

# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final appraisal document

### Entrectinib for treating ROS1-positive advanced non-small-cell lung cancer

#### 1 Recommendations

- 1.1 Entrectinib is recommended, within its marketing authorisation, as an option for treating ROS1-positive advanced non-small-cell lung cancer (NSCLC) in adults who have not had ROS1 inhibitors. It is recommended only if the company provides entrectinib according to the commercial arrangement (see section 2).

#### Why the committee made these recommendations

Evidence for entrectinib in ROS1-positive advanced NSCLC comes from a small study that did not compare entrectinib with anything else. It includes mostly people with previously treated disease. The evidence suggests that entrectinib is effective at shrinking tumours and slowing disease progression.

Two indirect comparisons of entrectinib, using evidence from a different kind of NSCLC, show that it is clinically effective compared with pemetrexed and platinum chemotherapy. But because the evidence is from a different population, this is uncertain.

However, the cost-effectiveness results are within the range NICE normally considers an acceptable use of NHS resources for end-of-life treatments. Therefore, entrectinib is recommended.

## 2 Information about entrectinib

### ***Anticipated marketing authorisation indication***

- 2.1 Entrectinib (Rozlytrek, Roche) is indicated as monotherapy ‘for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors’.
- 2.2 On 28 May 2020 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product entrectinib intended for the treatment of ROS1-positive advanced NSCLC.

### ***Dosage in the marketing authorisation***

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

### ***Price***

- 2.4 The list price for entrectinib is £5,160 for a 90-capsule pack of 200 mg capsules, and £860 for a 30-capsule pack of 100 mg capsules (excluding VAT, company submission). The company has a commercial arrangement (simple discount patient access scheme). This makes entrectinib 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 appraisal committee (section 6) considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

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- Pemetrexed with a platinum drug (PEM+PLAT) was the key comparator in this appraisal. In line with [NICE's position statement on appraising new cancer products: handling comparators and treatment sequences in the Cancer Drugs Fund](#), crizotinib was not a comparator in this appraisal (issue 1, see technical report pages 12 to 14).
- The relevant population was the STARTRK-2 subgroup of 78 patients who had:
  - a confirmed diagnosis of ROS1-positive non-small-cell lung cancer (NSCLC)
  - measurable disease at baseline
  - no minimum follow-up restriction
  - the licensed 600 mg entrectinib dose
  - no prior ROS1 inhibitor treatment.

Analyses based on the STARTRK-2 subgroup were appropriate for decision making (issue 2, see technical report pages 15 to 17).

- STARTRK-2, the key clinical trial, was a single-arm phase 2 basket trial. To compare entrectinib with PEM+PLAT, a matching-adjusted indirect comparison was done using data from the ASCEND-4 trial in anaplastic lymphoma kinase (ALK)-positive NSCLC. The results of the matching-adjusted indirect comparison were appropriate for decision making. However, there was a high level of uncertainty in the resulting progression-free survival and overall survival estimates because the evidence was from ALK-positive NSCLC and because of differences in the treatments people had before and after entrectinib in the ASCEND-4 and STARTRK-2 trials. It was not possible to estimate the direction or size of the effect the uncertainty had on the matching-adjusted indirect comparison results (issue 3, see technical report pages 18 to 23).
- The company modelled pemetrexed maintenance therapy only after pemetrexed with cisplatin in line with [NICE's technology appraisal guidance on pemetrexed for non-squamous NSCLC](#). In its base case it assumed no maintenance therapy. The ASCEND-4 trial was used to estimate progression-free survival with PEM+PLAT in the model. In that trial, pemetrexed maintenance therapy was used for approximately 8 cycles. To reflect current clinical practice and the clinical

evidence (ASCEND-4), the technical team considered results assuming that pemetrexed maintenance therapy was taken for 4, 6 or 8 cycles after an induction treatment with pemetrexed with either cisplatin or carboplatin (issue 6, see technical report pages 37 to 39).

- The company assumed a range of subsequent treatments in its model and only some patients had subsequent treatments. The cost of subsequent treatments was applied as one-off cost in the model. To reflect UK clinical practice, the technical team assumed that PEM+PLAT was the next treatment for all patients who progressed on entrectinib and considered scenario analyses assuming that 60% and 70% of patients were having subsequent therapy (issue 7, see technical report pages 40 to 43).
- The estimated progression-free survival utility value from STARTRK-2 was 0.73. A utility value for post-progression survival was not available. Given that only one set of utility data came from the trial and that the regression model had not been implemented correctly, the utilities used in [NICE's technology appraisal guidance on crizotinib for ROS1-positive advanced NSCLC](#) (0.81 for progression-free survival and 0.66 for post-progression survival) were appropriate for decision making (issue 8, see technical report pages 44 to 45).
- The healthcare costs based on values proposed by the ERG's clinical experts were appropriate for decision making (issue 9, see technical report pages 46 to 47).
- It considered that if entrectinib cannot be recommended for routine commissioning because of clinical uncertainty, it would be suitable for inclusion in the Cancer Drugs Fund (issue 10, see technical report pages 48 to 49).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 51), and took these into account in its decision making. It discussed the following issues (issue 4 and 5), which were outstanding after the technical engagement stage.

### ***Treatment pathway***

#### **ROS1-targeted treatment would be valued by both patients and clinicians**

3.1 ROS1 is a rare mutation that occurs in less than 2% of people with NSCLC. The committee was aware that patients would welcome an oral treatment that can delay chemotherapy. The patient experts considered that there was a significant unmet need for treatment for ROS1-positive NSCLC, and especially for people with brain metastases. [NICE's technology appraisal guidance on crizotinib for ROS1-positive advanced NSCLC](#) recommends crizotinib for use within the Cancer Drugs Fund as an option for treating ROS1-positive advanced NSCLC in adults. [NICE's guideline on lung cancer diagnosis and management](#) recommends pemetrexed with platinum chemotherapy (PEM+PLAT) on progression after crizotinib. In addition, [NICE's technology appraisal guidance on pemetrexed for non-squamous NSCLC](#) recommends maintenance treatment with pemetrexed for people whose disease did not directly progress after pemetrexed and cisplatin induction therapy. The committee was aware that pemetrexed maintenance is also used after pemetrexed and carboplatin induction therapy. In line with [NICE's position statement on appraising new cancer products: handling comparators and treatment sequences in the Cancer Drugs Fund](#), PEM+PLAT was the main comparator in this appraisal, because crizotinib is not recommended for routine commissioning. The committee concluded that a ROS1-targeted treatment would be valued by both patients and clinicians.

## ***Clinical evidence***

### **Evidence is available from 3 clinical studies**

3.2 The company based its analyses on 53 people with ROS1-positive advanced NSCLC from 2 phase 1 studies (ALKA and STARTRK-1) and 1 phase 2 study (STARTRK-2; excluding people who had less than 12-month follow-up data from the analyses). During the technical engagement stage it was agreed that the STARTRK-2 ROS1-positive NSCLC population was the relevant population for this appraisal. STARTRK-2 is an ongoing single-arm, multicentre basket trial (that is, a trial that included patients who had different types of cancer but the same

gene mutation). It recruited adults with advanced or metastatic solid tumours with various gene alterations (n=207) and included 78 people with ROS1-positive NSCLC. Most (73%) people had previous therapy for advanced disease and everyone had the licensed entrectinib dose. Data from the STARTRK-2 subgroup (May 2018 enrolment data cut-off) were used in this appraisal (including the model). After the technical engagement stage, the company submitted updated analyses (May 2019 enrolment data cut-off) which confirmed the original results from the STARTRK-2 subgroup. The results cannot be reported here because they are confidential. The company's pooled analyses from ALKA, STARTRK-1, and STARTRK-2 (including people with a minimum of 12 months' follow up) were also updated and are reported in the entrectinib summary of product characteristics. The updated pooled analyses included 94 people (not 53 as in the original dataset) because of longer follow up. No one was excluded from the updated analyses because of short follow up.

### **Entrectinib shows a high overall response rate and slows disease progression**

3.3 The primary efficacy endpoints in STARTRK-2 were objective response rate and duration of response. The survival data are immature (not yet complete). The results cannot be reported because they are confidential. The updated pooled analyses (n=94; May 2019 enrolment data cut-off), reported an overall response rate of 73.4% (95% confidence interval [CI] 63.3 to 82.0). The median progression-free survival for entrectinib was 16.8 months (95% CI 12.0 to 21.4). The committee considered that the STARTRK-2 subgroup was representative of NHS clinical practice. It noted that only a small number of people with ROS1-positive NSCLC were included in the basket trial and that the results were immature. However, the committee agreed that entrectinib produced a high overall response rate and slowed disease progression.

## **Entrectinib shows a high intracranial overall response rate in people with brain metastases**

3.4 Central nervous system metastases are common in advanced NSCLC. In the STARTRK-2 subgroup, 45% of people had brain metastasis when they entered the study and 8 people (10%) had measurable lesions. The results cannot be reported because they are confidential. Pooled analyses (with a minimum of 6 months of follow up; n=161) reported an intracranial overall response rate of 79.2% (95% CI 57.8 to 92.9) in 19 of 24 people with measurable central nervous system lesions at the start of the trial (46 people had brain metastases at the start of the trial). The clinical experts noted the anticipated benefit of entrectinib for treating and preventing advanced disease with central nervous system metastases. The committee agreed that entrectinib showed a high intracranial overall response rate in people with measurable central nervous system lesions.

## ***Modelling of overall survival and progression-free survival***

### **Evidence of effectiveness of the comparator, pemetrexed, is only available in ALK-positive advanced NSCLC**

3.5 In the absence of available data, the company used data from patients with ALK-positive disease as a proxy for ROS1-positive NSCLC. It explained that patients with ALK-positive and ROS1-positive NSCLC were similar in terms of demographics (for example, younger age, no or light smoking) and clinical characteristics (for example, adenocarcinoma histology). The company identified 2 studies that could be used for an indirect comparison of entrectinib with PEM+PLAT:

- ASCEND-4: an open-label, multicentre, randomised controlled trial comparing ceritinib with PEM+PLAT (with pemetrexed maintenance therapy) in ALK-positive advanced NSCLC (n=375).
- PROFILE 1014: an open-label, multicentre, randomised controlled trial comparing crizotinib with PEM+PLAT (without pemetrexed maintenance therapy) in ALK-positive advanced NSCLC (n=343).

In ASCEND-4, approximately 43% of patients had ceritinib after PEM+PLAT. Most patients (84%) had crizotinib after PEM+PLAT in PROFILE 1014. The committee was concerned about using proxy data, however in this instance the ERG and clinical experts agreed that this was acceptable because no ROS1-positive evidence was available. However, the committee highlighted the uncertainty the proxy data introduced to the estimated results. The committee agreed to explore the proxy data in its decision making. However, it considered the estimates from the indirect comparison to be uncertain.

**Both the ERG's and the company's approaches have considerable limitations**

3.6 An exponential distribution was applied to the STARTRK-2 data to estimate overall survival and progression-free survival beyond the observed data. To estimate the overall survival and progression-free survival for PEM+PLAT, the company first did a matching-adjusted indirect comparison using entrectinib (STARTRK-2; n=78) and crizotinib (PROFILE 1001; n=53) data in ROS1-positive NSCLC to estimate the crizotinib curve. Next, hazard ratios adjusted for crossover from PROFILE 1014 were applied to the crizotinib curve to estimate survival for PEM+PLAT. In PROFILE 1014 patients did not have pemetrexed maintenance therapy, as in UK clinical practice. The use of adjusted hazard ratios from PROFILE 1014 was critiqued during the technology appraisal of crizotinib for ROS1-positive advanced NSCLC and the proportional hazards assumption (the relative risk of an event is fixed irrespective of time) was not valid for progression-free survival, so any hazard ratios for progression-free survival should be interpreted with caution. Also, the ERG was concerned about the results from the matching-adjusted indirect comparison comparing entrectinib with crizotinib. The ERG considered that entrectinib and crizotinib have similar efficacy and preferred to assume the same progression-free survival and overall survival (a hazard ratio of 1 for both) in the company's approach. Because of the limitations of the company's approach, the ERG used a matching-adjusted indirect comparison of entrectinib (STARTRK-2; n=78)

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and PEM+PLAT (ASCEND-4; n=187) data to estimate the PEM+PLAT curve. ASCEND-4 patients had pemetrexed maintenance therapy in line with UK clinical practice. However, because of the high crossover to ceritinib after PEM+PLAT (ASCEND-4 results were not adjusted for crossover), the results likely overestimate overall survival and progression-free survival with PEM+PLAT compared with entrectinib. The committee agreed that both approaches have limitations but both should be considered for decision making.

### **The committee considers the likely survival estimate to be between the 2 approaches**

3.7 The progression-free survival results were similar using both approaches. Mean overall survival with entrectinib was the same because both approaches used entrectinib data from the STARTRK-2 subgroup. The entrectinib results and survival gains cannot be reported because they are confidential. The estimated mean overall survival with PEM+PLAT was 39.2 months using the ERG's approach and 15.6 months using the company's approach. The clinical experts considered the ERG's approach to overestimate and the company's approach to underestimate survival with PEM+PLAT. They also noted that the post-progression survival gain with entrectinib in the company's approach was implausibly high. The clinical experts agreed that the most likely survival values are somewhere between the 2 approaches. The committee agreed with the clinical experts and decided to consider both approaches in its decision making.

### ***End of life***

#### **Entrectinib meets both criteria to be considered a life-extending, end-of-life treatment compared with PEM+PLAT**

3.8 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 company's estimate of PEM+PLAT survival was less than 24 months and the ERG's estimate more than 24 months

(see section 3.7). The ERG's estimate was likely to be an overestimate because of people crossing over to have ceritinib in ASCEND-4 (see section 3.6). Entrectinib survival gains using both approaches were more than 3 months (results are confidential and cannot be reported here). The committee was aware that [NICE's guidance on crizotinib](#) considered it to meet both criteria to be considered a life-extending, end-of-life treatment when compared with PEM+PLAT at a similar point in the clinical pathway. The company, ERG, and clinical experts agreed that the life expectancy of patients who had treatment with PEM+PLAT was typically less than 24 months. Also, they all agreed that entrectinib could be expected to extend life by more than 3 months when compared with PEM+PLAT. The committee concluded that entrectinib meets both of NICE's criteria to be considered a life-extending, end-of-life treatment when compared with PEM+PLAT.

### ***Cost-effectiveness estimates***

#### **The cost-effectiveness estimates are within the range NICE normally considers an acceptable use of NHS resources for end-of-life treatments**

3.9 The technical team's preferred incremental cost-effectiveness ratio (ICER) for entrectinib (with the commercial arrangement applied) compared with PEM+PLAT was in the range of £37,910 to £42,572 per quality-adjusted life year (QALY) gained (see table 1 of the technical report). Using the company's approach to estimate progression-free survival and overall survival (while keeping all other assumptions the same and assuming the same efficacy for entrectinib and crizotinib), the company's preferred base-case post-technical engagement ICER was in the range of £21,607 to £23,457 per QALY gained. The decision-making ICERs used by the committee, which took account of all available confidential discounts including discounts for comparators and follow-up treatments, were higher. But these still remained within the range NICE normally considers an acceptable use of NHS resources for end-of-life treatments. The clinical experts explained that the 2 approaches to modelling were likely to

define the optimistic and pessimistic margins of survival benefit, with the true benefit lying somewhere in between (see section 3.7). The company also submitted some analyses using the updated clinical data (May 2019 enrolment data, see [section 3.2](#)). These analyses resulted in a small decrease in the company's and technical team's ICERs and confirmed the original results. Therefore, despite the immaturity and uncertainty with the data (see section 3.5), the committee was persuaded that the highest ICER for entrectinib compared with PEM+PLAT was likely to be below £50,000 per QALY gained.

### **Entrectinib is recommended for routine commissioning**

- 3.10 The committee concluded that entrectinib can be considered cost effective. Therefore it can be recommended for routine commissioning as an option for treating ROS1-positive advanced NSCLC.

## **4 Implementation**

- 4.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. 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 a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has ROS1-positive advanced non-small-cell lung cancer and the doctor responsible for their care thinks that entrectinib is the right treatment, it should be available for use, in line with NICE’s recommendations.

## **5 Review of guidance**

- 5.1 The guidance on this technology will be considered for review 3 years after publication. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh  
Chair, appraisal committee  
June 2020

## 6 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.

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.

### ***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 project managers.

#### **Marcela Haasova**

Technical lead

#### **Richard Diaz**

Technical adviser

#### **Gemma Barnacle and Gavin Kenny**

Project managers

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