# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

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

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using crizotinib for ROS1-positive advanced non-small cell lung cancer 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, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?



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**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 determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using crizotinib 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: Wednesday 7 February 2018

Second appraisal committee meeting: Wednesday 21 February 2018

Details of membership of the appraisal committee are given in section 7.



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# 1 Recommendations

1.1 Crizotinib is not recommended, within its marketing authorisation, for treating ROS1-positive advanced non-small-cell lung cancer (NSCLC) in adults.

1.2 This recommendation is not intended to affect treatment with crizotinib 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

ROS1-positive advanced NSCLC is a recently discovered subtype of non-small cell lung cancer, therefore not much is known about it and how well existing treatments work.

The main evidence on the effectiveness and safety of crizotinib in ROS1-positive advanced NSCLC comes from a small single arm study that included mostly people with previously treated disease that showed crizotinib can induce durable tumour shrinkage and slow disease progression, particularly in previously treated ROS1-positive advanced NSCLC. However, the lack of data comparing crizotinib with 'standard care' makes any assessment of relative effectiveness very challenging.

As a result of the limited clinical effectiveness data available from the ROS1-positive population (small single arm trial), the company presents results from 2 randomised controlled trials on crizotinib for ALK-positive advanced NSCLC (comparing crizotinib with chemotherapy) as proxy data for ROS1-positive advanced NSCLC. However, using data from a proxy population is far from ideal, and makes any estimates of cost effectiveness highly uncertain.


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Crizotinib meets NICE's criteria to be considered a life-extending end-of-life treatment for ROS1-positive advanced NSCLC.

Crizotinib is not recommended for previously treated ROS1-positive NSCLC, because the cost-effectiveness estimates are higher than what NICE normally considers acceptable for end-of-life treatments.

Crizotinib is not recommended for untreated ROS1-positive advanced NSCLC: although one cost-effectiveness estimate is possibly within the range that NICE normally considers acceptable for end-of-life treatments, it is highly uncertain because it is based on data from a proxy population.



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# 2 Information about crizotinib

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| **Marketing authorisation** | Crizotinib (Xalkori, Pfizer) as monotherapy is indicated 'for the treatment of adults with ROS1-positive advanced non-small-cell lung cancer (NSCLC)'. |
| **Dosage in the marketing authorisation** | 250 mg twice daily (500 mg daily) taken orally.<br>Dosing interruption and/or dose reduction may be needed based on individual safety and tolerability. If necessary, dose may be reduced to 200 mg twice daily and then 250 mg once daily.<br>An accurate and validated assessment for ROS1 should be done by laboratories with demonstrated proficiency in the specific test being utilised before starting crizotinib therapy. It is important that a well-validated and robust methodology is chosen to avoid false-negative or false-positive results.<br>For further details see the summary of product characteristics.<br>The summary of product characteristic states that there is limited information available in patients with ROS1-positive NSCLC with non-adenocarcinoma histology, including squamous cell carcinoma. |
| **Price** | The list price of crizotinib is £4,689 for 60 capsules (excluding VAT; British national formulary [BNF] online, accessed December 2017).<br>The company has agreed a patient access scheme with the Department of Health. If crizotinib had been recommended, this scheme would provide a simple discount to the list price of crizotinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS. |

# 3 Committee discussion

The appraisal committee (section 7) considered evidence submitted by Pfizer and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.



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## *Clinical need*

### The ROS1 oncogene is a recent discovery and both patients and clinicians would welcome a targeted therapy

3.1 The clinical experts observed that less than 2% of people with non-small-cell lung cancer have ROS1-positive advanced NSCLC. The ROS1 oncogene is found exclusively in non-squamous-cell lung cancer, mainly in tumours with adenocarcinoma histology. The committee noted that the ROS1 oncogene was only recently discovered; so limited information is available on the natural history, patient characteristics and the clinical effectiveness of chemotherapy for tumours that are ROS1-positive. The clinical experts highlighted that from the limited information available, there appear to be similarities between ROS1-positive advanced NSCLC and ALK-positive NSCLC: for example, both are most often seen in younger patients who do not smoke. In the absence of any targeted therapy until now, ROS1-positive advanced NSCLC is treated with cytotoxic chemotherapy that can cause unpleasant side effects. The committee noted the patient expert's statement that people with advanced or metastatic NSCLC often feel debilitated by multiple and distressing symptoms. It also noted that the clinical experts considered crizotinib a step-change in treatment because it is taken orally, and offers a marked improvement in quality of life. The committee concluded that crizotinib has a better safety profile than standard care (cytotoxic chemotherapy) and would be valued by both patients and clinicians.

## *ROS1 testing*

### ROS1 status should be tested upfront in all non-squamous NSCLC

3.2 The marketing authorisation for crizotinib states that it is necessary to have an accurate and validated assay for ROS1 before treatment with crizotinib is started. The company proposed initial testing with immunohistochemistry (IHC), and follow-up confirmation testing for positive cases with the highly accurate FISH (fluorescence in situ



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hybridisation) test. The clinical experts explained that only a few centres test for ROS1, and that assay methods vary. The committee discussed when ROS1 testing should be done: it could be done at diagnosis, along with testing for other mutations (such as EGFR and ALK), or later, once people have tested negatively for other mutations (because the different mutations are mutually exclusive). The clinical experts highlighted practical difficulties in testing different mutations at different stages because more biopsy samples might be needed. The committee also noted that any delay in diagnosing ROS1-positive advanced NSCLC would delay access to therapy. It agreed that testing for ROS1 status in all newly diagnosed non-squamous NSCLC would be the best strategy, in line with testing for other types of tumour expression in NSCLC.

## *Comparators*

3.3 The committee noted that crizotinib's UK marketing authorisation does not specify whether it should be used to treat squamous or non-squamous disease. It also noted that the summary of product characteristic states that there is limited information available in patients with ROS1-positive NSCLC with non-adenocarcinoma histology, including squamous cell carcinoma. The committee understood that the ROS1 oncogene is predominantly present in adenocarcinoma, which is a subtype of non-squamous NSCLC. It agreed that crizotinib would most likely be used in patients with non-squamous NSCLC in clinical practice in the NHS. In line with the final scope issued by NICE, the committee considered untreated and previously treated ROS1-positive advanced NSCLC separately when determining the most appropriate comparators for crizotinib.

### Untreated disease: pemetrexed plus platinum-based therapy is the appropriate comparator

3.4 The company considered that pemetrexed plus platinum-based chemotherapy (cisplatin or carboplatin) was the appropriate comparator for crizotinib in untreated ROS1-positive advanced NSCLC. As such, it


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excluded all other comparators identified in the final scope issued by NICE. The committee understood that NICE's guideline on lung cancer diagnosis and management recommends platinum-based combination chemotherapy for untreated disease (and docetaxel, gemcitabine, paclitaxel or vinorelbine alone for people who cannot tolerate combination chemotherapy). NICE's technology appraisal guidance on pemetrexed for the first-line treatment of NSCLC recommends pemetrexed plus cisplatin for adenocarcinoma or large-cell carcinoma. Pemetrexed is also recommended as maintenance treatment after pemetrexed plus cisplatin for locally advanced or metastatic non-squamous NSCLC in adults whose disease has not progressed (NICE technology appraisal guidance on pemetrexed maintenance treatment for non-squamous NSCLC after pemetrexed and cisplatin), and after platinum-based chemotherapy plus gemcitabine, paclitaxel or docetaxel (NICE technology appraisal guidance on pemetrexed for the maintenance treatment of NSCLC). The company excluded pemetrexed as maintenance treatment after pemetrexed plus cisplatin, stating that only around 15% of patients would be eligible. The committee understood that the ROS1 oncogene is most common in non-squamous NSCLC (see section 3.3). It also noted that patients newly diagnosed with ROS1-positive advanced NSCLC are generally young and physically fit, and so it was appropriate to exclude single-agent chemotherapy as a comparator (because this is only recommended for people who cannot tolerate combination chemotherapy). The committee concluded that pemetrexed plus platinum-based chemotherapy was the most appropriate comparator for crizotinib in untreated, ROS1-positive advanced NSCLC.

**Previously treated disease: it is inappropriate to exclude standard care docetaxel plus nintedanib as a comparator**

3.5 For crizotinib in previously treated ROS1-positive advanced NSCLC, the company considered docetaxel alone to be the best comparator. It excluded nintedanib plus docetaxel as a comparator, despite NICE's


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technology appraisal guidance on nintedanib for previously treated locally advanced, metastatic, or locally recurrent NSCLC recommending this as an option for previously treated disease. The company stated that it was not possible to compare crizotinib with nintedanib plus docetaxel, because data on nintedanib plus docetaxel were available only for unselected NSCLC. However, the committee understood that nintedanib plus docetaxel is more effective than docetaxel alone in this indication, such that it is considered standard care in the NHS for people who can tolerate it. The committee was not convinced by the company's rationale for excluding nintedanib plus docetaxel as a comparator. It concluded that the company should have included nintedanib plus docetaxel as a comparator, and agreed to consider this omission in its decision-making.

## *Clinical effectiveness*

### Evidence for crizotinib's effectiveness in ROS1-positive advanced NSCLC is extremely limited and there are no comparative data

3.6 The clinical-effectiveness evidence for crizotinib in ROS1-positive advanced NSCLC is from a small (n=53), single-arm study called PROFILE 1001. The trial was done at 8 sites across the US, Australia and South Korea. Only 7 patients had untreated disease; the other 46 had had at least 1 previous chemotherapy. Patients were followed-up for a median of 25.4 months. As determined by the investigators, 5 patients had complete response and 32 patients had partial response (according to Response Evaluation Criteria In Solid Tumours [RECIST]) giving an overall objective response rate of 69.8% (95% confidence interval [CI] 55.7 to 81.7). Median overall survival was not reached at the time of analysis and the company does not intend to carry out any interim analysis in the near future. Median progression-free survival was 19.8 months. The clinical experts stated that these results were clinically meaningful because, in unselected NSCLC, chemotherapy provides progression-free survival of around 5 months in untreated disease and just 3 months in previously treated disease. The committee noted that



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there is no available evidence on the effectiveness of crizotinib compared with chemotherapy for ROS1-positive advanced NSCLC. From the evidence available from PROFILE 1001, it concluded that crizotinib can induce durable tumour shrinkage and slow disease progression, particularly in previously treated ROS1-positive advanced NSCLC. However, the committee agreed that the lack of comparative data makes any assessment of comparative effectiveness (and any economic analysis) very challenging.

**The effectiveness of crizotinib compared with chemotherapy is based on its use in ALK-positive advanced NSCLC and so is highly uncertain**

3.7 Because of the limited clinical effectiveness data available for ROS1-positive advanced NSCLC, the company provided results from 2 randomised controlled trials that compared crizotinib with chemotherapy in untreated (PROFILE 1014) and previously treated (PROFILE 1007) ALK-positive NSCLC. The company stated that these results could be extrapolated to ROS1-positive advanced NSCLC. Both trials were considered during the development of previous NICE technology appraisal guidance (crizotinib for untreated ALK-positive advanced NSCLC and crizotinib for previously treated ALK-positive advanced NSCLC). The committee noted the ERG's comments that in both trials, the proportional hazards assumption was not valid for progression-free survival so any hazard ratios for progression-free survival should be interpreted with caution. The ERG also highlighted that the overall survival estimates were unreliable because of high rates of crossover, and that statistical methods for adjustment were not reported transparently. The committee agreed that the results showed crizotinib to be more effective than chemotherapy for ALK-positive NSCLC, but that its relative effectiveness in ROS1-positive advanced NSCLC remained uncertain.



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**The only comparative evidence for crizotinib in ROS1-positive advanced NSCLC is from proxy data in ALK-positive NSCLC**

3.8 The committee discussed the relevance of the PROFILE 1014 and PROFILE 1007 results to ROS1-positive advanced NSCLC. In its submission, the company strongly advocated that data from ALK-positive NSCLC could be used as a proxy for ROS1-positive advanced NSCLC. It stated that:

- The kinase domains of ALK and ROS1 share 77% of amino acids in the ATP-binding sites.
- Both ALK-positive and ROS1-positive advanced NSCLC are similar in terms of clinical behaviour including response to crizotinib, patient characteristics and histology (both are predominantly adenocarcinoma).
- The European Medicines Agency supported the generalisability of data from ALK-positive NSCLC to ROS1-positive advanced NSCLC when granting crizotinib's marketing authorisation in this indication.
- Twelve UK clinical experts from a company-sponsored advisory board agreed that the data were an appropriate proxy for ROS1-positive advanced NSCLC.

The clinical experts stated that in their experience ROS1-positive advanced NSCLC is even more sensitive to crizotinib than ALK-positive NSCLC. The committee acknowledged this, but noted the ERG's concern that any documented similarities between ALK-positive and ROS1-positive advanced NSCLC may not hold true as more patients with ROS1-positive advanced NSCLC are identified. The committee noted that median progression-free survival in the ROS1-positive trial (PROFILE 1001) and the ALK-positive trials (PROFILE 1014 and PROFILE 1007) differed enough (19.3 months compared with 10.9 months and 7.7 months respectively) to seriously question the comparability of the 2 patient populations. The committee was aware that there are no randomised trials planned for crizotinib in ROS1-positive advanced NSCLC and comparative data on efficacy is not expected. Furthermore, even the non-



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comparative data for its use in ROS1-positive advanced NSCLC were very limited, particularly for untreated disease. The committee agreed that using data from a proxy population was far from ideal, and considered whether it should accept analyses based on treatment effects from a proxy population. Having taken into account the relatively small patient population and the clinical experts' views on the innovative nature of crizotinib, the committee agreed to explore the proxy data in its decision-making. However, it stated that this should not set a precedent for the use of data from proxy populations in future appraisals.

## *Cost-effectiveness analyses*

### All cost-effective analyses are based on proxy data so results are extremely uncertain

3.9 The company presented cost-effectiveness analyses for crizotinib in untreated disease and previously treated disease using proxy data from PROFILE 1014 and PROFILE 1007 respectively. It also presented a scenario analysis using data from PROFILE 1001. However, even in this scenario analysis (which was based on the ROS1-positive trial), the company used hazard ratios from PROFILE 1014 and 1007 (the ALK-positive trials) to model the comparator treatment arms. The committee concluded that without any reliable evidence on the effectiveness of the comparator treatments in ROS1-positive advanced NSCLC, all of the cost-effectiveness estimates were inherently uncertain.

### The relationship between overall and progression-free survival is unclear, but the modelled overall survival is improbably high

3.10 The ERG had questioned the modelled overall survival gained with crizotinib (28.7 months for untreated disease and 16.3 months for previously treated disease), given that the modelled progression-free survival gain was considerably less (9.5 months for untreated disease and 5.7 months for previously treated disease). The committee recalled that the overall survival data from PROFILE 1014 and PROFILE 1007 were


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confounded by high crossover rates, and that adjustment methods had not been reported transparently (see section 3.6). The clinical experts explained that progression-free survival gains would be expected to result in some overall survival benefit, but the exact relationship is difficult to predict. Nevertheless, the experts agreed that a modelled overall survival gain almost 3 times higher than the modelled progression-free survival gain was most likely to be overestimate. The committee agreed that it had seen no evidence to support the large disparity between overall and progression-free survival.

**Neither of the ERG'S exploratory analyses model overall survival more accurately because of the company's use of proxy data**

3.11 To address the uncertainty in the overall survival benefit with crizotinib, the ERG did 2 scenario analyses:

- In the first, the ERG applied the hazard ratio for progression-free survival to the unadjusted (for crossover) overall survival curve of the crizotinib treatment arm.
- In the second, the ERG assumed no survival benefit other than survival gained in the progression-free state. For this scenario, the ERG adapted the overall survival curve for the comparator so as to make survival in the progressive states equal for both treatment arms. This means that any survival benefit was attributable to the survival benefit in the progression-free state.

For the first scenario analysis, the committee was not convinced that the hazard ratio from 1 outcome could be applied equally to another. The committee considered the ERG's second scenario analysis to be more informative in terms of overall survival modelling, but it did not agree with the way the ERG how implemented the analysis. The committee considered that adjusting the crizotinib overall survival curve (so as to make the survival gain in the post-progression state equal to the modelled survival in the post-progression state of the comparator arm) would have


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been a better approach. However, it accepted that the incremental benefit (life years gained and QALYs) would not be affected and the results would have been similar, if its preferred approach had been used by the ERG. Overall, the committee considered that some relative advantage for crizotinib after disease progression was plausible. It concluded that the overall survival gain for crizotinib was somewhere between the company's and ERG's estimates, but reiterated that this analysis was still based on a proxy population.

## *Utility values*

### The company underestimated the utility value for the comparator in untreated disease

3.12 The company used a utility value of 0.81 for people having crizotinib in both the progression-free and progressed disease states. For people having the pemetrexed plus platinum-based chemotherapy, the company used a utility value of 0.72. People subsequently having docetaxel or best supportive care were given utility values of 0.61 and 0.47 respectively. The committee noted that almost all the values used (with the exception of the utility value for people having pemetrexed plus platinum-based chemotherapy) were the same values accepted by the appraisal committees during the development of NICE technology appraisal guidance on crizotinib for ALK-positive NSCLC (crizotinib for untreated ALK-positive advanced NSCLC and crizotinib for previously treated ALK-positive advanced NSCLC). During the appraisal of crizotinib for untreated ALK-positive advanced NSCLC, the ERG had provided exploratory analyses using a utility value for people having pemetrexed plus platinum-based chemotherapy of 0.75 which was deemed appropriate by the committee at the time. The committee agreed that for consistency it would take this slightly higher utility value into account, and that this would decrease crizotinib's perceived cost effectiveness. The committee also noted that the company had not included disutility to account for any


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adverse reactions, and agreed that this would add further uncertainty to the results.

## *The most plausible ICERs*

**The company's analyses underestimate the ICERs for crizotinib compared with chemotherapy for both untreated and previously treated ROS1-positive advanced NSCLC**

3.13 The company presented incremental cost-effectiveness ratios (ICERs), using proxy data from patients with ALK-positive NSCLC, for crizotinib in untreated and previously treated ROS1-positive advanced NSCLC. The ICERs were presented as commercial in confidence and so cannot be reported here. Having acknowledged the limitations of the proxy data, the committee recalled the improbably high overall survival gain (see sections 3.10 and 3.11) and agreed that the ICERs presented by the company were likely to be severely underestimated.

**The most plausible ICERs for crizotinib are highly uncertain and not clearly within the range normally considered to be cost-effective use of NHS resources**

3.14 The committee agreed that the ICERs presented by both the company and the ERG were highly uncertain because of the use of proxy data from ALK-positive advanced NSCLC and uncertainties in the overall survival modelling. The committee agreed that, as a starting point for its discussion, it would consider ICERs at the mid-point between the company's base case and the ERG's exploratory analysis that assumed no survival benefit in progressed stages (see section 3.10). The committee recalled that for crizotinib in untreated disease, a higher utility value for people having pemetrexed plus platinum-based chemotherapy would further increase the ICER. For previously treated disease, a comparison with standard care (that is, nintedanib plus docetaxel) may increase the ICER further. The company had also underestimated the administration cost of crizotinib and treatment cost of pulmonary


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embolism, which may further affect the ICERs. The committee therefore considered that the most plausible ICERs for crizotinib in the company's main analysis (that extrapolated data for both crizotinib and the comparators from ALK-positive NSCLC) would be:

- For untreated disease, compared with pemetrexed plus platinum-based chemotherapy, would be around or just below £50,000 per quality-adjusted life year (QALY) gained. However, the committee agreed that this estimate came with far too much uncertainty to conclude on a figure below £50,000 without further evidence.
- For previously treated disease, compared with docetaxel, would be well above £50,000 per QALY gained. The committee agreed that had the comparison with nintedanib plus docetaxel been made, the ICER would have been even higher.

The committee also noted that the corresponding ICERs were higher in the company's PROFILE 1001 scenario analysis (that used data from ROS1-positive NSCLC population to model the intervention arm but extrapolated the relative effectiveness from ALK-positive NSCLC to model the comparator arm). Taking into account the ERG's exploratory analyses, the ICERs from the company's PROFILE 1001 scenario analysis would be:

- For untreated disease, compared with pemetrexed plus platinum-based chemotherapy, would be well above £50,000 per QALY gained.
- For previously treated disease, compared with docetaxel, would be well above £50,000 per QALY gained.

## *End of life*

### Crizotinib meets both criteria to be considered a life-extending treatment at the end of life

3.15 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's technology appraisal



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process and methods. The company stated that there is limited data on overall survival with chemotherapy in people with ROS1-positive advanced NSCLC. In the proxy population with ALK-positive NSCLC, median overall survival ranged from 6 months to 22 months and there is no evidence that it would be better in people with ROS1-positive advanced NSCLC. The company therefore considered that the life expectancy of people with ROS1-positive advanced NSCLC would be less than 24 months, thereby meeting the first criterion for an end-of-life treatment. The company also highlighted that median overall survival was not reached in PROFILE 1001, and median progression-free survival was 19.3 months, so overall survival with crizotinib in ROS1-positive advanced NSCLC would be at least 19.3 months. The committee agreed that crizotinib for ROS1-positive advanced NSCLC met the first criterion to be considered a life-extending treatment at the end of life. The committee noted that the mean overall survival gained with crizotinib, as estimated by the company's model, was 28.7 months in untreated disease and 16.3 months for previously treated disease. Therefore crizotinib may offer, on average, at least 3 months' extension to life compared with standard care. However, it noted the considerable uncertainty around the company's modelling of overall survival (see section 3.9) and considered that any estimate of an overall survival gain compared with standard care was very uncertain. The committee noted that crizotinib was considered life-extending for people with both untreated and previously treated ALK-positive NSCLC. Based on the clinical experts' testimony that the ALK-positive NSCLC population could be used as a proxy for people with ROS1-positive advanced NSCLC, the committee thought it likely that there was an overall survival gain with crizotinib of over 3 months. The committee concluded that crizotinib met both criteria to be considered a life-extending, end-of-life treatment.


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### Crizotinib cannot be recommended for routine use in the NHS

3.16 Despite meeting both end-of-life criteria, the most plausible ICERs for crizotinib compared with standard care in either the company's main analysis (that extrapolated data for both crizotinib and the comparators from the ALK-positive NSCLC trials, see section 3.14) or the PROFILE 1001 scenario analysis (that used data from ROS1-positive NSCLC population for crizotinib but extrapolated the relative effectiveness from ALK-positive NSCLC to model the comparator arms, see section 3.14) were not clearly within the range normally considered to be a cost-effective use of NHS resources. Given the wide range of plausible ICERs and the high level of uncertainty in the analyses, the committee concluded that it could not recommend crizotinib for routine use in the NHS to treat ROS1-positive advanced NSCLC.

## *Innovation*

### Crizotinib represents a step-change in the treatment of ROS1-positive advanced NSCLC

3.17 The company stated that crizotinib is innovative because it is the first targeted therapy for ROS1-positive advanced NSCLC. The US Food and Drug Administration also assigned crizotinib a breakthrough therapy designation, and the marketing authorisation was granted through a priority review. The committee emphasised that the European Medicines Agency had approved crizotinib in this indication based on just 1 single-arm study. The company highlighted that as an oral therapy, crizotinib gives patient more autonomy. Moreover, the company claimed that its quick and durable effect may have wider societal benefits that were not captured in the cost-effectiveness analysis. The committee agreed that crizotinib represents a step-change in the treatment of ROS1-positive advanced NSCLC. However, the committee concluded that there were no relevant additional benefits that had not been captured in the QALY.


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## *Cancer Drugs Fund*

### Crizotinib is a promising treatment but more data are needed to establish its clinical and cost effectiveness

3.18 Having concluded that crizotinib could not be recommended for routine use in the NHS to treat ROS1-positive advanced NSCLC, the committee considered if it could be recommended for use in the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides. It heard from the company that it would prefer crizotinib to be available for routine use in the NHS.

3.19 The committee was aware that the overall survival data from PROFILE 1001 were immature and no further analysis was expected in the near future. The company stated that some clinical experts consider further comparative trials to be unethical, because of crizotinib's efficacy in treating ROS1-positive advanced NSCLC in PROFILE 1001. The committee was aware that there are ongoing single-arm studies that will provide additional information on crizotinib in the ROS1-positive advanced NSCLC population. However, these studies would only partly address the uncertainties about crizotinib's relative clinical effectiveness because the studies do not include a relevant comparator.

### Crizotinib has plausible potential to be cost effective for untreated ROS1-positive advanced NSCLC

3.20 For previously treated ROS1-positive advanced NSCLC, the ICERs for crizotinib were well over £50,000 per QALY gained and highly uncertain because they were based on data from the proxy population (that is, people with ALK-positive NSCLC). Therefore, the committee considered that crizotinib did not have plausible potential to be cost effective for previously treated disease. However, the committee considered that crizotinib has plausible potential to be cost effective for untreated ROS1-


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positive advanced NSCLC because the ICERs (although based on the same proxy data) were around £50,000 per QALY gained.

**Using crizotinib in the Cancer Drugs Fund would provide important data and encourage standardisation of ROS1 testing**

3.21 The committee accepted that crizotinib is a promising treatment for ROS1-positive advanced NSCLC, and therefore agreed that it would like the company to consider a proposal for including crizotinib in the Cancer Drugs Fund. It agreed that this would allow further clinical data to be collected on the demographics of people with ROS1-positive advanced NSCLC, treatment length and the survival benefit (progression-free and overall) with crizotinib. These data would help to address the uncertainty around the comparability of ROS1-positive and ALK-positive advanced NSCLC populations (see sections 3.7 and 3.8) and the survival benefit with crizotinib (see sections 3.10 and 3.11). The committee agreed that prolonged follow-up of people having crizotinib would generate valuable scientific information in this disease area. The clinical experts commented that the clinical community would welcome an opportunity to contribute to this data collection if crizotinib were recommended for use in the Cancer Drugs Fund. The committee was aware that the existing evidence on crizotinib's clinical effectiveness in ROS1-positive NSCLC is mainly from previously treated disease. The committee agreed that if testing for ROS1 became routine practice, most people with ROS1-positive NSCLC would first have crizotinib and the number of people eligible for crizotinib as a later-line treatment would decrease over time. The committee agreed that although crizotinib did not have the plausible potential to be cost effect for previously treated disease, it was not reasonable to limit any company Cancer Drugs Fund proposal to people with untreated disease because this would leave a population with an unmet need. The committee therefore concluded that any company proposal for crizotinib's inclusion in the Cancer Drugs Fund should include both untreated and previously treated disease, but focus mainly on untreated disease.



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### *Equality*

**ROS1 testing at diagnosis would reduce potential inequitable access to targeted therapies**

3.22 The company commented that regional variations in access to ROS1 testing could lead to inequitable access, and advocated testing at diagnosis of all non-squamous NSCLC for ROS1 status. The company highlighted that sequential testing (that is, done after testing for EGFR and ALK) would also delay access to crizotinib. The committee agreed that variation in access to treatment does not normally constitute an equality issue under equality legislation. However, the committee considered this potential equality issue and agreed that if crizotinib is an available treatment option, ROS1 testing should be done at diagnosis to help prevent potential inequality of access.

## 4 Proposed date for review of guidance

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

Andrew Stevens and Stephen G O'Brien
Chairs, appraisal committee
January 2018


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# 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 C.

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

**Anwar Jilani**
Technical lead

**Nicola Hay**
Technical adviser

**Stephanie Yates**
Project manager

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