National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Selpercatinib for treating advanced thyroid cancer with RET alterations

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 *Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?)*	Butterfly Thyroid Cancer Trust (BTCT)	Yes	N/A
	Society for Endocrinology (SfE)	Yes	N/A
	Eli Lilly (company)	No. Lilly recommends the wording is revised to 'To appraise the clinical and cost effectiveness of selpercatinib within its marketing authorisation for advanced RET mutation-positive medullary thyroid cancer (MTC) and previously treated advanced RET fusion-positive thyroid cancer' to align with the expected marketing authorisation for selpercatinib.	This was discussed at the scoping workshop. Clinical expert opinion was that anaplastic thyroid cancer should be included within the RET-fusion positive population, and explained that anaplastic thyroid cancer usually presents

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			at an advanced, inoperable stage. The consensus was to leave the remit unchanged, so as not to exclude this patient group.
Timing Issues	BTCT	This cancer patient group has very limited treatment options, all of which have toxicity issues. New treatments which may be more effective and less toxic are needed.	Noted. Additional text on limited treatment options added to scope.
	SfE	There is an unmet need for less toxic and effective treatments for patients with advanced RET-mutation positive medullary thyroid cancers and other RET-fusion positive cancers, although this is a relatively small patient group. Treatment options for these patients are often limited.	After discussion on treatment pathway at the scoping workshop, the background section contains some additional details on currently available treatments, and notes the lack of treatment options in the paediatric setting.
	Eli Lilly	Timing is appropriate – Recommendations to the NHS should be as close to marketing authorisation as is feasible within the NICE appraisal programme.	No scope change required.
	BTCT	-	N/A
	SfE	-	N/A

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Additional comments on the draft remit	Eli Lilly	None.	N/A

Comment 2: the draft scope

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Background information	BTCT	Paragraph 2 is incorrect. RET fusions are found in approx 7%	Text in scope has been amended to acknowledge that the fusions are one of the causes, rather than one of the main causes.
	SfE	It is incorrect that fusions involving the RET gene are amongst the commonest causes of papillary thyroid cancer. Different genetic alterations usually underlie the pathogenesis of these cancers (2nd paragraph of the background)	Text in scope has been amended to acknowledge that the fusions are one of the causes, rather than one of the main causes.
	Eli Lilly	No comments.	N/A
The technology/ intervention *Is the description of the technology*	BTCT	Yes	N/A
	SfE	Yes	N/A
	Eli Lilly	The description of the technology is inaccurate and incomplete. Selpercatinib is currently being studied in single-arm phase 1/2 trial in people with	The scope aims to be as accessible and

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or technologies accurate?		advanced solid tumours with RET activations. Lilly recommends 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. It is administered orally.' 'Selpercatinib does not currently have a marketing authorisation in the UK for treating people with RET mutation-positive MTC or previously treated advanced RET fusion-positive thyroid cancer. Selpercatinib is currently being studied in single-arm phase 1/2 trial in people with advanced solid tumours with RET activations'	jargon-free as possible. The wording around the possible mechanism for selpercatinib inhibition of tumour cell growth has been amended slightly, but with the aim to still be as accessible as possible for a wide range of audiences.
Population *Is the population defined appropriately? Are there groups within this population that should be considered separately?*	BTCT	Should paediatric papillary cancers be considered?	Population for each indication in scope amended to 'people' rather than 'adults' or specifying an age category. This is to keep the population broad, in case the drug receives marketing authorisation in paediatric populations.

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	SfE	Yes	N/A
	Eli Lilly	The population is appropriately defined. The description does not make reference to a particular line of therapy for medullary thyroid cancer which aligns with the main trial for selpercatinib and its intended use in clinical practice as a line agnostic treatment. In the main global trial, LIBRETTO-001, previously treated RET fusion-positive thyroid cancer is defined [redacted]. Therefore, the eligible population in practice, and thus of interest for the appraisal, will be people with [redacted].	No change to scope required.
Comparators	BTCT	RAI is not a comparators and patients considered for this therapy would be RAI refractory [not effective] Consideration should be given to both RET DTC and MTC in the first line and also second line to currently licensed TKI drugs.	Scope has been amended to remove radioactive iodine as a comparator. TKI drugs included as comparators, in line with existing NICE guidance.
	SfE	Patients with differentiated thyroid cancer who would be a candidate for this drug would need to have radioiodine-refractory disease so using radioactive iodine as a comparator is not appropriate. Ideally Selpercatinib would need to be compared against other TKI-drugs such a Sorafenib/Lenvatinib or Cabozatinib in a first line as well as in a second line setting (following failure of other agents)	Scope has been amended to remove radioactive iodine as a comparator. TKI drugs included as comparators, in line

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			with existing NICE guidance.

	Eli Lilly	There are no current treatments on the market that specifically target RET-fusion positive advanced thyroid cancer and RET-mutation positive medullary thyroid cancer. In the absence of specific RET-targeted treatment, Lilly determine the following list as the current NHS standard of care in England and the most appropriate comparators for selpercatinib:
		• *For advanced RET mutation-positive MTC:*
		  ○ *cabozantinib*
		  ○ *best supportive care or palliative care (for those who have progressed beyond first-line systemic therapy)*
		• *For previously treated advanced RET fusion-positive thyroid cancer:*
		  ○ *best supportive care or palliative care*
		As explained above, the [redacted] Therefore, radioactive iodine is not an appropriate comparator since it would not be used again in patients who are already refractory to treatment.
			Scope has been amended to remove radioactive iodine as a comparator.

Outcomes	BTCT	Most important to look at quality of life and to see if this drug is better tolerated than those currently available.	No change to scope required – quality of life and adverse events already included in listed outcomes.
	SfE	Many of these drugs are known to have multiple toxic adverse effects. The capture of toxic side-effects and QoL outcomes are crucial.	No change to scope required – quality of life

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			and adverse events already included in listed 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) **Adverse effects of treatment** • Frequency, severity, and relatedness of Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) **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) (adults), PedsQL for teens (ages 13 to 17 years), PedsQL for children (age 12 years), and patient bowel diaries (MTC patients only). **Additional outcome measures**	Noted. No change to scope required.

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		• Best change in tumour size from baseline • Response by biochemical markers (e.g. calcitonin response)	
Economic analysis	BTCT	Genomics England Hubs and RET testing should become standard care at no additional cost	N/A
	SfE	Ideally these drugs should be tested alongside determination of genetic alterations in thyroid cancer and the application of pharmacogenomics. The access to molecular testing in this setting is not equitable across England.	Possible equality issue noted.
	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 alterations (gene fusion and gene mutation). However, it is anticipated that national genomic testing will be implemented by the time selpercatinib is launched in England.	Noted. No change to scope required.
Equality and Diversity	BTCT	No issues	N/A
	SfE	N/A	N/A
	Eli Lilly	No comment.	N/A

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Other considerations	BTCT	None	N/A
	SfE	RET-fusion genes have not been identified in poorly differentiated, follicular or anaplastic cancers so this treatment does not seem applicable in these setting	This was discussed at the scoping workshop – participants agreed that this statement was incorrect, and it is important that anaplastic thyroid cancer is considered due to lack of treatment options and poor outcomes. Scope unchanged, to retain these types of thyroid cancer.
	Eli Lilly	-	N/A
Innovation	BTCT	First data available suggests less toxicity this medicine would be beneficial to patients	Noted. No scope change required.
	SfE	Yes. If this drug proves less toxic than similar other drugs currently in use then that represents significant innovation.	Noted. No scope change required.
	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.	Noted. No change to scope required.

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		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. 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 RET-altered positive, TC 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	
Questions for consultation	BTCT	Existing treatments for this patient group are included in comparators. Cabozantenib is being tested via clinical trial second line setting for some DTC and MTC cancers	Ongoing clinical trials in this setting discussed at scoping workshop. Cabozantenib would not be approved by the time of this appraisal. Not

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			appropriate to include unlicensed comparators.
	SfE	There are other TKI agents currently being tested in clinical trial settings and comparison with these agents is warranted.	Ongoing clinical trials in this setting discussed at scoping workshop. Other TKI agents in the clinical trials discussed would not be approved by the time of this appraisal. Not appropriate to include unlicensed comparators.
	Eli Lilly	Our comments on comparators, outcomes, positioning in the treatment pathway and the appropriate populations for selpercatinib treatment have been captured above. Lilly believes there are no other MKI systemic treatments outside of those recommended by NICE technology appraisal for lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (TA535) and NICE technology appraisal for cabozantinib for treating medullary thyroid cancer TA516). In Thyroid Cancer best supportive care consists of non-systemic treatment options, additional monitoring and palliative care. In Technology Appraisal for Cabozantinib for treating medullary thyroid cancer (TA516) best supportive care was defined as: ***Medullary Thyroid Cancer, Best Supportive Care***	Noted. No change to scope required.

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Component	Rate/year PF and PD
Consultant outpatient	6
CT scans	2
MRI scans	1
Comm. Palliative care support	12
Palliative radiotherapy	2
Bisphosphonates for bone metastases (**IV + outpatient visit – for 5% pt. only**)	0.6
Palliative surgery	0.03

In Technology Appraisal of Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (TA535), best supportive care was defined as:

Differentiated thyroid cancer, Best Supportive Care	
Component	**Rate/quarter PF and PD**
Blood test	1
Coagulation test	1
Urine test	1
LFTs	1
TFTs	3
Protein test	1
Bone scan	1
MRI scan	1
CT scan	1
Regular Thyroxine (levo)	3.26
Calcium/Vit D	3
Oncologist outpatient visits	1

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		Lilly believes RET testing will become routine once the genetic testing hubs are fully implemented in England. Our comments on innovations have been captured above. Potential barriers for adoption include the delayed implementation of the nationwide genetic testing hubs in England.	
Additional comments on the draft scope	BTCT	-	N/A
	SfE	-	N/A
	Eli Lilly	None.	N/A

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

N/A