NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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www.nice.org.uk/guidance/ta911

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Selpercatinib is recommended with managed access as an option for treating RET fusion-positive advanced non-small-cell lung cancer (NSCLC) in adults, only if:

- it is untreated
- the conditions in the managed access agreement for selpercatinib 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

The scope for this appraisal was selpercatinib for untreated RET fusion-positive advanced NSCLC, which is narrower than its marketing authorisation. Selpercatinib is already recommended with managed access for previously treated RET fusion-positive advanced NSCLC (see NICE's technology appraisal guidance 760).

Standard treatment for untreated RET fusion-positive advanced NSCLC is pemetrexed plus platinum-based chemotherapy and pembrolizumab plus pemetrexed and platinum-based chemotherapy. Selpercatinib is another option.

Clinical trial evidence suggests that selpercatinib could be effective for untreated RET fusion-positive advanced NSCLC. But the results are uncertain because it was not compared directly with anything and the trial is continuing to collect results. Indirect comparisons with standard treatments suggest selpercatinib could increase how long people live and how long they have before their cancer gets worse. But the results from these are uncertain too.

Because the clinical-effectiveness evidence is uncertain, the cost-effectiveness estimates are also uncertain. The most likely estimates are higher than what NICE considers to be a

cost-effective use of NHS resources, even when considering the condition's severity and its effect on quality and length of life. So, selpercatinib cannot be recommended for routine use.

Selpercatinib could be cost effective if more evidence confirms that people live longer with treatment. Direct comparisons from the ongoing trial could help address the uncertainty about how long people live. So, selpercatinib is recommended for use with managed access.

2 Information about selpercatinib

Marketing authorisation indication

2.1 Selpercatinib (Retsevmo, Eli Lilly) is indicated for 'the treatment of adults with advanced RET fusion-positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor'.

2.2 Selpercatinib is also recommended with managed access for previously treated RET fusion-positive advanced NSCLC (see NICE's technology appraisal guidance 760).

Dosage in the marketing authorisation

2.3 The dosage schedule is available in the summary of product characteristics for selpercatinib.

Price

2.4 The list price for 56 capsules of selpercatinib (80 mg) is £4,368 (excluding VAT; BNF online, accessed February 2023). The company's estimated cost for a 28-day cycle of selpercatinib is £8,736.00.

2.5 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.

3 Committee discussion

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

Clinical management

Clinical need

3.1 The patient experts stated that people with RET fusion-positive non-small-cell lung cancer (NSCLC) tend to be younger and with fewer comorbidities. Because of this they tend to be diagnosed at a late stage, because they do not fit the profile of a typical person with lung cancer. The illness is characterised by breathlessness, cough and weight loss. The clinical experts explained that targeted treatment with tyrosine kinase inhibitors (TKIs) such as selpercatinib is associated with higher quality of life in this type of lung cancer compared with systemic chemotherapy. Because selpercatinib can cross the blood-brain barrier, it can be used to directly target brain metastases, which are more prevalent in people with this type of NSCLC. Another benefit is that, unlike current treatments, selpercatinib is an oral medicine. This means it can be taken at home instead of intravenously in hospital. A clinical expert said that evidence shows that immunotherapy, which is currently standard care in the NHS, has a poor response and has more side effects than targeted treatment. Selpercatinib is currently recommended with managed access for previously treated RET fusion-positive advanced NSCLC (see NICE's technology appraisal guidance on selpercatinib for previously treated RET fusion-positive advanced NSCLC, TA760). The clinical experts explained that targeted treatment would be an important addition to the treatment pathway for untreated RET fusion-positive advanced NSCLC. This is because people with this condition must have less well-tolerated and potentially less effective treatments options before becoming eligible for targeted treatment. The committee agreed that there is an unmet need for treatments for untreated RET fusion-positive advanced NSCLC. It concluded that people would welcome a

new oral treatment option.

RET fusion testing

3.2 The company did not include costs for genetic testing for RET fusions in its cost-effectiveness model. But a proportional cost associated with detecting RET fusion status was included in the model for the previously treated population in line with TA760. The committee was aware that RET fusion status is included in the 2020/2021 National Genomic Test Directory. The Royal College of Pathologists noted that testing for RET fusion status upfront is being done at many centres. But it noted that if pathology departments do not have funding to prepare tissue for genomic testing, individual trusts will need to fund this work. People having treatment at trusts that lack this funding do not have access to comprehensive testing. Instead, they have targeted testing, which may not include testing for RET fusion status. They said that the lack of funding will continue to create inequity of access to drugs between trusts, specifically for those that are only available after diagnostic confirmation. The professional organisation also noted that the lack of funding may affect turnaround times for RET testing, which may delay first-line treatment. The committee concluded that confirmation of RET fusion status is needed before starting on selpercatinib.

Squamous NSCLC

3.3 The company did not provide evidence for squamous NSCLC. It explained this was because RET fusions in squamous NSCLC are rare. Also, there were not many people with squamous NSCLC in the supplemental analysis set 1 (SAS1) of the LIBRETTO-001 trial (see section 3.5). It noted that the marketing authorisation for selpercatinib does not differentiate between squamous and non-squamous advanced NSCLC. The committee was aware that in TA760, clinical experts said that the NHS would expect to use selpercatinib in both squamous and non-squamous NSCLC. This is because they expect some level of response in the squamous type, despite the lack of evidence. The committee agreed that the recommendations in this technology appraisal would apply to both squamous and non-squamous advanced NSCLC.

Comparators

3.4 Expert oncologists practising in the NHS informed the company's choice of comparators. This was to ensure that the most relevant comparators in the UK were included. The expert oncologists stated that there is limited use of immunotherapies alone in clinical practice because they are less effective in cancer with RET fusion mutations. The company's comparators were aligned with the comparators in NICE's technology appraisal guidance on pralsetinib for treating RET fusion-positive advanced NSCLC. So, the company compared selpercatinib with pembrolizumab plus pemetrexed and platinum-based chemotherapy and pemetrexed plus platinum-based chemotherapy. The committee was satisfied with the company's comparators and considered that they were aligned with NHS practice.

Clinical effectiveness

LIBRETTO-001

3.5 LIBRETTO-001 is an ongoing multicentre, open-label, single-arm, phase 1 to 2 trial for selpercatinib in people with advanced solid tumours, including RET fusion-positive NSCLC tumours. The evidence for selpercatinib comes from the SAS1 dataset of LIBRETTO-001. The SAS1 dataset was a cohort within the trial that studied untreated RET fusion-positive NSCLC. The primary outcome of the trial is objective response rate (ORR). Secondary outcomes include progression-free survival (PFS), overall survival (OS) and health-related quality of life. A total of 796 people were enrolled in the trial and 356 had RET fusion-positive advanced NSCLC. Data from the 69 people from the SAS1 population was used in the analyses for this appraisal. ORR using the June 2021 data cut was 84% (95% confidence interval 73 to 92) and the median PFS was 22 months. The EAG stated that trial data for PFS and OS was relatively immature (42% had progression and 29% died), adding uncertainty to the results. The results suggest selpercatinib could be clinically effective. But the results are uncertain because of the immaturity of the data and because selpercatinib was not compared with other treatment options. The committee concluded that LIBRETTO-001

suggests selpercatinib could be clinically effective, but the data is uncertain.

Indirect treatment comparisons

3.6 Because LIBRETTO-001 is a single-arm trial, indirect treatment comparisons (ITCs) were needed to establish selpercatinib's efficacy compared with other treatments. The company did an ITC of selpercatinib compared with pemetrexed plus platinum-based chemotherapy using KEYNOTE-189. KEYNOTE-189 is a randomised controlled trial comparing pembrolizumab plus pemetrexed and chemotherapy with placebo plus pemetrexed and chemotherapy in people with untreated advanced non-squamous NSCLC. This study was selected by the company because it had access to the trial's individual patient data. This type of data was considered necessary to enable a population adjustment to match people based on individual characteristics. Using an adjustment method was essential because people with RET fusion-positive NSCLC are known for not smoking and being younger and healthier than people with other types of lung cancer. The EAG was concerned about the use of KEYNOTE-189 trial as a source for the ITC. This was because the baseline characteristics were not comparable to those in LIBRETTO-001. Also, people's RET fusion mutation status in KEYNOTE-189 was unknown. The EAG noted that it had found evidence in the literature suggesting that people with RET fusion-positive advanced NSCLC had more optimistic outcomes than those shown in KEYNOTE-189. A study by Drilon et al. (2016) suggests that people having treatment with pemetrexed can have a median PFS of 19 months, which is close to that of selpercatinib in LIBRETTO-001 (22 months) and considerably higher than KEYNOTE-189 (9 months). The EAG was concerned that this difference could overestimate the treatment effect of selpercatinib. The NHS England Cancer Drugs Fund clinical lead explained that the Drilon study had been done in a tertiary cancer hospital with a highly selected group of people (n=18) so recommended some caution when drawing conclusions from this trial. They explained that, although there are uncertainties in both trials presented, KEYNOTE-189 offered the benefit of being a large pivotal randomised controlled trial. The EAG also noted a study by Hess et al. (2021), which suggested that having a RET mutation increases the risk of

dying compared with not having one. Although the results of the Hess study are not statistically significant (hazard ratio [HR] 1.52, 95% confidence interval 0.95 to 2.43, p=0.08), it implies that having the mutation could lead to a worse prognosis. The clinical expert explained that it is currently difficult to state whether having a RET fusion mutation has a prognostic effect because it is rare, and the available evidence has mixed conclusions. But because brain metastases are more common in this population, having a RET fusion mutation is not expected to lead to better prognostic outcomes. Also, the EAG had concerns around the method of adjustment used for confounding. It agreed that the propensity score matching used in the company's base case was the most conservative. But it was still unclear about whether other methods would have led to results less favourable to selpercatinib. The committee noted that the results of the different methods of adjustment used were uncertain because of the uncertainties with the trial sources used in the ITC. The committee concluded that because of the uncertainties about RET fusion status and prognosis, the results of the ITC were uncertain.

Network meta-analysis

3.7 In addition to the ITC comparing selpercatinib with pemetrexed and platinum-based chemotherapy, the company did a network meta-analysis (NMA) to indirectly estimate the treatment effect of selpercatinib compared with pembrolizumab plus pemetrexed and platinum-based chemotherapy using:

- KEYNOTE-189, a randomised controlled trial comparing pembrolizumab plus pemetrexed and chemotherapy with placebo plus pemetrexed and chemotherapy
- KEYNOTE-189 Japan, a randomised control trial from Japan comparing pembrolizumab plus pemetrexed and chemotherapy with placebo plus pemetrexed and chemotherapy

- KEYNOTE-021, a randomised control trial comparing platinum-based chemotherapy with pemetrexed with or without pembrolizumab.

The company's base case was informed by the random effects model for all outcomes as it best fitted the data used. The results suggested that selpercatinib could improve ORR, PFS and OS compared with pemetrexed plus platinum-based chemotherapy and pembrolizumab plus pemetrexed and platinum-based chemotherapy. The exact results of this analysis cannot be shown here because they are confidential. The EAG had concerns about the results of the NMA. This is because the validity of the results partly depends on the choice of data informing the ITC (see section 3.6). If other sources had been used to inform the comparison with pemetrexed plus platinum-based chemotherapy, the NMA may have had different results. The committee concluded that the results of the NMA are uncertain, but they suggest that selpercatinib could be clinically effective.

Economic model

Company's modelling approach

3.8 The company used a partitioned survival model that included 3 health states: progression-free, progressed and death. The committee considered that the partitioned survival model is a standard approach to estimate the cost effectiveness of cancer drugs and is suitable for decision making.

Immature data and survival extrapolations

3.9 Because the data for PFS and OS from LIBRETTO-001 was relatively immature (42% of people had progression and 29% died), the extrapolated survival data from the economic model was uncertain. To explore this, the EAG did various scenario analyses looking at a range of plausible PFS and OS curves. It chose these curves based on plausible shape and best fit according to clinical expert opinion. The results of these scenarios provided a wide range of net monetary benefit results, confirming that the extrapolated data is substantially uncertain. The company highlighted that further data cuts from LIBRETTO-001 could

help validate the results from the latest data cut (June 2021). It also mentioned that LIBRETTO-431, a study comparing selpercatinib with pemetrexed plus platinum-based chemotherapy with or without pembrolizumab for first-line treatment of RET fusion-positive advanced NSCLC, could provide meaningful clinical-effectiveness data for selpercatinib. The committee considered that because of the immature data, the OS and PFS extrapolations are uncertain. The committee concluded that further data cuts from LIBRETTO-001 and the results from LIBRETTO-431 may address many of the uncertainties.

Choice of survival curves

3.10 The company selected the Gompertz curve to model PFS for selpercatinib compared with pemetrexed plus platinum-based chemotherapy. For the pembrolizumab plus pemetrexed and platinum-based chemotherapy arm, PFS was modelled using the HR from the NMA of pemetrexed plus platinum-based chemotherapy. For OS, the company selected the spline knot 1 curve for selpercatinib compared with pemetrexed plus platinum-based chemotherapy. For the pembrolizumab plus pemetrexed and platinum-based chemotherapy arm, OS was modelled applying the HR generated through the NMA. The EAG considered that the company's choice of survival curves for modelling treatment effectiveness was not transparent. It had concerns with the company's choice of a complex parametric survival curve to model OS (spline knot 1) instead of a standard parametric model. The company explained that it had selected its curves using clinical expert opinion. Because the data was immature (see section 3.9), using a visual and statistical fit of the parametric curves alone was insufficient to select the most appropriate curves. So expert opinion was needed to inform plausible survival at longer time horizons. The EAG was not convinced by the company's reason and highlighted that in some cases the company's curves were not close to the estimates suggested by its clinical experts. A clinical expert at the committee meeting highlighted that the company's chosen PFS and OS curves may have overestimated survival for selpercatinib compared with clinical practice. The clinical expert provided their own estimates of PFS and OS at different timepoints. The NHS England Cancer Drugs Fund clinical lead confirmed that these estimates would be plausible in UK clinical practice. But they cautioned

about putting too much emphasis on comparisons between trials and expectations from clinical practice, because of differences between people in these settings. The committee took this into consideration while noting the uncertainty around the company's choice of survival curves. The committee explained that it would instead prefer to see a range of plausible curves based on the committee's clinical experts estimates. The committee requested that the clinical experts exclude curves they felt led to implausible long-term survival estimates. For selpercatinib, the curves selected for PFS were:

- Weibull
- gamma
- stratified Weibull
- stratified gamma.

For OS, these were:

- Weibull
- gamma
- spline knot 3.

For pemetrexed plus platinum-based chemotherapy, a lognormal curve was selected to model PFS and an exponential curve was selected for OS. The committee concluded that a range of plausible curves, based on clinical expert opinion, would be considered in its decision making. But it noted that there was less uncertainty over the longer time horizons compared with selpercatinib.

Treatment effect waning

3.11 The company stated there was no evidence of treatment effect waning for selpercatinib in LIBRETTO-001 so it was not included in its base case. It explained that, if treatment waning were to happen, it would have been implicitly captured in the survival curves. The company noted that including waning would introduce additional uncertainty and that assumptions would be needed to inform the modelling. The company

also highlighted that no treatment effect waning had been included in the modelling for TA760. The EAG was not satisfied with the company's justification for not exploring treatment effect waning. It highlighted that the HR plots provided by the company showed a decreasing trend in hazard ratio for OS and PFS for selpercatinib compared with pemetrexed plus platinum-based chemotherapy, suggesting a potential treatment waning effect. The clinical expert explained that treatment waning is usually associated with immunotherapies when stopping rules have been applied. But TKIs such as selpercatinib are only used until disease progression, so a waning effect is not expected. It could also increase uncertainty if an arbitrary assumption was considered. For this reason, the clinical expert suggested to focus on the PFS data, which should account for the treatment effect waning. Based on this, the committee concluded that it was appropriate to exclude treatment effect waning from the modelling.

Subsequent treatments

3.12 The subsequent treatment distribution in the company's base case was based on UK clinical expert opinion. The EAG suggested that the treatments should have been modelled based on data from LIBRETTO-001. This is because the trial is the only empirical source that correlates with the effectiveness estimates from the trial. The company stated that the subsequent treatments used in the trial were not representative of clinical practice, because of a lack of data. The committee considered that subsequent treatments should reflect practice in the NHS. The committee concluded that the company's base case using clinical expert opinion was appropriate for decision making.

Severity modifier

QALY weighting

3.13 In its submission, the company provided evidence that untreated RET fusion-positive advanced NSCLC is a severe condition. The severity modifier allows the committee to give more weight to health benefits in the most severe conditions. The company provided absolute and

proportional quality-adjusted life year (QALY) shortfall estimates in line with NICE's health technology evaluation manual. Absolute QALY shortfall is the future health that is lost by people living with a condition, including quality and length of life, compared with the expected future health of people living without the condition, over their remaining lifetimes. Proportional QALY shortfall represents the proportion of future health that is lost by people living with the condition, including quality and length of life. To estimate the absolute and proportional QALY shortfalls, the company provided the QALYs of people without the condition over their remaining lifetime, based on the characteristics of people in the trial and the QALYs of people with the condition having current standard care. The company stated that, in line with the NICE reference case, the Hernandez-Alava (2017) study was used to inform the base-case analysis and some other sources were explored in scenarios. All analyses resulted in a QALY weight of 1.2. The EAG was able to reproduce the shortfall analysis, the absolute and proportional QALY shortfall and the QALY weight of 1.2. The committee concluded that the modifier for disease severity was met and was appropriate for decision making.

Cost-effectiveness estimates

ICER

3.14 Because of confidential discounts for selpercatinib and the comparators, the cost-effectiveness results are commercial in confidence and cannot be reported here. The committee preferred an analysis that included:

- the company's base case excluding its choice of survival curves
- an alternative range of plausible survival curves based on clinical expert estimates (see section 3.10).

Using the committee's preferred assumptions resulted in a range of incremental cost-effectiveness ratios (ICERs) that were above the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The committee noted the high level of uncertainty, specifically the:

- immature trial data (see section 3.5 and section 3.8)
- company's ITC and NMA (see section 3.6)
- choice of survival curves (see section 3.10).

Because of these uncertainties, the committee agreed that an acceptable ICER would be around £20,000 per QALY gained (using weighted QALYs) for a routine commissioning recommendation. It considered that with the available data, the most plausible ICERs had not been proven to be within the range NICE usually considers a cost-effective use of NHS resources, even when the severity modifier was applied. So, it concluded that selpercatinib could not be recommended for routine commissioning.

Managed access

Recommendation with managed access

3.15 Having concluded that selpercatinib could not be recommended for routine use, the committee then considered if it could be recommended with managed access. It discussed that:

- With appropriate commercial arrangements, selpercatinib has plausible potential to be cost effective when the modifier for disease severity is applied in some analyses.
- The key uncertainties relate to the immaturity of the pivotal clinical trial. New evidence could address the clinical uncertainty:
  - LIBRETTO-001 is ongoing and further data could help reduce uncertainties around long-term PFS and OS.
  - SIREN, a real-world evidence study observing selpercatinib's efficacy.
  - LIBRETTO-431, a randomised clinical trial comparing selpercatinib with pemetrexed plus platinum-based chemotherapy could also provide meaningful data on selpercatinib's efficacy.

- The company submitted a managed access proposal and expressed an interest in selpercatinib being considered for managed access.

  The committee concluded that selpercatinib met the criteria to be considered with managed access. It recommended selpercatinib with managed access for people with untreated RET fusion-positive advanced NSCLC, only if the conditions in the managed access agreement are followed. When the guidance is next reviewed the company should use the committee's preferred assumptions (unless new evidence shows otherwise), as set out in section 3.14.

Other factors

Innovation

3.16 The company, patient experts and clinical experts considered selpercatinib to be innovative. The clinical experts said that a targeted treatment for a specific mutation, such as selpercatinib, is the most appropriate in terms of tolerability and efficacy. Also, the clinical experts recalled that selpercatinib can cross the blood-brain barrier. This is important for managing brain metastases, which are more prevalent in people who have untreated RET fusion-positive advanced NSCLC. The committee recognised that selpercatinib is an innovative treatment.

4 Implementation

4.1 When NICE recommends a treatment as an option for use with managed access, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has untreated RET fusion-positive non-small-cell lung cancer 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 criteria in the managed access agreement.

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 with managed access. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use with managed access, 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, whichever is the later.

5 Evaluation committee members and NICE project team

Evaluation 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 highly specialised technologies evaluation committee and 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 evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Peter Jackson
Chair, highly specialised technologies evaluation committee

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), a technical adviser and a project manager.

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Accreditation