National Institute for Health and Care Excellence

Health Technology Evaluation
Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer [ID4056]
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	British Thoracic Oncology Group	Yes. This is an area of high unmet need in the lung cancer treatment landscape.	Comment noted. No action required.
	Eli Lilly and Company Limited	Yes.	Comment noted. No action required.
Wording	British Thoracic Oncology Group	Yes.	Comment noted. No action required.
	Eli Lilly and Company Limited	Yes.	Comment noted. No action required.
	British Thoracic Oncology Group	RET fusion positive NSCLC patients have no approved reimbursed targeted options in the first line. Many patients may never get to a subsequent treatment option due to the well documented attrition in lung cancer. The trial	Comment noted. In any appraisal NICE aims to publish guidance within

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Additional comments on the draft remit		data confirms the potent activity of the drug for treatment naïve patients. It is therefore of high urgency for this evaluation to take place to ensure suitable patients have access to the drug in the first line setting.	90 days of marketing authorisation. No action required.
	Eli Lilly and Company Limited	Please note, MHRA approval is expected in July 2022	Comment noted. In any appraisal NICE aims to publish guidance within 90 days of marketing authorisation. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Thoracic Oncology Group	Accurate and complete.	Comment noted. No action required.
	Eli Lilly and Company Limited	The description of NICE technology appraisal 584 for previously untreated, metastatic, non-squamous NSCLC is incomplete. NICE technology appraisal 584 states that this technology is recommended *as an option for untreated non-squamous NSCLC if the tumour expresses PD-L1 with less than 50% tumour proportion score and has no EGFR- or ALK-positive mutations* The description of NICE technology appraisal 770 is also incomplete for people with metastatic, squamous, NSCLC with PD-L1 TPS ≥50%. NICE technology appraisal 770 only recommends this technology for people if they have PD-L1 TPS ≥50% *and they need urgent clinical investigation*	Comment noted. The wording in the background section of the scope is not meant to be exhaustive. Scope unchanged.

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		References NICE [2019] Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. Available from https://www.nice.org.uk/guidance/ta584 NICE [2022] Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer. Available from https://www.nice.org.uk/guidance/ta770	
The technology/ intervention	British Thoracic Oncology Group	N/A	Comment noted. No action required.
	Eli Lilly and Company Limited	Typographical error on 'Retevmo'. Please amend to 'Retsevmo'	Comment noted. The scope has been updated to include the correct wording of the technology name.
Population	British Thoracic Oncology Group	Yes. This applies to RET fusion patients who are treatment naïve.	Comment noted. No action required.
	Eli Lilly and Company Limited	The population is appropriate defined. However, please note that although histology was not limited to non-squamous disease in the inclusion criteria for the main global study and for this appraisal, LIBRETTO-001, the majority of patients had [redacted]	Comment noted. Selpercatinib will be appraised within its marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted]	
Comparators	British Thoracic Oncology Group	Yes, they are the standard treatments. No single one can be considered the 'best alternative care'. The heterogeneity in treatment options is driven by patient factors, cancer factors and biomarker (PDL1 status) factors.	Comment noted.
	Eli Lilly and Company Limited	There are no current treatments routinely reimbursed for RET-fusion positive untreated advanced non-squamous NSCLC. In the absence of specific RET-targeted treatment, Lilly determines that treatments currently used for people without any identifiable biomarkers, other than those used for PD-1/PD-L1 patients, make up current NHS standard of care in England Please note, Pralsetinib for people with advanced RET fusion positive NSCLC [subject to ongoing NICE appraisal ID3875] has recently been recommended in the CDF and therefore cannot be considered a comparator for selpercatinib as per NICE's position statement on comparators currently in the CDF. Pemetrexed for the first-line treatment of non-small-cell lung cancer (NICE technology appraisal 181) should be a considered a comparator regardless of PD-L1 expression as stated in this guidance. Furthermore, recent draft guidance for Pralsetinib for people with advanced RET fusion positive NSCLC [subject to ongoing NICE appraisal ID3875] notes pemetrexed plus platinum chemotherapy and pembrolizumab combination with pemetrexed and platinum chemotherapy, as the only relevant comparators for this population. References	Comment noted. The comparators listed in the scope aims to be inclusive. A rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the appraisal committee.

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		NICE [2019] Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. Available from https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf NICE [2022] Pralsetinib for treating RET fusion-positive advanced non-small-cell lung cancer. Appraisal Consultation Document. Available from https://www.nice.org.uk/guidance/gid-ta10770/documents/129	
Outcomes	British Thoracic Oncology Group	Yes. Any CNS data would also be of use.	Comment noted. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate.
	Eli Lilly and Company Limited	Outcomes are appropriate.	Comment noted. No action required.
Economic analysis	British Thoracic Oncology Group	N/A	Comment noted. No action required.
	Eli Lilly and Company Limited	An economic analysis that addresses the requirements of the NICE reference case will be submitted. Cost-effectiveness results will be expressed as	Comment noted. Any issues relating to the costs of treatments and associated diagnostic

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		incremental cost per quality-adjusted life year, with a lifetime model horizon, considering costs from an NHS and PSS perspective. The cost of any generically available treatments will be taken into consideration in the base case analysis. Results will be presented using the list price for treatments in the base case due to the confidentiality of the PAS for certain treatments in NSCLC The economic analysis will consider sensitivity analyses for the costs for testing RET gene fusion. However, it is anticipated that national genomic testing will be implemented by the time selpercatinib is launched in the England.	testing can be considered by the appraisal committee.
Equality	British Thoracic Oncology Group	N/A	Comment noted. No action required.
	Eli Lilly and Company Limited	No concerns.	Comment noted. No action required.
Other considerations	British Thoracic Oncology Group	N/A	Comment noted. No action required.
	Eli Lilly and Company Limited	N/A	Comment noted. No action required.
Innovation	British Thoracic Oncology Group	Yes. Selpercatinib is an active agent against RET fusion NSCLC. The option to offer this to treatment naïve patients would be of great importance due to the high attrition of patients from line of therapy. Patients with driver	Comment noted. The appraisal committee will consider the innovative

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		mutations tend not to respond as well to conventional chemotherapy / immunotherapy and hence it is important to be able to offer the best and targeted treatment upfront. There is also the reduced burden of hospital visits and potential toxicities of chemotherapy / immunotherapy compared with an oral targeted drug with a preferable toxicity profile. Date for hospital / dayunit visits for chemotherapy / immunotherapy (as well as hospitalisation due to toxicities) should be available via SACT sata.	nature of the technology.
	Eli Lilly and Company Limited	Selpercatinib is a potent and selective RET inhibitor. Selpercatinib was at least 250-fold more selective for RET relative to other kinases. It strongly inhibited the in vitro growth of 4 cell lines harbouring endogenous RET gene alterations, with EC50 values less than 10 nM. In contrast, selpercatinib had 60- to 1300-fold less inhibitory anti-proliferative activity against 83 human cancer cell lines that lacked alterations in the endogenous RET gene. Administration results in an inhibition of cell growth of tumour cells that exhibit increased RET activity. It caused significant cytotoxicity in human cancer cell lines that harboured endogenous, clinically relevant RET gene alterations (IC50 1-10 nM) and was much less cytotoxic against human cancer cell lines without RET alterations (IC50 100-10,000 nM). NICE recommendation to use selpercatinib to selectively inhibit previously treated RET-altered positive solid tumours in England, Wales & NI made it the first RET kinase inhibitor on the market. This represented a first step towards establishing a new treatment paradigm for the advanced, non-squamous, RET fusion positive, NSCLC patient cohort.	Comment noted. The appraisal committee will consider the innovative nature of the technology.

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		EC50=half-maximal effective concentration; IC50=half maximal inhibitory concentration; nM=nanomolar References: Drilon AE, et al. ASCO 2018. Abstract 102. Drilon A et al. IASLC 2017. Abstract 10955. Gainor J, et al. ASCO 2019. Oral presentation	
Questions for consultation	British Thoracic Oncology Group	N/A	Comment noted. No action required.
	Eli Lilly and Company Limited	Which treatments are established clinical practice in the NHS for RET fusion-positive advanced non-small-cell lung cancer in people who have not received prior treatment? As per the recent committee determinations made in the draft guidance for Pralsetinib for people with advanced RET fusion positive NSCLC [ongoing NICE appraisal ID3875]. Pembrolizumab combinations [TA683] and Pemetrexed plus cisplatin/carboplatin [TA181] are the most appropriate comparators and current standard of care for patients that harbour a RET-fusion in non-squamous NSCLC. Would selpercatinib be a candidate for managed access? The Company believe selpercatinib in this indication may be a candidate for managed access given the majority of the evidence is based on single-arm phase 1/2 trial and there is a confirmatory phase 3 trial ongoing which will provide comparative and mature survival evidence, anticipated in the next few years.	Comment noted. See response in 'Comparators' section. Comment noted. No action required.

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		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. Please note, RET-fusions are rare in NSCLC occurring in 1-2% of NSCLC cases. The total prevalent population in England eligible with RET-fusion NSCLC is less than 1 in 50,000. It is also likely that the total eligible prevalent population for selpercatinib in all its indication <500 people. Our comments on the other questions have been captured above.	Comment noted. No action required.
Additional comments on the draft scope	British Thoracic Oncology Group	N/A	Comment noted. No action required.
	Eli Lilly and Company Limited	N/A	Comment noted. No action required.

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

Roche Products Ltd.