NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Contents

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1 Recommendations

1.1 Selpercatinib is recommended for use within the Cancer Drugs Fund as an option for treating RET fusion-positive advanced non-small-cell lung cancer (NSCLC) in adults who need systemic therapy after immunotherapy, platinum-based chemotherapy or both. It is recommended only if the conditions in the managed access agreement are followed.

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 clinician consider it appropriate to stop.

Why the committee made these recommendations

People with RET fusion-positive advanced NSCLC are usually offered docetaxel if they need systemic therapy after previous treatment. Sometimes they may be offered docetaxel with nintedanib.

Clinical trial evidence suggests some benefit for selpercatinib, but this is highly uncertain because the trial has not been running long enough. Also, selpercatinib is not directly compared with another treatment in the trial. It is compared indirectly with other treatments, but the results from this are also highly uncertain. Because of this, the estimates of cost effectiveness are very uncertain and selpercatinib cannot be recommended for routine use in the NHS.

Selpercatinib could be cost effective if further data shows that people live longer with treatment. Data from the trial of selpercatinib and from NHS practice would help address the uncertainty about clinical effectiveness. Selpercatinib is therefore recommended for use in the Cancer Drugs Fund.

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2 Information about selpercatinib

Marketing authorisation indication

2.1 Selpercatinib (Retsevmo, Eli Lilly) has a conditional marketing authorisation 'for the treatment of adults with advanced RET fusion-positive non-small-cell lung cancer (NSCLC) who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price for 60 capsules of selpercatinib (80 mg) is £4,680 (excluding VAT; BNF online, accessed July 2021). The company's estimated cost for a 28-day cycle of selpercatinib is £8,736.00.

2.4 The company has a commercial arrangement. This makes selpercatinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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3 Committee discussion

The appraisal committee considered evidence submitted by Eli Lilly, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that 1 issue was resolved during the technical engagement stage, and agreed that including genetic testing costs in the model was appropriate.

It discussed issues 1 to 13, which were identified in the ERG report. It also discussed the possibility of commissioning selpercatinib through the Cancer Drugs Fund.

New targeted treatment

People with RET fusion-positive advanced non-small-cell lung cancer would welcome a new treatment

3.1 The patient and clinical experts explained that the symptoms of advanced non-small-cell lung cancer (NSCLC; including breathlessness, cough, and weight loss) are hard to treat. Typical treatments for RET fusion-positive advanced NSCLC in the NHS are chemotherapy (such as platinum doublet chemotherapy) and immunotherapy (such as pembrolizumab). The clinical expert and the Cancer Drugs Fund clinical lead from NHS England explained that, for previously treated RET fusion-positive NSCLC, docetaxel is the main treatment. But they also explained that some people may also be offered nintedanib with docetaxel, and that these are the only standard treatments for this indication. They explained that use of docetaxel with nintedanib is decreasing because of its limited benefit and increased side effects compared with docetaxel alone. This leaves few options for people with RET fusion-positive advanced NSCLC. Selpercatinib is the first treatment targeted at RET fusion-positive advanced NSCLC and has shown high response rates in some people with this tumour type. The committee concluded that people with RET fusion-positive NSCLC would welcome the introduction

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of selpercatinib as a treatment option.

Comparators

The relevant comparators are docetaxel alone and docetaxel with nintedanib

3.2 In its original submission, the company provided evidence for a range of comparators based on the NICE scope for this appraisal. Through clinical advice and discussion at technical engagement, the company refined the list of comparators down to docetaxel alone and docetaxel with nintedanib. The ERG suggested that pemetrexed with carboplatin, and platinum doublet chemotherapy remained relevant comparators. The committee discussed atezolizumab as well. The company explained that advice to both itself and ERG had been clear that people would most likely have immunotherapies first. The company said it was advised that people who have immunotherapies first are not then offered them second line, meaning this class of therapy is irrelevant for this indication. The company said it was also advised that pemetrexed with carboplatin and platinum doublet chemotherapy are rarely used second line. The committee concluded that docetaxel was the main comparator and that docetaxel with nintedanib was also an appropriate comparator for people with RET fusion-positive NSCLC.

Clinical evidence

The direct clinical evidence for selpercatinib is uncertain because it depends on 1 single-arm study

3.3 The evidence for selpercatinib comes from the LIBRETTO-001 clinical trial. This is a single-arm, open-label, multicentre phase 1 to 2 trial including people with advanced solid tumours with RET activations. The primary outcome of the trial is objective response rate. Secondary outcomes include progression-free survival (PFS), overall survival (OS) and health-related quality of life. A total of 329 people with RET fusion-positive advanced NSCLC were enrolled, and:

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- data from 253 people was used in the analyses
- 184 people were enrolled with second-line advanced NSCLC that had been treated with platinum chemotherapy (known as the integrated analysis set [IAS])
- data from 105 people was used in the first data cut (described as the primary analysis set).

  In the primary analysis set, the objective response rate was 63.8% and the median PFS was 16.53 months. Other trial results were confidential, but the company reported evidence that showed similar results for the primary analysis set and IAS groups. The ERG stated that the small number of survival events in LIBRETTO-001 and the short follow-up times meant that there was uncertainty around the impact of selpercatinib on survival. Also, some PFS and OS data was not evaluable. The company was able to provide additional evidence from a later data cut. This gave about 3 more months of data, the results from which were consistent with the results from the IAS. However, the ERG considered that this did not overcome the uncertainty because the data was still immature. The ERG also noted that the company had not included this additional data in its cost-effectiveness modelling using its original data set. The committee agreed that basing the evidence on 1 single-arm study meant that there was uncertainty in the data for selpercatinib, particularly because the data was immature.

The trial population is generalisable to the NHS population

3.4 The trial population included people who had had platinum chemotherapy, some people who had also had immunotherapy, and some people who had also had a multikinase inhibitor (MKI) such as cabozantinib. The ERG said it would have been more appropriate to provide data for people who had only had chemotherapy and people who had only had immunotherapy. The ERG also said people were unlikely to be offered MKIs in the NHS as part of treatment for RET fusion-positive NSCLC. This is because MKIs do not have a UK marketing authorisation for this indication specifically. The clinical expert said the trial population did reflect the NHS population for this indication. The company provided data to show that the trial groups who had and had not had MKI treatment had similar responses. The ERG acknowledged that the data

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for the IAS MKI-naive group was similar to the data for the IAS overall. The committee accepted that the LIBRETTO-001 trial population was generalisable to the NHS population of people with RET fusion-positive advanced NSCLC.

Recommendations in this technology appraisal should apply to people with squamous and non-squamous advanced NSCLC

3.5 The marketing authorisation for selpercatinib does not differentiate between people with squamous and non-squamous advanced NSCLC. However, because of the rarity of RET gene fusions in squamous NSCLC, clinical advice, and the very small number of people with squamous NSCLC in the LIBRETTO-001 trial, the company did not present any evidence on using selpercatinib to treat these tumours. The clinical expert said they might expect some difference in the effectiveness of selpercatinib in treating squamous advanced NSCLC. This is because people with squamous NSCLC may be older, have a higher chance of being smokers and be less fit. However, the clinical expert expected there would still be some level of response. The Cancer Drugs Fund clinical lead said that the NHS would expect to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC. The committee agreed that the recommendations in this technology appraisal would apply to both squamous and non-squamous advanced NSCLC. This is because of the wording of the marketing authorisation and because the squamous population is so small.

Indirect treatment comparison

The populations included in the trials used in the network meta-analyses (NMAs) are relevant for the indirect treatment comparison (ITC)

3.6 Because LIBRETTO-001 was a single-arm trial, an ITC was needed to establish the relative efficacy of selpercatinib. The ERG stated that trials used for the ITC were unlikely to have contained substantial numbers of people with RET fusion-positive advanced NSCLC. This was because the

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mutation is rare (1% to 2% of people with NSCLC). Also, testing was not done for RET fusion status in these trials, which the company acknowledged as a limitation of the data. The company did its ITC using NMA. This method allows for the relative effects estimated in different studies to be pooled if studies are sufficiently similar. To overcome the limitations noted by the ERG, and to ensure the selected trials were comparable, a suitable cohort of people was needed as a control arm for LIBRETTO-001. The company simulated a control arm (that is, people having docetaxel with placebo), referred to as the pseudo-control arm, by using data from the REVEL NSCLC randomised controlled trial. The aim was to allow for the LIBRETTO-001 data to be compared with the other trials in the ITC. The committee noted that the other trial data was not adjusted for RET status. The clinical expert said that the effect of RET fusion on treatment effectiveness for people with advanced NSCLC is unknown. However, the clinical expert thought it may become clear over time as more testing is carried out for this form of lung cancer. The committee accepted that, in the absence of a direct comparator population with RET fusion-positive NSCLC, the NMA trial populations were relevant for the ITC.

Removing the adjustment for RET status from the simulated control arm for docetaxel is appropriate

3.7 In the company's original submission, the Flatiron clinic-genomic database was used to provide a range of prognostic factors (such as RET fusion status, age, smoking history and cancer histology). This was to adjust the control arm extracted from the REVEL randomised controlled trial to match the LIBRETTO-001 population. The company said this process had generated a relevant control arm for LIBRETTO-001, simulating the effect of using docetaxel with placebo to treat RET fusion-positive advanced NSCLC. The ERG said the methods used by the company needed multiple statistical steps, and each step created additional uncertainty. The company changed its approach after technical engagement, and the ERG pointed out that several issues either remained or had been created by using the new propensity score-matching approach. It also pointed out that the additional data provided by the company from a later point of the LIBRETTO-001 trial had not been used in the NMAs. Doing this would have ensured as much data as

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possible was informing the ITC. The ERG emphasised that there was still too much uncertainty in the NMAs to make conclusions on the relative efficacy of selpercatinib and the comparators. The committee agreed that simulating the control arm using the company's approach did generate uncertainty for the relative efficacy of selpercatinib. It agreed that, in principle, using a simulated control arm was acceptable. The committee considered that there was not enough evidence to understand the effect of RET fusion status on survival. So, it thought that the relative clinical-effectiveness estimates may have lacked validity. In response to consultation, the company reported new evidence from the scientific literature. It argued this showed that RET fusion status was not prognostic, so the simulated control arm should be generated without adjustment for RET status. The company provided updated survival results for the simulated control arm without adjustment for RET status. It used these results in its NMA. The ERG said that scientific literature identified by the company was not designed to show whether RET fusion status was prognostic, and that the results were not conclusive. However, it thought that the analysis from the company that had shown its results without adjusting the simulated comparator for RET fusion status could be informative. The ERG said that there were still several issues in addition to those with the generation of the revised simulated control arm. These included:

- statistical concerns about the violation of the proportional hazards assumption in some of the trials in the NMA
- that the people in the trials (other than LIBRETTO-001) were not tested for RET fusion-positive status

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- that fewer people were included in the company's propensity score-matching approach than in its original approach.

  The clinical expert commented that there is uncertainty about whether RET status does affect outcomes. However, the clinical expert explained that, in their experience, they would expect RET fusion-positive NSCLC to respond similarly to treatment as other forms of NSCLC. The clinical expert also reminded the committee that people with RET fusion mutations tend to access treatment at an earlier age, which would improve outcomes. The ERG emphasised that it was not possible to mitigate all uncertainty in estimating the effect of selpercatinib and the simulated control arm. The Cancer Drugs Fund clinical lead commented that there is uncertainty about the prognostic effects of RET fusion mutations. However, they noted that the company had adjusted the data for other covariates, such as demographic factors, that are known to affect survival. The committee concluded that, based on the limited data available, it was appropriate to remove the adjustment for RET status from the simulated control arm. But it also noted that significant uncertainty remained from this and other sources.

The company's economic model

The company's model is appropriate for decision making

3.8 The company used a partitioned-survival economic model that included 3 health states: progression-free, progressed and death. The committee concluded that the model was generally appropriate and consistent with the models used in other appraisals for NSCLC, including:

- NICE's technology appraisal guidance on atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy
- NICE's technology appraisal guidance on osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer

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- NICE's technology appraisal guidance on nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy.

  The committee concluded that the company's economic model was suitable for decision making.

The company's survival extrapolations for people having selpercatinib are plausible but uncertain

3.9 In the company's original submission, extrapolation of PFS and OS for selpercatinib came from LIBRETTO-001 and the NMA (see section 3.6). The different extrapolation distributions were ranked using statistical methods, and also considered by clinical advisers to the company. The company based its conclusions for the selpercatinib arm on the Spline/Knot1 OS extrapolation. This was because its clinical advisers believed this extrapolation fitted most closely to their expectation of clinical reality, even though it was not objectively the best fit. The committee noted that clinical expert opinions drew little on experience of the rare RET fusion-positive form of NSCLC. It also noted that there is little long-term experience of using selpercatinib in the NHS. The ERG said that selection based on clinical advice rather than statistical tests, was open to bias. The direction and magnitude of any bias was not clear from the data. The ERG did not select a preferred alternative base-case extrapolation function because it thought the data and NMAs were too uncertain to make this possible. It noted that the Gompertz alternative extrapolation would match the clinical evidence most closely, and would be just as appropriate a selection of extrapolation as Spline/Knot1. However, it noted that it resulted in substantially different cost-effectiveness results. A different approach was used for PFS with selpercatinib, in that the stratified Gompertz distribution was used to fit the data. The committee discussed the differences in the extrapolated OS estimations presented and that this was, in part, caused by the short follow up of the LIBRETTO-001 trial. The ERG said that, based on its inspection of extrapolations fit to the LIBRETTO-001 data, OS for selpercatinib appeared to have been overestimated by the company. The clinical expert and Cancer Drugs Fund clinical lead supported this view. The committee acknowledged the uncertainty in PFS and OS estimates, particularly in the wide range of extrapolations for selpercatinib. In

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response to consultation, the company provided updated survival extrapolations for selpercatinib based on the results from its updated NMA and presented the updated results. It was again possible to fit a wide range of extrapolations to the data. The company repeated the process used in its original submission for choosing extrapolation curves. It selected the stratified Gompertz distribution for PFS, and the unstratified Gompertz for OS. The ERG commented that, based on the selpercatinib Kaplan–Meier curve of the data in LIBRETTO-001, the extrapolated OS for selpercatinib appeared to have been overestimated. The ERG reiterated that several other distributions also fitted the data. The Cancer Drugs Fund clinical lead and clinical expert commented that the 5-year survival estimates appeared to be similar to those seen in clinical practice for other targeted lung cancer therapies. They explained that the predicted survival may have been high, for example, the 38.8% survival predicted at 5 years using the company's Gompertz extrapolation. But they thought that this was plausible based on experience with other targeted treatments. The company acknowledged that its revised PFS and OS extrapolations may still have overestimated the effect of selpercatinib. However, it commented that the uncertainty could have been reduced with more mature data from LIBRETTO-001. The committee concluded that there was still uncertainty about long-term survival with selpercatinib and that more mature data from LIBRETTO-001 would provide more robust long-term survival estimates. However, it agreed that, based on the opinions of the clinical expert and the Cancer Drugs Fund clinical lead, the survival benefits from selpercatinib at 5 years were not unreasonable. So, the committee concluded that it was appropriate to consider the company's survival estimates for selpercatinib in its decision making.

The modelled OS for the simulated control arm is plausible but there is still uncertainty

3.10 In the company's original submission, the estimates of PFS and OS for docetaxel came from the simulated control arm and NMA (see section 3.6 and section 3.7). The ERG considered that the extrapolation of survival in the control arm was likely to have been longer than expected in clinical practice. The clinical expert said they would have expected OS to be about 9 to 10 months for docetaxel, rather than the

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higher values seen in the survival extrapolations in the original submission. They explained that it is feasible that people with RET fusion-positive advanced NSCLC could have greater OS than people with other forms of advanced NSCLC. This is particularly because they tend to be younger and non-smokers, which might explain some of the higher-than-expected OS in the docetaxel arm. However, they noted that there was no evidence to support this. The company explained that the increase in OS from 9 months in the simulated control arm was because of the adjustment processes for RET fusion status used in its generation. The committee agreed that the survival estimates for the control arm were implausibly long, and that this would mean the conclusions based on the model were not robust. In response to consultation, the company provided revised survival extrapolations for the simulated control arm without adjustment for RET fusion status. The company considered that the updated survival extrapolations fitted more closely to the clinical expert's estimates (that is, 9 to 10 months). The ERG reiterated its opinion that there was still a lot of uncertainty. It did not think that simply removing the adjustment for RET fusion status would have accounted for all the uncertainty (see section 3.7). The ERG thought that the company had succeeded in reducing survival estimates for the simulated control arm, which had been considered to be too high. However, it pointed out that, because of limited data, the long-term survival for this group was still uncertain. The clinical expert considered the revised survival extrapolations to be more plausible. This was because of the low number of people in the stimulated control arm who were expected to be alive at 5 years and beyond. The committee agreed that the company's revised survival extrapolations for the simulated control arm were clinically plausible and appropriate for decision making. However, it also agreed that the survival estimates were still uncertain. This was because of the lack of evidence on whether RET status is a prognostic factor, so whether it should have been adjusted for in the stimulated control arm.

The economic model should use time to discontinuation (TTD) when calculating the cost of selpercatinib

3.11 The original company model used PFS to calculate the cost of selpercatinib. The ERG said that using an extrapolation based on the TTD data in LIBRETTO-001 would be more accurate. The company

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subsequently used an estimate for TTD in its updated model. The ERG preferred to incorporate a parametric extrapolation for TTD into the original model. The company stated that the ERG's approach overestimated TTD, and therefore costs, because the data was immature. The clinical expert said that the costs of selpercatinib would be higher if estimated using TTD rather than PFS. The reason is that it is common for a treatment to be continued even if there is disease progression because progression does not mean there is no benefit from the treatment. This could be because:

- an initially large tumour is substantially reduced, so progression of this tumour would be less than without treatment or

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- 1 or more secondary tumours have progressed but there is still a positive effect on the primary tumour from having the treatment.

  The clinical expert advised that it would be unlikely that people would still be on the treatment 2 years after progression. In response to consultation, the company provided further information on its original approach. It explained that it had got the mean time from progression to stopping treatment from the LIBRETTO-001 trial. It then added this value to the PFS curve to calculate cost of selpercatinib. The company also provided scenario analyses for various fixed time points between PFS and stopping treatment with selpercatinib. It based this on LIBRETTO-001 data to show that modelling TTD might overestimate the time on treatment, and so overestimate costs of selpercatinib. The ERG considered that this did not include new evidence. It reminded the committee that TTD is the usual basis for calculating costs in other NICE technology appraisals. The ERG also highlighted that more data was available for TTD than OS. So, it thought that there could have been an inconsistency in the company's arguments that OS data was sufficiently reliable to use within the economic model but not TTD data. The clinical expert said that people would continue using selpercatinib for as long as it was beneficial. The clinical expert explained that there would not be a single predicable value for time from progression to stopping treatment. The Cancer Drugs Fund clinical lead said that the company's scenario analysis comparing PFS extrapolations with various TTD extrapolations showed an inconsistency between the company's separate results for OS and TTD. This inconsistency resulted in a longer OS but shorter TTD (the results are confidential and cannot be reported here). When the details of the results were considered by the committee and the experts, they were not plausible. The Cancer Drugs Fund clinical lead considered that the expected OS for people with RET fusion-positive NSCLC closely aligned with the ERG's TTD extrapolation. The company considered that this extrapolation of TTD was an overestimate. It thought that the uncertainty associated with TTD could be reduced with further data from the ongoing trial and validation from external data. The committee noted consultation comments had stated that it would be inconsistent with previous NICE technology appraisals to use PFS rather than TTD. It concluded that the cost of selpercatinib should be based on an extrapolation of the TTD data in LIBRETTO-001.

The cost of genetic testing for RET fusions should be

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incorporated into the economic model

3.12 The company did not include costs for genetic testing for RET fusions into its original cost-effectiveness model. This was because it expects such testing to be done routinely within the NHS. The Cancer Drugs Fund clinical lead confirmed that testing for RET fusions is available in the NHS as a fluorescent in-situ hybridisation test. However, access to this test is not routine or part of normal screening at the NHS Genomic Medicine Service. The clinical expert said that next-generation sequencing screening panels would be adapted to include testing for RET fusions when possible. However, at the time of this appraisal for selpercatinib, this was not considered routine. Therefore, NHS England provided a suitable cost per test to the company, and the company included this in its economic model. The committee noted the response to consultation from a commentator that the cost of testing should have been shown as a percentage of the overall testing costs. The commentator said that this percentage should have represented the additional costs compared with the testing costs without testing for RET fusion status. The committee agreed that incorporating the cost of genetic testing for RET fusions was appropriate.

Utility values in the economic model

The progressed disease (PD) utility value used by the company is acceptable in the absence of more robust data

3.13 The ERG pointed out that the company's approach to utility values used in the model was inconsistent. In general, the company took its utility values from NICE's technology appraisal guidance on nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy. However, it used the utility value for PD of 0.688 from the company's base-case analysis in the nivolumab appraisal, rather than that appraisal committee's preferred value for PD of 0.569. The ERG was concerned that 0.688 was high, preferring 0.569. For the appraisal of selpercatinib, the company collected health-related quality-of-life data in the LIBRETTO-001 trial. However, it used the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire

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rather than EQ-5D to collect this data. The company followed a method reported in the literature to map EORTC to EQ-5D, and the calculated PD value was higher than 0.688. So, the company decided to use the midpoint between 0.569 and 0.688 in its model, which was 0.628. The ERG said this approach was arbitrary and maintained its view that the utility value of 0.569 from the nivolumab appraisal was appropriate for this population. The clinical expert stated that people with RET fusion-positive advanced NSCLC tend to be younger and have never smoked. So, they thought it was feasible they might have generally higher utility values than people with other forms of lung cancer. The committee decided that the PD value of 0.628 used by the company in the revised model was acceptable for decision making in absence of more robust data.

Cost-effectiveness estimates

The most plausible incremental cost-effectiveness ratio (ICER) is outside the range normally considered a cost-effective use of NHS resources

3.14 In response to consultation, the company presented a revised base case, which included an updated commercial arrangement for selpercatinib. The pairwise ICER was:

- £55,119 per quality-adjusted life year (QALY) gained for selpercatinib compared with docetaxel

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- £48,800 per QALY gained for selpercatinib compared with docetaxel plus nintedanib (not accounting for the confidential discount which applies to nintedanib and increases the ICER).

  The ERG did a fully incremental analysis. This was a combined single analysis in which nintedanib with docetaxel was compared with docetaxel alone, which was then compared with selpercatinib alone. In this analysis, docetaxel alone and selpercatinib alone 'extendedly dominated' docetaxel with nintedanib (that is, nintedanib with docetaxel was less effective and had a higher ICER than selpercatinib). This meant the relevant comparison was between docetaxel and selpercatinib. The company also presented scenario analyses using its revised PFS curves for calculating the cost of selpercatinib. In these, the ICERs ranged from £54,006 to £59,540 per QALY gained for selpercatinib compared with docetaxel (see section 3.11). The ERG made 1 change to the base case. It modelled the costs of selpercatinib based on TTD rather than PFS. The ERG's pairwise ICERs were £76,210 per QALY gained for selpercatinib compared with docetaxel, and £71,978 per QALY gained for selpercatinib compared with docetaxel with nintedanib (not accounting for the confidential discount that applies to nintedanib, which increases the ICER). The ERG maintained that the data underpinning the cost-effectiveness model was uncertain because of the issues mentioned in section 3.3, section 3.6, section 3.7, section 3.9 and section 3.10. The committee acknowledged the large range of plausible ICERs because of data immaturity and modelling assumptions. It was aware that modelling the cost of selpercatinib based on TTD rather than PFS was a key driver of cost effectiveness. It reiterated its opinion that the cost of selpercatinib should have been based on TTD rather than PFS. It therefore concluded that the most plausible ICERs for selpercatinib compared with docetaxel would be closer to the ERG's ICER of £76,210 per QALY gained. This was because this ICER incorporated its preferred assumption. It concluded that this was outside the range normally considered a cost-effective use of NHS resources.

There are no additional benefits that are not captured in the cost-effectiveness analysis

3.15 The committee noted that, unlike docetaxel, selpercatinib is an oral drug, and it specifically targets RET fusion-positive NSCLC. It agreed that selpercatinib would be beneficial. The committee considered that the

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model structure should have been able to capture the benefits and costs of selpercatinib in terms of health-related quality of life and QALYs gained. It did not think that it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

End of life

Life expectancy for people with RET fusion-positive NSCLC having standard care is less than 2 years

3.16 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. In the company's original submission, the base-case estimate for the median OS for people offered docetaxel was less than 24 months, and an estimate of the mean was not provided. However, the company explained that it thought this to be an overestimate compared with clinical expert opinion, which was 9 to 10 months. The ERG's estimates for OS for people offered docetaxel with or without nintedanib were higher than those of the company, that is, above 24 months. The company thought that the ERG's extrapolations for survival were overestimates. The committee noted the comments from the clinical expert. It considered that the expected survival of people with RET fusion-positive advanced NSCLC who were not offered selpercatinib might be much less than 24 months in practice. In the company's response to consultation, the modelled estimates for OS with docetaxel (without adjustment for RET status in the simulated control arm) were closer to the survival estimates expected by the clinical expert. The ERG reiterated that there was a lack of data to show that removing the adjustment for RET status was the correct approach, so there was still uncertainty. The committee accepted that there was uncertainty in how the simulated control arm was generated. But it agreed that the updated OS results for docetaxel were plausible and concluded that the short life expectancy criterion was met.

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Selpercatinib is likely to extend life by more than 3 months

3.17 In its original base case, the company estimated that selpercatinib would extend life expectancy by much more than 3 months (the company's modelled estimates are confidential and cannot be presented here). The ERG thought that this was feasible according to the data, but highly uncertain because of the difference between clinical expert opinion and company estimates. The committee recalled its concerns about the uncertainty in the OS estimates generated using the company's original model. It concluded that the company's estimate of extending life expectancy was not reliable and so the life extension criterion was not met. This was because of its concerns with the original NMA and the lack of robust results from the model. In response to consultation, the company presented updated OS estimates for selpercatinib and the simulated control arm based on the generation of the revised control arm, and updated NMAs. A wide range of extrapolations could be made from the results, so the committee agreed that there was uncertainty about the extent of the additional survival gain from selpercatinib compared with the simulated control arm. However, it concluded that it was likely that people having selpercatinib would benefit from an extension to life of more than 3 months.

Conclusion

Selpercatinib is not recommended for routine use in the NHS

3.18 The committee was aware that the evidence base will necessarily be weaker for some rare indications such as RET fusion-positive advanced NSCLC because of the low number of people with the condition. The committee recalled that there are no targeted treatments currently available for RET fusion-positive advanced NSCLC, as discussed in section 3.1. It noted the clinical- and cost-effectiveness evidence was highly uncertain because of the immaturity of the data from the LIBRETTO-001 trial. It also noted that there was still uncertainty about the ITC using NMAs based on the simulated control arm. Selpercatinib met NICE's end of life criteria. However, the committee's preferred ICER was well above the range normally considered a cost-effective use of

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NHS resources, even considering the end of life criteria. Therefore, it could not recommend selpercatinib for routine use for previously treated RET fusion-positive advanced NSCLC.

Cancer Drugs Fund

Selpercatinib should be included in the Cancer Drugs Fund

3.19 Having concluded that selpercatinib could not be recommended for routine use, the committee then considered whether it could be recommended for treating RET fusion-positive advanced NSCLC within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum):

- The company had expressed that it thought the Cancer Drugs Fund may be appropriate for selpercatinib.
- The key uncertainties were the accuracy and clinical feasibility of the extrapolations of OS, PFS and TTD for selpercatinib. Further data collection in the ongoing LIBRETTO-001 trial may reduce the uncertainties in the OS, PFS and TTD extrapolations (see section 3.9).

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- Further data collection in the ongoing LIBRETTO-001 trial would not reduce the uncertainty in the OS and PFS extrapolations for docetaxel, which are based on the simulated control arm. Data from other sources might confirm the effect of RET fusion status on survival in people with advanced NSCLC but would not remove other sources of uncertainty. The committee agreed that this uncertainty would not be fully resolved by data collection in the Cancer Drugs Fund (see section 3.10).

  The company proposed a confidential commercial arrangement for use of selpercatinib within the Cancer Drugs Fund. The committee noted there was uncertainty about the extrapolations of OS, PFS and TTD for selpercatinib, and the extrapolations of OS and PFS for docetaxel, which were based on the simulated control arm. However, it was satisfied that, with the commercial access agreement applied, selpercatinib has plausible potential to be cost effective (the cost-effectiveness estimates are confidential and cannot be reported here). The committee concluded that selpercatinib met the criteria for inclusion in the Cancer Drugs Fund. It therefore recommended the drug for use within the Cancer Drugs Fund for treating RET fusion-positive advanced NSCLC in adults who need systemic therapy after immunotherapy, platinum-based chemotherapy or both, if the conditions in the managed access agreement are followed. It also stated that, when the guidance is next reviewed, the company should use the committee's preferred assumptions (unless new evidence indicates otherwise), as set out in section 3.14.

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4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has RET fusion-positive advanced non-small-cell lung cancer and needs systemic therapy after immunotherapy, platinum-based chemotherapy or both, and the doctor responsible for their care thinks that selpercatinib is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) - A new deal for patients, taxpayers and industry.

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 use in the Cancer Drugs Fund, 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. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. The NHS England and NHS Improvement 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 the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales,

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whichever is the later.

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5 Appraisal committee members and NICE project team

Appraisal committee members

This topic was evaluated as a single technology appraisal by the highly specialised technologies evaluation committee. Because of this, some members of the technology appraisal committees were brought in to provide additional expertise to the committee. The 4 technology appraisal committees are standing advisory committees of NICE.

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

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

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

Stephen Norton
Technical lead

Nicola Hay, Christian Griffiths and Victoria Kelly
Technical advisers

Gavin Kenny
Project manager

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Accreditation

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