NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Crizotinib for untreated anaplastic lymphoma kinase-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 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?

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 (FAD).
- Subject to any appeal by consultees, the FAD 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: 22 June 2016

Second appraisal committee meeting: 6 July 2016

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

1 Recommendations

1.1 Crizotinib is not recommended within its marketing authorisation, that is, for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults.

1.2 This guidance is not intended to affect the position of patients whose treatment with crizotinib was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Crizotinib (Xalkori, Pfizer) is an inhibitor of the anaplastic lymphoma kinase (ALK) tyrosine kinase receptor and its variants.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)'

2.2 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.

2.3 The recommended dosage of crizotinib is 250 mg twice daily. The list price of crizotinib is £4,689 for 60 capsules (excluding VAT; British national formulary online, accessed February 2016). 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 Evidence

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.

4 Committee discussion

The appraisal committee reviewed the data available 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. The committee noted 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 of value to people with ALK-positive NSCLC.

4.2 The committee considered the population relevant to this appraisal. The committee 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

relatively rare in people with squamous advanced NSCLC (0.1%) but is common in people with non-squamous advanced NSCLC. The committee heard that ALK-mutation testing is routinely done in this population. 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 would first have a platinum-based chemotherapy (as described in NICE's guideline on lung cancer: diagnosis and management and NICE's technology appraisal on pemetrexed for the first-line treatment of non-small-cell lung cancer). The committee was aware that pemetrexed can be given in combination with cisplatin or carboplatin. The committee queried whether it was appropriate to pool the combinations and heard from the clinical experts that both treatments are considered to have equal efficacy, although carboplatin is associated with less toxicity.
- 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 was no biological reason to expect a different response with crizotinib in this group, but the committee was aware that there was little evidence specific to this group of patients.
- The committee heard from the clinical experts that after a set number of cycles of pemetrexed with either cisplatin or carboplatin, some people who do well may have further pemetrexed but without platinum (that is, pemetrexed maintenance therapy). The clinical experts estimated that

NSCLC responds to pemetrexed maintenance therapy in about 5% to 10% of patients, and noted that the drug is currently available through the Cancer Drugs Fund.

The committee concluded that platinum-based chemotherapy was the most relevant comparator for crizotinib. The committee also concluded that although platinum-based chemotherapy with pemetrexed followed by pemetrexed maintenance therapy alone was not included in the final NICE scope and the company's decision problem for this appraisal, it could be a relevant comparator because it is often used in clinical practice.

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 noted the ERG's comments that the trial population underpinning this evidence (PROFILE 1014) is younger and has 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 patient characteristics in PROFILE 1014 accurately reflect the patient population in England, and so the committee concluded that PROFILE 1014 was suitable for its decision-making.

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. It noted the ERG's critique that the proportional hazards assumptions needed for a Cox proportional hazard model may not be valid because the 2 treatment regimens are administered differently (in the trial 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 is clinically effective and increases progression-free survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC.

4.7 The committee discussed crossover in PROFILE 1014. It noted there was a high rate of patients crossing over from chemotherapy to crizotinib. The committee was aware that because most of this crossover occurred at or after disease progression, it would not affect progression-free survival, but would affect overall survival. The company presented evidence using 2 different methods to adjust overall survival for crossover (the rank preserving structural failure time method and the 2-stage method) 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. The committee recognised that there was some uncertainty about the confounders that were unmeasured

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 the most appropriate to use.

4.8 The committee discussed the overall survival benefits associated with crizotinib. 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 crossover was accounted for using the 2-stage method. 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 is uncertain because of relatively immature data and the high proportion of crossover of patients moving from chemotherapy to crizotinib. On balance, the committee concluded that crizotinib very likely increases overall survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC

Cost effectiveness

4.9 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: progression free, progressed disease and death. The model included either crizotinib or chemotherapy as the first treatment, followed by docetaxel and then best supportive care.The committee noted that the model was consistent with the approaches used for other appraisals in NSCLC. However, the ERG had concerns with several aspects of the company's model:

- In the model, 54% of patients had pemetrexed with cisplatin and 46% had pemetrexed with carboplatin. The ERG's clinical expert suggested that in NHS practice, around 30% of people would have cisplatin and 70% would have carboplatin. The ERG presented cost-effectiveness results based on 25% of people having cisplatin and 75% having carboplatin. The committee recalled that carboplatin and cisplatin are considered equally effective (see section 4.3) and differences in costs are marginal. The committee concluded that this had a minimal impact on cost effectiveness, and did not consider it further.
- The ERG was concerned that the company discounted costs and benefits annually instead of a per cycle basis. The committee concluded that a per-cycle discount rate (as in the ERG's exploratory analysis) could be more accurate, but that the company's approach of discounting annually was reasonable and consistent with the advice in NICE's guide to the methods of technology appraisal.
- The ERG identified an error where the company included time zero as a complete cycle. The committee heard from the company that this was a mistake and that the ERG corrected this in its exploratory analyses.

4.10 The committee discussed the company's approach to modelling overall and progression free survival. It noted that, to generate more realistic survival estimates, the company had adjusted PROFILE 1014 data to reflect the characteristics of patients in a retrospective cohort study from North America (Davis et al. 2015). The committee identified this as a source of uncertainty because the method for adjustment was unclear, but it noted from the company's sensitivity analyses that it was a conservative assumption. The committee concluded that it was satisfied with the company's approach.

4.11 The committee considered the extrapolation of overall survival and progression free survival in the company's model.

- It noted that the company had assumed proportional hazards between treatments. The committee recalled that the hazard ratios were likely to change over time and that the assumption of proportional hazards was unlikely to hold. The committee recalled that the company had individual patient data from PROFILE 1014 and therefore could have modelled each treatment group independently (see section 4.6). 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 was aware that the company's base case used a generalised gamma curve for progression-free survival and a Weibull curve for overall survival. The committee noted that during clarification the company submitted separate parametric curves for each treatment group, and that the ERG presented cost-effectiveness results using these (that is, progression free survival: crizotinib, log-normal curve; chemotherapy, generalised gamma curve. Overall survival: crizotinib, generalised gamma curve; chemotherapy, exponential curve). It noted that the ERG was unable to identify any particular curve as being clinically the most appropriate and therefore selected curves using the lowest Akaike information criterion.

The committee concluded that because individual patient data were available and because the assumption of proportional hazards was unlikely to hold, it preferred the ERG's approach that used separate parametric curves for each treatment. The committee also concluded that using the lowest Akaike information criterion to select the best curve was acceptable in this instance.

4.12 The committee discussed the time on treatment assumed by the company in its model:

- The committee heard from the clinical experts that they sometimes continue to offer crizotinib after a person's disease has progressed based on radiographic criteria (RECIST) if the person is still benefiting from treatment. The committee recognised that this was accounted for in the company's model and agreed it was appropriate.
- The committee noted that the company modelled the median time on treatment from PROFILE 1014. It noted the ERG's concern that the mean (not median) time is needed for accurate modelling. The committee recognised that the ERG took this into account in its exploratory analyses. The committee's preference was to use the mean time on treatment.
- The committee noted the ERG's concern that the company underestimated the time on treatment in its model because it was shorter than the time on treatment in PROFILE 1014. The ERG noted that this was because of the way that the proportion of people who died was calculated. The committee recognised that the ERG took this into account in its exploratory analyses. The committee's preference was to use to the time on treatment taken from PROFILE 1014.
- The committee was concerned with the way the company estimated time on treatment with crizotinib from 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 because of the availability of relevant data, the ERG did not adjust the analyses using the same approach used by the company to reflect the population in England for progression-free and

overall survival (see section 4.10). Therefore, the committee agreed that the ERG's exploratory analysis may have overestimated the time on treatment with crizotinib and therefore also the incremental cost-effectiveness ratio (ICER). On balance, the committee concluded that it would have preferred to see an adjusted parametric survival curve to estimate time on treatment with crizotinib. It also concluded that although the ERG may have overestimated the ICER, in the absence of relevant data for an alternative approach, it was appropriate.

4.13 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 lung cancer: diagnosis and management), however 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 receive 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. However, it recognised this was only available through the Cancer Drugs Fund.

Therefore, the committee was unclear on whether the company's model accurately reflects second-line treatment for people with ALK-positive NSCLC. The committee was aware that the ERG presented analyses without second-line treatment because of the lack of data on time on second-line treatment. It noted that the ERG considered that the overall effect on the ICER would be small. On balance, the committee concluded that, in the absence of robust data and uncertainty about second-line

treatments, excluding second-line treatment from the model was the most robust approach.

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

- The company applied a lower utility (academic in confidence) for platinum-based chemotherapy than crizotinib for the progression-free health state in its model. The committee noted that this may underestimate the utility associated with platinum-based chemotherapy because health-related quality-of-life data were only collected for patients during chemotherapy, and not after chemotherapy had finished. Therefore the health-related quality-of-life of people who were no longer receiving chemotherapy was not captured, despite these patients being included in this health state. The committee also noted the ERG's view that people who finish chemotherapy have fewer adverse events and a better quality of life than people taking chemotherapy. The committee was aware that the ERG presented analyses with a higher utility value for the progression-free health state with a platinum-based chemotherapy (also academic in confidence) and concluded that this was appropriate.
- The committee noted that the company applied a utility value (academic in confidence) when a patient's disease progresses and they continue crizotinib. It noted that this value was an average of the utility for first-line treatment with crizotinib (before disease progression) and the utility for second-line treatment with docetaxel (after disease progression). The committee noted that this utility was higher than the utility for people taking chemotherapy before disease progression. It noted the ERG's concern that although the utility value was plausible (because there would be benefits from crizotinib but also worsening symptoms because of disease progression), it was not based on evidence. However, in the absence of health-related quality-of-life data, the committee concluded that the company's approach was acceptable.

- The committee noted that the company applied a 'transition utility' when a person moves to a new health state. It noted the ERG's concern that transition utilities double-count utility, because utilities are based on an average across patients in the health state and already include patients who have just entered the health state and patients who have remained in the health state for longer. The committee heard from the company that it agreed with the ERG's critique. The committee was aware that the ERG presented analyses without the transition utility and concluded that this was appropriate.

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

- The committee considered the appropriate cost for ALK-testing in the model. The committee noted that that the ERG considered that the company 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) and so agreed that the ERG may have overestimated the cost. The committee concluded that the true cost for ALK-mutation testing was likely to be between the company's cost (commercial in confidence) and ERG's cost of £4500.
- The committee considered the costs associated with wasting crizotinib. It noted that the company assumed no drug wastage when a patient stopped treatment, but the ERG considered this to be unrealistic: when a patient starts a pack of crizotinib or chemotherapy, it would not be reused by another patient. The committee recognised that the ERG took this into account in its exploratory analyses. The committee concluded that wastage should be included.

- The committee discussed administration costs related to 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. The committee recognised that the ERG took this into account in its exploratory analyses. The committee concluded that administration costs should be included.
- The committee discussed the monitoring costs related to crizotinib and chemotherapy and noted that the company included the cost of computed tomography and chest X-ray in its model. It noted that these costs were the same for both crizotinib and chemotherapy. The committee heard from the clinical experts that people having crizotinib after disease progression might be monitored more frequently compared with those having chemotherapy. However, in the absence of evidence, it concluded that the company's approach was appropriate.

4.16 The committee considered the cost-effectiveness results for crizotinib compared with pemetrexed plus either cisplatin or carboplatin for people with advanced ALK-positive NSCLC and considered the following ICERs:

- Company base case: £47,620 per quality-adjusted life year (QALY) gained.
- ERG's preferred base-case analysis: £74,792 per QALY gained
  - assumes proportional hazards between treatment groups for progression-free survival and overall survival.
- ERG's stratified model: £89,754 per QALY gained
  - assumes proportional hazards between treatment groups
  - baseline prognostic factors estimated independently for each treatment group.

- ERG's independent parametric curves analysis: £130,364 per QALY gained
  - no longer assumes proportional hazards between treatment groups
  - baseline prognostic factors estimated independently for each treatment group
  - see section 4.11 for details of the parametric curves.

The committee recalled its preferred assumptions relating to time on treatment (see sections 4.12 and 4.13), utilities (see section 4.14), costs (see section 4.15), and overall and progression-free survival (see section 4.7). It concluded that the ERG's exploratory analysis using independent parametric curves for each treatment (with an estimated ICER of £130,364 per QALY gained) most closely reflected the committee's preferred assumptions. However, the committee acknowledged that this used some assumptions that the committee did not prefer (such as using an unadjusted time on treatment with crizotinib, a higher cost for ALK-mutation testing [(£4,500]), and discounting per cycle) and therefore appreciated that the analysis overestimated the ICER. On balance, the committee concluded that even after accounting for these assumptions, the most plausible ICER was unlikely to be at a level at which crizotinib could be considered a cost-effective use of NHS resources. It therefore concluded that it could not recommend crizotinib as a cost-effective use of NHS resources.

End of Life

4.17 The committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are sufficiently robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.18 The committee discussed whether crizotinib for untreated ALK-positive advanced NSCLC met the end-of-life criteria.

- It considered the life expectancy criteria. It noted that the company's model (using data from PROFILE 1014) showed that the life expectancy of people with ALK-positive NSCLC is a median 13.8 months and a mean 17.9 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 4.10), 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, it noted the evidence showing that crizotinib is likely to extend life by an additional 3 months compared with a platinum-based chemotherapy: PROFILE 1014 showed an extension to life of a median 7.9 months and a mean of 11.1 months with crizotinib compared with platinum-based chemotherapy. 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 3 months mean survival benefit.

The committee concluded that both the life expectancy and the extension-to-life criteria were met. The committee further concluded that because the most plausible ICER was substantially above £50,000 per QALY gained, it could not recommend crizotinib as a cost-effective use of NHS resources.

Innovation

4.19 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 patients value oral therapies. The committee further noted that the company did not incorporate the expected benefits of crizotinib to patient's 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.

4.20 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 the technology 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		
Crizotinib is not recommended within its marketing authorisation, that is, for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults. The committee concluded that the ERG's exploratory analysis using independent parametric curves for each treatment most closely reflected the committee's preferred assumptions. The incremental cost-effectiveness ratio (ICER) was £130,364 per quality-adjusted life year (QALY) gained for crizotinib compared with pemetrexed plus either cisplatin or carboplatin. The committee acknowledged that the ERG's exploratory analysis used some assumptions that the committee did not prefer. It concluded that even after accounting for these assumptions, the most plausible ICER was unlikely to be at a level at which crizotinib could be considered a cost-effective use of NHS resources.		1.1, 4.16
Current practice		

Clinical need of patients, including the availability of alternative treatments	The committee noted that the prognosis for advanced NSCLC is poor, and that there is no cure and concluded that additional treatment options would be of value to people with ALK-positive NSCLC.	4.1
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard that crizotinib could potentially extend life and improve quality of life. It concluded that crizotinib is clinically effective and increases progression-free survival and very likely increases overall survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC. The committee recognised the size of the benefit for overall survival is uncertain because of relatively immature data and the high proportion of crossover of patients moving from chemotherapy to crizotinib. The committee concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of QALYs.	4.1, 4.6, 4.8, 4.19
What is the position of the treatment in the pathway of care for the condition?	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)'.	2.1

Evidence for clinical effectiveness		
Availability, nature and quality of evidence Relevance to general clinical practice in the NHS	The committee heard from the company and the clinical experts that the patient characteristics in PROFILE 1014 accurately reflect the patient population in England, and so the committee concluded that PROFILE 1014 was suitable for its decision-making.	4.5
Uncertainties generated by the evidence	The committee concluded that crizotinib is clinically effective and increases progression-free survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC. The committee recognised that the size of the benefit for overall survival is uncertain because of relatively immature data and the high proportion of crossover of patients moving from chemotherapy to crizotinib. On balance, the committee concluded that crizotinib very likely increases overall survival compared with pemetrexed plus either cisplatin or carboplatin in people with ALK-positive NSCLC.	4.6, 4.8

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	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.	4.3
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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 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 crossover was accounted for using the 2-stage method. It noted that applying different methods to account for crossover did not vary the hazard ratio substantially.	4.6, 4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The committee noted that the model was consistent with the approaches used for other appraisals in NSCLC. However, the ERG had concerns with several aspects of the company's model.	4.9

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee considered the assumptions relating to time on treatment, utilities, costs, and overall and progression-free survival. It concluded that the ERG's exploratory analysis using independent parametric curves for each treatment most closely reflected the committee's preferred assumptions.	4.9, 4.11 to 4.16
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The committee noted that the company applied a lower utility for platinum-based chemotherapy than crizotinib for the progression-free health state and that this may underestimate the utility associated with platinum-based chemotherapy. The committee also noted that people who finish chemotherapy have fewer adverse events and a better quality of life than people taking chemotherapy. It noted that the utility value when a patient's disease progresses and they continue crizotinib was an average the utility for first-line treatment with crizotinib (without before disease progression) and the utility for second-line treatment with docetaxel (after disease progression).It also noted that the company applied a 'transition utility' when a person moves to a new health state. The committee concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of QALYs.	4.14, 4.19

Are there specific groups of people for whom the technology is particularly cost effective?	The committee heard that the ALK-positive mutation is relatively rare in people with squamous advanced NSCLC (0.1%) but common people with non-squamous advanced NSCLC.	4.2
What are the key drivers of cost effectiveness?	The committee was aware that the time on treatment and the approach to second-line treatment affects the ICER.	4.12, 4.13
Most likely cost-effectiveness estimate (given as an ICER)	The committee concluded that the ERG's exploratory analysis using independent parametric curves for each treatment (with an estimated ICER of £130,364 per QALY gained), most closely reflected the committee's preferred assumptions. However, the committee acknowledged that this used some assumptions that the committee did not prefer and therefore appreciated that the analysis overestimated the ICER. On balance, the committee concluded that even after accounting for these assumptions, the most plausible ICER was unlikely to be at a level at which crizotinib could be considered a cost-effective use of NHS resources.	4.16
Additional factors taken into account		

Patient access schemes (PPRS)	The committee concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of crizotinib.	4.20
End-of-life considerations	The committee concluded that both the life expectancy and the extension to life criteria were met.	4.17, 4.18
Equalities considerations and social value judgements	The following potential equality issues were identified during the scoping process: • 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. 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, and so were not considered equality issues.	-

5 Recommendations for research

5.1 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.

6 Proposed date for review of guidance

6.1 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.

Amanda Adler
Chair, appraisal committee
May 2016

7 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

Raisa Sidhu
Technical Adviser

Jeremy Powell
Project Manager

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