NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175)

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment 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 comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- The population specified in the scope was 'adults with locally advanced or metastatic non-small-cell lung cancer that has progressed following prior chemotherapy'. Clinical practice has changed since the publication of NICE technology appraisal guidance 162 (Erlotinib for the treatment of non-small-cell lung cancer). EGFR-TK mutation testing is now typically carried out at diagnosis to determine whether people have EGFR-TK mutation positive or negative tumours. Treatment decisions are driven by EGFR-TK mutation status, as well as disease stage, histology, performance status, co-morbidities and patient preference. The EGFR-TK mutation-positive population receive either erlotinib or gefitinib as a first-line treatment and that re-treatment with an EGFR-TK inhibitor following disease progression is unlikely. For people whose disease tests negative for EGFR-TK mutations, third generation platinum doublet chemotherapy or monotherapy are given as first-line treatment, and following disease progression these patients are given erlotinib or docetaxel. What population (that is, EGFR-TK mutation-

unknown, EGFR-TK mutation-positive, EGFR-TK mutation-negative) do the Committee consider relevant to developing guidance in the review of technology appraisals 162 and 175?

- The BR21 trial compares erlotinib with best supportive care in a population with EGFR-TK mutation-unknown status (at randomisation). Median progression-free survival (2.2 compared with 1.8 months) and median overall survival (6.7 compared with 4.7 months) were statistically significantly longer in people treated with erlotinib compared with best supportive care. Are the results of the BR21 trial in a population with EGFR-TK mutation-unknown status relevant to the decision-making?
- The retrospective subgroup analysis of the EGFR-TK mutation-negative population from the BR21 trial showed no statistically significant differences in median overall survival between erlotinib and best supportive care treatment groups (7.9 compared with 3.3 months). What is the Committee's view on the robustness of the retrospective subgroup analysis of the BR21 trial for the EGFR-TK mutation-negative population?
- The TAILOR trial directly compares erlotinib with docetaxel in the EGFR-TK mutation-negative population. Median progression-free survival was statistically significantly lower with erlotinib compared with docetaxel (2.4 compared with 2.9 months) and no statistically significant differences in median overall survival were estimated between treatment groups (5.4 compared with 8.2 months). The Assessment Group were uncertain whether the multicentre Italian TAILOR trial reflected clinical practice in England. It included 2 regimens of docetaxel (either 75 mg/m2 every 3 weeks or weekly infusions of 35mg/m2). The authors of the TAILOR trial noted that the regimens have similar efficacy but the latter regimen would not be used in English clinical practice. Is the TAILOR trial generalisable to clinical practice in England?
- No trials were identified that were conducted solely in the EGFR-TK mutation-positive population. The Assessment Group only identified retrospective (posthoc) subgroup analyses which included small numbers of patients and diverse outcomes, were poorly reported and had poor statistical power. The Assessment

Group did acknowledge that the median overall survival results reported in the manufacturer's posthoc analysis of the first-line IPASS trial in patients who receive an EGFR-TK inhibitor compared with patients who do not receive an EGFR-TK inhibitor following failure of first-line chemotherapy, are longer than estimates previously reported in trials of gefitinib, erlotinib or chemotherapy treatment but this finding needs to be validated by evidence from an independent RCT because it would represent an important therapeutic advance. The Assessment Group concluded that the evidence base in the EGFR-TK mutation-positive is not sufficiently robust to inform decision-making. What is the Committee's view on the clinical effectiveness data available for the EGFR-TK mutation-positive population?

- The manufacturers and the Assessment Group did not conduct a mixed treatment comparisons because of heterogeneity in important clinical factors (such as ethnicity and performance status) between trials. The Assessment Group commented that conducting a mixed treatment comparison was likely to increase rather than reduce uncertainty. Is it appropriate to conduct a mixed treatment comparison?

Cost effectiveness

- Cost effectiveness evidence is only presented for the EGFR-TK mutation-unknown and EGFR-TK mutation-negative populations. Therefore, no cost effectiveness analysis is presented for the EGFR-TK mutation-positive population because of (in the view of the Assessment Group) a lack of sufficiently robust clinical effectiveness evidence. Can a recommendation be made for the EGFR-TK mutation-positive population?
- The final scope for the appraisal included docetaxel and best supportive care as comparators. What is the most appropriate comparator for erlotinib and gefitinib?
- The Assessment Group considered that standard parametric functions were invalid for modelling the progression-free survival and overall survival data because they assume a single continuous disease and treatment effect. It therefore chose to use a 3-phase spline model for each comparison. Is the survival modelling carried out by the Assessment Group appropriate?

- The manufacturer (Roche Products) used EQ-5D utility values measured in people with non-small-cell lung cancer associated with the anaplastic lymphoma kinase (ALK) gene in its economic analysis. The Assessment Group considered the use of utility values from Nafees et al. (2008), which use the standard gamble technique in the UK general population (n=100), to be more appropriate. The Assessment Group weighted these results by response rates and the incidence of adverse reactions. Nafees et al. (2008) included a number of vignettes relating to second-line non-small-cell lung cancer. How appropriate are the utility values used in the manufacturer's submission and assessment report?
- The manufacturer (Roche Products) only included costs relating to adverse reactions that occurred in more than 5% of patients in the BR21 trial. The Assessment Group included costs and disutilities associated with 7 adverse reactions from the Nafees et al. (2008) study. Have adverse reactions been sufficiently captured in the cost effectiveness analyses presented by the manufacturer (Roche Products) and Assessment Group?
- Using the intent-to-treat data from the BR21 trial, the manufacturer (Roche Products) and Assessment Group estimated ICERs of £51,036 and £61,132 per QALY gained respectively for the comparison of erlotinib with best supportive care in the EGFR-TK mutation-unknown population. What is the most plausible ICER for erlotinib compared with best supportive care in the EGFR-TK mutation-unknown population?
- Using the retrospective subgroup data from the BR21 trial, the manufacturer (Roche Products) and Assessment Group estimated ICERs of £58,579 and £54,687 per QALY gained respectively for the comparison of erlotinib with best supportive care in the EGFR-TK mutation-negative population. What is the most plausible ICER for erlotinib compared with best supportive care in the EGFR-TK mutation-negative population?
- The Assessment Group's estimated ICER for erlotinib compared with docetaxel in the EGFR-TK mutation-negative population was sensitive to changes in the incidence of febrile neutropenia in the docetaxel group. In the Assessment Group's base-case analysis, the incidence of febrile neutropenia in the docetaxel group was 3.9% (1.1% to 8.3%), taken from

the TAILOR trial. The manufacturer of erlotinib (Roche Products) considered the incidence rate of febrile neutropenia in the docetaxel group to be low compared with other trials, such as, the INTEREST (approximately 10%) and JMEI (approximately 13%) trials. The manufacturer commented that this may be related to the inclusion of a fitter patient population or the use of weekly treatment schedules in the TAILOR trial. However, the Assessment Group considered that because docetaxel has been used for many years it is likely that its associated adverse reactions are better managed and more frequently avoided than in the past because of increased clinical awareness. In NICE technology appraisal 162, the Committee considered an estimate of 5.95% from the Decision Support Unit to be the most plausible incidence rate from those presented. What is the most plausible incidence rate of febrile neutropenia in the docetaxel group?

- Using the data from the TAILOR trial, the Assessment Group's economic model estimated incremental cost savings of £1653 and an incremental QALY loss of 0.108 for erlotinib compared with docetaxel in the EGFR-TK mutation-negative population. This resulted in an ICER of £15,359 per QALY gained for docetaxel compared with erlotinib. In an extreme sensitivity analysis, the Assessment Group included a utility 'bonus' increment associated with oral delivery; this increased the ICER from £15,359 to £26,176 per QALY gained. What is the most plausible ICER for erlotinib compared with docetaxel in the EGFR-TK mutation-negative population?

1 Background: clinical need and practice

1.1 In England and Wales approximately 33,000 people are diagnosed with lung cancer each year. Around 72% (approximately 20,000) of lung cancers are non-small-cell lung cancers, which can be further classified into 3 histological sub-types: large-cell undifferentiated carcinoma; squamous cell carcinoma; and adenocarcinoma. The majority of lung cancers are diagnosed in the later stages, with 21% presenting with locally and regionally advanced disease (stage IIIB) and 48% presenting with

advanced disease (stage IV) in which the cancer has spread to other parts of the body. For people presenting with non-small-cell lung cancer stage IIIB the 5-year survival rate is around 7% to 9%, for people presenting with non-small-cell lung cancer stage IV the 5-year survival rate varies from 2% to 13%.

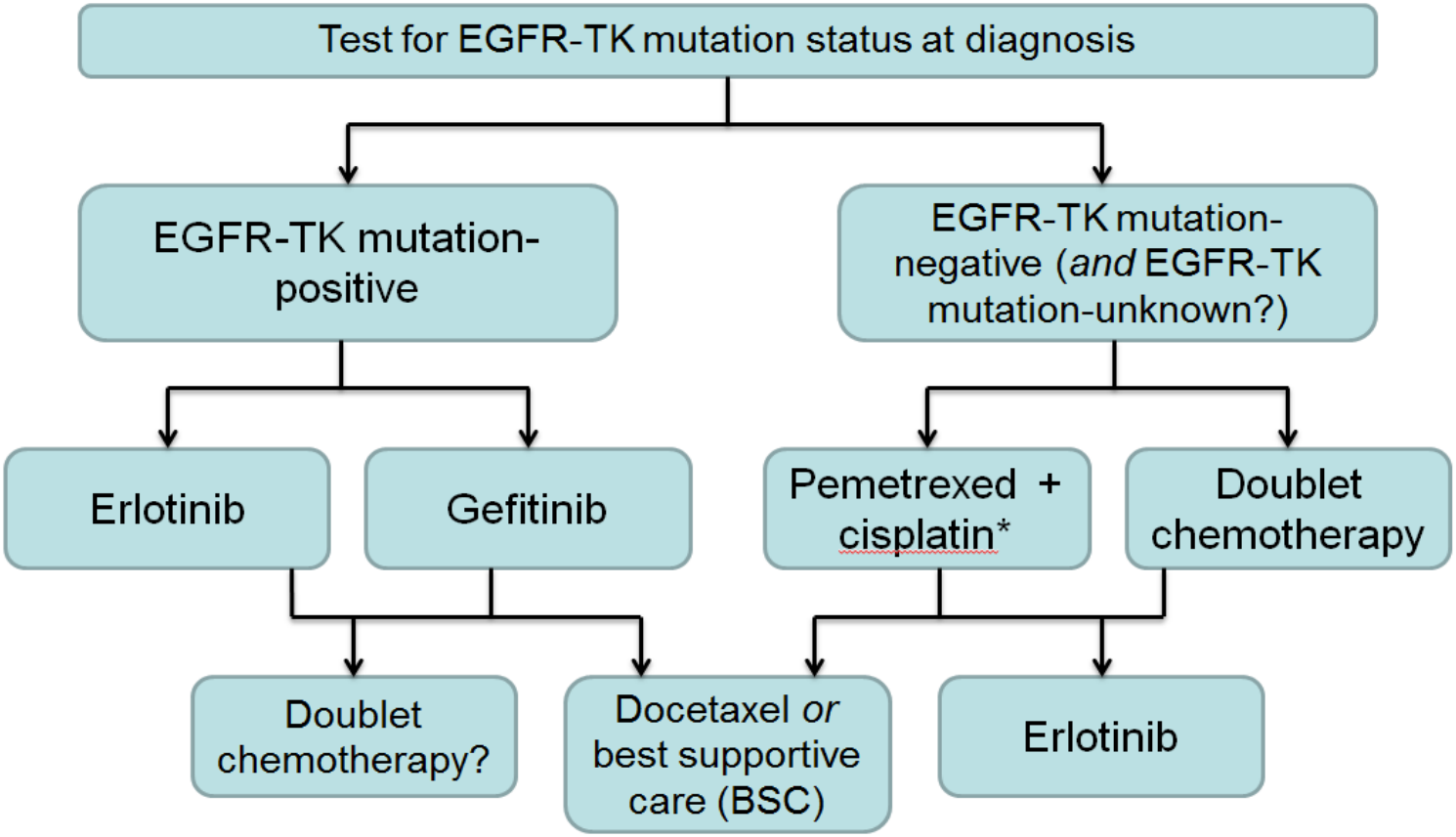
1.2 Non-small-cell lung cancer can either test positive for an epidermal growth factor receptor tyrosine kinase mutation (EGFR-TK mutation-positive tumours) or test negative for an EGFR-TK mutation (EGFR-TK mutation-negative tumours). The EGFR-tyrosine kinase is a selective target for inhibiting cancer. In normal cells, EGFR-TK is controlled and therefore the overexpression of EGFR-TK is considered a critical factor in the development and malignancy of non-small-cell lung cancer tumours. Overexpression of EGFR has been detected in 10 to 15% of non-small-cell lung cancers.

1.3 For the majority of people with non-small-cell lung cancer, the aims of therapy are to prolong survival and improve quality of life. For people with locally advanced or metastatic non-small-cell lung cancer in whom relapse has occurred following prior chemotherapy, NICE recommends that docetaxel monotherapy should be considered if second-line therapy is appropriate (NICE clinical guideline 121; see Appendix A). NICE also recommends erlotinib with a patient access scheme as a second line treatment option for non-small-cell lung cancer as an alternative to docetaxel (NICE technology appraisal guidance 162; see Appendix A). Erlotinib is not recommended for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer in patients for whom docetaxel is unsuitable (that is, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy. Pemetrexed is not recommended for treating locally advanced or metastatic non-small-cell lung cancer after prior chemotherapy (NICE technology appraisal guidance 124; see Appendix A). NICE was unable to make a recommendation for gefitinib as a second-line treatment option for

people with non-small-cell lung cancer because the manufacturer did not provide an evidence submission (Terminated NICE technology appraisal guidance 175; see Appendix A).

1.4 Clinical practice has changed since the publication of NICE technology appraisal 162 because the identification of a tumour's EGFR-TK mutation status has become an important prognosis factor. In the NHS, most people with non-small-cell lung cancer obtain a histological diagnosis for their tumour before first-line therapy to ensure the most appropriate treatment regime is considered. People with non-small-cell lung cancer whose tumours are likely to test positive for EGFR-TK mutations (that is, people who have the following factors: female, never-smoker and adenocarcinoma histology) are now also tested for EGFR mutation status at diagnosis. NICE recommends first-line treatment with an EGFR-TK inhibitor (either erlotinib or gefitinib) in people with non-small-cell lung cancer whose disease tests positive for EGFR-TK mutations (Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer [NICE technology appraisal guidance 192], Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer [NICE technology appraisal 258]). In clinical practice, re-treatment with an EGFR-TK inhibitor is unlikely to be considered in patients whose disease tests negative for EGFR-TK mutations and has progressed following first-line treatment. Consequently EGFR-TK mutation status is increasingly being considered in the design of lung cancer clinical trials (for example, prospective recruitment of for EGFR-TK mutation-positive or EGFR-TK mutation-negative populations, or using EGFR-TK mutation status as a stratification factor).

Figure 1: Treatment pathway for non-small-cell lung cancer [adapted from NICE clinical guideline 121, Roche Product's evidence submission page 8 and professional statements]



Note: *option for patients with predominantly non-squamous non-small-cell lung cancer

2 The technologies

Erlotinib

2.1 Erlotinib (Tarceva, Roche Products) is an orally administered inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK). It blocks the signal pathways in cell proliferation and slows the growth and spread of the tumour. Erlotinib has a UK marketing authorisation for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer after the failure of at least 1 prior chemotherapy regimen.

2.2 The summary of product characteristics lists the following adverse reactions for erlotinib: infection, anorexia, keratoconjunctivitis sicca, conjunctivitis, dyspnoea, cough, diarrhoea, nausea, vomiting, stomatitis, abdominal pain, rash, pruritus, dry skin and fatigue. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The recommended dosage is 150 mg once daily. The price for a pack (30 tablets per pack) of 150 mg tablets is £1631.53 (excluding VAT; 'British National Formulary' [BNF] edition 66). Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of erlotinib has agreed a patient access scheme with the Department of Health. The level of discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Gefitinib

2.4 Gefitinib (Iressa, AstraZeneca) is an orally active EGFR-TK inhibitor that blocks the signal pathways involved in cell proliferation. By blocking EGFR-TK, gefitinib helps to slow the growth and spread of the cancer. Gefitinib has a UK marketing authorisation for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer with activating mutations of EGFR-TK.

2.5 The summary of product characteristics states that when assessing the EGFR-TK mutation status of a patient, it is important that a well-validated and robust method is chosen to avoid false-negative and false-positive determinations.

2.6 The summary of product characteristics lists the following common and very common adverse reactions for gefitinib: diarrhea, skin reactions, anorexia, conjunctivitis, blepharitis, dry eye, haemorrhage, interstitial lung disease, vomiting, nausea, stomatitis, dehydration, dry mouth, elevations in alanine aminotransferase, elevations in total bilirubin, nail disorder, alopecia, asymptomatic laboratory elevations in blood creatinine, proteinuria, cystitis and asthenia. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.7 The recommended dosage is 250 mg once daily. The price for a pack (30 tablets per pack) of 250 mg tablets is £2167.71 (excluding VAT; 'British National Formulary' [BNF] edition 66). Costs may vary in different settings because of negotiated procurement discounts.

Summary of the technologies

Table 1: Summary description of technologies

Non-proprietary name	Erlotinib	Gefitinib
Proprietary name	Tarceva	Iressa
Manufacturer	Roche Products	Astra Zeneca
Dose	150 mg once daily	250 mg once daily
Acquisition cost (BNF edition 66)	£1631.53 (30 tablets)	£2167.71 (30 tablets)
Patient access scheme	[redacted]	No

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of erlotinib and gefitinib within their licensed indications for treating non-small-cell lung cancer following prior chemotherapy (review of NICE technology appraisals 162 and 175).

	Final scope issued by NICE	Additional comments or specifications in the Assessment Group's protocol
Population	Adults with locally advanced or metastatic non-small-cell lung cancer that has progressed following prior chemotherapy	
Intervention	• Erlotinib • Gefitinib	
Comparators	Erlotinib and gefitinib should be compared with each other and with: • Docetaxel • Best supportive care	

The Assessment Group (AG) noted that gefitinib has a UK marketing authorisation for treating people with non-small-cell lung cancer who test positive for EGFR-TK mutations. It commented that people with non-small-cell lung cancer who test negative for EGFR-TK mutations are therefore not eligible for treatment with gefitinib. The patent for Docetaxel expired in 2010. The list price of Docetaxel is approximately 90% less than that considered in NICE technology appraisals 162 and 175.

Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life
Economic evalu	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.
Other considerations	Guidance will only be issued in accordance with the marketing authorisations. If the evidence allows, subgroups such as those defined by histology (squamous/ non squamous) and EGFR mutation status. The appraisal should consider the implications of mutational testing. The availability of any patient access schemes for the interventions and comparators should be taken into account in the analysis.

3.2 The Assessment Group commented that the increased significance of EGFR-TK mutation status in non-small-cell lung cancer has raised questions about how to treat EGFR-TK mutation-positive or mutation-negative patients. The Assessment Group suggested that the current pathway for EGFR-TK mutation testing varies across England, but the rates of testing are improving each year. It further noted that most people with non-small-cell lung cancer have an EGFR-TK mutation test before first-line therapy and that very few patients need to have an EGFR-TK mutation test before second-line therapy.

The Assessment Group stated that most of the EGFR-TK mutation-positive population receive either erlotinib or gefitinib as a first-line treatment and that re-treatment with an EGFR-TK inhibitor following disease progression is unlikely. Docetaxel is given as a second-line treatment. The Assessment Group noted that the patient population eligible for treatment with an EGFR-TK inhibitor following prior chemotherapy is likely to be small. For the EGFR-TK mutation-negative population, third generation platinum doublet chemotherapy or monotherapy are given as first-line treatment, and following disease progression these patients are given erlotinib or docetaxel.

4 Clinical-effectiveness evidence

4.1 The Assessment Group conducted a systematic review of the literature to identify studies evaluating the clinical effectiveness and safety of erlotinib and gefitinib for treating adults with locally advanced or metastatic non-small-cell lung cancer that has progressed following prior chemotherapy. It identified 12 randomised controlled trials (RCTs): 2 trials comparing erlotinib with docetaxel (DELTA, n=301; TAILOR, n=222), 1 trial comparing erlotinib with chemotherapy (TITAN, n=424), 1 trial comparing erlotinib with best supportive care (BR21, n=731), 1 trial comparing gefitinib with erlotinib (Kim et al. 2012, n=96), 6 trials comparing gefitinib with docetaxel (Bhatnagar et al. 2012, n=30;

INTEREST, n=1466; ISTANA, n=161; Li et al. 2010, n=98; SIGN, n=141; V-15-32, n=490) and 1 trial comparing gefitinib with best supportive care (ISEL, n=1692).The Assessment Group did not identify any additional trials relevant to the scope that were not identified in the manufacturer's submissions.

4.2 The Assessment Group commented that overall the trials were of reasonable methodological quality. Two of the studies were conference abstracts (Bhatnagar et al. 2012; DELTA) and therefore limited details were reported about each of the trial designs and methods used. The Assessment Group highlighted that, of the published RCTs, only BR21 and ISEL were double-blind and the remaining RCTs were open-label. In all of the published RCTs, patient characteristics were comparable between trial groups and included more than 80% of randomised patients in their final analyses. However, the Assessment Group noted that in Kim et al. (2012), the patient characteristics for the historical control group that was used to estimate the efficacy of erlotinib and gefitinib (rather than directly comparing both groups) were not reported. All but 1 of the published RCTs stated that an intention-to-treat analysis was conducted (Li et al. 2010).

4.3 Five trials were conducted internationally, 1 was a multicentre trial in Italy (TAILOR) the remaining 6 trials were conducted in Asian countries (Bhatnagar et al. 2012; DELTA; ISTANA; Kim et al. 2012; Li et al. 2010; V-15-32), 3 of which were multicentre (DELTA; ISTANA; V-15-32). The phase of Bhatnagar et al. (2012) and Li et al. (2010) were unknown, 2 of the trials were phase II (Kim et al. 2012; SIGN), and the remaining 8 trials were phase III. The dosages of erlotinib and gefitinib were consistent with the licensed indications across the trials. In the 9 trials that included docetaxel as a comparator the dosages were: 75mg m^2 every 3 weeks in 6 of the trials (Bhatnagar et al. 2012; INTEREST; ISTANA; Li et al. 2010; SIGN; TAILOR); 60mg m^2 every 3 weeks, which is the standard dose in Japan, in 2 of the trials (DELATA; V-15-32); and at the treating physician's

discretion in the TITAN trial. Because the choice of chemotherapy (docetaxel or pemetrexed) was at the discretion of the physician, patients were not randomised in the TITAN trial and the trial investigators only published aggregated outcomes for chemotherapy and considered any disaggregated comparison of erlotinib with docetaxel or pemetrexed to be unreliable. Median follow-up ranged from 7.2 months (ISEL) to 33 months (TAILOR).

4.4 The median age of patients in the RCTs ranged from 49 to 61 years. The majority of patients: were male (except for Kim et al. 2012); had stage IV disease (except for Li et al. 2010); had received 1 prior chemotherapy (except for BR21 and ISEL); and had a performance status of 0 or 1 assessed by the Eastern Cooperative Oncology Group (ECOG) scoring system. The main histological type across the RCTs was adenocarcinoma, however, the ratio of adenocarcinoma to other histological subtypes varied. Patients included in the Kim et al. (2012) and TAILOR trials were tested for EGFR-TK mutation status before study entry, but it was unclear if EGFR-TK status was known at the time of randomisation in the DELTA trial. The 6 RCTs conducted in Asia exclusively included patients of East Asian ethnicity but the majority of patients included in the remaining trials were white (except for SIGN).

4.5 The Assessment Group considered the overall population (patients who disease has EGFR-TK mutation-unknown status) and 2 subgroups based on EGFR-TK mutation status:

- EGFR-TK mutation-positive population.
- EGFR-TK mutation-negative population.

Clinical practice has changed since the publication of NICE technology appraisal 162 (Erlotinib for the treatment of non-small-cell lung cancer [NICE technology appraisal guidance 162]) because the identification of a patient's EGFR-TK mutation status has become an important prognostic

factor. Consequently EGFR-TK mutation status is increasingly being considered in the design of non-small-cell lung cancer trials (for example, prospective recruitment of for EGFR-TK mutation-positive or EGFR-TK mutation-negative populations, or using EGFR-TK mutation status as a stratification factor). A substantial number of the published trials conducted in patients with non-small-cell lung cancer therefore did not consider mutation status in their design or the recruitment, and consequently are limited to retrospective subgroup analyses (see table 2 for a summary of trials included in the Assessment Group's review of the clinical effectiveness evidence). The manufacturer of gefitinib focused its evidence submission on the EGFR-TK mutation-positive population because the licensed indication for gefitinib is for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer with activating mutations of EGFR-TK. The Assessment Group also considered that the 3 trials published since the European Medicines Agency granted marketing authorisation for gefitinib were insufficiently robust to make recommendations that may result in a change to current clinical practice (Bhatnagar et al. 2012; Kim et al. 2012; Li et al. 2010).

EGFR-TK mutation-unknown population (overall population)

Erlotinib

4.6 Three trials of erlotinib were identified by the Assessment Group that presented outcome data for the EGFR-TK-unknown population. No statistically significant differences in median progression-free survival were estimated between erlotinib compared with docetaxel (DELTA: 2.0 compared with 3.2 months; hazard ratio [HR] 1.22, 95% confidence interval [CI] 0.97 to 1.55) and erlotinib compared with either docetaxel or pemetrexed (TITAN: 6.3 compared with 8.6 weeks; HR 1.19, 95% CI 0.97 to 1.46). The BR21 trial showed a statistically significantly longer median progression-free survival with erlotinib compared with best supportive care (2.2 compared with 1.8 months; HR 0.61, 95% CI 0.51 to 0.74).

4.7 No statistically significant differences in median overall survival were estimated between erlotinib compared with docetaxel (DELTA: 14.8 compared with 12.2 months; HR 0.91, 95% CI 0.68 to 1.22) and erlotinib compared with either docetaxel or pemetrexed (TITAN: 5.3 compared 5.5 months; HR 0.96, 95% CI 0.78 to 1.19). The BR21 trial showed a statistically significantly longer median overall survival with erlotinib compared with best supportive care (6.7 compared 4.7 months; HR 0.7, 95% 0.58 to 0.85).

4.8 Response rates were reported for 2 of the 3 trials (BR21; TITAN). The response rates were higher for erlotinib compared with best supportive care (BR21: 8.9% compared with <1%) and erlotinib compared with either docetaxel or pemetrexed (TITAN: 7.8% compared with 6.3%).

4.9 Patients treated with erlotinib experienced a statistically significantly higher health-related quality of life compared with patients receiving best supportive care when measured by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 in the BR21 trial. No statistically significant differences in health-related quality of life were estimated between erlotinib and docetaxel when measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire in the TITAN trial.

4.10 The manufacturer of erlotinib stated that the most common grade 3 to 4 adverse reactions associated with erlotinib are skin rash (approximately 5 to 9%) and diarrhoea (approximately 0.6 to 6%) but are easily manageable. It commented that life-threatening adverse reactions are very rare and erlotinib is better tolerated compared with chemotherapy. The Assessment Group stated that it considered that the adverse reactions reported in the trials appear to be consistent with the information available for erlotinib in its summary of product characteristics (see section 2.2).

Gefitinib

4.11 Gefitnib is only licensed for treating adult patients with locally advanced or metastatic non-small-cell lung cancer who test positive for EGFR-TK mutations (see section 2.4). NICE can only appraise treatments within their licensed indications, therefore the trial evidence available for the EGFR-TK mutation-unknown population is not applicable to the technology appraisal. However, the Assessment Group did identify 7 trials of gefitinib for treating non-small-cell lung that has progressed following prior chemotherapy. Please refer to tables 4, 6 and 8 in the overview and pages 43 to 46 of the Assessment Group report for further details.

EGFR-TK mutation-positive population

Erlotinib

4.12 No trials of erlotinib were identified by the Assessment Group that were solely conducted in EGFR-TK mutation-positive population. Two trials were identified that reported retrospective subgroup analyses of the EGFR-TK mutation-positive population (BR21; TITAN). Only 1 of the 2 trials reported results for progression-free survival. No statistically significant differences in median progression-free survival were found for erlotinib compared with either docetaxel or pemetrexed (TITAN: median progression-free survival in month not reported [NR]; HR 0.71, 95% CI 0.13 to 3.97). No statistically significant differences in median overall survival were found for erlotinib compared with:

- Best supportive care (BR21: 10.9 compared with 8.3 months; HR 0.55, 95% CI 0.25 to 1.19)
- Either docetaxel or pemetrexed (TITAN: 19.3 compared with NR months; HR 1.19, 95% CI 0.12 to 11.49).

Gefitinib

4.13 The Assessment Group did not identify any trials of gefitinib that were conducted solely in an EGFR-TK mutation-positive population. Four trials were identified that retrospectively reported a subgroup analysis of the

EGFR-TK mutation-positive population (INTEREST; ISEL; Kim et al 2012; V-15-32). Limited data for progression-free survival were available. The INTEREST trial showed statistically significantly longer median progression-free survival for patients receiving gefitinib than patients receiving docetaxel (7 compared with 4.1 months; HR 0.16, 95% CI 0.05 to 0.49). A smaller proportion of patients treated with gefitinib compared with best supportive care experienced disease progression in the ISEL trial (11 out of 21 patients compared with 4 out of 5 patients; median progression-free survival NR; HR NR).

4.14 No statistically significant differences in median overall survival were found between gefitinib and docetaxel in the INTEREST trial (14.2 compared with 16.6 months; HR 0.83, 95% CU 0.41 to 1.67). A smaller proportion of patients treated with gefitinib compared with best supportive care died in the ISEL trial (7 out of 21 patients compared with 3 out of 5 patients; median overall survival NR; HR NR). The manufacturer of gefitinib presented the results of a posthoc analysis of the IPASS trial comparing the EGFR-TK mutation-positive population who received subsequent EGFR-TK inhibitor treatment and those who did not receive subsequent EGFR-TK inhibitor treatment following the failure of first-line chemotherapy. Median overall survival was lower in patients who did not receive subsequent EGFR-TK inhibitor treatment compared with patients who did receive subsequent EGFR-TK inhibitor treatment ([redacted]). The Assessment Group stated that the median overall survival results reported in the manufacturer's posthoc analysis of the first-line IPASS trial are longer than estimates previously reported in trials of gefitinib, erlotinib or chemotherapy treatment and therefore this finding needs to be validated by evidence from an independent RCT because it would represent an important therapeutic advance.

4.15 Three of the 4 trials presented data for each treatment group (INTEREST; Kim et al. 2012; V-15-32). Results suggested that patients randomised to

receive gefitinib had a higher response rate compared with patients randomised to receive docetaxel or erlotinib, but tests of statistical significance were only presented in 1 trial (INTEREST, p=0.04).

EGFR-TK mutation-negative population

Erlotinib

4.16 Four trials of erlotinib were identified by the Assessment Group that included either: patients known to be EGFR-TK mutation-negative (TAILOR); patients with and without EGFR-TK mutations whose EGFR-TK status were known prior to randomisation (DELTA); or retrospectively reported a subgroup analysis of the EGFR-TK mutation-negative population (BR21; TITAN).

4.17 Three of the 4 trials reported results for median progression-free survival. Median progression-free survival was statistically significantly lower with erlotinib compared with docetaxel in 2 of the 3 trials (TAILOR: 2.4 compared with 2.9 months; HR 1.39, 95% CI 1.06 to 1.82, DELTA: 1.3 months compared with 2.9 months; HR 1.44, 95% CI 1.08 to 1.92). In the remaining trial, no statistically significant differences in median progression-free survival were estimated between patients randomised to erlotinib compared with patients randomised to either docetaxel or pemetrexed (TITAN: median progression-free survival in months NR; HR 1.25, 95% CI 0.88 to 1.78).

4.18 No statistically significant differences in overall survival were estimated between erlotinib compared with:

- best supportive care (BR21: 7.9 compared with 3.3 months; HR 0.74, 95% 0.52 to 1.05)
- docetaxel (TAILOR: 5.4 compared with 8.2 months; HR 1.28, 95% CI 0.95 to 1.96, DELTA: 9.0 compared with 9.2 months; HR 0.98, 95% CI 0.69 to 1.39)

- docetaxel or pemetrexed (TITAN: 6.6 compared with 4.4 months; HR 0.85, 95% CI 0.59 to 1.22).

Only the TAILOR trial reported the response rates for each treatment group and the results showed a statistically significantly lower response rate for erlotinib compared with docetaxel (3.0% compared with 15.5%; p=0.003).

4.19 Because the TAILOR trial (conducted in 52 hospitals in Italy) is the only published study providing head-to-head evidence for erlotinib and docetaxel in the EGFR-TK mutation-negative population, the Assessment Group further considered its relevance to clinical practice in England. It noted that:

- Two regimens of docetaxel were administered (either 75 mg/m^2 every 3 weeks or weekly infusions of 35mg/m^2), and the latter regimen would not be used in English clinical practice.

- A poorer performance status is linked to poorer outcomes, and a higher proportion of patients with a performance status of 2 would be treated in routine clinical practice in England than included in the TAILOR trial (7%).

- There are differences in other important prognostic factors between the erlotinib and docetaxel treatment groups that are possible modifiers of trial outcome in favour of docetaxel including: never-smokers (17% compared with 27%), squamous cell histology (28% compared with 21%) and adenocarcinoma histology (63% compared with 75%).

- The manufacturer of erlotinib (Roche Products) considered the rates of haematological toxicity in the docetaxel group to be low compared with other trials, such as, the INTEREST and JMEI trials. The manufacturer commented that this may be related to the inclusion of a fitter patient population or the use of weekly treatment

schedules. However, the Assessment Group considered that because docetaxel has been used for many years it is likely that its associated adverse reactions are better managed and more frequently avoided than in the past because of increased clinical awareness.

The Assessment Group concluded that the TAILOR study is a large, high quality RCT, but it is uncertain about the extent to which it reflects clinical practice in England and whether the results are likely to be mirrored in an English clinical population. The Assessment Group also noted that the primary endpoint of TAILOR changed at the first planned interim analysis from 'biomarkers of EGFR-TK amplification, protein expression and KRAS mutations' to 'overall survival' because these biomarkers were found to have no effect.

Gefitinib

4.20 Gefitnib is not licensed for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer who test negative for EGFR-TK mutations (see section 2.4). NICE can only appraise treatments within their licensed indications, therefore the trial evidence available for this population is not applicable to the technology appraisal.

Mixed treatment comparison

4.21 The manufacturers and the Assessment Group did not conduct a mixed treatment comparison. The manufacturer of gefitinib and the Assessment Group commented that it would be inappropriate to estimate the relative treatment effectiveness of erlotinib or gefitinib using a mixed treatment comparison because the presence of heterogeneity in important clinical factors between the trials is likely to increase rather than reduce uncertainty. Clinical and statistical weaknesses stated by the Assessment Group that precluded conducting a mixed treatment comparison included:

- Patient characteristics between trials which were not considered sufficiently similar. For example, ethnicity (Asian populations

compared with non-Asian populations), the proportion of patients with a performance status of 0 or 1 compared with a performance status of 2 or more, and the proportion of patients who had received 1 prior chemotherapy compared with 2 or more prior chemotherapies.

- A lack of outcome data for each of the patient populations.
- Several trials which only reported either unadjusted or adjusted analyses and combination of these results may not be directly comparable.
- The use of a Cox proportional hazards model to estimate hazard ratios in trials of erlotinib and gefitinib compared with the comparator treatment appears to be violated in 6 of the trials because the Kaplan-Meir plot crosses, which is a sufficient condition to reject proportionality.

Summary of the trials included and their results (Assessment Group clinical effectiveness review)

Table 2: Summary of trials identified by the Assessment Group

Trial	Design	Intervention	Comparator	Patient population	Retrospective EGFR subgroup data available
Bhatnagar et al. (2012)	RCT	Gefitinib	Docetaxel	EGFR-TK mutation-unknown	No
BR21	Placebo-controlled phase III RCT	Erlotinib	Placebo	EGFR-TK mutation-unknown	Yes
DELTA	Open-label phase III RCT	Erlotinib	Docetaxel	EGFR-TK mutation-positive and EGFR-TK mutation-negative	Yes
INTEREST	Open-label phase III RCT	Gefitinib	Docetaxel	EGFR-TK mutation-unknown	Yes
ISEL	Placebo-controlled phase III RCT	Gefitinib and best supportive care	Placebo and best supportive care	EGFR-TK mutation-unknown	Yes
ISTANA	Open-label phase III RCT	Gefitinib	Docetaxel	EGFR-TK mutation-unknown	No
Kim et al. (2012)	Open-label, non-comparative phase II RCT	Gefitinib	Erlotinib	EGFR-TK mutation-positive and 2 out of 3 factors associated with EGFR-TK mutations	Yes
Li et al. (2010)	RCT	Gefitinib	Docetaxel	EGFR-TK mutation-unknown	No
SIGN	Open-label phase II RCT	Gefitinib	Docetaxel	EGFR-TK mutation-unknown	No
TAILOR	Open-label phase III RCT	Erlotinib	Docetaxel	EGFR-TK mutation-negative only	Yes
TITAN	Open-label phase III RCT	Erlotinib	Docetaxel or pemetrexed	EGFR-TK mutation-unknown	Yes
V-15-32	Open-label phase III RCT	Gefitinib	Docetaxel	EGFR-TK mutation-unknown	Yes

Table 3: Summary of overall survival results – Patients treated with erlotinib for non-small-cell lung cancer that has progressed following prior chemotherapy

Comparison: erlotinib *versus* (trial)	% of deaths (number of events/number randomised)	% of deaths (number of events/number randomised)	Median survival (months)	Hazard ratio (95% CI)	*p-value*
EGFR-TK mutation-unknown status (overall population)					
versus BSC (BR21)	77.46 (378/488)	86.01 (209/243)	6.7 vs 4.7	0.7 (0.58 to 0.85)	<0.001
versus docetaxel (DELTA)	NR	NR	14.8 vs 12.2	0.91 (0.68 to 1.22)	0.527
versus docetaxel/ pemetrexed (TITAN)	NR	NR	5.3 vs 5.5	0.96 (0.78 to 1.19)	0.73
EGFR-TK mutation-positive population					
versus BSC (BR21)	NR	NR	10.9 vs 8.3	0.55 (0.25 to 1.19)	0.12
versus docetaxel/ pemetrexed (TITAN)	NR	NR	19.3 vs NR	1.19 (0.12 to 11.49)	0.88
EGFR-TK mutation-negative population					
versus BSC (BR21)	NR	NR	7.9 vs 3.3	0.74 (0.52 to 1.05)	0.09
versus docetaxel (DELTA)	NR	NR	9.0 vs 9.2	0.98 (0.69 to 1.39)	0.914
versus docetaxel (TAILOR)	NR	NR	5.4 vs 8.2	Adjusted: 1.37 (1.00 to 1.89) Unadjusted: 1.28 (0.95 to 1.96)	0.05 0.10
versus docetaxel/pemetrexed (TITAN)*	NR	NR	6.6 vs 4.4	0.85 (0.59 to 1.22)	0.37

CI=confidence interval; NR=not reported.

* Without the 30 patients with squamous cell carcinoma who received PEM (HR= 0.93; CI=0.75 to 1.17, p=0.544)

Table 4: Summary of overall survival trial results – Patients treated with gefitinib for non-small-cell lung cancer that has progressed following prior chemotherapy

Comparison: gefitinib *versus* (trial)	% of deaths (number of events/number randomised)	% of deaths (number of events/number randomised)	Median survival (months)	Hazard ratio (95% CI)	*p-value*
EGFR-TK mutation-unknown status (overall population)					
versus BSC (ISEL)	NR	NR	5.6 vs 5.1	0.89 (0.77 to 1.02)	0.087
versus docetaxel (INTEREST)	82.02 (593/723)	81.13 (576/710)	7.6 vs 8	PP: 1.02 (0.91 to 1.15) ITT: 1.015 (0.901 to 1.143)	0.47 NS
versus docetaxel (ISTANA)	81.71 (67/82)	74.68 (59/79)	14.1 vs 12.2	0.87 (0.61 to 1.24)	0.4370
versus docetaxel (Li et al. 2010)	NR	NR	7.1 vs 6.9	NR	NR
versus docetaxel (SIGN)	NR	NR	7.5 vs 7.1	0.97 (0.61 to 1.52)	0.88
versus docetaxel (V-15-32)	63.67 (156/245)	61.48 (150/244)	11.5 vs 14	1.12 (0.89 to 1.4)	0.33
EGFR-TK mutation-positive population					
versus BSC (ISEL)	33.33 (7/21)	60 (3/5)	NR	NR	NR
versus docetaxel (INTEREST)	72.73 (32/44 over both groups)		14.2 vs 16.6	0.83 (0.41 to 1.67)	0.60
EGFR-TK mutation-negative population					
versus BSC (ISEL)	70.45 (93/132)	64.91 (37/57)	NR	NR	NR
versus docetaxel (INTEREST)	84.98 (215/253 over both groups)		6.4 vs 6.0	1.02 (0.78 to 1.33)	0.91

CI=confidence interval; NR=not reported; PP=per protocol; ITT=intention-to-treat; NS=not stated.

Table 5: Summary of progression-free survival trial results – Patients treated with erlotinib for non-small-cell lung cancer that has progressed following prior chemotherapy

Comparison: erlotinib *versus* (trial)	% of deaths (number of events/number randomised)	% of deaths (number of events/number randomised)	Median survival (months)	Hazard ratio (95% CI)	*p-value*
EGFR-TK mutation-unknown status (overall population)					
versus BSC (BR21)	92.21 (450/488)	95.47 (232/243)	2.2 vs 1.8	0.61 (0.51 to 0.74)	< 0.001
versus docetaxel (DELTA)	NR	NR	2.0 vs 3.2	1.22 (0.97 to 1.55)	0.092
versus docetaxel/ pemetrexed (TITAN)	92.61 (188/203)	83.26 (184/221)	6.3 weeks vs 8.6 weeks	1.19 (0.97 to 1.46)	0.089
EGFR-TK mutation-positive population					
versus docetaxel/ pemetrexed (TITAN)	NR	NR	NR	0.71 (0.13 to 3.97)	NR
EGFR-TK mutation-negative population					
versus docetaxel (DELTA)	NR	NR	1.3 vs 2.9	1.44 (1.08 to 1.92)	
versus docetaxel (TAILOR)	NR	NR	2.4 vs 2.9	Adjusted: 1.41 (1.05 to 1.89) Unadjusted: 1.39 (1.06 to 1.82)	0.02 0.01
versus docetaxel/ pemetrexed (TITAN)	90.67 (68/75)	79.73 (59/74)	NR	1.25 (0.88 to 1.78)	0.20

CI=confidence interval; NR=not reported.

Table 6: Summary of progression-free survival trial results – Patients treated with gefitinib for non-small-cell lung cancer that has progressed following prior chemotherapy

Comparison: gefitinib *versus* (trial)	% of deaths (number of events/number randomised)	% of deaths (number of events/number randomised)	Median survival (months)	Hazard ratio (95% CI)	*p-value*
EGFR-TK mutation-unknown status (overall population)					
versus BSC (ISEL)	NR	NR	3.0 vs 2.6	0.82 (0.73 to 0.92)	0.0006
versus docetaxel (INTEREST)	82.02 (593/723)	76.62 (544/710)	2.2 vs 2.7	1.04 (0.93 to 1.18)	NR
versus docetaxel (ISTANA)	74.39 (61/82)	74.68 (59/79)	3.3 vs 3.4	Adjusted: 0.634* (0.459 to 0.875) Unadjusted: 0.729* (0.533 to 0.988)	0.0441 0.0134
versus docetaxel (SIGN)	NR	NR	3 vs 3.4	0.94 (0.64 to 1.39)	0.76
versus docetaxel (V-15-32)	90.00 (180/200)	84.49 (158/187)	2 vs 2	0.9 (0.72 to 1.12)	0.335
versus erlotinib (Kim et al. 2012)	NR	NR	4.9 vs 3.1	NR	NR
EGFR-TK mutation-positive population					
versus BSC (ISEL)	52.38 (11/21)	80 (4/5)	NR	NR	NR
versus docetaxel (INTEREST)	NR	NR	7 vs 4.1	0.16 (0.05 to 0.49)	0.001
versus erlotinib (Kim et al. 2012)	NR	NR	11.9 over both groups	NR	NR
EGFR-TK mutation-negative population					
versus BSC (ISEL)	84.09 (111/132)	85.96 (49/57)	NR	NR	NR
versus docetaxel (INTEREST)	NR	NR	1.7 vs 2.6	1.24 (0.94 to 1.64)	0.14
versus erlotinib (Kim et al. 2012)	NR	NR	2.8 months overall	NR	NR

CI=confidence interval; NR=not reported; *90% CI used.

Table 7: Summary of response rate trial results – Patients treated with erlotinib for non-small-cell lung cancer that has progressed following prior chemotherapy

Comparison: erlotinib *versus* (trial)	% Response rate in intervention group (number responded/number randomised)	% Response rate in control group (number responded/number randomised)	% Overall response rate (number responded/number randomised)	*p-value*
EGFR-TK mutation-unknown status (overall population)				
versus BSC (BR21)	8.9 (NR)	< 1 (NR)	NR	NR
versus docetaxel/ pemetrexed (TITAN)	7.88 (16/203)	6.33 (14/221)	NR	NR
EGFR-TK mutation-positive population				
versus BSC (BR21)	NR	NR	26.67 (4/15)	0.035
EGFR-TK mutation-negative population				
versus BSC (BR21)	NR	NR	6.93 (7/101)	NR
versus docetaxel (TAILOR)	3 (3/100)	15.46 (15/97)	NR	0.003

CI=confidence interval; NR=not reported.

Table 8: Summary of response rate trial results – Patients treated with gefitinib for non-small-cell lung cancer that has progressed following prior chemotherapy

Comparison: gefitinib *versus* (trial)	% Response rate in intervention group (number responded/number randomised)	% Response rate in control group (number responded/number randomised)	% Overall response rate (number responded/number randomised)	*p-value*
EGFR-TK mutation-unknown status (overall population)				
versus BSC (ISEL)	8 (77/959)	1 (6/480)	7.28 (3.1 to 16.9)	<0.0001
versus docetaxel (INTEREST)	9.10 (NR)	7.60 (NR)	1.22 (0.82 to 1.84)	0.33
versus docetaxel (ISTANA)	28.10 (NR)	7.60 (NR)	NR	NR
versus docetaxel (Li et al. 2010)	22.44 (11/49)	18.75 (9/48)	NR	NR
versus docetaxel (SIGN)	13.24 (9/68)	13.70 (10/73)	NR	NR
versus docetaxel (V-15-32)	22.50 (45/200)	12.80 (24/187)	2.14 (1.21 to 3.78)	0.009
versus erlotinib (Kim et al. 2012)	47.92 (23/48)	39.58 (19/48)	NR	NR
EGFR-TK mutation-positive population				
versus BSC (ISEL)	NR	NR	37.50 (6/16)	NR
versus docetaxel (INTEREST)	42.11 (8/19)	21.05 (4/19)	NR	0.04
versus docetaxel (V-15-32)	66.67 (6/9)	45.45 (5/11)	NR	NR
versus erlotinib (Kim et al. 2012)	66.70 (NR)	62.50 (NR)	76.47 (13/17)	NR
EGFR-TK mutation-negative population				
versus BSC (ISEL)	NR	NR	2.59 (3/116)	NR
versus docetaxel (INTEREST)	6.60 (7/106)	9.76 (12/123)	NR	0.37
versus erlotinib (Kim et al. 2012)	NR	NR	25.00 (8/32)	NR

CI=confidence interval; NR=not reported; *ISEL reported objective response rate.

5 Comments from other consultees

5.1 The professional group stated that approximately 25% of people who are treated with first-line chemotherapy subsequently recieve second-line treatment in the UK. The professional and patient groups commented that gefitinib is not used in clinical practice for treating non-small-cell lung cancer that has progressed following prior chemotherapy, but is used for the first-line treatment of people with non-small-cell lung cancer with activating mutations of EGFR-TK. The patient group noted that gefitinib may be given after chemotherapy in unusual cases because the health system has failed to provide a timely diagnosis. The professional and patient groups explained that, in clinical practice, erlotinib is used for treating non-small-cell lung cancer that has progressed following prior chemotherapy. The professional group commented that docetaxel is only used in the fittest patients but the patient group stated that because of its toxicity, it understood that docetaxel is no longer used in the second-line setting.

5.2 The professional group noted that there are 3 internationally recognised guidelines for treating non-small-cell lung cancer that offer advice on second-line therapy (American Society of Clinical Oncology; European Society of Medical Oncology; National Comprehensive Cancer Network US). It stated that there is no restriction in any of these guidelines on the second-line use of EGFR-TK inhibitors according to EGFR-TK mutation status.

5.3 The professional group noted that EGFR-TK plays an important role in the development and progression of non-small-cell lung cancer. It commented that evidence suggests that 30% of people with non-small-cell lung cancer do not have an adequate tissue diagnosis and up to 5% of samples sent for EGFR-TK mutation analysis fail due to insufficient or poor quality DNA. Therefore, EGFR-TK status is unknown in a significant proportion of patients.

5.4 The professional and patient groups identified a number of advantages of treating non-small-cell lung cancer with EGFR-TK inhibitors. They explained that EGFR-TK inhibitors have a more favourable side effect and tolerability profile compared with chemotherapy, including a lower incidence of grade 3 and 4 events that result in hospitalisation and can be life-threatening. The professional and patient groups commented that because EGFR-TK inhibitors are orally administered, there are no repeated day case admissions as seen with intravenous chemotherapies. The professional group highlighted that EGFR-TK inhibitors provide a second-line treatment option for people with non-small-cell lung cancer in whom best supportive care would generally be the only option. It commented that patients treated with EGFR-TK inhibitors do not need growth factor support compared with 50% of patients treated with docetaxel in the second-line setting. The patient group noted that because this population has a short life expectancy, spending additional time away from the hospital setting is important.

5.5 The professional group acknowledged that EGFR-TK inhibitors are associated with side effects, for example, rash and diarrhoea but that these are manageable. In patients who test negative for an EGFR-TK mutation who are fit enough to recieve second-line chemotherapy, the professional group stated that there may be a benefit with chemotherapy compared with EGFR-TK inhibitors but considered that the current evidence base is immature [note: at the time of receiving professional and patient groups statements, the TAILOR trial had not been published].

5.6 The patient group was aware that the patent for docetaxel has expired and highlighted its concern that ‘cost will form the core of this appraisal’ because it considered that there is ‘no new clinical evidence available’. It continued to state that this may set a precedent and was worried about the potential effect on future patient care in the cancer community. The professional group commented that any change in NICE guidance that may result in an increased use of chemotherapy would impact the

treatment delivery of chemotherapy units because EGFR-TK inhibitors are administered in the outpatient setting. It also noted that people with non-small-cell lung cancer treated with chemotherapy are reviewed more frequently in the outpatient setting compared with patients treated with EGFR-TK inhibitors (every 3 weeks compared with every 4 weeks respectively). Furthermore, the increased toxicity associated with chemotherapy would increase the use of inpatient services alongside those associated with its administration. The professional group considered that each provider of oncology services would need to assess the potential impact of any change in guidance for people with non-small-cell lung cancer and how any increase in demand is provided.

6 Cost-effectiveness evidence

6.1 The Assessment Group carried out a systematic review of existing cost effectiveness evidence and identified 11 papers for inclusion in its review, but did not quality assess these studies because they were not directly relevant to UK decision-making. For further details on the results of the cost effectiveness review please see section 6.1.4 of the Assessment Group report. Only 1 manufacturer (Roche Products [erlotinib]) provided an economic model to support its submission. Both the manufacturer of erlotinib and the Assessment Group's economic models only considered the population with EGFR-TK mutation-unknown status and 1 of the 2 subgroups relevant to the technology appraisal (that is, the EGFR-TK mutation-negative population). The EGFR-TK mutation-positive population was not considered because no trials were identified that solely assessed the relative effectiveness of erlotinib or gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (see sections 4.16 and 4.17). This precluded an assessment of the cost-effectiveness of gefitinib because its licensed indication is for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer with activating mutations of EGFR-TK.

Manufacturer's economic model (Roche Products)

6.2 The manufacturer submitted a partitioned survival model that only assessed the cost effectiveness of erlotinib with best supportive care. The manufacturer stated that it was not possible to demonstrate that erlotinib is cost effective compared with docetaxel following the availability of generic docetaxel and therefore this comparison was excluded from the analyses. The manufacturer conducted the economic analysis from an NHS and personal social services perspective and the model had a cycle length of 1-week and a time horizon of 6 years. Costs and health effects were discounted at an annual rate of 3.5%.

6.3 The manufacturer's economic model included 3 health states: progression-free disease, progressed disease and death. The population was assumed to be the same as that recruited to the BR21 trial, and data from this study were used to estimate progression-free survival and overall survival. No extrapolation of progression-free survival data was required, as by 18 months, all patients on best supportive care had progressed and for erlotinib only 2 patients remained free of disease progression. These 2 patients were assumed to experience disease progression at the next cycle. For overall survival, data were extrapolated from weeks 70 and 78 for erlotinib and best supportive care respectively.

6.4 The manufacturer's economic model incorporated the patient access scheme for erlotinib (see table 1, section 2) and took into account the mean treatment duration based on the BR21 trial (9.57 weeks). Other costs considered in the manufacturer's economic model were related to: a pharmacist dispensing a prescription of erlotinib every 30 days (£18.20); supportive care for progression-free disease (£85 per week) and progressed disease (£220 per week); and managing adverse reactions (the manufacturer only included adverse reactions that occurred in more than 5% of patients in the BR21 trial).

6.5 The manufacturer used pooled chemotherapy EQ-5D utility values from the PROFILE-1007 trial of crizotinib for both the erlotinib and best

supportive care treatment groups (Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene [NICE technology appraisal guidance 296]). The manufacturer noted that the utility values were relatively high for people with non-small-cell lung cancer and that the population in PROFILE-1007 included anaplastic lymphoma kinase (ALK) positive patients who were younger and less fit compared with patients enrolled in the BR21 trial. The utility values used for the progression-free disease and progressed disease health states were 0.747 and 0.610 respectively.

6.6 The manufacturer presented deterministic pairwise incremental cost-effectiveness ratios (ICERs) for erlotinib compared with best supportive care for: the overall population (EGFR-TK mutation-unknown); and a subgroup analysis of the EGFR-TK mutation-negative population. For the overall population, the manufacturer's economic model estimated incremental costs and incremental quality-adjusted life years (QALYs) of £7529 and 0.148 respectively, resulting in an ICER of £51,036 per QALY gained. For the EGFR-TK mutation-negative population, the manufacturer's economic model estimated incremental costs and incremental QALYs of £7490 and 0.128 respectively, resulting in an ICER of £58,579 per QALY gained.

6.7 The manufacturer carried out univariate sensitivity analysis to determine the impact to the ICER from changes in the parameters included in its economic model for the EGFR-TK mutation-unknown population. The results of the univariate sensitivity analysis showed that the ICER was most sensitive to changes in the utility values used for the 'progression-free disease' and 'progressed disease' health states. The manufacturer also presented the results of a probabilistic sensitivity analysis that showed that there is a 0% probability of erlotinib being cost effective compared with best supportive care in the EGFR-TK mutation-unknown population if the maximum acceptable ICER was £30,000 per QALY gained. The probabilistic sensitivity analysis estimated incremental

costs and incremental QALYs of £7490 and 0.147 respectively, resulting in an ICER of £50,825 per QALY gained. The manufacturer did not carry out any sensitivity analyses for its economic model that included the EGFR-TK mutation-negative population.

Independent Assessment Group's economic model

6.8 The Assessment Group developed a partitioned survival model to assess the cost effectiveness of erlotinib with:

- Best supportive care in the EGFR-TK mutation-unknown population
- Best supportive care in the EGFR-TK mutation-negative population
- Docetaxel in the EGFR-TK mutation-negative population.

The model had a cycle length of 3 days and a lifetime time horizon. The model included 3 health states: progression-free disease, progressed disease and death. The Assessment Group conducted the economic analysis from an NHS and personal social services perspective. Costs and health effects were discounted at an annual rate of 3.5% and a half-cycle correction was applied.

6.9 Using the manufacturer's Kaplan-Meier data from the intent-to-treat analysis of the BR21 trial, the Assessment Group estimated progression-free survival and overall survival for the EGFR-TK mutation-unknown population treated with erlotinib and best supportive care. The Assessment Group noted that standard parametric functions were invalid because they assume a single continuous disease and treatment effect throughout the duration of the trial, and data from BR21 showed that different disease and treatment effects were occurring during certain periods of the trial. Therefore it fitted a 3-phase spline model with two 'knot' points following examination of the cumulative hazard plots. The Assessment Group noted that the transitions between phases in the treatment groups occur at different time points between the first two phases but at a common time point between phases 2 and 3. The event

risk (progression or death) within each phase was found to be approximately constant in both treatment groups and for both the progression-free survival and overall survival models, the long-term event risk (phase 3) showed the same hazard rate for both groups in the trial.

6.10 The Assessment Group used published Kaplan-Meier data from the TAILOR trial to estimate progression-free survival and overall survival for patients treated with erlotinib and docetaxel in the EGFR-TK mutation-negative subgroup. The Assessment Group noted that the progression-free survival and overall survival data from the TAILOR trial showed similar relationships to that observed in the BR21 trial and therefore applied a similar 3-phase spline model with two knot points. The Assessment Group explained that:

- in the first phase the event risks are very similar in both treatment groups
- in the second phase patients are subject to increase risk of an event but at differential treatment efficacy leading to the survival curves diverging
- in the final phase the event risks reduce substantially in both treatment groups.

It commented that the transitions between phases occur at similar times from randomisation in both treatment groups. The main structural differences between the survival models for each treatment group were observed in the final phase. The Assessment Group stated that the event risk for progression-free survival remained higher in the erlotinib group, suggesting that progression-free survival outcomes continue to diverge indefinitely. For overall survival, the mortality risk stabilised at the same level between treatment groups once all patients experienced disease progression, suggesting that post-progression survival is unrelated to previous treatments.

6.11 Using the manufacturer's data from the posthoc subgroup analysis of the BR21 trial, the Assessment Group were able to estimate progression-free survival and overall survival for the EGFR-TK mutation-negative population treated with erlotinib and best supportive care. The Assessment Group commented that the analysis for the EGFR-TK mutation-negative population was less reliable than the results for the EGFR-TK mutation-unknown population because of the risk of imbalances between baseline patient characteristics and its smaller sample size.

6.12 The Assessment Group's economic model included the patient access scheme for erlotinib. The cost of generic docetaxel was taken from the electronic Market Information Tool (eMIT) which includes information on the prices paid by approximately 95% of NHS Trusts for generic medicines, and therefore the eMIT price reflected the price of docetaxel relevant to the NHS. The dose of docetaxel was also estimated based on the mean body surface area. Resource use and unit costs for administrating erlotinib and docetaxel were based on a nurse-led outpatient visit and in the day-case setting respectively. For the comparison of erlotinib with docetaxel, the Assessment Group assumed that treatment continued until disease progression or death. For the comparison of erlotinib with best supportive care the mean treatment duration was based on the BR21 trial data but the Assessment Group noted that no statistically significant differences were estimated between the length of progression-free survival and the time-on-treatment. Other costs considered in the Assessment Group's economic model were related to: supportive care for progression-free disease (£72 per week), progressed disease (£135 per week) and for terminal disease assumed to last 14 days per patient (£3952 per patient); managing adverse reactions.

6.13 The Assessment Group noted several concerns with the utility values from the PROFILE-1007 trial used by the manufacturer:

- Results were not published or peer-reviewed.

- No assessment of bias was possible because no information was available on the patients completing the EQ-5D.

- The utility values include the effects of treatment-related adverse reactions for a treatment not considered in this technology appraisal and are measured in a different population (adults with non-small-cell lung cancer associated with an ALK fusion gene).

The Assessment Group used alternative utility values from Nafees et al. (2008) in which utility values were measured in a sample of the UK general population (n=100) using the standard gamble technique. The Assessment Group adjusted the progression-free disease for each treatment based on the degree of response and the incidence of adverse reactions. This provided utility values of: 0.6450 and 0.6225 for the 'progression-free disease' health state for erlotinib and docetaxel respectively in the EGFR-TK mutation-negative subgroup; 0.6351 and 0.6353 for erlotinib and best supportive care respectively in both the EGFR-TK mutation-unknown population and the EGFR-TK mutation-negative subgroup. Utility values for the 'progressed disease' health state and the 'terminal period' (last 2 weeks of life) were 0.4734 and 0.2488 respectively. In its base case, no adjustment to the utility values were made by the Assessment Group to reflect potential differences in patient preferences for oral therapy compared with intravenous therapy. For further details about utility values used in the Assessment Group's base-case analysis, please refer to pages 105 to 106 of the Assessment Group's report.

6.14 The Assessment Group's economic model included costs and disutilities associated with 7 adverse reactions: diarrhea, fatigue, neutropenia, febrile neutropenia, hair loss, nausea and skin rash. The Assessment Group pooled the available grade 3 and 4 adverse reaction data from all published trials to estimate the incidence rate for each adverse reaction in the EGFR-TK mutation-unknown population. It used the incidence rate for

each adverse reaction from the TAILOR trial for the EGFR-TK mutation-negative population. For further details please refer to pages 99, 104 and 105 of the Assessment Group's report.

Table 9: Incidence of adverse reactions included in the Assessment Group's economic modeling of erlotinib compared with best supportive care [see table 41 of the Assessment Group report]

Adverse reaction: Mean % (95% CI)	Pooled analysis	
	Erlotinib	BSC
Diarrhoea	3.7 (2.6 to 4.9)	0.7 (0.3 to 1.4)
Fatigue	9.9 (8.1 to 11.8)	11.0 (9.0 to 13.1)
Febrile neutropenia	0.0 (0.0 to 0.2)	0.0 (0.0 to 0.2)
Hair loss	0.0 (0.0 to 0.2)	0.0 (0.0 to 0.2)
Nausea	3.4 (2.4 to 4.6)	1.8 (1.1 to 2.8)
Neutropenia	0.0 (0.0 to 0.2)	0.0 (0.0 to 0.2)
Skin rash	8.1 (6.5 to 9.9)	0.1 (0.0 to 0.4)

Table 10: Incidence of adverse reactions included in the Assessment Group's economic modeling of erlotinib compared with docetaxel [see table 42 of the Assessment Group report]

Adverse reaction: Mean % (95% CI)	TAILOR	
	Erlotinib	Docetaxel
Diarrhoea	2.8 (0.6 to 6.7)	1.9 (0.2 to 5.3)
Fatigue	5.6 (2.1 to 10.7)	9.6 (4.8 to 15.9)
Febrile neutropenia	0.0 (0.0 to 2.4)	3.9 (1.1 to 8.3)
Hair loss	0.0 (0.0 to 2.4)	14.4 (8.4 to 21.8)
Nausea	0.9 (0.0 to 3.4)	2.9 (0.6 to 6.8)
Neutropenia	0.0 (0.0 to 2.4)	20.2 (13.1 to 28.4)
Skin rash	14.0 (8.1 to 21.2)	0.0 (0.0 to 2.4)

6.15 In the Assessment Group's base-case analyses deterministic pairwise ICERs were presented. In the analysis for erlotinib compared with best supportive care for the EGFR-TK mutation-unknown population, the Assessment Group's economic model estimated an incremental overall survival benefit of 2.1 months, of which 1.7 months occurred before disease progression. The estimated incremental costs and incremental QALYs were £6314 and 0.103 respectively, resulting in an ICER of £61,132 per QALY gained. The results of the Assessment Group's univariate sensitivity analysis showed that the ICER was insensitive to changes in most parameters. The ICER was most sensitive to changes in baseline utility value for 'progression-free disease' taken from Nafees et al. (2008) and the incidence of febrile neutropenia. The Assessment Group carried out a probabilistic sensitivity analysis that showed that there was a 0% probability of erlotinib being cost effective compared with best supportive care in the EGFR-TK mutation-unknown population if the maximum acceptable ICER was £30,000 per QALY gained. The Assessment Group estimated a probabilistic ICER of £59,973 per QALY gained. Please see table 11 for a summary of disaggregated results and pages 116 to 120 of the Assessment Group's report for further details.

6.16 The Assessment Group's base-case analysis for erlotinib compared with docetaxel for the EGFR-TK mutation-negative subgroup estimated an incremental overall survival loss of 2.5 months, of which 1.5 months occurred before disease progression. It estimated incremental cost savings of £1653 and an incremental QALY loss of 0.108. Despite the availability of generic docetaxel, the total costs per patient are higher for docetaxel compared with erlotinib because of increased costs for treatment administration and the management of adverse reactions. For docetaxel compared with erlotinib, the Assessment Group estimated an ICER of £15,359 per QALY gained. The results of the univariate sensitivity analysis showed that the ICER was insensitive to changes in most parameters. The ICER was most sensitive to changing the price of docetaxel from the eMIT price to the list price, and the incidence of febrile

neutropenia. The Assessment Group carried out a probabilistic sensitivity analysis that showed that there was a 91% probability of docetaxel being cost effective compared with erlotinib in the EGFR-TK mutation-negative population if the maximum acceptable ICER was £30,000 per QALY gained. For docetaxel compared with erlotinib, the Assessment Group estimated a probabilistic ICER of £12,719 per QALY gained. Please see table 12 for a summary of disaggregated results and pages 107 to 110 of the Assessment Group's report for further details.

6.17 The Assessment Group's base-case analyses for erlotinib compared with best supportive care for the EGFR-TK mutation-negative subgroup estimated an incremental overall survival benefit of 2.2 months and estimated that all of the survival benefit occurred before disease progression. It estimated incremental costs and incremental QALYs of £6362 and 0.116 respectively, resulting in an ICER of £54,687 per QALY gained. The results of the univariate sensitivity analysis showed that the ICER was most sensitive to changes in the choice of survival model parameters (especially for overall survival), utility values and the incidence of key adverse reactions. The Assessment Group carried out a probabilistic sensitivity analysis that showed that there was a 0% probability of erlotinib being cost effective compared with best supportive care in the EGFR-TK mutation-negative subgroup if the maximum acceptable ICER was £30,000 per QALY gained. The Assessment Group estimated a probabilistic ICER of £54,184 per QALY gained. Please see table 13 for a summary of disaggregated results and pages 111 to 115 of the Assessment Group's report for further details.

6.18 The Assessment Group conducted a scenario analysis exploring the potential impact of including a utility benefit associated with delivery of oral treatment, given that oral therapies are generally more preferable to patients than intravenous therapies. This scenario analysis is only relevant to the comparison of erlotinib (oral) with docetaxel (intravenous) and the utility benefit is intended to represent a reduction in pain, anxiety and

disruption to everyday activities due to switching to an oral treatment. The Assessment Group's scenario analysis assumed the utility value for the progression-free disease health state for erlotinib was equal to that of the general population at the equivalent mean age. This resulted in an increase in the 'progression-free disease' utility value for patients treated with erlotinib from 0.645 to 0.8. The estimated ICER comparing docetaxel with erlotinib in the EGFR-TK mutation-negative subgroup increased from £15,359 to £26,176 per QALY gained (see section 6.15). The Assessment Group concluded that this scenario analysis is extremely optimistic and indicates that any realistic estimation of utility benefit associated with oral delivery is very unlikely to significantly impact the size of the estimated ICER when comparing docetaxel with erlotinib.

Summary of the manufacturer's (Roche) and the Assessment Group's base-case cost effectiveness results

Table 11: Erlotinib compared with best supportive care in the EGFR-TK mutation-unknown population (BR21 intent-to-treat population) [page 64 to 65 of Roche Products evidence submission and page 118 of the Assessment Group report]

	Manufacturer (Roche Products)			Assessment Group		
	Erlotinib	**BSC[a]**	**Incremental**	**Erlotinib**	**BSC[a]**	**Incremental**
LYs* (total)	0.867	0.656	0.212	0.851	0.675	0.176
Progression-free survival	0.367	0.232	0.135	0.374	0.235	0.140
Post-progression survival	0.501	0.424	0.077	0.477	0.441	0.036
QALYs (total)**	0.579	0.432	0.148	0.4484	0.3452	0.1033
Progression-free survival	0.274	0.173	0.101	0.2369	0.1488	0.0881
Post-progression survival	0.305	0.259	0.046	0.2116	0.1963	0.0152
Costs (total)	£13,522	£5993	£7529	£14,446	£8133	£6314
Drug	[redacted]	£0	[redacted]	[redacted]	£0	[redacted]
Administration	[redacted]	£0	[redacted]	[redacted]	£0	[redacted]
Adverse reactions	[redacted]	£113	[redacted]	[redacted]	£562	[redacted]
Progression-free survival BSC	[redacted]	£1020	[redacted]	[redacted]	£872	[redacted]
Post-progression survival BSC	[redacted]	£4860	[redacted]	[redacted]	£6699	[redacted]
Incremental-cost effectiveness ratio	**£51,036 per QALY gained**			**£61,132 per QALY gained**		

* LYs = life years; ** QALYs = quality-adjusted life years; [a] BSC = best supportive care; NR = not reported

Table 12: Erlotinib compared with docetaxel in the EGFR-TK mutation-negative subgroup (TAILOR trial) [page 107 of the Assessment Group report]

	Manufacturer (Roche Products)			Assessment Group		
	Erlotinib	**DOC[a]**	**Incremental**	**Erlotinib**	**DOC[a]**	**Incremental**
LYs* (total)	NR	NR	NR	0.967	1.178	(0.211)
Progression-free survival	NR	NR	NR	0.287	0.409	(0.122)
Post-progression survival	NR	NR	NR	0.679	0.769	(0.089)
QALYs (total)**	NR	NR	NR	0.4863	0.5939	(0.1076)
Progression-free survival	NR	NR	NR	0.1850	0.2535	(0.0685)
Post-progression survival	NR	NR	NR	0.3013	0.3403	(0.0391)
Costs (total)	NR	NR	NR	£14,049	£15,702	(£1653)
Drug	NR	NR	NR	[redacted]	£340	[redacted]
Administration	NR	NR	NR	[redacted]	£2305	[redacted]
Adverse reactions	NR	NR	NR	[redacted]	£2783	[redacted]
Progression-free survival BSC	NR	NR	NR	[redacted]	£1524	[redacted]
Post-progression survival BSC	NR	NR	NR	[redacted]	£8749	[redacted]
Incremental-cost effectiveness ratio (docetaxel compared with erlotinib)			**NR**			**£15,359 per QALY gained**

* LYs = life years; ** QALYs = quality-adjusted life years; [a] DOC = docetaxel; NR = not reported

Table 13: Erlotinib compared with best supportive care in the EGFR-TK mutation-negative subgroup (BR21 trial) [page 71 to 72 of Roche Products evidence submission and page 112 of the Assessment Group report]

	Manufacturer (Roche Products)			Assessment Group		
	Erlotinib	**BSC[a]**	**Incremental**	**Erlotinib**	**BSC[a]**	**Incremental**
LYs* (total)	0.850	0.682	0.168	0.859	0.676	0.184
Progression-free survival	0.409	0.222	0.187	0.407	0.223	0.184
Post-progression survival	0.441	0.460	(0.019)	0.453	0.454	(0.001)
QALYs (total)**	0.574	0.447	0.128	0.4579	0.3416	0.1163
Progression-free survival	0.305	0.166	0.139	0.2575	0.1413	0.1163
Post-progression survival	0.269	0.281	(0.012)	0.2004	0.2004	0.000
Costs (total)	£13,853	£6361	£7490	£14,437	£8075	£6362
Drug	[redacted]	£0	[redacted]	[redacted]	£0	[redacted]
Administration	[redacted]	£0	[redacted]	[redacted]	£0	[redacted]
Adverse reactions	[redacted]	£113	[redacted]	[redacted]	£533	[redacted]
Progression-free survival BSC	[redacted]	£979	[redacted]	[redacted]	£827	[redacted]
Post-progression survival BSC	[redacted]	£5270	[redacted]	[redacted]	£6715	[redacted]
Incremental-cost effectiveness ratio	**£58,579 per QALY gained**			**£54,687 per QALY gained**		

* LYs = life years; ** QALYs = quality-adjusted life years; [a] BSC = best supportive care; NR = not reported

7 End-of-life considerations

Criterion	Data available
Treatment is indicated for patients with a short life expectancy, normally less than 24 months	**Median overall survival** *EGFR-TK mutation-unknown population:* The BR21 trial showed a statistically significantly longer median overall survival with erlotinib compared with best supportive care (6.7 compared 4.7 months; HR 0.7, 95% 0.58 to 0.85). *EGFR-TK mutation-negative population:* No statistically significant differences in median overall survival were estimated between erlotinib compared with: • Best supportive care (retrospective subgroup analysis of BR21: 7.9 compared with 3.3 months; HR 0.74, 95% 0.52 to 1.05). • Docetaxel (TAILOR: 5.4 compared with 8.2 months; HR 1.28, 95% CI 0.95 to 1.96, DELTA: 9.0 compared with 9.2 months; HR 0.98, 95% CI 0.69 to 1.39). **Mean overall survival** *EGFR-TK mutation-unknown population:* For erlotinib compared with best supportive the mean overall survival estimated by the: • Manufacturer's economic model were 9.12 compared with 7.60 months respectively. • Assessment Group's economic model were 10.21 compared with 8.10 months respectively. *EGFR-TK mutation-negative population:* For erlotinib compared with best supportive care, the Assessment Group's economic model estimated mean overall survival of 10.31 compared with 8.11 months respectively. For erlotinib compared with docetaxel, the Assessment Group's economic model estimated mean overall survival of 11.60 compared with

	14.13 months respectively.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	See data presented above.
The treatment is licensed or otherwise indicated for small patient populations	Number of people diagnosed with lung cancer in 2011 in England [National Lung Cancer Audit Report 2012]: 31,765 Approximately 72% of lung cancers are non-small-cell lung cancers [National Lung Cancer Audit Report 2012]: 22,871 Approximately 21% present with locally and regionally advanced disease (stage IIIB) and 48% presenting with advanced disease (stage IV) [source: NICE final scope]: 15,781 Proportion of people with stage III and stage IV lung cancer who receive chemotherapy as first-line treatment is reported between 23% [source: NICE costing statement TA258 erlotinib first-line] to 33% [source: AG report]: 3630 to 5208 Proportion of people with stage III and stage IV lung cancer without activating mutations of EGFR-TK (EGFR-TK mutation-negative) is reported to be between 85% to 90%: 4427 (85% of 5208). Note: In NICE TA227 (Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer), erlotinib did not meet the end-of-life criteria because the cumulative population for erlotinib was not considered small. “The Appeal Panel had concluded that it was appropriate, according to the supplementary advice, to add together the potential patient populations covered by the marketing authorisation for different indications rather than on the basis of actual or recommended use. The Committee therefore considered that the true size of the cumulative population potentially eligible for treatment with erlotinib according to its UK marketing authorisations was not small”

8 Equality issues

8.1 One consultee suggested that erlotinib and gefitinib are used more frequently for treating locally advanced or metastatic non-small-cell lung cancer in women and people of south and east Asian ethnicity. The Appraisal Committee will consider implications of access to the different patient groups when developing guidance. However, the issue of more frequent use of erlotinib and gefitinib in people of south or east Asian ethnicity and in women is not an equalities issue that can be addressed within a NICE technology appraisal. Uptake of the guidance is not part of the Appraisal Committee's considerations.

8.2 The manufacturer of erlotinib commented that people with non-small-cell lung cancer whose disease is not suitable for treatment with docetaxel have a high burden of illness and unmet need because of a lack of alternative treatment options. In the view of the manufacturer, this should be considered by the Appraisal Committee because society prefers to allocate resources to those patients with high burden of illness and high unmet need. This equality issue was also highlighted by a professional group. The professional group stated that if there is a change in NICE guidance, it will disadvantage some subgroups of patients with non-small-cell lung cancer (namely EGFR-TK mutation-negative). It explained that there are a significant proportion of patients who are not fit enough to take second line chemotherapy but currently benefit from treatment with second-line erlotinib.

8.3 No further equalities issues were highlighted in NICE technology appraisal guidance 162 (Erlotinib for the treatment of non-small-cell lung cancer [NICE technology appraisal guidance 162]) or during consultation of the draft scope of this technology appraisal (review of NICE technology appraisals 162 and 175).

9 Innovation

Erlotinib

9.1 The manufacturer of erlotinib stated that erlotinib provided a step change in the treatment of non-small-cell lung cancer when NICE recommended it for use in technology appraisal 162 (Erlotinib for the treatment of non-small-cell lung cancer [NICE technology appraisal guidance 162]). It explained that erlotinib is an oral drug that allows patients at the end of life to be treated at their home, and commented that this:

- releases capacity in chemotherapy units;
- reduces the burden of intravenous infusions, and;
- allows patients to spend their last months with family and friends.

Gefitinib

9.2 The manufacturer of gefitinib considered that gefitinib is an innovative treatment for people with locally advanced or metastatic non-small-cell lung cancer with activating mutations of EGFR-TK that has been previously treated with platinum-based chemotherapy. The manufacturer stated it offers substantial health-related quality of life benefits compared with standard or care, including:

- higher objective response rates;
- significantly longer profession-free survival;
- improved tolerability, and;
- improved quality of life.

The manufacturer acknowledged that the evidence available for gefitinib in the population relevant to this technology appraisal is limited and that

there may be insufficient evidence to allow a robust comparison with the alternative treatments.

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer. NICE diagnostics guidance 9 (2013). http://guidance.nice.org.uk/DG9
- Quality standard for lung cancer. Quality Standard 17 (2012). http://guidance.nice.org.uk/QS17
- Lung cancer: The diagnosis and treatment of lung cancer (an update of clinical guideline 24). NICE clinical guideline 121 (2011). http://guidance.nice.org.uk/CG121
- Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer. Terminated NICE technology appraisal guidance 175 (2009). http://guidance.nice.org.uk/TA175
- Erlotinib for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 162 (2008). http://guidance.nice.org.uk/TA162
- Pemetrexed for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 124 (2007). http://guidance.nice.org.uk/TA124

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Afatinib for the treatment of EGFR-TK mutation positive non-small-cell lung cancer. Publication date to be confirmed.

NICE pathways

- There is a NICE pathway on non-small-cell lung cancer, which is available from http://pathways.nice.org.uk/pathways/lung-cancer/treatment-for-non-small-cell-lung-cancer

Appendix B: Clinical efficacy section of the draft European public assessment report

Erlotinib

- Initial marketing authorisation documents including scientific discussion (relevant to this technology appraisal):

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_before_authorisation/human/000618/WC500033992.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000618/WC500033991.pdf

- Changes to marketing authorisation and SPC since initial authorisation of the medicine:

http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000618/WC500109251.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000618/WC500033993.pdf

Gefitinib

- Initial marketing authorisation documents including scientific discussion (relevant to this technology appraisal):

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001016/WC500036361.pdf

- Changes to SPC since initial authorisation of the medicine:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/001016/WC500070343.pdf