NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Selpercatinib for treating advanced thyroid cancer with RET alterations

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of selpercatinib within its marketing authorisation for treating advanced RET fusion-positive thyroid cancer and advanced RET mutation-positive medullary thyroid cancer (MTC).

Background

Cancer of the thyroid, a small gland at the base of the neck, can cause pain and difficulties in swallowing and breathing.[1] There are several types of thyroid cancer, including the most common, papillary and follicular, as well as the rarer medullary thyroid cancer (MTC) and anaplastic thyroid cancer.

Some thyroid cancers can be caused by alterations in the RET (or 'rearranged during transfection') gene, which can lead to uncontrolled cell growth. Mutations in the RET gene are present in many MTC cases (RET mutation-positive), and chromosomal rearrangements (or 'fusions') involving the RET gene are one of the most common causes of papillary thyroid cancer (RET fusion-positive).[2,3]

Thyroid cancer is uncommon and can occur at any age, but is most often diagnosed in people from their 20s through to their 60s. Between 2013 and 2017, more than 15,000 people in England were diagnosed with thyroid cancer,[4] and it is around three times more common in women than in men.[5] The 'differentiated' thyroid cancers (papillary and follicular) represent 90% of all thyroid cancers.[6] MTC is rarer, and accounts for approximately 3% (adult) to 10% (paediatric) of thyroid cancers.[7] MTC arises from a different type of cell than other thyroid cancers. It can run in families, frequently spreads to lymph nodes in the neck, and typically has poorer long-term outcomes.[8] For example, UK 5-year survival for MTC is 75% in males compared to 90% for papillary thyroid cancer (90% and 95% respectively in females).[9,10]

British Thyroid Association guidelines indicate that usual treatment for thyroid cancer in the UK is surgery to remove part or all of the thyroid.[7] Surgery may be followed by a number of systemic and non-systemic treatments, according to the size and type of cancer and factors such as evidence of local or distant disease.[7] Treatment options may include radioactive iodine, external beam radiotherapy, or targeted drugs.[7] These drugs inhibit proteins that are involved in signalling within cells, in order to stop thyroid cancer growing and spreading.

For differentiated thyroid cancer, surgery followed by radioactive iodine is the most common treatment approach. If the cancer doesn't respond to radioactive iodine, then levatinib and sorafenib (multi-kinase inhibitors) are recommended options (technology appraisal 535). They represent possible systemic treatments for some people with advanced RET fusion-positive thyroid cancer whose disease has progressed following prior treatment.

Cabozantinib (a tyrosine kinase inhibitor) is recommended for progressive medullary thyroid cancer in adults with unresectable, locally advanced or metastatic disease (technology appraisal 516). At the time of that appraisal, it was not appropriate to make a recommendation based on RET mutation tumour status, as the required test was not routinely carried out. Vandetanib is not recommended for medullary thyroid cancer (technology appraisal 550). This means cabozantinib is the only currently recommended systemic treatment for people with advanced MTC who can't have surgery, regardless of whether or not their cancer is RET-mutation positive.

The technology

Selpercatinib (brand name unknown, Lilly) is an oral RET inhibitor, and does not currently have a marketing authorisation in the UK for advanced RET fusion-positive thyroid cancer or advanced RET mutation-positive MTC. It binds to cancer cells which have a genetic alteration in the RET protein, and this binding inhibits RET receptor signalling. This disrupts tumour growth.

It has been studied in an open label single arm clinical trial as monotherapy for advanced RET mutation-positive MTC and advanced RET fusion-positive solid tumours.

Intervention(s)	Selpercatinib
Population(s)	• Adults with advanced RET fusion-positive thyroid cancer who require systemic therapy and whose disease has progressed following prior treatment • People aged 12 years and over with advanced RET mutation-positive medullary thyroid cancer (MTC) who require systemic therapy

Comparators	• For advanced RET fusion-positive thyroid cancer which has progressed following prior treatment:
	  ○ lenvatinib and sorafenib (for differentiated thyroid cancer which did not respond to radioactive iodine)
	  ○ radioactive iodine
	  ○ best supportive care or palliative care
	• For advanced RET mutation-positive MTC:
	  ○ cabozantinib
	  ○ best supportive care or palliative care (for those who have progressed beyond first-line systemic therapy)

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account. The use of selpercatinib is conditional on the presence of RET mutation or fusion. The economic modelling should include the costs associated with diagnostic testing for RET mutation/fusion in people with advanced MTC/advanced thyroid cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.
Other considerations	If the evidence allows, the following subgroups will be considered. These include different types of thyroid cancer within advanced RET fusion-positive thyroid cancer, such as papillary carcinoma, follicular carcinoma, poorly differentiated carcinoma and anaplastic carcinoma. The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Cabozantinib for treating medullary thyroid cancer (2018). NICE Technology Appraisal 516. Review date 2020.

	Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine (2018). NICE Technology Appraisal 535. Review date 2021. Vandetanib for treating medullary thyroid cancer (2018). NICE Technology Appraisal 550. Review date 2021. Appraisals in development (including suspended appraisals): Selumetinib for treating differentiated thyroid cancer. NICE technology appraisals guidance [ID1079]. Publication date to be confirmed. Guidelines in development: Thyroid cancer: assessment and management. Publication expected April 2022. Related Interventional Procedures: Minimally invasive video-assisted thyroidectomy (2014). NICE interventional procedures guidance 499. Intraoperative nerve monitoring during thyroid surgery (2008). NICE interventional procedures guidance 255. Related NICE Pathways: Endocrine cancers (2018) NICE pathway https://pathways.nice.org.uk/pathways/endocrine-cancers
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 9 Adult specialist endocrinology services, Chapter 109 Specialist endocrinology and diabetes services for children. Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1, 4. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for selpercatinib been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for advanced RET fusion-positive thyroid cancer? Are any multi-kinase inhibitors or tyrosine kinase inhibitors routinely used which are not listed in the comparators?

Which treatments are considered to be established clinical practice in the NHS for advanced RET-mutation-positive medullary thyroid cancer? Are any multi-kinase inhibitors or tyrosine kinase inhibitors routinely used which are not listed in the comparators?

Are any of the listed comparators not appropriate? How should best supportive care be defined?

Are the outcomes listed appropriate?

Is testing for RET status routine in thyroid cancer (not just for hereditary disease)? Is RET status currently used to inform treatment decisions for thyroid cancer in NHS practice?

Are the subgroups suggested in 'other considerations' appropriate? Are there any other subgroups of people in whom selpercatinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider selpercatinib will fit into the existing NICE pathway, endocrine cancers?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which selpercatinib will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider selpercatinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of selpercatinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

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.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1 Macmillan Cancer Support (2017) Understanding thyroid cancer. Accessed April 2020.

2 National Institute of Health (2020) RET gene. Accessed April 2020.

3 Li AY, McCusker MG, Russo A et al. (2019) RET fusions in solid tumors. Cancer Treatment Reviews 81, 101911.

4 Office for National Statistics (2019) Cancer survival in England - adults diagnosed. Accessed May 2020.

5 National Cancer Intelligence Network (2020) Thyroid cancer – trends by sex, age and histological type. Accessed April 2020.

6 Cancer Research UK (2018) Types of thyroid cancer. Accessed April 2020.

7 British Thyroid Association (2014). Guidelines for the management of thyroid cancer. Clinical Endocrinology 81: Suppl 1.

8 American Thyroid Association (2020) Medullary thyroid cancer. Accessed May 2020.

9 Cancer Research UK (2018). Thyroid cancer – survival. Accessed May 2020.

10 Dal Maso L, Tavilla A, Pacini F et al. (2017). Survival of 86,690 patients with thyroid cancer: A population-based study in 29 European countries from EUROCARE-5. European Journal of Cancer 77, May 2017, 140-152.

