National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score

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
Wording	BTOG-NCRI-ACP-RCP-RCR	The wording is appropriate	Thank you, your comment has been noted. No changes to the scope are needed.
	MSD UK	The wording of this remit is likely to reflect the population included in KEYNOTE-042 trial, the pivotal study that provides the main evidence for this appraisal. [redacted]	Thank you, your comment has been noted. No changes to the scope are needed.
Timing Issues	BTOG-NCRI-ACP-RCP-RCR	Keynote 042 study looking at PDL1 positive patients (>1%) has not reported. This study is recruiting patients.	Thank you for your comment. Results from Keynote 042 will be provided by the

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			company during the development of this appraisal as part of the company submission. No changes to the scope are needed.
	MSD UK	There is a significant need for new, and effective, therapies for patients with lung cancer.	Thank you, your comment has been noted. No changes to the scope are needed.
Additional comments on the draft remit	BTOG-NCRI-ACP-RCP-RCR	Currently approval is for pembrolizumab for untreated lung cancer patients >50% PDL1 expression. Secondline after chemotherapy offered to those <50%. All PDL1 positive lung cancer patients should receive at some point in treatment pathway.	Thank you, your comment has been noted. No changes to the scope are needed.

Comment 2: the draft scope

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Background information	BTOG-NCRI-ACP-RCP-RCR	Accurate background information	Thank you for your comment.
	MSD UK	No comments	Thank you.

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The technology/ intervention	BTOG-NCRI-ACP-RCP-RCR	Accurate description of pembrolizumab	Thank you for your comment.
	MSD UK	Yes	Thank you for your comment.
Population	BTOG-NCRI-ACP-RCP-RCR	Population of lung cancer patients with enough tissue for PDL1 testing	Thank you for your comment. It is anticipated that practical issues, such as PD-L1 testing will be discussed at the appraisal committee meeting. No changes to the scope are needed.
	MSD UK	As described above, the population of interest for this indication will include patients with advanced or metastatic NSCLC whose tumours express PD-L1 (tumour proportion score ≥1%) who have received no prior systemic chemotherapy treatment and in whom EGFR or ALK-directed therapy is not indicated.'	Thank you, your comment has been noted. The population section has been amended.
	Royal College Of Pathologists	As this drug already has an approval for patients with at least 50% positive staining for tumours, the NHS has already set up and pays for the relevant antibody test (current companion diagnostic is 22C3). However, there are increasing amounts of published data on other antibody tests being comparable and this is something that might require discussion if this appraisal goes beyond scoping.	Thank you for your comment. It is anticipated that practical issues, such as PD-L1 testing will be discussed at the appraisal committee meeting. No changes to the scope are needed.
Comparators	BTOG-NCRI-ACP-RCP-RCR	Comparators:	Thank you for your comment. The comparators listed in the scope are those currently

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		Platinum doublet chemotherapy with pemetrexed, gemcitabine, vinorelbine, paclitaxel (US mainly) Pemetrexed maintenance until PD for Nonsquamous lung cancers	used in UK clinical practice. Pemetrexed maintenance treatment is already included in the list of comparators. The appraisal committee will discuss the relevant comparator during the development of this appraisal. No changes to the scope are needed.
	MSD UK	MSD agrees with the following two proposed comparators: • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only) o with or without pemetrexed maintenance treatment (following cisplatin-containing regimens only) However, MSD believes that single agent chemotherapy (docetaxel, gemcitabine, paclitaxel, or vinorelbine; for people for whom platinum combination therapy is not appropriate) should not be considered appropriate comparators. This position is supported by the fact that based on recent market shares observed in the UK, less than 3% of	Thank you for your comment. We agree that single-agent chemotherapy can be removed from the scope as a comparator. In technology appraisal 447 the clinical experts highlighted that it is mainly used as an option for previously treated disease. The scope has been updated to reflect this.

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		patients are unsuitable to receive platinum containing chemotherapy as first-line therapy; and in discussion with clinical oncologists they cannot see why these patients would behave differently from patients treated with platinum containing chemotherapy in the first-line setting.	
Outcomes	BTOG-NCRI-ACP-RCP-RCR	• overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life. All appropriate outcomes	Thank you, your comment has been noted. No changes to the scope are needed.
	MSD UK	MSD agrees with the proposed outcome measures. In addition, it is known that the response to immunotherapies (immuno-oncology drugs) may be delayed, but once triggered, is likely to be durable, bringing unquantifiable long term survival benefit for a subset of patients. This benefit is not captured by the proposed outcome measures, thus MSD suggests the inclusion of “Duration of Response” as an additional outcome measure.	Thank you for your comment. Duration of response has been added as an outcome.
Economic analysis	BTOG-NCRI-ACP-RCP-RCR	Chemotherapy/pembrolizumab combination is now FDA/EMA approved. Likley to be used for low PDL1 expressors	Thank you, your comment has been noted. No changes to the scope are needed.
	MSD UK	No comments.	Thank you.
Equality and Diversity	BTOG-NCRI-ACP-RCP-RCR	No equality issues	Thank you for your comment. It is anticipated that issues

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		As long as PDL1 testing is available to all lung cancer patients	such as PD-L1 testing will be discussed at the appraisal committee meeting. No changes to the scope are needed.
	MSD UK	No comments.	Thank you.
Other considerations	BTOG-NCRI-ACP-RCP-RCR	Immunotherapy doublet with PD1/PDL1 antibodies and CTLA4 antibodies is being tested in 1st line patients with any level of PDL1 including negative. Clinical trials completed recruitment.	Thank you, your comment has been noted. No changes to the scope are needed.
	MSD UK	No comments.	Thank you.
Innovation	BTOG-NCRI-ACP-RCP-RCR	The Keynote 042 data is not in the public domain yet. The study is still recruiting.	Thank you for your comment. Results from Keynote 042 should be provided by the company during the development of this appraisal as part of the company submission. No changes to the scope are needed.
	MSD UK	MSD considers pembrolizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits. Pembrolizumab was the first anti PD-1 pathway targeting agent to be approved with a companion diagnostic to identify patients whose tumours express PD-L1 as determined by a validated test.	Thank you, your comment has been noted. No changes to the scope are needed.

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		Incorporation of pembrolizumab as first-line treatment for all patients whose tumours express PD-L1 (with TPS ≥1%), would represent a step-change in the management of advanced NSCLC.	
Questions for consultation	BTOG-NCRI-ACP-RCP-RCR	Pembrolizumab is not licensed for this first line indication for PDL1>1%	Thank you for your comment. The appraisal will be scheduled in order to provide timely guidance upon this technology receiving its marketing authorisation for this indication.
	MSD UK	Q: 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? Re: The ongoing clinical trial will assess efficacy in subgroups of participants with different levels of PD-L1 tumour expression. Q: Where do you consider pembrolizumab will fit into the existing NICE pathway, Lung cancer? Re: Pembrolizumab is expected to displace the use of chemotherapy as first-line therapy in patients with metastatic NSCLC whose tumours express PD-L1. Q: 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? Re: With the approach taken, by looking at an enriched population based on PD-L1 expression there is a potential to focus the treatment on the most appropriate patients. This will not be captured in the QALYs	Thank you, your comments have been noted. No changes to the scope are needed. The scope identifies principal measures of health outcome(s) that will be relevant for the estimation of clinical effectiveness. That is,

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		since the cost savings that will occur will refer to patients not treated with pembrolizumab. Additionally the benefits for carers/family will not be captured, nor any of the societal benefits from selected individuals returning to work or remaining in work for longer. Q: Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.	they measure health benefits and adverse effects that are important to patients and/or their carers. The clinical outcome measures usually quantify an impact on survival or health-related quality of life that translates into quality-adjusted life years (QALYs) for the evaluation of cost effectiveness. The committee will take into account the potential innovative nature of the technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure.

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		Re: MSD estimates that data will be available from the following multicentre, international, randomised, phase III trial: *"Study of MK-3475 (Pembrolizumab) Versus Platinum-based Chemotherapy for Participants With PD-L1-positive Advanced or Metastatic Non-small Cell Lung Cancer (MK-3475-042/KEYNOTE-042)" - NCT02220894* MSD estimates that the data that will be available can present some challenges given that the standard of care includes a variety of combinations of platinum based chemotherapy, and some of those have not been recommended by NICE for use in the UK. This is expected to also have implications in terms of heterogeneity of any indirect treatment comparisons that may be conducted. Q: To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. Re: MSD does not consider that there will be any barriers to adoption of this technology since pembrolizumab in additional NSCLC indications is already recommended by NICE. Q: Would it be appropriate to use the cost comparison methodology for this topic? Re: MSD does not consider the cost comparison methodology is appropriate for this topic. Q: Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?	

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		Re: MSD anticipates that pembrolizumab will offer significant additional clinical efficacy over current comparators, at incremental cost. Q: Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Re: Yes, the primary outcome measure of overall survival used in the pivotal KEYNOTE-042 trial remains the most clinically relevant endpoint for a cancer study. Q: Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year? Re: MSD is not aware of any substantial new evidence for the comparator technologies considered.	
Additional comments on the draft scope	British Thoracic Society	The British Thoracic Society welcomes the appraisal of Pembrolizumab for untreated PD-L1 positive non-small-cell lung cancer with at least 1% tumour proportion score ID1247. We note the draft scope and have no additional points to make. We look forward to seeing the appraisal report.	Thank you, your comments have been noted. No changes to the scope are needed.
	MSD UK	Within the cover letter for the draft scope consultation (dated 17 November 2017), expected timings for the appraisal are indicated, with a February 2018 start and mid-April submission deadline. Based on our current estimated regulatory filing date of [redacted] we would suggest these proposed timings are inappropriate.	Thank you for your comment. The appraisal will be scheduled in order to provide timely guidance upon this technology receiving its marketing authorisation for this indication.