National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Selpercatinib for RET fusion-positive advanced non-small-cell lung cancer

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	Eli Lilly	Yes	Comment noted. No action required.
	British Thoracic Oncology Group	Yes	Comment noted. No action required.
	Roche	None	Comment noted. No action required.
Timing Issues	Eli Lilly	Timing is appropriate – Recommendations to the NHS should be as close to marketing authorisation as is feasible within the NICE appraisal programme.	Comment noted. No action required.
	British Thoracic Oncology Group	This is a drug for patients with advanced lung malignancy who have limited treatment options. A targeted therapy such as this has the potential to improve life expectancy in an area of unmet need.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Roche	None	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Eli Lilly	Lilly has noted that the description for people who progress after first-line treatment receiving atezolizumab with bevacizumab, carboplatin and paclitaxel, is incomplete. Lilly recommends using the following *wording* to accurately capture the correct population eligible for treatment under Technology Appraisal 584: "People with non-squamous NSCLC who progress after platinum-based therapy have treatment with platinum doublet (TA181) or pemetrexed with carboplatin. They can also receive chemotherapy with docetaxel and the multikinase inhibitor nintedanib (TA347). People with PD-L1 <50% could also have atezolizumab with bevacizumab, carboplatin and paclitaxel, *only when targeted therapy for epidermal growth factor receptor (EGFR)-positive or anaplastic lymphoma kinase (ALK)-positive NSCLC has failed* (TA584)" Lilly also notes that the % description of patients from the National Lung Cancer Audit (2017) with stage IIIB or IV disease refers to people who received systemic anti-cancer treatment. Lilly recommends revising the wording to "*In 2017, 39,201 people were diagnosed with NSCLC in England & Wales, and around 57% had stage IIIB or stage IV disease"* ***References***	Comment noted. The wording in the background section of the scope has been updated to clarify the treatment pathway based on histology (squamous and non-squamous) and PD-L1 status. First- and second-line treatments are included. The recommendation on EGFR and ALK positive population from TA584 has been noted in the comparator section of the scope. The statistics on the overall incidence and

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		National Institute of Health and Care Excellence (2019). Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. NICE Technology Appraisal 584 [TA584] *National Lung Cancer Audit: Annual report 2018 (for the audit period 2017) (2019). Royal College of Physicians*	stage of lung cancer have been updated in the background section.
	British Thoracic Oncology Group	Yes	Comment noted. No action required.
	Roche	Penultimate paragraph suggests that patients who progress after platinum-based chemotherapy may receive further platinum doublet chemotherapy; this is incorrect, as patients would not receive platinum-based chemotherapy in consecutive lines of treatment. It also suggests that the combination of atezolizumab with bevacizumab, carboplatin and paclitaxel is second-line therapy; this is incorrect as it is a first-line therapy according to its licence and position in the NICE pathway.	Comment noted. The wording in the background section of the scope has been updated to clarify the treatment pathway based on histology (squamous and non-squamous) and PD-L1 status. First- and second-line treatments are included. The recommendation on EGFR and ALK positive population from TA584 has been noted in the comparator section of the scope..

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The technology/ intervention	Eli Lilly	The description of the technology is incomplete. Lilly recommends specifying the trial included people with RET-activations, and to use the following wording: *'Selpercatinib (brand name unknown, Eli Lilly) is a small molecule inhibitor of the rearranged during transfection (RET) receptor tyrosine kinase. Chromosomal rearrangements involving in-frame fusions of RET with various partners can result in constitutively activated chimeric RET fusion proteins that can act as oncogenic drivers, promoting cell proliferation and survival in tumour cell lines. Point mutations in RET can also result in constitutively activated RET proteins that can promote cell growth and survival in tumour cell lines. Administration of selpercatinib can thus cause inhibition of cell growth of tumour cells that exhibit increased RET activity'* *'Selpercatinib does not currently have a marketing authorisation in the UK for treating people with RET fusion positive advanced non-small-cell lung cancer. Selpercatinib is currently being studied in single-arm phase 1/2 trial in people with advanced solid tumours with RET activations.'*	Comment noted. Wording added to specify the effect of selpercatinib on tumour cells. Wording added to specify that the trial includes people with RET activations.
	British Thoracic Oncology Group	Yes – however need clarity if approval is being sought for first line or later line usage (or both)	Comment noted. Details about the treatment line in which selpercatinib is anticipated to be used is currently confidential and will not be included in the technology section of the scope.
	Roche	None	Comment noted.

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Population	Eli Lilly	The population is appropriately defined. The description does not make reference to a particular line of therapy which aligns with the main global trial for selpercatinib and its intended use in clinical practice as a line agnostic treatment. Selpercatinib should be considered in people with advanced RET-fusion positive NSCLC who have either untreated or previously treated disease. However, please note that although histology was not limited to non-squamous disease in the inclusion criteria for the main global study, LIBRETTO-001, the majority of patients had non-squamous NSCLC. There was only [redacted]. Additionally, biomarkers status by PD-1/PD-L1 was not an exclusion criterion in the trial. Therefore, the eligible population in practice, and thus of interest for the appraisal, will be [redacted] For people who had received treatment previously, the main global trial, LIBRETTO-001, defined these patients as previously receiving platinum-based therapy or PD-1/PD-L1 immunotherapy, or both. [redacted]. Therefore, it is anticipated that selpercatinib will be used in practice for [redacted] and will be the target population for the appraisal as well as people who are [redacted].	Comment noted. Selpercatinib will be appraised within its marketing authorisation.
	British Thoracic Oncology Group	Yes	Comment noted.
	Roche	None	Comment noted.
Comparators	Eli Lilly	There are no current treatments on the market for the treatment of RET-fusion positive advanced non-squamous NSCLC. In the absence of specific RET-targeted treatment, Lilly determines that treatments currently used for	Comment noted. The comparators listed in the scope aims to be

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		people without any identifiable biomarkers, other than those used for PD-1/PD-L1 patients, make up current NHS standard of care in England Lilly notes that the comparators should be limited to those treatments used for non-squamous NSCLC. The most appropriate comparators for selpercatinib for the appraisal should be listed as below: ***People with untreated non-squamous NSCLC:*** • *Pembrolizumab, with pemetrexed and platinum chemotherapy (TA557, Cancer Drugs Fund – currently under review)* ***People with previously treated non-squamous NSCLC:*** • *Atezolizumab* • *Docetaxel, with or without nintedanib* • *Best supportive care* Lilly strongly recommends adding TA557 as a relevant comparator as it is currently undergoing its CDF review [ID1584]. It is likely a recommendation on this technology will be released before selpercatinib is launched in the UK. Non-squamous NSCLC systemic anticancer treatment algorithms produced for NICE guideline 122 indicates pembrolizumab combinations (TA557) as a treatment option for untreated disease regardless of biomarker status. [redacted]	inclusive. A rationale should be provided for excluding any comparators from the evidence submission, which can be considered by the appraisal committee. However, the scope has been updated to include established clinical management for untreated and previously treated NSCLC.

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		For previously treated non-squamous NSCLC, atezolizumab combinations (TA584) is only recommended as a second-line treatment for people who have had EGFR or ALK-targeted treatment at first line. Therefore, it is not a relevant comparator for selpercatinib. Non-squamous NSCLC systemic anticancer treatment algorithms in NICE guideline 122 indicates atezolizumab, and docetaxel with or without nintedanib are relevant treatments for people with non-squamous NSCLC regardless of biomarker status. Pemetrexed plus carboplatin is a treatment for people who have previously received pembrolizumab monotherapy therefore it is not a relevant comparator for selpercatinib, since the eligible population for the appraisal will be people that have [redacted] Therefore, Lilly recommends adding atezolizumab (TA520) and removing platinum doublet from the comparator list since being superseded by more recent NICE recommendations. *Market research data conducted on all available treatments available in NSCLC used in the UK, including targeted treatments *References* *National Institute of Health and Care Excellence (2019). Lung cancer: diagnosis and management. NICE Guideline 122 [NG122]* *Lilly data on file, Internal market research (2019)*	
	British Thoracic Oncology Group	**Untreated disease**	Comment noted. The comparators listed in

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		I appreciate that pembrolizumab, pemetrexed and platinum chemotherapy (NICE 557) and pembrolizumab, carboplatin and paclitaxel (NICE 600) are only available via the cancer drug fund, however these would be the most commonly used regimes 1st line for non-squamous and squamous NSCLC patients in the NHS for PDL1 < 50%. These regimes would be more appropriate comparators For PDL1 > 50% I agree single agent pembrolizumab is the most commonly used for both histological subtypes. **After previous chemotherapy treatment** The comparator for PDL1 >50% for both squamous and non-squamous should be platinum doublet chemotherapy Based on what I have stated for 'untreated disease' The comparator for PDL1<50% for squamous should be Docetaxel and for non-squamous Docetaxel plus Nintedanib. Atezolizumab, bevacizumab, carboplatin and paclitaxel should not be a comparator here as it is for treatment naïve patients Best supportive care would also be an appropriate comparator	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. However, the scope has been updated to include established clinical management for untreated and previously treated NSCLC.
	Roche	Atezolizumab with bevacizumab, carboplatin and paclitaxel is listed for patients with PD-L1 <50%, after previous chemotherapy; in accordance with its licence and the NICE pathway, this combination should not be listed here, as it is a first-line therapy.	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

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			considered by the appraisal committee. However, the scope has been updated to include established clinical management for untreated and previously treated NSCLC.
Outcomes	Eli Lilly	Outcomes are appropriate. The anticipated outcome measures to be considered in the submission to assess clinical benefit of selpercatinib include: **Survival** • Progression free survival • Overall survival **Response rate** • Objective Response Rate (ORR), Duration of Response (DOR), CNS Objective Response Rate (CNS ORR), CNS Duration of Response (CNS DOR), time to any and best response, Clinical Benefit Rate (CBR) **Time to treatment discontinuation** **Adverse effects of treatment** • Frequency, severity, and relatedness of Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)	Comment noted. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate.

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		Health-related quality of life • Changes from baseline in disease-related symptoms and HRQoL, as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) **Additional outcome measures** • Best change in tumour size from baseline	
	British Thoracic Oncology Group	Yes	Comment noted.
	Roche	None	Comment noted.
Economic analysis	Eli Lilly	An economic analysis that addresses the requirements of the NICE reference case will be submitted. Cost-effectiveness results will be expressed as 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.	Comment noted. Any issues relating to the costs of treatments and associated diagnostic testing can be considered by the appraisal committee.
	British Thoracic Oncology Group	n/a	Comment noted.

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	Roche	None	Comment noted.
Equality and Diversity	Eli Lilly	No comment.	Comment noted. No action required.
	British Thoracic Oncology Group	n/a	Comment noted. No action required.
	Roche	None	Comment noted. No action required.
Other considerations	Eli Lilly	No comment	Comment noted. No action required.
	British Thoracic Oncology Group	n/a	Comment noted. No action required.
	Roche	None	Comment noted. No action required.
Innovation	Eli Lilly	Selpercatinib has shown promising activity in advanced RET positive solid tumours. The U S Food and Drug Administration granted accelerated approval to selpercatinib on the 08/05/2020. It also received orphan designation. 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 harboring endogenous *RET* gene alterations, with EC_{50} 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.	Comment noted. The appraisal committee will consider the innovative nature of the technology.

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		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 harbored endogenous, clinically relevant *RET* gene alterations (IC_{50} 1-10 nM) and was much less cytotoxic against human cancer cell lines without *RET* alterations (IC_{50} 100-10,000 nM). NICE approval to use selpercatinib to selectively inhibit RET-altered positive solid tumours in England, Wales & NI would make it the first RET kinase inhibitor on the market. This would represent a first step towards establishing a new treatment paradigm for the advanced, non-squamous, RET fusion positive, NSCLC patient cohort. EC_{50}=half-maximal effective concentration; IC_{50}=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	
	British Thoracic Oncology Group	This technology stands to provide a significant benefit to this group of patients based on the LIBRETTO-001 study outcomes	Comment noted. The appraisal committee will consider the innovative nature of the technology.
	Roche	None	Comment noted.
Questions for consultation	Eli Lilly	Our comments on comparators, outcomes, positioning in the treatment pathway and the appropriate populations have been captured above.	Comments on comparators, outcomes, positioning in the treatment pathway, and

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		Best supportive care may be defined as described in NICE Guidelines 122 for Lung cancer: diagnosis and management (2019). It consists of palliative care and palliative radiotherapy, additional monitoring requiring additional health care resources, and a tailored regimen to control symptoms as endobronchial obstruction. Our comments on innovations have been captured above Cost comparison is not appropriate for this topic. TA557 is expected to receive routine commissioning (ID1584). This will be considered the new standard of care for untreated non-squamous NSCLC regardless of PD-L1 TPS and thus a relevant comparator for selpercatinib Potential barriers for adoption include the delayed implementation of the nationwide genetic testing hubs in England.	populations noted in sections above. The committee will consider the definition of best supportive care based on the company submission and current NICE guidance. Any potential barriers for adoption will be considered in the appraisal.
	British Thoracic Oncology Group	None	Comment noted.
	Roche	None	Comment noted.

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

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