

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

Technology appraisal guidance

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

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1 Recommendations

- 1.1 Crizotinib is recommended for use within the Cancer Drugs Fund as an option for treating ROS1-positive advanced non-small-cell lung cancer (NSCLC) in adults, only if the conditions in the [managed access agreement](#) are followed.
- 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 type of NSCLC and there are limited data about how well existing treatments work.

Evidence for crizotinib in ROS1-positive advanced NSCLC comes from a small, single-arm study that included mostly people with previously treated disease. Although the study showed crizotinib to be effective at shrinking tumours and slowing disease progression, the lack of data comparing it with other treatments makes the size of the benefit uncertain.

Because of the limited evidence in ROS1-positive NSCLC, the company presented data from 2 randomised controlled trials for crizotinib in ALK-positive NSCLC instead (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 the assessment of clinical and cost effectiveness highly uncertain.

Crizotinib meets NICE's criteria to be considered a life-extending end-of-life treatment, but there are uncertainties in the clinical- and cost-effectiveness estimates. For previously treated disease, the range of cost-effectiveness estimates was broader than for untreated disease and all estimates are higher than what NICE normally considers acceptable for end-of-life treatments. Crizotinib therefore cannot be recommended for routine use in the NHS to treat ROS1-positive advanced NSCLC.

Crizotinib is innovative but there were no relevant additional benefits that had not been captured in the quality-adjusted life-year calculations. Collecting further data on its use in the Cancer Drugs Fund would help address uncertainties in crizotinib's survival benefit, and the comparability of

ROS1-positive and ALK-positive advanced NSCLC. Using crizotinib in a managed approach would also encourage standardisation of ROS1 status testing in non-squamous NSCLC. Therefore, crizotinib can be recommended for use within the Cancer Drugs Fund to treat ROS1-positive NSCLC.

2 Information about crizotinib

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	<p>250 mg twice daily (500 mg daily) taken orally.</p> <p>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.</p> <p>An accurate and validated assessment for ROS1 should be done by laboratories with demonstrated proficiency in the specific test being used before starting crizotinib therapy. It is important that a well-validated and robust methodology is chosen to avoid false-negative or false-positive results.</p> <p>For further details see the summary of product characteristics.</p> <p>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.</p>
Price	<p>The list price of crizotinib is £4,689 for 60 capsules (excluding VAT; British national formulary [BNF] online, accessed December 2017).</p> <p>The company has a commercial arrangement. This makes crizotinib 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.</p>

3 Committee discussion

The appraisal committee ([section 5](#)) 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.

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 (NSCLC) have ROS1-positive advanced NSCLC. The ROS1 oncogene is thought to be found almost exclusively in non-squamous NSCLC, 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 hybridisation) test. The clinical experts explained that only a few centres test for ROS1, and that assay methods vary. The committee understood that although the marketing authorisation for crizotinib did not specify non-squamous disease, ROS1-positive NSCLC is almost exclusively seen in non-squamous tumours (see [section 3.1](#)) and therefore the testing would most likely be in people with non-squamous tumours only. 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 and the risk of delayed or missed diagnoses with sequential testing. 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

There are different comparators for crizotinib in untreated and previously treated disease

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 mainly 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 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. 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 understood that the ROS1 oncogene is most common in non-squamous NSCLC and 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 technology appraisal guidance on [nintedanib for previously treated locally advanced, metastatic, or locally recurrent NSCLC](#) recommending this as an option for previously treated NSCLC of adenocarcinoma histology. 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. In

response to consultation, the company further explained that using pooled chemotherapy in the analysis (that is, docetaxel or pemetrexed in line with treatment options in PROFILE 1007) is a conservative approach because pemetrexed is more effective than docetaxel. However, the committee understood that nintedanib plus docetaxel is more effective than docetaxel alone for treating adenocarcinoma, 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, because it is thought that the ROS1 oncogene is most common in non-squamous NSCLC and agreed to consider this omission in its decision-making.

Clinical effectiveness

Direct evidence for crizotinib's effectiveness in ROS1-positive advanced NSCLC is extremely limited because 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. Most patients (96%) had NSCLC of adenocarcinoma histology but 2 patients had non-adenocarcinoma histology. 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. From the evidence available from PROFILE 1001, the committee agreed that crizotinib can induce durable tumour shrinkage and slow disease progression, particularly in previously treated ROS1-positive advanced NSCLC. In response to consultation, the company highlighted that its original submission included

results from a UK clinical audit by the Royal Marsden and other small studies in ROS1-positive advanced NSCLC that supported the efficacy and safety of crizotinib. The committee noted that the clinical audit reported a median progression-free survival of 12.1 months for both untreated and previously treated disease, and that the OxOnc study reported a median overall survival of 32.5 months at the data cut-off in July 2016 (median overall survival was not reached in the other studies). The committee also noted that although the OxOnc study recruited more patients than PROFILE 1001, it was done in Asia and therefore may not be applicable to UK settings. The committee noted that there is no available evidence on the effectiveness of crizotinib compared with chemotherapy for ROS1-positive advanced NSCLC and concluded 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 was aware that in both the PROFILE 1014 and PROFILE 1007 trials, progression-free survival was statistically significantly longer with crizotinib compared with chemotherapy (pemetrexed plus platinum for untreated disease and pemetrexed plus docetaxel for previously treated disease). The committee was also aware that the overall survival results (unadjusted for patient crossover) from PROFILE 1014 and PROFILE 1007 suggested that there were no statistically significant differences between crizotinib and chemotherapy in each of these trials. However, the crossover-adjusted hazard ratio results suggested that crizotinib statistically significantly improved overall survival compared with chemotherapy in patients with ALK-positive advanced NSCLC. The committee noted the ERG's comments that in both trials, 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. 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.

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 committee considered the histology of ALK-positive NSCLC. It understood that the inclusion criteria in PROFILE 1014 specified non-squamous NSCLC and most patients (93%) in PROFILE 1007 had adenocarcinoma histology. The ALK-positive mutation is more common in people with non-squamous advanced NSCLC than in people with squamous advanced NSCLC and that the testing for the ALK mutation is routinely done in the non-squamous population only. The committee therefore accepted the company's view that both are predominantly of adenocarcinoma histology. 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-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 regarded this approach as very unusual and stated that this should not set a precedent for the use of data from proxy populations in future appraisals.

Cost-effectiveness analyses

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

3.9 The committee recognised that the company had presented a revised base-case analysis in response to consultation incorporating some of the committee's preferred assumptions, and a number of scenario analyses that explored alternative values for the overall and post-progression survival benefit of crizotinib. All analyses included a higher utility value for people taking pemetrexed plus platinum-based chemotherapy (see [section 3.12](#)) and higher costs for treating pulmonary embolism (see [section 3.13](#)). It also incorporated testing costs for untreated disease and assumed sequential testing for previously treated disease (see [section 3.2](#)). The committee understood that all the testing costs were for non-squamous NSCLC only.

- The revised base case incorporated an overall survival benefit for crizotinib of 18.2 months for untreated disease and 20.9 months for previously treated disease.
- The scenario analyses incorporated a range of values for the overall and post-progression survival benefit of crizotinib explored the impact of excluding testing

- costs.

The committee noted that the revised analyses still extrapolated data for both crizotinib and the comparators from ALK-positive NSCLC and that it had not presented a revised analysis of the PROFILE 1001 scenario (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). It considered that even with the new analyses, there was still a high degree of uncertainty because of the use of proxy data. Without any reliable evidence on the effectiveness of the comparator treatments in ROS1-positive advanced NSCLC (see [section 3.6](#)), the committee concluded that all of the cost-effectiveness estimates were associated with uncertainty that needed to be accounted for in its decision-making.

Overall survival

The relationship between overall and progression-free survival is unclear and the size of crizotinib's overall survival benefit is difficult to establish

3.10 The ERG had questioned the company's original modelled overall survival gain with crizotinib (see [table 1](#)), 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 confounded by high crossover rates, and that adjustment methods had not been reported transparently (see [section 3.7](#)). 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 an overestimate. In its response to consultation and based on clinical expert opinion, the company reported analyses using a range of values for overall and post-progression survival to explore the additional survival benefit with crizotinib.

Table 1 Summary of the company's analyses

Analysis	Survival gain for crizotinib (months)			
	Untreated disease		Previously treated disease	
	OS	PPS	OS	PPS

Original base case	28.7	19.2	16.3	10.7
Revised base case	18.2	9.6	20.9	15.2
Scenarios (adapted from ERG)	9.5*	0*	5.8*	0.1*
			16.3	10.7
Other scenarios	13.1	3.6	16.2	10.5
<p>Abbreviations: ERG, evidence review group; OS, overall survival; PPS, post-progression survival.</p> <p>* The company considered that these scenarios were not clinically plausible.</p> <p>Survival gains are from the ERG's critique of the company's response to consultation. The company presented further analyses but these were marked as commercial in confidence so cannot be reported here.</p>				

The company highlighted that that overall survival gains of at least 13.1 months for untreated disease and at least 16.2 months for previously treated disease had been accepted for crizotinib in the ALK-positive population (see NICE technology appraisal guidance on [crizotinib for untreated ALK-positive advanced non-small-cell lung cancer](#) and [crizotinib for previously treated ALK-positive advanced NSCLC](#)) and considered these clinically plausible. The ERG agreed that some post-progression clinical benefit with crizotinib was plausible, but noted that the size of the benefit was highly uncertain and the company's estimates of survival gain were not adequately justified. The committee understood that compared with its original analyses, the company's revised base case included a more conservative post-progression benefit for untreated disease but a larger benefit for previously treated disease (see [table 1](#)). The committee concluded that even with the new analyses from the company, there was considerable uncertainty around the size of survival benefit in the progression free and progressed states because the relationship between overall survival and progression-free survival is unclear.

The mid-point between the ERG's and company's new scenario analyses for overall survival modelling is preferred

3.11 To explore the uncertainty in the overall survival benefit with crizotinib, the ERG did 2 scenario analyses in its critique of the company's original submission:

- 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 to make survival in the progressed state 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 implemented the analysis. The committee considered that adjusting the crizotinib overall survival curve (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 been a better approach. Overall, the committee considered that some relative advantage for crizotinib after disease progression was plausible. In its response to consultation, the company did 4 scenario analyses to explore the clinical plausibility of each of the overall survival models (see [section 3.10](#)). This included the company's amendments to the ERG's second scenario analysis that adapted the overall survival curve for crizotinib and included a clinical benefit for crizotinib in the progressed state. The committee understood that these scenarios improved the cost effectiveness of crizotinib for both untreated and previously treated disease. The committee was aware from correspondence with 1 of the clinical experts who had attended the first committee meeting that the company's modelled survival benefits for untreated and previously treated disease were plausible for this small group of young patients with few comorbidities. The expert explained that response to crizotinib in patients with the ROS1-positive mutation is similar to patients with the ALK-positive mutation, so an average survival benefit of 24 months is reasonable for both untreated and previously treated disease. The committee concluded that the overall survival gain for crizotinib was somewhere between the company's new scenario analyses using the lower bounds of clinical benefit (that is, an overall survival benefit of 13.1 months for untreated disease and 16.2 months for previously treated disease) and the ERG's estimates assuming no benefit in the progressed state, but reiterated that this analysis was still based on a proxy population and therefore considerable uncertainty remained.

Utility values

The company's new utility values for the comparator in untreated disease are appropriate for decision-making

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 adverse reactions, and agreed that this would add further uncertainty to the results. In response to consultation, the company preferred to use a utility of 0.75 for pemetrexed plus platinum-based chemotherapy when patients were not taking treatment and 0.72 when patients were taking treatment. The committee noted that this approach had only a small effect on the cost-effectiveness results and concluded that the utility values used in the company's new analyses were appropriate for decision-making.

Costs

It is appropriate to include revised costs for treating pulmonary embolism and administering crizotinib

- 3.13 The company included higher costs for treating pulmonary embolism as part of its revised base case, noting that these costs were consistent with values used during the development of NICE technology appraisal guidance on [ceritinib for untreated ALK-positive NSCLC](#). The ERG noted that including higher costs for treating pulmonary embolism had only a small effect on the cost effectiveness of crizotinib. The committee understood that the company did not change the administration costs of crizotinib in its revised base case, and noted that including the NHS reference cost for delivering oral chemotherapy (HRG code

SB11Z) increased the incremental cost-effectiveness ratios (ICERs) for both untreated and previously treated disease. It also understood that a similar administration cost using HRG code SB11Z was included in a previous NICE technology appraisal in the ALK-positive population ([crizotinib for previously treated ALK-positive advanced NSCLC](#)). The committee concluded that it was appropriate to include higher costs for treating pulmonary embolism and administering crizotinib.

The most plausible ICERs

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

3.14 The committee agreed that the new ICERs presented by the company were highly uncertain because of the use of proxy data from ALK-positive advanced NSCLC and uncertainties in the overall survival extrapolation. For previously treated disease, the committee noted that the ICER range was broader than for untreated disease. The committee recalled that, as a starting point for its discussion, it would consider ICERs at the mid-point between the company's new scenario that included a clinical benefit for crizotinib in the progressed state (assuming an overall survival gain of 13.1 months for untreated disease and 16.2 months for previously treated disease) and the ERG's scenario assuming no survival benefit in the progressed state (see [section 3.11](#)). Having considered that some post-progression clinical benefit with crizotinib was plausible but the size was uncertain (see [section 3.10](#)), and having established its preferred assumptions for upfront testing costs (see [section 3.2](#)) and higher administration costs (see [section 3.13](#)), the committee considered that the most plausible ICERs would be:

- For crizotinib compared with pemetrexed plus platinum-based chemotherapy in untreated disease: around or above £50,000 per quality-adjusted life year (QALY) gained (the exact ICERs were presented as commercial in confidence and therefore cannot be presented here). 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 crizotinib compared with docetaxel in previously treated disease: well above £50,000 per QALY gained (the exact ICERs were presented as commercial in confidence and therefore cannot be presented here). The committee agreed that had

- crizotinib been compared with nintedanib plus docetaxel, the ICER would be even higher.

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 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 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 in the company's revised base case, was 18.2 months for untreated disease and 20.9 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 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.

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 the company's revised base case were not

clearly within the range normally considered to be a cost-effective use of NHS resources. Given 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 calculations.

Cancer Drugs Fund

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

3.18 Having concluded that crizotinib could not be recommended for routine use in the NHS to treat ROS1-positive NSCLC, the committee considered whether 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](#). The committee was aware that the overall survival data from PROFILE 1001 were immature and no further analysis was expected in 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 NSCLC in PROFILE 1001. The committee was aware that there

are ongoing single-arm observational studies that will provide additional information. However, these studies would only partly address the uncertainties about crizotinib's relative clinical effectiveness. The committee agreed with NHS England that because ROS1-positive lung cancer has only recently been described, and information on the population characteristics, natural history and prognosis is limited, it would be of great value to collect data about the use of crizotinib in ROS1-positive advanced NSCLC through the Cancer Drugs Fund. The committee concluded that collecting data on the demographics of people with ROS1-positive advanced NSCLC, treatment length and disease progression on crizotinib would help to address the uncertainties around the survival benefit and the comparability of ROS1-positive and ALK-positive advanced NSCLC populations. The clinical experts commented that the clinical community would welcome an opportunity to contribute to this data collection through the Cancer Drugs Fund; the representative from NHS England indicated that such data could be collected for up to 5 years. The committee further concluded that crizotinib's use through the Cancer Drugs Fund would also encourage standardisation of ROS1 testing.

Crizotinib is recommend for use in the Cancer Drugs Fund for both untreated and previously treated ROS1-positive NSCLC

3.19 Having determined that the most plausible ICER for crizotinib in untreated disease was around or above £50,000 per QALY gained, the committee concluded that crizotinib had plausible potential to represent cost effectiveness through its use in the Cancer Drugs Fund. The ICER based on the current evidence is higher than the range normally considered to be a cost-effective use of NHS resources, but the committee considered that crizotinib's clinical effectiveness was promising and its use through the Cancer Drugs Fund would provide important data to resolve the clinical uncertainties and encourage standardisation of ROS1 testing. For previously treated disease, the committee noted that the ICER range was broader than for untreated disease. The committee noted that when 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 therefore agreed that it would not make a distinction between untreated and previously treated disease in its recommendations. The committee concluded that it could recommended crizotinib as an option for use within the Cancer Drugs Fund to treat ROS1-positive NSCLC, only if the

conditions in the managed access agreement are followed.

Crizotinib is most likely to be used in the Cancer Drugs Fund for non-squamous NSCLC only

3.20 The committee further considered the population for which crizotinib would most likely be used within the Cancer Drugs Fund. It recalled that: in clinical practice, crizotinib is most likely to be used for non-squamous NSCLC; the comparators chosen by the company were for non-squamous NSCLC; the trial results from PROFILE 1001 and the ALK-positive proxy data from PROFILE 1014 and 1007 were almost exclusively in people with non-squamous histology and predominately in adenocarcinoma; and the testing costs included in the cost-effectiveness analysis were based on a non-squamous lung cancer population. The committee was aware that the incidence of ROS1 in squamous NSCLC is around 1.7% to 1.8%, but recognised that testing of ROS1 status in all patients with NSCLC would be very costly for the Cancer Drugs Fund. It accepted that ROS1 testing and the use of crizotinib in the Cancer Drugs Fund would be in people with non-squamous NSCLC only.

Other factors

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

3.21 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 becomes an available treatment option, ROS1 testing should be done at diagnosis to help prevent potential inequality of access.

4 Implementation

- 4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has ROS1-positive non-small-cell lung cancer (NSCLC) and the doctor responsible for their care thinks that crizotinib is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in [NHS England's Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#).
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination or agreement of a managed access agreement by the NHS in Wales, whichever is the latter.

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

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Accreditation

