NICE National Institute for Health and Care Excellence

NICE guidance

Pralsetinib for treating RET fusion-positive advanced non-small-cell lung cancer

Technology appraisal guidance
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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.

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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 Pralsetinib is not recommended, within its marketing authorisation, for treating RET fusion-positive advanced non-small-cell lung cancer (NSCLC) in adults who have not had a RET inhibitor before.

1.2 This recommendation is not intended to affect treatment with pralsetinib 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

Usual treatment for untreated RET fusion-positive advanced NSCLC is pembrolizumab with pemetrexed and chemotherapy, or platinum-based chemotherapy with or without pemetrexed. Usual treatment for previously treated RET fusion-positive advanced NSCLC is docetaxel chemotherapy or docetaxel with nintedanib.

The clinical evidence for pralsetinib suggests it could be clinically effective, but its benefit is uncertain because it was not compared directly with any usual NHS treatments. The results from indirectly comparing pralsetinib with some usual treatments suggest that pralsetinib could increase the time before the NSCLC gets worse and how long people live.

Pralsetinib meets NICE's criteria to be a life-extending treatment at the end of life for people with previously treated NSCLC, but not for untreated NSCLC. Because of the uncertainty in the clinical evidence, the estimates of cost effectiveness are uncertain and too high to be considered a cost-effective use of NHS resources. So pralsetinib cannot be recommended for routine use.

Pralsetinib is a new treatment and more data on its clinical effectiveness is being collected from 1 ongoing trial and 1 new trial. Collecting more data from these trials through a managed access agreement in the Cancer Drugs Fund may resolve some uncertainty in the clinical evidence. But NICE was advised that it was not possible to put a managed access agreement in place, meaning pralsetinib cannot be recommended for use in the Cancer Drugs Fund.

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2 Information about pralsetinib

Marketing authorisation indication

2.1 Pralsetinib (Gavreto, Roche) is indicated for 'the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for 120 capsules of pralsetinib (100 mg) is £7,044 (excluding VAT, company submission).

2.4 The company has a commercial arrangement, which would have applied if the technology had been recommended.

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3 Committee discussion

The appraisal committee considered evidence submitted by Roche, 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.

Treatment pathway and clinical practice

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

3.1 A clinical expert stated that RET fusion-positive advanced non-small-cell lung cancer (NSCLC) particularly affects young people who do not smoke and who do not typically fit the profile of people with lung cancer. So, people often tend to be diagnosed at a late stage. The patient experts highlighted that people with this condition have a poor prognosis which has a significant impact on family and carers. The illness is characterised by breathlessness, cough and weight loss, which can be difficult to manage without treatment. The clinical experts explained that pralsetinib is a once daily oral pill that has a clear advantage over intravenous treatment, which is normally given in hospital. The committee agreed that there is an unmet need in this patient population. It concluded that people with RET fusion-positive advanced NSCLC would welcome a new oral treatment option.

RET fusion status is not yet routinely identified in clinical practice

3.2 The clinical experts stated that there is no treatment pathway specific to RET fusion-positive advanced NSCLC because testing for RET fusion status has not been universally introduced (which is expected to change within 18 months). Also, until recently there were no targeted treatments in the UK. The clinical experts explained that RET fusion status is included in the 2020/2021 National Genomic Test Directory. However, this genetic screening has not yet been implemented at all hospitals and

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is typically only available at large centres. The experts further explained that test results might not be available at or soon after diagnosis, so decisions about first-line treatment are usually made without knowing RET fusion status. The clinical experts explained that if RET fusion status is unknown, the person will typically be offered pembrolizumab plus pemetrexed and chemotherapy as first-line treatment. If RET fusion status is known, they suggested that people would usually have platinum-based chemotherapy with or without pemetrexed. But the company explained in its consultation response that it had received input from clinical experts that suggested that pembrolizumab plus pemetrexed and chemotherapy may be more likely to be used in clinical practice nationally. A professional organisation noted that immunotherapy is believed to be less effective in cancer with oncogene drivers such as RET fusion than in the broader advanced NSCLC population. Second-line treatment for people whose RET fusion status is known is usually docetaxel monotherapy or docetaxel plus nintedanib. The clinical experts noted that use of docetaxel plus nintedanib is decreasing because of the limited benefit and increased side effects compared with docetaxel alone. The committee concluded that RET fusion status is not routinely identified in the NHS at present, and confirmation of RET fusion status influences which treatments would be considered relevant comparators.

Population and subgroups

Considering the untreated and treated subgroups separately is appropriate

3.3 The company submission included data for RET fusion-positive advanced NSCLC categorised in 2 subgroups: untreated, and previously treated (having had systemic treatment before). The committee concluded that the company's approach considering 2 subgroups was appropriate.

Pralsetinib's clinical evidence is based on non-squamous NSCLC alone

3.4 The company did not present information for squamous NSCLC. It

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explained that this was because there is a low incidence of people with RET fusion-positive squamous advanced NSCLC. Also, only a small number of people with squamous NSCLC were included in the clinical trial. Therefore, it chose the comparators for this appraisal using current standard care for this population in NICE's non-squamous treatment pathway. At consultation, the company explained that the marketing authorisation for pralsetinib does not differentiate between non-squamous and squamous NSCLC. The committee concluded that it was aware of the histological difference and determined it had not seen evidence for the squamous population, and that it would factor this into its decision making.

Comparators

The company's comparators are aligned with NHS practice

3.5 The company did not compare pralsetinib to all the comparators in the NICE scope. Based on clinical advice, the company refined the list of comparators and categorised them by treatment subgroup: untreated or previously treated. The company had been advised that people only have immunotherapies if they have not had treatment before. Also, it had excluded atezolizumab, bevacizumab, and carboplatin plus paclitaxel because they are used minimally. The clinical expert agreed with the company in excluding immunotherapy in people whose cancer had relapsed. After consultation, the company updated its comparators to better align with NHS practice (see section 3.2). For the untreated subgroup, these were:

- platinum-based chemotherapy with or without pemetrexed
- pembrolizumab plus pemetrexed and chemotherapy.

For the previously treated subgroup, the company's updated comparators were:

- docetaxel monotherapy

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- docetaxel plus nintedanib.

The committee was satisfied with the company's updated comparators, and considered that they were aligned with NHS practice (see section 3.2).

Clinical effectiveness

Clinical evidence for pralsetinib's effectiveness is uncertain because it is based on 1 single-arm study

3.6 The evidence for pralsetinib came from the ARROW clinical trial. This is a single-arm, open-label, non-randomised, multicentre, phase 1 and 2 trial for advanced, unresectable, RET fusion-positive NSCLC and other RET-altered solid tumours. The primary outcome of the trial is objective response rate. Secondary outcomes include duration of response, clinical benefit rate, disease control rate, progression-free survival, and overall survival. The trial recruited people from 79 centres in 13 countries, including 13 patients from the UK. It enrolled 310 people with RET fusion-positive advanced NSCLC, which provided the clinical evidence for the company's base-case cost-effectiveness analysis. Objective response rate using the November 2020 data cut was 69% (95% confidence interval: 62 to 75), and was higher for the untreated subgroup (79%) than the previously treated subgroup (64%). The median progression-free survival and overall survival results are confidential and cannot be shown here. The results suggest pralsetinib could be clinically effective. But this is uncertain because of the lack of comparative data to directly assess pralsetinib's effectiveness compared with other systemic treatment options. Also, the ERG assessed the quality of the ARROW study using the Downs and Black checklist, a scale used to assess the quality of studies. The quality of the trial was marked down in all 4 sections of the scale: reporting, external validity, internal validity, and confounding. The ERG explained that based on the results of the assessment, the trial does not appear to be a well-conducted, non-comparative observational study. The committee concluded that data from the ARROW study is relevant and suggests pralsetinib could be clinically effective, but it is uncertain because it comes from 1 single-arm study.

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The trial population is likely to be generalisable to the NHS population

3.7 The ERG was concerned about the small number of patients enrolled in the UK centres in the ARROW study. It said this could affect the generalisability of the trial to the population having treatment for RET fusion-positive advanced NSCLC in the NHS. The clinical expert said the trial population did reflect the NHS population for this indication. The committee considered that the ARROW trial population is likely to be generalisable to the NHS population.

The indirect treatment comparison results are uncertain

3.8 Because ARROW is a single-arm trial, indirect treatment comparisons were needed to establish the efficacy of pralsetinib compared with other treatments. Because of the lack of available clinical trial evidence about RET fusion-positive tumours, the company used data from people with wild type tumours (that is, tumours without a gene mutation or rearrangement, or of unknown mutation status). However, people with RET fusion-positive tumours have different characteristics to those with wild type tumours. Namely, their cancer is usually non-squamous, they are usually younger and have likely never smoked. So, the company adjusted the data to account for the different characteristics and reduce bias in the results. However, the lack of individual patient data meant some of the comparisons were naive. After consultation, the company updated its comparative analyses with the updated comparators (see section 3.5) using the committee's preferred methodology for the indirect treatment comparison:

- naive comparison for pembrolizumab plus pemetrexed and chemotherapy (using KEYNOTE-189, a randomised controlled trial comparing pembrolizumab plus pemetrexed and chemotherapy with placebo plus pemetrexed and chemotherapy)
- propensity score weighting analysis for platinum-based chemotherapy with or without pemetrexed (using IMpower132, a randomised controlled trial comparing atezolizumab plus platinum-based chemotherapy with chemotherapy alone)

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- propensity score weighting analysis assuming equal efficacy between docetaxel monotherapy and docetaxel plus nintedanib (using the OAK trial, an open-label randomised controlled study comparing atezolizumab with docetaxel in patients with locally advanced or metastatic NSCLC who are having or who have had platinum-based chemotherapy).

  The ERG noted that there were methodological problems with the systematic literature review, including baseline differences between the studies and the ARROW trial, which was a particular concern for the validity of the naive comparisons. Also, the search methods were not described, no other methods of adjustment were considered, and overlap was not explicitly assessed. So, the ERG considered that the results of the indirect treatment comparison needed to be regarded with caution. The company included an assumption of equal efficacy between docetaxel monotherapy and docetaxel plus nintedanib for the comparison in the previously treated subgroup. The committee acknowledged that the benefit of adding nintedanib to docetaxel is perceived to be limited (see section 3.2) but considered assuming no additional benefit to be implausible. The committee concluded that the results of the indirect treatment comparisons were uncertain.

The company's economic model

The company's model is appropriate for decision making

3.9 The company used a partitioned survival model that included 3 health states: progression-free, progressed disease and death. At consultation, the company updated its model in response to the committee's concerns, by:

- updating its comparators (see section 3.5)
- updating the model with the committee's preferred methodology for the indirect treatment comparison (see section 3.8)
- removing the proportional hazards assumption for the lifetime benefit of pralsetinib, except for pembrolizumab plus pemetrexed and chemotherapy

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- using independent curves to model survival (see section 3.11).

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

The model assumes a constant treatment benefit which may be implausible

3.10 The company model assumed that the benefit of pralsetinib compared with standard care could be characterised by a proportional hazards relationship over the full period of the model, which the committee considered implausible. After consultation, the company removed the proportional hazards assumption from the model for the comparisons with platinum-based chemotherapy with or without pemetrexed, docetaxel monotherapy and docetaxel plus nintedanib (see section 3.8). Instead, it fitted independent curves to model overall and progression-free survival for pralsetinib compared with the main comparators in all subgroups. However, it did not remove the proportional hazards assumption for pembrolizumab plus pemetrexed and chemotherapy. The company considered this to be a pragmatic approach to maintain simplicity in the model. The ERG considered that the company's model was improved. But some uncertainty still remained, because a constant treatment effect is still seen throughout the model, the trial data is immature, and the sample size used was small. The committee concluded that the assumption of pralsetinib's constant benefit over time may be implausible, particularly because there is no trial evidence beyond 18 months.

The overall survival and progression-free survival extrapolations are uncertain, but acceptable for decision making

3.11 Given that the ARROW trial did not include comparators, the company did an indirect treatment comparison to estimate the relative effectiveness of pralsetinib compared with other treatments (see section 3.8). To estimate survival for pralsetinib beyond the data collection period, the company used parametric models to extrapolate survival for both the untreated and previously treated subgroups. To estimate survival for the main comparators, the company fitted independent

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curves to model overall survival and progression-free survival, where patient-level data was available. The curve selection aligned with the NICE technical guidance on survival analysis. For the untreated subgroup, the company used exponential curves for overall survival and generalised gamma curves for progression-free survival and time to treatment discontinuation. For the previously treated subgroup, exponential curves were also used to model overall survival. Weibull curves were used for progression-free survival and time to treatment discontinuation. The committee was aware that there is a lack of available clinical trial evidence about RET fusion-positive tumours. It recalled that the company used data from patients with wild type tumours in its indirect treatment comparisons (see section 3.8). Because the overall survival and progression-free survival extrapolations are based on these data, the extrapolations are uncertain. Noting this uncertainty, the committee agreed that, on balance, this approach was reasonable based on the limited data available. The committee concluded that the overall survival and progression-free survival extrapolations were uncertain, but acceptable for decision making.

End of life

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.

The end of life criteria are met for previously treated RET fusion-positive advanced NSCLC

3.12 The committee accepted that people with previously treated RET fusion-positive advanced NSCLC are unlikely to live for longer than 24 months. The clinical experts explained that it is likely that pralsetinib will extend life for more than 3 months. In addition, the model estimated an undiscounted mean overall survival gain for pralsetinib compared with the comparators of more than 3 months (the exact results are confidential and cannot be reported here). Despite the uncertainty in the clinical data, and how this was incorporated into the company's economic model, the committee agreed it was likely that this criterion was met. So, the committee concluded that the end of life criteria had

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been met for this subgroup.

The end of life criteria are not met for untreated RET fusion-positive advanced NSCLC

3.13 The committee recalled that treatments in the untreated subgroup are pembrolizumab plus pemetrexed and chemotherapy, and platinum-based chemotherapy with or without pemetrexed (see section 3.5). The committee was aware that, nationally, clinicians may be more likely to prescribe pembrolizumab plus pemetrexed and chemotherapy for untreated RET fusion-positive advanced NSCLC. At consultation, the company acknowledged that people having pembrolizumab plus pemetrexed and chemotherapy tend to live longer than 24 months. On balance, the committee concluded that the end of life criteria were not met for untreated RET fusion-positive advanced NSCLC.

Cost-effectiveness estimates

An acceptable ICER would be at the lower end of the range normally considered a cost-effective use of NHS resources

3.14 NICE's guide to the methods of technology appraisal notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (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 and whether the technology meets the criteria for consideration as a 'life-extending treatment at the end of life'. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted the uncertainties informing the cost-effectiveness estimates, including the primary clinical evidence being from a single-arm trial (see section 3.6), limitations with the indirect treatment comparisons (see section 3.8) and a constant treatment benefit for pralsetinib applied throughout the modelled time horizon (see section 3.10). Because of these uncertainties, the committee considered the maximum acceptable ICER would be at the lower end of the range normally considered a cost-effective use of NHS resources.

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Pralsetinib is not recommended for routine use in the NHS

3.15 Because of confidential discounts for pralsetinib and its comparators, the cost-effectiveness results are commercial in confidence and cannot be reported here. The committee recalled that the end of life criteria were met in the previously treated group, but not the untreated group (see section 3.13). The committee noted the uncertainties with clinical and cost-effectiveness evidence, and that its preferred cost-effectiveness estimates were above the maximum ICERs considered a cost-effective use of NHS resources for the untreated and treated groups. Therefore, it concluded it could not recommend pralsetinib for routine use in the NHS.

Cancer Drugs Fund

Data from AcceleRET could address some clinical uncertainties

3.16 Having concluded that pralsetinib could not be recommended for routine use for either subgroup, the committee considered if it could be recommended for use in the Cancer Drugs Fund. Although the ongoing single-arm ARROW trial would provide further data on progression-free and overall survival for pralsetinib, the committee agreed this will not address the key uncertainties about pralsetinib's relative clinical effectiveness. It was aware that another trial had started. This is AcceleRET, an open-label, randomised, phase 3 study of pralsetinib compared with standard care in untreated RET fusion-positive advanced NSCLC (standard care being platinum-based chemotherapy plus pemetrexed with or without pembrolizumab in non-squamous disease and platinum-based chemotherapy plus gemcitabine in squamous disease). Progression-free survival is the primary outcome, and overall survival is included as a secondary outcome. The committee concluded that data from the AcceleRET trial would resolve some uncertainty for the untreated subgroup by providing direct comparative evidence against other systemic treatments and longer progression-free and overall survival estimates (estimated to be 32 months).

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Pralsetinib is not recommended for use in the Cancer Drugs Fund

3.17 Having established that data collection could address some of the clinical uncertainty, the committee considered whether there was plausible potential for satisfying the criteria for routine commissioning. It agreed that, based on current data from ARROW and the commercial arrangement submitted as part of the company's consultation response, pralsetinib had the potential to be cost effective. It concluded that pralsetinib met the criteria to be considered for inclusion in the Cancer Drugs Fund. The committee was aware that 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 specifies that final acceptance into the Cancer Drugs Fund depends on a managed access agreement being in place. NICE has been informed that it was not possible for a managed access agreement to be finalised by the company and NHS England. So, pralsetinib cannot be recommended for use within the Cancer Drugs Fund for RET fusion-positive NSCLC.

Other factors

There are no equality issues

3.18 No equality or social value judgement issues were identified.

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4 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

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), a technical adviser and a project manager.

Anne Murray-Cota
Technical lead

Caron Jones
Technical adviser

Kate Moore
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