

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer

1 Recommendations

- 1.1 Crizotinib is recommended, within its marketing authorisation, as an option for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults. The drug is recommended only if the company provides it with the discount agreed in the patient access scheme.

2 The technology

Description of the technology	Crizotinib (Xalkori, Pfizer) is an inhibitor of the anaplastic lymphoma kinase (ALK) tyrosine kinase receptor and its variants.
Marketing authorisation	Crizotinib has a marketing authorisation in the UK which includes 'the first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC)'.
Adverse reactions	The summary of product characteristics lists the following as the most common adverse reactions associated with crizotinib: visual disorder, diarrhoea, nausea, vomiting, constipation, oedema, fatigue, decreased appetite, neutropenia, elevated aminotransferases, anaemia, leukopenia, neuropathy, dysgeusia, dizziness, bradycardia, abdominal pain and rash. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	The recommended dosage of crizotinib is 250 mg twice daily.
Price	The list price of crizotinib is £4,689 for 60 capsules (excluding VAT; 'British national formulary' [BNF] online, accessed February 2016).

	The company has agreed a patient access scheme with the Department of Health. This scheme provides 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 does not constitute an excessive administrative burden on the NHS.
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3 Evidence

The appraisal committee ([section 8](#)) 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.

4 Committee discussion

The appraisal committee reviewed the data on the clinical and cost effectiveness of crizotinib, having considered evidence on the nature of untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) and the value placed on the benefits of crizotinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee considered the nature of the condition noting that the prognosis for advanced NSCLC is poor, and that there is no cure. The committee heard from the clinical and patient experts that crizotinib could potentially extend life and improve quality of life. The committee concluded that additional treatment options would be valuable to people with ALK-positive NSCLC.

4.2 The committee considered the population relevant to this appraisal and noted that the marketing authorisation includes adults with ALK-positive advanced NSCLC, whereas the company's base case focused on non-squamous ALK-positive advanced NSCLC. The committee heard

from a clinical expert that the ALK-positive mutation is more common in people with non-squamous advanced NSCLC than in people with squamous advanced NSCLC. It heard that testing for the ALK-mutation is routinely done in the non-squamous population. Because the ALK-positive mutation is relatively rare in people with squamous advanced NSCLC, the committee concluded that the population in the company's submission, that is, people with non-squamous advanced NSCLC, accurately reflects people with ALK-positive advanced NSCLC seen in UK clinical practice.

4.3 The committee considered the treatment pathway for people with untreated ALK-positive NSCLC and the comparators relevant to this appraisal:

- The committee heard from the clinical experts that most people with ALK-positive NSCLC in England would first have a platinum-based chemotherapy (as described in NICE's guideline on [diagnosing and managing lung cancer](#) and NICE's technology appraisal on [pemetrexed for first-line treatment of non-small-cell lung cancer](#)). The committee was aware that pemetrexed can be given in combination with either cisplatin or carboplatin, which the experts considered to be equally effective. The committee concluded that platinum-based chemotherapy was the most relevant comparator for crizotinib.
- The committee noted that the company's submission only compared crizotinib with platinum-based chemotherapy, and therefore did not consider people who could not take platinum-based chemotherapy. It heard from clinical experts that there is no biological reason to expect a different response with crizotinib in this group.

4.4 The committee discussed whether testing for the ALK-mutation is established practice in the NHS. It heard from the clinical experts that ALK-mutation testing is needed before starting crizotinib, and that all people with non-squamous disease are tested. The committee concluded that the cost of ALK-mutation testing should be taken into account.

Clinical effectiveness

4.5 The committee considered the clinical-effectiveness evidence for crizotinib. It acknowledged that the main trial presented by the company was PROFILE 1014, which investigated whether crizotinib prolongs progression-free survival compared with pemetrexed plus either cisplatin or carboplatin in people with locally advanced, recurrent or metastatic non-squamous NSCLC. The committee was aware that crizotinib treatment continued until (and in some cases beyond) disease progression, whereas pemetrexed with either cisplatin or carboplatin was given for a maximum of 6 cycles. At disease progression, the trial allowed patients to switch treatment groups. The committee noted the ERG's comments that the trial population was younger and had a higher proportion of patients who do not smoke compared with other studies of NSCLC. The committee heard from the company and the clinical experts that the patients' characteristics in PROFILE 1014 reflected people with ALK-positive NSCLC in England, and so the committee concluded that PROFILE 1014 was suitable for its decision-making.

Progression-free survival

4.6 The committee discussed the results of PROFILE 1014 and the primary outcome measure of progression-free survival:

- It noted that progression was determined using radiographic criteria, specifically the Response Evaluation Criteria in Solid Tumours (RECIST). The committee heard from the clinical experts that radiographic criteria are the gold standard for monitoring NSCLC.
- The committee noted that crizotinib increased progression-free survival compared with pemetrexed with either cisplatin or carboplatin (hazard ratio [HR] 0.45; 95% confidence interval [CI] 0.35 to 0.60).
- The committee was aware that the company used a Cox proportional hazards model to estimate the hazard ratio for progression-free survival. It noted the ERG's critique that in this case, the proportional

hazards assumptions needed to analyse data using a Cox proportional hazards model may not hold because the 2 treatment regimens are given differently (in PROFILE 1014, crizotinib was given until progression whereas platinum-based chemotherapy [the control group] was given for a finite number of cycles). The ERG stated that this did not have a large effect on cost effectiveness, but because patient-level data were available, the company could have modelled the data using separate independent parametric curves with fewer assumptions.

On balance, the committee concluded that crizotinib increases progression-free survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC.

Overall survival

- 4.7 The committee discussed the results of PROFILE 1014 and the secondary outcome measure of overall survival. It noted the ERG's comments that the results for overall survival were based on relatively immature data, that is, that few patients had died at the time of data analysis. It also noted that a high proportion of patients crossed over from chemotherapy to crizotinib. The committee was aware that because crossover occurred at or after disease progression, it would not affect progression-free survival, but would affect overall survival. The committee concluded that it was appropriate for the company to adjust for crossover when estimating the size of the benefit on overall survival associated with crizotinib.
- 4.8 The committee discussed the methods for adjusting for crossover in PROFILE 1014. The company presented evidence using different methods to adjust overall survival for crossover (rank preserving structural failure time, iterative parameter estimation, and 2-stage methods) and presented a range of analyses which accounted for different confounders. The committee recognised that the company had used the 2-stage

method for its cost-effectiveness analyses. It was aware that there was some uncertainty about whether all confounders were measured at the time of crossover, but noted that the ERG agreed this was the most appropriate approach because it did not assume a common treatment effect (that is, that the treatment effect is the same regardless of when a person starts treatment). The committee concluded that the 2-stage method was appropriate.

- 4.9 The committee discussed the size of the benefits associated with crizotinib on overall survival. The committee noted that crizotinib increased overall survival compared with pemetrexed plus either cisplatin or carboplatin (HR 0.62; 95% CI 0.41 to 0.96), when using the 2-stage method to account for crossover. It noted that applying different methods to account for crossover did not vary the hazard ratio substantially. It noted the ERG's comments that the results for overall survival were based on relatively immature data (that is, few patients had died at the time of data analysis). The committee recognised that the size of the benefit was uncertain because of relatively immature data and the high proportion of patients crossing over from chemotherapy to crizotinib. On balance, the committee concluded that crizotinib is very likely to increase overall survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC, but the size of the increase is uncertain.

Cost effectiveness

- 4.10 The committee considered the approach and structure of the company's economic model. The company used a semi-Markov model structure with 3 health states: the progression-free health state, progressed-disease health state and death. The model included either crizotinib or chemotherapy as the first treatment, followed by docetaxel and then best supportive care. The committee concluded that the model was consistent with the approaches used for other appraisals in NSCLC.

Clinical parameters and treatment effect

- 4.11 The committee discussed the company's approach to modelling overall and progression-free survival. It noted that, to generate more realistic survival estimates relevant to the UK population, the company had adjusted PROFILE 1014 data to reflect the characteristics of patients in a retrospective cohort study from the US and Canada (Davis et al. 2015). The committee discussed whether the characteristics of patients in the study reflected those of patients in England and noted from the company's sensitivity analyses that the assumptions were conservative. The committee concluded that it was satisfied with the company's approach.
- 4.12 The committee considered whether assuming proportional hazards between treatments was appropriate for extrapolating progression-free and overall survival to estimate how long, on average, crizotinib extended the progression-free period and delayed death. The committee noted consultation comments from the company that the recommended statistical checks in NICE's [Decision Support Unit technical support document 14](#), including log-cumulative hazard plots for overall survival, had shown that the proportional hazards assumptions held. The committee recalled the different methods of administration between treatments (see section 4.6) and noted that the log-cumulative hazard plots for each treatment were not parallel. The committee therefore disagreed with the company, noting that the hazard ratios were likely to change over time and that the assumption of proportional hazards was unlikely to hold. The committee was aware that NICE's [Decision Support Unit technical support document 14](#) suggests using separate parametric curves for each treatment group. The committee concluded that using separate parametric curves for each group was appropriate.
- 4.13 The committee considered whether the parameters used to adjust the parametric curves to the UK population should be the same or different for both treatments (that is, use independent covariate stratification). The

committee noted comments received during consultation that there is no evidence suggesting a difference in prognosis between treatments or that covariates (such as age or sex) influence outcomes depending on treatment. The committee heard from the ERG that stratifying covariates independently uses fewer assumptions, and noted that it had a minor effect on the incremental cost-effectiveness ratios (ICERs). On balance, the committee agreed that it was appropriate to adjust each treatment for the population separately and concluded that using independent prognostic covariates was appropriate.

4.14 The committee discussed which parametric curves for extrapolating progression-free and overall survival it considered most plausible:

- The committee was aware that the company's base case used a generalised gamma distribution for progression-free survival and a Weibull distribution for overall survival. It noted that the ERG presented exploratory analyses using separate parametric curves for each treatment (that is: progression-free survival – a log-normal distribution for crizotinib and a generalised gamma distribution for chemotherapy; overall survival – a generalised gamma distribution for crizotinib; and an exponential distribution for chemotherapy). The committee recognised that different parametric distributions predicted a range of differences in progression-free and overall survival. The committee noted comments received from the company during consultation that the overall survival increase using the ERG's selected distributions was implausible (0.8 months increased survival with crizotinib compared with chemotherapy). It heard from the clinical experts that they expected no less than a 6-month increase in overall survival with crizotinib. The committee agreed that that curves used in the ERG's exploratory analysis (that is: progression-free survival – a log-normal distribution for crizotinib and a generalised gamma distribution for chemotherapy; overall survival – a generalised gamma distribution for

crizotinib; and an exponential distribution for chemotherapy) were not plausible.

- The committee considered statistical tests of model fit and noted that, based on either the Akaike information criterion (AIC) or the Bayesian information criterion (BIC), there were no large differences between the distributions. It noted comments received from the company during consultation that the exponential distribution (for both crizotinib and chemotherapy) had the lowest cumulative AIC and BIC. The committee agreed that it did not consider adding AIC and BIC scores together to be routine statistical practice, and that selecting parametric curves for extrapolation should not be based on statistical methods alone.
- To extrapolate overall survival, the committee noted that the company, in its response to the appraisal consultation document, preferred the exponential distribution for crizotinib, and the exponential or Weibull distributions for chemotherapy. The company provided its 4 criteria for selecting parametric curves:
 - Overall survival with chemotherapy must be less than 24 months; the committee agreed that this was reasonable given the committee's discussion of end-of-life criteria (see section 4.21).
 - The mean overall-survival gain with crizotinib must be more than 7.1 months based on an estimate from PROFILE 1007, a trial used in NICE's technology appraisal guidance for [crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene](#). The company suggested that crizotinib should be more effective as a first-line treatment for NSCLC than as a second-line treatment. However, the committee recognised that PROFILE 1007 was based on a different population, a different comparator (docetaxel), and a different duration of treatment. The committee was also aware that in NICE's technology appraisal guidance for [crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion](#)

[gene](#), overall survival was uncertain because of cross-over between treatments. The committee heard from the company that although several years of additional follow-up data was collected for PROFILE 1014, the next reanalysis will be done when median overall is reached (as per protocol). The committee agreed that the dataset for overall survival remained incomplete and that the gain in overall-survival data was uncertain.

- The mean gain must be more than the median gain in overall survival: the committee heard from the clinical experts that some people on crizotinib live longer than expected, and agreed that this criterion is plausible and appropriate.
- The mean gain in overall survival should be clinically plausible; the committee agreed that this criterion was appropriate.

The committee acknowledged there was uncertainty about the size of the average gain in overall survival. It was aware that the company planned to do more analyses and emphasised the need for mature overall-survival data. The committee noted that using different parametric curves for overall survival had a major effect on the ICERs. Given the limited data available, the committee agreed to use the same distribution for both treatments to minimise the differences in assumptions between treatments. The committee noted that the exponential, log-normal and log-logistic distributions had a median overall-survival gain of more than 6 months and a mean overall-survival gain higher than the median overall-survival gain, and agreed that these distributions were all plausible and considered these for its decision making.

- 4.15 The committee discussed the time on treatment assumed in the company's model. The committee was concerned about the way in which the company estimated time on crizotinib treatment using PROFILE 1014. The company assumed that people taking crizotinib stopped treatment at the end of the trial (that is, they were censored), and applied this in the

model. The ERG considered that this substantially underestimated the time on treatment after progression. The committee agreed that it was inappropriate to assume that patients in the trial who stopped treatment because the trial ended would also stop treatment in real life, and preferred the ERG's analyses using a parametric survival curve, that accounts for censoring, to estimate the mean duration of treatment. However, it noted that the ERG did not adjust the analyses to reflect the population in England because it did not have access to the relevant data. The committee noted that in response to the appraisal consultation document, the company presented a revised analysis reflecting the population in England. The committee agreed that this was appropriate.

4.16 The committee discussed the approach to second-line treatment in the company's model:

- Docetaxel: the committee noted that the company assumed that everyone with progressed disease had docetaxel (as described in NICE's guideline on [diagnosing and managing lung cancer](#)), but it heard from the clinical experts that some people are not fit enough for second-line docetaxel. It also noted the ERG's comments that in PROFILE 1014, people went on to have a wide range of therapies (other than docetaxel) after disease progression.
- Second-line crizotinib: the committee noted that the company did not include second-line crizotinib in its model. It heard from the clinical experts that people who have first-line platinum-based chemotherapy may go on to have second-line crizotinib. The committee was aware that crizotinib is not recommended in NICE's technology appraisal for [previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene](#), and that second-line treatment with crizotinib was only available through the Cancer Drugs Fund.

- Second-line ceritinib: the committee was aware that ceritinib is recommended in NICE's technology appraisal guidance for [previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer](#). The committee noted that ceritinib is considered as an option after treatment with crizotinib.

Therefore, the committee was unclear on whether the company's model accurately reflected second-line treatment for people with ALK-positive NSCLC in England. However, the committee was also aware that the ERG presented analyses without second-line treatment because of sparse data on time on second-line treatment, which suggested that the effect on the ICER would likely be small. On balance, the committee concluded that, in the absence of robust data and because of uncertainty about second-line treatments, excluding second-line treatment from the model was the most robust approach.

Utilities

4.17 The committee discussed the utility values used in the company's model:

- The company applied a lower utility for the progression-free health state in its model for platinum-based chemotherapy (0.72) than it did for crizotinib (0.81). The committee noted that this may underestimate the utility associated with platinum-based chemotherapy because health-related quality-of-life data were collected for patients only during chemotherapy, but not after chemotherapy had finished. The committee was aware that the ERG presented analyses with a higher utility value (0.81) for the progression-free health state with a platinum-based chemotherapy. In its response to the appraisal consultation document, the company accepted that it had underestimated the utility value for chemotherapy and suggested a higher utility value of 0.75. The committee heard from the ERG that the revised utility value also underestimated the utility decrement associated with chemotherapy

because it included minor and not major adverse events, and that the data were based only on people on treatment. The committee heard from the clinical experts that people treated with cisplatin can have ongoing peripheral neuropathy and a lower quality of life compared with people taking oral treatments. On balance, the committee concluded that the utility value was closer to 0.75 than 0.81 and that the company's revised utility was appropriate.

- The committee noted that the company applied a utility value (0.74) for the period after a patient's disease has progressed but they continue to take crizotinib. It noted that this value averaged the utility for first-line treatment with crizotinib (before disease progression, 0.81) and the utility for second-line treatment with docetaxel (after disease progression, 0.66). It noted that this was not based on evidence. In its response to the appraisal consultation document, the company used a higher utility value (0.78) estimated from PROFILE 1014. The ERG stated that there was a risk of attrition bias for this estimate (that is, sicker patients were lost to follow-up earlier and not included in the analysis), which reduced the difference in the health-related quality of life of patients before and after progression. The committee heard from the clinical experts that despite progression, a patient on crizotinib may not have symptoms of lung cancer. The committee concluded that the utility value for the period after a patient's disease has progressed but the patient continues to take crizotinib was uncertain but likely to be between 0.74 and 0.78.

Costs

4.18 The committee discussed the costs used in the company's model:

- The committee considered the appropriate cost for ALK-testing in the model and noted that the ERG considered that the company had underestimated the cost of testing. The committee heard from the ERG that a recent Cancer Research UK study reported the cost of

ALK-mutation testing as £153 per patient. The ERG estimated that the cost of identifying a person with the ALK mutation was around £4,500, because over 29 people with NSCLC need to be tested to identify 1 person with the mutation. The committee heard from a clinical expert that the cost of immunohistochemistry was between £50 and £100 (excluding laboratory costs). In its response to the appraisal consultation document, the company assumed a cost of £75 for immunohistochemistry, increasing the cost of identifying a person with the ALK mutation to £2,380. The ERG suggested that the company underestimated the cost because it excluded laboratory costs. The committee heard from the company that the sequence of tests is a recent change, so the costs of ALK-mutation testing were still uncertain. Although the true cost for ALK-mutation testing is unknown, the committee considered that the cost of ALK-mutation testing was between £2,380 and £4,500.

- The committee discussed administration costs for crizotinib, and noted that the company did not include them in its model. It heard from the clinical experts that there would be administration costs, and also noted that these costs were included in NICE's technology appraisal on [crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene](#) (£163.85). The committee recognised that the ERG took this into account in its exploratory analyses. However, the committee agreed with consultation comments from the company that the lower administration cost (£14.40) used in the NICE technology appraisal on [ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer](#) was more appropriate than the cost used by the ERG in its exploratory analyses (£163.85).

4.19 The committee considered 4 results for the cost-effectiveness of crizotinib compared with pemetrexed plus either cisplatin or carboplatin for people with advanced ALK-positive NSCLC:

- Company's revised base case: £49,186 per quality-adjusted life year (QALY) gained that:
 - assumes proportional hazards without independent covariate stratification
 - reflects changes to the original company submission:
 - ◇ higher patient access scheme discount
 - ◇ alternative utility values (see section 4.17)
 - ◇ adjusted time on treatment (see section 4.15)
 - ◇ adjusted administration costs and ALK-mutation testing costs (see section 0).
- Company's independent parametric curve analysis: £47,921 per QALY gained that:
 - no longer assumes proportional hazards between treatment groups, but uses independent exponential curves for both treatments
 - adjusts each treatment for the population separately (independent covariate stratification).
- ERG's revised exploratory analysis: £58,029 per QALY gained that:
 - assumes proportional hazards without independent covariate stratification
 - reflects changes to the company's revised analysis:
 - ◇ higher utility for platinum-based chemotherapy for the progression-free health state (0.81 rather than 0.75)
 - ◇ lower utility when a patient's disease progresses and they continue crizotinib (0.74 rather than 0.78)
 - ◇ higher ALK-mutation testing cost (£4,500 rather than £2,380)
 - ◇ higher administration cost for crizotinib (£163.85 rather than £14.40).
- ERG's independent parametric curves analysis: £55,131 per QALY gained that:
 - no longer assumes proportional hazards between treatment groups but uses independent exponential curves for both treatments

- adjusts each treatment for the population separately (independent covariate stratification).

The committee recalled its preferred assumptions relating to time on treatment (see sections 4.15), utilities (see section 4.17), costs (see section 0), proportional hazards (see section 4.12), independent covariate stratification (see section 4.13), and extrapolation (see section 4.14). It concluded that the company's independent parametric curve analysis (with an estimated ICER of £47,291 per QALY gained) most closely reflected the committee's preferred assumptions and noted that the ICERs for other alternative curves (such as the log-normal and log-logistic distributions for both treatments) were similar. However, the committee acknowledged that this used some assumptions that the committee did not prefer or that the committee considered to be uncertain (such as the utility value for the period after a patient's disease has progressed but the patient continues to take crizotinib, and the cost of testing for an ALK mutation), and therefore acknowledged that uncertainty on the cost effectiveness of crizotinib remained fairly large. The committee was aware that it needed to be increasingly certain of the cost effectiveness of a technology as the technology's effect on NHS resources increases, as described in NICE's [guide to the methods of technology appraisal](#). It recalled that ALK-positive mutation is rare in people with advanced NSCLC and considered the effect of adopting the technology as relatively small. On balance, the committee concluded that even after accounting for the uncertainty in the cost effectiveness, the most plausible ICER was likely to be at a level at which crizotinib could be considered a cost-effective use of NHS resources when the end-of-life criteria to apply.

End-of-life considerations

- 4.20 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [final Cancer Drugs Fund technology appraisal process and methods](#).
- 4.21 The committee discussed whether crizotinib for untreated ALK-positive advanced NSCLC met the end-of-life criteria.
- It considered the life expectancy criterion and noted that the company's revised model (using data from PROFILE 1014 and an exponential distribution for overall survival for both treatments) showed that the life expectancy of people with ALK-positive NSCLC is a median 14.8 months and a mean 20.8 months with platinum-based chemotherapy. The committee was aware that the data from PROFILE 1014 were adjusted so that the trial population reflected the patient population in a retrospective cohort study (Davis et al. 2015; see section 4.11), and considered this to be a conservative assumption. The committee agreed that the short life expectancy criterion was met.
 - The committee discussed the life-extension criterion and noted the evidence that crizotinib is likely to extend life by an additional 3 months compared with a platinum-based chemotherapy. The company's revised model (using data from PROFILE 1014 and an exponential distribution for overall survival for both treatments) showed an extension to life of a median 9.9 months and a mean of 13.1 months with crizotinib compared with platinum-based chemotherapy. Crizotinib extended life by a median or mean of at least 3 months compared with platinum-based chemotherapy when using other parametric survival curves (such as a log-normal or log-logistic distribution for both treatments). The committee heard from the ERG that the estimates of overall survival were highly uncertain because the data were considered immature and because of extensive crossover from

chemotherapy to crizotinib. The committee considered that although the size of the benefit was unclear, it could be sufficiently confident that crizotinib would offer at least an additional mean survival benefit of 3 months.

The committee concluded that both the life expectancy and the extension-to-life criteria were met.

Innovation

4.22 The committee considered whether crizotinib is an innovative treatment. It noted that the company considered crizotinib as innovative because the current standard of care for advanced NSCLC is intravenous chemotherapy every 3 weeks. It also noted that crizotinib is the only available oral therapy and that people value oral therapies. The committee further noted that the company did not incorporate the expected benefits of crizotinib to patients' carers in its model. However, the committee noted that it had not been presented with evidence about the extent to which these benefits were realised in practice. The committee concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of QALYs.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.23 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of crizotinib in this appraisal.

Summary of appraisal committee's key conclusions

TAXXX	Appraisal title: Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer	Section
Key conclusion		
<p>Crizotinib is recommended, within its marketing authorisation, as an option for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults.</p> <p>The committee concluded that the company's independent parametric curve analysis (with an estimated incremental cost-effectiveness ratio [ICER] of £47,291 per quality-adjusted life year [QALY] gained) most closely reflected the committee's preferred assumptions and noted that the ICERs for other alternative curves (such as the log-normal and log-logistic distributions for both treatments) were similar. However, the committee acknowledged that this used some assumptions that the committee did not prefer or that the committee considered to be uncertain and therefore acknowledged that uncertainty on the cost effectiveness of crizotinib remained fairly large. On balance, the committee concluded that even after accounting for the uncertainty in the cost effectiveness, the most plausible ICER was likely to be at a level at which crizotinib could be considered a cost-effective use of NHS resources when the end-of-life criteria to apply.</p>		1.1, 4.19
Current practice		

<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The committee noted that the prognosis for advanced non-small-cell lung cancer (NSCLC) is poor and that there is no cure, and concluded that additional treatment options would be valuable for people with anaplastic lymphoma kinase (ALK)-positive NSCLC.</p>	<p>4.1</p>
<p>The technology</p>		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The committee concluded that crizotinib increases progression-free survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC. The committee concluded that crizotinib is very likely to increase overall survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC, but the size of the increase is uncertain.</p> <p>The committee concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of QALYs.</p>	<p>0, 4.9, 4.22</p>
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>The committee was aware that crizotinib has a marketing authorisation in the UK for ‘the first-line treatment of adults with anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC)’.</p>	<p>2</p>
<p>Evidence for clinical effectiveness</p>		

<p>Availability, nature and quality of evidence</p> <p>Relevance to general clinical practice in the NHS</p>	<p>The committee heard from the company and the clinical experts that the patients' characteristics in PROFILE 1014 reflected people with ALK-positive NSCLC in England, and so the committee concluded that PROFILE 1014 was suitable for its decision-making.</p>	<p>4.5</p>
<p>Uncertainties generated by the evidence</p>	<p>The committee recognised that the company had used the 2-stage method for its cost-effectiveness analyses. It was aware that there was some uncertainty about whether all confounders were measured at the time of crossover.</p> <p>The committee concluded that crizotinib is very likely to increase overall survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC, but the size of the increase is uncertain.</p>	<p>4.8, 4.9</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The committee heard that there was no biological reason to expect a different response with crizotinib in people who cannot take platinum-based chemotherapy, but was aware that there was little evidence specific to this group of patients.</p>	<p>4.3</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The committee noted that crizotinib increased progression-free survival compared with pemetrexed with either cisplatin or carboplatin (hazard ratio [HR] 0.45; 95% confidence interval [CI] 0.35 to 0.60).</p> <p>The committee noted that crizotinib increased overall survival compared with pemetrexed plus either cisplatin or carboplatin (HR 0.62; 95% CI 0.41 to 0.96), when using the 2-stage method to account for crossover. It noted that applying different methods to account for crossover did not vary the hazard ratio substantially.</p>	<p>0, 4.9</p>
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The committee concluded that the model was consistent with the approaches used for other appraisals in NSCLC.</p>	<p>4.10</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The committee recalled its preferred assumptions relating to time on treatment, utilities, costs, proportional hazards, independent covariate stratification, and extrapolation. It concluded that the company’s independent parametric curve analysis most closely reflected the committee’s preferred assumptions. It acknowledged that this used some assumptions that the committee did not prefer or that the committee considered to be uncertain (such as the utility value for the period after a patient’s disease has progressed but the patient continues to take crizotinib, and the cost of testing for an ALK mutation), and therefore acknowledged that uncertainty on the cost effectiveness of crizotinib remained fairly large.</p>	<p>4.12– 4.19</p>
<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they</p>	<p>The committee concluded that the utility value for the progression-free health state for platinum-based chemotherapy was closer to 0.75 than 0.81 and that the company’s revised utility was appropriate.</p> <p>The committee concluded that the utility value for the period after a patient’s disease has progressed but the patient continues to take crizotinib was uncertain but likely to be between 0.74 and 0.78.</p> <p>The committee concluded that it had not been presented with any additional evidence of</p>	<p>4.17, 4.22</p>

<p>been considered?</p>	<p>benefits that were not captured in the measurement of QALYs.</p>	
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The committee heard from a clinical expert that the ALK-positive mutation is more common in people with non-squamous advanced NSCLC than in people with squamous advanced NSCLC</p>	<p>4.2</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The committee noted that using different parametric curves for overall survival had a major effect on the ICERs.</p> <p>The committee was also aware that analyses without second-line treatment suggested that the effect on the ICER would likely be small.</p> <p>The committee noted that the ICERs for parametric survival curves (such as the log-normal and log-logistic distributions for both treatments) were similar.</p>	<p>4.14, 4.16, 4.19</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The committee concluded that the company's independent parametric curve analysis (with an estimated ICER of £47,291 per QALY gained) most closely reflected the committee's preferred assumptions and noted that the ICERs for other alternative distributions (such as the log-normal and log-logistic distributions for both treatments) were similar. However, the committee acknowledged that this used some assumptions that the committee did not prefer or that the committee considered to be uncertain and therefore acknowledged that uncertainty on the cost effectiveness of crizotinib remained fairly large. On balance, the committee concluded that even after accounting for the uncertainty in the cost effectiveness, the most plausible ICER was likely to be at a level at which crizotinib could be considered a cost-effective use of NHS resources when the end-of-life criteria to apply.</p>	<p>4.19</p>
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>The committee concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of crizotinib.</p>	<p>4.23</p>
<p>End-of-life considerations</p>	<p>The committee concluded that both the life expectancy and the extension to life criteria were met.</p>	<p>4.20, 4.21</p>

<p>Equalities considerations and social value judgements</p>	<p>The following potential equality issues were identified during the scoping process:</p> <ul style="list-style-type: none"> • That testing could be restricted to people with a diagnosis of adenocarcinoma. • That there could be inequitable access if regional variations in ALK-mutation testing exist. <p>The potential equality issues identified during the scoping process were noted by the Committee. None of these issues related to protected characteristics, as defined by the Equalities Act (2010), and so were not considered equality issues.</p>	<p>-</p>
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5 Implementation

- 5.1 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.
- 5.2 The Welsh Assembly Minister for Health and Social Services has 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 3 months of the guidance being published.

- 5.3 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 untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer 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.
- 5.4 The Department of Health and Pfizer have agreed that crizotinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to **[NICE to add details at time of publication]**

6 Recommendations for research

- 6.1 The committee was aware that follow-up for PROFILE 1014 was ongoing and that the next planned analysis of the trial would be done when median survival has been reached. The committee agreed that this additional analysis would give useful data on overall survival with crizotinib for people with untreated ALK-positive non-small-cell lung cancer.

7 Review of guidance

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

Amanda Adler
Chair, appraisal committee
August 2016

8 Appraisal committee members, guideline representatives and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

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.

Jasdeep Hayre

Technical Lead

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