National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Pembrolizumab with pemetrexed and platinum chemotherapy for untreated metastatic non-squamous non-small-cell lung cancer [ID1173]

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	Merck Sharp & Dohme (MSD)	In order to be consistent with the anticipated licence indication, please amend: *"in combination with chemotherapy within its marketing authorisation for treating advanced, metastatic, non-squamous non-small-cell lung cancer"* to *"in combination with pemetrexed and platinum within its marketing authorisation, for the first-line treatment of patients with metastatic non-squamous NSCLC".*	Thank you for your comment. The remit and the title have been amended to reflect the anticipated license indication.
	Royal College of Pathologist (RCP)	Yes	Comments noted. No action required.
	BTOG-NCRI-ACP-RCP-RCR	Progression free survival only currently in the public arena. Overall survival not reached. Meaningful difference in PFS as below.	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing issues	MSD	MSD believes that the scoping and provisional scheduling of this appraisal topic is premature. Please note that the EU regulatory submission, filed in March 2017, was based on data from the Phase I/II study KEYNOTE-021G, which had a primary endpoint of objective response rate (ORR). There is an ongoing Phase III trial (KEYNOTE-189) in the relevant patient population covered by this planned appraisal. [redacted]	Thank you for your comment. The timelines for this appraisal will be revised to allow the inclusion of important data in the submission.
	RCP	Urgent	Thank you for your comment. The timelines for this appraisal will be revised to allow the inclusion of important data in the submission.
	BTOG-NCRI-ACP-RCP-RCR	Currently chemotherapy (platinum/pemetrexed) only offered to PDL1<50% to advanced NSCLC	Comments noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	MSD	No additional comments	Noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	RCP	Ok	Comments noted. No action required.
	BTOG-NCRI-ACP-RCP-RCR	Background information is accurate and true reflection of practice	Comments noted. No action required.
The technology/ intervention	MSD	No additional comments	Noted. No action required.
	RCP	Yes	Comments noted. No action required.
	BTOG-NCRI-ACP-RCP-RCR	Pembrolizumab and platinum/pemetrexed chemotherapy in non-squamous cell NSCLC	Thank you for your comment. The remit, the title and the PICO table have been amended to reflect the anticipated license indication.
Population	MSD	No additional comments	Noted. No action required.
	RCP	If the levels of expression of PD-L1 are relevant to consideration for therapy, this will have implications for histopathology	Thank you for your comment. The population is currently defined in line with the broader trial population. The appraisal committee will take into account any additional requirements

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			associated with identifying potential subgroups of interest.
	BTOG-NCRI-ACP-RCP-RCR	Population defined is from Keynote 021 Cohort G of an open label multi-arm first line study. • EGFR/ALK non-mutated • Irrespective of PDL1 expression 123 patients treated with pembrolizumab/carboplatin/pemetrexed	Comments noted. No action required.
Comparators	MSD	No additional comments - we agree with the proposed comparators	Comments noted. No action required.
	BTOG-NCRI-ACP-RCP-RCR	• Carboplatin/pemetrexed (no maintenance) • Cisplatin/pemetrexed followed by pemetrexed maintenance • PDL1>50%: Pembrolizumab alone Valid comparators	Comments noted. No action required.
Outcomes	MSD	MSD agrees with the proposed outcome measures. However, 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. The outcome ‘duration of response’ has been added to the list of outcomes.
	BTOG-NCRI-ACP-RCP-RCR	Outcomes measures all valid. Median overall survival not achieved at time of writing	Comments noted. No action required.

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Economic analysis	MSD	No additional comments	Noted. No action required.
	RCP	The level of expression testing will have significant implications for pathology as the tests are currently “companion diagnostics” and relatively expensive (and time consuming)	Thank you for your comment. Any additional resource needed for this technology will be incorporated in the economic analyses for the committee’s consideration.
	BTOG-NCRI-ACP-RCP-RCR	This space will also be contended by immunotherapy combinations: Eg. Ipilumimab/nivolumab, nivolumab/chemo	Comments noted. No action required.
Equality and Diversity	MSD	No additional comments	Noted. No action required.
	BTOG-NCRI-ACP-RCP-RCR	None identified	Comments noted. No action required.
Other considerations	MSD	No additional comments	Noted. No action required.
	RCP	The impact on laboratory staff to deal with the increased immunohistochemistry also needs to be considered as a cost implication	Thank you for your comment. Any additional resource needed for this technology will be incorporated in the economic analyses for

Section	Consultee/ Commentator	Comments [sic]	Action
			the committee's consideration.
	BTOG-NCRI-ACP-RCP-RCR	Toxicity is likely to be greater: Immune-mediated adverse reactions occurred with pembrolizumab including pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis. Pembrolizumab can also cause severe or life-threatening infusion-related reactions	Thank you for your comment. Adverse effects of treatment is included as an outcome in the scope and will be discussed during the appraisal.
Innovation	MSD	No additional comments	Noted. No action required.
	BTOG-NCRI-ACP-RCP-RCR	Data on which FDA approval based, is included below	Comments noted. No action required.
Questions for consultation	MSD	**Question:** Is pembrolizumab likely to be used in combination with third generation chemotherapy and platinum in people with non-squamous non-small-cell lung cancer? **Answer:** The anticipated licence will only cover pembrolizumab in combination with pemetrexed and platinum, for the first-line treatment of patients with metastatic non-squamous NSCLC **Question:** Is pembrolizumab likely to be used only in people with stage IV non-squamous non-small-cell lung cancer? **Answer:** Yes, as we anticipate that the licence will specify "patients with advanced, metastatic non-squamous NSCLC".	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Question: Have all relevant comparators for pembrolizumab been included in the scope? **Answer:** Yes, we believe all relevant comparators have been considered **Question:** Which treatments are considered to be established clinical practice in the NHS for untreated stage IV non-squamous non-small-cell lung cancer? **Answer:** With the exception of pembrolizumab, we believe all comparators listed are considered to be established clinical practice in the NHS for untreated stage IV non-squamous non-small-cell lung cancer. **Question:** Are the outcomes listed appropriate? **Answer:** We consider the outcomes listed are appropriate. We have additionally suggested one further outcome (duration of response) for consideration – please see above. **Question:** Are the subgroups suggested in 'other considerations 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? **Answer:** We consider the suggested subgroups to be appropriate **Question:** Where do you consider pembrolizumab will fit into the existing NICE pathway, Lung cancer? **Answer:** We anticipate that pembrolizumab in combination with chemotherapy will be positioned as an alternative first-line treatment option for patients with metastatic non-squamous NSCLC	

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	BTOG-NCRI-ACP-RCP-RCR	1. Pembrolizumab and chemotherapy likely to be used in the fitter population 2. Comparators included **3.** Pembro/chemo combination likely to be for fitter patients who are PDL1<50% or PDL1 negative **4.** Unlikely to be given to patients PDL1>50% as pembrolizumab first line less toxic and highly effective	Comments noted. No action required.
Any additional comments on the draft scope	BTOG-NCRI-ACP-RCP-RCR	Main Evidence: Keynote 021: Pembrolizumab plus pemetrexed/carboplatin demonstrated an objective response rate (ORR) that was nearly double the ORR of pemetrexed/carboplatin alone: 55% (95% confidence interval [CI] = 42–68) compared to 29% (95% CI = 18–41), respectively. All responses were partial responses. Among patients who received pembrolizumab plus pemetrexed/carboplatin, 93% had a duration of response of 6 months or more (range = 1.4+ to 13.0+ months) compared to 81% who received pemetrexed/carboplatin alone (range = 1.4+ to 15.2+ months). In addition, findings demonstrated an improvement in PFS (hazard ratio [HR] = 0.53; 95% CI = 0.31–0.91, P = .0205), with a median PFS of 13.0 months (95% CI = 8.3–not estimable) for patients treated with pembrolizumab plus pemetrexed/carboplatin compared to 8.9 months (95% CI = 4.4–10.3) with pemetrexed/carboplatin alone.	Comments noted. No action required.

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

No consultees/commentators indicated that they had no comments.