NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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.

Contents

This guidance replaces TA296.

1 Recommendations

1.1 Crizotinib is recommended, within its marketing authorisation, as an option for previously treated 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 Information about crizotinib

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

Marketing authorisation

2.2 Crizotinib has a marketing authorisation in the UK which includes 'adults with previously treated ALK-positive advanced non-small-cell lung cancer'.

Adverse reactions

2.3 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

2.4 The recommended dosage of crizotinib is 250 mg twice daily.

Price

2.5 The list price of crizotinib is £4,689 for 60 capsules (excluding VAT; BNF online, accessed October 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.

3 Committee discussion

Evidence

3.1 The appraisal committee (section 6) considered evidence submitted by Pfizer and a review of this submission by the evidence review group. This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. It focused on cost-effectiveness analyses using a revised patient access scheme, which provides a simple discount to the list price of crizotinib. The level of the discount is commercial in confidence.

3.2 See the committee papers for full details of the Cancer Drugs Fund reconsideration evidence and the history for full details of the evidence used for NICE's original technology appraisal guidance on crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene.

Discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of crizotinib, having considered evidence on the nature of non-small-cell lung cancer 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.

Clinical effectiveness (NICE technology appraisal guidance 296)

3.3 The committee heard from clinical experts and patient experts that there are limited treatment options for people with non-small-cell lung cancer whose disease has progressed after chemotherapy. It heard from the patient experts and clinical experts that non-small-cell lung cancer associated with an anaplastic

lymphoma kinase (ALK) fusion gene is an uncommon subtype of non-small-cell lung cancer and noted the views of the patient experts and clinical experts on the severity of the disease. The committee also heard from the clinical experts and patient experts that people with ALK-positive non-small-cell lung cancer would particularly value the availability of an effective targeted therapy and the convenience of an oral formulation; neither of these features apply to docetaxel. It also heard from the clinical experts that most patients would tolerate the side effects associated with crizotinib. The committee concluded that crizotinib offers potential benefits to people with ALK-positive non-small-cell lung cancer.

3.4 The committee discussed the decision problem as presented in the company's submission. It noted that this was the same as the scope for the appraisal, except that the scope listed erlotinib as a comparator, but the company had not included a comparison of crizotinib and erlotinib in the submission. The committee understood that erlotinib is a treatment that targets the activated epidermal growth factor receptor (EGFR) gene mutation in non-small-cell lung cancer and that it is very rare for people with non-small-cell lung cancer to have both the EGFR mutation and ALK fusion gene. It therefore accepted the company's position that an EGFR-targeted medicine would not be expected to be standard of care in clinical practice for patients with ALK-positive disease. The committee was aware of a comment received during consultation that if crizotinib were not available, ALK testing would not be carried out and patients would be likely to receive erlotinib as second-line treatment in preference to docetaxel. However, the committee did not consider this to be a reason for insisting on a comparison between crizotinib and erlotinib, given that the decision problem, as defined in the NICE scope, was to appraise crizotinib in a population of patients with ALK-positive disease. Therefore, the committee agreed with the company's position that erlotinib should not be considered as a comparator for crizotinib for previously treated ALK-positive non-small-cell lung cancer. It also noted that pemetrexed was not in the scope and was not a valid comparator as a second-line treatment because patients are likely to have pemetrexed before being considered for crizotinib. The committee was also aware that pemetrexed is not recommended by NICE as a second-line treatment. It concluded that docetaxel and best supportive care are the appropriate comparators for crizotinib.

3.5 The committee discussed the characteristics of the population in the PROFILE 1007 trial. It noted that most of the trial population had been diagnosed

with adenocarcinoma, had a good performance status, was relatively young and had never smoked. The committee considered that these characteristics generally indicate better prognosis and therefore discussed whether the trial population represented people with ALK-positive non-small-cell lung cancer in clinical practice. It heard from the clinical experts that the modest benefits of docetaxel in PROFILE 1007 were consistent with what would be expected in clinical practice. The committee noted the lack of evidence available either to determine the survival of patients with ALK-positive disease who had not received treatment with crizotinib or to assess the separate impact on survival of the features of non-small-cell lung cancer that accompany ALK-positive disease (young age, mainly women, nearly always adenocarcinoma, and a high proportion of people who have never smoked). Although it questioned whether such patients might have a better prognosis than patients with ALK-negative disease because of these favourable prognostic factors, the committee accepted that the PROFILE 1007 population was likely to be similar to people considered for treatment with crizotinib in UK clinical practice.

3.6 The committee considered treatment duration with crizotinib. It noted that a large proportion of patients in PROFILE 1007 continued to receive crizotinib treatment after radiographically determined disease progression. It noted that the summary of product characteristics states that 'prolongation of treatment after objective disease progression in selected patients may be considered on an individual basis, but no additional benefit has been demonstrated'. The committee discussed whether treatment would be discontinued on radiographic disease progression in clinical practice. It heard from the clinical experts that if a tumour has progressed, it would indicate reduced sensitivity to treatment and there would be a need to switch to another therapy. However, at present there is no standard third-line therapy. Without further treatment options, the committee understood that symptomatic progression, rather than radiographic progression, is likely to be the trigger for treatment change or discontinuation. The committee was informed of an abstract presented at the American Society of Clinical Oncology reporting that 53% of patients in PROFILE 1001 and PROFILE 1005 received crizotinib after disease progression for at least 2 weeks (range 2 to 84 weeks, median 10 weeks). The committee was persuaded by the evidence from PROFILE 1007 and the American Society of Clinical Oncology abstract that treatment would most likely continue until symptomatic progression. It did not find any reason from the evidence provided by the clinical experts to suggest

that treatment would routinely stop at radiographic progression. The committee therefore concluded that the treatment protocol of PROFILE 1007, in which patients could continue treatment after radiographic progression, reflected the likely treatment duration for crizotinib in UK clinical practice.

3.7 The committee discussed the evidence for the clinical efficacy of crizotinib. It noted the median progression-free survival gains of 4.7 and 5.1 months with crizotinib compared with chemotherapy and docetaxel respectively from PROFILE 1007, and considered that this represented a noteworthy extension to progression-free survival in advanced non-small-cell lung cancer. It noted the objective response rate of around 65% and considered this to be a very high response rate for a second-line non-small-cell lung cancer treatment. The committee went on to discuss the overall survival estimates from PROFILE 1007. It noted that the results did not identify a statistically significant difference in overall survival between crizotinib and chemotherapy. However, the committee acknowledged that this was based on relatively immature data and subject to a high rate of crossover from chemotherapy to crizotinib. It heard from the company that more mature and therefore more reliable overall survival data would be available for PROFILE 1007. However, it noted that this would not be within the timeframe of this appraisal. The committee therefore considered the results of the company's crossover analyses in which the estimate of overall survival gain with crizotinib compared with chemotherapy ranged from 5.8 months to 21.7 months. The committee considered that the range of results from the crossover analyses suggested a high degree of uncertainty around the estimate of overall survival gain. It heard from the clinical experts that the estimated gain in overall survival with treatment might be expected to be 8 or 9 months. The committee noted that this was approximately midway between the results of the rank-preserving structural failure time (RPSFT) method and the company's chosen method for crossover analysis (inverse probability of treatment and censoring weighted 5; IPTCW5) as discussed in section 3.10. It therefore accepted that treatment with crizotinib would result in an overall survival gain compared with docetaxel but the exact size of the gain was uncertain because of the immaturity of the PROFILE 1007 data and the impact of crossover in the study. Overall, the committee concluded that, based on the evidence for progression-free survival and response rate, crizotinib is a clinically efficacious treatment for ALK-positive advanced non-small-cell lung cancer compared with chemotherapy.

3.8 The committee noted the number of adverse events associated with crizotinib treatment from the PROFILE studies. However, it was advised by the patient experts and clinical experts that crizotinib would be tolerated by most people with non-small-cell lung cancer. The committee concluded that crizotinib is associated with some adverse reactions but these would be tolerable for most patients and generally easily managed.

3.9 The committee discussed the results of the company's mixed treatment comparison in which crizotinib was compared with best supportive care. It noted the evidence review group's (ERG's) assertion that there were substantial underlying differences in the populations of patients with non-small-cell lung cancer in the included studies. The committee was aware of the company's comment that the median progression-free survival values in the chemotherapy arms of the different trials included in the network were consistent. However, the committee remained concerned about the relevance of the trial populations to a population of people with ALK-positive non-small-cell lung cancer who would receive best supportive care. This was because the trials in the mixed treatment comparison included patients who were well enough for chemotherapy, and therefore their prognostic factors would not represent those of patients receiving best supportive care. In addition, only PROFILE 1007 was carried out in patients with ALK-positive non-small-cell lung cancer; the other trials were in unselected disease. Therefore, the committee concluded that the results from the mixed treatment comparison were subject to uncertainty given the significant heterogeneity in the included studies. It further concluded that the resulting hazard ratio for overall survival for crizotinib compared with best supportive care should be viewed with considerable caution and that as a result, the relative effect of crizotinib compared with best supportive care remained an area of substantial uncertainty.

3.10 The committee discussed the company's preferred approach to crossover (IPTCW5) in more detail, noting that this had been used to obtain the overall survival hazard ratio for docetaxel. The committee noted the ERG's main concern that the different approaches to crossover had resulted in survival gain for crizotinib varying between 5.8 months (using the RPSFT method) and 21.7 months (using the real world data method). The ERG reiterated its concern at the meeting that this variation suggested a high degree of uncertainty associated with all the results from the various crossover analyses. The committee discussed

the company's justification for preferring one method, noting that, of the different statistical methods, IPTCW5 gave the most favourable overall survival benefit for crizotinib. It heard from the company that the decision was based on their view that the chemotherapy overall survival which resulted from using the hazard ratio from the IPTCW5 method applied to the extrapolated overall survival data for crizotinib, most closely reflected the overall survival from other trials of docetaxel and pemetrexed. Therefore, the company asserted that the IPTCW5 method was the most appropriate based on the face validity of the results. However, the committee was concerned that the other trials of second-line treatment with pemetrexed or docetaxel were in potentially very different populations of patients. The committee noted that the company's chosen method resulted in a modelled progression-free survival gain of 5.7 months, and an overall survival gain of 12.3 months for crizotinib and that this large gain in overall survival compared with progression-free survival was not supported by any evidence. The committee also considered the application of the company's method of adjustment for crossover, questioning why the type of chemotherapy had not been included as a covariant, given that pemetrexed had been given as the first choice treatment in the chemotherapy group. It heard from the company that this had not been considered. The committee considered that this could lead to flaws in the analysis. It did not accept the company's assertion of face validity to justify using one particular crossover adjustment method because it remained concerned that the choice of data and parametric extrapolation method also influenced the outcome. The committee concluded that the company's application of the chosen method for adjusting for crossover (IPTCW5) produced an overly optimistic overall survival benefit for crizotinib, for which there was no supporting evidence.

3.11 The committee further discussed the most likely projection of the overall survival benefit for crizotinib compared with docetaxel. It discussed comments by the company that it is biologically plausible that the overall survival to progression-free survival ratio would be higher with targeted therapy than with chemotherapy. The clinical experts confirmed that in some patients there was a dramatic response to treatment and that targeted therapies such as crizotinib could reduce tumour size to below that at the beginning of therapy. Therefore, at progression, the size of the tumour could still be smaller than at the beginning of therapy and as a result, benefit would continue into the progressed disease stage. The committee was persuaded by this evidence. It went on to discuss the

outcome from the RPSFT method, in which the overall survival benefit for crizotinib was 5.8 months. In view of the evidence from the clinical experts relating to the expected gain in survival with crizotinib (see section 3.7), the committee concluded that the RPSFT method might underestimate overall survival. The committee recognised the limitations of the crossover adjustment methods, particularly when applied to a small trial with crossover in both directions and with immature data. It considered that the IPTCW2 method, which resulted in an overall survival benefit of 7.1 months, may be a reasonable assumption given the lack of robust data. This method produced a result between the 2 extremes of the IPTCW5 and RPSFT methods, broadly in agreement with clinical opinion (see section 3.7). The committee concluded that the exact gain in overall survival from treatment with crizotinib was very uncertain and an exact value could not be reliably established from the available data; however for the purposes of the economic model the IPTCW2 was the most reasonable method on which to base its decision.

Cost effectiveness (NICE technology appraisal guidance 296)

3.12 The committee discussed the utility estimates in the model. It welcomed the collection of EQ-5D data in PROFILE 1007. The committee noted that the baseline utility estimates were different between the groups at entry into the study, and specifically that the mean baseline utility value for crizotinib was higher than for chemotherapy. The company confirmed that this had not been adjusted for in the model. The committee also noted the difference in utility values between crizotinib and chemotherapy for the progressed disease health state and observed that these post-progression utilities had been measured at the outset of the progressed disease state and continued at that value until death. It first discussed whether a treatment benefit with crizotinib might be expected to continue after treatment was stopped. The committee heard from the clinical experts that patients with progressed disease would continue to have some additional health-related quality-of-life benefit for some time after treatment was withdrawn compared with those on chemotherapy, but that this would deteriorate over time. It accepted that some utility benefit might be expected from crizotinib discontinued at disease progression, though there are no data to suggest how great a benefit this might be or for how long it would persist. The committee was also aware that there might be a utility benefit of continuing

crizotinib, but there were no data to show whether such continued treatment benefits patients or for how long. The committee considered the company's revised model, incorporating a step change in post-progression utilities. It recognised that this was a more conservative assumption than in the original model because the initial difference in post-progression utility reduced rather than persisted over time. However, the company did not justify the approach used to model a reduction in post-progression utilities. The ERG commented that, without any further evidence, the size and duration of post-progression benefit remained uncertain. In addition the approach used by the company to characterise the reduction is likely to overestimate the quality-adjusted life year (QALY) benefits because of the impact of discounting and of differences in the baseline values. The committee concluded that the company's revised post-progression utilities represented a partial solution to the estimation of these values but that the utility estimates in the post-progression health state remained uncertain because of the lack of utility data in the post-progression period.

3.13 The committee discussed the cost estimates in the company's economic model.

- The committee noted that CT scans were performed every 6 weeks in PROFILE 1007. The committee heard from the clinical experts that on average, patients would initially have a CT scan every 2 months and this would probably be reduced to every 3 months at a later stage if the patient was clearly benefitting from treatment. The committee considered that the costs of CT scans in the original model had been underestimated. It noted that in the revised base-case model the company updated the costs to assume a CT scan every 3 months for all patients in the progression-free health state.
- The committee noted that the costs of docetaxel in the model were based on its use in the post hoc subgroup in PROFILE 1007 (presented as confidential in the company's submission and not reported here). Based on the clinical experts' opinion, the committee thought it very unlikely that in England and Wales, patients would receive more than 6 cycles of docetaxel. The committee noted that in the revised base-case model the company capped the costs of docetaxel at 6 cycles.
- The committee considered the administration costs, noting that the model assumed no cost to the NHS associated with administration of crizotinib. It

agreed that there would be some administrative costs to the NHS associated with treatment with crizotinib and that the SB11Z healthcare resource group code for oral chemotherapy of £126 should have been included for each crizotinib treatment cycle in the progression-free state. The committee considered the company's view that no administration costs would be incurred because this treatment is taken at home and that this administration cost had not been included in other appraisals involving oral chemotherapies. The committee was also aware of current inconsistencies in the healthcare resource group codes highlighted by the ERG, who pointed out that the administration cost for docetaxel was £102. However, the committee agreed that an administration cost was appropriate for crizotinib and since SB11Z was the only available healthcare resource group code for oral chemotherapy cost it accepted this value as appropriate. The committee recognised that this cost is not a key driver of the cost effectiveness of crizotinib.

- Finally, the committee considered the acquisition cost of docetaxel, noting the substantial discrepancy between the published price in the BNF and the range of prices paid by the NHS across the country as reported in the electronic Market Information Tool (eMIT) from the NHS Commercial Medicines Unit. It noted the company's view that the eMIT costs did not meet NICE's criteria for inclusion in the base case. However, the committee agreed that the eMIT costs were appropriate because the NICE methods guide states that a reduced price should be used in the base case when nationally available price reductions exist.

  Overall, the committee agreed that the costs in the revised base-case model were likely to be underestimated in favour of crizotinib because of the use of the BNF price for docetaxel and the exclusion of crizotinib administration costs. The committee considered the impact of these 2 parameter inputs and noted that the ERG had carried out exploratory analyses. These analyses demonstrated that the use of the eMIT price for docetaxel would increase the incremental cost-effectiveness ratio (ICER) by about £5,000 per QALY gained and including the £126 crizotinib administration cost would increase the ICER by about £2,200 per QALY gained. The committee concluded that the impact of these factors would increase the ICER in the company's revised base-case model.

3.14 The committee further considered the cost-effectiveness estimates of crizotinib compared with docetaxel. It expressed a preference to base its decision on probabilistic estimates of the ICER whenever possible. In addition, the committee decided that the most relevant ICER would assume the same treatment duration for crizotinib as in PROFILE 1007 (see section 3.6). The committee considered the company's revised base-case probabilistic estimate of the ICER of £70,000 per QALY gained. It was aware that this was based on the company's preferred method for adjusting for crossover (IPTCW5). Based on its earlier discussions about the approach to crossover (see sections 4.8 and 4.9) the committee then considered the probabilistic estimates of the ICER using the IPTCW2 and RPSFT methods, available from the ERG's exploratory analyses (£96,000 and £111,800 per QALY gained respectively). The committee considered that, given the limited evidence, it was reasonable to assume that the ICER would be closer to £96,000 per QALY gained because the overall survival gain obtained using IPTCW2 was broadly in agreement with clinical opinion. However, the committee noted that these estimates did not use the eMIT price for docetaxel or an administration cost of £126 for crizotinib (see section 3.13). The committee was aware that when the ERG had carried out these 2 amendments to the company's revised base case individually, the combined result was to increase the ICER by approximately £7,000 per QALY gained. The committee therefore concluded that the ICER on which to base a decision for crizotinib compared with docetaxel would be more than £100,000 per QALY gained.

3.15 The committee further considered the cost-effectiveness estimates of crizotinib compared with best supportive care. In line with its consideration of the ICER for the comparison with docetaxel, the committee expressed a preference for a probabilistic estimate of the ICER and one that assumed the same treatment duration for crizotinib as in PROFILE 1007. The committee considered the company's revised base-case probabilistic estimate of the ICER of £50,200 per QALY gained. It was aware that this was based on the company's preferred approach to crossover (IPTCW5). Having previously concluded that the IPTCW5 method would be overly optimistic towards crizotinib, the committee reasoned that this ICER would be likely to be underestimated. In addition, the committee had reservations that this ICER was based on a hazard ratio from a mixed treatment comparison in which the patients in the included trials had been eligible for chemotherapy (see section 3.9). The committee considered that this introduced substantial uncertainty around any estimates of the ICER. The

committee therefore concluded that the ICER on which to base a decision for crizotinib compared with best supportive care would be more than £50,200 per QALY gained. However, the committee further concluded that this ICER was associated with substantial uncertainty, which it was not possible to quantify because of the lack of a robust mixed treatment comparison between crizotinib and best supportive care.

Innovation (NICE technology appraisal guidance 296)

3.16 The committee considered whether crizotinib offers benefits because of its innovative nature, as the first targeted drug for ALK-positive non-small-cell lung cancer. It heard from the company that crizotinib is innovative because the ability to target patients who are most likely to benefit can be seen as a step change in the management of non-small-cell lung cancer. It further heard from the clinical experts and patient experts that crizotinib delivers high response rates and a substantial benefit in at least progression-free survival in lung cancer and is also well tolerated, particularly when compared with current standard cytotoxic therapy for non-small-cell lung cancer. The committee agreed with these observations but considered that the potential extension to life and the convenience of an oral treatment compared with intravenous second-line therapy would already be captured in the QALY calculation. The committee was not made aware of any significant and substantial impact on health-related benefits which are not already captured in the QALY calculation, and therefore concluded that no additional value judgements needed to be made for innovation.

End-of-life considerations (NICE technology appraisal guidance 296)

3.17 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 and that are licensed for indications that affect small numbers of people with incurable illnesses. 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.
- The treatment is licensed or otherwise indicated for small patient populations.

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

3.18 The committee considered the life expectancy of patients with advanced non-small-cell lung cancer associated with an ALK fusion gene. It noted the results from the company's statistical crossover analyses, which gave a range of estimates between 20 and 27 months for the chemotherapy group. Based on its discussions around the crossover methods explored by the company (see section 3.10), it considered that there was some uncertainty around these estimates. It further acknowledged that there is a lack of overall survival data for patients with ALK-positive non-small-cell lung cancer who have not received treatment with crizotinib. However, on balance, the committee considered that the life expectancy of patients with ALK-positive non-small-cell lung cancer after first-line chemotherapy would be less than 24 months. It then discussed the criterion relating to extension to life. The committee noted that the median progression-free survival results from PROFILE 1007 indicated an extension to life of 4.7 months for crizotinib compared with chemotherapy, and that this was not affected by crossover. It agreed that crizotinib would extend life by an additional 3 months. The committee then considered the size of the population, noting the company's estimate of around 500 patients. It accepted that crizotinib is licensed for a small population. The committee accepted that, on the basis of these 3 criteria, the supplementary advice from NICE for life-extending treatments could be considered for crizotinib, even though there was considerable uncertainty in the exact overall survival gain, and therefore in the resulting ICER.

3.19 The committee considered its recommendations to the NHS. Based on the most plausible ICERs (see sections 4.12 and 4.13), the committee concluded that even

allowing for the supplementary advice to the committee for life-extending treatments, the size of additional weight that would need to be assigned to the QALY gains would be too great for crizotinib to be considered a cost-effective use of NHS resources. Also, the committee was not satisfied that the assumptions used in the economic modelling for the comparison with best supportive care, in particular the hazard ratio from the mixed treatment comparison, were plausible and robust. The committee concluded that treatment with crizotinib for previously treated ALK-positive advanced non-small-cell lung cancer should not be recommended for use within the NHS.

Equality issues (NICE technology appraisal guidance 296)

3.20 The committee considered whether its recommendations were associated with any potential issues related to equality. The committee noted the potential equality issue raised during scoping that testing could be restricted to patients with a diagnosis of adenocarcinoma. The committee heard from the clinical experts that there is currently no established ALK testing strategy in UK clinical practice. The committee then considered the potential equality issues raised by clinical experts during consultation. The clinical experts were concerned that, if this treatment is not recommended, patients in the NHS will not have access to a targeted therapy that is routinely available elsewhere and so survival rates in England and Wales will continue to lag behind other countries. Lung cancer patients are also a particularly disadvantaged group, with a high proportion from more socially disadvantaged groups. The committee discussed whether these potential equality issues affected NICE's duties under the equality legislation and concluded that its recommendations do not have a particular impact on any of the groups whose interests are protected by the legislation and that there was no need to alter or add to its recommendations.

Cancer Drugs Fund reconsideration

3.21 This appraisal was a Cancer Drugs Fund reconsideration of the published NICE technology appraisal guidance on crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. Crizotinib has been available through the Cancer Drugs Fund because it was not

recommended in the original guidance. In its revised submission updating its cost-effectiveness analysis, the company:

- re-analysed data for overall survival using more mature data from PROFILE 1007
- included a revised patient access scheme (a simple discount to the list price as in NICE's technology appraisal guidance on crizotinib for untreated anaplastic lymphoma kinase-positive non-small-cell lung cancer)
- applied the same values for post-regression utility for crizotinib and docetaxel
- did not present new analyses comparing crizotinib with best supportive care
- updated all unit costs data to 2016 values (including the eMIT price for docetaxel)
- assumed in its base case that clinicians would not continue to offer crizotinib after disease progression, and
- presented scenario analyses to address areas of uncertainty.

Clinical management

3.22 The committee recognised that the treatment pathway for ALK-positive non-small-cell lung cancer has changed since the publication of NICE's technology appraisal guidance on crizotinib (NICE technology appraisal guidance 296). New treatments recommended by NICE are now available. For example, crizotinib is recommended as a treatment option for untreated (that is, first-line treatment) anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in adults (see NICE's technology appraisal guidance on crizotinib for untreated anaplastic lymphoma kinase-positive non-small-cell lung cancer) and ceritinib is recommended for treating advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer in adults who have previously had crizotinib (see NICE's technology appraisal guidance on ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer). Before crizotinib was recommended as first-line treatment, it was available as a second- or subsequent-line treatment, after platinum-based combination chemotherapy,

through the Cancer Drugs Fund. The committee heard from clinical experts that now that crizotinib is recommended for untreated disease, significantly fewer patients would have crizotinib as a second-line treatment. Also, the committee heard from the clinical experts that they would like to offer crizotinib as an option to patients whose ALK-positive tumour status became known after they had received first-line chemotherapy. The committee concluded that the changes in the treatment pathway resulted in a smaller population for crizotinib as second-line treatment.

New analyses

3.23 The company submitted a new model which included all the committee's preferred assumptions, except treatment with crizotinib extending beyond disease progression (the company included treatment after progression only as a scenario analysis). The company also included a revised patient access scheme. The model compared crizotinib with docetaxel only, but used evidence from the combined docetaxel and pemetrexed arm of PROFILE 1007. The resulting ICERs cannot be reported here because they are commercial in confidence. The committee discussed the lack of analyses comparing crizotinib with best supportive care in the company submission. The company proposed that if crizotinib were cost effective compared with docetaxel, it would also be cost effective compared with best supportive care. The ERG commented that although some uncertainty existed, the company's statement appeared reasonable. The committee concluded that if crizotinib were cost effective compared with docetaxel, it would also be cost effective compared with best supportive care.

3.24 The committee discussed the company's approach to crossover using the more mature overall survival data from PROFILE 1007. The mature data were based on median follow-up of 51 and 53 months, by which time 67% and 73% of patients had died in the crizotinib and chemotherapy arms respectively. This compared with the company's original submission based on a median follow-up of 12.2 months in each arm, when 28% and 27% of patients had died in the crizotinib and chemotherapy arms respectively. The committee noted that in the mature dataset there was a higher proportion of patients who switched to other treatments when their disease progressed. In the chemotherapy arm (n=174),

87% and 64% of patients in the mature and the previous dataset, respectively, switched from chemotherapy to crizotinib or other drugs. The committee was aware that the company had revisited the most appropriate method for modelling overall survival when using the mature data. The company argued that because of the high degree of crossover, the small number of patients remaining on chemotherapy in the control arm, and the variation in post-progression therapies, the IPTCW method was no longer appropriate. The company therefore adjusted the survival data using the RPSFT method. Unlike IPTCW, the RPSFT method relies on the assumption of a 'common treatment effect', meaning that a therapy is as effective when given later (for example, at progression) as it would be earlier (before progression). The committee asked the company whether it had tested this assumption. The company was unable to satisfactorily answer the committee. The ERG agreed that the RPSFT method was a better choice than the IPTCW approach, but it noted that the company had not explored other methods, for example the iterative parameter estimation and 2-stage methods. Noting that in the analyses the hazard ratio declined from 0.79 (adjusted for crossover, less mature data) to 0.38 (adjusted for crossover, more mature data), the ERG highlighted that the more mature data suggested that crizotinib (compared with docetaxel) appeared to be much more effective than in the company's original submission. The committee agreed that irrespective of the method of crossover adjustment used, and despite the longer follow-up, the size of the overall survival estimate associated with crizotinib is uncertain.

3.25 The committee considered the ERG's scenario analyses, which used 2 different estimates of overall survival hazard ratio:

- In the first scenario, the ERG used an overall survival hazard ratio of 0.49, which the ERG chose to be the same value as the progression-free survival hazard ratio reported in PROFILE 1007. Progression-free survival is normally not affected by crossover, because crossover usually happens after progression. Also, according to the ERG, the hazard ratio for overall survival is normally less strongly associated with a treatment than is progression-free survival.
- The second scenario used an overall survival hazard ratio of 0.60, which reflected the hazard ratio for overall survival reported in the NICE technology appraisal guidance on crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer. The ERG assumed that in this

scenario crizotinib was equally effective in delaying death in people with either untreated or previously treated disease.

The committee noted that both scenarios increased the ICERs. Further scenario analyses presented by both the company and the ERG assumed that crizotinib continues to be given beyond disease progression. These analyses again increased the ICERs. Because of the uncertainty around the estimate of overall survival, the committee agreed, the ERG's scenario analyses rather than the company's base-case model are more appropriate for decision making. The committee preferred the ERG's first scenario (with an overall survival hazard ratio of 0.49) because it used PROFILE 1007 data and the hazard ratio for progression-free survival was not confounded by crossover. The committee heard from the clinical experts that because ceritinib is now recommended third line after crizotinib, clinicians would be unlikely to offer continued treatment with crizotinib after disease progression. However, the committee was aware that the evidence from PROFILE 1007 included treatment with crizotinib after progression, and therefore the estimates of effectiveness (as well as the costs) reflect this. The committee considered that if a shorter duration of treatment were assumed than seen in the trial, then it would also be reasonable to assume lower effectiveness. Therefore, for consistency between the effectiveness and the cost estimates, the committee chose to consider analyses which included crizotinib treatment after progression, as in the original appraisal. The committee concluded that its preferred base case was the ERG's scenario analysis including an overall survival hazard ratio of 0.49 and allowing for crizotinib treatment after progression.

3.26 The committee considered the most plausible ICER for crizotinib compared with docetaxel for people with previously treated ALK-positive advanced non-small-cell lung cancer. It noted that the updated analyses submitted by the company included the costs of administering crizotinib, which were estimated using the costs for administering chemotherapy. The committee was aware that the company did not think that it was appropriate to include these costs and that it considered the resulting ICER to be conservative, that is, higher than it would otherwise be. The committee also heard from the ERG that the company used what the ERG considered to be a conservative health utility assumption after progression on crizotinib (including the treatment after progression scenario).

The committee concluded that the most plausible ICER for crizotinib compared with docetaxel would be less than £50,000 per QALY gained including the revised patient access scheme, assuming a hazard ratio of 0.49 for overall survival and allowing for crizotinib treatment after progression. The committee had previously concluded that if crizotinib were cost effective compared with docetaxel, it was also likely to be cost effective compared with best supportive care.

End-of-life considerations

3.27 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. It noted the committee's previous conclusion that the end-of-life criteria had been met (see section 3.18). The criterion that the treatment is licensed or otherwise indicated for small patient populations is no longer relevant. The committee did not see new evidence to change its original decision and considered the end-of-life criteria to be fulfilled.

Conclusion

3.28 Taking into account the new cost-effectiveness analyses, which apply to a population that is likely to be getting smaller, including the revised patient access scheme, and considering the end-of-life criteria, the committee recommended crizotinib as a cost-effective use of NHS resources for people with previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer.

Summary of appraisal committee's key conclusions

Key conclusion (Cancer Drugs Fund reconsideration of NICE technology appraisal guidance 296)

- Section 1.1: Crizotinib is recommended, within its marketing authorisation, as an option for previously treated 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.

- Section 4.19 and 4.26: The committee understood that in the company's Cancer Drugs Fund (CDF) reconsideration submission, it provided an updated cost-effectiveness analysis. The committee concluded that allowing for the supplementary advice to the committee for life-extending treatments, crizotinib was a cost-effective use of NHS resources.

Current practice (NICE technology appraisal guidance 296)

Clinical need of patients, including the availability of alternative treatments

- Section 4.1: The committee heard from clinical experts and patient experts that there are limited treatment options for people with non-small-cell lung cancer whose disease has failed chemotherapy.
- The committee also heard from the clinical experts and patient experts that people with anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer would particularly value the availability of an effective targeted therapy and the convenience of an oral formulation; neither of these features apply to docetaxel.

The technology (NICE technology appraisal guidance 296)

How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?

- Section 4.14: The committee considered that the potential extension to life and the convenience of an oral treatment compared with intravenous second-line therapy would already be captured in the quality-adjusted life year (QALY) calculation. The committee was not made aware of any significant and substantial impact on health-related benefits which are not already captured in the QALY calculation, and therefore concluded that no additional value judgements needed to be made for innovation.

What is the position of the treatment in the pathway of care for the condition?

- Section 4.2: The committee concluded that docetaxel and best supportive care are the appropriate comparators for crizotinib.

Adverse reactions

- Section 4.6: The committee noted the number of adverse reactions associated with crizotinib treatment from the PROFILE studies. The committee concluded that crizotinib is associated with some adverse reactions but these would be tolerable for most patients and generally easily managed.

Evidence for clinical effectiveness (NICE technology appraisal guidance 296)

Availability, nature and quality of evidence

- Section 3.2: The main evidence came from 1 multicentre, randomised phase III efficacy and safety study in patients with previously treated ALK-positive non-small-cell lung cancer (PROFILE 1007).

Relevance to general clinical practice in the NHS

- Section 4.3: The committee accepted that the PROFILE 1007 population was likely to be similar to people considered for treatment with crizotinib in UK clinical practice.
- Section 4.4: The committee concluded that the treatment protocol of PROFILE 1007, in which patients could continue treatment after radiographic progression, reflected the likely treatment duration for crizotinib in UK clinical practice.

Uncertainties generated by the evidence

- Sections 4.5, 4.8 and 4.9: The committee acknowledged that the overall survival data from the crizotinib studies were relatively immature and, for PROFILE 1007, subject to a high rate of crossover from chemotherapy to crizotinib. The committee heard from the company that more mature and therefore more reliable overall survival data would be available for PROFILE 1007. However, it noted that this would not be within the timeframe of this appraisal. The committee concluded that the exact gain in overall survival from treatment with crizotinib was very uncertain and an exact value could not be reliably established from the available data.

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?

- Subgroups of patients receiving treatment with crizotinib were not in the scope, or identified during the appraisal.

Estimate of the size of the clinical effectiveness including strength of supporting evidence

- Section 4.5: The committee noted the median gain in progression-free survival of 5.1 months with crizotinib compared with docetaxel from PROFILE 1007, and considered that this represented a noteworthy extension to progression-free survival in advanced non-small-cell lung cancer.
- The committee accepted that treatment with crizotinib would result in an overall survival gain compared with docetaxel but the exact size of the gain was uncertain because of the immaturity of the PROFILE 1007 data and the impact of crossover in the study.
- Overall, the committee concluded that, based on the evidence for progression-free survival and response rate, crizotinib is a clinically efficacious treatment for ALK-positive non-small-cell lung cancer compared with chemotherapy.

Evidence for cost effectiveness (NICE technology appraisal guidance 296)

Availability and nature of evidence

- Section 3.2: The company developed a 3-state model, which it referred to as a semi-Markov area-under-the-curve analysis. The model used estimates of treatment effectiveness from PROFILE 1005, PROFILE 1007 and a mixed treatment comparison.

Uncertainties around and plausibility of assumptions and inputs in the economic model

- Section 4.8: The committee discussed the company's justification for preferring one crossover adjustment method, noting that, of the different statistical methods, inverse probability of treatment and censoring weighted 5 (IPTCW5) gave the most favourable overall survival benefit for crizotinib. The committee noted that the company's chosen

method resulted in a modelled progression-free survival gain of 5.7 months, and an overall survival gain of 12.3 months for crizotinib and that this large gain in overall survival compared with progression-free survival was not supported by any evidence. The committee concluded that the company's application of the chosen method for adjusting for crossover (IPTCW5) produced an overly optimistic overall survival benefit for crizotinib, for which there was no supporting evidence.

- Section 4.7: The committee concluded that the results from the mixed treatment comparison were subject to uncertainty given the significant heterogeneity in the included studies. It further concluded that the resulting hazard ratio for overall survival for crizotinib compared with best supportive care should be viewed with considerable caution and that as a result, the relative effect of crizotinib compared with best supportive care remained an area of substantial uncertainty.

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?

- Section 4.10: The committee discussed the utility estimates in the model. It noted that the baseline utility estimates were different between the groups at entry into the study, and specifically that the mean baseline utility value for crizotinib was higher than for chemotherapy. The company confirmed that this had not been adjusted for in the model.

- The committee also noted the difference in utility values for the progressed disease health state between crizotinib and chemotherapy and observed that these post-progression utilities had been measured at the outset of the progressed disease state and continued at that value until death. The committee accepted that some utility benefit might be expected from crizotinib discontinued at disease progression, though there are no data to suggest how great a benefit this might be or for how long it would persist. The committee concluded that the company's revised post-progression utilities represented a partial solution to the estimation of these values but that the utility estimates in the post-progression state remained uncertain because of the lack of data in the post-progression period.

What are the key drivers of cost effectiveness?

- Sections 4.9 to 4.13: The committee considered the most plausible cost-effectiveness estimates of crizotinib compared with docetaxel and best supportive care. The

committee agreed that the exact gain in overall survival from treatment with crizotinib was very uncertain and an exact value could not be reliably established from the available data; however for the purposes of the economic model the IPTCW2 was the most reasonable method on which to base its decision. This method produced a result between the 2 extremes of the IPTCW5 and rank-preserving structural failure time (RPSFT) methods, broadly in agreement with clinical opinion (see section 4.5). For the comparison with best supportive care, the committee concluded that the incremental cost-effectiveness ratio (ICER) was associated substantial uncertainty, which it was not possible to quantify because of the lack of a robust mixed treatment comparison between crizotinib and best supportive care.

Most likely cost-effectiveness estimate (given as an ICER) (NICE technology appraisal guidance 296)

- Sections 4.12 and 4.13: The committee concluded that the ICER on which to base a decision for crizotinib compared with docetaxel would be more than £100,000 per QALY gained.
- The committee concluded that the ICER on which to base a decision for crizotinib compared with best supportive care would be more than £50,200 per QALY gained. However, the committee further concluded that this ICER was associated with a substantial amount of uncertainty, which it was not possible to quantify because of the lack of a robust mixed treatment comparison between crizotinib and best supportive care.

Additional factors taken into account (NICE technology appraisal guidance 296)

Patient access schemes (PPRS)

- Section 2.5: The company has agreed a patient access scheme with the Department of Health. This involves a discount applied to the list price of crizotinib. 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.

End-of-life considerations

- Sections 4.16 and 4.17: The committee accepted that the supplementary advice from NICE for life-extending treatments could be considered for crizotinib compared with chemotherapy, even though there was considerable uncertainty in the exact overall survival gain, and therefore in the resulting ICER.

Equalities considerations and social value judgements

- Section 4.18: The committee concluded that its recommendations do not have a particular impact on any of the groups whose interests are protected by the legislation and that there was no need to alter or add to its recommendations.

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Current practice

- Section 4.20: The committee noted that the treatment pathway for ALK-positive non-small-cell lung cancer has changed since the original appraisal (NICE technology appraisal 296). New treatments recommended by NICE are now available.

Evidence for clinical effectiveness

- Section 4.22: The committee noted that more mature data were available in the CDF reconsideration submission.

Evidence for cost effectiveness

- Sections 4.19 and 4.21: The company submitted a new model which included all the committee's preferred assumptions, except treatment with crizotinib extending beyond disease progression. The committee noted that no analyses comparing crizotinib with best supportive care were presented in the CDF reconsideration submission.

- Sections 4.23 and 4.24: The committee concluded that the most plausible ICER for crizotinib compared with docetaxel would be less than £50,000 per QALY gained including the revised patient access scheme, assuming a hazard ratio of 0.49 for

overall survival and allowing for crizotinib treatment after progression.

Additional factors taken into account

- Section 4.19: The committee acknowledged that the CDF reconsideration submission included the patient access scheme as in NICE's technology appraisal guidance on crizotinib for untreated anaplastic lymphoma kinase-positive non-small-cell lung cancer.
- Section 4.25: The committee considered the end-of-life criteria to be fulfilled.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 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 previously treated 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.

4.4 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 pfizerNICEaccount@pfizer.com.

5 Appraisal committee members and NICE project team

Appraisal committee members

NICE technology appraisal 296

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Cancer Drugs Fund reconsideration of NICE technology appraisal 296

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the minutes of the appraisal committee meeting, which are posted on the NICE website.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology

analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

NICE technology appraisal 296

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