NICE National Institute for
Health and Care Excellence

Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer

Technology appraisal guidance
Published: 27 June 2012

www.nice.org.uk/guidance/ta258

Your responsibility

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

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

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

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1   Erlotinib is recommended as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer (NSCLC) if:

- they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation **and**

- the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012).

2 The technology

2.1 Erlotinib (Tarceva, Roche Products) is an active inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK). It blocks the signal pathways involved in cell proliferation and slows the growth and spread of the tumour. It has a UK marketing authorisation 'for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with EGFR activating mutations'.

2.2 The summary of product characteristics lists the following adverse reactions to erlotinib: diarrhoea, rash, anorexia, gastrointestinal perforation, keratitis and rare cases of hepatic failure. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 Erlotinib is given orally at a recommended dosage of 150 mg/day. The cost of a pack of 30 (150-mg) tablets is £1,631.53 (excluding VAT; BNF, edition 63). Dosage reductions (typically to 100 or 50 mg/day) are possible if the clinician considers it appropriate, and erlotinib is also available in tablet strengths of 100 mg and 25 mg. The manufacturer of erlotinib has agreed a patient access scheme (revised in 2012) with the Department of Health in which a confidential discount from the list price is applied to original invoices. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Page 5 of 33

3 The manufacturer's submission

The Appraisal Committee considered evidence submitted by the manufacturer of erlotinib (Roche Products) and a review of this submission by the Evidence Review Group (ERG).

Decision problem

3.1   The manufacturer's approach to the decision problem was in line with the NICE scope for the population, intervention, outcomes and the economic evaluation. The manufacturer's submission focussed on a comparison of erlotinib with gefitinib for first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC. The manufacturer's submission did not include pemetrexed plus cisplatin or carboplatin as a comparator because of the declining use in clinical practice of this combination for first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC and the absence of suitable data for comparison in this population.

Clinical effectiveness

3.2   The manufacturer identified 2 randomised controlled trials (EURTAC and OPTIMAL) that compared erlotinib with platinum doublet chemotherapy as first-line treatment for patients with locally advanced or metastatic EGFR-TK mutation-positive NSCLC. The manufacturer based its evidence submission on the EURTAC trial with the OPTIMAL trial as supporting evidence. No studies were identified that compared erlotinib directly with gefitinib in this patient population, and so the manufacturer presented an indirect treatment comparison to assess the relative effectiveness of erlotinib and gefitinib.

3.3   The EURTAC trial was a European-based, open-label, phase 3, randomised trial of first-line erlotinib treatment compared with platinum doublet chemotherapy for patients with stage 3b or stage 4 NSCLC and EGFR-TK mutation-positive tumours. The trial included 173 randomised patients and was conducted in 42 centres in Spain, France and Italy. Patients were screened for EGFR-TK mutations and those with EGFR-TK mutation-positive tumours were randomised to receive

either 150 mg of erlotinib orally once a day or 1 of the following standard platinum-based chemotherapy regimens: cisplatin or carboplatin plus docetaxel; cisplatin or carboplatin plus gemcitabine. In the randomisation, patients were stratified according to Eastern Cooperative Oncology Group (ECOG) status (either ECOG=0, or ECOG=1 or 2) and the mutation type (deletion in exon 19 or mutation in exon 21 L858R). Treatment continued until disease progression, unacceptable adverse reactions, death, or until 4 chemotherapy cycles were completed. Following disease progression, patients were allowed to cross over in either direction, if clinically appropriate.

3.4   The primary outcome examined in the EURTAC trial was the length of progression-free survival. This was assessed as the time from randomisation to the first occurrence of progressive disease or death from any cause. Secondary outcomes included overall survival, best overall response, disease control, health-related quality of life and safety. Best overall response was defined in terms of the number of patients with either a complete or partial response (as defined by the Response Evaluation Criteria in Solid Tumours [RECIST] version 1 criteria) and disease control included patients with either a complete or partial response and those with stable disease for at least 6 weeks.

3.5   The manufacturer's submission described the results of the intention-to-treat analysis for all randomised patients. The median and 95% confidence limits of progression-free and overall survival between the erlotinib and the platinum doublet chemotherapy arms were obtained from the Kaplan–Meier estimate of the survival function. A 2-sided log-rank test was used to assess the difference in outcomes between the 2 treatment arms. A Cox proportional hazards model was used to estimate the hazard ratio and 95% confidence intervals.

3.6   The EURTAC trial included 153 patients at the time of the interim analysis and 173 at the updated analysis. For the updated analysis there were 86 patients in the erlotinib arm and 87 in the platinum doublet chemotherapy arm. Data for progression-free survival and overall survival from the EURTAC trial are still being collected. Both the interim and updated analyses showed that progression-free survival was statistically significantly longer for patients treated with erlotinib than for patients treated with platinum doublet chemotherapy. In the updated analysis, the median progression-free survival in the platinum doublet chemotherapy arm was 5.2 months compared with 9.7 months in the erlotinib

arm. The risk of disease progression or death was statistically significantly reduced (by 63%, HR 0.37, 95% CI 0.25 to 0.54, p<0.0001) for patients in the erlotinib arm. In the updated analysis the manufacturer reported overall survival results for 69 (40%) events. The median overall survival was 19.5 months in the platinum doublet chemotherapy arm and 19.3 months in the erlotinib arm (hazard ratio 1.04 [95% CI 0.65 to 1.68], p=0.8702). More patients in the platinum doublet chemotherapy arm received second and further-line treatments than patients in the erlotinib arm (77% [n=67] compared with 45% [n=39]). In the platinum doublet chemotherapy arm, 66 of the 67 patients received at least 1 treatment with either erlotinib or gefitinib. In the updated analysis, the best overall response (as defined in section 3.4) was statistically significantly greater in the erlotinib arm than the platinum doublet chemotherapy arm (58.1% [95% CI 47.0% to 68.7%] compared with 14.9% [95% CI 8.2% to 24.2%], p<0.0001).

3.7 The manufacturer submitted the results of the OPTIMAL trial, which was carried out in 22 centres in China, as additional evidence. The OPTIMAL trial was a multicentre, open-label, phase 3, randomised trial of first-line erlotinib treatment compared with platinum doublet chemotherapy for chemotherapy-naive patients with stage 3b or stage 4 NSCLC whose tumours were EGFR-TK mutation-positive. Patients were randomised (n=165) to receive either 150 mg of erlotinib orally once daily or gemcitabine plus cisplatin chemotherapy. Treatment continued until disease progression, unacceptable adverse reactions or death, or until 4 chemotherapy cycles were completed. Following disease progression, patients were allowed to cross over in either direction, if clinically appropriate.

3.8 In the most recent analysis from the OPTIMAL trial, progression-free survival was statistically significantly longer in patients treated with erlotinib than in patients treated with platinum doublet chemotherapy. The median progression-free survival in the platinum doublet chemotherapy arm was 4.6 months (95% CI 4.21 to 5.42) compared with 13.7 months (95% CI 10.58 to 15.28) in the erlotinib arm. The risk of progression or death was statistically significantly reduced (by 84%, HR 0.16; 95% CI 0.10 to 0.26, p<0.0001) for patients in the erlotinib arm. The overall survival data from the OPTIMAL trial were not presented because too few deaths had been recorded at the time of the analysis.

3.9 The manufacturer did not perform a meta-analysis of progression-free survival from the EURTAC and OPTIMAL trials because heterogeneity between the

treatment effects was identified using an assessment of heterogeneity recommended by the Cochrane Collaboration. The manufacturer noted that factors possibly contributing to the heterogeneity included: the different ethnicity of the patients in the trials; better adherence in the OPTIMAL trial and poorer efficacy of the comparator in the OPTIMAL trial.

3.10   A systematic review identified 4 randomised controlled trials comparing gefitinib with various doublet chemotherapy regimens in East Asian populations (IPASS, First-SIGNAL, WJTOG3405 and NEJGSG002). The data from the gefitinib trials were pooled by assuming that the doublet chemotherapy was of equal efficacy in each of the 4 trials (Ku et al. 2011). Across the 4 studies, the estimated hazard ratio for median progression-free survival was 0.45 (95% CI 0.38 to 0.55, $p<0.001$).

3.11   For the indirect comparison of erlotinib with gefitinib the manufacturer assumed that the platinum doublet chemotherapy arms of the EURTAC and OPTIMAL trials could be linked to the gefitinib meta-analysis using platinum doublet chemotherapy as the anchor point. From an assessment of the similarities and differences between the studies, the manufacturer concluded that ethnicity is the key factor for the differences and so a robust indirect comparison should involve studies based in an East Asian population. The manufacturer presented results from 4 possible indirect comparisons of the 2 erlotinib trials and combinations of them against the gefitinib meta-analysis. In the indirect comparisons the hazard ratio for median progression-free survival varied between 0.36 (95% CI 0.22 to 0.59) and 0.82 (95% CI 0.54 to 1.26) depending on the combination of studies chosen. In the manufacturer's view the hazard ratio for progression-free survival from the indirect comparison of EURTAC with the gefitinib meta-analysis (hazard ratio 0.82 [95% CI 0.54 to 1.26]) was the most appropriate estimate of the clinical effectiveness of erlotinib compared with gefitinib in patients with EGFR-TK mutation-positive NSCLC in England and Wales.

3.12   The manufacturer stated that there were insufficient data on health-related quality of life collected in the EURTAC trial for any analysis to be done. In the OPTIMAL trial, quality of life was assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and the Trial Outcome Index. Results were presented from 128 (83.2%) patients and demonstrated that approximately 70% of patients receiving first-line erlotinib experienced

significant, clinically relevant improvements in quality of life compared with 30% of patients receiving platinum doublet chemotherapy across all FACT-L scales measured.

3.13 The incidence and nature of adverse reactions to erlotinib in the EURTAC and OPTIMAL trials were consistent with previously collected data on the use of erlotinib for first-line maintenance treatment and relapsed NSCLC. The manufacturer noted the longer duration of active treatment with erlotinib compared with chemotherapy and that the extended treatment period may also have increased the number of adverse reactions reported. In the EURTAC trial, patients in the erlotinib arm had a typical treatment duration of 9 to 10 months before progression or unacceptable adverse reactions, whereas patients in the chemotherapy arm received a maximum of 4 cycles over approximately 3 months. Most of the reported adverse reactions in both arms were grade 1 or grade 2 (432 out of 527 events [82.0%] in the chemotherapy arm and 621 out of 681 events [91.2%] in the erlotinib arm). Fewer patients experienced grade 3 or 4 events in the erlotinib arm (31 patients [41.3%]) than in the chemotherapy arm (49 patients [66.2%]).

3.14 In the EURTAC trial, low grade skin reactions and diarrhoea were the most commonly reported adverse reactions in patients who received erlotinib. Skin reactions were mainly mild or moderate, with 5% of patients experiencing grade 3 rash and 1% experiencing dry skin. No grade 4 skin reactions were reported. Diarrhoea was also mainly mild or moderate, with 4% of patients experiencing grade 3 diarrhoea.

Cost effectiveness

3.15 The manufacturer presented a de novo economic analysis that assessed the cost effectiveness of erlotinib compared with gefitinib for the first-line treatment of EGFR mutation-positive NSCLC. In line with the NICE reference case, outcomes were expressed in terms of quality-adjusted life years (QALYs), an NHS and personal social services perspective was adopted, and costs and benefits were discounted at 3.5%. The treatments compared in the model were first-line erlotinib (one 150-mg tablet daily until disease progression) or gefitinib (one 250-mg tablet daily until disease progression). No second-line treatments were

included because the second-line treatment options were considered identical for both erlotinib and gefitinib. The manufacturer presented a semi-Markov economic model with 3 health states: progression-free survival, progressed disease and death. The model had a 10-year time horizon and a cycle length of 1 month.

3.16   The manufacturer considered that the EURTAC study was more representative of the outcomes expected in UK clinical practice than the OPTIMAL study and so the clinical data in the model were derived from the EURTAC trial and the indirect comparison of erlotinib (EURTAC trial) and gefitinib (Ku et al. 2011). An area under the curve approach was used to calculate the proportion of patients in the progression-free survival health state each month. For erlotinib, the estimated survival curve for the progression-free state was based on the observed EURTAC data up to month 16 and was then extrapolated assuming an exponential distribution. For gefitinib, the progression-free survival curve was derived by transforming the erlotinib survival curve using the hazard ratio for progression-free survival (HR 0.82) from the indirect comparison of erlotinib (EURTAC trial) and gefitinib (Ku et al. 2011). The same transition probabilities, derived from the EURTAC data, were used for both erlotinib and gefitinib for the transition between the progression-free survival health state and death and between the progressed disease health state and death.

3.17   Utilities in the model were based on values from the study of Nafees et al. (2008). These utility values were estimated using the standard gamble approach with 105 members of the UK general public who were asked to value health-state descriptions of patients receiving second-line chemotherapy for NSCLC. These values have been used in 4 previous NICE appraisals of drugs for NSCLC (pemetrexed for the first-line treatment of NSCLC, pemetrexed for the maintenance treatment of NSCLC, gefitinib for the first-line treatment of locally advanced or metastatic NSCLC, and erlotinib monotherapy for the maintenance treatment of NSCLC). The utility values for the progression-free survival health state were treatment dependent and were calculated from the response rate and the incidence of adverse reactions (grade 3 or 4 rash; grade 3 or 4 diarrhoea). The utility value for the progression-free health state for patients receiving erlotinib (0.661) was based on the response rate in the EURTAC trial (58.10%). The value for patients receiving gefitinib (0.656) was based on a gefitinib response rate (28.23%) which was estimated indirectly by applying the relative

response from the gefitinib meta-analysis to the chemotherapy response rate observed in the EURTAC trial (14.9%). The utility decrement value for progressed disease (-0.1798 relative to the progression-free survival stable disease baseline value of 0.6532) was taken from the study of Nafees et al. (2008) and assumed that the choice of first-line treatment had no influence on the utility patients experienced post progression.

3.18   The manufacturer included costs associated with drug acquisition and administration, best supportive care, terminal care, monitoring and adverse reactions in the economic model. These were estimated from a range of secondary sources such as reference costs, BNF and submissions for previous NICE technology appraisals. The monthly cost of erlotinib with the list price (see section 2.3) was £1,631.53 based on a daily dose of 150 mg. The manufacturer also presented analyses based on the erlotinib drug cost with the earlier 14.5% discount and with the revised patient access scheme. Under the terms of the gefitinib patient access scheme approved by the Department of Health, there is a single fixed cost of £12,200 per patient when the third monthly pack of gefitinib is supplied. In the base-case analysis, the proportion of patients for whom the £12,200 payment was made was derived by applying the hazard ratio for progression-free survival from the indirect comparison of erlotinib and gefitinib (HR 0.82) to the 'time to last dose' curve generated from the EURTAC data. This results in approximately 76% patients incurring the fixed cost for gefitinib. No administration cost for the erlotinib patient access scheme was included in the economic model because it is a simple discount. For the gefitinib patient access scheme, the manufacturer assumed that the administration cost includes a one-off £70 cost (patient registration, invoicing and query management) and an ongoing monthly cost of £35 (completion of request pack and payment reconciliation).

3.19   Results from the manufacturer's base-case analyses (including the discount under the patient access scheme as revised in 2012) for erlotinib compared with gefitinib show an incremental cost-effectiveness ratio (ICER) of £21,874 per QALY gained. From deterministic sensitivity analyses for a range of parameters, the manufacturer identified the main factors affecting the cost effectiveness as the hazard ratio for progression-free survival for gefitinib and the proportion of patients for whom the gefitinib patient access scheme payment was needed. Varying the hazard ratio for progression-free survival from the indirect

comparison from 0.36 to 0.58 resulted in an ICER between £15,712 and £16,552 per QALY gained. When the proportion of patients incurring the fixed charge for gefitinib was varied from 85% to 100%, the ICER was always less than £10,066 per QALY gained. The manufacturer also presented a probabilistic sensitivity analysis which resulted in an ICER of £25,791 per QALY gained for erlotinib compared with gefitinib. There was a 36% probability of erlotinib being cost effective if the maximum acceptable ICER was £20,000 per QALY gained; the probability was 63% if the maximum acceptable ICER was £30,000 per QALY gained.

Evidence Review Group comments

3.20   The ERG stated that without consideration of pemetrexed in combination with another drug (doublet chemotherapy) as a comparator, the evidence presented in the manufacturer's submission was incomplete and did not allow a full evaluation of erlotinib as set out in the decision problem. The ERG considered pemetrexed-based doublet chemotherapy a valid comparator because almost all patients whose tumours are EGFR-TK mutation-positive have non-squamous lung cancer. In addition, some of these will be treated with pemetrexed-based doublet chemotherapy in hospitals that do not routinely test for EGFR and also in situations when delaying treatment to await EGFR-TK status would be detrimental to the patient's health. The ERG stated that the difference in efficacy between pemetrexed and gefitinib has become clearer since the publication of NICE's technology appraisal guidance on gefitinib for the first-line treatment of locally advanced or metastatic NSCLC. The ERG stated that pemetrexed is the only first-line treatment for patients with non-squamous cell lung cancer which has demonstrated a statistically significant gain in overall survival when compared with third-generation chemotherapy. Recently published updates to a randomised controlled trial of gefitinib have reported no overall survival gain for gefitinib compared with third-generation chemotherapy.

3.21   In the ERG's view, the EURTAC trial was well-designed and suitably powered to demonstrate its primary objective. It considered the inclusion and exclusion criteria to be reasonable and the baseline characteristics of patients in EURTAC trial to reflect patients in UK clinical practice who would be considered eligible for treatment with an EGFR-TK inhibitor. The ERG was unable to comment definitively

on the quality of the supporting evidence from the OPTIMAL trial because the clinical study report was not made available.

3.22 The ERG considered that the use of conventional proportional hazards methods to estimate hazard ratios in either the gefitinib or erlotinib trials compared with any other drug is problematic. The assumption of proportional hazards was not tested by the manufacturer. The ERG presented plots of the hazard rates for gefitinib and erlotinib and comparators, which suggested an assumption of proportional hazards was not valid. A comparison of the cumulative hazards for each of the 6 trials of a tyrosine kinase inhibitor (either gefitinib or erlotinib) compared with platinum doublet chemotherapy showed 2 separate phases. During the first 4 months of treatment (corresponding approximately to the period of standard chemotherapy), there is very little difference in hazards between intervention and comparator arms. However, in the following 2 to 3 months the slopes of the lines in all trial arms increase, but with the comparator arms diverging rapidly from the erlotinib or gefitinib arms. A more appropriate method of estimating the relative efficacy involves treating these 2 time periods as separate phases (equivalent to active therapy followed by observation and maintenance therapy) and deriving separate hazard ratios for each phase (using a landmark analysis for the second phase). In the ERG's view, relative efficacy should be estimated using this approach and the estimates obtained explored in a revised economic model.

3.23 The ERG highlighted that the manufacturer identified heterogeneity between the EURTAC and OPTIMAL trials by comparing the median progression-free survival. In the ERG's view the heterogeneity identified by the manufacturer is simply a consequence of using this outcome measure. A comparison of the Kaplan–Meier curves for progression-free survival from the 2 trials shows close correspondence in the comparator arms. The 2 erlotinib arms follow very similar trends although they are slightly separated. Crucially, across successive time periods the gradients of the cumulative hazard curves are very similar. The ERG concluded that the balance of evidence favours including results from both EURTAC and OPTIMAL trials in any indirect comparison.

3.24 The ERG was not convinced that any of the 4 options for the indirect comparison described by the manufacturer are appropriate. It believed that data from the EURTAC and OPTIMAL trials should be pooled and that revised relative efficacy

measures be used (see section 3.22). From an analysis of the progression-free survival and the cumulative hazard curves, the ERG showed that after 12 months the results for patients in the IPASS trial (gefitinib compared with doublet chemotherapy) diverge from the other gefitinib trials. The ERG recommended that a sensitivity analysis that excludes the IPASS data should be undertaken as part of the indirect comparison.

3.25   The ERG was only able to offer a limited critique of the cost-effectiveness results submitted by the manufacturer because of its concerns about the structure of the model. In the ERG's view pemetrexed plus cisplatin should be included as a comparator and there was also an argument for including the 4 third-generation platinum doublets (docetaxel, gemcitabine, paclitaxel and vinorelbine) in a full evaluation as in NICE's technology appraisal guidance on gefitinib for the first-line treatment of locally advanced or metastatic NSCLC. In the ERG's view, the omission of all comparators other than gefitinib has resulted in a simple model structure without a robust, multi-way economic comparison that would most likely have reduced the probability of erlotinib appearing as the most cost-effective option.

3.26   The ERG highlighted that the current model yielded an overall survival benefit for patients with EGFR-TK mutation-positive NSCLC receiving first-line erlotinib compared with those receiving gefitinib, which has not been demonstrated by the published evidence from randomised controlled trials. The submitted model does not include any data on overall survival and after disease progression all surviving patients are assumed to follow the same post-progression course and incur the same costs. The direct consequence of the simple model structure is that most of the estimated difference in progression-free survival between patients receiving gefitinib and those receiving erlotinib is preserved by a common post-progression phase, which translates into a similar difference in overall survival.

Revised economic analyses following consultation

3.27   Additional evidence was provided by the manufacturer in response to NICE's request in the appraisal consultation document for an updated economic model and analyses. The updated model included, as requested, an assumption of equal

progression-free survival and equal utilities for the progression-free survival health state for the 2 treatments (erlotinib and gefitinib). The manufacturer provided analyses exploring the sensitivity of the cost-effectiveness results to varying the proportion of patients (equally for erlotinib and gefitinib) in the progression-free survival health state at day 60 (for whom the fixed charge for gefitinib is incurred under the patient access scheme). The proportion in the base case was 80%, which was the proportion of patients still receiving erlotinib at the start of the third month of the EURTAC trial. In the sensitivity analyses, the proportion was varied, equally for erlotinib and gefitinib, from the base case to 100%. The costs in the model were not modified. Results from the updated model showed that erlotinib becomes more cost effective than gefitinib when at least 91% of patients incur the gefitinib fixed charge. In the manufacturer's view the proportion of patients incurring the gefitinib fixed charge at day 60 is likely to be more than 90%, as demonstrated in each of the 4 gefitinib trials. Also, data from recent market surveys in Europe and the UK indicate that at least 95% of patients receiving gefitinib have 60 or more days of treatment (and thus incur the fixed charge).

3.28 The ERG explored the analyses using the manufacturer's updated model and confirmed that the Committee's requests specified in the appraisal consultation document had been implemented. However, the ERG noted that the manufacturer assumed the same rates of adverse reactions for the 2 treatments (erlotinib and gefitinib) when calculating the utility value. The ERG showed that when the same utility value is used for both treatments and the different rates of adverse reactions are retained in the updated model, there is a small additional cost of £5.24 per patient for erlotinib treatment. The ERG was concerned that the cost of administering the gefitinib patient access scheme (a mean cost of £438 per patient over the treatment period) was overstated in the manufacturer's model. The ERG assumed that pack ordering and reconciliation would be needed only once a year and estimated a mean cost for administering the gefitinib patient access scheme of between £111 and £118 per patient. The ERG explored the impact of updating the manufacturer's model with these costs and included the adverse reaction rates for each treatment. The ERG's results demonstrated that erlotinib is cost effective compared with gefitinib when 95% or more of patients receiving gefitinib incur the fixed charge for gefitinib.

3.29 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 erlotinib, having considered evidence on the nature of locally advanced or metastatic EGFR-TK mutation-positive NSCLC and the value placed on the benefits of erlotinib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical practice

4.2   The Committee discussed the clinical need of patients with locally advanced or metastatic EGFR-TK mutation-positive NSCLC. It heard from the clinical specialists that the main aim of treatment is to extend progression-free and overall survival with the fewest adverse reactions and with the best quality of life possible for the remaining months of life. The clinical specialists also highlighted that for this patient population an oral treatment with a tyrosine kinase inhibitor, such as gefitinib or erlotinib, is usually associated with an improved quality of life compared with platinum doublet chemotherapy.

4.3   The Committee heard from the clinical specialists that current UK clinical practice for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC is to use gefitinib as recommended in NICE's technology appraisal guidance on gefitinib for the first-line treatment of locally advanced or metastatic NSCLC. The Committee also heard that chemotherapy with pemetrexed plus carboplatin or cisplatin may be used as a second-line treatment and is rarely used as first-line treatment for this patient population. The Committee accepted that gefitinib is current standard practice in England and Wales for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.

4.4   The Committee discussed the availability of EGFR testing to inform the first-line treatment of locally advanced or metastatic NSCLC. It heard from the clinical specialists that EGFR testing is standard practice for this patient population

across almost all the NHS. The Committee accepted that EGFR testing is standard practice in England and Wales when making decisions about the first-line treatment of locally advanced or metastatic NSCLC.

4.5   The Committee discussed the use of tyrosine kinase inhibitors in clinical practice for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC. It heard from clinical specialists that in their opinion erlotinib and gefitinib are very similar treatments with similar efficacy and levels of adverse reactions. The clinical specialists highlighted that having the choice of 2 similar treatments enables better management of adverse reactions. The Committee also heard from the clinical specialists that the adverse reactions associated with both these treatments are much less common than those associated with chemotherapy but may vary (for example, rash may be more common with erlotinib and interstitial lung disease may be more common with gefitinib). Erlotinib offers the advantage of being able to vary the dosage by using tablets of different dose strength. The Committee also heard that the patient access scheme for gefitinib is not straightforward and that hospitals may find the patient access scheme for erlotinib easier to administer. The Committee concluded that further first-line treatment options for patients with locally advanced or metastatic EGFR-TK mutation-positive NSCLC would be valuable for clinical practice.

Clinical effectiveness

4.6   The Committee considered the evidence submitted by the manufacturer on the clinical effectiveness of erlotinib. The Committee agreed with the manufacturer that although pemetrexed plus cisplatin or carboplatin was listed as a comparator in the scope, recent changes in the clinical pathway since the publication of NICE's technology appraisal guidance on gefitinib for the first-line treatment of locally advanced or metastatic NSCLC in 2011 have resulted in the use of gefitinib for first-line treatment for most patients with EGFR-TK mutation-positive NSCLC, as confirmed by the clinical specialists (see section 4.3). The Committee concluded that gefitinib is the appropriate comparator for this appraisal.

4.7   The Committee noted that the evidence of clinical effectiveness of erlotinib in locally advanced or metastatic EGFR-TK mutation-positive NSCLC was based on

the EURTAC trial with supporting evidence from the OPTIMAL trial. The Committee noted that both trials provided evidence of increased progression-free survival compared with doublet chemotherapy. The Committee agreed that the EURTAC trial provided evidence relevant to clinical practice in the NHS in England and Wales. The Committee concluded that the evidence from the EURTAC trial demonstrated that erlotinib increased progression-free survival compared with doublet chemotherapy.

4.8 The Committee considered the indirect comparison presented by the manufacturer. The hazard ratio for progression-free survival used in the model (0.82, 95% CI 0.54 to 1.26) was obtained by comparing the EURTAC trial with the gefitinib meta-analysis. The Committee noted the wide confidence intervals around the estimated hazard ratio for progression-free survival, but recognised the difficulties in constructing a robust indirect comparison given the limited number of studies in this patient population and the heterogeneity between the studies. The Committee discussed the heterogeneity between the trials and the possible prognostic factors that may have influenced heterogeneity, such as ethnic group and class of mutation (exon 19 deletion compared with mutation in exon 21 L858R). It heard from the clinical specialists that the difference in the response rate in the chemotherapy arms between the EURTAC and OPTIMAL trials was within the acceptable range for this group of patients. The Committee noted that the ERG had pointed out the similarities in the curves for progression-free survival from the EURTAC and OPTIMAL trials and the difference between the results from the IPASS trial and the other gefitinib trials after 12 months of treatment. The Committee heard from the ERG that the gefitinib trials had not been uniformly reported so it was not possible to be certain whether the differences were caused by factors such as differing variables in multivariate analyses or small patient numbers. The Committee also discussed the ERG's comments about the difficulties associated with using the proportional hazards assumption for these data and the possibility of using revised efficacy outcomes. The Committee was not convinced that an indirect comparison could be used with the existing data, to support the assumption that erlotinib was more effective than gefitinib, given the heterogeneity of the populations included and the variations in prognostic factors within the populations. In addition, the Committee noted the clinical specialists' view that erlotinib and gefitinib are very similar treatments with similar efficacy for locally advanced or metastatic EGFR-TK mutation-positive NSCLC (see section 4.5). The Committee concluded that

there was insufficient evidence to suggest a difference in clinical effectiveness between erlotinib and gefitinib in the model and therefore the most appropriate value for the hazard ratio for progression-free survival between the treatments is 1.

4.9   The Committee discussed the overall survival data from the trials. It noted that the data for overall survival were incomplete (either not available for all patients or not known) for the EURTAC and OPTIMAL trials and therefore no comparison of overall survival benefit for erlotinib and gefitinib was available. It also noted the ERG's concerns about whether there was an overall survival benefit for treatment with a tyrosine kinase inhibitor compared with doublet chemotherapy in light of the recently published final results from the IPASS trial (gefitinib compared with doublet chemotherapy). Because of the similarities in the treatments and the lack of data on overall survival, the Committee was not convinced of a survival benefit for erlotinib compared with gefitinib for patients with locally advanced or metastatic EGFR-TK mutation-positive NSCLC.

4.10   The Committee considered the adverse reactions experienced by patients receiving treatment for locally advanced or metastatic NSCLC. It noted that data from the EURTAC trial demonstrated that fewer patients in the erlotinib arm experienced grade 3 or 4 events compared with the chemotherapy arm. Low grade skin reactions (rash grade 3, 5%) and diarrhoea (grade 3, 4%) were the most commonly reported adverse reactions associated with erlotinib. The clinical specialists confirmed that the adverse reactions associated with erlotinib and gefitinib were generally modest but slightly different. The Committee concluded that the adverse reactions associated with erlotinib were relatively mild in most patients and that from a clinical perspective there may be some advantage to having a choice of tyrosine kinase inhibitors for this patient group.

4.11   The Committee noted the lack of quality-of-life data from the EURTAC trial and heard from the clinical specialists that a common problem with studies in this patient population is the failure to complete questionnaires. The Committee was disappointed that there were insufficient quality-of-life data from the EURTAC trial for analysis. Because erlotinib and gefitinib are both oral tyrosine kinase inhibitors with similar efficacy and comparable adverse reactions, the Committee concluded that the health-related quality of life of patients would be similar for the 2 treatments.

Cost effectiveness

4.12   The Committee considered the manufacturer's original cost-effectiveness analysis and the ERG's critique. It noted that the manufacturer used a semi-Markov model to evaluate the cost effectiveness of erlotinib compared with gefitinib. The clinical data used in the model were derived mainly from the EURTAC trial and the indirect comparison of data from the EURTAC trial with the gefitinib meta-analysis described by Ku et al. (2011). The Committee was aware of the ERG's concerns that the structure of the model allowed the benefit in progression-free survival to be translated into an overall survival benefit in the economic model. Given the uncertainties associated with the hazard ratio for progression-free survival obtained from the indirect comparison (described in sections 3.22 to 3.25 and 4.8), as well as the lack of evidence demonstrating an overall survival benefit for erlotinib compared with gefitinib (see section 4.9), the Committee concluded that the cost effectiveness of erlotinib compared with gefitinib could be best assessed from an analysis which assumes equal clinical benefit between the treatments and focuses on their differential costs.

4.13   The Committee discussed the utility values used within the original model and noted that the utility value for the progression-free survival health state was 0.661 for erlotinib and 0.656 for gefitinib. It noted that the difference was mainly a result of difference in the response rates (58% for erlotinib compared with 28% for gefitinib) used in the calculation. The Committee heard from the ERG that the response rate from the gefitinib meta-analysis was 71.5% (Ku et al. 2011). The Committee heard from the manufacturer that the difference in utility values (0.005, <1%) used for the 2 treatments made little difference to the results from the model. However, the Committee saw little clinical justification for the difference in the utilities in the manufacturer's original model, and concluded that an analysis incorporating identical utility values for patients receiving erlotinib and patients receiving gefitinib in the progression-free survival health state should be used as a basis for its decision making.

4.14   The Committee acknowledged that, following its request for further clarification in the appraisal consultation document, the manufacturer had provided an updated economic model which incorporated equal progression-free survival and utilities for erlotinib and gefitinib. The results from the model depended on the costs of the drugs, the cost of administering the gefitinib patient access scheme

and the proportion of patients on gefitinib who incurred the fixed charge on day 60. The Committee discussed the uncertainties in the clinical evidence which led to this request for an economic model based on there being no difference in the clinical benefit between the treatments. The Committee acknowledged the limitations of this type of economic model which incorporates no uncertainties about survival. The Committee concluded that, although the assumption of equal clinical benefit could be a conservative estimate of the clinical effectiveness of erlotinib, the updated economic model was in line with clinical opinion (see section 4.5), reflected the absence of any clinical data from direct comparisons, and allowed a direct comparison of the costs of the 2 treatments.

4.15   The Committee considered the impact of the cost of administering the gefitinib patient access scheme on the results from the updated economic model. When the mean administration cost changed from £438 per patient in the manufacturer's updated model to £111 to £118 in the ERG's exploratory analysis, erlotinib was cost effective when the proportion of patients incurring the fixed charge for gefitinib increased from 91% to 95%. The Committee acknowledged that the time taken to complete the online forms for the gefitinib patient access scheme was much shorter than that estimated by the manufacturer and that the typical administration costs for patient access schemes of this type were likely to be nearer to the ERG's estimate rather than the manufacturer's. This remained despite the possibility of additional reporting costs associated with the gefitinib patient access scheme which were not included in the ERG's analyses. The Committee understood that there may not be complete uptake of the gefitinib patient access scheme across the NHS, that some trusts may pay the list price for gefitinib and that this has not been considered in the updated model, which assumed all patients on gefitinib for more than 60 days would incur the fixed charge. The Committee concluded that the administration costs of the gefitinib patient access scheme were likely to be nearer the ERG's estimates rather than the manufacturer's, and that there may be some additional savings not included in the updated model because of the incomplete uptake of the gefitinib patient access scheme across the NHS.

4.16   The Committee considered the impact of the proportion of patients who receive gefitinib for more than 60 days (and would therefore incur the fixed charge) on the results from the updated economic model. Both the manufacturer and the ERG presented sensitivity analyses incorporating different costs for administering

the gefitinib patient access scheme (see section 4.15). The Committee discussed the evidence on the proportion of patients who receive gefitinib for more than 60 days (and incur the fixed charge). The Committee was disappointed that there was not more reliable evidence available from the NHS. The Committee heard from clinical specialists that nearly all patients on gefitinib survive until day 60 when the third pack is issued. The Committee noted that the base-case analysis presented by the manufacturer used a proportion of 80%, which was the proportion of patients in the EURTAC trial who had completed 60 days of erlotinib treatment. There were about 88% of erlotinib patients in the EURTAC trial who were in the progression-free survival health state on day 60 but this included some patients who had not completed 60 days of treatment. The sensitivity analysis presented by the manufacturer identified that erlotinib became cost effective compared with gefitinib when 91% of patients incurred the fixed charge for gefitinib. The ERG's exploratory analysis estimated this proportion to be 95%. The Committee discussed the results from the updated analyses and on balance agreed that the sums of money either saved or spent are small given the uncertainties associated with the analysis. The Committee concluded that at the price agreed under the patient access scheme (as revised in 2012) erlotinib should be recommended as an option for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC.

Other considerations

4.17   The Committee discussed whether it needed to consider the 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. It noted that the manufacturer did not make a case for erlotinib to be considered as an end-of life treatment in the submission. The Committee also heard from the manufacturer that in its view erlotinib does not meet the criteria for an end-of-life treatment. The Committee noted that in NICE's technology appraisal guidance on erlotinib monotherapy for the maintenance treatment of NSCLC, erlotinib did not meet the end-of-life criteria because the cumulative population for erlotinib was not considered small. The Committee therefore concluded that erlotinib did not need to be considered as a life-extending, end-of-life treatment.

4.18   The Committee discussed whether erlotinib should be considered an innovative technology, or if there were any significant and substantial health benefits which were not included in the economic model. It noted that the manufacturer did not make a case for erlotinib to be considered innovative, and did not identify any additional health benefits not included in the economic model. The Committee heard from the manufacturer that erlotinib is not considered a major change in treatment for locally advanced or metastatic EGFR-TK mutation-positive NSCLC, but is an incremental advance. The manufacturer stated that the oral administration and the straightforward patient access scheme gave value to erlotinib. The Committee concluded that erlotinib could not be considered to show significant innovation and that no additional health benefits had been identified which had not been adequately captured by the economic model.

4.19   The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations. The Committee noted that no equality issues were included in the manufacturer's submission. It also noted that the reduced adverse reactions associated with tyrosine kinase inhibitors compared with those associated with chemotherapy raised during the scope consultation was not an equalities issue for this appraisal. No equalities issues were identified by the Committee. Given that the recommendations did not differentiate between any groups of people, the Committee concluded that its recommendations did not limit access to the technology for any specific group compared with other groups and that there was no need to alter or add to its recommendations.

5 Implementation

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

5.2   [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

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

5.4   When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer and the healthcare professional responsible for their care thinks that erlotinib is the right first-line treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

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.

Professor Peter Clark (Chair)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology

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

Professor Darren Ashcroft
Professor of Pharmacoepidemiology, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Ian Campbell
Honorary Consultant Physician, Llandough Hospital

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor in Health Economics, University of Sheffield

Dr Martin Duerden

Assistant Medical Director, Betsi Cadwaladr University Health Board

Gillian Ells

Prescribing Advisor, NHS Sussex Downs and Weald

Dr Jon Fear

Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

Paula Ghaneh

Senior Lecturer and Honorary Consultant, 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 Hutton

Professor of Health Economics, University of York

Professor Peter Jones

Emeritus Professor of Statistics, Keele University

Dr Steven Julious

Senior Lecturer in Medical Statistics, University of Sheffield

Dr Vincent Kirkbride

Consultant Neonatologist, Regional Neonatal Intensive Care Unit, Sheffield

Rachel Lewis

Advanced Nurse Practitioner, Manchester Business School

Professor Paul Little

Professor of Primary Care Research, University of Southampton

Professor Katherine Payne

Professor of Health Economics, University of Manchester

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge

GP and Consultant in Medicines Management, NHS Lothian

Dr Peter Selby

Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Murray D Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

Paddy Storrie

Lay member

Dr Lok Yap

Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust

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.

Dr Bernice Dillon

Technical Lead

Dr Bhash Naidoo

Technical Adviser

Kate Moore

Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Bagust A, Beale S, Blundell M, et al. Erlotinib for the first-line treatment of EGFR-TK mutation positive non-small cell lung cancer, December 2011

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). Manufacturers or sponsors were also invited to make written submissions. Professional or specialist, patient or carer groups, and other consultees, had the opportunity to give their expert views. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Roche

Professional or specialist, and patient or carer groups:

- Roy Castle Lung Cancer Foundation

- British Thoracic Society

- Cancer Research UK

- Royal College of Nursing

- Royal College of Pathologists

- Royal College of Physicians

Other consultees:

- Department of Health

- Welsh Government

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

- British National Formulary

- Commissioning Support Appraisal Services

- Department of Health, Social Services and Public Safety – Northern Ireland

- Healthcare Improvement Scotland

- AstraZeneca UK

- Lilly UK

- Pfizer

- Liverpool Reviews and Implementation Group

- National Institute for Health Research Health Technology Assessment Programme

- British Thoracic Oncology Group

- National Collaborating Centre for Cancer

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

- Professor Michael Lind, Foundation Professor of Oncology, nominated by Lilly – clinical specialist

- Dr Sanjay Popat, Consultant Medical Oncologist, nominated by Royal College of Physicians – clinical specialist

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

- Roche Products Ltd

ISBN: 978-1-4731-6714-8