National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab for adjuvant treatment of resected non-small-cell lung cancer [ID3907]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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
Appropriateness	MSD UK (company)	MSD consider it appropriate to refer this topic to NICE for appraisal.	Thank you for your comment. No action required.
Wording	MSD UK (company)	MSD consider it appropriate to refer this topic to NICE for appraisal.	Thank you for your comment. No action required.
Timing Issues	MSD UK (company)	Despite the availability of treatments with curative intent (e.g., surgery), there is a high unmet need for this population that would benefit from new treatments aiming at reducing the risk of recurrence and improving survival outcomes. Based on this, the current appraisal should be carried out in line with current NICE scheduling, to allow timely patient access after the indication has obtained regulatory approval.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit		No comments	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	MSD UK (company)	The background information is accurate and comprehensive	Thank you for your comment. No action required.
The technology/ intervention	MSD UK (company)	Yes, the draft scope wording accurately reflects the intervention	Thank you for your comment. No action required.
Population	MSD UK (company)	MSD suggest that the description of the population be amended as follows (amendment in italics) “Adults with NSCLC who have undergone *complete* surgical resection with or without adjuvant chemotherapy”, as no evidence of disease (NED) at clinical examination and baseline radiological assessment was required by the trial protocol prior to randomisation. With regard to subgroups, MSD believe that subgroups by stage should not be considered separately for the following reasons: • Whilst stage was a stratification factor in the PEARLS/KEYNOTE-091 trial (the pivotal trial supporting this appraisal), the trial was not powered to detect differences in treatment effects in these subgroups and, considering the smaller sample size and the inherent exploratory nature of	Comments noted. The technology will be appraised according to its marketing authorisation. Staging remains as a subgroup for consideration. No action required.

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		subgroup analyses, no valid and reliable conclusions can be drawn about the effectiveness of the technology in these subgroups. • Current standard of care (SoC) for NSCLC patients after complete surgical resection with or without adjuvant chemotherapy is the same regardless of stage of cancer prior to surgery and therefore clinical effectiveness and cost effectiveness of the technology in these subgroups would be evaluated in comparison with same SoC. Analysis of subgroups by stage was not included in the final scope of the appraisal for a similar indication [ID3852].	
Comparators	MSD UK (company)	MSD agree that active monitoring reflects the standard of care in the UK for adults with NSCLC who have undergone complete surgical resection with or without adjuvant chemotherapy, and therefore is considered the best alternative care. It should be noted that in the PEARLS/KEYNOTE-091 trial (the pivotal trial supporting this appraisal), pembrolizumab was compared to placebo to allow an unbiased evaluation of the outcomes. Both arms underwent regular disease evaluation (active monitoring) such as chest/upper abdomen CT scan and brain CT and/or MRI if clinically indicated. Randomisation to pembrolizumab or placebo occurred among patients who had no evidence of disease after completion of a radical treatment plan (surgery with or without adjuvant chemotherapy). Patients for whom adjuvant chemotherapy prior to pembrolizumab was not considered to be appropriate would not receive cisplatin-based chemotherapy as alternative treatment to pembrolizumab, and therefore “Cisplatin-based chemotherapy” is not considered a relevant comparator in this population. MSD would like to note that atezolizumab only has obtained a marketing authorisation for adult patients with Stage II to IIIA NSCLC whose tumours	Comments noted. The scope has been updated to note that atezolizumab is only licensed for people whose tumours express PD-L1 with a tumour proportion score of at least 50%. The scope has been updated to state that active monitoring is established clinical practice.

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		have PD-L1 expression on ≥ 50% of tumour cells (TC) following platinum-based adjuvant chemotherapy.	
Outcomes	MSD UK (company)	Response rate is not considered an appropriate outcome for the evaluation of an adjuvant treatment and was not collected in the KEYNOTE-091 trial, and therefore will not be included as an outcome in the submission. The remainder of the outcomes are considered relevant as they capture the most important health-related benefits (and harms) of the technology.	Thank you for your comment. Response rate has been removed as an outcome in the scope.
	Roche	Response rate is not an appropriate outcome - not possible in this stage of NSCLC due to surgery	Thank you for your comment. Response rate has been removed as an outcome in the scope.
Economic analysis		No comments	
Equality and Diversity	MSD UK (company)	MSD do not consider that 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 the treatment will be licensed or could lead to recommendations that have a different impact on people protected by the equality legislation or could have any adverse impact on people with a particular disability or disabilities.	Thank you for your comment. No action required.
Other considerations		No comments	
Innovation	MSD UK (company)	MSD consider pembrolizumab to be innovative in its potential to make a significant and substantial positive impact on health-related benefits. No	Thank you for your comment. Innovation

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		treatment is currently available as part of the standard of care and patients would benefit from a new adjuvant treatment aiming at improving patients' outcomes. This technology would represent a 'step-change' in the management of the condition. Surgery is a treatment with curative intent and pembrolizumab has the potential to improve the probability that surgery is genuinely curative. This is an important outcome for all stakeholders. MSD expect that the health-related quality of life benefits of receiving adjuvant pembrolizumab treatment will be captured within the QALY calculation. PEARLS/KEYNOTE-091 trial (NCT02504372), a randomised, triple-blinded phase III trial evaluating pembrolizumab versus placebo in participants with stage IB/II-IIIA NSCLC who have undergone surgical resection with or without adjuvant chemotherapy, will inform the evidence base for this submission**.**	will be considered in more detail as part of the full appraisal. No action required.
Questions for consultation	MSD UK (company)	**Question: Have all relevant comparators for pembrolizumab for adjuvant treatment of fully resected non-small-cell lung cancer with and without adjuvant treatment been included in the scope?** Answer: Yes, all relevant comparators have been included in the scope. Please see MSD additional comments under 'comparators' section. **Question: Are all people with fully resected UICC v7 stage II to IIIA (and stage IB with a tumour size of 4 cm or greater) suitable for adjuvant therapy?** Answer: Based on feedback from UK clinical experts, it is our understanding that some of the people with fully resected stage IB (tumour size of 4 cm or greater) to IIIA NSCLC may not be suitable for adjuvant chemotherapy as they are not fit enough due to comorbidities (e.g., cardiovascular diseases). Patient choice is also an important factor alongside 'suitability'. The	Comments noted. Please see relevant sections of this document for related response

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		proportion of patients receiving adjuvant chemotherapy varies greatly across centres, ranging from 10% to 80%. **Question: How should 'established clinical management without pembrolizumab' be defined?** Answer: Currently, established clinical management of people with fully resected stage IB (tumour size of 4 cm or greater) to IIIA NSCLC after receiving adjuvant chemotherapy (if suitable), is active monitoring which includes CT scan repeated every 3-6 months, with interval between scans extending after 1 year. No alternative treatment is available for this population. **Question: What considerations are made in determining whether pembrolizumab is used before or after adjuvant chemotherapy?** Answer: Pembrolizumab has been evaluated as adjuvant treatment in NSCLC patients after they have received adjuvant chemotherapy or without prior adjuvant chemotherapy as per relevant local guidelines. The effectiveness of pembrolizumab before adjuvant chemotherapy has not been evaluated and therefore it is not known. **Question: Is there a routine test to detect the biomarker PD-L1 in resected samples?** Answer: Routine PD-L1 testing in early-stage lung cancer is understood to be widely available as part of the care pathway. It consists of immunohistochemical (IHC) assay, with the most common being 22C3, SP263, SP142 and 28-8. **Question: Are the outcomes listed appropriate?**	

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		Answer: Response rate is not considered an appropriate outcome for the evaluation of an adjuvant treatment and was not collected in the PEARLS/KEYNOTE-091 trial, and therefore will not be included as an outcome in the submission. The remainder of the outcomes are considered relevant as they capture the most important health-related benefits (and harms) of the technology. **Question: 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?** Answer: MSD believe that subgroups by stage should not be considered separately for the following reasons: • Whilst stage was a stratification factor in the PEARLS/KEYNOTE-091 trial, the trial was not powered to detect differences in treatment effects in these subgroups and, considering the smaller sample size and the inherent exploratory nature of subgroup analyses, no valid and reliable conclusions can be drawn about the effectiveness of the technology in these subgroups. • Current standard of care (SoC) for NSCLC patients after complete surgical resection with or without adjuvant chemotherapy is the same regardless of stage of tumour so clinical effectiveness and cost effectiveness of the technology in these subgroups would be evaluated in comparison with same SoC. • Analysis of subgroups by stage was not included in the final scope of the appraisal for a similar indication [ID3852]. **Question: NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.**	

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		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 pembrolizumab 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.** Answer: Please see MSD comments under 'equality' section. **Question: Do you consider pembrolizumab 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)?** Answer: MSD consider pembrolizumab to be innovative in its potential to make a significant and substantial positive impact on health-related benefits. No treatment is currently available as part of the standard of care and patients would benefit from a new adjuvant treatment aiming at improving patients' outcomes. This technology would represent a 'step-change' in the management of the condition. Surgery is a treatment with curative intent and	

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		pembrolizumab has the potential to improve the probability that surgery is genuinely curative. This is an important outcome for all stakeholders. • **Do you consider that the use of pembrolizumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Answer: MSD expect that the health-related quality of life benefits of receiving adjuvant pembrolizumab treatment will be captured within 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.** Answer: PEARLS/KEYNOTE-091 trial (NCT02504372), a randomised, triple-blinded phase III trial evaluating pembrolizumab versus placebo in participants with stage IB/II-IIIA NSCLC who have undergone surgical resection with or without adjuvant chemotherapy, will inform the evidence base for this submission. **Question: NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on NICE's health technology evaluation processes is available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation).** Answer: Single Technology Appraisal process is considered appropriate for the appraisal of this topic.	

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		Question: NICE's health technology evaluations: the manual states the methods to be used where a cost comparison case is made. • **Would it be appropriate to use the cost-comparison methodology for this topic?** • **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** Answer: A cost-comparison methodology is not deemed appropriate for this topic as the new technology has shown to provide greater health benefits than currently relevant comparators and the costs are likely to be higher. • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Answer: The primary outcome of the trial is still considered relevant, appropriate and will be a key driver of the economic model. • **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?** Answer: MSD will conduct a systematic literature review (SLR) that aims to identify all relevant evidence about comparators published until search date. With regard to the currently relevant comparator (i.e., active monitoring), MSD do not anticipate new evidence from ongoing trials to be available within the timelines of this appraisal.	
	Roche	What considerations are made in determining whether pembrolizumab is used before or after adjuvant chemotherapy? Trial design should be considered - it should also be noted that KEYNOTE-091 allowed patients to receive chemotherapy as an option. However the disease free survival subgroup analysis, currently suggests that the patients who did not receive adjuvant chemotherapy prior to pembrolizumab treatment	Comments noted. Subgroup analysis by PD-L1 expression will be considered subject to evidence availability.

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		did not perform as well (Paz-Ares, et al. ESMO Plenary 2022 (Abs VP3-2022)). Is there a routine test to detect the biomarker PD-L1 in resected samples? TC based PD-L1 assays are the most commonly used in the UK (22C3 and SP263). 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? PD-L1 expression subgroups - data from KEYNOTE-091 trial suggests that it may not be as effective in the ≥50% patients (Paz-Ares, et al. ESMO Plenary 2022 Abs VP3-2022)	
Additional comments on the draft scope		No comments	

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