NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

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

1.2 People currently receiving crizotinib that is not recommended according to 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Crizotinib (Xalkori, Pfizer) is a selective small-molecule inhibitor of the anaplastic lymphoma kinase (ALK) receptor tyrosine kinase and its oncogenic variants (that is, ALK fusion events and selected ALK mutations). It has been granted a conditional UK marketing authorisation for treating 'adults with previously treated 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 treatment: visual impairment, diarrhoea, nausea, vomiting,
constipation, oedema, fatigue, decreased appetite, neutropenia and elevated aminotransferases. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The acquisition cost of crizotinib is £4689 for 1 pack of 60×200 mg (or 250 mg) capsules (30-day supply) (excluding VAT; ‘British national formulary’ [BNF] edition 64). The summary of product characteristics states that the recommended dose of crizotinib is 250 mg twice daily (500 mg daily) taken continuously. It further states that ‘Treatment should be continued until disease progression or unacceptable toxicity. Prolongation of treatment after objective disease progression in selected patients may be considered on an individual basis but no additional benefit has been demonstrated’. Assuming treatment until disease progression, the cost of a course of treatment would be £37,512 using the median progression-free survival in the study PROFILE 1007 as the number of cycles of treatment (that is, 7.7 months or 8 packs of capsules), or £46,890 using the number of treatment cycles calculated from the duration of progression-free survival in the manufacturer’s economic model (that is, 9.6 months or 10 packs of capsules). Using the median number of crizotinib treatment cycles started in PROFILE 1007 (that is, 10.5 months or 11 packs of capsules) the cost of a course of treatment would be £51,579.

Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of crizotinib 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. The manufacturer has agreed that the patient access scheme will
remain in place until any review of this NICE technology appraisal guidance is published.

3 The manufacturer’s submission

The Appraisal Committee (section 8) considered evidence submitted by the manufacturer of crizotinib and a review of this submission by the Evidence Review Group (ERG; section 9).

3.1 The manufacturer presented evidence on the clinical effectiveness of crizotinib used within the marketing authorisation and in line with the appraisal scope. The manufacturer explained that a comparison with erlotinib, which was a comparator in the scope, was not considered valid because erlotinib acts as an epidermal growth factor receptor (EGFR) inhibitor and EGFR mutation does not tend to occur with anaplastic lymphoma kinase (ALK) translocation. Therefore, the evidence provided in the submission considered comparisons of crizotinib with the 2 remaining comparators in the scope, namely docetaxel and best supportive care.

3.2 The main evidence came from 1 multicentre, randomised phase III efficacy and safety study in patients with advanced or metastatic previously treated ALK-positive non-small-cell lung cancer (PROFILE 1007). In this study, 347 patients were randomised on a 1:1 basis to receive either crizotinib 250 mg twice daily or chemotherapy (pemetrexed 500 mg/m² [58%]; or docetaxel 75 mg/m² [42%] if the patient had already received treatment with pemetrexed earlier in their treatment pathway and met eligibility criteria for liver function and peripheral neuropathy). Treatment continued until disease progression, which was defined using the Response Evaluation Criteria in Solid Tumours (RECIST) of independent radiology review, unacceptable toxicity or withdrawal of consent. Patients in the study could continue treatment after
radiographical progression at the discretion of the investigator. After disease progression, crossover was allowed in both directions.

3.3 The primary outcome in PROFILE 1007 was progression-free survival (PFS). Secondary outcomes included overall survival, objective response rate, duration of response, disease control rate, medication-related adverse events and health-related quality of life (lung cancer specific symptoms and general health status). The primary outcome was reported for the intention-to-treat population and for a post hoc subgroup in which crizotinib was compared with docetaxel in the chemotherapy group. Overall survival was not reported for the subgroup; the manufacturer stated that this was because of the immaturity of these data.

3.4 The median age of patients recruited into PROFILE 1007 was 51 years in the crizotinib arm, compared with 49 years in the chemotherapy arm. Most patients had adenocarcinoma (94.2% in the crizotinib arm; 92.0% in the chemotherapy arm) and had never smoked (62.4% in the crizotinib arm; 63.8% in the chemotherapy arm). The Eastern Cooperative Oncology Group (ECOG) performance status for patients in PROFILE 1007 was predominantly 0 (approximately 39%) or 1 (52%); only 9% were performance status 2.

3.5 The intention-to-treat analysis showed that treatment with crizotinib led to a statistically significant increase in median PFS of 4.7 months compared with chemotherapy (7.7 months in the crizotinib arm [95% confidence interval (CI) 6.0 to 8.8] compared with 3.0 months in the chemotherapy arm [95% CI 2.6 to 4.3]; hazard ratio [HR] for progression 0.49; 95% CI 0.37 to 0.64; p<0.0001). In the post hoc subgroup analysis, crizotinib was associated with a statistically significant increase in median PFS of
5.1 months compared with docetaxel (7.7 months in the crizotinib arm [95% CI 6.0 to 8.8] compared with 2.6 months in the docetaxel arm [95% CI presented as confidential]; HR for progression 0.30; 95% CI 0.21 to 0.43; p<0.0001).

3.6 Median overall survival results from PROFILE 1007 were based on an interim analysis with a cut-off date of March 2012, at which point 28% of the target events (death) had been observed in the crizotinib arm and 27% in the chemotherapy arm. In this analysis, crizotinib was not found to prolong overall survival compared with chemotherapy (20.3 months in the crizotinib arm compared with 22.8 months in the chemotherapy arm, HR 1.02; 95% CI 0.68 to 1.54; p=0.54). The manufacturer stated that these results were likely to have been significantly affected by crossover in the trial (the percentages of patients who crossed over between the treatment arms were reported as confidential data and cannot be reported here). Overall survival data were not presented for the docetaxel subgroup because of the immaturity of the data. The objective response rate was reported for the full population and the docetaxel subgroup. For the full population, the objective response rates were 65.3% (95% CI 57.7% to 72.4%) for crizotinib and 19.5% (95% CI 13.9% to 26.2%) for the chemotherapy group; the objective response rate ratio was 3.4 (95% CI 2.4 to 4.7, p<0.0001). For the docetaxel subgroup, the objective response rate was 65.7% for crizotinib and 6.9% for docetaxel (the 95% confidence intervals and relative risk were reported as confidential). Median duration of follow-up was 12.2 months in PROFILE 1007.

3.7 The manufacturer explored the effect of crossover using different approaches including the rank-preserving structural failure time (RPSFT) method, the inverse probability of treatment and censoring weighted (IPTCW) method and the use of a case-
matched hazard ratio from ‘real world data’. In addition, the manufacturer explored 5 different versions of the IPTCW method, which differed in terms of how missing values were imputed. The RPSFT and IPTCW methods used data from PROFILE 1007. The ‘real world data’ method used a published case-matched analysis in which some crizotinib-treated patients with ALK-positive non-small-cell lung cancer from PROFILE 1001 (a single arm safety study of 149 patients treated with crizotinib) were case-matched to patients with ALK-positive non-small-cell lung cancer who did not receive crizotinib (control group) from a retrospective analysis. The hazard ratios for death for crizotinib compared with chemotherapy were 0.83 for the RPSFT method and 0.36 for the real world data method. The remaining hazard ratios for the IPTCW methods were presented as confidential and therefore cannot be reported here. The hazard ratios were applied to the economic model to provide modelled mean survival times for chemotherapy. For the RPSFT method, the modelled mean survival time for chemotherapy was 26.9 months, giving an absolute gain in overall survival for crizotinib compared with chemotherapy of 5.8 months. For the real world data method, the modelled mean survival time for chemotherapy was 11.3 months, giving an absolute gain in overall survival for crizotinib compared with chemotherapy of 21.7 months. The manufacturer decided not to use the real world data method because of limitations in the analysis from which the hazard ratio resulted, and preferred the IPTCW method with last observation carried forward for up to 56 days to impute values for missing data (referred to as IPTCW5) for the base-case analysis. This method gave a modelled mean survival of 33 months for crizotinib, and 20.8 months for chemotherapy, giving an absolute gain in overall survival for crizotinib compared with chemotherapy of 12.3 months.
The overall survival hazard ratio resulting from this method was reported as confidential and cannot be reported here.

3.8 Non-comparative evidence for crizotinib was presented from the ongoing, single-arm studies PROFILE 1001 (n=149) and PROFILE 1005 (n=901). In PROFILE 1005, efficacy data were analysed from a subgroup of the population in the study (n=261), whereas the safety analysis was performed using data from all patients. The median duration of follow-up for the subgroup was 14.2 months. The manufacturer called the subgroup the ‘mature population’; these patients had been confirmed as having ALK-positive non-small-cell lung cancer by the central laboratory and had been recruited first, so the length of follow-up was longer than for the full population (the percentage of events [death] observed in this subgroup by the cut-off date, January 2012, was reported as confidential and cannot be reported here). Endpoints for both PROFILE 1001 and PROFILE 1005 included PFS and overall survival; in addition, PROFILE 1005 assessed health-related quality of life through the EQ-5D questionnaire. Median PFS for the PROFILE 1005 subgroup at data cut-off (54% disease progression using RECIST criteria events observed) was 8.1 months (95% CI 6.8 to 9.7). Median overall survival for the subgroup was presented as confidential and therefore cannot be reported here.

3.9 The manufacturer reported adverse reactions for PROFILE 1001, PROFILE 1005 and PROFILE 1007. Pooled analyses from the PROFILE studies were provided separately for hepatotoxicity and testosterone concentrations. In PROFILE 1001, 98% of patients (n=117) experienced at least 1 adverse reaction; 47% of patients (n=56) reported an adverse reaction with a severity of grade 3 or greater and 7% (n=8) discontinued as a result of an adverse reaction. In PROFILE 1005, the most common adverse reactions
(occurring in 10% or more patients) were: gastrointestinal disorders (for example, nausea 47%, vomiting 39% and diarrhoea 41%) and visual impairment 52%. Grade 3 or 4 adverse reactions were reported in 25.6% of patients, most frequently neutropenia (n=50 [5.5%]), increased alanine aminotransferase (n=36 [4.0%]) and fatigue (n=18 [2.0%]). Of the 198 deaths in the study, 4 were considered treatment-related by the investigators. Most of the adverse reaction data from PROFILE 1007 were presented as confidential and cannot therefore be reported. However, the manufacturer released selected data from PROFILE 1007; the most common adverse reactions were diarrhoea (n=103 [59.9%]), vision disorder (n=103 [59.9%]) nausea (n=94 [57.7%]), vomiting (n=80 [46.5%]) and constipation (n=73 [42.4%]).

3.10 In PROFILE 1007, quality of life was measured through the European Organization for the research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and EQ-5D questionnaire. The overall difference in change from baseline scores in global quality of life and functioning domains was found to be significantly different between the 2 treatment groups, with a statistically significantly greater improvement observed for crizotinib compared with chemotherapy (p<0.0001). In the study, baseline EQ-5D scores were higher in the crizotinib group than in the chemotherapy group. The mean EQ-5D index scores were presented as confidential and cannot be reported here.

3.11 The manufacturer carried out a systematic review, which did not identify any direct comparative evidence for crizotinib compared with best supportive care. It therefore conducted a mixed treatment comparison to attempt to provide overall survival and PFS hazard ratios for this comparison. To build a network of studies, the manufacturer stated that it was necessary to include studies that
included patients with ALK-negative non-small-cell lung cancer. Four studies were identified for inclusion in the mixed treatment comparison: PROFILE 1007 (comparing crizotinib with docetaxel or pemetrexed), JMEI and GFPC 05-06 (comparing docetaxel with pemetrexed), and TAX-317 (comparing docetaxel with best supportive care). The manufacturer assessed the extent to which the differences in age, disease stage, performance status, form of treatment, crossover and not using intention-to-treat analysis in GFPC 05-06 were potential sources of heterogeneity. A fixed-effects model was chosen because of the small number of studies in the network. Two analyses were carried out, differing in how crizotinib was connected to the network, and using either the docetaxel (analysis 1) or pemetrexed (analysis 2) subgroup of the chemotherapy arm from PROFILE 1007 as the link with the other studies.

3.12 Data on PFS were not available for all studies in the mixed treatment comparison and therefore, overall survival was the only outcome considered. Crossover-adjusted hazard ratios were not available for crizotinib compared with the subgroups (docetaxel and pemetrexed), and the manufacturer therefore assumed that the overall survival hazard ratios of crizotinib compared with docetaxel, and crizotinib compared with pemetrexed, were equivalent. The overall survival hazard ratio for crizotinib compared with chemotherapy from PROFILE 1007, adjusted for crossover using the manufacturer’s preferred IPTCW5 method, was used as a proxy for both comparisons. The results of the mixed treatment comparison were presented as confidential and cannot be reported here. The manufacturer concluded that the results of analyses 1 and 2 were consistent with each other, and that crizotinib has a statistically significant effect on overall survival compared with best supportive care.
3.13 The manufacturer developed a 3 state model, which it referred to as a semi-Markov area-under-the-curve analysis. The 3 states in the model were progression-free disease, progressed disease and death. All patients entered the model after failure of 1 chemotherapy regimen, but were considered progression free because they had not reached the criterion for further progression. After each 30-day cycle, patients remained in their present state or moved from progression free to either progressed disease or death, or from progressed disease to death. Patients in the progressed disease health state received best supportive care in line with current clinical practice. Life years were generated by the model according to the proportion of patients in the progression free and progressed disease states at each cycle and summing these over the lifetime time horizon (15 years in the base case). All patients were assumed to have ALK-positive non-small-cell lung cancer because testing was assumed to have been performed before, or during, first-line treatment. The model provided pairwise comparisons between crizotinib and docetaxel, best supportive care or pooled chemotherapy (docetaxel and pemetrexed).

3.14 The manufacturer’s model used estimates of treatment effectiveness (PFS and overall survival) from different sources. PFS for crizotinib and docetaxel was extrapolated by fitting a Weibull distribution (crizotinib) or a log-normal distribution (docetaxel) to the Kaplan-Meier plots from PROFILE 1007; PFS for best supportive care was assumed to be equal to docetaxel in PROFILE 1007; overall survival for crizotinib was extrapolated by fitting a Weibull distribution to the Kaplan-Meier plot for the subgroup (called the ‘mature population’) from PROFILE 1005. Overall survival for docetaxel was estimated by applying the crossover-adjusted hazard ratio between crizotinib and pooled chemotherapy from PROFILE 1007 (see section 3.7) to the
crizotinib overall survival curve (from PROFILE 1005). For best supportive care, overall survival was estimated by applying a generated hazard ratio between crizotinib and best supportive care from the mixed treatment comparison (see section 3.11) to the crizotinib overall survival curve (from PROFILE 1005). Using these data sources, the proportion of patients in the progressed disease health state was calculated as the difference between overall survival and PFS.

3.15 Resource use in the model included costs relating to drug acquisition (according to BNF 63 prices), administration (docetaxel only) and monitoring, treating adverse reactions, ALK testing, and costs of best supportive care, routine medical management and terminal care. The average treatment duration for crizotinib was derived from PROFILE 1007. In the base-case analysis, treatment was assumed to stop on progression to the progressed disease health state (assessed radiographically every 6 weeks), which occurred after a median duration of 33 weeks. A scenario analysis was performed assuming length of treatment until discontinuation as observed in PROFILE 1007 (the number of weeks was presented as confidential and cannot be reported here). A half-cycle correction was applied to the crizotinib acquisition costs, which effectively assumed no wastage was incurred by patients who moved to the progressed disease health state at the midpoint of any monthly cycle. Treatment with docetaxel was assumed to continue until disease progression. The administration cost of docetaxel was £102.11 per cycle; no administration costs were included in the total cost for crizotinib or best supportive care. The model included the cost of CT scans by health state and assumed that 30% of patients received 0.75 scans per month in the progression-free health state and 5% of patients received 0.75 scans per month in the progressed disease health state. The
only adverse event considered in the model was neutropenia, rates of which were taken from PROFILE 1007. The costs of treating neutropenia were attributed to treatment with docetaxel only, because it was assumed that neutropenia from treatment with crizotinib could be managed without incurring any additional cost, by dose reduction or temporary discontinuation of treatment. For the costs of ALK testing the model’s base-case testing strategy was to test the entire non-small-cell lung cancer population using immunohistochemistry (IHC) and confirm equivocal results (IHC 1+ and 2+) using a fluorescence in-situ hybridisation (FISH) test. The manufacturer calculated the cost of each testing strategy as the expected cost per patient to identify 1 patient with ALK-positive non-small-cell lung cancer from a cohort of patients with all types of non-small-cell lung cancer. The manufacturer assumed an ALK-positive non-small-cell lung cancer prevalence of 5%, resulting in a multiplication factor of 20 for testing the entire non-small-cell lung cancer cohort. The unit cost of IHC was £25 and the unit cost of a FISH test was reported as confidential and therefore cannot be reported here. The total cost of ALK testing in the model was £630.06 for each patient receiving treatment with crizotinib.

3.16 Utility values for the progression-free and progressed disease health states were derived from EQ-5D data collected in PROFILE 1007. For the progression-free health state, utilities were calculated (for crizotinib and docetaxel separately) as the average EQ-5D index value at each time point in PROFILE 1007 weighted by the number of patients still on treatment at that time. The health state utility values were reported as confidential and cannot be reported here. The utility values for progressed disease were taken from EQ-5D data collected when treatment was discontinued. Because utility values were not available for best supportive care from the trial, these were assumed to be equal to the utility values for
baseline chemotherapy for progression-free disease and the end of treatment utility values for chemotherapy for progressed disease. No disutility for adverse events associated with treatment was applied in the model.

3.17 In the manufacturer’s base-case analysis, the modelled PFS for crizotinib was 9.6 months, compared with 3.9 months for both docetaxel and best supportive care (incremental benefit for crizotinib of 5.7 months). The modelled time in the progressed disease health state was 23.4 months for crizotinib and 16.8 months for both docetaxel and best supportive care (incremental benefit for crizotinib of 6.6 months). The modelled 12-month survival probability for crizotinib was 67.7%, compared with 54.4% for docetaxel and 34.6% for best supportive care. The base-case analysis resulted in a deterministic incremental cost-effectiveness ratio (ICER) of £41,544 per quality-adjusted life year (QALY) gained for crizotinib compared with docetaxel (incremental costs of £40,227 and incremental QALYs of 0.968) and £35,455 per QALY gained for crizotinib compared with best supportive care (incremental costs of £48,128 and incremental QALYs of 1.357).

3.18 The manufacturer undertook a series of one-way deterministic sensitivity analyses to test the robustness of the results by varying several parameters used in the economic evaluation. Hazard ratios for overall survival (for crizotinib compared with docetaxel, and crizotinib compared with best supportive care) were varied between the upper and lower limits of the 95% confidence interval. Other parameters, including the utility values for progression-free and progressed disease for all treatments, administration costs of chemotherapy and the costs of diagnostic testing were varied between 20% below and 20% above the base-case value. From the results, the manufacturer highlighted that the ICER for crizotinib
was very sensitive to the hazard ratios for overall survival, which affected the absolute QALYs for both the crizotinib and comparator arm. This increased the ICER from the base case of £41,544 per QALY gained to £239,699 per QALY gained in the comparison with docetaxel, and from the base case of £35,455 per QALY gained to £82,289 per QALY gained in the comparison with best supportive care. The results were also sensitive to utility values for the progressed disease and progression-free health states for crizotinib, docetaxel and best supportive care; using a lower utility value for crizotinib for progressed disease (with utility values for other treatments remaining as in the base case), the ICER increased to £47,939 per QALY gained for crizotinib compared with docetaxel and £39,184 per QALY gained for crizotinib compared with best supportive care. The manufacturer also carried out a series of scenario analyses using different extrapolation methods, different estimates for utility, different treatment duration and different treatment effects. The most pronounced impact on the ICER was observed with a treatment duration for crizotinib based on PROFILE 1007; with this change alone, the ICER increased to £63,785 per QALY gained for crizotinib compared with docetaxel and £51,662 per QALY gained for crizotinib compared with best supportive care. The manufacturer concluded from the deterministic and scenario analyses that the key driver of the cost effectiveness of crizotinib was the overall survival hazard ratios for crizotinib compared with the comparators in the model (derived from the crossover analyses and mixed treatment comparison). In addition, the model was sensitive, although to a much smaller extent, to variations in the utility value, the method of overall survival and PFS extrapolation, treatment duration, and using a 10-year (instead of 15-year) time horizon.
3.19 The manufacturer undertook probabilistic sensitivity analyses in which the probability of crizotinib being cost effective at a threshold of £50,000 per QALY gained was 64% compared with docetaxel and 81% compared with best supportive care. At a threshold of £30,000 per QALY gained, the probability fell to below 20% and 30% for the comparisons respectively.

3.20 The manufacturer indicated that crizotinib fulfils the criteria to be assessed as an end-of-life treatment, because the patient population covered by the marketing authorisation is likely to be small (around 550 patients in the UK), current expected survival is only 6–8 months, and the results of the crossover-adjusted overall survival analysis suggested extension to life of more than 3 months.

Evidence Review Group comments

3.21 The ERG considered that the manufacturer had identified all the available evidence on the clinical effectiveness of crizotinib. It considered that the major limitation of the clinical-effectiveness evidence submitted by the manufacturer was the lack of overall survival data for crizotinib. This was because of the immaturity of the available survival data. The ERG considered the manufacturer’s use of the term ‘mature’ in relation to the PROFILE 1005 subgroup to be misleading. It considered that the data could not be considered mature for either PROFILE 1007 or PROFILE 1005 given the low overall survival rates (28% in PROFILE 1007, percentage in PROFILE 1005 presented as confidential). The ERG also considered that the higher overall survival event rate in PROFILE 1005 may reflect the poorer performance status of the patients in this study, rather than the maturity of the data. In addition, both studies had a similar duration (PROFILE 1005 was slightly shorter), and the median time to follow-up was only...
2 months longer for PROFILE 1005 than for PROFILE 1007 (14.2 compared with 12.2 months).

3.22 The ERG raised issues relating to the comparability of the populations within PROFILE 1007, and between PROFILE 1007 and PROFILE 1005. Within PROFILE 1007, the ERG’s main concern related to the differences between patient characteristics in the chemotherapy subgroups (docetaxel and pemetrexed). Between PROFILE 1007 and PROFILE 1005, the ERG noted some significant differences in the baseline characteristics of patients. In particular, the ERG considered that the number and type of previous therapies received and ECOG performance status could affect treatment response.

3.23 The ERG considered there to be a lack of a randomised comparison between crizotinib and docetaxel on which to draw robust conclusions of relative efficacy. This was because, in PROFILE 1007, pemetrexed was both an additional comparator and the treatment of choice in the comparator arm of the study. The ERG considered that this would lead to selection bias. It stated that including data from pemetrexed in the PROFILE 1007 comparator arm would increase the power of the efficacy outcomes, but would potentially underestimate the incidence of drug-related adverse reactions (because docetaxel is associated with greater toxicity than pemetrexed).

3.24 The ERG considered the manufacturer’s different approaches to adjusting for crossover. It noted that the manufacturer had excluded 2 methods that produced estimates favouring chemotherapy as clinically implausible. The ERG challenged this justification on the basis that there are occasions when a benefit in PFS may not translate into a benefit in overall survival. With regard to the manufacturer’s preferred method of adjusting for crossover
(IPTCW), the ERG pointed out that observational methods such as IPTCW are sensitive to the proportion of patients who cross over and to the number of patients. The ERG stated that the small number of patients and degree of crossover in PROFILE 1007 make it difficult to derive reliable overall survival estimates using the IPTCW method and it therefore felt that the manufacturer’s preferred estimates had questionable validity. The ERG questioned the plausibility of the results of the IPTCW5 (the manufacturer’s preferred crossover-adjustment method), given that the absolute survival gain with crizotinib from the crossover analysis (12.3 months) was more than double that of the PFS gain with crizotinib (5.7 months). The ERG also raised concerns about applying the RPSFT method to the PROFILE 1007 data, because this method only produces unbiased estimates when treatment effect is not time dependent, that is, independent of the number of previous treatments. However, the ERG noted that the RPSFT method resulted in a gain of 5.8 months in overall survival for crizotinib compared with chemotherapy, and considered that this result was consistent with what might be expected given the gain in PFS with crizotinib. Therefore the ERG considered the RPSFT method to have greater face validity and to be a more appropriate choice of method of adjusting for crossover for the base-case analysis.

3.25 The ERG raised concerns about using PFS, the primary endpoint of PROFILE 1007, as a surrogate for overall survival in the absence of mature data. The ERG highlighted that there is a complex relationship between PFS and overall survival in cancer generally, including lung cancer, and PFS may not accurately predict overall survival across populations and treatments. The ERG explained that, in the manufacturer’s submission, the gains in PFS were derived by fitting parametric curves to PFS data from
PROFILE 1007 and the gains in overall survival were derived by using a parametric curve fitted to the overall survival data from crizotinib in PROFILE 1005 and applying a crossover-adjusted hazard ratio for docetaxel to this data set. The predicted overall survival gains for crizotinib were higher than would be expected, given the available evidence of the relationship between PFS and overall survival seen in patients with non-small-cell lung cancer. The ERG did not consider that it was plausible for post-progression survival to be prolonged greatly by crizotinib unless crizotinib was continued after radiographical progression and was still having an effect. The ERG questioned the validity of the estimated overall survival advantage of crizotinib compared with chemotherapy in the manufacturer’s analysis because of the lack of overall survival benefit demonstrated so far in PROFILE 1007, the small number of patients and the large estimated overall survival benefit compared with that of PFS.

3.26 The ERG questioned the reliability of the results from the manufacturer’s mixed treatment comparison, based on major differences between the populations in the included trials. There were differences in:

- the proportion of patients with squamous cell histology (GFPC 05-06 and JMEI included patients with squamous cell histology)
- the median age of the populations in the non-crizotinib studies (GFPC 05-06, JMEI and TAX-317), which was 7–12 years older than in PROFILE 1007
- the proportion of patients with adenocarcinoma (50% in the non-crizotinib studies compared with 93% in PROFILE 1007)
- the percentage of women (30–35% in the non-crizotinib studies compared with 55% in PROFILE 1007).
3.27 The ERG noted that overall survival was the key driver of the cost effectiveness of crizotinib, and, given the concerns raised previously about the maturity of the overall survival data in PROFILE 1005 (see section 3.21), the ERG considered that these concerns would have to be weighed against the potential impact of all other assumptions and approaches applied in the manufacturer’s model. With regard to extrapolation of overall survival in the manufacturer’s base-case analysis, the ERG considered that it would be equally plausible (and possibly a more appropriate choice given its better statistical fit) to use an exponential, instead of Weibull distribution, for extrapolating overall survival.

3.28 The ERG commented that the manufacturer’s assumption in the model that treatment stops on evidence of radiographic progression may not represent what happens in clinical practice. The ERG highlighted that radiographic assessment may have led to earlier identification of progression and crossover of treatment in PROFILE 1007 than would occur in clinical practice. The ERG noted that using the actual treatment duration of crizotinib in PROFILE 1007 would increase the duration of treatment and costs. In the manufacturer’s scenario analysis, using treatment duration as in PROFILE 1007, the ICER for crizotinib compared with docetaxel increased from the base case of £41,544 per QALY gained to £63,785 per QALY gained.

3.29 The ERG raised concerns about the validity of the assumptions made about health-related quality of life in the model. The ERG pointed out that the model assumed a higher utility value in progressed disease for patients who had received crizotinib than for those who had received docetaxel (and best supportive care); patients were assumed to maintain a post-progression health-
related quality of life benefit at the end of treatment throughout the time spent in the progressed disease health state. The ERG questioned the validity of the assumption that utility at the end of treatment reflected the average utility experienced during the entire progressed disease health state. The ERG explained that the utility of progressed disease is assumed to be independent of time spent in the state. The ERG was not convinced that patients maintain a different health-related quality of life benefit in the progressed disease state (and certainly not for the entire duration of this disease state), and commented that this assumption was not justified or discussed by the manufacturer. The ERG stated that, in the base case, post-progression utility would be a key driver of cost effectiveness because the post-progression health state accounted for approximately 57% of the incremental gain in QALYs. The ERG also noted that progression-free health state utilities were higher than previously reported in non-small-cell lung cancer, and if these differences are real, this could reflect a finding that patients with ALK-positive disease are generally healthier than patients with ALK-negative disease. In addition, the ERG stated that the manufacturer had not adjusted for the different baseline utilities between treatments (the estimate of baseline utility was numerically higher for crizotinib than for chemotherapy), and that no justification had been given for not doing so.

3.30 The ERG commented that the drug acquisition cost for docetaxel in the model (based on the BNF 63) does not reflect the average price paid across England and Wales through procurement contracts. Using information from the Commercial Medicines Unit (Electronic Market Information Tool [eMIT]), a usage weighted average of the price paid for a generic drug such as docetaxel can be estimated and would be a more appropriate source for this cost in the model. The ERG also highlighted that the manufacturer’s submission did
not explicitly describe or justify the treatment duration for docetaxel (the median number and range of cycles in PROFILE 1007 was presented as confidential and cannot be reported here). Clinical advisers to the ERG suggested that it is unlikely that more than 6 cycles of treatment with docetaxel would be given in clinical practice. Consequently, the ERG raised concern that the costs of docetaxel would be overestimated in the manufacturer’s analysis.

3.31 The ERG highlighted that the manufacturer had applied a half-cycle correction to the costs of crizotinib in the model. This implied that there is no wastage associated with crizotinib, that unused capsules would be reclaimed from patients who have progressed at the midpoint of any treatment cycle. The ERG considered that, by removing the half-cycle correction, it was possible to explore the influence of this assumption on the results of the model. This was undertaken in alternative scenario analyses (see section 3.34). The ERG’s preferred assumption was to remove the half-cycle correction for the costs of crizotinib from the model.

3.32 The ERG accepted that the primary target population for testing for ALK would be patients with non-small-cell lung cancer with adenocarcinoma histology, and particularly with EGFR-negative disease. However, the ERG noted that ALK fusion can be observed with non-small-cell lung cancer of a different histology. Clinical advisers to the ERG commented that it is likely that, in the UK, only patients with adenocarcinoma would have ALK testing. However, histopathologists advising the ERG expressed a desire to see more widespread testing to identify all NSCLC patients with the ALK fusion gene. The ERG estimated that approximately 100 patients would be missed if screening was confined to adenocarcinoma patients, although it cautioned that there is considerable uncertainty around this estimate. With regard to the type of test, the ERG
considered it reasonable to suggest the use of IHC with subsequent confirmation of equivocal results using FISH testing. However, the ERG stressed the lack of clarity as to the timing of the testing strategy (because of uncertainty about the prevalence of the ALK fusion gene in non-adenomatous non-small-cell lung cancer) and highlighted that this would impact on the cost-effectiveness estimates.

3.33 The ERG explored an alternative approach to modelling overall survival. It noted that the manufacturer had considered proportional hazards models, namely exponential, Weibull and Gompertz models. The ERG agreed with the manufacturer that the Gompertz distribution did not provide an adequate fit to the data. However, the Weibull and exponential functions appeared to offer similar fits. The ERG commented that because there is a lack of evidence to assess external validity, it might have been more appropriate to choose the exponential distribution given the higher internal validity (a better statistical fit) than the Weibull function selected by the manufacturer. Using the exponential survival function in the base case, the ICER for crizotinib compared with docetaxel would increase from £41,554 to £44,643 per QALY gained.

3.34 The ERG carried out exploratory analyses using alternative parameters and assumptions for 5 areas of uncertainty in the manufacturer’s model that the ERG considered to be drivers of cost effectiveness. These were:

- the method of adjusting for crossover in the hazard ratio estimates of overall survival (comparing the ERG’s preferred method of RPSFT with IPTCW5)
- crizotinib treatment duration (using the same duration of treatment as in PROFILE 1007, rather than the
manufacturer’s base-case assumption of treatment until RECIST progression)

- post-progression utility values (using the same utility values for all treatments)
- the acquisition cost of docetaxel (using the cost as reported in eMIT rather than the BNF 63) and
- removing the half-cycle correction for crizotinib acquisition costs.

Using different combinations of these amendments, the ICER for crizotinib compared with docetaxel ranged between £63,770 per QALY gained (using the IPTCW5 crossover-adjustment method, assuming crizotinib treatment until RECIST progression, the BNF 63 price for docetaxel and the post-progression crizotinib utility value for both treatments) and £204,315 per QALY gained (using the RFSPT crossover-adjustment method, crizotinib treatment duration as in PROFILE 1007, the eMIT price for docetaxel and the crizotinib post-progression utility values for both treatments). Substituting the crizotinib post-progression utility values with pooled chemotherapy post-progression utility values, the ICER was £181,095 per QALY gained. The ICER for crizotinib compared with best supportive care ranged between £46,824 per QALY gained (using the IPTCW5 crossover-adjustment method, assuming treatment until RECIST progression and assuming pooled chemotherapy post-progression utility values for both treatments) and £80,535 per QALY gained (using the RPSFT crossover-adjustment method, crizotinib treatment as in PROFILE 1007 and pooled chemotherapy post-progression utility values).

Manufacturer’s additional evidence after consultation

3.35 After consultation the manufacturer presented additional evidence, which included:
• Overlaid Kaplan-Meier overall survival curves for crizotinib-treated patients in PROFILE 1007, PROFILE 1005 and PROFILE 1001. The manufacturer stated that the curves showed that the rates of overall survival were very similar between the PROFILE 1007 and 1005 populations.

• Results of the mixed treatment comparison applying the IPTCW2 crossover-adjustment method. The results were presented as confidential and cannot be reported here.

• Revised base-case ICERs from the economic model, which included the patient access scheme for crizotinib (see section 2.3) and amendments to the estimates described in section 3.36.

3.36 For the revised base-case cost-effectiveness analysis, the model included some amendments to the estimates:

• Post-progression utility for crizotinib was amended to include a step decrease in the utility estimate at the mid-point (10 months) of the post-progression phase.

• Acquisition and administration costs of docetaxel were applied for a maximum of 6 treatment cycles, to reflect the Committee’s belief that patients in England and Wales are unlikely to undergo more than 6 cycles of treatment with docetaxel.

• Monitoring costs in the progression-free health state were increased from £241.44 to £257.80, to reflect the frequency of CT scanning expected in UK routine clinical practice.

• The half-cycle correction was removed from the acquisition costs of crizotinib to reflect the assumption that unused crizotinib capsules would be wasted for those patients that transition before the end of each monthly cycle.
3.37 The manufacturer presented cost-effectiveness results from the revised economic model, with and without the patient access scheme. Only results with the patient access scheme are reported here. The revised base-case analysis, assuming treatment duration as in PROFILE 1007 and the IPTCW5 crossover-adjustment method, resulted in deterministic ICERs of £65,925 per QALY gained for crizotinib compared with docetaxel and £47,914 per QALY gained for crizotinib compared with best supportive care. Probabilistic ICERs were £70,046 per QALY gained for crizotinib compared with docetaxel and £50,230 per QALY gained for crizotinib compared with best supportive care.

ERG comments on the manufacturer’s additional evidence at consultation

3.38 The ERG considered that the manufacturer’s response to consultation largely reflected amendments to the model to address the Committee’s concerns rather than introduce new data. The only new information included in the revised economic model was the patient access scheme. The ERG checked the manufacturer’s revisions to the model and obtained similar results for the revised base-case ICERs for crizotinib compared with docetaxel and compared with best supportive care. It also identified outstanding issues that had not been addressed by the manufacturer and conducted exploratory analyses to evaluate the impact of each of these changes separately on the manufacturer’s deterministic revised base-case ICER of £65,925 per QALY gained for crizotinib compared with docetaxel.

- The ERG incorporated the eMIT acquisition price for docetaxel into the revised model with treatment duration as in PROFILE 1007 and obtained a deterministic ICER of £70,996 per QALY gained for crizotinib compared with docetaxel.
• The ERG considered the PFS data and pre-progression utility estimates based on the pooled chemotherapy arm of PROFILE 1007 more appropriate than the data from the docetaxel subgroup. Cost-effectiveness analysis with the revised model updated with PFS and utility estimates from the pooled chemotherapy arm resulted in a deterministic ICER of £67,508 per QALY gained for crizotinib compared with docetaxel.

• The ERG noted that the manufacturer’s estimate for the cost per FISH screening test had increased from £113 in their response to clarification and this had not been included in the revised model. The increased cost of the FISH test was marked confidential and cannot be reported here. Using the revised cost per FISH test resulted in a deterministic ICER of £66,288 per QALY gained for crizotinib compared with docetaxel.

• The ERG incorporated the oral chemotherapy administration cost of £126 per month into the revised model and obtained a deterministic ICER of £68,215 per QALY gained. However, the ERG also highlighted that this administration cost for crizotinib was higher than the administration cost for docetaxel (£102) used in the model.

• The ERG investigated the impact of changing the crossover-adjustment method from the IPTCW5 method used by the manufacturer. Using the treatment duration as in PROFILE 1007 and the IPTCW2 crossover-adjustment method resulted in a deterministic ICER of £89,961 per QALY gained for crizotinib compared with docetaxel and a probabilistic ICER of £95,985 per QALY gained for crizotinib compared with docetaxel. Using the RPSFT method to adjust for crossover gave a deterministic ICER of £99,664 per QALY gained for
crizotinib compared with docetaxel and a probabilistic ICER of £111,795 per QALY gained for crizotinib compared with docetaxel.

The ERG also explored cost-effectiveness results from the revised model assuming treatment duration as in PROFILE 1007 and including both the eMIT docetaxel cost and the increased FISH screening test costs with different crossover-adjustment methods. The deterministic ICER for crizotinib compared with docetaxel increased from £71,358 per QALY gained using the IPTCW5 method to £108,022 per QALY gained using the RPSFT method. Similarly, the deterministic ICER for crizotinib compared with best supportive care increased from £48,149 per QALY gained using the IPTCW5 method to £55,157 per QALY gained using the RPSFT method.

3.39 Full details of all the evidence are in the manufacturer’s submission and the ERG report.

4 Consideration of the evidence

4.1 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 specialists. It also took into account the effective use of NHS resources.

4.2 The Committee heard from clinical specialists and patient experts that there are limited treatment options for people with non-small-cell lung cancer whose disease has progressed following chemotherapy. It heard from the patient experts and clinical specialists 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 specialists on the severity of the disease. The Committee also heard from the clinical specialists 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 specialists 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.

4.3 The Committee discussed the decision problem as presented in the manufacturer’s submission. It noted that this was the same as the scope for the appraisal, with the exception that the appraisal scope listed erlotinib as a comparator, but the manufacturer 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 manufacturer’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 was 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 manufacturer’s position that erlotinib should not be considered as a comparator for crizotinib for treating previously treated ALK-positive non-small-cell lung cancer. It also noted that pemetrexed was not in the scope and not a valid comparator as a second-line treatment because patients are likely to have been treated with 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.

4.4 The Committee discussed the characteristics of the population in PROFILE 1007. It noted that most of the trial population had been diagnosed with adenocarcinoma, had a good performance status, were 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 specialists 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 ascertain 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 on account 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.

4.5 The Committee considered treatment duration with crizotinib. It noted that a large proportion of patients in PROFILE 1007 continued to receive treatment with crizotinib 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 specialists 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 2–84 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 specialists 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.
The Committee discussed the evidence for the clinical efficacy of crizotinib. It noted the median gains in PFS 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 PFS 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 manufacturer that more mature and therefore more reliable overall survival data would be available for PROFILE 1007 at [confidential information removed on 250313 at the request of the company]. However, it noted that this would not be within the timeframe of this appraisal. The Committee therefore considered the results of the manufacturer’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 specialists 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 RPSFT method and the manufacturer’s chosen method (IPTCW5) as discussed in section 4.9. It therefore accepted that treatment with crizotinib would result in an overall survival gain compared with docetaxel but the exact magnitude 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, on the basis of the evidence for PFS and response rate, crizotinib is a clinically efficacious treatment for ALK-positive advanced non-small-cell lung cancer compared with chemotherapy.

4.7 The Committee noted the number of adverse events associated with crizotinib treatment from the PROFILE studies (see section 3.9). However, it was advised by the patient experts and clinical specialists 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.

4.8 The Committee discussed the results of the manufacturer’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 manufacturer’s comment that the median PFS 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 NSCLC 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 NSCLC; 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.

4.9 The Committee discussed the manufacturer’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 manufacturer’s justification for preferring 1 method, noting that, of the different statistical methods, IPTCW5 gave the most favourable overall survival benefit for crizotinib. It heard from the manufacturer 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 manufacturer 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 manufacturer’s chosen method resulted in a modelled PFS gain of
5.7 months, and an overall survival gain of 12.3 months for crizotinib and that this large gain in OS compared with PFS was not supported by any evidence. The Committee also considered the application of the manufacturer’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 manufacturer that this had not been considered. The Committee considered that this could lead to flaws in the analysis. It did not accept the manufacturer’s assertion of face validity to justify the use of 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 manufacturer’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.

4.10 The Committee further discussed the most likely projection of the overall survival benefit for crizotinib compared with docetaxel. It discussed comments by the manufacturer that it is biologically plausible that the overall survival to PFS ratio would be higher with targeted therapy than with chemotherapy. The clinical specialists 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
specialists relating to the expected gain in survival with crizotinib (see section 4.6), 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 4.6). 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.

4.11 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 manufacturer 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 benefit of treatment with crizotinib might be expected to continue after treatment was stopped. The Committee heard from the clinical specialists that patients with progressed disease would continue to experience some additional
health-related quality of life benefit for some time after treatment
could 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 benefit to utility of
continuing crizotinib, but there were no data to show whether such
continued treatment benefits patients or for how long. The
Committee considered the manufacturer’s revised model,
incorporating a step change in post-progression utilities (see
section 3.36). 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 manufacturer did not justify the approach used to
model a reduction in post-progression utilities. The ERG
commented that, without any further evidence, the magnitude and
duration of post-progression benefit remained uncertain. In addition
the approach used by the manufacturer to characterise the
reduction is likely to overestimate the QALY benefits because of
the impact of discounting and of differences in the baseline values.
The Committee concluded that the manufacturer’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.

4.12 The Committee discussed the cost estimates in the manufacturer’s
economic model.

- The Committee noted that CT scans were performed every
  6 weeks in PROFILE 1007. The Committee heard from the
clinical specialists 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 (see section 3.36) the manufacturer 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 manufacturer’s submission and not reported here). On the basis of the clinical specialists’ 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 (see section 3.36) the manufacturer 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 manufacturer’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 ‘British National Formulary’ (BNF) and the range of prices paid by the NHS across the country as reported in the electronic Market Information Tool (eMIT) from the Commercial Medicines Unit of the NHS. It noted the manufacturer’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 (see section 3.38). These analyses demonstrated that the use of the eMIT price for docetaxel would increase the ICER by about £5000 per QALY gained and including the £126 crizotinib administration cost would increase the ICER by about £2200 per QALY gained. The
Committee concluded that the impact of these factors would increase the ICER in the manufacturer’s revised base-case model.

4.13 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 of crizotinib as in PROFILE 1007 (see section 4.5). The Committee considered the manufacturer’s revised base-case probabilistic estimate of the ICER of £70,000 per QALY gained. It was aware that this was based on the manufacturer’s preferred method for adjusting for crossover (IPTCW5). Based on its earlier discussions regarding the approach to crossover (see sections 4.9 and 4.10) 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 4.12). The Committee was aware that when the ERG had carried out these 2 amendments to the manufacturer’s revised base case individually, the combined result was to increase the ICER by approximately £7000 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.
4.14 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 manufacturer’s revised base-case probabilistic estimate of the ICER of £50,200 per QALY gained. It was aware that this was based on the manufacturer’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 4.8). 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.

4.15 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 manufacturer 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 specialists and patient experts that crizotinib delivers high
response rates and a substantial benefit in at least PFS 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.

4.16 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.
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 manufacturer’s statistical crossover analyses, which gave a range of estimates between 20 and 27 months for the chemotherapy group. On the basis of its discussions around the crossover methods explored by the manufacturer (see section 4.9), 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 PFS 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 manufacturer’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 three 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.

The Committee considered its recommendations to the NHS. On the basis of the most plausible ICERs (see sections 4.13 and 4.14), the Committee concluded that even allowing for the supplementary advice to the Committee for life-extending treatments, the magnitude 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. Furthermore, 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.

4.19 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 specialists that there is currently no established ALK testing strategy in UK clinical practice. The Committee then considered the potential equality issues raised by clinical specialists during consultation. The clinical specialists 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 impacted on 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.

Summary of Appraisal Committee’s key conclusions
Key conclusion

On the basis of the most plausible ICERs, the Committee concluded that even allowing for the supplementary advice to the Committee for life-extending treatments, the magnitude of additional weight that would need to be assigned to the QALY gains for people with previously treated ALK-positive NSCLC would be too great for crizotinib to be considered a cost-effective use of NHS resources.

The Committee accepted that treatment with crizotinib would result in an overall survival gain compared with docetaxel but the exact magnitude of the gain was uncertain because of the immaturity of the PROFILE 1007 data and the impact of crossover in the study.

The Committee concluded that, on the basis of the evidence for PFS and response rate, crizotinib is a clinically efficacious treatment for ALK-positive non-small-cell lung cancer compared with chemotherapy.

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, and for crizotinib compared with best supportive care would be more than £50,200 per QALY gained.

Current practice

Clinical need of patients, including the availability of alternative treatments

The Committee heard from clinical specialists 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 specialists 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.

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 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.
<table>
<thead>
<tr>
<th>What is the position of the treatment in the pathway of care for the condition?</th>
<th>The Committee concluded that docetaxel and best supportive care are the appropriate comparators for crizotinib.</th>
<th>4.3</th>
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<tr>
<td>Adverse reactions</td>
<td>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 were generally easily managed.</td>
<td>4.7</td>
</tr>
</tbody>
</table>

### Evidence for clinical effectiveness

| Availability, nature and quality of evidence | The main evidence came from 1 multi-centre, randomised phase III efficacy and safety study in patients with previously treated ALK-positive non-small-cell lung cancer (PROFILE 1007). | 3.2 |
| Relevance to general clinical practice in the NHS | The Committee accepted that the PROFILE 1007 population was likely to be similar to people considered for treatment with crizotinib in UK clinical practice. 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. | 4.4, 4.5 |

| Uncertainties generated by the evidence | The Committee acknowledged that the overall survival data from the crizotinib studies was relatively immature and, in the case of PROFILE 1007, subject to a high rate of crossover from chemotherapy to crizotinib. The Committee heard from the manufacturer that more mature and therefore more reliable overall survival data would be available for PROFILE 1007 at [confidential information removed on 250313 at the request of the company]. 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. | 4.6, 4.9, 4.10 |

| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | Subgroups for 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 | The Committee noted the median gain in PFS of 5.1 months with crizotinib compared with docetaxel from the PROFILE 1007 study, and considered that this represented a noteworthy extension to PFS 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 magnitude 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, on the basis of the evidence for PFS and response rate, crizotinib is a clinically efficacious treatment for ALK-positive non-small-cell lung cancer compared with chemotherapy. | 4.6 |

<p>| Evidence for cost effectiveness | Availability and nature of evidence | The manufacturer 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. | 3.13, 3.14 |</p>
<table>
<thead>
<tr>
<th>Uncertainties around and plausibility of assumptions and inputs in the economic model</th>
<th>The Committee discussed the manufacturer’s justification for preferring 1 crossover-adjustment method, noting that, of the different statistical methods, IPTCW5 gave the most favourable overall survival benefit for crizotinib. The Committee noted that the manufacturer’s chosen method resulted in a modelled PFS gain of 5.7 months, and an overall survival gain of 12.3 months for crizotinib and that this large gain in OS compared with PFS was not supported by any evidence. The Committee concluded that the manufacturer’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. 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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>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?</td>
<td>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 manufacturer 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 manufacturer’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 very uncertain.</td>
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<td>4.11</td>
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<tr>
<td>Question</td>
<td>Answer</td>
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<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Are there specific groups of people for whom the technology is particularly cost effective?</td>
<td>Not applicable</td>
</tr>
<tr>
<td>What are the key drivers of cost effectiveness?</td>
<td>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 RPSFT methods, broadly in agreement with clinical opinion (see section 4.6). For the comparison with best supportive care, the Committee concluded that the ICER was associated substantial uncertainty, which it is not possible to quantify because of the lack of a robust mixed treatment comparison between crizotinib and best supportive care.</td>
</tr>
<tr>
<td>Most likely cost-effectiveness estimate (given as an ICER)</td>
<td>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.</td>
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because of the lack of data in the post-progression period.
Additional factors taken into account

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<tr>
<th>Additional factors taken into account</th>
<th>Details</th>
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<tr>
<td>Patient access schemes (PPRS)</td>
<td>The manufacturer of crizotinib 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.</td>
<td>2.3</td>
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<tr>
<td>End-of-life considerations</td>
<td>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.</td>
<td>4.17</td>
</tr>
<tr>
<td>Equalities considerations and social value judgements</td>
<td>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.</td>
<td>4.19</td>
</tr>
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5 Implementation

5.1 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.
6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the NICE website.

Published

- Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. NICE technology appraisal guidance 192 (2010).
- Pemetrexed for the maintenance of non-small-cell lung cancer. NICE technology appraisal guidance 190 (2010).

7 Review of guidance

7.1 The guidance on this technology will be considered for review by the Guidance Executive in May 2016. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Brian Shine
Chair, Appraisal Committee
July 2013
8 Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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.

Dr Brian Shine (Chair)
Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Professor Jonathan Michaels (Vice Chair)
Professor of Clinical Decision Science, University of Sheffield

Professor Kathryn Abel
Director of Centre for Women’s Mental Health, University of Manchester

Dr Aomesh Bhatt
Regulatory and Medical Affairs Director Europe and North America, Reckitt Benckiser
Final appraisal determination – Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene
Christopher Earl
Surgical Care Practitioner, Wessex Neurological Centre at Southampton University Hospital

Gillian Ells
Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh
Professor and Honorary Consultant Surgeon, University of Liverpool

Dr Susan Griffin
Research Fellow, Centre for Health Economics, University of York

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Professor John Henderson
Professor of Paediatric Respiratory Medicine, University of Bristol and Bristol Royal Hospital for Children

Dr Paul Hepple
General Practitioner, Muirhouse Medical Group

Professor Peter Jones
Emeritus Professor of Statistics, Keele University

Dr Tim Kinnaird
Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Emily Lam
Lay Member

Terrance Lewis
Lay member
Final appraisal determination – Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene

Issue date: August 2013
B  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.

Helen Tucker and Bernice Dillon
Technical Lead

Joanne Holden
Technical Adviser

Kate Moore
Project Manager
9 Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Reviews and Dissemination/Centre for Health Economics:


B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Pfizer

II Professional/specialist and patient/carer groups:

- Roy Castle Lung Cancer Foundation
- British Thoracic Society
- Cancer Research UK
- National Lung Cancer Forum for Nurses
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:
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- Department of Health
- Greater Manchester PCT Cluster
- Southampton, Hampshire, Isle of Wight and Portsmouth PCT Cluster
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- British Thoracic Oncology Group
- NHS Centre for Reviews and Dissemination and Centre for Health Economics, York
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on crizotinib by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Fiona Blackhall, Consultant Medical Oncologist, nominated by Pfizer – clinical specialist
- Dr Sanjay Popat, Consultant Medical Oncologist, nominated by Royal College of Physicians and Pfizer – clinical specialist
- Dr Jesme Fox, nominated by Roy Castle Lung Cancer Foundation – patient expert

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Pfizer