NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Although the Institute has noted the ERG report is a limited critique of the manufacturer's submission it decided to present the information for discussion at the Appraisal Committee meeting to allow for the production of timely guidance for the NHS.

Key issues for consideration

Clinical effectiveness

- What is the current pathway of care for people with previously untreated, locally advanced or metastatic non-small-cell lung cancer (NSCLC) that is epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive?

- The manufacturer did not consider pemetrexed plus cisplatin or carboplatin as a comparator for patients with non-squamous NSCLC as specified in the scope. The ERG believes a full evaluation of erlotinib is not possible without this comparison. Does the Committee consider the exclusion of pemetrexed plus cisplatin or carboplatin as a comparator to be acceptable? Is gefitinib therefore the only relevant comparator for

erlotinib in the EGFR-TK mutation-positive locally advanced or metastatic NSCLC patient population?

- In the absence of any head-to-head trial data the manufacturer undertook an indirect comparison of the clinical effectiveness of erlotinib with gefitinib in EGFR-TK mutation-positive patients. The ERG stated that for a robust comparison an extended evidence network is required, incorporating erlotinib, gefitinib and pemetrexed-based chemotherapy and linked via RCTs to the four third-generation chemotherapy doublet treatments (docetaxel, gemcitabine, paclitaxel and vinorelbine). Does the Committee consider the use of an indirect comparison with a limited network of comparators and RCTs to be appropriate?

- In constructing the indirect comparison the manufacturer assumed that all third-generation doublet chemotherapy treatments are equally clinically effective in patients with EGFR-TK mutation-positive, locally advanced or metastatic NSCLC. Does the Committee consider this to be appropriate?

- Does the Committee agree that heterogeneity exists between the EURTAC and OPTIMAL trials and so pooling of results is not appropriate?

- Does the Committee consider that the manufacturer's indirect comparison of EURTAC with the pooled results from the four gefitinib studies is robust given the differences between EURTAC and the gefitinib studies in terms of trial design and population (such as number of cycles of chemotherapy, previous chemotherapy allowed, male/female, never smokers, performance status, lung cancer stage, recurrence post-surgery, type of mutation and ethnicity) and the differences in response to tyrosine kinase inhibitors (TKIs) and chemotherapy?

- For the indirect comparison of erlotinib with gefitinib which of the four possible options discussed by the manufacturer best represents the clinical effectiveness of these drugs in the EGFR-TK mutation-positive, locally advanced or metastatic NSCLC patient population in England and Wales?

- Recent published results have shown no overall survival benefit for gefitinib compared with the third-generation doublet chemotherapy treatments. What is the Committee's view of the overall survival data from the EURTAC trial, given that estimates were based on results of 40% (69 patients) maturity?

- What is the Committee's view on the use of the Cox proportional hazards method to calculate the hazard ratios of the TKIs compared with doublet chemotherapy treatment?

- There are no quality of life data available from the EURTAC trial. The manufacturer has presented quality of life data from the OPTIMAL trial (considered by the manufacturer to display heterogeneity in comparison with EURTAC). Does the Committee consider the quality of life data from the OPTIMAL trial to be relevant to the EGFR-TK mutation-positive NSCLC patient population in England and Wales?

- Is there a significant difference in toxicity between erlotinib and gefitinib?

Cost effectiveness

- The ERG believes the manufacturer's model does not provide reliable evidence of clinical and cost effectiveness, and a full evaluation of erlotinib is not possible without including additional comparators. Does the Committee agree that the model needs to include additional

comparators such as pemetrexed plus cisplatin or carboplatin for patients with non-squamous NSCLC (as specified in the scope)?

- The current structure of the economic model does not include overall survival data and relies on the progression-free survival (PFS) benefit obtained from an indirect comparison of the EURTAC study with the gefitinib meta-analysis via a network anchored on doublet chemotherapy. Does the Committee agree with the hazard ratio of 0.82 for PFS benefit between erlotinib and gefitinib used in the model?

- The ERG notes that the simple structure of the model for the progressive disease state results in a translation of this PFS benefit into an overall survival benefit. The ERG states there is no evidence of any overall survival advantage for either of the EGFR-TKI therapies (gefitinib or erlotinib) over doublet chemotherapy. The overall survival data from the EURTAC study is still immature. Does the Committee consider that trial data for overall survival benefit should be incorporated into the economic model?

- The current economic model compares erlotinib with gefitinib and does not include second-line treatments because the manufacturer states that there is no difference in the second-line treatment options for patients who progress having received an EGFR-TKI as first-line treatment. Does the Committee consider that second-line treatments should be included in the model if an extended model with more comparators is used?

- The manufacturer's model assumes approximately 76% of gefitinib patients survive past day 60, and therefore incur the fixed cost of £12,200 for gefitinib under the patient access scheme. Sensitivity analyses varied this proportion from approximately 85% to 100%. Does the Committee consider the base case of 76% is an acceptable

proportion as it is based on the use of the PFS HR of 0.82 applied to the analysis of time of last dose of erlotinib?

- Does the Committee agree with the calculation of differential utilities for PFS for erlotinib (0.661) and gefitinib (0.656) and the method of calculating these by assuming a response rate of 58% for erlotinib and 28% for gefitinib?

- The population specified in the scope is adults with previously untreated EGFR-TK mutation-positive, locally advanced or metastatic NSCLC. The ERG considers that not all patients will have timely access to EGFR testing. Does the Committee consider that the model should include EGFR testing costs?

1 Background: Clinical need and practice

1.1 Around 85–90% of lung cancers are non-small-cell lung cancers, and the remainder are small-cell lung cancers. The main types of NSCLC are squamous cell carcinoma (45%), adenocarcinoma (45%) and large cell carcinoma (10%). Approximately a third of people with NSCLC present with local potentially resectable disease and surgery will be suitable for about 50% of these people. About 30% of people present with locally and regionally advanced disease (Stage IIIb) and 40% present with advanced disease (Stage IV), in which there are distant metastases or a pleural or pericardial effusion.

1.2 In England and Wales 34,949 people were diagnosed with lung cancer in 2008. Estimates of the number of people who receive first-line chemotherapy for inoperable NSCLC vary between 1320 and 6447 per year. EGFR receptors are over-expressed in a number of tumours, including NCSLC. Activating EGFR mutations

occur in about 30% of Asian patients and 10–15% of white patients. Lung cancer incidence and mortality rates are strongly associated with smoking and socio-economic deprivation. The manufacturer estimates that around 400 patients per year will be eligible for first-line treatment with erlotinib, and the ERG agrees with this estimate.

1.3 Survival from lung cancer is very low because it is difficult to treat and is often diagnosed late. In England and Wales there were 30,254 deaths in 2008 from lung cancer. The prognosis for people with NSCLC is poor, with a one-year survival rate of 28% and a five-year survival rate of 8%.

1.4 One third of people with NSCLC have disease that is suitable for potentially curative surgical resection, but for most people with NSCLC cure is not possible and the aims of therapy are to prolong survival and improve quality of life. Treatment may include radiotherapy and supportive care with or without chemotherapy. NICE has published 'Lung cancer: the diagnosis and treatment of lung cancer' (NICE clinical guideline 121). It recommends that chemotherapy should be offered to people with stage III or IV NSCLC and a good performance status. This should be a combination of docetaxel, gemcitabine, paclitaxel or vinorelbine, plus carboplatin or cisplatin. People who are unable to tolerate a platinum combination may be offered single-agent chemotherapy (see appendix A). 'Pemetrexed for the first-line treatment of non-small-cell lung cancer' (NICE technology appraisal guidance 181) recommends pemetrexed in combination with cisplatin as an option for the first-line treatment of locally advanced or metastatic NSCLC if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (see appendix A). 'Gefitinib for the first-line treatment of locally

advanced or metastatic non-small-cell lung cancer' (NICE technology appraisal guidance 192) recommends gefitinib as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if they test positive for the EGFR-TK mutation (see appendix A). Erlotinib is recommended as an alternative to docetaxel as a second-line treatment option for patients with NSCLC on the basis that it is provided by the manufacturer at an overall treatment cost equal to that of docetaxel in 'Erlotinib for the treatment of non-small-cell lung cancer' (NICE technology appraisal guidance 162). Erlotinib monotherapy is not recommended as a maintenance treatment for people with locally advanced or metastatic NSCLC who have stable disease after platinum-based first-line chemotherapy in 'Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer' (NICE technology appraisal guidance 227). Bevacizumab was referred to NICE for appraisal for the treatment of unresectable advanced, metastatic or recurrent NSCLC, but no evidence submission was received from the manufacturer so NICE was unable to recommend the use of bevacizumab for this indication to the NHS 'Bevacizumab for the treatment of non-small-cell lung cancer' (NICE technology appraisal 148).

2 The technology

2.1 Erlotinib (Tarceva, Roche Products) is an orally administered, active inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK). It has a UK marketing authorisation 'for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations'. For further information see the summary of product characteristics.

2.2 The summary of product characteristics lists the following adverse reactions for erlotinib: diarrhoea, rash, anorexia, gastrointestinal bleeding, liver function test abnormalities and keratitis. 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 tablets (150 mg) is £1631.53 (excluding VAT; British National Formulary [BNF] edition 62). Dosage reductions (typically to 100 or 50 mg/day) are possible if the clinician considers it appropriate, and erlotinib is also available in tablet sizes of 100 mg and 25 mg. The manufacturer of erlotinib has agreed a patient access scheme with the Department of Health. This consists of a confidential [redacted] discount applied to the list price, therefore the acquisition cost of erlotinib is [redacted] for a pack of 30 tablets [150 mg]). The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of erlotinib, within its licensed indication, for the first-line treatment of EGFR-TK mutation-positive locally advanced or metastatic non-small-cell lung cancer

Decision problem

Population	Adults with previously untreated EGFR-TK mutation-positive locally advanced or metastatic NSCLC
Intervention	Erlotinib
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life

3.2 The manufacturer's approach to the decision problem was in line with the NICE scope for the population, intervention and outcomes considered. However the manufacturer did not address all the comparators specified in the scope and the ERG also commented on the absence of EGFR mutation testing costs in the economic evaluation.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Comparators	• Gefitinib For people with non-squamous NSCLC of adenocarcinoma or large cell carcinoma histology: • Pemetrexed in combination with cisplatin or carboplatin	• Gefitinib

3.3 The manufacturer's submission did not include pemetrexed in combination with cisplatin or carboplatin as a comparator. In the submission, the manufacturer stated that market research indicates that an EGFR-TKI (either erlotinib or gefitinib) is currently used in the first-line treatment of 95% of UK patients with an EGFR-TK mutation-positive tumour and only around 5% of patients receive doublet chemotherapy. The manufacturer considered that this scale of uptake in the first year since the

publication of NICE technology appraisal guidance 192 (TA192) implies that although pemetrexed plus platinum chemotherapy may have been an appropriate comparator to gefitinib in TA192, this is no longer the case. In addition, a lack of data on the efficacy of pemetrexed plus cisplatin in EGFR-TK mutation-positive NSCLC patients made an indirect comparison with traditional doublet chemotherapy impossible in TA192. The manufacturer considered the declining use in clinical practice of pemetrexed plus cisplatin 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 as sufficient reasons not to consider pemetrexed plus platinum chemotherapy as a comparator in the submission.

3.4 The ERG stated that without consideration of pemetrexed-based 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 rationale for this opinion was based on a number of reasons:

- The ERG considered pemetrexed-based doublet chemotherapy a valid comparator because almost all EGFR-TK mutation-positive patients have non-squamous lung cancer. This was demonstrated by the high proportion of patients (94.8–100%) with non-squamous disease in the six major trials involving EGFR-TK inhibitor drugs (gefitinib or erlotinib) for locally-advanced or metastatic NSCLC.
- The ERG stated that some patients will be treated with pemetrexed-based doublet chemotherapy in hospitals that do not routinely test for EGFR, or when delaying treatment would be detrimental to the patient's health. The manufacturer's own

market research has demonstrated that up to 10% of UK clinicians do not have access to EGFR mutation testing. Clinical advisers to the ERG have confirmed that EGFR testing is not routinely performed in all hospitals in England and Wales.

- In TA192 the Committee concluded that it was likely that gefitinib was no less efficacious than pemetrexed plus cisplatin, and that pemetrexed plus cisplatin was the relevant comparator for gefitinib. The ERG considered that, because gefitinib and pemetrexed-based doublet chemotherapy are believed to be equally efficacious, both treatments should be compared with erlotinib as stated in the final scope, to fully address the decision problem.
- The ERG stated that the difference in efficacy between pemetrexed and gefitinib is becoming clearer since the publication of TA192. Pemetrexed is the only first-line treatment for patients with non-squamous lung cancer which has demonstrated a statistically significant overall survival gain when compared with a third-generation chemotherapy treatment. Recently published updates to an RCT involving gefitinib have reported that there is no overall survival gain for gefitinib compared with third-generation chemotherapy treatments.

	Final scope issued by NICE	Decision problem addressed in the submission
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective. Costs of any additional mutation testing required for this treatment should be considered in the economic analysis.	As per scope, except no additional testing costs are considered

3.5 The ERG considered the economic analysis to have been addressed as described in the scope, however it noted that not all patients will have timely access to EGFR testing. The ERG considered that some EGFR-TK mutation-positive patients will be treated with pemetrexed in hospitals that do not routinely test for EGFR status, or when delaying treatment is not in the best interests of the patient, and so pemetrexed should have been included as a comparator in the economic model. The manufacturer stated that EGFR testing has become standard care in the UK over the last two years for patients with locally advanced or metastatic NSCLC and so it did not need to be considered as an additional cost.

3.6 The clinical specialists agreed that EGFR-TK mutation-positive patients with advanced NSCLC are currently treated with gefitinib in accordance with TA192. A clinical specialist commented that pemetrexed and cisplatin combination chemotherapy is not an appropriate comparator as it is not generally given for EGFR-TK mutation-positive patients. The clinical specialists also stated that most patients with advanced non-squamous NSCLC already have

their tumours tested for EGFR mutations so no additional testing or training would be required.

3.7 The manufacturer's submission has positioned this technology as a first-line treatment for chemotherapy-naive patients with locally advanced or metastatic EGFR-TK mutation-positive NSCLC. This is in line with the marketing authorisation.

4 Clinical-effectiveness evidence

4.1 The manufacturer identified two RCTs (EURTAC and OPTIMAL) that compared erlotinib with platinum doublet chemotherapy as a first-line treatment for patients with EGFR-TK mutation-positive locally advanced or metastatic NSCLC. No studies were identified that compared erlotinib directly with gefitinib for these patients, and so the manufacturer presented an indirect treatment comparison to assess the relative effectiveness of erlotinib compared with gefitinib. A systematic literature review revealed four RCTs comparing gefitinib with platinum doublet chemotherapy as a first-line treatment for patients with EGFR-TK mutation-positive NSCLC. The manufacturer also presented the results from a pooled analysis of observational studies.

EURTAC study

4.2 The manufacturer presented the EURTAC study as the basis of the evidence submission because this is the only European-based, phase III, randomised trial of first-line erlotinib treatment compared with platinum doublet chemotherapy for patients with stage IIIb or stage IV NSCLC whose tumours are EGFR mutation-positive. The study was conducted in 42 centres in Spain, France and Italy. The trial was unblinded and independent review centre-based assessments were used to rule out any investigator-related bias in the interim analysis. Patients were screened for EGFR mutations.

Those with EGFR mutation-positive tumours (deletion in exon 19 or mutation in exon 21 L858R) were then randomised to receive either 150 mg of erlotinib orally once per day or one of four platinum-based chemotherapy regimes. Patients in the platinum-based chemotherapy arm received one of the following standard platinum doublet chemotherapy regimens at the clinicians' choice:

- Cisplatin plus docetaxel. The dosage was cisplatin 75 mg/m^2 and docetaxel 75 mg/m^2 on day 1, with repeat cycles every 3 weeks;
- Cisplatin plus gemcitabine. The dosage was cisplatin 75 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on days 1 and 8, with repeat cycles every 3 weeks;
- Carboplatin plus docetaxel. The dosage was docetaxel 75 mg/m^2 on day 1 and carboplatin with area under the plasma concentration curve (AUC) = 6 on day 1, with repeat cycles every 21 days;
- Carboplatin plus gemcitabine. The dosage was gemcitabine 1000 mg/m^2 on days 1 and 8 and carboplatin with AUC = 5 on day 1, with repeat cycles every 21 days.

Randomisation was stratified according to Eastern Cooperative Oncology Group (ECOG) status (ECOG = 0, 1 or 2) and the mutation type (deletion in exon 19 or mutation in exon 21 L858R). Treatment continued until disease progression, unacceptable toxicity, death, or until four chemotherapy cycles were completed. Following disease progression, patients were allowed to cross over at their clinician's discretion. Recruitment to the trial was stopped on the advice of the independent data monitoring committee when the results of the interim analysis, based on data cut-off on 2 August 2010, were made known. Results from the interim analysis

and an updated analysis, based on data cut-off on 26 January 2011, are presented in the submission.

4.3 From the updated analysis, 1275 patients were screened and 174 were randomised, 88 to platinum doublet chemotherapy and 86 to the erlotinib arm. One patient received chemotherapy before randomisation. Baseline characteristics were generally well-balanced between the erlotinib (n = 86) and platinum doublet chemotherapy (n = 87) arms: median age (65 versus 65 respectively), gender (33% versus 22% male), ECOG = 1 score at baseline (45% versus 52%) and non-smokers (26% versus 14%).

4.4 The primary outcome examined in EURTAC was duration of PFS. This was assessed from the date of randomisation to the first occurrence of progressive disease (both radiological and clinical progression) or death from any cause. The Response Evaluation Criteria in Solid Tumours (RECIST) criteria, which are based on tumour measurement rather than investigator assessment, were used to calculate PFS. Secondary outcomes included overall survival, best overall response, disease control, health-related quality of life and safety.

4.5 The manufacturer's submission describes the results of the intention-to-treat analysis on all randomised patients. Kaplan–Meier survival methodology was used to calculate median and 95% confidence limits of PFS and overall survival between the erlotinib and the platinum doublet chemotherapy arms. A two-sided log-rank test was used for testing 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.

EURTAC results

4.6 The EURTAC trial included 153 patients at the interim analysis and 173 at the updated analysis. Both the interim and updated analysis showed that PFS for patients treated with erlotinib was statistically significantly longer than for patients treated with platinum doublet chemotherapy. For the interim analysis the median PFS in the platinum doublet chemotherapy arm was 5.2 months, compared with 9.4 months in the erlotinib arm and the risk of having a PFS event (progression or death, whichever occurs first) was significantly reduced by 58% (hazard ratio [HR] 0.42, 95% confidence intervals [CI] 0.27 to 0.64, $p < 0.0001$) for patients in the erlotinib arm. One year after randomisation, 12% of patients in the platinum doublet chemotherapy arm and 37% of patients in the erlotinib arm were alive and progression-free. In the updated analysis the median PFS in the platinum doublet chemotherapy arm was 5.2 months compared with 9.7 months in the erlotinib arm and the risk of having a PFS event was significantly reduced by 63% (HR 0.37, 95% CI 0.25 to 0.54, $p < 0.0001$) for patients in the erlotinib arm. One year after randomisation, 11% of patients in the platinum doublet chemotherapy arm and 40% of patients in the erlotinib arm were alive and progression-free. These data are summarised in table 1.

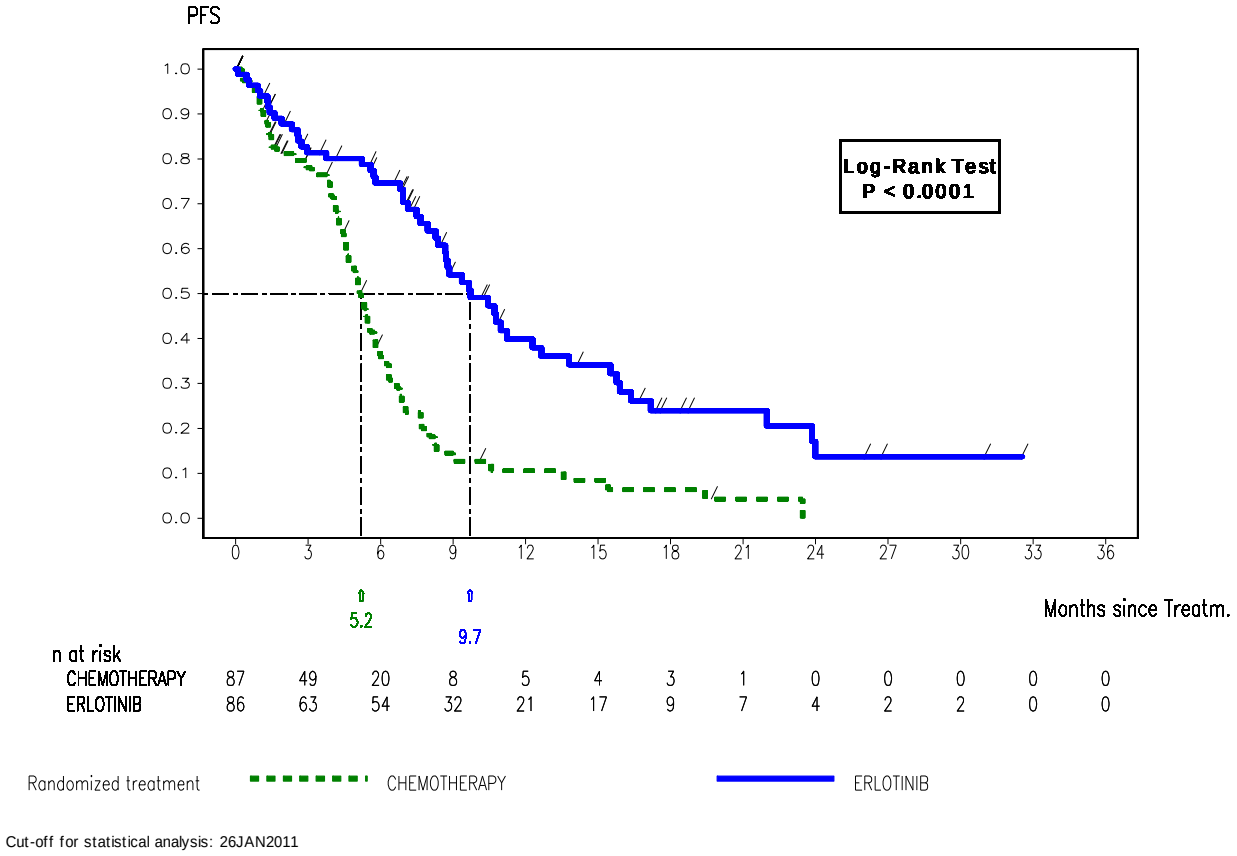
Table 1: Progression-free survival results from the EURTAC study

Parameter	Interim analysis (Data cut-off 2 August 2010)		Updated analysis (Data cut-off 26 January 2011)	
	Platinum doublet chemotherapy (n = 76)	Erlotinib (n = 77)	Platinum doublet chemotherapy (n = 87)	Erlotinib (n = 86)
Patients with event	47 (61.8%)	45 (58.4%)	59 (67.8%)	52 (60.5%)
Patients without event$^{\Delta}$	29 (38.2%)	32 (41.6%)	28 (32.2%)	34 (39.5%)
Median time to event* (months)	5.2	9.4	5.2	9.7
95% CI for median time to event*	4.4 to 5.8	7.9 to 12.3	4.5 to 6.0	8.4 to 12.6
p-value (log-rank test)	< 0.0001		< 0.0001	
Hazard ratio	0.42		0.37	
95% CI for hazard ratio	0.27 to 0.64		0.25 to 0.54	
1-year estimate				
Patients remaining at risk	5	17	5	21
Event-free rate*	0.12	0.37	0.11	0.4
95% CI for rate*	0.02 to 0.21	0.24 to 0.51	0.02 to 0.19	0.28 to 0.52

Key: CI, confidence interval; Δ, censored; *, Kaplan-Meier estimate.
Source: adapted from manufacturer's submission, table 20, pages 99 and 100.

4.7 In the updated analyses, the Kaplan-Meier curves for PFS begin to separate after 6 weeks and remain separated (see figure 1). The PFS Kaplan-Meier curves for the interim analysis are similar.

Figure 1: Kaplan-Meier curves for progression-free survival from EURTAC study (updated analysis)

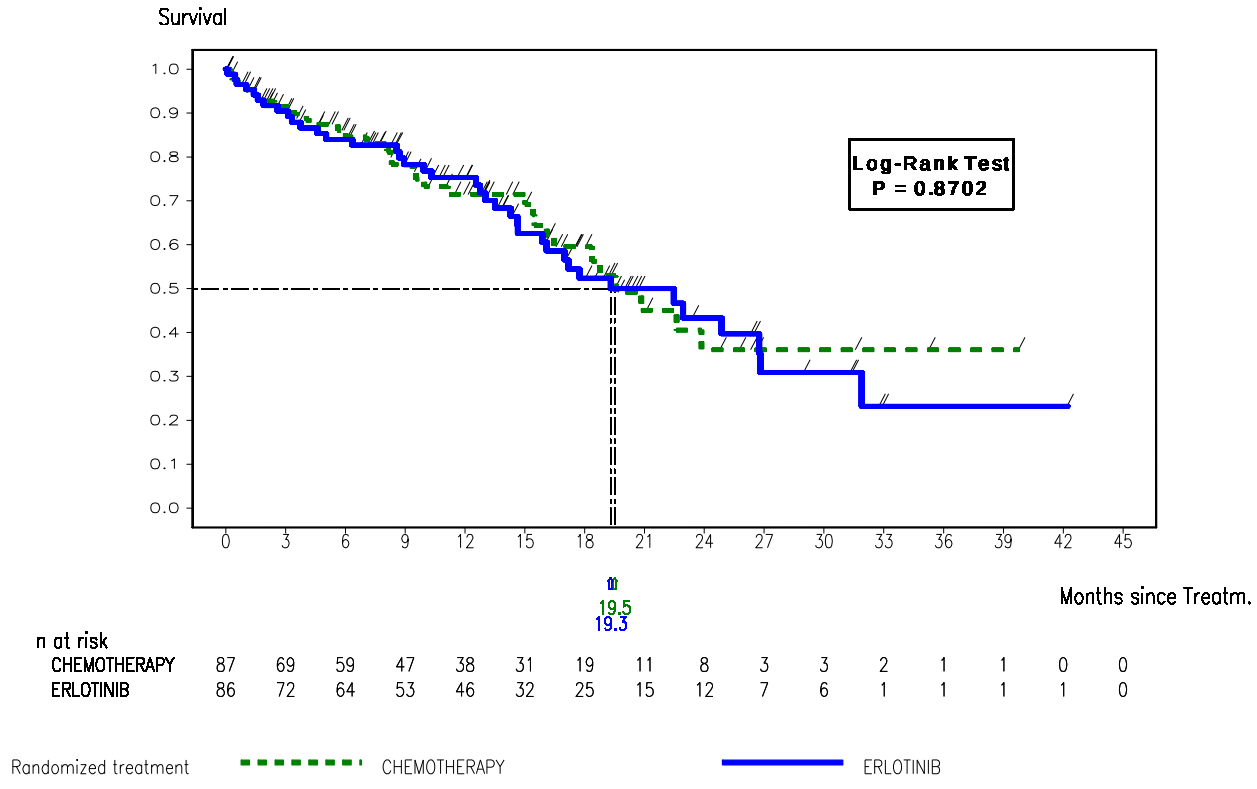


Cut-off for statistical analysis: 26JAN2011

4.8 Both the interim and updated analyses showed similar results for the secondary outcomes. Only the results from the updated analysis are described here (results from the interim analysis are described on pages 102–107 of the manufacturer's submission). The overall survival data from EURTAC are still maturing. In the updated analysis 69 patients (40%) had died. The median time to death was 19.5 months in the platinum doublet chemotherapy arm and 19.3 months in the erlotinib arm (see figure 2). The hazard ratio was 1.04 (95% CI 0.65 to 1.68, p = 0.8702). The 1-year event-free rate was 71% in the platinum doublet chemotherapy arm and 75% in the erlotinib arm. The 2-year event-free rate was 36% in the platinum doublet chemotherapy arm and 43% in the erlotinib arm. More patients in the platinum doublet chemotherapy arm received

second and further-line treatments compared to the erlotinib arm. (77% (n = 67) vs 45% (n = 39)). In the platinum doublet chemotherapy arm 66 of the 67 patients received at least one treatment with either erlotinib or gefitinib. The manufacturer noted in the submission that the trial was not powered to show an overall survival difference. In addition, because of the high level of cross over from platinum doublet chemotherapy to an EGFR-TKI post-progression, it is unlikely that the overall survival results will reach statistical significance.

Figure 2: Kaplan-Meier curves of overall survival from EURTAC study (updated analysis)



Cut-off for statistical analysis: 26JAN2011

4.9 In the updated analysis the proportion of responders was significantly greater in the erlotinib arm compared with the platinum

doublet chemotherapy arm (58.1% [95% CI 47.0% to 68.7%] versus 14.9% [95% CI 8.2% to 24.2%], $p < 0.0001$). There was no significant difference in disease control between the arms (65.5% platinum doublet chemotherapy versus 77.9% erlotinib). No results were presented for health-related quality of life from the EURTAC trial because completion rate of the questionnaire was low and the data were considered by the manufacturer to be inconclusive.

OPTIMAL study

4.10 The manufacturer presented the OPTIMAL study, carried out in 22 centres in China, as additional evidence in the submission. This was a multi-centre, 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. Randomisation of patients was stratified according to histology (adenocarcinoma versus non-adenocarcinoma), mutation type (exon 19 deletion or exon 21 L858R) and smoking status (smokers versus non-smokers). Patients were randomised to receive either 150 mg of erlotinib orally once daily or gemcitabine plus cisplatin chemotherapy. Treatment continued until disease progression, unacceptable toxicity or death, or until four chemotherapy cycles were completed. Following disease progression, patients were allowed to cross over at their clinician's discretion.

4.11 In the OPTIMAL trial 549 patients were screened and 165 were randomised. Nine patients refused platinum doublet chemotherapy after being randomised to that arm and one patient was excluded from the trial by the investigator because of rapid progression of malignant pleural effusion. Baseline characteristics were generally well-balanced between the erlotinib (n = 82) and gemcitabine plus carboplatin (n = 72) arms: median age (57

versus 59 respectively), gender (42% versus 40% male), adenocarcinoma (88% versus 86%), non-smokers (72% versus 70%) and clinical stage IV (87% versus 93%).

4.12 The primary outcome examined in OPTIMAL was duration of PFS. This was assessed from the date of randomisation to the first occurrence of progressive disease or death from any cause. The RECIST criteria were used to calculate PFS. Secondary outcomes included tumour response and time to progression, overall survival, health-related quality of life and safety.

4.13 In the most recent analysis from the OPTIMAL study, the PFS in patients treated with erlotinib was statistically significantly longer than for patients treated with platinum doublet chemotherapy. The median PFS in the platinum doublet chemotherapy arm was 4.6 months compared with 13.7 months in the erlotinib arm and the risk of having a PFS event (progression or death, whichever occurs first) was significantly reduced by 84% (HR 0.16; 95% CI 0.10 to 0.26, $p < 0.0001$) for patients in the erlotinib arm. In the OPTIMAL study quality of life data were based on the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and the Trial Outcome Index. Results were presented from 128 (83.2%) patients participating in the trial and pre-planned analysis 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.

Meta-analysis

4.14 There was no meta-analysis of the PFS results from the EURTAC and OPTIMAL studies because the manufacturer identified heterogeneity between the treatment effects using an assessment

of heterogeneity recommended by the Cochrane Collaboration. The manufacturer reported that a minimal overlap in the confidence intervals of the estimates of the PFS hazard ratios from EURTAC and OPTIMAL suggested heterogeneity. Results from statistical tests also suggested heterogeneity between the PFS hazard ratios: chi-squared test ($p = 0.007$) and the I^2 statistic ($I^2 = 86\%$). To explain possible causes of the heterogeneity, the manufacturer compared the population, intervention, comparators, outcomes and study design of the two trials. The manufacturer concluded that it is difficult to precisely identify the cause of the heterogeneity but that possible contributing factors included:

- The different ethnic mix of the patients in the studies. OPTIMAL was conducted in Chinese centres and all the EURTAC centres were in Europe. In previous NICE technology appraisal guidance (TA227) it was stated that Asian patients are known to respond better to lung cancer treatments than other races.
- Better compliance and adherence in the OPTIMAL study compared with EURTAC. For example, dose reduction because of adverse events in OPTIMAL occurred in 4.8% of patients compared with 13.1% in EURTAC, and the discontinuation rate was 1.2% in OPTIMAL compared with 13.1% in EURTAC.
- An underperforming comparator in the OPTIMAL study. A simple cross-trial comparison of the median PFS of patients given gemcitabine plus carboplatin in OPTIMAL was slightly lower than that for the doublet chemotherapy arm in EURTAC (4.6 months versus 5.2 months).

Indirect treatment comparison

4.15 The manufacturer presented an indirect comparison to compare the clinical effectiveness of erlotinib with gefitinib because there

was no direct evidence. A systematic review identified four RCTs comparing gefitinib with various doublet chemotherapy therapies (IPASS, First-SIGNAL, WJTOG3405 and NEJGSG002). Data were extracted and analysed for clinical efficacy based on PFS, overall survival and best overall response outcomes (see table 2). The data from the gefitinib studies were pooled by assuming that the doublet chemotherapy arms in each of the four trials are of equal efficacy and Ku et al (2011) have published the results. Across the four studies, the estimated PFS hazard ratio is 0.45 (95% CI, 0.38 to 0.55, p<0.001).

Table 2: Summary of results from gefitinib RCTs and meta-analysis

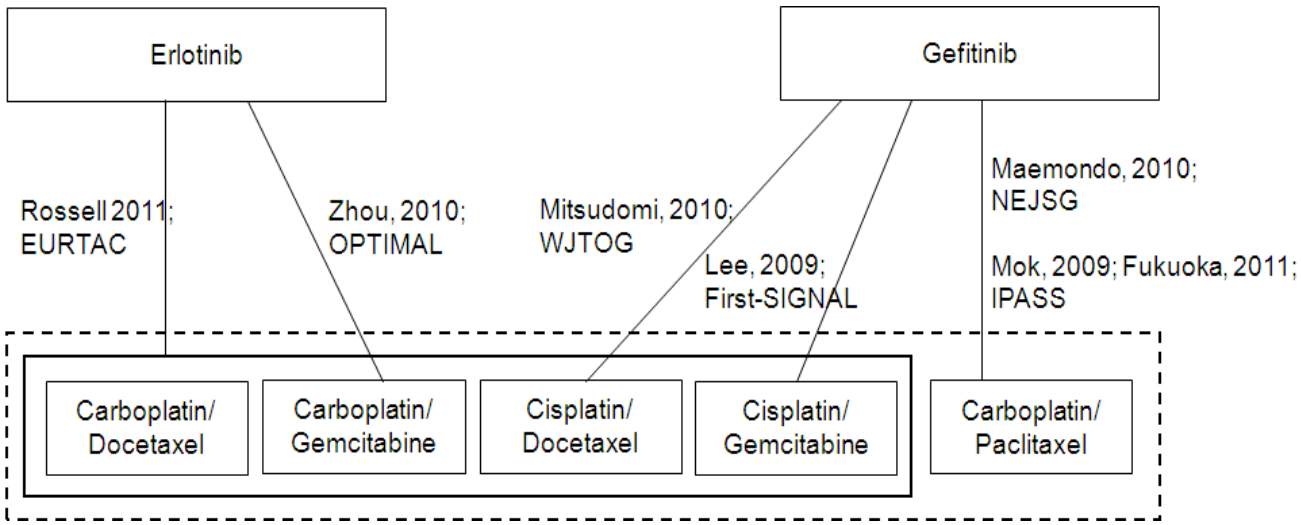
Parameter	Platinum doublet chemotherapy arm	Gefitinib arm	
	Median progression-free survival		**HR (95% CI) *p value***
IPASS	6.3 months	9.5 months	0.48 (0.36–0.64) *p < 0.0001*
WJTOG3405	6.3 months	9.2 months	0.489 (0.336–0.710) *p < 0.0001*
NEJGSG002	5.4 months	10.8 months	0.30 (0.22–0.41) *p < 0.0001*
First-SIGNAL	6.7 months	8.4 months	0.613 (0.308–1.221) *p = 0.084*
	Best overall response		**Odds ratio (95% CI) *p value***
IPASS	47.3%	71.2%	2.75 (1.65–4.60) *p = 0.0001*
WJTOG3405	32.2%	62.1%	*(12.6-47.1) p < 0.0001*
NEJGSG002	30.7%	73.7%	*p < 0.0001*
First-SIGNAL	37.5%	84.6%	9.167 (2.109–39.847) *p < 0.002*
	Median overall survival		**HR (95% CI) *p value***
IPASS	21.9 months	21.6 months	0.90 (0.79–1.02) *p = 0.109*
WJTOG3405	Not reached	30.9 months	n/a
NEJGSG002	23.6 months	30.5 months	*p = 0.31*
First-SIGNAL	26.5months	30.6 months	*p = 0.648*
Lung cancer symptoms and health-related quality of life (HRQoL)	**Patients with clinically relevant Improvements in QoL during the study EGFR-TK mutation patients only**		
PS, smoking history and gender as covariates	**Platinum doublet chemotherapy arm**	**Gefitinib arm**	**Odds ratio (95% CI) *p value***
IPASS – Total FACT-L	44.5	70.2	3.01 (1.79–5.07) *p < 0.0001*
IPASS – TOI	38.3	70.2	3.96 (2.33–6.71) *p < 0.0001*
IPASS – LCSS	53.9	75.6	2.70 (1.58–4.62) *p = 0.0003*
WJTOG3405	Not reported		
NEJGSG002	Not reported		
First-SIGNAL	Not reported		

Source: manufacturer's submission page 146.

The manufacturer's rationale for assuming the doublet chemotherapy arms were of equal efficacy was based the work by Ku and colleagues and the commentary in the evidence submission for TA192. In addition the manufacturer assumed that the chemotherapy arms of EURTAC and OPTIMAL can be linked to the network using doublet chemotherapy as the anchor point. This network is depicted in figure 3. More extensive and detailed information for all the trials is presented in the manufacturer's

submission, pages 160–163. The adjusted indirect comparison methodology developed by Bucher was used to conduct the indirect comparison.

Figure 3: Network of randomised clinical trials



Source: Manufacturer's submission page 157

4.16 The manufacturer presented results from four possible indirect comparisons, of the two erlotinib trials and combinations of them, against the gefitinib meta-analysis described by Ku and colleagues. The resulting indirect comparison PFS hazard ratios of erlotinib compared with gefitinib 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 (see table 3).

Table 3: Progression free survival hazard ratio for erlotinib compared with gefitinib, calculated by indirect comparison

Comparison	Indirect PFS hazard ratio erlotinib vs gefitinib	Erlotinib			Gefitinib		
		Name	PFS hazard ratio	95% CI for PFS HR	Name	PFS hazard ratio	95% CI for PFS HR
OPTIMAL compared with Ku et al. (2011)	0.36 (CI 0.22 to 0.59)	OPTIMAL	0.162	0.102 to 0.26	Ku et al. (2011)	0.45	0.38 to 0.55
Fixed effects pooled estimate of EURTAC/OPTIMAL compared with Ku et al. (2011)	0.58 (CI 0.41 to 0.81)	Fixed effect pooling EURTAC/ OPTIMAL	0.26	0.2 to 0.35	Ku et al. (2011)	0.45	0.38 to 0.55
Random effects pooled estimate of EURTAC/OPTIMAL compared with Ku et al. (2011)	0.56 (CI 0.24 to 1.28)	Random effect pooling EURTAC/ OPTIMAL	0.25	0.11 to 0.56	Ku et al. (2011)	0.45	0.38 to 0.55
EURTAC and Ku et al. (2011)	0.82 (CI 0.54 to1.26)	EURTAC	0.37	0.25 to 0.54	Ku et al. (2011)	0.45	0.38 to 0.55

Key: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Source: manufacturer's submission pages 166–168.

The manufacturer considered that the indirect PFS hazard ratio based on a comparison of EURTAC with the gefitinib meta-analysis (PFS hazard ratio 0.82 [95% CI 0.54 to 1.26]) is the most representative of the clinical effectiveness of erlotinib compared with gefitinib in the EGFR-TK mutation-positive NSCLC patient population in England and Wales.

Non-RCT evidence

4.17 The manufacturer presented the results of a pooled analysis of observational data from 1434 EGFR-TK mutation-positive patients published by Paz-Ares et al (2010). In the analysis, median PFS was reported as 13.2 months for patients treated with erlotinib, 9.8 months for patients treated with gefitinib and 5.9 months for patients treated with doublet chemotherapy.

Safety

4.18 The safety profile of erlotinib in the EURTAC and OPTIMAL trials was consistent with previously collected data in the earlier indications for erlotinib in the first-line maintenance and relapsed NSCLC settings. 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 reported adverse events. In EURTAC, patients in the erlotinib arm had a typical treatment duration of 9 to 10 months until progression or unacceptable toxicity, whereas patients in the chemotherapy arm received a maximum of four cycles over approximately 3 months. Most of the reported adverse events 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%]) compared with the chemotherapy arm (49 patients [66.2%]).

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

mainly mild to moderate, with 4% of patients experiencing grade 3 diarrhoea.

4.20 The manufacturer reported an increased incidence of infections and infestations for patients in the erlotinib arm compared with the chemotherapy arm (49.3% versus 16.2% respectively). The manufacturer noted this increase is the result of the incidence of paronychia (16%) and folliculitis (8%) which occurred only in the erlotinib arm. However, these were not life-threatening and represented modest inconvenience and discomfort to patients, unlike the infections that can accompany periods of chemotherapy induced immunosuppression

Health-related quality of life

4.21 Insufficient health-related quality of life data were collected in EURTAC for any analysis to be done. The manufacturer presented quality of life data from the OPTIMAL study. These data showed that patients receiving first-line erlotinib experienced significantly greater improvements in quality of life compared with patients receiving platinum double chemotherapy across all scales measured.

Evidence Review Group comments

4.22 The ERG identified issues with the manufacturer's submission early in the STA process. The issues highlighted were the absence of the pemetrexed with cisplatin comparator, the incomplete indirect comparison, patient treatment pathways not in-line with current NICE guidance and survival gain in the economic model that is not demonstrated by the clinical evidence. Following discussions, the ERG agreed to proceed with a critique of the submission. The ERG did not formulate clarification questions and presented a limited critique of the submission.

4.23 The ERG was of the opinion that without appropriate consideration of pemetrexed as a comparator, the evidence presented in the manufacturer's submission is incomplete and does not allow a full evaluation of erlotinib as set out in the decision problem. The ERG states that pemetrexed is the only treatment that has demonstrated an overall survival gain in patients with non-squamous NSCLC when compared with third-generation chemotherapy treatment, and must therefore be included as part of any clinical-effectiveness assessment for this patient population.

4.24 The ERG considered the EURTAC trial to be a well-designed trial suitably powered to demonstrate its primary objective. It considered the inclusion and exclusion criteria to be reasonable and that the baseline characteristics of the patients in EURTAC reflect the patients in UK clinical practice who would be considered eligible for treatment with an EGFR-TKI. The manufacturer's detailed descriptions and the evidence included in the clinical study report both indicate that the trial is of good quality.

4.25 The ERG considered that the use of conventional proportional hazards methods to estimate hazard ratios in the gefitinib and erlotinib trials compared with any other drug is problematic; the hazard ratio may not be accurate and should be viewed with caution. The ERG is aware that the Kaplan–Meier plots of PFS in the TKIs (gefitinib and erlotinib) have a different pattern to those for third-generation chemotherapy drugs, and so the proportional hazards assumption may be invalid for all PFS comparisons between these two types of treatments.

4.26 The ERG noted that the overall survival data are immature at both the interim and updated analysis time points in the EURTAC study. No difference in overall survival between erlotinib and doublet chemotherapy was reported in EURTAC, however the updated analysis showed that more patients had died in the erlotinib arm (38 [44%] versus 31 [35%]). The ERG was also aware that recent gefitinib publications have shown only a PFS benefit, with no overall survival benefit compared with doublet chemotherapy.

4.27 The ERG was unable to comment definitively on the quality of evidence from the supporting OPTIMAL trial as the clinical study report was not made available. The ERG noted similar concerns from the European Medicines Agency in the published European public assessment report (EPAR) for this technology.

4.28 The ERG questioned the generalisability of the quality of life results presented from the OPTIMAL study. There were a number of significant differences between the OPTIMAL and EURTAC trials, such as the chemotherapy regimens in the control arms, the race of the patients and the size of the PFS benefit. The ERG also noted that no quality of life data were presented that compare erlotinib with any of the comparators specified in the scope (gefitinib or for patients with non-squamous NSCLC, pemetrexed plus cisplatin or carboplatin).

4.29 The ERG noted that the manufacturer identified heterogeneity between the OPTIMAL and EURTAC results which precluded a pooled analysis of the two trials. The manufacturer stated that the EURTAC study is the most relevant for the assessment of the clinical effectiveness of erlotinib in England and Wales. The ERG noted that the manufacturer also presented exploratory meta-

analyses of both random and fixed effects of the two trials and claimed both produce broadly consistent and highly significant point estimates of the pooled PFS hazard ratio of erlotinib versus doublet chemotherapy.

4.30 The ERG highlighted concerns in relation to the indirect comparison between erlotinib and gefitiinib presented by the manufacturer. The ERG disagreed with restricting the network for the indirect comparison to EGFR-TK mutation-positive patients and believed a more robust mixed treatment comparison could be constructed, linking erlotinib, gefitinib and pemetrexed via the third-generation doublets. In addition the assumption, made by the manufacturer, that all doublet chemotherapies have the same efficacy may not be valid in EGFR mutation positive patients. The ERG was not aware or any clinical evidence to support this assumption. While the ERG acknowledged that the Bucher's adjusted indirect comparison methodology was valid, in the ERG's opinion it would have been preferable to have based the indirect comparison on the individual hazard ratios from the relevant studies.

4.31 The ERG noted the greater number of incidences of dyspnoea in the erlotinib arm compared with the chemotherapy arm (31 [41.3%] versus 19 [25.7%])

5 Comments from other consultees

5.1 The professional organisations and clinical specialists stated that patients with advanced NSCLC and proven EGFR-TK mutation-positive status were currently treated with gefitinib in accordance with TA192. A clinical specialist commented that combination pemetrexed and cisplatin chemotherapy is not an appropriate comparator because it is not generally given for patients with

proven EGFR-TK mutation over gefitinib. The clinical specialists confirmed that treatment is usually carried out in specialist cancer clinics.

5.2 The clinical specialists stated that most patients with advanced non-squamous NSCLC already have their tumours tested for EGFR mutations so no additional testing or training would be required.

5.3 A clinical specialist commented that the EURTAC and OPTIMAL trials reflected UK practice at the time the trials were taking place. However, gefitinib has since become standard care for these patients, and although there are no trials comparing erlotinib with gefitinib cross-trial comparisons demonstrated similar efficacy and toxicity.

5.4 A clinical specialist considered that both gefitinib and erlotinib have differing side effect profiles. Gefitinib causes less rash but more interstitial lung disease compared with erlotinib. If both were available for first-line treatment for mutation-positive patients the clinician could change treatments in patients experiencing undue side effects from one or other drug. Another clinical specialist considered erlotinib is associated with skin rash and diarrhoea and these are similar to the toxicities associated with gefitinib.

5.5 A clinical specialist considered that the toxicity of erlotinib was mild and that it significantly improved quality of life compared with platinum-doublet chemotherapy treatment. Because erlotinib is a tablet that can be administered in an outpatient setting it has an advantage over chemotherapy, which requires day-case or overnight admission and toxicity management that may require inpatient care. The different tablet strengths of erlotinib simplify dose modification, whereas gefitinib is available as a single

strength tablet, limiting dose modification to reducing frequency. However, a clinical specialist noted that the need for dose modification is uncommon in treatment with either erlotinib or gefitinib.

6 Cost-effectiveness evidence

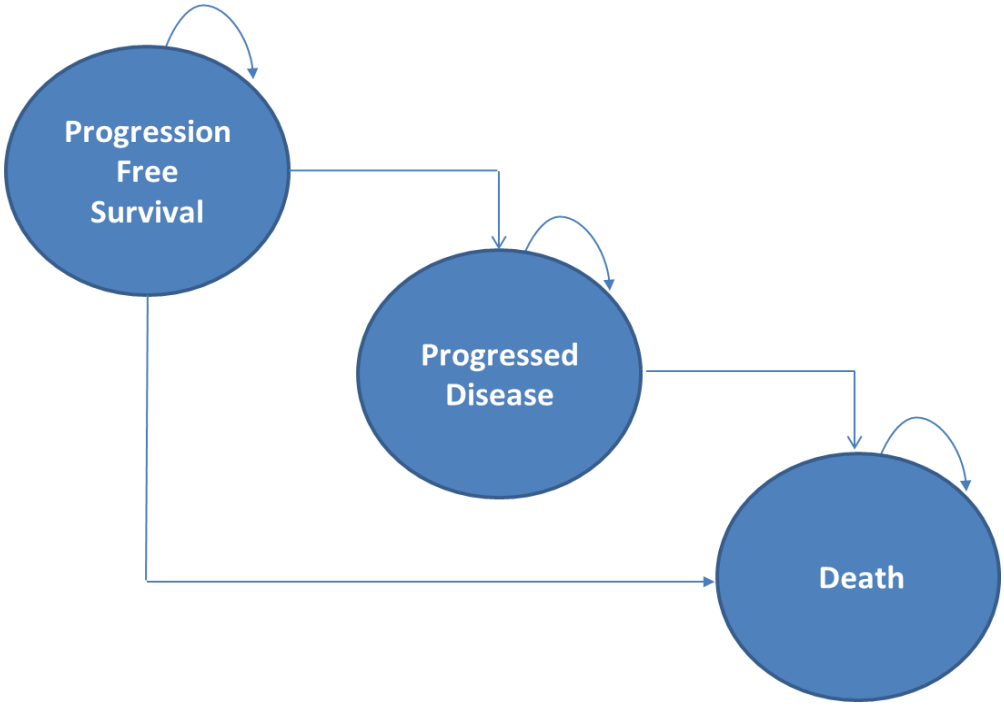
6.1 The manufacturer's systematic review did not identify any published studies that evaluated the cost effectiveness of erlotinib compared with gefitinib in the first-line treatment of EGFR-TK mutation-positive NSCLC.

6.2 The manufacturer presented a de novo economic analysis that assessed the cost effectiveness of erlotinib compared with gefitinib for the first-line treatment of EFGR mutation-positive NSCLC. The population considered is consistent with the marketing authorisation and the scope of this appraisal. In line with the NICE reference case, outcomes were expressed in terms of life years and quality-adjusted life years, 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), and no second-line treatments were considered.

Economic model structure

6.3 The manufacturer presented a semi-Markov economic model with three health states: progression-free survival (PFS), progressed disease (PD), and death.. The model had a 10-year time horizon and a cycle length of one month. All patients entered the model in the PFS health state and every month, they either remained in the same state or progressed to a worse state.

Figure 4: Economic model structure



Source: manufacturer's submission page 193

Clinical evidence

6.4 All the clinical data for the model were based on the EURTAC trial results. An area under the curve approach was used to calculate the proportion of patients in the PFS state each month. For erlotinib, the curve for the PFS state was based on the observed EURTAC data up to month 16 and was then extrapolated using an exponential function. The PFS curve for gefitinib was derived by transforming the erlotinib curve using the PFS hazard ratio obtained from the indirect comparison of erlotinib and gefitinib (HR 0.82 based upon the comparison of EURTAC and Ku et al. 2011). This approach assumes proportional hazards between gefitinib and erlotinib. The manufacturer considered it to be a conservative approach because the PFS benefit used is based on an indirect comparison that compares erlotinib in a white

population with gefitinib in an Asian population. Identical transition probabilities derived from the EURTAC data were used for both erlotinib and gefitinib for the transition between PFS and death (0.0142) and progressed disease and death (0.0757). Key patient parameters such as age and gender mix were based on the EURTAC data.

Utility values in manufacturer's economic model

6.5 Because no appropriate health-related quality-of-life data were collected in the EURTAC trial, the manufacturer conducted a systematic review for studies on health-related quality of life in metastatic or advanced NSCLC health technology evaluations. The manufacturer considered the utility values from the Nafees study to be the most appropriate for this appraisal. These utility values were estimated using the standard gamble approach in 105 members of the UK general public. They have been used in four previous NICE technology appraisals (TA181, TA190, TA192, TA227) and allow the disutility of adverse events to be incorporated into an economic model.

6.6 The PFS utility value for erlotinib (0.661) was derived by combining the EURTAC response rate (58.10%) and the incidence of grade 3 or 4 diarrhoea (4%) and rash (5.3%) observed in the EURTAC trial with the appropriate Nafees values. The PFS utility value for gefitinib (0.656) was derived by combining an estimated indirect gefitinib response rate (28.23%) and the incidence of grade 3 or 4 diarrhoea (3.8%) and rash (2.3%) observed in the IPASS trial with the appropriate Nafees values. The confidence intervals for the erlotinib and gefitinib PFS utility values were not derived explicitly. The indirect gefitinib response rate was estimated by applying the relative response from the gefitinib meta-analysis described by Ku et al. (2011)

(1.895 gefitinib versus chemotherapy) to the chemotherapy response rate observed in the EURTAC study (14.9%). The utility value for progressed disease (−0.1789, 95% CI −0.2223 to −0.1373) was taken from the Nafees study and assumed that the first-line treatment choice had no influence upon the utility patients experienced post-progression.

Costs in manufacturer's economic model

6.7 The manufacturer included costs associated with drug acquisition and administration, best supportive care, terminal care, monitoring and adverse events in the economic model. These were estimated from a range of secondary sources such as reference costs, BNF and previous NICE technology appraisal submissions, and the key costs are shown in table 4.

Table 4: Key costs in economic model

Cost type	Cost	Included elements	Value (95% CI if used)	Source
Drug costs	Dispensing costs	Pharmacy costs per pack of erlotinib/gefitinib dispensed	£13 (£6.63 to £19.37)†	MS section 6.5.5.2
	Erlotinib drug costs		30 x 150 mg = £1631.53 30 x 100 mg =£1324.14 30 x 25 mg = £378.33 With [redacted] discount in the PAS scheme: 30 x 150 mg = [redacted] 30 x 100 mg= [redacted] 30 x 25 mg= [redacted]	BNF 62 list price MS table 6, section 1.10
	Gefitinib PAS fixed cost payment		£12,200	MS section 6.5.5.1.2
	Gefitinib PAS administration cost	(1) setup cost per patient (2) monthly ongoing	£70 (†) £34	MS section 6.5.5.3
Care costs for health states	Monthly PFS BSC cost (including monitoring)	Supportive care plus CT assessment of response every three months	£181.46	MS section 6.5.6
	Monthly progressive disease BSC cost	Supportive care plus CT assessment of response every three months whilst on 2nd line treatment (estimate based upon SATURN RCT in NICE TA227)	£160.06	MS section 6.5.6
	Terminal phase best supportive care	Supportive care	£2,588.25	MS section 6.5.6
Care costs for adverse events	Rash		£116	Roche 2006 cited in Brown et al. 2009 (NICE TA192 ERG report)
	Diarrhoea		£867	Eli Lilly 2009 cited in Brown et al. 2009 (NICE TA192 ERG report)

Key: BSC, best supportive care; CI, confidence interval; CT, computed tomography; MS, manufacturer's submission; PAS, patient access scheme; PFS, progression-free survival; RCT, randomised controlled trial; †, Gamma distribution applied under assumption standard error was a quarter of base-case value.

Source: manufacturer's submission pages 238-242.

6.8 The manufacturer included the costs of drug treatment, including drug acquisition, administration and monitoring costs. Under the terms of the erlotinib patient access scheme approved by the Department of Health, the monthly cost of erlotinib was [redacted] based on a daily dose of 150 mg. Under the terms of the gefitinib patient access scheme approved by the Department of Health for gefitinib, there is a single fixed cost of £12,200 per patient when the third monthly pack of gefitinib is supplied. This means that patients who need less than 3 months of treatment do not incur a charge and that there are no further costs for those patients who survive longer than three months and require additional packs of gefitinib. In the base case, the proportion of patients for whom the £12,200 payment was required was derived by applying the indirect comparison PFS hazard ratio of erlotinib versus gefitinib (HR 0.82 based upon the comparison of EURTAC and Ku et al. 2011) to the 'time to last dose' curve generated for erlotinib. This proportion was then multiplied by the fixed cost payment in order to estimate the expected cost of gefitinib.

6.9 The costs of EGFR mutation testing were not included in the model because the manufacturer considered that EGFR testing is current standard UK practice. The model did not include second-line treatment costs because the manufacturer considered that in current standard UK practice the options and costs of second-line therapy are identical for patients with progressive disease who received first-line treatment with either gefitinib or erlotinib.

Results from manufacturer's economic model

6.10 Results from the manufacturer's base-case analyses (including the patient access scheme discount) for erlotinib compared with

gefitinib show an incremental cost-effectiveness ratio (ICER) of £21,874 per QALY gained (incremental QALYs [redacted]; incremental cost [redacted]) and £16,317 per life year gained (see table 5).

Table 5: Base-case results from the manufacturer's economic model

Drug	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£ per QALY gained)
Gefitinib	£16,046	1.796	1.015				
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,874

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; Inc., incremental.

Source: manufacturer's submission page 258.

6.11 Deterministic sensitivity analysis was presented for a wide range of parameters including transitional probabilities, utilities, resources and general parameters such as time horizon (base-case 10 years, range 5–20 years) etc. The five parameters which had the largest impact on the ICER are presented in table 6. Results were also presented for four scenario analyses which considered the relative efficacy of gefitinib and erlotinib, the proportion of patients incurring the gefitinib patient access scheme charge, the point of transition from observed PFS Kaplan–Meier curve to modelled tail and the point of transition from observed 'Time to last dose' Kaplan–Meier curve to modelled tail. The manufacturer concluded from the sensitivity analyses that the key drivers of the cost-effectiveness results were the indirect comparisons of erlotinib and gefitinib and the proportion of patients for whom the gefitinib patient access scheme payment was required.

Table 6: Results of deterministic sensitivity analysis

Parameter or scenario	Baseline variable value	Value or range varied	Cost per QALY gained
Impact of PAS scheme	Confidential discount	BNF 62 list price	£74,300
Gefitinib PAS per patient administration costs	£70 set-up and £34 monthly ongoing	50%	£24,204
		200%	£17,213
Erlotinib: monthly probability of disease progression (after month 16)	0.085977	±10% from the base case	£19,232–£24,800
Gefitinib: monthly probability of disease progression (after month 16)	0.104567	±10% from the base case	£23,915–£20,471
Monthly PFS BSC costs (including monitoring)	£181.46	±95% CI† from the base case	£20,062–£23,685
Relative efficacy of erlotinib and gefitinib	EURTAC vs Ku et al.: PFS HR for erlotinib vs gefitinib = 0.82	• OPTIMAL vs Ku et al.: 0.36 • EURTAC/OPTIMAL random effects pooling vs Ku et al.: 0.56 • EURTAC/OPTIMAL fixed effects pooling vs Ku et al.: 0.58	£15,712–£16,552
Proportion of patients incurring gefitinib PAS charge	EURTAC erlotinib 'time to last dose' curve 3 month value with indirect PFS HR applied (0.82)	• EURTAC erlotinib PFS curve 3 month value with indirect PFS HR applied (0.82) • IPASS gefitinib PFS curve 3 month value (95%) • 100% of patients 'activate' the PAS	[redacted] to £10,066
Point of transition from observed PFS KM curve to modelled 'tail'	After month 16	Month 5 to month 30	£14,826–£21,524
Point of transition from observed 'Time to last dose' erlotinib KM curve to modelled tail	After day 300	Day 150 to day 600	£19,418–£24,958

Key: BNF, British National Formulary; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier; PAS, patient access

scheme; PFS, progression-free survival; QALY, quality-adjusted life year.
Source: adapted from ERG report page 49.

6.12 The manufacturer undertook a probabilistic sensitivity analysis based on 2500 simulations to investigate the mean ICER. A scatterplot (incremental cost versus QALY) and a cost-effectiveness acceptability curve based on the patient access scheme costs are included in the ERG report (the graphs presented in the manufacturer's submission do not include the patient access scheme). Compared with gefitinib, the probability of erlotinib being cost effective at £20,000 per QALY gained was 35.8%. The probability of erlotinib being cost effective at £30,000 per QALY gained was 62.76%.

Evidence Review Group comments

6.13 The ERG was only able to offer a limited critique of the economic evidence submitted by the manufacturer because of concerns about the submitted model. It believes further information and analyses are required in order to allow a fair assessment of the cost effectiveness of erlotinib as first-line treatment for EGFR-TK mutation-positive patients.

6.14 The ERG considered that pemetrexed plus cisplatin should be included as a comparator and that there was also an argument for including the four third-generation platinum doublets (docetaxel, gemcitabine, paclitaxel and vinorelbine) in a full evaluation similar to that carried out for the gefitinib appraisal. The ERG considered that the omission of all comparators other than gefitinib has resulted in a simple model structure and avoided a robust, multi-way economic comparison which would most likely have reduced

the probability of erlotinib appearing as the most cost-effective option.

6.15 The ERG highlighted that if pemetrexed were to be included as a comparator in the economic evaluation, the costs and benefits of second-line treatments would also have to be considered.

6.16 The ERG noted that the current model yielded overall survival benefit for EGFR-TK mutation-positive patients receiving first-line treatment with erlotinib and gefitinib, and that this is not demonstrated by the published RCT evidence. The submitted model does not include any overall survival data or parameters, but relies on PFS data directly and thorough projective modelling to represent the effects of erlotinib and chemotherapy on patient outcomes. Following disease progression all surviving patients are assumed to be subject to the same post-progression survival experience and costs. The direct consequence of this simple structure is that most of the estimated difference in PFS between gefitinib and erlotinib is preserved via a common post-progression phase, and therefore translates into a similar difference in overall survival.

6.17 The ERG rejected the suggestion that the lack of overall survival benefit in the gefitinib and erlotinib trials was explained by the large-scale crossover of patients after disease progression. It believes that there is no validated objective evidence which confirmed that the improvement in PFS will lead to a corresponding gain in overall survival. The ERG highlighted that if the estimated overall survival gain is removed from the manufacturer's base-case results the ICER comparing erlotinib with gefitinib increases to over £50,000 per QALY gained (including the patient access scheme discount).

6.18 Overall, the ERG considered that in order for the decision problem to be appropriately addressed, the model needs to be modified by the manufacturer to provide ICERs for the full list of available treatments, to incorporate the results of an extended PFS mixed treatment comparison using a more comprehensive and robust evidence network, and to include the costs and benefits of second-line treatments. In addition, the logic of the model should be modified to include meta-analysis results from available overall survival data for EGFR-TK inhibitors, without assuming that PFS gains automatically convert to overall survival gains, and a wider range of scenario analyses should be explored covering the assumptions and uncertainties identified.

7 End-of-life considerations

7.1 The manufacturer did not make a case for erlotinib to be considered as an end-of-life treatment. However, discussion of erlotinib as an end-of-life treatment might prove useful to the Committee at the first Appraisal Committee meeting.

Criterion	**Data available**
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	At the updated analysis for the EURTAC study, where 69 (40%) patients had died, the median survival in the doublet chemotherapy comparator arm was 19.5 months. The latest results for the overall survival of the EGFR mutation-positive patients in the Iressa Pan-Asia study (IPASS) based in East Asia, is 21.6 months in the gefitinib arm (based on 104 events) and 21.9 months in the carboplatin plus paclitaxel arm (based on 95 events).
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an	No trial data exists which directly compares erlotinib with gefitinib. The manufacturer used an indirect comparison between the EURTAC trial and a meta-analysis of the

additional 3 months, compared with current NHS treatment	four gefitinib RCTs to calculate a PFS hazard ratio of 0.82 (0.54 to 1.26)for erlotinib compared with gefitinib. This benefit is used in the economic model.The predicted life years gained from the economic modelling is [redacted], reflecting a gain in overall survival of approximately [redacted] months However the ERG highlight that that there is no evidence for an overall survival benefit for erlotinib compared with gefitinib.
The treatment is licensed or otherwise indicated for small patient populations	Erlotinib is licensed for a number of other indications: • monotherapy for maintenance treatment of patients with locally advanced or metastatic non-small-cell lung cancer with stable disease after four cycles of standard platinum-based first-line chemotherapy, (see TA 227) • the treatment of patients with locally advanced or metastatic non-small-cell lung cancer after failure of at least one prior chemotherapy regimen. (See TA 162) • the treatment of patients with metastatic pancreatic cancer in combination with gemcitabine. In TA227, the Committee considered that the true size of the cumulative population potentially eligible for treatment with erlotinib according to its UK marketing authorisations (at that time) was not small. • It noted that the manufacturer had indicated that 6700 patients receive first-line chemotherapy in the UK (some of these patients would receive erlotinib as maintenance treatment rather than as a second-line therapy). • It also noted that most of the 7000 patients with pancreatic cancer present with metastatic disease and erlotinib would potentially be indicated

	for this population.

8 Equalities issues

8.1 No equalities issues were identified during submission. During consultation on the draft scope, consultees highlighted that drugs such as erlotinib and gefitinib (tyrosine kinase inhibitors) are less toxic than standard chemotherapy and therefore they provide additional treatment options for some patients (such as those who are less fit or elderly) who might have otherwise been denied treatment. During the scoping workshop it was acknowledged that this was not a specific equalities issue but that the Committee would consider the health needs of all patients included in the population under consideration in the appraisal

9 Innovation

9.1 The manufacturer did not make a case for erlotinib to be considered in terms of innovation.

10 Authors

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With input from the Lead Team (John Radford, Paula Ghaneh and Alison Hawdale)

Appendix A: Supporting evidence

Related NICE guidance

Published

- Lung cancer: The diagnosis and treatment of lung cancer. NICE clinical guideline 121 (2011). Available from www.nice.org.uk/guidance/CG121
- Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 227 (2011). Available from www.nice.org.uk/guidance/TA227
- Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. NICE technology appraisal guidance 192 (2010). Available from www.nice.org.uk/guidance/TA192
- Pemetrexed for the maintenance treatment of non-small-cell lung cancer. NICE technology appraisal guidance 190 (2010). Available from www.nice.org.uk/guidance/TA190
- Pemetrexed for the first-line treatment of non-small-cell lung cancer. NICE technology appraisal guidance 181 (2009). Available from www.nice.org.uk/guidance/TA181
- Erlotinib for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 162 (2008), Available from www.nice.org.uk/guidance/TA162
- Bevacizumab for the treatment of non-small-cell lung cancer (terminated appraisal). NICE technology appraisal 148 (2008).

Recommendations from 'Lung cancer: The diagnosis and treatment of lung cancer (update of NICE clinical guideline 24)' (NICE clinical guideline 121 [2011])

Chemotherapy for non-small-cell lung cancer

1.4.40 Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky

score of 80–100), to improve survival, disease control and quality of life. **[2005]**

1.4.41 Chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. **[2005]**

1.4.42 Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. **[2005]**

1.4.43 Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. **[2005]**

Recommendations from '**Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer' (NICE technology appraisal guidance 192 [2010])**

1.1 Gefitinib 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 gefitinib at the fixed price agreed under the patient access scheme**.**

Recommendations from **'Pemetrexed for the first-line treatment of non-small-cell lung cancer' (NICE technology appraisal guidance 181 [2009])**

1.1 Pemetrexed in combination with cisplatin is recommended as an option for the first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) only if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.

1.2 People who are currently being treated with pemetrexed for NSCLC but who do not meet the criteria in 1.1 should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.