Pharmacoeconomics Review Article

Title page

Crizotinib for untreated anaplastic lymphoma kinase-positive non-small-cell lung cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal

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Abstract

As part of the National Institute for Health and Care Excellence's (NICE) Single Technology Appraisal (STA) process the manufacturer of crizotinib submitted evidence on the clinical and cost effectiveness of crizotinib in untreated anaplastic lymphoma kinase-positive (ALK positive) non-small cell lung cancer (NSCLC). Crizotinib has previously been assessed by NICE for patients with previously treated ALK positive NSCLC (TA 296). It was not approved in this previous appraisal, but had been made available through the cancer drugs fund (CDF). As part of this new appraisal the company included a price discount patient access scheme (PAS). The Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Appraisal Group at the University of York was commissioned to act as the independent Evidence Review Group (ERG). This article provides a description of the company's submission, and the ERG's review and summarises the resulting NICE guidance issued in August 2016. The main clinical effectiveness data were derived from a multicentre randomised controlled trial (RCT): PROFILE 1014, which compared crizotinib to pemetrexed chemotherapy in combination with carboplatin or cisplatin in patients with untreated non-squamous ALK-positive NSCLC. In the trial crizotinib demonstrated improvements in progression-free survival (PFS) and overall survival (OS). The company's economic model was a three state 'area under the curve' Markov Model. The base-case incremental cost-effectiveness ratio (ICER) was estimated to be greater than £50,000 per QALY gained (excluding the PAS discount). The ERGs assessment of the evidence submitted by the company raised a number of concerns. In terms of the clinical evidence, the OS benefit was highly uncertain due to the cross-over permitted in the trial and the immaturity of the data; only 26% of events had occurred by the data cut off point. In the economic modelling the most significant concerns related to the analysis of OS and assumptions made regarding the duration of therapy. The ERG exploratory re-analysis of the OS data relaxed the assumption of proportional hazards made in the company submission, which demonstrated significant uncertainty regarding the OS gains from crizotinib. The ERG reconfigured the economic model so that duration of therapy was based on the area under the curve analysis of the PROFILE 1014 trial, dramatically increasing the cost associated with implementing crizotinib and consequently, substantially increasing the ICER. At the first appraisal meeting, the NICE Appraisal Committee concluded that crizotinib while clinically effective was not sufficiently cost effective for use in the National Health Service (NHS). Following the consultation, the company offered a revised PAS, and conducted extensive re-analysis, resulting in a revised base-case ICER of £47,291 per QALY gained. The NICE Appraisal Committee concluded that crizotinib was likely to be a cost-effective use of NHS resources, despite the uncertainty that persists around a number of factors, namely the long-term survival benefit of crizotinib. Crizotinib was therefore recommended, as an option for untreated ALK-positive advanced NSCLC in adults.

Key Points for Decision Makers

- The main clinical effectiveness data were derived from a multicentre randomised controlled trial (RCT), which demonstrated improvements in progression-free survival (PFS) and overall survival (OS) for crizotinib compared with pemetrexed chemotherapy in combination with carboplatin or cisplatin in patients with untreated anaplastic lymphoma kinase-positive (ALK-positive) non-small cell lung cancer (NSCLC).
- The base-case incremental cost-effectiveness ratio (ICER) was estimated to be greater than £50,000 per quality adjusted life year (QALY) gained excluding the patient access scheme (PAS) discount.

- The Evidence Review Group (ERG) critique of the evidence submitted by the company raised a number of concerns regarding the clinical data supporting the claimed OS benefits. The ERG also considered that the assumption made by the company regarding duration of treatment significantly underestimated total time on treatment (and hence total costs).
- The ERG's exploratory analyses focused on alternative approaches to analysing the OS data and reconfiguration of the economic model to better account for time spent on treatment.
- Crizotinib was recommended as an option for untreated ALK-positive advanced NSCLC in adults once a patient access scheme was agreed.

1. Introduction

Guidance on which treatments should be offered to patients on the NHS in England is issued by the National Institute for Health and Care Excellence (NICE). The role of the NICE technology appraisal programme is to assess treatments and make recommendations based on the cost-effectiveness of the technology. Single technology appraisals (STAs) are designed to appraise a single technology, with a single indication. Evidence is submitted by the manufacturer of the technology and is then reviewed and critiqued by an independent Evidence Review Group (ERG). A NICE appraisal committee then consider the evidence submitted by the company, additional evidence supplied by patient, clinical and NHS commissioning experts, as well as the review conducted by the ERG.

Crizotinib has previously been assessed by NICE for patients with previously treated ALK positive locally advanced or metastatic non-small-cell lung cancer (TA 296) [1]. It was not approved but was made available through the cancer drugs fund (CDF). However, the company subsequently submitted evidence for crizotinib to be considered in a different population: patients with previously *untreated* ALK-positive locally advanced or metastatic non-small cell lung cancer (NSCLC).

This article summarises the critique conducted by the ERG of the company's submission. The issues raised during the review and the committee's decision making process are also summarised. Full details of the appraisal and the relevant documents can be found on the NICE website [2].

2. The Decision Problem

Lung cancer is a highly prevalent disease, with 33,027 reported cases in England and Wales in 2014 [3]. It is characterised by abnormal or uncontrolled growth of lung cells [4] and is grouped into two categories: small-cell (SCLC) and non-small-cell (NSCLC), which make up 15% and 85% of patients respectively [5]. Within NSCLC there are three main sub-categories: large-cell undifferentiated carcinoma (10-15%), adenocarcinoma (40%) and squamous cell carcinoma (25-30%). The anaplastic lymphoma kinase (ALK) fusion gene is active in approximately 3-5% of NSCLC patients, [6] [7] with the vast majority of cases being found in adenocarcinomas.

Lung cancer is a major cause of mortality and morbidity in the UK. Symptoms of NSCLC include: coughing, chest pain, weight loss and loss of appetite, shortness of breath (dyspnoea) and fatigue. Once it has spread to distant organs NSCLC can also result in bone pain, nervous system changes, yellowing of the skin (jaundice), and lumps near the surface of the body [4]. The symptom burden therefore has a significant impact on patients' quality of life, with around 90% of patients experiencing two or more disease-related symptoms which may result in psychological distress [8]. In some cases the disease can result in the development of brain metastases, which severely increases patients' mortality risk [9]. As symptom onset often occurs once the cancer has developed, prognosis is poor for those with advanced NSCLC, with current survival rates for lung cancer being the second lowest out of 20 common cancers in England and Wales [5]. Between 7-24% with stage 3 NSCLC and 2-13% with stage 4 NSCLC are estimated to survive for five years or more [10].

Current NICE guidance (CG121) recommends pemetrexed chemotherapy in combination with carboplatin or cisplatin given intravenously, for first line treatment in patients with inoperable advanced NSCLC who have a good performance score [11]. Several RCTs have shown median overall survival to be somewhere between 7.8 and 11.8 months for patients treated with pemetrexed chemotherapy [12-14]. Evidence for survival times amongst ALK-positive NSCLC patients is limited, however there are some limited data which suggests that survival times for these patients may in fact be higher as many are younger and non-smokers. A small retrospective analysis of 36 ALK-positive patients in a Phase I clinical trial, many of whom had received prior therapy, reported a median overall survival of 20 months (95% CI 13, 26) in these patients [13].

Crizotinib is an oral receptor tyrosine kinase (RTK) inhibitor which acts against anaplastic lymphoma kinase (ALK) and its oncogenic variants. It is targeted at adults with ALK-positive advanced NSCLC, and has been approved for use in 87 countries. In September 2013 guidance was issued which did not recommend crizotinib for people with previously treated ALK-positive NSCLC (TA296), however, the treatment was made available through the CDF. Crizotinib has recently been granted European Union marketing authorisation for use in the first-line setting. The manufacturer recommends a twice daily dose of 250mg, which is to be taken continuously until disease progression or unacceptable toxicity. In order for patients to be offered crizotinib they must be screened to identify whether they are ALK-positive.

3. The Independent Evidence Review Group (ERG) Review

The company submitted evidence to NICE on the use of crizotinib in the first-line treatment of patients with non-squamous ALK-positive NSCLC. The ERG reviewed the submission received by NICE and assessed whether or not the submission conformed to NICE methodological guidelines, critiqued the company's interpretation and analysis of the evidence, and checked for the existence of other evidence or alternative interpretations of the evidence.

3.1 Clinical evidence

The company's submission included a systematic review which was conducted in order to identify RCT and non-RCT studies that investigated the efficacy and safety of crizotinib. One multi-centre Phase III open label RCT was identified (PROFILE 1014) [15] which compared crizotinib with pemetrexed chemotherapy in combination with carboplatin or cisplatin in patients with untreated non-squamous ALK-positive NSCLC.

In the trial crizotinib demonstrated a statistically significant improvement in progression-free survival (PFS), with a median of 10.9 months (95% CI 8.3, 13.9), compared with a median of 7.0 months (95% CI 6.8, 8.2) for chemotherapy. Additionally, crizotinib had a statistically significant greater tumour response, with an objective response rate of 74% (95% CI 67, 81) versus chemotherapy, which had a rate of 45% (95% CI 37, 53). Additionally crizotinib had a shorter time to response, and a greater duration of response compared to chemotherapy.

At the time of the data-cut off, median overall survival (OS) had not been reached as just 26% of patients had died since randomisation. At the time of the data-cut off median follow-up for those assigned to crizotinib was 17.4 months, and 16.7 months for patients assigned to chemotherapy, a difference which was not found to be statistically significant. However, 70% of patients who were initially assigned to chemotherapy were later permitted to cross-over following progression and receive crizotinib. The company therefore utilised nine different methods to adjust for the presence of cross-over, using variations of the rank preserving structural time model (RPSFTM), the iterative parameter estimation method (IPE) and the two stage method. All nine resulted in hazard ratios which demonstrated increased overall survival for patients receiving crizotinib relative to chemotherapy, with hazard ratios ranging from 0.571 to 0.674. In most cases the confidence intervals were wide, with only four demonstrating a statistically significant benefit.

A number of different measures were utilised to measure health-related quality of life (HRQoL) including EQ-5D and the lung cancer-specific module EORTC QLQ LC-13. These measures demonstrated that patients had improved quality of life on both crizotinib and chemotherapy compared to baseline, with greater improvements found in those treated with crizotinib.

There was little difference in the numbers of patients suffering a treatment related adverse event between the two randomised groups, with 98.2% of crizotinib and 92.9% of pemetrexed chemotherapy patients experiencing at least one. Within these patients, 35.1% in the crizotinib arm, and 39.1% in the chemotherapy group experienced grade 3 or 4 adverse events. Adverse events leading to permanent discontinuation occurred in 12% and 14% in the crizotinib and chemotherapy groups respectively. The most frequently reported adverse events in the crizotinib group compared to the chemotherapy group were vision disorders (71% vs 9%), diarrhoea (61% vs 13%) and oedema (49% vs 12%). Conversely the most reported adverse events for chemotherapy compared to those on crizotinib were fatigue (38% vs 29%), anaemia (32% vs 9%) and neutropenia (30% vs 21%).

Two non-randomised studies were also included in the submission: PROFILE 1001 [16] and Davis et al. 2015 [17]. PROFILE 1001 was a single arm, open-label, Phase I study where 24 patients received first-line therapy of 250mg twice daily crizotinib, resulting in a median PFS of 18.3 months (95% CI, 8.3 to 'not reached') at the latest data cut-off point. Davis et al. 2015[17] was a retrospective cohort study of 210 American and Canadian patients with confirmed ALK-positive NSCLC on both first and second line crizotinib therapy which reported a median PFS of 9.6 months (95% CI 8.4, 10.8), and median OS of 2 years (95% CI 1.5, 'not reached').

A pooled analysis of safety data was also conducted drawing from data from PROFILE's 1014 and 1001, as well as PROFILE's 1005 and 1007 which investigated crizotinib as a second-line therapy. The company submission reported that the pooled analysis (n= 1,699) showed that the safety profile was relatively consistent across all trials and lines of therapy. The most frequently reported adverse events experienced on crizotinib were vision disorders (62%), nausea (57%), and diarrhoea (54%). The European Medicines Agency (EMA) determined that the adverse event profile of crizotinib therefore presents a clinically significant but manageable burden to patients [18].

3.2 Critique of Clinical Evidence

The ERG highlighted a number of issues with the clinical evidence presented by the company.

3.2.1. Trial Design

PROFILE 1014 was a well conducted trial, and the potential bias in the trial resulting from the open-label nature of the study is likely mitigated by the trials use of the objective measure for disease progression the Response Evaluation Criteria In Solid Tumors (RECIST) criteria. However, progression in practice is determined by the worsening of symptoms and not the RECIST criteria, which means that the results seen in the trial may not be reflected in clinical practice. Additionally, the trial permitted treatment decisions post disease progression, which put the trial at high risk of bias for OS.

3.2.2 Overall Survival Data

The ERG highlighted four main issues with the survival data presented by the company.

Firstly, the data, particularly OS data are immature. At the time of the data cut-off point at 18 months, deaths had occurred in just 26% of those who underwent randomisation.

Secondly, the methods by which the company adjusted for the issue of patients switching therapies beyond progression suffer from limitations and may result in bias. The RPSFTM and IPE method both assume a common treatment effect, meaning that the timing of a treatment does not affect its benefit. This may not hold as those who switched on to the experimental drug when they were at a more advanced stage may not have the same benefit as those who received the treatment from randomisation. The RPSFTM and IPE method also have problems when the comparator treatment used in the RCT is active (i.e. it prolongs survival) [19]. Alternatively the two-stage method assumes that there are no unmeasured confounders, and that that there is no time dependant confounding between the time of disease progression and time of switching. The ERG could not select a method that they considered to be the most appropriate with any certainty.

Thirdly, the cross-over methods adjusted for those patients who switched from chemotherapy to crizotinib; however, it did not adjust for the patients who switched from crizotinib to receive other therapies.

Fourthly, there are imbalances in the two treatment arms in the numbers who went on to receive follow-up therapy and also the therapies people went on to receive. The aim of the appraisal was to evaluate the effect of first-line therapies alone, but due to the switching rules and the imbalances in follow-on therapy it is difficult to assess whether the outcomes of the trials reflect this.

Finally, the company analysed the survival data by fitting one parametric model to the data, therefore making the assumption of Cox proportional hazards, which assumes a constant proportional treatment effect between the two treatment arms. However, an inspection of the log-cumulative hazard plots for OS which plot log hazards against the log of time appeared to show the curves diverging, i.e. not proportional. This divergence may be explained by the different ways in which the two treatments are administered, as patient's received crizotinib continuously for a mean period of 23.7 months, whereas those in the chemotherapy arm received treatment in fixed cycles for a mean of 3.9 months. The NICE Decision Support Unit (DSU) guidance on the interpretation of proportional hazards outlines that an assumption of proportional hazards is reasonable when the majority of events have taken place in the trial, and in the absence of patient level data, neither of which is true in this scenario [19]. The ERG therefore considered that it was more appropriate to fit separate parametric models for each treatment arm.

3.2.3 Trial Population

In addition to these issues, the survival data results for chemotherapy from PROFILE 1014 differ from those reported in alternative studies, with PROFILE 1014 patients reporting longer survival times. After cross-over adjustment one year survival probabilities were around 65-75%, while 18 month survival probabilities were around 65-70% depending on the method of adjustment. These estimates can be compared to those reported in other trials of advanced non-squamous NSCLC: for pemetrexed chemotherapy + cisplatin, 1 year survival was 50% and 18 month survival was 35%, [12] and for pemetrexed chemotherapy + carboplatin 1 year survival was 40% and 18 month survival was 20% [14]. It is unclear whether these differences can be attributed to the patients in PROFILE 1014 being unrepresentative of the population seen in practice, or whether the ALK-positive population performs better than the general non-squamous NSCLC population.

3.2.4 Trial Comparators

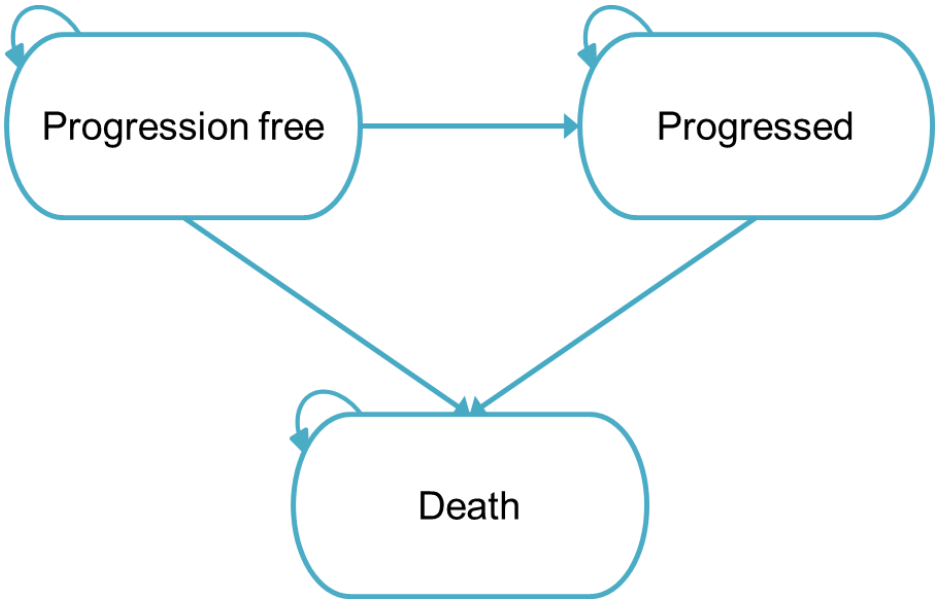
The ERG had concerns that not all comparators used in clinical practice were included in the analysis. Specifically, pemetrexed maintenance therapy was not included as a comparator. Pemetrexed maintenance therapy, which involves giving chemotherapy patients further cycles of therapy, is available via the cancer drugs fund to all patients who received pemetrexed chemotherapy with cisplatin (30% of all patients). The ERG considered that the exclusion of maintenance therapy means that an important comparator used in a significant proportion of patients was excluded from consideration.

3.3 Cost-effectiveness evidence

The model submitted by the company was a three health state model (Figure 1) which the company refers to as a semi-Markov "area under the curve" analysis. The three states are: progression free, progressed and death. Transitions between states are not explicitly incorporated into the analysis using probabilities but the proportion of patients in each state is determined by using estimates of survival over time. Patients are assumed to receive either crizotinib or pemetrexed chemotherapy in combination with cisplatin or carboplatin as first-line treatments. Once patients progress (as defined by RECIST) they are moved onto second-line treatment (docetaxel) and then third-line best supportive care before death. However, in the model patients who receive crizotinib therapy first-line

may continue therapy beyond progression if in the view of the treating clinician they are deemed to still be benefitting from treatment.

Figure 1: Model structure (Figure 17, Pg.122 in the Company Submission)



The duration of treatment for patients who discontinue therapy at progression is based on time to progression which was calculated from an extrapolation of PFS data from PROFILE 1014. However, this extrapolation was adjusted using the base-line characteristics of patients from the Davis et al. 2015 [17] study, as the company claimed these patients are more representative of patients typically found in UK practice. Duration of treatment for patients who continue treatment beyond progression was also linked to time to progression, but it was assumed that patients treated with crizotinib receive a further 4 cycles of therapy based on data from the PROFILE 1014 trial.

The population analysed in the economic model were patients with ALK-positive NSCLC of non-squamous histology, which is consistent with PROFILE 1014. The economic perspective was the National Health Service (NHS) and Personal Social Services (PSS) in accordance with the NICE reference case. The time horizon was 15 years which was stated to represent a lifetime horizon and costs and benefits in the model were discounted at an annual rate of 3.5% as per the NICE reference case.

Patients receiving crizotinib who were in the progression-free state were assumed to derive a greater utility benefit, than those in the progression-free state treated with chemotherapy based on the EQ-5D data taken from the PROFILE 1014 trial. It was assumed that those who progressed but were still being treated with crizotinib would receive a higher utility than those who move onto second-line therapy. A utility value was therefore applied which was a mid-point between the pre-progression utility and the post-progression second-line therapy utility value. Additionally, a mid-point transitional utility was applied for one cycle when patients moved between health states to reflect a gradual worsening of quality of life.

The economic model assumes patients receive a dose of two 250mg tablets daily, in line with PROFILE 1014. The dosing of pemetrexed chemotherapy with cisplatin was based on body surface area, while pemetrexed with carboplatin was selected using a target under the curve method.

Administration costs were included for pemetrexed but not for crizotinib on the basis that it is an oral therapy and does not require hospital admission. Costs were also included for NHS resource use associated with routine medical care, monitoring and supportive care, and adverse event management.

Costs for ALK testing were also included in the base-case analysis, with a testing strategy that involved providing all non-squamous NSCLC patients with an ImmunoHistoChemistry (IHC) test, and giving those who scored +1 or +2 a confirmatory fluorescence in situ hybridisation (FISH) test which is considered the gold-standard for testing.

The company presented results for the base case analysis based on the November 2013 cut of the PROFILE 1014 data, and supplied results with and without an unapproved confidential patient access scheme (PAS) which was applied to the list price of crizotinib. Without the PAS, crizotinib had an incremental cost-effectiveness (ICER) of greater than £50,000 per QALY gained. The probabilistic analysis showed that crizotinib had a 0% chance of being considered cost-effective at this threshold.

3.4 Critique of the Cost-effectiveness Evidence

The ERG highlighted a number of issues with the company's cost-effectiveness evidence.

3.4.1 Model Validation

The ERG identified a significant number of errors and potential inconsistencies in the company's de novo cost-effectiveness model, which they identified and corrected for early in the STA process. Many of the errors were minor in their nature; however, they raised questions concerning the internal validity of the model and they could have been easily identified prior to submission.

3.4.2 Proportional Hazards and Immature Survival Data

The issues surrounding overall survival around the variation in second-line therapy received, the assumption of Cox proportional hazards, the adjustment made for cross-over and the immaturity of the data have a profound impact on the cost-effectiveness of crizotinib. To attempt to correct for these issues the ERG fitted two independent parametric survival functions to the Kaplan-Meier plots of PFS and OS for the crizotinib and pemetrexed chemotherapy arms of PROFILE 1014. The ERG attempted to select the most appropriate parametric functions based on the Akaike information criterion (AIC) and Bayesian information criterion (BIC) criteria of goodness of statistical fit and clinical plausibility. However, there was little difference between the AIC and BIC values despite the curves producing a wide range of values for OS gain and clinical plausibility was difficult to assess due to the lack of data available to inform the analysis.

3.4.3 Treatment Duration

The ERG made adjustments to the estimation of patients' time on treatment beyond progression. The company model assumed that patients received a further 4 cycles of crizotinib (conditional on the patient being alive) based on a median of 3.1 months reported in PROFILE 1014. The ERG considered the use of a median time on treatment to be inappropriate and had concerns regarding the implementation of time on treatment in the model. The ERG in its analysis sought to correct for these issues and modelled time on treatment using the Kaplan-Meier discontinuation curves to which the ERG fitted a series of parametric survival curves. Based on the AIC and BIC criteria, the exponential curve was selected, which generated a mean time on crizotinib post progression of 11.73 months. This overcame the issues of using a median instead of a mean value which is incorrect practice, and the implementation issues in the company model.

Similar issues were identified in the model relating to time on second-line docetaxel (which in the company model was informed from PFS data from PROFILE 1007). The ERG was, however, unable to obtain a treatment discontinuation curve for second-line therapy, and it was uncertain whether second-line therapy would in fact be offered in practice. Due to these issues the ERG removed second-line treatment in the ERG base-case and patients were assumed to move directly onto BSC.

3.4.4 Administration Costs

The company's model assumed that crizotinib would not accrue any ongoing administration costs as it is an oral therapy, and therefore does not require hospital admission. The ERG questioned this but found there to be inconsistency across previous NICE appraisals over whether administration costs should be included for oral therapies. The oral therapy nintedanib for previously treated locally advanced, metastatic or locally recurrent NSCLC (TA347) [20] was considered to not incur administration costs, but in the appraisal of crizotinib for previously treated NSCLC ALK-positive patients (TA 296) [1] it was judged that administration costs should be included. The ERG considered the previous crizotinib appraisal to be the most relevant and reflecting TA 296, applied an administration cost of £163 in each cycle of the model.

3.4.5 Additional Issues

In addition to the principal issues outlined above the ERG also identified a number of other issues, which included:

- Choice of comparator therapies, in particular the failure to include pemetrexed maintenance therapy and crizotinib as a second-line therapy which, while not included in the final NICE scope, are available via the CDF and are therefore representative of current UK practice.
- The ERG considered that the utility values for pre-progressed pemetrexed chemotherapy patients who have completed treatment were likely to be underestimated due to limitations in the follow-up of these patients during the PROFILE 1014 trial.
- The ERG had concerns regarding the assumption that patients whose disease progressed would for one cycle experience a utility that was a mid-point between the pre-progression and post-progression utility, as this led to the potential double-counting of utility.
- The ERG had concerns regarding the assumption that pemetrexed chemotherapy patients receive a six cycle regimen of chemotherapy based on PROFILE 1014. The clinical advisors to the ERG stated that although the aim may be to offer six cycles this is not always achievable and patients typically receive 4 cycles of therapy. Furthermore, the SmPC for pemetrexed in combination with platinum-based chemotherapy allows for between 4 and 6 cycles of chemotherapy [21].
- The company model assumed no drug wastage for either crizotinib or comparator therapies. The ERG considered this inappropriate and thought it was likely to underestimate the ICER due to the higher costs of crizotinib.
- The ERG considered that the company had underestimated the cost of ALK testing and identified an alternative cost based on a large survey of UK testing facilities which estimated much higher unit costs [22].

3.5 Conclusions of the ERG's Review

PROFILE 1014 showed crizotinib to have a significant benefit in terms of median PFS compared to the pemetrexed chemotherapy group (HR 0.45, 95% CI 0.35 to 0.60). The OS data were immature and median OS was not reached, with an unadjusted hazard ratio for death with crizotinib of 0.821 (0.536 to 1.255). A number of methods of adjustment for crossover were implemented, with hazard ratios

ranging from 0.571 to 0.674. However, not all were statistically significant and there was substantial crossover which wasn't completely accounted for. Furthermore, there is evidence to suggest that the assumption of Cox proportional hazards to model survival does not hold. There also remain uncertainties surrounding the clinical characteristics and prognosis of a typical population of patients with advanced non-squamous ALK-positive NSCLC and the comparability of the populations in PROFILE 1014 with the UK ALK-positive NSCLC population. The economic model contained a number of errors and potentially over-stated the cost-effectiveness of crizotinib through the way time spent on treatment, administration costs and ALK testing costs were implemented.

The ERGs base-case analysis with a PAS applied found that in a variety of scenarios crizotinib could not be considered a cost-effective therapy. However, these results were highly uncertain due to the immaturity of the OS data, with different combinations of parametric functions used to model survival producing a wide range of ICER values.

4 NICE Guidance

4.1 Preliminary guidance

The NICE appraisal committee considered whether crizotinib should be given NHS approval and whether it met NICE's end of life criteria. On balance the committee concluded that crizotinib is clinically effective and increases PFS, and likely increases OS compared with pemetrexed chemotherapy plus either cisplatin or carboplatin in people with ALK-positive NSCLC. However, the committee believed that the results presented in the ERG's analysis most closely reflected the committee's preferred assumptions, while also acknowledging that these results likely overestimated the ICER. The preliminary NICE recommendation was that although crizotinib may meet the end of life criteria it is not a cost-effective option for the first-line treatment of ALK-positive non-squamous NSCLC, even with the PAS applied.

4.1.1 Company's Response to Preliminary Guidance

The company rejected the ERGs argument regarding the utility value used for pre-progression pemetrexed chemotherapy patients, and presented new data to support a lower utility value, claiming that those on crizotinib experience a greater reduction in symptom burden. Additionally, the company also revised upward the utility value used for patients continuing to receive crizotinib therapy beyond progression, presenting new EQ-5D data to support the change. The company also rejected the ERGs estimate of ALK testing costs, and instead pointed to information that was provided by a pathologist at the appraisal committee meeting who stated that an IHC test would likely cost £50-100. The company therefore assumed a midpoint of £75, which increased the cost per positively identified patient from the company's original base-case to £2,380.

The company accepted that there may be administration costs associated with crizotinib, however they reiterated the inconsistency in related NICE submissions, and objected to the value used by the ERG. The company stated that due to the similarities between crizotinib, and the recently appraised ceritinib (TA395) [23]that it would be appropriate to include the same administration cost for crizotinib that was accepted by NICE in this instance. Therefore the company included a dispensary cost of £14.40 in each cycle of the model. The company also included an increased the PAS discount which was applied to the list price of crizotinib.

The company revised the ERG's changes to time on treatment, which were based on the survival curve for time on treatment from PROFILE 1014, by adjusting time on treatment using the "real-world" patient characteristics identified in Davis et al. 2015[17]. This ensured that time on treatment was estimated in a way that was consistent with the modelling of PFS and OS.

The company considered that the committee's preferred analysis underestimated the OS gains from crizotinib as it implied a mean OS gain of just 0.8 months. The company stated that the OS gain will be at least 7.1 months as this value was accepted by the committee in the second-line appraisal of crizotinib for NSCLC, and that the value of 0.8 months contradicts the opinion of clinical experts which claim a benefit of 7.1-13 months. The company supplied new analyses where the proportional hazards assumption was relaxed, but also included results where proportional hazards was assumed, as they believed that the tests that they had conducted indicated that the proportional hazards assumption was appropriate. The curves were then adjusted using data from Davis et al. 2015 [17] to ensure the curves were more reflective of patients found in practice.

The company incorporated all of the above changes and used a range of parametric functions in order to model PFS and OS, assuming proportional hazards in some instances, while modelling the curves

independently in others. The company then excluded all scenarios which generated an OS gain of less than 7.1 months as they deemed this clinically implausible, and all scenarios where the mean life expectancy on pemetrexed chemotherapy was greater than 24 months as this would result in the end of life criteria no longer holding. This left eleven possible combinations of independent curves and four possible choices of parametric functions if proportional hazards were assumed, with ICERs ranging from £31,708 to £49,186 per QALY. The company further excluded curves which produced what they deemed as implausibly large OS estimates for crizotinib, and those which produced mean OS values greater than the median OS values as they claimed this contradicted clinical expert opinion. If mean OS is greater than median OS then this would imply no tail in the survival curve which seemed unlikely. This resulted in two possible curve pairings when separate curves were modelled and four when proportional hazards were assumed. The company's preferred independent parametric curve analysis generated an ICER of £47,921 per QALY and their preferred model making use of the proportional hazards assumption produced an ICER of £49,186 per QALY when the PAS was applied.

4.1.2 ERG Critique of the Response Submitted by the Company

Table 1 summaries the assumptions used in each version of the model including the ERG's re-analysis following the company's appraisal consultation document (ACD). The ERG incorporated the new analysis presented by the company regarding time on treatment, but rejected a number of other assumptions including revisions made to administration costs and ALK testing costs, and revisions to utility values for pre-progressed pemetrexed patients following discontinuation of treatment and crizotinib patients continuing to receive treatment beyond progression.

Table 1 Summary of model assumptions

Parameter	Assumption in company base-case	Committee's preferred analysis	Assumption in revised company model	Assumption in ERG re-analysis
Utility values for pre-progression pemetrexed patients (once off treatment)	Assumes constant utility score of 0.72 for pre-pre-progressed pemetrexed patients	Assumes a utility score of 0.81 for pemetrexed patients who have completed treatment, but not progressed.	Assumes a utility score of 0.75 for pemetrexed patients who have completed treatment, but not progressed.	Assumes a utility score of 0.81 for pemetrexed patients who have completed treatment, but not progressed.
Time on treatment with crizotinib	Assumes patients receive crizotinib beyond pre-progression for maximum of 4 cycles (mean 2.2)	Time on treatment is estimated from unadjusted parametric curve based on time on treatment in the PROFILE 1014 study.	Time on treatment is estimated from parametric curve adjusted using real world data.	Time on treatment is estimated from parametric curve adjusted using real world data.
Crizotinib administration costs	No administration costs included	Administration costs of £163.85 per month included.	Administration costs of £14.40 per month included.	Administration costs of £163.85 per month included.
ALK testing costs	Cost of ALK testing based on file data.	Cost of ALK testing based on Cancer Research UK survey. Cost of testing per ALK patient is £4500.	Cost of ALK testing based on expert testimony. Cost of testing per ALK patient is £2379.89.	Cost of ALK testing based on Cancer Research UK survey. Cost of testing per ALK patient is £4500.

Post-progression utility score for crizotinib patients when still on treatment	Assumes a utility score of 0.74 based on improved symptom control and lower toxicity	Assumes a utility score of 0.74.	Assumes a utility score of 0.78 based on analysis of HRQoL data from PROFILE 1014.	Assumes a utility score of 0.74.
PFS and OS extrapolation	Assumes proportional hazard and common covariates for prognostic factors in each treatment group.	Separate curves are fitted to treatment and comparator and prognostic factors are stratified independently for each treatment group.	Assumes proportional hazard and common covariates for prognostic factors in each treatment group.	Separate curves are fitted to treatment and comparator and prognostic factors are stratified independently for each treatment group.

ERG evidence review group, *PFS* progression free survival, *OS* overall survival, *ALK* Anaplastic lymphoma kinase, *HRQoL* health-related quality of life

Importantly the ERG also rejected the company's defence of the use of proportional hazards, and highlighted that the assumption places a constraint on the data. The DSU document on this methods issue suggests that where individual patient level data are available it is generally more appropriate to fit separate curves [19]. This is because it is generally a more conservative position and avoids the potential for bias resulting from imposing the proportional hazards assumption. Similarly the ERG rejected the company's claim that the independent covariate stratification of survival curves is inappropriate and highlighted that this method required fewer assumptions than the alternative method adopted by the company.

In interpreting the OS data and the criteria used by the company to select from all possible survival curves the ERG also highlighted a number of issues. The company argued that mean OS for pemetrexed chemotherapy should not exceed 24 months as the committee had accepted that crizotinib met the end of life criteria. However, the ERG noted that this was not based on evidence but simply the opinion the committee gave with the information they were presented with at the time. The company also argued that mean OS gain should exceed 7.1 months, as this was the committees opinion of the OS gains when crizotinib was given as a second line therapy in PROFILE 1007. The ERG consider this assumption reasonable given evidence on the relative magnitude of PFS gains across PROFILE 1007 and 1014. However, this assumption was not entirely unproblematic because patients in second-line setting received therapy for a different duration of time, the comparator was docetaxel rather than pemetrexed, and because patients who receive second line treatment are likely to be different in their characteristics to those who receive first-line therapy. The ERG also agreed with the company that mean OS should be plausible given expectations on the survival of advanced ALK-positive NSCLC patients. However, due to the lack of evidence on OS for ALK-positive NSCLC patients the ERG considered it difficult to judge what should be considered as plausible. The ERG therefore consider a wider range of curves plausible than the company in their response.

When proportional hazards were assumed the ERGs revised base-case using the updated PAS generated an ICER of £58,029 per QALY gained. When the assumption of proportional hazards was relaxed, then assuming that the mean OS gain exceeded 7.1 months the estimated ICER was found to lie between £35,972 and £57,035 per QALY. The ICER assuming the company's preferred curve selection was £55,131 per QALY.

4.2 Final NICE Guidance

Following the consultation on the preliminary guidance, the NICE Appraisal Committee released the following final guidance to the NHS (TA406) [2]:

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

The committee agreed with many of the ERGs adjustments, however, concluded that the company’s assumed utility values, administration costs, and ALK testing costs were valid. It therefore concluded that the company’s independent parametric curve analysis, which generated an ICER of £47,291 per QALY gained, most closely reflected the committee’s preferred assumptions, and noted that the ICERs for other alternative curves were similar. However, the committee acknowledged that the uncertainty surrounding the cost-effectiveness of crizotinib was extensive, and that the company’s analysis did not incorporate all of the committees preferred assumptions.

5 ERG Conclusion

This STA highlighted the important role the ERG plays in the appraisal process and in particular the role it can play in error checking, identifying sub-optimal methods and questioning the validity of assumptions. The ERG was able to identify a significant number of calculation errors in the submitted company model that brought into question the internal validity of the analysis.

This STA also highlighted a number of general issues potentially important to future appraisals. Firstly, as with many cancer models, OS was a key parameter in estimating cost-effectiveness. The evidence provided in support of OS gains was, however, subject to a number of limitations many of which directly arose due the design of the PROFILE 1014 trial. The most significant of these issues related to the immature data-set that was available, which created significant uncertainty regarding the magnitude of OS gains, and in the opinion of the ERG meant that OS could not be meaningfully estimated. This uncertainty led to a wide range of potential estimates of cost-effectiveness, both above and below threshold values.

Secondly, crizotinib, unlike chemotherapy is not given in a fixed treatment regimen and patients are treated up to and even beyond progression of disease. As such, time on treatment is an important determinant of overall drug acquisition costs and consequently estimated cost-effectiveness. The ERG was however, critical of the approach taken by the company to model time on treatment. The ERG made significant revisions to the economic model to rectify these issues which had a significant impact on the estimated ICER.

Finally, this STA highlighted past inconsistencies in previous NICE appraisals regarding the application of administration costs for oral therapies. While not instrumental in the current analysis a more consistent approach by NICE committees would provide guidance for future submission and help avoid unnecessary confusion.

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Compliance with Ethical Standards

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