

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Selpercatinib for advanced thyroid cancer with RET alterations untreated with a targeted cancer drug in people 12 years and over

1 Recommendations

1.1 Selpercatinib is recommended as an option for treating:

- advanced RET-mutant medullary thyroid cancer and
- advanced RET fusion-positive thyroid cancer that is refractory to radioactive iodine (if radioactive iodine is appropriate).

It is for people 12 years and over and is recommended only if:

- the cancer has not been treated with a targeted cancer drug, and
- the company provides it according to the commercial arrangement (see [section 2](#)).

1.2 This recommendation is not intended to affect treatment with selpercatinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Why the committee made these recommendations

This evaluation focuses on RET-mutant medullary thyroid cancer and RET fusion-positive thyroid cancer for people whose cancer has not been treated with a targeted

cancer drug. NICE has separately evaluated selpercatinib for thyroid cancer that has been treated with a targeted cancer drug (see [NICE technology appraisal guidance 742](#)).

People may have surgery to remove all or part of the thyroid before starting drug treatments. Usual treatments for RET-mutant medullary thyroid cancer include cabozantinib (a targeted cancer drug) and best supportive care (routine care and monitoring). Usual treatments for RET fusion-positive thyroid cancer that is refractory to radioactive iodine include targeted cancer drugs (lenvatinib or sorafenib) and best supportive care. Selpercatinib is a targeted cancer drug.

The main clinical trial supporting this evaluation did not directly compare selpercatinib with usual treatment. Indirect comparisons suggest that people having selpercatinib live longer and have longer before their cancer gets worse than people having usual treatment. But this is uncertain.

The most likely cost-effectiveness estimates are below what NICE considers an acceptable use of NHS resources. So selpercatinib is recommended.

2 Information about selpercatinib

Marketing authorisation indication

2.1 Selpercatinib (Retevmo, Eli Lilly) is indicated for ‘the treatment of adults and adolescents 12 years and older with advanced RET-mutant medullary thyroid cancer’ and ‘adults and adolescents with advanced RET fusion-positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate)’.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the [summary of product characteristics for selpercatinib](#).

Price

- 2.3 The list price is £2,184 for 56 capsules of 40 mg selpercatinib and £4,368 for 56 capsules of 80 mg.
- 2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes selpercatinib available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The [evaluation committee](#) considered evidence submitted by Eli Lilly, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The condition

Effects on quality of life

- 3.1 Thyroid cancer has different subtypes. RET-activating fusions and mutations are important in different types of thyroid cancer. The clinical experts explained that medullary thyroid cancer, in which RET mutations are relatively common and associated with poorer outcomes, accounts for about 4% of thyroid cancers. RET fusions in other thyroid cancers are less common and it is unclear whether they are associated with poorer outcomes. The clinical experts explained that because RET mutations are more common in medullary thyroid cancer, and the likelihood of the disease progressing to advanced disease is higher than in other thyroid cancers, most people who would be offered selpercatinib would have RET-mutant medullary thyroid cancer. The patient organisation submissions explained that symptoms associated with thyroid cancer (such as diarrhoea, bone pain, fatigue and weight loss) can prevent people from leaving the house and have a significant impact on quality of life. Existing treatment options can cause significant side effects that also affect the ability to continue usual daily activities. The committee

concluded that there is an unmet need for more treatment options for thyroid cancer that are effective and well tolerated.

Clinical management

Comparators

3.2 For RET-mutant medullary thyroid cancer, after a partial or full thyroidectomy or radiotherapy, most people have cabozantinib, as recommended in [NICE's technology appraisal guidance on cabozantinib for treating medullary thyroid cancer](#). Some people will have best supportive care (BSC) if they cannot have cabozantinib, including people aged 12 to 17 years. For differentiated RET fusion-positive thyroid cancer, after a partial or full thyroidectomy, followed by radioactive iodine, [NICE's technology appraisal guidance on lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine](#) recommends lenvatinib and sorafenib. For people who cannot have lenvatinib or sorafenib, including people aged 12 to 17 years and people with undifferentiated RET fusion-positive thyroid cancer, the only treatment option is BSC. For RET fusion-positive thyroid cancer, the company stated that lenvatinib was the main comparator, because it had received clinical advice that about 5% to 10% of people would have sorafenib in NHS clinical practice. The clinical experts agreed that most people would have lenvatinib, because healthcare professionals view it as more effective than sorafenib and offer treatment with lenvatinib first. They explained that the most likely reason people would have sorafenib is if they could not tolerate lenvatinib. The committee decided that sorafenib should be considered as a comparator because some people do have it and it is recommended by NICE. The committee concluded that cabozantinib and BSC are used for RET-mutant medullary thyroid cancer, and that lenvatinib, sorafenib and BSC are used for RET fusion-positive thyroid cancer. But it acknowledged that most people with RET-mutant medullary thyroid cancer would have cabozantinib, and most people with

RET fusion-positive thyroid cancer would have lenvatinib, so these are the most relevant comparators.

Clinical effectiveness

Data sources

3.3 The company's evidence for selpercatinib came from the phase 1 and 2 single-arm trial LIBRETTO-001. The company also noted a phase 3 trial, LIBRETTO-531, which compared selpercatinib with cabozantinib or vandetanib in untreated locally advanced or metastatic medullary thyroid cancer with a RET alteration. Both trials included adults, but people aged 12 years and over could be included where permitted by local regulatory authorities. The company stated that the data from LIBRETTO-531 was too immature to be used in this evaluation.

Indirect treatment comparisons

3.4 To compare selpercatinib with cabozantinib and BSC in RET-mutant medullary thyroid cancer, the company did a matched-adjusted indirect treatment comparison. This used any-line data (that is, from people whose cancer had been previously treated with a systemic therapy and those whose cancer was untreated with systemic therapy) from LIBRETTO-001 and from the EXAM trial. EXAM compared cabozantinib with placebo, and the company used the placebo arm as a proxy for BSC in its analysis. The results suggested that progression-free survival (PFS) and overall survival (OS) were improved with selpercatinib compared with cabozantinib (hazard ratio for PFS 0.08, $p < 0.001$; hazard ratio for OS 0.20, $p < 0.001$) and compared with BSC (hazard ratio for PFS 0.05, $p < 0.001$; hazard ratio for OS 0.11, $p < 0.001$). The EAG noted a number of uncertainties in the company's matched-adjusted treatment comparison, including that:

- the company could not adjust for many of the important prognostic factors and effect modifiers it had identified because of a lack of data
- data on OS was only available for the RET M918T mutation-positive subgroup in EXAM (a specific type of RET mutation)

- the matched-adjusted treatment comparisons were not done in the relevant population for this evaluation (cancer untreated with systemic therapy)
- 21.5% of people having cabozantinib in EXAM previously had kinase inhibitor treatment
- using the placebo arm from EXAM as a proxy for BSC was not reasonable for OS because 49.5% of people had subsequent systemic therapies.

To compare selpercatinib with lenvatinib, sorafenib and BSC in RET fusion-positive thyroid cancer, the company did naive, unadjusted indirect comparisons using any-line data from LIBRETTO-001, and data from the SELECT and DECISION trials. SELECT compared lenvatinib with placebo, and DECISION compared sorafenib with placebo. The company used the placebo-arm data from SELECT as a proxy for BSC, and because 87.8% of people in the placebo arm crossed over to have lenvatinib, it adjusted the Kaplan–Meier OS curves for crossover. The results from the indirect treatment comparison in RET fusion-positive thyroid cancer suggested that PFS and OS were improved with selpercatinib compared with lenvatinib, sorafenib and BSC. The company considers the exact results to be confidential so they cannot be reported here. But the EAG cautioned that the populations in LIBRETTO-001, SELECT and DECISION were very different, particularly in the number of previous treatments, time from diagnosis and severity of disease, and that the RET fusion status was unknown in SELECT and DECISION. The indirect treatment comparison did not account for any of these differences. The EAG also advised that some of the proportional hazards assumptions appeared violated, so the reported hazard ratios may not be accurate. The committee concluded it was likely that selpercatinib improved PFS and OS compared with cabozantinib, lenvatinib, sorafenib and BSC. But it was uncertain by how much, because of the many uncertainties in the indirect treatment comparisons.

Economic model

OS estimates with selpercatinib

3.5 The company presented a partitioned survival model with 3 health states: progression-free, progressed-disease and death. To model OS for selpercatinib, the company fitted 19 parametric distributions to the OS curve for selpercatinib from the matched-adjusted indirect comparison. It elicited clinical expert opinion on the proportions of people likely to be alive at 10 years and 20 years after each treatment. The clinical experts provided ranges of plausible values; the company considers the figures to be confidential so they cannot be reported here. The company selected a stratified Weibull function for selpercatinib in RET-mutant medullary thyroid cancer. It applied an adjustment factor of 2 at 5 years, so that the values predicted by the model for 10-year and 20-year survival matched the clinical experts' opinion. To model OS for selpercatinib in RET fusion-positive thyroid cancer, the company fitted 20 parametric distributions to the OS data from LIBRETTO-001 for the any-line RET fusion-positive thyroid cancer population. The company chose a piecewise exponential distribution and applied a 1.2 adjustment factor at 5 years, to be consistent with its approach for RET-mutant medullary thyroid cancer. At the first committee meeting, the company explained that it had applied the adjustment factor at 5 years because that was the end of the trial data. The EAG explained that it had applied the adjustment factor at 18 months so that the function better fitted the Kaplan–Meier data. The clinical experts at the committee meeting explained that it was difficult to estimate the 10-year and 20-year OS for people having the different treatments because the treatments were relatively new and the disease is rare. The committee was concerned that the company's method of adjusting the survival curves was crude and not based on trial data. But it noted that the adjustments did reduce the estimates of OS with selpercatinib to be more in line with expert opinion. So it was more of a conservative approach than not applying the adjustment factors. It concluded that the OS extrapolations were uncertain, but the company's extrapolations were in

line with the clinical experts' estimates and so could be used for decision making.

Sorafenib in the model

3.6 For RET-mutant medullary thyroid cancer, the company included cabozantinib and BSC as comparators in the economic model. For RET fusion-positive thyroid cancer, the company included lenvatinib and BSC as comparators in its base case. It did not originally include sorafenib because it considered that only a small number of people would have sorafenib in NHS clinical practice. But in response to consultation on the draft guidance, the company presented a scenario analysis that included sorafenib. The company highlighted that the results from the indirect comparison indicated that PFS was higher with lenvatinib than with sorafenib, but that OS was higher with sorafenib, which it considered to be implausible. It cited clinical advice that the efficacy of lenvatinib is greater than that of sorafenib, and also presented results from a study by Kim et al. (2023) that suggested PFS was higher with lenvatinib than sorafenib. The clinical experts at the committee meetings also considered the OS results from the indirect comparison to be implausible. The company selected a piecewise exponential curve to extrapolate OS for sorafenib from the Kaplan–Meier data in DECISION. It applied an adjustment factor of 2.7 at 26 months to align the survival estimates predicted by the model with estimates provided to the company by clinical experts. This meant that after the adjustment factor was applied, the OS curve for lenvatinib was higher than the curve for sorafenib. The committee concluded that the results were uncertain but were in line with the clinical experts' estimations and so could be used for decision making.

OS with BSC and cabozantinib in RET-mutant medullary thyroid cancer

3.7 To extrapolate OS for BSC in RET-mutant medullary thyroid cancer, the company used placebo-arm data from the RET M918T population from EXAM and fitted a stratified Weibull distribution to the Kaplan–Meier curve. Kaplan–Meier curves for OS were not available for the overall RET-

mutant subgroup in EXAM, but clinical opinion to the company suggested outcomes with placebo would be similar for both subgroups. Because cabozantinib may be more effective in the RET M918T population, the company then generated an OS curve for cabozantinib by applying the hazard ratio from EXAM (in the RET-mutant medullary thyroid cancer population) to the BSC extrapolation. The company consulted clinical experts to elicit a range of survival estimates at 10 years and 20 years for people with RET-mutant medullary thyroid cancer having cabozantinib. The EAG preferred to apply the same hazard ratio from EXAM to the stratified spline 1 knot extrapolation for BSC to obtain an OS curve for cabozantinib. It considered that this predicted a 10-year OS that was more in line with the values suggested by the company's clinical experts. The committee agreed that the EAG's extrapolation of cabozantinib was more in line with the clinical experts' estimates of OS. So, it concluded that it was more appropriate to use the EAG's method of generating an OS curve for cabozantinib.

Utility values

Source of utility values

3.8 The company sourced utility values for the economic model from a vignette study by [Fordham et al. \(2015\)](#). The mean health state utility value was 0.8 in the progression-free state and 0.5 in the progressed-disease state. The EAG advised that 0.8 seemed high for the progression-free health state and was close to general population values. When age- and sex-matched to the RET-mutant medullary thyroid cancer population, the general population utility value was 0.845. When matched to the RET fusion-positive thyroid cancer population, the general population utility is 0.857. The EAG also considered that the utility value of 0.5 for the progressed-disease health state seemed low compared with the progression-free state because it received clinical advice that progression is often picked up by tests rather than a change in symptoms. It preferred to use utility values mapped from the RET fusion-positive thyroid cancer

population from LIBRETTO-001. The company considers these values to be confidential so they cannot be reported here. But, the utility value for the progression-free state was lower than the company's, and the utility value for the progressed-disease state was higher than the company's. The company noted that the EAG's method was based on very small numbers of people from the trial with a small number of assessments. And for the progressed-disease health state, people were still taking selpercatinib when the assessments were done. It also noted that the utility values from Fordham et al. (2015) had been accepted in previous NICE technology evaluations for treatments for thyroid cancer. The clinical experts explained that after progression, symptoms such as diarrhoea and bone pain can return. The committee agreed that quality of life would be worse in the progressed-disease state. But it did not consider it had been presented with evidence for a reduction as large as that in the values from Fordham et al. (2015) included in the company's model. The committee also noted that the utility value used in [NICE's technology appraisal guidance on selpercatinib for treating advanced thyroid cancer with RET alterations](#) was 0.8 for people whose cancer had progressed after treatment with a systemic therapy. The committee acknowledged that the utility values from Fordham et al. (2015) had been accepted in previous NICE evaluations. But it was aware that EQ-5D methods are preferred where available, as stated in [NICE's health technology evaluations manual](#). The committee considered that the large reduction in the utility value between the progression-free and the progressed-disease health states in the company's model was implausible. The committee also agreed that the utility values mapped from LIBRETTO-001 were more plausible. So, the committee concluded that the utility values mapped from LIBRETTO-001 should be used in the model.

Costs

Relative dose intensity

3.9 The company included a relative dose intensity multiplier in the model, to reflect dose reductions because of treatment toxicity. The EAG advised that because cabozantinib and lenvatinib have a flat price for all recommended doses, the costs of these treatments should have instead been adjusted for dose adherence; that is, the proportion of days on which people had treatment. This data was not available, so the EAG provided scenarios in which the relative dose intensity was removed for cabozantinib, lenvatinib and selpercatinib, or just for cabozantinib and lenvatinib. When the relative dose intensity was removed, dose reductions did not result in treatment cost reductions. The committee agreed that because selpercatinib has different prices for different doses, dose reductions would result in treatment cost reductions. So, it concluded that in the absence of adherence data, relative dose intensity should be removed in the model for cabozantinib and lenvatinib, but not for selpercatinib. The committee also noted that an analysis comparing selpercatinib with sorafenib in the RET fusion-positive thyroid cancer population should not include relative dose intensity for sorafenib.

Severity

3.10 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight (a severity modifier) to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with [NICE's health technology evaluations manual](#). For RET-mutant medullary thyroid cancer, the company considered that a severity modifier of 1.2 should be applied to the comparisons with BSC and cabozantinib. But when including the utility values mapped from LIBRETTO-001 (see [section 3.8](#)) or using its preferred method of modelling cabozantinib OS (see [section](#)

[3.7](#)), the EAG calculated that the QALY shortfall changed such that a severity modifier should not apply for the comparison with cabozantinib. The committee noted that both of these amendments were its preferred assumptions. For RET fusion-positive thyroid cancer, the company considered that a severity modifier would apply to the comparison with BSC but not with lenvatinib or sorafenib. The committee's preferred assumptions did not change the calculations of QALY shortfall enough to change the conclusions about whether a severity modifier would apply. So, the committee concluded that in a pairwise analysis, a severity modifier of 1.2 could be applied to the comparisons with BSC for both populations, but not to the comparisons with cabozantinib, lenvatinib or sorafenib. The committee also considered that the severity of the condition could be greater in people aged 12 to 17 years. But it noted that it had not been provided with severity modifier calculations separately for this subgroup.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.11 [NICE's health technology evaluations manual](#) notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the uncertainty in the indirect treatment comparisons (see [section 3.4](#)) and the OS modelling (see [section 3.6](#) and [section 3.7](#)). But the committee also acknowledged that thyroid cancer is rare, and the population that could be eligible for selpercatinib includes children and young people with thyroid cancer. The difference between the quality of life of people with the condition and people in the general population is likely to be greater for children and

young people than for adults. The patient expert also highlighted that RET-mutant medullary thyroid cancer is hereditary so there can be a disproportionate effect on one family if multiple members of the family have the condition. They also highlighted that selpercatinib is generally better tolerated than current treatments. Because of these factors, the committee was willing to accept a higher degree of uncertainty and concluded that an acceptable ICER would be around £30,000 per QALY gained.

Preferred assumptions

3.12 After consultation, the company updated its base case to incorporate all of the committee's preferred assumptions. These were:

- including sorafenib in the model (see [section 3.5](#))
- using utility values mapped from LIBRETTO-001 (see [section 3.8](#))
- using a piecewise exponential distribution to extrapolate OS for selpercatinib, with an adjustment factor of 2 at 5 years for RET-mutant medullary thyroid cancer and of 1.2 at 5 years for RET fusion-positive thyroid cancer (see [section 3.5](#))
- basing cabozantinib OS extrapolation on a stratified spline 1 knot distribution for BSC (RET-mutant medullary thyroid cancer only; see [section 3.7](#))
- removing relative dose intensity for cabozantinib, lenvatinib and sorafenib (see [section 3.9](#))
- applying a severity modifier of 1.2 only to the comparisons with BSC (see [section 3.10](#)).

The cost-effectiveness estimates are confidential because of confidential commercial discounts for selpercatinib, cabozantinib and lenvatinib. For RET-mutant medullary thyroid cancer, the ICER compared with the most relevant comparator, cabozantinib (see [section 3.2](#)) was below £30,000 per QALY gained. For RET fusion-positive thyroid cancer, the ICER compared with the most relevant comparator, lenvatinib (see [section 3.2](#))

was below £30,000 per QALY gained. The committee noted that people aged 12 to 17 years could not have lenvatinib or cabozantinib, but that it had not been presented with separate ICERs for this group.

Conclusion

Recommendation

3.13 For both the RET-mutant medullary thyroid cancer population and the RET fusion-positive thyroid cancer population, the committee agreed that the most plausible cost-effectiveness estimates were below the range that NICE considers to be a cost-effective use of NHS resources. It noted that it was not presented with ICERs separately for people aged 12 to 17 years, but understood that this group was expected to be small and it agreed that the recommendation should include this group (see [section 3.14](#)). So, it recommended selpercatinib for advanced RET-mutant medullary thyroid cancer and advanced RET fusion-positive thyroid cancer that has not been treated with a targeted cancer drug and is refractory to radioactive iodine (if radioactive iodine is appropriate) in people 12 years and older.

Equality considerations

3.14 Stakeholders stated that:

- women are more likely to be diagnosed with thyroid cancer than men
- children should have access to selpercatinib, and
- that there could be regional variation in molecular testing for RET alterations.

Age and sex are protected under the Equality Act 2010. The committee noted that it could only evaluate selpercatinib within its marketing authorisation indications, which were for people aged 12 and over. The committee noted that issues related to differences in regional availability of genetic testing cannot be addressed in a technology appraisal.

Because the committee recommended selpercatinib in line with its

marketing authorisation, it did not consider that its recommendations had a different impact on people protected by the equality legislation than on the wider population. So, the committee concluded that these were not potential equality issues.

4 Implementation

- 4.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide

funding and resources for it within 2 months of the first publication of the final draft guidance.

- 4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced thyroid cancer with RET alterations and the healthcare professional responsible for their care thinks that selpercatinib is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

This topic was evaluated as a single technology evaluation by the [highly specialised technologies evaluation committee](#), which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The [minutes of each evaluation committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

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