NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using pralsetinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: February 2022

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using pralsetinib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 24 March 2022.

Second appraisal committee meeting: 7 April 2022.

Details of membership of the appraisal committee are given in section 5.

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 advanced NSCLC when RET fusion status is unknown is pembrolizumab plus pemetrexed and chemotherapy. Untreated advanced NSCLC when RET fusion status is known is usually treated with chemotherapy alone. Usual treatment for those who have already had treatment is docetaxel with or without nintedanib (whether RET fusion status is known or not).

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 indirect comparisons of pralsetinib compared with some usual treatments are highly uncertain, while comparisons with other usual treatments were not provided.

The above limitations in the clinical evidence mean the results from the economic model are very uncertain. Because of this it is not possible to determine a cost-effectiveness estimate for pralsetinib. So, it cannot be recommended for routine use.

Because of the issues with the economic model, pralsetinib's potential for use in the Cancer Drugs Fund could not be assessed. So pralsetinib cannot be recommended for use in the Cancer Drugs Fund.

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.

Price

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

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

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, have fewer comorbidities 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 symptoms of 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 a clear 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 Genomics Test Directory. However, this genetic screening has not yet been implemented at all hospitals and 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 first line. However, if their RET fusion status has been confirmed to be positive, the clinical experts indicated that first-line treatment is usually platinum-based chemotherapy with or without pemetrexed. Although pembrolizumab combination might also be offered, a professional organisation noted that immunotherapy is believed to be less effective in cancer with oncogene drivers such as RET fusion compared with 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 docetaxel and nintedanib use is decreasing due to 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

Untreated and treated subgroups were considered separately

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 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, the comparators chosen for this appraisal were determined using current standard care for this population in NICE's non-squamous treatment pathway. The committee was aware of the histological difference and determined it had not seen evidence for the squamous population.

Comparators

The company's comparators are incomplete and not 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 group: untreated or previously treated. For the untreated subgroup, the company's choice of comparators were:

- pembrolizumab monotherapy

- pembrolizumab plus pemetrexed and chemotherapy.

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

- docetaxel monotherapy
- docetaxel plus nintedanib
- platinum-based chemotherapy with or without pemetrexed.

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. But they highlighted that platinum-based chemotherapy with or without pemetrexed was missing as first-line treatment. The expert explained that this comparator had been presented as a second-line treatment, but it would usually be used as first-line treatment in RET fusion-positive NSCLC. The committee recalled that it had heard from the clinical experts that, in the NHS, once people have a confirmed RET fusion-positive status they would likely be offered platinum-based chemotherapy with or without pemetrexed as a first-line treatment (see section 3.2). The committee considered that platinum-based chemotherapy with or without pemetrexed was a relevant comparator in the untreated subgroup. It noted that platinum-based chemotherapy with or without pemetrexed was not a relevant comparator for the previously treated subgroup. The committee considered that the comparators presented by the company were not aligned with NHS practice and concluded that the company's analyses were incomplete.

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 and 13 countries, including 13 patients from the UK. A total of 310 people with RET fusion-positive advanced NSCLC were enrolled, 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. This is because of the lack of comparative data to assess pralsetinib's effectiveness with other systemic treatment options. Also, the ERG did a quality assessment 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 pralsetinib's clinical evidence is uncertain because it comes from 1 single-arm study.

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

3.7 The ERG raised its concerns regarding the low 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 and explained that RET fusion-positive advanced NSCLC affects people similarly, regardless of ethnicity. The committee considered that the ARROW trial population is likely to be generalisable to the NHS population.

The indirect treatment comparison results are highly uncertain

3.8 Because ARROW is a single-arm trial, an indirect treatment comparison was 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 patients with wild type tumours (that is, tumours without a gene mutation or rearrangement or unknown mutation status). The company used the Flatiron database (a nationwide US observational database derived from electronic health record data) and a systematic literature review to inform the comparison. 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. The company did 3 types of comparative analysis:

- propensity score weighting using Flatiron for:
  - pembrolizumab plus pemetrexed and chemotherapy
  - pembrolizumab monotherapy
- propensity score weighting using the OAK trial (a phase 3 multicentre randomised controlled trial comparing atezolizumab with docetaxel) for:
  - docetaxel monotherapy
- naive comparisons for:

- docetaxel plus nintedanib (using LUME-Lung 1, a phase 3 multicentre randomised controlled trial comparing nintedanib with docetaxel)
- platinum-based chemotherapy with or without pemetrexed (using GOIRC, a randomised phase 2 study comparing pemetrexed with pemetrexed plus carboplatin and pooled analysis from the NVALT7 trial, a randomised phase 2 study comparing progression-free survival of pemetrexed alone with pemetrexed plus carboplatin).

The ERG noted that there were methodological problems with the systematic literature review, including baseline differences between studies and the ARROW trial, which was a particular concern for the validity of the naive comparisons. The GOIRC study included more women than LUME-LUNG 1 (72% compared with 37%). There was an imbalance of people with brain metastases in ARROW and LUME-LUNG 1 (37% compared with 8% respectively). The GOIRC trial reported the lowest European Co-operative Oncology Group score among all the studies presented. Metastatic disease was not reported in any of the studies. The committee expressed concerns about the appropriateness of the real-world data in the Flatiron database, due to the challenges in assessing its quality. It was not persuaded that the data sources for the comparators should have been selected primarily according to the availability of individual patient data. It also noted that an indirect treatment comparison of clinical trial data to with real-world data can be expected to introduce bias because the care that people have in each setting is likely to be different (for example, the intensity and quality of monitoring and care would be expected to be greater in a clinical trial). For these reasons, the hazard ratio results of the indirect treatment comparison may have overestimated the relative clinical effectiveness of pralsetinib. The ERG agreed with the committee and further added that the issues previously raised about the comparators also apply to these

results (see section 3.5). The committee concluded that the results of the indirect treatment comparisons were highly uncertain.

Propensity score weighting analysis should have been done for platinum-based chemotherapy with or without pemetrexed

3.9 The company presented a naive comparison between pralsetinib and platinum-based chemotherapy with and without pemetrexed using GOIRC and NVALT7. However, there was no adjustment for confounding in this analysis. The ERG was concerned that the company presented this naive comparison despite having access to the Flatiron database, which was used to inform other comparisons. The ERG explained that this comparison should have been made using the Flatiron database because platinum-based chemotherapy with or without pemetrexed was used more (16.1%) than pembrolizumab plus pemetrexed and chemotherapy (14.1%) and pembrolizumab monotherapy (7.6%). The company highlighted that it only considered this comparison in the previously treated setting and that the Flatiron data for this subgroup was not adjustable. Nevertheless, the clinical expert reminded the committee that platinum-based chemotherapy with or without pemetrexed is a fundamental comparator that is missing from the company's analysis for the untreated disease (see section 3.5). They added that naive estimates are likely to underestimate the effectiveness of platinum-based chemotherapy with or without pemetrexed. The committee concluded that propensity score weighting analysis should have been done for platinum-based chemotherapy with or without pemetrexed.

The company's economic model

The company's model is not appropriate for decision making

3.10 The company used a partitioned survival model that included 3 health states: progression-free, progressed disease and death. The committee agreed that the model was not appropriate for decision making for the following reasons:

- First, there were concerns about the validity of the model due to the large difference between the deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) seen for all the comparators. The company nor the ERG were able to provide an explanation for this.
- Second, the committee noticed that the model did not use the relevant comparators used in the NHS (see section 3.5).
- Third, the validity of the clinical inputs of the model is highly uncertain because of the assessment of relative treatment benefit (see section 3.8).
- Fourth, the company's model assumes a constant proportional benefit of pralsetinib over the lifetime of patients, which is implausible and leads to over optimistic estimates (see section 3.11).
- Fifth, the overall survival and progression-free survival extrapolations are implausible (see section 3.12).

The committee concluded that the company's economic model was not suitable for decision making.

The model assumes a constant treatment benefit which is implausible

3.11 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. This was despite the evidence from ARROW only including 9.5 months of median follow-up time in the untreated population. The ERG explained that the hazard ratios used by the company are based on a small sample size, immature data, and highly uncertain indirect treatment comparison results. So, it explained that it is unrealistic to assume a constant and unending treatment effect for pralsetinib. The ERG reiterated that there had been no justification provided for this assumption besides the landmark estimates, which were underestimated in the comparator extrapolations (see section 3.12). The committee considered that the company had not adequately validated the proportional hazards assumption in its submission or economic model. It noted that the combination of the large size of the

modelled hazard ratio for pralsetinib's relative treatment effect and proportional hazards assumption led to an unrealistic cost-effectiveness model. The committee considered that proportional hazards is a strong assumption and it is unreasonable to apply this over the full time horizon of the model given the immature and highly uncertain data available on relative effectiveness. The committee concluded that the assumption of pralsetinib's constant benefit over time is implausible, and the model needs adjusting to account for this.

The overall survival and progression-free survival extrapolations are implausible

3.12 Given that the ARROW trial did not include comparators, the company did an indirect treatment comparison to estimate 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. Survival for the comparators was estimated by applying the hazard ratios from the indirect treatment comparison to the extrapolated survival for the pralsetinib arm. Given that Cox proportional hazard ratios from the indirect treatment comparison were used as the measure of treatment effect, the modelling approach assumed a proportional hazards relationship between pralsetinib and comparators over the full period of the model. In the selection of the parametric model for extrapolation, the company considered statistical fit, visual assessment, and expert opinion on the clinical plausibility of the extrapolation. The ERG explained that because of the immaturity of data and small statistical differences, the survival curves were created using clinical expert landmark predictions. This added uncertainty to the results. Also, the company's survival curves overpredicted the benefit of pralsetinib and underpredicted the benefit of the comparators. For example, in the untreated subgroup at 3 years, pralsetinib (55%) exceeded the clinical experts' prediction for overall survival (50%). The comparator survival curves were lower (19% and 16%) than the predicted

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landmark survival (30% and 25%). To explore the uncertainty, the ERG produced a scenario using an alternative set of hazard ratios at 3 years. These hazard ratios resulted in overall survival and progression-free survival curves that better reflected the clinical expert advice. The ERG's calibration reduced the underprediction of the comparator survival curves. The committee was reminded that the evidence used to inform the extrapolations came from a single-arm trial compared with real-world evidence and that the data from the indirect treatment comparison was highly uncertain (see section 3.6 and section 3.8). Taking into account these uncertainties plus the implausibility of a lifetime relative treatment benefit (see section 3.11), the committee agreed that the extrapolations presented could not be considered sufficiently reliable for decision making. The committee concluded that the overall survival and progression-free survival extrapolations are implausible.

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 people with previously treated RET fusion-positive advanced NSCLC

3.13 The committee accepted that people with previously treated RET fusion-positive advanced NSCLC are unlikely to live 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 that exceeded 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 the end of life criteria had been met for this subgroup.

There is not enough evidence to conclude if people with untreated RET fusion-positive advanced NSCLC meet the end of life criteria

3.14 The committee recalled that it had heard from the clinical experts that platinum-based chemotherapy with or without pemetrexed would typically be offered as a first-line treatment when RET fusion-positive status had been confirmed (see section 3.2). However, it was unable to consider if the end of life criteria applied to this group because it had not been provided with the relevant comparison. The committee was aware that pembrolizumab plus pemetrexed and chemotherapy might also be offered. It recalled its concerns about the validity and reliability of the clinical data used for this comparator (see section 3.8) and that the modelling of overall survival may be underestimated (see section 3.12). The committee agreed that it had not been presented with sufficient evidence to decide if the end of life criteria had been met for people with untreated RET fusion-positive advanced NSCLC, so it could not make a robust conclusion about this subgroup.

Cost-effectiveness estimates

A plausible ICER could not be determined because of problems with model so pralsetinib is not recommended for routine use

3.15 The committee agreed that there were problems with the company's modelling approach in terms of the comparators used and modelling of comparator effectiveness. It noted the high level of uncertainty in the model, particularly around the:

- choice of comparators (see section 3.5)
- results of the indirect treatment comparisons (see section 3.8)
- comparator overall survival extrapolations (see section 3.12)
- assumption of proportional hazards over the full time horizon of the model (see section 3.11)
- overall validity of the model owing to the discrepancy between the deterministic and probabilistic ICERs (see section 3.10).

Because of this, the committee did not consider the analyses presented by either the company or ERG to be suitable for decision making and was unable to select a most plausible ICER or range of ICERs. Pralsetinib is therefore not recommended for routine use in the NHS.

Cancer Drugs Fund

Pralsetinib cannot be recommended through the Cancer Drugs Fund

3.16 Having concluded that pralsetinib could not be recommended for routine use for either subgroup, the committee considered if it could be recommended within the Cancer Drugs Fund. The committee discussed if the clinical uncertainties identified in the company's modelling could be addressed by collecting more data in the Cancer Drugs Fund. The committee was aware that the ongoing single-arm ARROW trial would provide further data on progression-free and overall survival for pralsetinib. But it agreed this could not address any of the substantial uncertainty about pralsetinib's clinical effectiveness compared with the relevant comparators in either untreated or previously treated RET fusion-positive advanced NSCLC. It was also 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 (platinum-based chemotherapy plus pemetrexed with or without pembrolizumab in non-squamous disease and platinum-based chemotherapy plus gemcitabine in squamous disease). The committee noted that progression-free survival is the primary outcome, and that overall survival is included as a secondary outcome. However, it was unclear if the comparative data collected within the relevant timeframe would be sufficiently mature to robustly resolve the uncertainty around the pralsetinib's longer-term effectiveness. Also, it recalled that the comparators used by the company were not aligned with NHS practice (see section 3.5) and that as a result, it was unable to determine if pralsetinib had plausible potential to be cost effective. It concluded that

pralsetinib did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Lindsay Smith
Chair, appraisal committee
February 2022

5 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.

Issue date: February 2022

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ISBN: [to be added at publication]