National Institute for Health and Care Excellence

Health Technology Evaluation

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated unresectable advanced malignant pleural mesothelioma

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	Company (MSD)	MSD believe that it is appropriate to refer this topic to NICE for appraisal, and that the STA cost-comparison is appropriate. The NICE Guide to the methods of technology appraisal states that a cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication. To establish clinical similarity, we are conducting clinical systematic literature reviews, and network meta-analysis to estimate the relative efficacy and safety of pembrolizumab plus chemotherapy against other first-line treatments for unresectable, advanced, or metastatic malignant pleural mesothelioma in adults, which include nivolumab plus ipilimumab (TA818) and pemetrexed plus cisplatin (TA135).	Thanks for your comments

Section	Stakeholder	Comments [sic]	Action
	Mesothelioma UK	Appropriate	Thanks for your comment
	British Thoracic Oncology Group	Agree its appropriate	Thanks for your comment
	The Association of Respiratory Nurses	Highly appropriate to consider given evidence from phase 3 trials suggesting improved response rates, progression free and overall survival	Thanks for your comment
Wording	Company (MSD)	We suggest that dates are added for the NICE technology appraisal guidance referred to in paragraph 3 (TA818 and TA135). The TA818 guidance was published in August 2022, and recommends nivolumab plus ipilimumab for patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and thus supersedes guidance TA135 (published January 2008) for patients in this subpopulation. The recommendation for pemetrexed plus cisplatin (TA135) still applies for patients outside of the ECOG score of 0-1 subgroup, such as those who are considered to have advanced disease and for whom surgical resection is considered inappropriate. Of note, pemetrexed plus cisplatin/carboplatin was the comparator against which nivolumab plus ipilimumab demonstrated cost effectiveness in TA818. We also suggest adding (to paragraph 3) the date on which the relevant guidelines were published. The British Thoracic Society guidelines were published in March 2018 and have not been updated since the introduction of nivolumab plus ipilimumab (TA818 guidance published August 2022), thus recommendations in relation to nivolumab plus ipilimumab have not been captured for this patient population. Expert opinion is that the recommendations in this guideline are now outdated and largely irrelevant when it comes to treatment decision making. Oncologists follow the most up-to-date technology assessment guidance issued by NICE.	Thank you for your comments. While nivolumab and ipilimumab may now be used more in clinical practice for patients with ECOG status of 0 or 1, TA135 guidance has not been changed since TA818 has published. However, the publication dates of TA818 and TA135 have been added. The ESMO clinical practice guidelines have not been added. The

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		We also recommend the inclusion of the most recent European Society for Medical Oncology (ESMO) Clinical Practise Guidelines,[1] which recommend nivolumab plus ipilimumab as first-line treatment for malignant pleural mesothelioma patients with an ECOG status of 0-1.	background section is intended to be a brief summary of the background to disease area and treatment pathway, and where available, clinical practice guidelines that are specific to NHS practice are referenced, rather than those that apply to wider regions. However, as the British Thoracic Society guidelines are now outdated, these have been removed.
	Mesothelioma UK	No comments	No response needed
	British Thoracic Oncology Group	No comment	No response needed
	The Association of Respiratory Nurses	Clear and concise	Thanks for your comment

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Timing	Company (MSD)	Given the unmet need for additional clinically effective treatments for malignant pleural mesothelioma in the NHS, the timelines proposed for this appraisal are considered suitable.	Thanks for your comment
	Mesothelioma UK	Not urgent	Thanks for your comment
	British Thoracic Oncology Group	Not urgent	Thanks for your comment
	The Association of Respiratory Nurses	New and emerging evidence Patient awareness	Thanks for your comment

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Company (MSD)	NA	No response needed
	Mesothelioma UK	Looks fine	Thanks for your comment
	British Thoracic Oncology Group	It looks ok	Thanks for your comment

Section	Consultee/ Commentator	Comments [sic]	Action
	The Association of Respiratory Nurses	Appropriate	Thank you for your comment
Population	Company (MSD)	MSD suggest amending the population to: adults with untreated unresectable advanced malignant pleural mesothelioma if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.	Thanks for your comment. The population is kept broad at this stage.
	Mesothelioma UK	Yes	Thanks for your comment
	British Thoracic Oncology Group	yes	Thanks for your comment
	The Association of Respiratory Nurses	Yes clearly defined	Thank you for your comment
Subgroups	Company (MSD)	At this time MSD do not expect there to be any specific subpopulations narrower than the target population described above in whom pembrolizumab may provide greater clinical benefits or more value for money.	Thanks for your comment
	Mesothelioma UK	Subgroups are represented	Thanks for your comment
	British Thoracic Oncology Group	The proposed subgroups are appropriate	Thanks for your comment

Section	Consultee/ Commentator	Comments [sic]	Action
	The Association of Respiratory Nurses	Is ECOG performance status considered	Thanks for your comment. ECOG status has been added as a subgroup.
Comparators	Company (MSD)	We propose that the relevant comparator for pembrolizumab plus chemotherapy in this indication is nivolumab plus ipilimumab, for the reasons described below: Based on NICE guidelines (TA818), nivolumab plus ipilimumab is recommended for untreated unresectable malignant pleural mesothelioma in adults with an ECOG performance status of 0 or 1, which was the clinical trial population in the pivotal CheckMate 743 trial.[2] Due to the restricted patient population in the clinical trial, the company did not consider best supportive care a relevant comparator, which was accepted by the NICE Committee. Similarly, the population investigated in the pivotal clinical trial evaluating pembrolizumab, KEYNOTE-483, was those with an ECOG score of 0 or 1. As discussed above, NICE guidance TA818 supersedes guidance TA135, and thus the recommendation for pemetrexed (plus cisplatin or carboplatin) as first-line treatment applies to patients outside of the ECOG 0-1 status subgroup. In addition, from our discussions with clinical experts, it is clear that nivolumab + ipilimumab is the first-line treatment of choice. Clinical experts have stated in our discussions 'chemotherapy alone has no place in the first-line treatment of mesothelioma', and that 'denying access to immunotherapy for mesothelioma patient would be criminal'. Chemotherapy alone is reserved in the first-line treatment of mesothelioma only when a patient is contraindicated for immunotherapy. These patients would also be contraindicated to pembrolizumab and are therefore not a relevant group in this appraisal. Pembrolizumab+chemotherapy is an alternative treatment option for patients who would otherwise have had nivolumab+ipilimumab. Therefore,	Thanks for your comments. The population for the scope is 'Adults with untreated unresected advanced malignant pleural mesothelioma'. As nivolumab with ipilimumab is only recommended in people with ECOG PS of 0 or 1, some people within the population for this appraisal will not be eligible for nivolumab with ipilimumab and may have pemetrexed with cisplatin/carboplatin. As noted in NICE's health technology evaluations manual (section 2.2.12), 'The scope identifies all potentially relevant comparators that are

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		pemetrexed plus cisplatin/carboplatin is not a relevant comparator to pembrolizumab. In addition, the ESMO Clinical Practice Guidelines recommend nivolumab plus ipilimumab as first-line treatment for patients with an ECOG status of 0 or 1. Pemetrexed+platinum is recommended as second-line treatment if disease progresses. The consensus among clinicians from our discussions was that chemotherapy is reserved for subsequent lines of therapy. Therefore, pemetrexed+platinum chemotherapy is not a suitable comparator for pembrolizumab. As pembrolizumab aims to treat the same patient population as nivolumab plus ipilimumab, nivolumab plus ipilimumab is the most suitable comparator.	established practice in the NHS. It considers issues likely to be discussed by the committee when selecting the most appropriate comparator. At this stage of the evaluation, identifying comparators should be inclusive.' As noted above, TA135 guidance has not been changed since TA818 has published.
	Mesothelioma UK	Currently – Ipilimumab and Nivolumab are the standard of care access through Blueteq Criteria and remains the only route to immunotherapy	Thanks for your comment. The population for the scope is 'Adults with untreated unresected advanced malignant pleural mesothelioma'. As nivolumab with ipilimumab is only recommended in people with ECOG PS of 0 or 1, some people within the population for this

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			appraisal will not be eligible for nivolumab with ipilimumab and may have pemetrexed with cisplatin/carboplatin. As noted in NICE's health technology evaluations manual (section 2.2.12), 'The scope identifies all potentially relevant comparators that are established practice in the NHS. It considers issues likely to be discussed by the committee when selecting the most appropriate comparator. At this stage of the evaluation, identifying comparators should be inclusive.
	British Thoracic Oncology Group	Nivolumab + ipilimumab is the main standard of care 1st line in England. Blueteq criteria allow this as the only way to access immunotherapy for mesothelioma patients. Those unfit for nivo-ipi might get pemetrexed with platinum. We feel carboplatin is used more than cisplatin.	Thanks for your comment. The population for the scope is 'Adults with untreated unresected advanced malignant pleural

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			mesothelioma'. As nivolumab with ipilimumab is only recommended in people with ECOG PS of 0 or 1, some people within the population for this appraisal will not be eligible for nivolumab with ipilimumab and may have pemetrexed with cisplatin/carboplatin. As noted in NICE's health technology evaluations manual (section 2.2.12), 'The scope identifies all potentially relevant comparators that are established practice in the NHS. It considers issues likely to be discussed by the committee when selecting the most appropriate comparator. At this stage of the evaluation, identifying comparators should be inclusive.

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	The Association of Respiratory Nurses	Yes	Thank you for your comment
Outcomes	Company (MSD)	We consider these as the appropriate outcomes to be assessed in this appraisal.	Thank you for your comment
	Mesothelioma UK	Yes	Thank you for your comment
	British Thoracic Oncology Group	Yes they are appropriate	Thank you for your comment
	The Association of Respiratory Nurses	Outcome measures appropriate Could have considered QoL, PROMs	Thank you for your comment. The outcome in the scope on health-related quality of life will capture QoL and PROMS.
Equality	Company (MSD)	Malignant pleural mesothelioma predominantly affects elderly male individuals; more than 50% of diagnosis occur in people aged 75 and older, and between 2016 and 2018 83% of diagnoses were in men.[3] Therefore, it is important to note that the age and sex of most patients in this indication is a protected characteristic. Historically, malignant pleural mesothelioma cases are linked to those who work in construction or manufacturing who are exposed to asbestos directly in the workplace.[4] Whilst this is still the case, there is growing evidence of other occupations developing asbestos-related diseases from other workplace areas that contain asbestos, such as hospitals and schools. Incidental	Thank you for your comment. These have been listed in the Equalities Impact Assessment and will be considered by the committee during the appraisal.

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		exposure to asbestos has been seen in teachers, doctors, nurses and other employees who do not come into direct contact with asbestos.[6]	
	Mesothelioma UK	No issues raised	Thank you for your comment
	British Thoracic Oncology Group	No issues here	Thank you for your comment
	The Association of Respiratory Nurses	No concerns identified	Thank you for your comment
Questions for consultation	Company (MSD)	Where do you consider pembrolizumab with pemetrexed and platinum-based chemotherapy will fit into the existing care pathway for untreated unresectable advanced malignant pleural mesothelioma? • MSD response: We consider pembrolizumab with pemetrexed and platinum-based chemotherapy to be an alternative first-line treatment option for patients with untreated unresectable malignant pleural mesothelioma with an ECOG performance status of 0 or 1. We consider pembrolizumab plus pemetrexed and platinum-based chemotherapy to be a direct competitor to nivolumab plus ipilimumab. In practice, would pembrolizumab with pemetrexed be offered with any platinum-based chemotherapies other than cisplatin? • MSD response: We would like to correct the wording of the question as pembrolizumab with pemetrexed would be offered with cisplatin or carboplatin, as per the clinical trial population in KEYNOTE-483.[5] Of patients in the pembrolizumab plus chemotherapy arm (N=222), 42% received cisplatin only, 43% carboplatin only, and 14% of patients switched from cisplatin to carboplatin treatment due to cisplatin-	Thanks for your comments. As noted above, the population for the scope is 'Adults with untreated unresected advanced malignant pleural mesothelioma'. As nivolumab with ipilimumab is only recommended in people with ECOG PS of 0 or 1, some people within the population for this appraisal will not be eligible for nivolumab

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		related adverse events.[5] The NICE Committee in TA818 stated that carboplatin as first choice and cisplatin if not tolerated better reflects UK current clinical practice. Would pembrolizumab with pemetrexed and platinum-based chemotherapy be a candidate for managed access? • MSD response: at present, MSD is submitting this appraisal for routine commissioning route. Do you consider that the use of pembrolizumab with pemetrexed and platinum-based chemotherapy can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? • MSD response: We do not consider that there will be 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 committee to take account of these benefits. MSD response: relevant inputs in support of the submission will be taken from the final KEYNOTE-483 trial data.	with ipilimumab and may have pemetrexed with cisplatin/carboplatin. As noted in NICE's health technology evaluations manual (section 2.2.12), 'The scope identifies all potentially relevant comparators that are established practice in the NHS. It considers issues likely to be discussed by the committee when selecting the most appropriate comparator. At this stage of the evaluation, identifying comparators should be inclusive. The scope refers to platinum-based chemotherapy so would capture cisplatin or carboplatin.

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	Mesothelioma UK	using chemotherapy in combination with immunotherapy in the first line setting could be used an alternative to immunotherapy only	Thank you for your comment. The population for the scope is 'Adults with untreated unresected advanced malignant pleural mesothelioma'. As nivolumab with ipilimumab is only recommended in people with ECOG PS of 0 or 1, some people within the population for this appraisal will not be eligible for nivolumab with ipilimumab and may have pemetrexed with cisplatin/carboplatin. As noted in NICE's health technology evaluations manual (section 2.2.12), 'The scope identifies all potentially relevant comparators that are established practice in the NHS. It considers issues likely to be discussed by the committee when

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			selecting the most appropriate comparator. At this stage of the evaluation, identifying comparators should be inclusive.
	British Thoracic Oncology Group	We feel this combination of chemotherapy+ immunotherapy will be a potential 1st line option as an alternative to dual immunotherapy (nivo=ipi). We feel this treatment will be offered with carboplatin predominantly. There is a body of evidence showing carboplatin and cisplatin are equivalent in efficacy. Cisplatin uses a chemo chair for most of the day while carboplatin is a <1hr infusion.	Thank you for your comments.
	The Association of Respiratory Nurses	Please consider effect on QoL/ PROMs given adverse effects and short time limited progression free and overall survival	Thank you for your comment. The outcome in the scope on health-related quality of life will capture QoL and PROMS.

Reference from company:

1. Popat S, Baas P, Faivre-Finn C, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(☆). *Ann Oncol*. 2022; 33(2):129-42.
2. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. *Lancet*. 2021; 397(10272):375-86.
3. Physicians RCo. National Mesothelioma Audi. 2020. Available at: https://www.rcplondon.ac.uk/projects/national-mesothelioma-audit. Accessed: February 2024.

4. England N. Mesothelioma. 2022. Available at: https://www.nhs.uk/conditions/mesothelioma/. Accessed: Feb 2024.
5. Chu Q, Perrone F, Greillier L, et al. Pembrolizumab plus chemotherapy versus chemotherapy in untreated advanced pleural mesothelioma in Canada, Italy, and France: a phase 3, open-label, randomised controlled trial. *Lancet*. 2023; 402(10419):2295-306.
6. Mesothelioma UK. Clearing The Air: The costs and benefits of removing asbestos from UK schools and hospitals. Available from [last accessed 14 Feb 2024]: https://www.mesothelioma.uk.com/downloads/clearing-the-air-the-costs-and-benefits-of-removing-asbestos-from-uk-schools-and-hospitals/?wpdmdl=20853