

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

Technology appraisal guidance

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## 1 Guidance

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 £1631.53 (excluding VAT; 'British national formulary' [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.

### 3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of erlotinib (Roche Products) and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).

#### *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 two 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 III, randomised trial of first-line erlotinib treatment compared with platinum doublet chemotherapy for patients with stage IIIb or stage IV 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 one 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 four 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 two-sided log-rank test was used to assess the difference in outcomes between the two 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 one 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 III, randomised trial of first-line erlotinib treatment compared with platinum doublet chemotherapy for chemotherapy-naive patients with stage IIIb or stage IV 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 four 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 four 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 four trials (Ku et al. 2011). Across the four 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 four possible indirect comparisons of the two 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 9–10 months before progression or unacceptable adverse reactions, whereas patients in the chemotherapy arm received a maximum of four cycles over approximately 3 months. Most of the reported adverse reactions in both arms were grade 1 or grade 2 (432/527 events [82.0%] in the chemotherapy arm and 621/681 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 three 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 four previous NICE appraisals of drugs for NSCLC ([Pemexetred for the first-line treatment of non-small-cell lung cancer \[NICE technology appraisal guidance 181\]](#), [Pemexetred for the maintenance treatment of non-small-cell lung cancer \[NICE technology appraisal guidance 190\]](#), [Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer \[NICE technology appraisal guidance 192\]](#), [Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer, \[NICE technology appraisal guidance 227\]](#)). 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 £1631.53 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 [Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer](#) (NICE technology appraisal guidance 192). 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 six trials of a tyrosine kinase inhibitor (either gefitinib or erlotinib) compared with platinum doublet chemotherapy showed two 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 2–3 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 two time periods as separate phases (equivalent to active therapy followed by observation/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 two trials shows close correspondence in the comparator arms. The two 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 four 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 four third-generation platinum doublets (docetaxel, gemcitabine, paclitaxel and vinorelbine) in a full evaluation as in [Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer](#) (NICE technology appraisal guidance 192). 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 two 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 four 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 two 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, which are available from [www.nice.org.uk/guidance/TA258](http://www.nice.org.uk/guidance/TA258)



## 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 technology appraisal guidance 192. 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 two 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 technology appraisal guidance 192 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 two 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 two 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 two 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 £111–118 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 [Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer](#) (NICE technology appraisal guidance 227) 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.

### *Summary of Appraisal Committee's key conclusions*

TA258	Appraisal title: Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer	Section
<b>Key conclusion</b>		
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: <ul style="list-style-type: none"> <li>• they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation and</li> <li>• the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012).</li> </ul>		1.1
The Committee concluded that gefitinib was the comparator for this appraisal.		4.6



<p>The Committee concluded there was insufficient evidence to suggest a difference in clinical effectiveness between erlotinib and gefitinib and it heard from clinical specialists that erlotinib and gefitinib are very similar treatments with similar efficacy. The Committee concluded that the cost effectiveness of erlotinib compared with gefitinib could be best assessed from the updated economic model which assumes equal clinical benefit for the treatments and focuses on their differential costs.</p>		<p>4.3, 4.8, 4.12</p>
<p>The Committee agreed that the results from the economic model showed that on balance the sums of money lost or saved are small given the uncertainties in the analysis, and so it recommended erlotinib as a treatment option.</p>		<p>4.16</p>
<p><b>Current practice</b></p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>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.</p>	<p>4.2</p>
	<p>Current standard practice in England and Wales for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive NSCLC is gefitinib.</p>	<p>4.3</p>
<p><b>The technology</b></p>		
<p>Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The oral method of administration and less common adverse reactions with either erlotinib or gefitinib offers an advantage for patients compared with chemotherapy. Erlotinib offers the advantage of being able to vary the dosage by using tablets of different dose strength.</p>	<p>4.2, 4.5</p>
	<p>The manufacturer confirmed that erlotinib is not considered a major change in treatment, but is an incremental advance. The Committee concluded that erlotinib could not be considered to show significant innovation.</p>	<p>4.18</p>

What is the position of the treatment in the pathway of care for the condition?	Erlotinib has a UK marketing authorisation 'for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer with EGFR activating mutations'.	2.1
	The Committee heard from clinical specialists the current UK clinical practice for this indication is to use gefitinib as recommended by NICE technology appraisal guidance 192.	4.3
Adverse reactions	The adverse reactions associated with erlotinib and gefitinib were 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.	4.10
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The evidence of clinical effectiveness was derived from the EURTAC trial (a European-based, open-label, randomised trial of first-line erlotinib treatment compared with platinum doublet chemotherapy for patients with stage IIIb or stage IV NSCLC and EGFR-TK mutation-positive tumours). Additional evidence was provided by the OPTIMAL trial (a Chinese-based open-label randomised trial of first-line erlotinib treatment compared with platinum doublet chemotherapy for chemotherapy-naive patients with stage IIIb or stage IV NSCLC whose tumours were EGFR-TK mutation-positive).	3.2, 3.3, 3.7
	There was no evidence from a direct comparison of erlotinib and gefitinib.	3.1
Relevance to general clinical practice in the NHS	The Committee agreed that the EURTAC trial provided evidence relevant to clinical practice in the NHS in England and Wales.	4.7
Uncertainties generated by the evidence	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.	4.8

	The Committee noted that the overall survival data from the trials were incomplete. The Committee was not convinced of a survival benefit for erlotinib compared with gefitinib.	4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee did not consider any subgroups.	-
Estimate of the size of the clinical effectiveness including strength of supporting evidence	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. 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. 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.	4.8
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The manufacturer originally submitted a semi-Markov model to evaluate the cost effectiveness of erlotinib compared with gefitinib. The clinical data for this model were derived from the EURTAC trial and the indirect comparison.	3.15, 3.16
	In response to NICE's request in the appraisal consultation document, the manufacturer submitted an updated model. This model assumed equal progression-free survival and equal utilities for the progression-free survival health state for the two treatments (erlotinib and gefitinib).	3.27

Uncertainties around and plausibility of assumptions and inputs in the economic model	In the Committee's view, the survival benefit for erlotinib compared with gefitinib was uncertain.	4.8, 4.9
	The Committee concluded that the cost effectiveness of erlotinib compared with gefitinib could be best assessed from the updated economic model which assumes equal clinical benefit for the treatments and focuses on their differential costs.	4.12
	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 two treatments.	4.14
	The Committee concluded that the administration costs of the gefitinib patient access scheme were likely to be nearer the ERG's estimates 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.	4.15

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee saw little clinical justification for the difference in the utilities for the progression-free survival health state for erlotinib and gefitinib in the original economic model and requested that they be made identical in the updated model.</p> <p>No significant and substantial health-related benefits that have not been captured by the QALY calculation were identified either in the submission or at the Committee meeting. The Committee concluded that no additional health benefits had been identified which had not been adequately captured by the economic model.</p>	<p>4.13</p> <p>4.18</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee did not consider any subgroups.</p>	<p>-</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>In the Committee's view the main factors affecting cost effectiveness were the difference in efficacy between erlotinib and gefitinib and the proportion of patients incurring the fixed charge for gefitinib under the patient access scheme.</p>	<p>4.12,</p> <p>4.16</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>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.</p>	<p>4.16</p>

<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	The Committee noted the patient access scheme (as revised in 2012) for erlotinib based on a confidential discount on the list price. It noted that hospitals may find the patient access scheme for erlotinib easier to administer than the scheme for gefitinib.	2.3, 4.5,
	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.	4.15
End-of-life considerations	The Committee noted that the manufacturer did not make a case for erlotinib to be considered as an end-of-life treatment. The Committee also noted that in <a href="#">Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer</a> (NICE technology appraisal guidance 227) erlotinib did not meet the end-of-life criteria because the cumulative population was not considered small. The Committee therefore concluded that erlotinib did not need to be considered as a life-extending, end-of-life treatment.	4.17
Equalities considerations and social value judgements	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 equalities issues were raised in the submission or at the meeting. 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.	4.19

## 5 Implementation

- 5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- 5.2 The technology in this appraisal may not be the only treatment for non-small-cell lung cancer recommended in NICE guidance, or otherwise available in the NHS. Therefore, if a NICE technology appraisal recommends use of a technology, it is as an option for the treatment of a disease or condition. This means that the technology should be available for a patient who meets the clinical criteria set out in the guidance, subject to the clinical judgement of the treating clinician. The NHS must provide funding and resources (in line with section 5.1) when the clinician concludes and the patient agrees that the recommended technology is the most appropriate to use, based on a discussion of all available treatments.
- 5.3 NICE has developed [tools](#) to help organisations put this guidance into practice (listed below).
- A costing statement explaining the resource impact of this guidance.
  - Audit support for monitoring local practice.
- 5.4 The Department of Health and the manufacturer have agreed that erlotinib will be offered to the NHS under a patient access scheme (as revised in 2012) which makes erlotinib available with a discount on the list price applied to original invoices. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Roche Customer Care (0800 731 5711).

## 6 Related NICE guidance

### Published

- [Lung cancer: The diagnosis and treatment of lung cancer](#). NICE clinical guideline 121 (2011).
- [Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer](#). NICE technology appraisal guidance 227 (2011).
- [Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer](#). NICE technology appraisal guidance 192 (2010).
- [Pemetrexed for the maintenance treatment of non-small-cell lung cancer](#). NICE technology appraisal guidance 190 (2010).
- [Pemetrexed for the first-line treatment of non-small-cell lung cancer](#). NICE technology appraisal guidance 181 (2009).
- [Erlotinib for the treatment of non-small-cell lung cancer](#). NICE technology appraisal guidance 162 (2008).
- [Bevacizumab for the treatment of non-small-cell lung cancer \(terminated appraisal\)](#). NICE technology appraisal 148 (2008).



## 7 Review of guidance

- 7.1 The guidance on this technology will be considered for review in April 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Andrew Dillon  
Chief Executive  
June 2012

## **Appendix A: Appraisal Committee members and NICE project team**

### *A Appraisal Committee members*

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four 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

***B NICE project team***

Each technology appraisal is assigned to a team consisting of one 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

## Appendix B: Sources of evidence considered by the Committee

A 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

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

I Manufacturer/sponsor:

- Roche

II Professional/specialist and patient/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

III Other consultees:

- Department of Health
- Welsh Government

IV 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

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on 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

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

- Roche Products Ltd

## Changes after publication

February 2014: minor maintenance

## About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE [single technology appraisal](#) process. We have produced a [summary of this guidance for patients and carers](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

### Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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