NICE National Institute for Health and Care Excellence

NICE guidance

Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy

Technology appraisal guidance
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Your responsibility

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

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

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

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

Contents

This guidance replaces TA175 and TA162.

1 Recommendations

1.1 Erlotinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer that has progressed in people who have had non-targeted chemotherapy because of delayed confirmation that their tumour is epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation-positive, only if the company provides erlotinib with the discount agreed in the patient access scheme revised in the context of NICE's technology appraisal guidance 258 on erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer.

1.2 Erlotinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours of unknown EGFR-TK mutation status, only if:

- the result of an EGFR-TK mutation diagnostic test is unobtainable because of an inadequate tissue sample or poor-quality DNA and
- the treating clinician considers that the tumour is very likely to be EGFR-TK mutation-positive and
- the person's disease responds to the first 2 cycles of treatment with erlotinib and
- the company provides erlotinib with the discount agreed in the patient access scheme revised in the context of NICE's technology appraisal guidance 258 on erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer.

1.3 Erlotinib is not recommended for treating locally advanced or metastatic non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are EGFR-TK mutation-negative.

1.4 Gefitinib is not recommended for treating locally advanced or metastatic

non-small-cell lung cancer that has progressed after non-targeted chemotherapy in people with tumours that are EGFR-TK mutation-positive.

1.5 People whose treatment with erlotinib or gefitinib is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 Information about the technologies

Information about erlotinib

2.1 Erlotinib (Tarceva, Roche Products) is an inhibitor of epidermal growth factor receptor tyrosine kinase (EGFR-TK). It blocks the signal pathways involved in cell proliferation and helps to slow the growth and spread of tumours. 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 as the most common 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 Erlotinib is given orally at a recommended dosage of 150 mg once daily. The cost for a 30-tablet pack of 150-mg tablets is £1,631.53 (excluding VAT; BNF, accessed online September 2015). Costs may vary in different settings because of negotiated procurement discounts. Roche Products has agreed a patient access scheme with the Department of Health, with a simple discount applied at the point of purchase or invoice. 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.

Information about gefitinib

2.4 Gefitinib (Iressa, AstraZeneca) is an EGFR-TK inhibitor. It blocks the signal pathways involved in cell proliferation and helps to slow the growth and spread of tumours. Gefitinib has a UK marketing authorisation for the treatment of adults with 'locally advanced or metastatic non-small-cell lung cancer with activating mutations of EGFR-TK'.

2.5 The summary of product characteristics lists the following as common and very common adverse reactions for gefitinib: diarrhoea, 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.

2.6 Gefitinib is given orally at a recommended dosage of 250 mg once daily. The cost for a 30-tablet pack of 250-mg tablets is £2,167.71 (excluding VAT; BNF, accessed online September 2015). Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

Clinical need and practice

3.1 Approximately 32,000 people are diagnosed with lung cancer in England each year. Around 72% of lung cancers are non-small-cell lung cancers, which can be further classified into 3 histological subtypes: large-cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma. Most lung cancers are diagnosed in the later stages, with 21% of people presenting with locally and regionally advanced disease (stage 3B) and 48% presenting with advanced disease (stage 4) in which the cancer has spread to other parts of the body. The 5-year survival rates for people presenting with stage 3B or stage 4 non-small-cell lung cancer are around 7% to 9% and 2% to 13% respectively.

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

3.3 For most 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 that has progressed after chemotherapy, NICE's previous guideline on lung cancer (now replaced by NICE's guideline on lung cancer: diagnosis and management) recommends that docetaxel monotherapy should be considered if second-line therapy is appropriate. NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer recommends erlotinib with a patient access scheme as a second-line treatment option for non-small-cell lung cancer as an alternative to docetaxel. It does not recommend erlotinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer in patients for whom docetaxel is unsuitable (that is, if there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy. In the terminated

NICE technology appraisal on gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer, 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 company did not provide an evidence submission.

3.4 Clinical practice has changed since the publication of NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer because the identification of a tumour's EGFR-TK mutation status has become an important prognostic 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 that the most appropriate treatment regimen is considered. People with non-small-cell lung cancer are also tested for EGFR-TK mutation status at diagnosis. NICE recommends first-line treatment with an EGFR-TK inhibitor in people with non-small-cell lung cancer whose tumour tests positive for EGFR-TK mutations (see NICE's technology appraisal guidance on gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer and afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer). In clinical practice, re-treatment with an EGFR-TK inhibitor is unlikely to be considered for patients whose tumour tests positive for EGFR-TK mutations and has progressed after 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 EGFR-TK mutation-positive or EGFR-TK mutation-negative populations, or using EGFR-TK mutation status as a stratification factor).

Evidence and interpretation

The Appraisal Committee considered evidence from a number of sources.

Clinical effectiveness

3.5 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 after chemotherapy. It identified 12 randomised controlled trials: 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=1,466; 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=1,692). The Assessment Group did not identify any additional trials relevant to the scope that were not identified in the companies' submissions.

3.6 The Assessment Group commented that overall, the trials were of reasonable methodological quality. Two of the studies were reported in conference abstracts (Bhatnagar et al. 2012; DELTA) and therefore limited details were available about each of the trial designs and methods used. The Assessment Group highlighted that, of the published randomised controlled trials, only BR21 and ISEL were double-blind and the remaining randomised controlled trials were open-label. In all of the published randomised controlled trials, 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 randomised controlled trials (Li et al. 2010) stated that an intention-to-treat analysis was conducted.

3.7 Five trials were conducted internationally, 1 was a multicentre trial in Italy (TAILOR) and the remaining 6 trials were conducted in Asian countries (Korea, South Korea, India, China and Japan; 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). In all the trials, the dosages of erlotinib and gefitinib were consistent with the licensed dosages. In the 9 trials that included docetaxel as a comparator, the dosages were: 75 mg/m^2 every 3 weeks in 6 of the trials (Bhatnagar et al. 2012; INTEREST; ISTANA; Li et al. 2010; SIGN; TAILOR); 60 mg/m^2 every 3 weeks (which is the standard dose in Japan) in 2 of the trials (DELTA; 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. The TITAN trial investigators only published aggregated outcomes for chemotherapy and considered any disaggregated comparison of erlotinib with docetaxel or pemetrexed to be unreliable. Across all the 12 trials, median follow-up ranged from 7.2 months (ISEL) to 33 months (TAILOR).

3.8 The median age of patients in the randomised controlled trials ranged from 48 to 67 years. Most patients were male (except for Kim et al. 2012); had stage 4 disease (except for Li et al. 2010); had 1 previous chemotherapy regimen (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 randomised controlled trials was adenocarcinoma but the ratio of adenocarcinoma to other histological subtypes varied. Patients included in the Kim et al. (2012) and TAILOR trials were tested for epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation status before study entry, but it was unclear whether EGFR-TK status was known at the time of randomisation in the DELTA trial. The 6 randomised controlled trials conducted in Asia exclusively included patients of East Asian family origin but most patients included in the remaining trials were white (except for SIGN).

3.9 The Assessment Group considered 3 populations: people whose tumours test positive for EGFR-TK mutations, people whose tumours test negative for EGFR-TK mutations and people whose tumours are of unknown EGFR-TK mutation status. Clinical practice has changed since the publication of previous NICE technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer because the identification of a tumour's EGFR-TK mutation status has become an important prognostic factor. Many of the published trials conducted in patients with non-small-cell lung cancer therefore did not consider mutation status in their design or recruitment, and consequently were limited to retrospective subgroup analyses of the EGFR-TK mutation-positive or EGFR-TK mutation-negative populations. AstraZeneca focused its evidence submission on the EGFR-TK mutation-positive population because gefitinib is only licensed for this population. The Assessment Group also considered that the 3 trials (Bhatnagar et al. 2012; Kim et al. 2012; Li et al. 2010) published since the European Medicines Agency granted the marketing authorisation for gefitinib were not sufficiently robust to make recommendations that could result in a

change to current clinical practice.

EGFR-TK mutation-positive population

Erlotinib

3.10 No trials of erlotinib were identified by the Assessment Group that were solely conducted in an 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 docetaxel or pemetrexed (TITAN: median progression-free survival in months not reported, hazard ratio [HR] 0.71, 95% confidence interval [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 months for erlotinib compared with 8.3 months for best supportive care, HR 0.55, 95% CI 0.25 to 1.19)
- docetaxel or pemetrexed (TITAN: 19.3 months for erlotinib, not reported for docetaxel or pemetrexed, HR 1.19, 95% CI 0.12 to 11.49).

Gefitinib

3.11 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 who had gefitinib than those who had docetaxel (7 months compared with 4.1 months, HR 0.16, 95% CI 0.05 to 0.49). A smaller proportion of patients who had gefitinib experienced disease progression compared with best supportive care in the ISEL trial (11 out of 21 patients compared with 4 out of 5 patients, median progression-free survival not reported, HR not reported).

3.12 No statistically significant differences in median overall survival were found between gefitinib and docetaxel in the INTEREST trial (14.2 months compared with 16.6 months respectively, HR 0.83, 95% CI 0.41 to 1.67). A smaller proportion of patients who had gefitinib died compared with best supportive care in the ISEL trial (7 out of 21 patients compared with 3 out of 5 patients, median overall survival not reported, HR not reported). AstraZeneca also presented the results of a post hoc analysis in a first-line trial (IPASS) that compared patients whose disease had progressed on chemotherapy (paclitaxel and carboplatin) and who had subsequent EGFR-TK inhibitor treatment (n=83), with those who did not have subsequent EGFR-TK inhibitor treatment (n=46). Median overall survival was lower in patients who did not have subsequent EGFR-TK inhibitor treatment compared with patients who did (the company labelled the data as academic in confidence, so it cannot be presented here). The Assessment Group stated that the median overall survival results for patients treated after chemotherapy with an EGFR-TK inhibitor, reported in the company's post hoc analysis of the IPASS trial, were longer than estimates previously reported in trials of gefitinib, erlotinib or chemotherapy treatment. The Assessment Group concluded that this finding therefore needs to be validated by evidence from an independent randomised controlled trial, because it would represent an important therapeutic advance.

3.13 Three of the 4 trials that retrospectively reported a subgroup analysis of the EGFR-TK mutation-positive population presented response rates for each treatment group (INTEREST; Kim et al. 2012; V-15-32). Results suggested that patients randomised to have gefitinib had a higher response rate compared with those randomised to have docetaxel or erlotinib, but results of statistical significance were only presented in 1 trial (INTEREST; gefitinib compared with docetaxel, p=0.04).

EGFR-TK mutation-negative population

Erlotinib

3.14 Four trials of erlotinib were identified by the Assessment Group that included patients known to be EGFR-TK mutation-negative (TAILOR), patients with and without EGFR-TK mutations whose EGFR-TK status was known before randomisation (DELTA), or patients whose EGFR-TK status was retrospectively

reported in a subgroup analysis of the EGFR-TK mutation-negative population (BR21; TITAN).

3.15 Three of the 4 trials reported results for median progression-free survival. This was statistically significantly lower with erlotinib compared with docetaxel in 2 of the 3 trials (TAILOR: 2.4 months 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 not reported, HR 1.25, 95% CI 0.88 to 1.78).

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

- best supportive care (BR21: 7.9 months for erlotinib compared with 3.3 months for best supportive care, HR 0.74, 95% CI 0.52 to 1.05)
- docetaxel (TAILOR: 5.4 months for erlotinib compared with 8.2 months for docetaxel, HR 1.28, 95% CI 0.95 to 1.96; DELTA: 9.0 months for erlotinib compared with 9.2 months for docetaxel, HR 0.98, 95% CI 0.69 to 1.39)
- docetaxel or pemetrexed (TITAN: 6.6 months for erlotinib compared with 4.4 months for docetaxel or pemetrexed, 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). No patients who had erlotinib (n=100) in the TAILOR trial had a complete response to treatment, compared with 5 patients in the docetaxel group (n=97). In the erlotinib group there was a partial response to treatment in 3 patients, compared with 10 patients in the docetaxel group.

3.17 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 35 mg/m^2), and the latter regimen would not be used in clinical practice in England.
- A poorer performance status is linked to poorer outcomes, and the TAILOR trial enrolled a lower proportion of patients with a performance status of 2 or more (approximately 7%) than would be treated in routine clinical practice in England.
- 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 people who have: never smoked (17% compared with 27%); squamous cell histology (28% compared with 21%); and adenocarcinoma histology (63% compared with 75%).
- Roche Products considered the rates of haematological toxicity in the docetaxel group to be low compared with other trials. The company 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 randomised controlled trial, 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 the clinical population. The Assessment Group also noted that the primary end point 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

3.18 Gefitinib is not licensed for the treatment of adults with locally advanced or metastatic non-small-cell lung cancer whose tumours test negative for EGFR-TK mutations (see section 2.4). NICE can only appraise treatments within their

licensed indications, so the trial evidence available for gefitinib in this population is not applicable to this technology appraisal.

EGFR-TK mutation-unknown population

Erlotinib

3.19 The Assessment Group identified 3 trials of erlotinib that presented outcome data for the EGFR-TK mutation-unknown population. No statistically significant differences in median progression-free survival were estimated between erlotinib and docetaxel (DELTA: 2.0 months compared with 3.2 months respectively, HR 1.22, 95% CI 0.97 to 1.55) and erlotinib compared with either docetaxel or pemetrexed (TITAN: 6.3 weeks compared with 8.6 weeks respectively, 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 months compared with 1.8 months respectively, HR 0.61, 95% CI 0.51 to 0.74).

3.20 No statistically significant differences in median overall survival were estimated between erlotinib compared with docetaxel (DELTA: 14.8 months compared with 12.2 months respectively, HR 0.91, 95% CI 0.68 to 1.22) and erlotinib compared with either docetaxel or pemetrexed (TITAN: 5.3 months compared with 5.5 months respectively, 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 months compared with 4.7 months, HR 0.7, 95% CI 0.58 to 0.85).

3.21 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 less than 1%) and erlotinib compared with either docetaxel or pemetrexed (TITAN: 7.9% compared with 6.3%).

3.22 Patients who had erlotinib experienced a statistically significantly higher health-related quality-of-life score compared with patients who had best supportive care when measured by the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire (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.

3.23 Roche Products stated that the most common grade 3 to 4 adverse reactions associated with erlotinib are skin rash (approximately 5% to 9% of patients) and diarrhoea (approximately 0.6 to –6% of patients) but these are easily manageable. It commented that life-threatening adverse reactions are very rare and erlotinib is better tolerated than 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

3.24 Gefitinib is only licensed for treating adults 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 gefitinib in the EGFR-TK mutation-unknown population is not applicable to this technology appraisal.

Mixed treatment comparison

3.25 The companies and the Assessment Group did not conduct a mixed treatment comparison. AstraZeneca 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 would be likely to increase rather than reduce uncertainty. The Assessment Group stated that the clinical and statistical weaknesses that precluded conducting a mixed treatment comparison included:

- Patient characteristics between trials that were not considered sufficiently similar. For example, family origin, 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 1 chemotherapy regimen compared with 2 or more chemotherapy regimens.

- A lack of outcome data for each of the patient populations.
- Several trials only reported either unadjusted or adjusted analyses, and combining unadjusted and adjusted results may be inappropriate because they 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 appeared to be violated in 6 of the trials because the Kaplan–Meier plots crossed, which is a sufficient condition to reject proportionality.

Cost effectiveness

Published studies

3.26 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 decision-making in England. Only Roche Products provided an economic model to support its submission. Both Roche Products 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 after chemotherapy in this population (see sections 3.10 and 3.11). This meant it was not possible to assess the cost effectiveness of gefitinib because it is only licensed for the treatment of EGFR-TK mutation-positive locally advanced or metastatic non-small-cell lung cancer.

Company's economic model (Roche Products: erlotinib)

3.27 The company submitted a partitioned survival model that only assessed the cost effectiveness of erlotinib compared with best supportive care. The company

stated that it was not possible to demonstrate that erlotinib is cost effective compared with docetaxel following the availability of generic docetaxel and so this comparison was excluded from the analyses. The company 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%.

3.28 The company'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 needed because by 18 months, all patients on best supportive care had disease progression and only 2 patients on erlotinib had progression-free disease. These 2 patients were assumed to experience disease progression at the next cycle. For overall survival, data were extrapolated from week 70 for erlotinib and from week 78 for best supportive care.

3.29 The company's economic model incorporated the patient access scheme for erlotinib and took into account the mean treatment duration based on the BR21 trial (19.57 weeks). Other costs considered in the company'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 company only included adverse reactions that occurred in more than 5% of patients in the BR21 trial).

3.30 The company used pooled chemotherapy EQ-5D utility values from the PROFILE-1007 trial of crizotinib for both the erlotinib and best supportive care treatment groups (NICE's previous technology appraisal guidance on crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene [now replaced by NICE's technology appraisal guidance on crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer]). The company noted that the utility values were relatively high for people with non-small-cell lung cancer and that the population in PROFILE-1007 included patients with anaplastic lymphoma kinase (ALK)-positive disease who were younger and less fit than 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.

3.31 The company presented deterministic pairwise incremental cost-effectiveness ratios (ICERs) for erlotinib compared with best supportive care for the EGFR-TK mutation-unknown population and a subgroup analysis of the EGFR-TK mutation-negative population. For the EGFR-TK mutation-unknown population, the company's economic model estimated incremental costs and incremental quality-adjusted life years (QALYs) of £7,529 and 0.148 respectively, resulting in an ICER of £51,036 per QALY gained. For the EGFR-TK mutation-negative population, the incremental costs and incremental QALYs were £7,490 and 0.128 respectively, resulting in an ICER of £58,579 per QALY gained.

3.32 The company carried out univariate sensitivity analysis to determine the impact on 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 company also presented the results of a probabilistic sensitivity analysis, which showed that at £30,000 per QALY gained, there is a 0% probability of erlotinib being cost effective compared with best supportive care in the EGFR-TK mutation-unknown population. The probabilistic sensitivity analysis estimated incremental costs and incremental QALYs of £7,490 and 0.147 respectively, resulting in an ICER of £50,825 per QALY gained. The company did not carry out any sensitivity analyses for its economic model that included the EGFR-TK mutation-negative population.

Assessment Group's economic model

3.33 The Assessment Group did not undertake a detailed examination of the company's economic model. Instead, it developed a partitioned survival model to assess the cost effectiveness of erlotinib compared with:

- best supportive care in the EGFR-TK mutation-unknown population
- docetaxel in the EGFR-TK mutation-negative population
- best supportive care in the EGFR-TK mutation-negative population.

3.34 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.

3.35 Using the company's Kaplan–Meier data from the intention-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 the use of standard parametric functions was not appropriate because they assumed 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, after examining the cumulative hazard plots, the Assessment Group fitted a 'piecewise' survival model with 3 phases. The piecewise approach was chosen to reflect the observed change in event risk both after treatment with erlotinib had started and after disease progression when treatment had stopped. The Assessment Group noted that the transitions between phases in the treatment groups occur at different time points between the first 2 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, and the long-term event risk (phase 3) showed the same hazard rate for both groups in the trial.

3.36 The Assessment Group used published Kaplan–Meier data from the TAILOR trial to estimate progression-free survival and overall survival for patients who had erlotinib and docetaxel in the EGFR-TK mutation-negative population. 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 piecewise model. The Assessment Group explained that:

- in the first phase, the event risks were very similar in both treatment groups
- in the second phase, patients in both treatment groups had an increased event risk compared with their event risk in the first phase, but the event risk was different for patients who had erlotinib and those who had docetaxel,

leading to the survival curves diverging

- in the final phase, the event risks reduced substantially in both treatment groups.

It commented that the transitions between phases occurred 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 continued 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.

3.37 Using the company's data from the post hoc subgroup analysis of the BR21 trial, the Assessment Group was 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.

3.38 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 average prices paid by approximately 95% of NHS trusts in England for generic medicines. Therefore, the eMIT price reflected the price of docetaxel relevant to the NHS. The dose of docetaxel was also estimated based on mean body surface area for men and women, and a weighted average cost was used. Resource use and unit costs for administering erlotinib were based on a nurse-led outpatient visit and those for docetaxel were based on a day case setting. 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), terminal disease assumed to last 14 days per patient (£3,952 per patient), and managing adverse reactions.

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

- 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 included the effects of treatment-related adverse reactions for a treatment not considered in this technology appraisal and measured in a different population (adults with non-small-cell lung cancer that is anaplastic lymphoma kinase positive).

  The Assessment Group used alternative utility values from Nafees et al. (2008), which were measured in a sample of the UK general population (n=100) using the standard gamble technique. The Assessment Group adjusted the utility values for 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 population, and 0.6351 and 0.6353 for erlotinib and best supportive care respectively in the EGFR TK mutation unknown and the EGFR TK mutation-negative populations. Utility values for the 'progressed disease' health state and the 'terminal period' (last 2 weeks of life) were independent of treatment: 0.4734 and 0.2488 respectively. In its base case, no adjustment to the utility values was made by the Assessment Group to reflect potential differences in patient preferences for oral therapy compared with intravenous therapy.

3.40 The Assessment Group's economic model included costs and disutilities associated with 7 adverse reactions: diarrhoea, 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.

3.41 Deterministic pairwise ICERs were presented in the Assessment Group's base-case analyses. 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 £6,314 and 0.103 respectively, resulting in an ICER of £61,132 per QALY gained. The results of the univariate sensitivity analysis showed that the ICER was not sensitive 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). The Assessment Group carried out a probabilistic sensitivity analysis, which showed that at £30,000 per QALY gained, there is a 0% probability of erlotinib being cost effective compared with best supportive care in the EGFR-TK mutation-unknown population. The Assessment Group estimated a probabilistic ICER of £59,973 per QALY gained.

3.42 The Assessment Group's original base-case analysis for erlotinib compared with docetaxel in the EGFR-TK mutation-negative population 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 £1,653 and an incremental QALY loss of 0.108. For erlotinib compared with docetaxel, the Assessment Group estimated an ICER of £15,359 saved per QALY lost (that is, erlotinib was less effective but also less costly than docetaxel). The results of the univariate sensitivity analysis showed that the ICER was not sensitive to changes in most parameters. The ICER was most sensitive to changing the incidence and cost of febrile neutropenia. The base-case results of the cost-effectiveness analyses presented in the Assessment Group's original report and addendum 1 for erlotinib compared with docetaxel in the EGFR-TK mutation-negative population have been superseded. The Assessment Group corrected an error in its economic model that had led to an overestimation in the cost of treating febrile neutropenia.

3.43 The Assessment Group conducted a scenario analysis in the original base-case

analysis (see section 3.42) 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 caused by switching to an oral treatment. The Assessment Group's scenario analysis assumed that 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 the 'progression-free disease' utility value for patients who had erlotinib increasing from 0.645 to 0.8. When erlotinib was compared with docetaxel in the EGFR-TK mutation-negative population, the estimated ICER increased from £15,359 to £26,176 saved per QALY lost. 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 have a substantial impact on the size of the estimated ICER when comparing docetaxel with erlotinib.

3.44 The Assessment Group presented results for the corrected base-case analysis for erlotinib compared with docetaxel in the EGFR-TK mutation-negative population. This analysis also used an incidence of febrile neutropenia of 6.35% estimated from patients who had the 3-weekly docetaxel regimen in the TAILOR trial (reflective of the docetaxel regimen used in clinical practice in England). The corrected economic model estimated that in the base-case analysis, erlotinib was dominated by docetaxel (that is, docetaxel gave more QALYs and cost less than erlotinib): the Assessment Group estimated incremental costs of £545 and an incremental QALY loss of 0.1076. The Assessment Group noted that the incremental costs become £0 when the incidence rate of febrile neutropenia included in the economic model was assumed to be 16.2% (equal cost but more QALYs for docetaxel). It further noted that the ICER for erlotinib compared with docetaxel in the EGFR-TK mutation-negative population only exceeded £30,000 saved per QALY lost when the incidence rate of febrile neutropenia was assumed to be more than 63% in the economic model. The Assessment Group carried out a probabilistic sensitivity analysis, which showed that at £0 per QALY gained, there is less than a 1% probability of erlotinib being cost effective compared with docetaxel in the EGFR-TK mutation-negative population.

3.45 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 £6,362 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) and utility values. The Assessment Group carried out a probabilistic sensitivity analysis, which showed that at £30,000 per QALY gained, there is a 0% probability of erlotinib being cost effective compared with best supportive care in the EGFR-TK mutation-negative population. The Assessment Group estimated a probabilistic ICER of £54,184 per QALY gained.

Consideration of the evidence

3.46 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of erlotinib and gefitinib, having considered evidence on the nature of non-small-cell lung cancer and the value placed on the benefits of erlotinib and gefitinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

3.47 The Committee heard from the clinical experts and the patient expert about the nature of locally advanced and metastatic non-small-cell lung cancer that has progressed after chemotherapy. The patient expert emphasised that extending survival and improving quality of life are important to people with non-small-cell lung cancer, as is spending less time at the hospital because they have a short life expectancy. The clinical experts commented that the number of people with non-small-cell lung cancer that has progressed after chemotherapy who are of good fitness is generally low, and very few of these people have an ECOG performance status score of 0 or 1. First-line chemotherapy is suitable for only 50% of people with a performance status of 2 and subsequently 25% of this population will go on to have further treatment. The Committee recognised the importance of having clinically effective and tolerable treatment options for people with non-small-cell lung cancer that has progressed after chemotherapy.

3.48 The Committee discussed the role of EGFR-TK mutation testing. It was aware that the identification of a tumour's EGFR-TK mutation status is an important prognostic factor and determines treatment choice in the first-line setting. It noted that NICE's diagnostics guidance on EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer describes which tests for EGFR-TK mutations are clinically and cost effective for informing first-line treatment decisions. The clinical experts stated that most patients have a mutation test before starting first-line treatment and emphasised the importance of testing all patients. They explained that the time to diagnosis of EGFR-TK mutation status (and consequently treatment initiation) generally ranges from 7 to 10 days but varies between regions, partly because some patients have their disease managed across several hospitals. The clinical experts further noted that at diagnosis and initiation of subsequent treatments, the patient is informed that EGFR-TK inhibitors are a targeted therapy for tumours that test positive for EGFR-TK mutations. The Committee concluded that a timely diagnosis of EGFR-TK mutation status has an important role in ensuring that patients are given the most appropriate treatment.

3.49 The Committee considered the clinical pathway for the EGFR-TK mutation-positive population. The clinical experts stated that most patients have an EGFR-TK inhibitor as first-line treatment in line with NICE's technology appraisal guidance on gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer and erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer. The clinical experts commented that erlotinib and gefitinib are very similar treatments with comparable efficacy and side effects, but the Committee was aware that gefitinib only has a marketing authorisation for treating the EGFR-TK mutation-positive population. It noted that erlotinib has a broader marketing authorisation for treating non-small-cell lung cancer that has progressed after chemotherapy and therefore, it is licensed for treating EGFR-TK mutation-positive, mutation-negative and mutation-unknown populations. The Committee also heard from the clinical experts that the adverse reactions associated with both these treatments are much less common than those associated with chemotherapy, although rash may be more common with erlotinib and interstitial lung disease may be more common with gefitinib. The clinical experts stated that the use of EGFR-TK inhibitors for re-treating non-small-cell lung cancer after first-line EGFR-TK inhibitor treatment has failed

is not common in clinical practice in England because of reduced sensitivity of the tumour to these treatments. They also explained that the EGFR-TK mutation-positive population generally includes people who have never smoked and who are younger and fitter than the EGFR-TK mutation-negative population, which means that platinum-doublet chemotherapy is still suitable for them after first-line treatment. The Committee understood from the clinical experts that some patients have stable disease and it is possible to wait for 2 weeks for the diagnostic test result, but a small proportion of patients with aggressive disease need immediate treatment before EGFR-TK mutation status is confirmed. The clinical experts explained that these patients will complete a course of platinum-doublet chemotherapy and have an EGFR-TK inhibitor afterwards. The Committee concluded that although most patients with EGFR-TK mutation-positive tumours have first-line treatment with an EGFR-TK inhibitor and their disease is unlikely to be re-treated with these agents, a small number of patients may have a delayed diagnosis of EGFR-TK mutation-positive status. For this subgroup, subsequent treatment with an EGFR-TK inhibitor after non-targeted chemotherapy is considered to be appropriate in clinical practice.

3.50 The Committee considered the clinical pathway for the EGFR-TK mutation-negative population. It understood from the clinical experts that the EGFR-TK mutation-negative population have first-line treatment with platinum-doublet chemotherapy and not EGFR-TK inhibitors. The Committee was aware that gefitinib does not have a UK marketing authorisation for treating the EGFR-TK mutation-negative population. The clinical experts explained that the choice of treatment in patients whose non-small-cell lung cancer has progressed after chemotherapy depends on their performance status. Patients with a performance status of 0 or 1 are offered a choice between erlotinib and docetaxel in line with NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer. The Committee heard from the clinical experts that in clinical practice, docetaxel is preferred despite its toxicity because in their opinion, docetaxel is clinically effective compared with erlotinib. However, the clinical experts acknowledged that some clinicians and patients prefer erlotinib despite its mechanism of action being targeted at EGFR-TK mutation-positive tumours. They confirmed that in clinical practice, docetaxel is not suitable for patients with a performance status of 2 (that is, less fit than patients with a performance status of 0 or 1) because of the drug's toxicity (in particular, it leading to febrile neutropenia). These people are offered erlotinib or

best supportive care, even though NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer does not recommend erlotinib for people for whom docetaxel is unsuitable. The clinical experts highlighted that suitability of docetaxel is a grey area because of differing dosing possibilities and the importance of patient choice. The Committee concluded that in clinical practice, treatment varies for patients depending on performance status and does not fully reflect existing NICE guidance.

3.51 The Committee considered the clinical pathway for patients with unknown EGFR-TK mutation status. It understood from the clinical experts that an adequate tissue sample is unable to be taken in 30% of patients with non-small-cell lung cancer and up to 5% of samples sent for EGFR-TK mutation analysis fail because of insufficient or poor-quality DNA. The clinical experts commented that an element of clinical judgement is needed when treating these patients but they would generally follow the same clinical pathway as the EGFR-TK mutation-negative population (see section 3.50). Patients in whom the disease has progressed after non-targeted chemotherapy may have erlotinib if their patient characteristics suggest that their tumour may be mutation-positive (for example, people who have never smoked or are light smokers, women, people of Asian family origin and people with adenocarcinoma histology). The Committee concluded that the EGFR-TK mutation-unknown population is diminishing because of the increasing role of EGFR-TK mutation testing but there is a small group of patients in whom diagnosis of EGFR-TK mutation status is not possible.

Clinical effectiveness

EGFR-TK mutation-positive population

3.52 The Committee discussed the clinical effectiveness evidence for gefitinib in the EGFR-TK mutation-positive population. It understood that there were no trials of gefitinib solely conducted in this population whose disease has progressed after non-targeted chemotherapy but some clinical effectiveness evidence is available from several retrospective analyses. The Committee discussed the retrospective analyses, including 2 from second-line trials of gefitinib (ISEL and INTEREST) and 1 from the first-line IPASS trial of gefitinib. The Committee was aware that the

ISEL trial compared gefitinib and best supportive care but did not report the median survival for each treatment group and presented a pooled estimate, so the results were not meaningful for assessing the relative effectiveness. It noted that the INTEREST trial showed statistically significantly longer median progression-free survival with gefitinib compared with docetaxel but there was no statistically significant difference in median overall survival. The Committee also noted that in the post hoc analysis of the IPASS trial, the median overall survival of patients who had subsequent EGFR-TK inhibitor treatment was longer compared with those who did not have it. The Committee heard from the Assessment Group that in the post hoc analysis of the IPASS trial, 37 of the 46 patients who did not have subsequent EGFR-TK inhibitor treatment did not have any treatment at all and therefore the results were heavily weighted against the comparator group (that is, the 'no subsequent EGFR-TK inhibitor' group). The Assessment Group considered that the evidence available for the EGFR-TK mutation-positive population was weak and not sufficiently robust to inform decision-making. The Committee agreed that these retrospective analyses were based on small patient numbers, were subject to imbalances in baseline patient characteristics (and so were highly selective) and lacked statistical power. AstraZeneca acknowledged the limitations of the retrospective analyses. The Committee was aware that established practice is to treat patients with EGFR-TK mutation-positive tumours with EGFR-TK inhibitors in the first-line setting (see section 3.49). However, the Committee was aware that a small proportion of the EGFR-TK mutation-positive population may have a delayed diagnosis of EGFR-TK mutation status and, depending on their fitness, may need immediate treatment with non-targeted chemotherapy (see section 3.49). It heard from the clinical experts that when a tumour tests positive for EGFR-TK mutations, the disease responds to treatment with EGFR-TK inhibitors to the same degree irrespective of whether the person has had non-targeted chemotherapy or not. The Committee was persuaded that the EGFR-TK mutation-positive population would gain a clinical benefit from treatment with EGFR-TK inhibitors if they have had chemotherapy because of a delayed diagnosis of EGFR-TK mutation status. The Committee's preliminary conclusion was that for the small proportion of the EGFR-TK mutation-positive population who had a delayed diagnosis and needed immediate treatment with non-targeted chemotherapy, treatment with gefitinib is clinically appropriate if a diagnosis of EGFR-TK mutation-positive status has been confirmed and the disease has progressed after chemotherapy. However, the Committee considered its preliminary conclusion further in the context of the

cost-effectiveness evidence (see section 3.64).

3.53 The Committee discussed the clinical effectiveness evidence for erlotinib in the EGFR-TK mutation-positive population. It understood that there were no trials of erlotinib solely conducted in this population but that clinical effectiveness evidence was available from 2 retrospective analyses of the BR21 and TITAN trials. The Committee noted that neither of these analyses reported statistically significant differences between erlotinib and the comparator group (that is, best supportive care in the BR21 trial and a pooled comparator of patients randomised to either docetaxel or pemetrexed in the TITAN trial). It recognised that these retrospective analyses of erlotinib were subject to the same weaknesses identified in the retrospective analyses of gefitinib but was persuaded by the clinical experts that the EGFR-TK mutation-positive population would gain a clinical benefit from treatment with EGFR-TK inhibitors after chemotherapy (see section 3.52). The Committee concluded that for the small proportion of the EGFR-TK mutation-positive population who had a delayed diagnosis and needed immediate treatment with non-targeted chemotherapy, second-line treatment with erlotinib is clinically appropriate if EGFR-TK mutation-positive status has been confirmed and the disease has progressed after chemotherapy.

EGFR-TK mutation-negative population

3.54 The Committee discussed the clinical effectiveness evidence available for the EGFR-TK mutation-negative population, comparing the EGFR-TK inhibitors with best supportive care. It noted that gefitinib does not have a UK marketing authorisation for treating the EGFR-TK mutation-negative population and therefore it could not be considered as a treatment option for this population. The Committee understood that only 1 retrospective analysis was available from the BR21 trial, comparing erlotinib and best supportive care in the EGFR-TK mutation-negative population. It was aware that the BR21 trial was completed in 2004 before EGFR-TK mutation testing became established practice and part of clinical decision-making. It also noted that the trial formed part of the evidence base for NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer. The Committee heard from the company that many of the patients enrolled in the BR21 trial had already had first-line or second-line chemotherapy and that docetaxel was unsuitable for them because their performance status was poor. The Committee acknowledged that the BR21

trial did not report statistically significant differences in median overall survival between erlotinib and best supportive care but median overall survival was numerically longer for erlotinib (see section 3.16). It heard from the Assessment Group that the sample sizes were larger in the retrospective analysis of the BR21 trial in the EGFR-TK mutation-negative population than in the retrospective analyses of the trials in the EGFR-TK mutation-positive population, but the results were still less reliable than the main intention-to-treat analysis of the BR21 trial because of the risk of imbalances in baseline patient characteristics. The Committee heard from the clinical experts that erlotinib is now essentially regarded as a targeted therapy for mutation-positive patients only. It concluded that the evidence only weakly suggests that erlotinib may be clinically effective compared with best supportive care in the EGFR-TK mutation-negative population for whom docetaxel is unsuitable.

3.55 The Committee considered the clinical effectiveness evidence available for the EGFR-TK mutation-negative population comparing erlotinib with docetaxel. It understood that clinical effectiveness evidence was available from 2 retrospective subgroup analyses of the DELTA and TITAN trials and the TAILOR trial conducted specifically in the EGFR-TK mutation-negative population. The Committee noted that:

- DELTA showed statistically significantly longer median progression-free survival in patients who had docetaxel compared with those who had erlotinib, but TITAN did not show any statistically significant differences between groups for median progression-free survival.
- No statistically significant differences were estimated between the erlotinib group and the comparator group for median overall survival in both DELTA and TITAN.

The Committee again acknowledged the weaknesses of retrospective subgroup analyses (see section 3.52) and noted that the TITAN trial presented the results of erlotinib compared with a pooled comparator (that is, patients were randomised to either docetaxel or pemetrexed in the comparator group), and that pemetrexed was not specified in the scope of this technology appraisal. The Committee was aware that the TAILOR trial showed statistically significantly longer median progression-free survival and longer (but not statistically significant) median overall survival with docetaxel

compared with erlotinib (see sections 3.15 and 3.16). It acknowledged that the TAILOR trial confirmed the Committee's conclusions on the clinical effectiveness of erlotinib compared with docetaxel in NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer. In the absence of head-to-head evidence comparing erlotinib with docetaxel, the Committee for NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer concluded that 'erlotinib could not reasonably be considered to have an overall survival benefit when compared with docetaxel, and that a progression free survival benefit with docetaxel was more probable'. The Committee acknowledged that, despite erlotinib being targeted at the EGFR TK mutation positive population, the TAILOR trial indicated that in some patients with confirmed EGFR TK mutation-negative status their disease partially responded to treatment with erlotinib. The Committee further considered the generalisability of the TAILOR trial to clinical practice in England. The Committee discussed the concern that the TAILOR trial enrolled a lower proportion of patients with a performance status of 2 or more (approximately 7%) than is treated in clinical practice. It understood from the clinical experts that patients with a performance status of 2 or more would not be offered docetaxel (see section 3.50) and therefore the low proportion of patients with a performance status of 2 or more in the TAILOR trial reflects clinical practice. The Committee acknowledged that the TAILOR trial included a docetaxel weekly regimen that is not used in clinical practice in England and understood from the clinical experts that using a weekly dose (and consequently weekly hospital visits) may lead to fewer episodes of febrile neutropenia. At the second Appraisal Committee meeting, the Committee heard from the Assessment Group that all episodes of febrile neutropenia in the TAILOR trial occurred in patients who had the 3 weekly docetaxel regimen (approximately 60% of patients in the docetaxel group were using this regimen). The Committee understood that only considering patients who had the 3 weekly docetaxel regimen increased the Assessment Group's estimate of the incidence of febrile neutropenia from 3.85% (whole docetaxel group) to 6.35% (3 weekly docetaxel regimen only). However, the Committee heard from the clinical experts that increasing the frequency of docetaxel infusion had become more common in clinical practice in the preceding 12 months because of the results from the TAILOR trial. The Committee considered that the results of the TAILOR trial were relevant to people in England with

non-small-cell lung cancer whose disease had progressed after chemotherapy and whose tumours tested negative for EGFR TK mutations. The Committee concluded that based on the available evidence and clinical practice in England, erlotinib is less clinically effective than docetaxel in the EGFR TK mutation negative population.

EGFR-TK mutation-unknown population

3.56 The Committee discussed the clinical effectiveness evidence available for the EGFR-TK mutation-unknown population. It noted that gefitinib does not have a UK marketing authorisation for treating this population and therefore it could not be considered as a treatment option for this population. For erlotinib, it understood that clinical effectiveness evidence was available from 3 trials (BR21, DELTA and TITAN), in which the intention-to-treat populations included patients whose tumours were not tested before randomisation. For the EGFR-TK mutation-unknown population, the Committee noted that the BR21 trial showed statistically significantly longer median progression-free survival and median overall survival for erlotinib compared with best supportive care. It commented that the DELTA and TITAN trials showed no statistically significant differences between erlotinib and docetaxel for median progression-free survival and median overall survival. The Committee understood that the diminishing population of unknown EGFR-TK mutation-status generally follow the same clinical pathway as the EGFR-TK mutation-negative population (see section 3.51). The Committee noted the mean estimates of incremental survival it had been presented with, which compared erlotinib with best supportive care for the EGFR-TK mutation-unknown (see section 3.41) and the EGFR-TK mutation-negative populations (see section 3.42), and concluded that these were similar.

3.57 The Committee discussed the BR21 intention-to-treat population and its relevance to decision-making. It understood from the clinical experts that certain clinical characteristics are strong predictors of mutation status (see section 3.51). It noted that the overall results of the BR21 intention-to-treat population are likely to be poorer than the results of a population whose tumours have a high probability of testing positive for EGFR-TK mutations. The Committee concluded that, in the EGFR-TK mutation-unknown population, it is likely that erlotinib is more clinically effective compared with best supportive care in people who have clinical characteristics similar to those with confirmed EGFR-TK mutation-positive

status than in those who do not.

Cost effectiveness

3.58 The Committee discussed the cost-effectiveness analyses presented by the companies and the Assessment Group. It noted that:

- Roche Products and the Assessment Group did not present any cost-effectiveness estimates for the EGFR-TK mutation-positive population because of the weaknesses in clinical effectiveness data (see sections 3.52 to 3.53).
- No cost-effectiveness estimates were presented for gefitinib because it only has a UK marketing authorisation for treating the EGFR-TK mutation-positive population.
- Roche Products did not present cost-effectiveness estimates comparing erlotinib with docetaxel because it did not consider that it was possible to show that erlotinib was cost effective following the availability of generic docetaxel.

  The Committee concluded that it was only presented with cost effectiveness estimates for erlotinib in the EGFR TK mutation negative and EGFR TK mutation-unknown populations.

EGFR-TK mutation-negative population

3.59 The Committee discussed the Assessment Group's ICERs for the comparison of erlotinib with docetaxel in the EGFR-TK mutation-negative population. The Committee was aware of the conclusion in NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer stating although 'the difference in benefit between docetaxel and erlotinib was uncertain in the absence of direct comparisons, erlotinib could be acceptable if the total costs of treatment were lower or equal to those of docetaxel'. It noted that since the publication of NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer, the results of the first published trial directly comparing erlotinib with docetaxel in patients whose tumours tested

negative for EGFR-TK mutations had become available (that is, the TAILOR trial). Additionally, the price of docetaxel had reduced by approximately 90%. The Committee acknowledged that the direct evidence from the TAILOR trial showed that erlotinib was less clinically effective than docetaxel (see section 3.55). It also considered, however, that the benefits of docetaxel were diminished by it resulting in febrile neutropenia in some patients. The Committee considered what rate of febrile neutropenia experienced by patients having docetaxel should inform the economic model. It considered comments received during consultation and the additional data on the incidence of febrile neutropenia presented by the Assessment Group in its second addendum. It understood that the 3-weekly docetaxel regimen is established clinical practice in England and that the incidence of febrile neutropenia was approximately 6.35% in patients who had this regimen in the TAILOR trial. It also heard from some consultees that the incidence can be much higher in clinical practice than that reported in clinical trials. Finally, the Committee heard from the company that it considered the rate of febrile neutropenia in patients who had docetaxel to be approximately 15% in clinical practice but not as high as suggested by some consultees (that is, up to 40%). The Committee heard from the Assessment Group that erlotinib was still dominated (that is, docetaxel gave more QALYs and cost less than erlotinib) by docetaxel when increasing the incidence of febrile neutropenia from the rate observed in patients who had the 1-weekly docetaxel regimen (3.85%) to the rate observed in patients who had the 3-weekly docetaxel regimen (6.35%) in the TAILOR trial. The Committee understood from the Assessment Group that erlotinib only became cost neutral (at a health loss) compared with docetaxel when the rate of febrile neutropenia was equal to 16.2%. The Committee also highlighted that the ICER only exceeded £30,000 saved per QALY lost when the incidence rate of febrile neutropenia was assumed to be more than 63% and therefore erlotinib would only be considered cost effective at much higher incidence rates than those suggested by consultees during consultation on the first appraisal consultation document. The Committee acknowledged that there was considerable variability, and therefore uncertainty, around the most plausible incidence rate for febrile neutropenia but agreed that the most robust estimate was 6.35%. The Committee concluded that, for all incidence rates of febrile neutropenia suggested during the course of the appraisal, erlotinib did not represent a cost-effective use of NHS resources for the EGFR-TK mutation-negative population.

3.60 The Committee discussed the estimated ICERs for the comparison of erlotinib and best supportive care in the EGFR-TK mutation-negative population for whom docetaxel is unsuitable. It noted that the Assessment Group's economic model estimated lower incremental costs and fewer incremental QALYs compared with the company's economic model but the estimated base-case ICERs were similar for the comparison of erlotinib with best supportive care (£54,700 per QALY gained and £58,600 per QALY gained respectively). The Committee understood that the ICERs were robust to changes in all parameters included in the respective economic models. The Committee therefore concluded that erlotinib is not a cost-effective use of NHS resources in the EGFR-TK mutation-negative population for whom docetaxel is unsuitable.

EGFR-TK mutation-unknown population

3.61 The Committee discussed the estimated ICERs for the comparison of erlotinib and best supportive care in the EGFR-TK mutation-unknown population. It acknowledged that the Assessment Group's estimated base-case ICER was higher than the company's base-case ICER but both were over £50,000 per QALY gained (£61,100 per QALY gained and £51,000 per QALY gained respectively). The Committee understood that the ICERs were robust to changes in all parameters included in the respective economic models. The Committee therefore concluded that erlotinib is not cost effective compared with best supportive care in the EGFR-TK mutation-unknown population.

3.62 The Committee was aware that it had not been presented with any cost-effectiveness analyses comparing erlotinib with docetaxel in the EGFR-TK mutation-unknown population. The Committee highlighted from its earlier deliberations that the mean estimates of incremental survival for erlotinib compared with best supportive care in EGFR-TK mutation-negative and EGFR-TK mutation-unknown populations were similar. It was therefore persuaded that the mean estimates of incremental survival comparing erlotinib with docetaxel in the EGFR-TK mutation-unknown population were likely to be similar to those it had been presented with for the EGFR-TK mutation-negative population (see section 3.55). It agreed that, in patients for whom docetaxel is suitable, the ICERs for erlotinib compared with docetaxel in the EGFR-TK mutation-unknown population are likely to be similar to those it had been presented with for the EGFR-TK mutation-negative population. The Committee therefore concluded that

erlotinib compared with docetaxel is not a cost-effective use of NHS resources in the EGFR-TK mutation-unknown population.

3.63 The Committee was persuaded, however, that some patients whose disease is of unknown EGFR-TK mutation status can be recognised by clinical experts as having a high likelihood of testing positive for EGFR-TK mutations. It agreed that for these patients, the economic modelling may well underestimate the benefits of erlotinib. The Committee concluded that for the EGFR-TK mutation-unknown population with clinical characteristics suggestive of EGFR-TK mutation-positive tumours, the ICER for erlotinib compared with best supportive care is likely to be lower than those estimated by the company and the Assessment Group.

Overview of the Appraisal Committee's conclusions and recommendations

EGFR-TK mutation-positive population

3.64 The Committee discussed the most plausible ICER for each of the populations. It noted that cost-effectiveness estimates were not presented for each population considered in the appraisal so it had to use its judgement on whether erlotinib represented an equitable and cost-effective use of NHS resources in these circumstances. The Committee was aware that a small population with EGFR-TK mutation-positive tumours are offered EGFR-TK inhibitors after chemotherapy in clinical practice because of a delayed diagnosis. It noted that no trials were solely conducted in this population and that the clinical effectiveness evidence was limited to retrospective subgroup analyses that were not sufficiently robust for decision-making. The Committee commented that it had not been presented with cost-effectiveness estimates for either gefitinib or erlotinib in the EGFR-TK mutation-positive population and therefore it could not approximate the most plausible ICER. It highlighted that the population in the final scope for this appraisal included 'adults with locally advanced or metastatic non-small-cell lung cancer that has progressed following prior chemotherapy' and therefore concluded that it could only make recommendations for erlotinib and gefitinib for the EGFR-TK mutation-positive population at the time of (or after) disease progression after non-targeted chemotherapy because of a delayed diagnosis. The Committee considered patients whose tumours test positive for EGFR-TK mutations and who switch from chemotherapy to either erlotinib or gefitinib

before disease progression because of a delayed diagnosis to be an extension of the first-line population for whom NICE has recommended erlotinib and gefitinib (see NICE's technology appraisal guidance on gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer and erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer). The Committee noted that in NICE's technology appraisal guidance on gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, there was both robust evidence and an agreed patient access scheme. It understood from the Department of Health that the fixed-price patient access scheme for gefitinib would not apply to the EGFR-TK mutation-positive population whose disease had progressed after chemotherapy. In the absence of either robust evidence or a patient access scheme for the use of gefitinib for treating non-small-cell lung cancer that has progressed after chemotherapy, the Committee agreed that it could not recommend gefitinib in this population. The Committee agreed, however, that because erlotinib is provided with the discount agreed in the patient access scheme, the EGFR-TK mutation-positive population should have the option of treatment with erlotinib after chemotherapy once their disease has progressed because it would be unfair to disadvantage this small group of people because of a delayed diagnosis.

EGFR-TK mutation-negative population

3.65 The Committee considered the population whose tumours test negative for EGFR-TK mutations and for whom docetaxel is suitable (performance status of 0 or 1). The Committee acknowledged that there is evidence to suggest that some tumours that test negative for EGFR-TK mutations may respond to erlotinib treatment (see section 3.55), and that spending less time at the hospital is important to people (see section 3.47). However, it was aware that direct evidence comparing erlotinib with docetaxel showed erlotinib to be less clinically effective. The Committee noted that although erlotinib was considered to be better tolerated than docetaxel, the health-related quality of life and the cost associated with managing adverse reactions had been accounted for in the cost-effectiveness estimates. The Committee was aware that the price of both erlotinib and docetaxel had changed since the publication of NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer, and the Assessment Group's economic model estimated that

erlotinib resulted in higher costs with fewer QALYs (that is, a health loss) compared with docetaxel. The Committee concluded that taking all these factors into account, erlotinib could not be recommended for the EGFR-TK mutation-negative population for whom treatment with docetaxel is suitable.

3.66 The Committee considered the population of people whose tumours test negative for EGFR-TK mutations and for whom docetaxel is unsuitable (that is, those with a performance status of 2). The Committee stated that without new clinical effectiveness evidence and consistent with the recommendation in NICE's previous technology appraisal guidance on erlotinib for the treatment of non-small-cell lung cancer, erlotinib after chemotherapy did not represent a cost-effective use of NHS resources in people with non-small-cell lung cancer whose tumours test negative for the EGFR-TK mutation and for whom docetaxel is unsuitable, with the most plausible ICER likely to be over £50,000 per QALY gained compared with best supportive care. The Committee considered a comment received from the company on the appraisal consultation document, stating that based on the Assessment Group's base-case ICER in this population "the QALY multiplier needed for approval was not substantially above that quoted in the Value Based Assessment consultation document (2.7 compared with 2.5 respectively) given the 'high burden of illness' and 'wider societal impact' associated with non-small-cell lung cancer". The Committee noted that in the Value Based Assessment consultation document, it was proposed that burden of illness and wider societal impact would be added to the existing set of modifiers that an Appraisal Committee is able to take into account, and that 2.5 represents the maximum weighting that the Appraisal Committee should consider when taking into account the cumulative impact of all the modifiers. However, the Committee was aware that following consultation on value based assessment of technologies, no changes to NICE's guide to the methods of technology appraisal are being made in the short term and that the current end-of-life treatments protocol is being retained in its current form, while NICE carries out further work. Based on NICE's current methods for appraising technologies and the ICERs presented, the Committee concluded that erlotinib could not be recommended for this population.

EGFR-TK mutation-unknown population

3.67 The Committee noted that the EGFR-TK mutation-unknown population is

diminishing because of the increasing role and advances in testing of EGFR-TK mutation-status. The Committee highlighted its conclusions that the clinical effectiveness and cost effectiveness of erlotinib in the EGFR-TK mutation-unknown and EGFR-TK mutation-negative populations were likely to be similar compared with docetaxel (see section 3.56), and therefore erlotinib could not be considered a cost-effective use of resources in this population (see section 3.62). The Committee noted that the ICERs for erlotinib compared with best supportive care were over £50,000 per QALY gained in the EGFR-TK mutation-unknown population for whom treatment with docetaxel is not suitable, and therefore erlotinib could not be considered a cost-effective use of resources in this population. However, the Committee highlighted its conclusion that the ICER for erlotinib compared with best supportive care was likely to be lower than those estimated by the company and the Assessment Group in the EGFR-TK mutation-unknown population with clinical characteristics suggestive of EGFR-TK mutation-positive tumours. The Committee acknowledged that a patient's EGFR-TK mutation status may be unobtainable in clinical practice because of inadequate tissue samples. It heard from the clinical experts that if a person's disease is likely to respond to EGFR-TK inhibitor treatment, that it will do so by 2 cycles of treatment. The Committee considered that it would be unfair to disadvantage this small group of people. It therefore concluded that erlotinib should be recommended as a treatment option in the EGFR-TK mutation-unknown population with clinical characteristics suggestive of EGFR-TK mutation-positive tumours if their disease has progressed after non-targeted chemotherapy, and that people should be able to continue treatment until disease progression if their tumours have responded after 2 cycles.

3.68 The Committee considered whether there were any health-related quality-of-life benefits that were not adequately captured in the QALY calculation. The Assessment Group's report recognised that a drug taken orally may provide people with non-small-cell lung cancer with a valuable alternative to intravenous docetaxel. The benefit of an oral mode of treatment was not captured in the Assessment Group's base-case analysis comparing erlotinib with docetaxel but was explored in a scenario analysis (see section 3.43). The Committee was aware of the Assessment Group's comments that it was an extremely optimistic scenario analysis applying the maximum possible patient health utility increment and that any realistic estimation of utility benefit was very unlikely to have a substantial impact on the size of the ICER. The Committee noted that the

Assessment Group's scenario analysis was not plausible but acknowledged that some people may have a preference for erlotinib because it is orally administered. However, it concluded that including a plausible estimation of the health-related quality-of-life benefits of oral treatment would not change its conclusion about the cost effectiveness of erlotinib in the EGFR-TK mutation-negative population for whom docetaxel is suitable.

3.69 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all of the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- 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.
- The treatment is licensed or otherwise indicated for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.

  In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

3.70 The Committee discussed whether erlotinib fulfilled the criteria for a life-extending, end-of-life treatment. It was aware that Roche Products did not make a case for erlotinib meeting the end-of-life criteria in its submission. The Committee noted that the median overall survival of patients with non-small-cell lung cancer after chemotherapy in the trials was 5 to 8 months. It considered that the life expectancy of patients with non-small-cell lung cancer after chemotherapy was less than 24 months. The Committee went on to consider whether erlotinib met the extension-to-life criterion. It understood that:

- In the TAILOR trial and the Assessment Group's economic modelling, patients

who had erlotinib experienced shorter progression-free survival and shorter overall survival compared with patients who had docetaxel in the EGFR-TK mutation-negative population.

- The clinical effectiveness evidence for erlotinib compared with best supportive care in the EGFR-TK mutation-negative population for whom docetaxel was not suitable was considered not to be sufficiently robust for decision-making because there was a risk of imbalances in baseline patient characteristics between the groups (see section 3.54), no statistically significant differences were shown between the groups, and the Assessment Group's economic analysis for this population estimated an incremental mean survival gain of 2.2 months.

- The incremental estimates of median and mean survival (from the BR21 trial and Assessment Group's economic model respectively) for erlotinib compared with best supportive care were both less than 3 months in the EGFR-TK mutation-unknown population.

  The Committee was not convinced that the extension to life of patients to whom erlotinib could be offered was at least an additional 3 months. Having established that erlotinib did not meet the extension-to-life criterion, the Committee decided that it was not necessary to make a decision about the population size criterion. It concluded, on this basis, that erlotinib did not fulfil the criteria for being a life-extending, end-of-life treatment.

3.71 The Committee considered whether its recommendations were associated with any issues related to the equality legislation and the requirement for fairness. It noted a comment received in response to the appraisal consultation document that recommending erlotinib for use in a subgroup of patients whose tumours are likely to test positive for EGFR-TK mutations based on sex, race or smoking status is discriminatory. Firstly, the Committee considered that the clinical benefit of EGFR-TK inhibitors is greater in tumours that test positive for EGFR-TK mutations than in those that test negative for EGFR-TK mutations. It agreed that given its recommendation for use of erlotinib in the EGFR-TK mutation-positive population, it would be unfair to not recommend erlotinib for the small group of patients who are unable to obtain a diagnosis of EGFR-TK mutation status but who are likely to have EGFR-TK mutation-positive tumours based on recognised factors. In addition, patients whose disease is not likely to test positive for

EGFR-TK mutations are likely to have alternative effective treatment options; for example, patients suitable for docetaxel are potentially having a more clinically effective therapy than erlotinib (that is, docetaxel as supported by the results of the TAILOR trial). Therefore, the Committee agreed that its recommendations do not constitute detrimental treatment of patients whose disease is likely to test negative for EGFR-TK mutations and therefore its recommendations were fair and did not constitute an equality issue.

Relevance of the Pharmaceutical Price Regulation Scheme 2014

3.72 The Appraisal Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism (which requires participating companies to provide a financial rebate to the Department of Health for any expenditure on branded medicines over a set threshold) when assessing the cost-effectiveness of erlotinib and gefitinib. The Appraisal Committee noted NICE's position statement on this matter. It also noted the Department of Health's view that the PPRS 2014 contained no provisions requiring NICE to adopt a particular approach or method for technology appraisals, or to make an adjustment to its considerations to take account of the payment mechanism. It discussed the comment from Roche Products stating that, while the current NHS expenditure on branded medicines remains over the set threshold, the reimbursement mechanism effectively means that there is no additional cost to the NHS if erlotinib was recommended. The Committee also noted the company's proposal for the Committee to issue positive guidance on erlotinib conditional on Roche Products remaining in the 2014 PPRS; the spend level within the scheme remaining above the agreed growth levels; and that guidance is reviewed at the start of the 2019 PPRS.

3.73 The Committee considered the principle of the argument put forward by Roche Products that erlotinib is cost-neutral to the NHS because of current PPRS overspend. The Committee and the company agreed that, in theory, this argument would apply equally to all medicines covered by the 2014 PPRS. The Committee therefore discussed the validity of this argument considering the possible implications for patients, the healthcare system and pharmaceutical companies. The Committee noted that the calculation of the total rebate was not

allocated to specific drugs or companies; the burden of the financial rebate for any drugs that are not cost effective would be borne not just by the specific company, but by all companies participating in the 2014 PPRS. The Committee agreed this would be unfair, and it also carried the risk of distorting the drugs market by creating a potentially inflationary cycle; because pharmaceutical companies would have less incentive to take into account cost effectiveness. Patients may then increasingly receive medicines that are not cost effective. In addition, the Committee considered that the payments made under the 2014 scheme were not mandated to be allocated to local drug budgets and so would not automatically or routinely allow local commissioners or NHS England to revise their assessment of the opportunity costs of branded medicines. The Committee concluded that, as it stands, the 2014 PPRS does not remove the opportunity cost from funding treatments that are not considered to be cost effective according to the normal methods of technology appraisals.

3.74 The Appraisal Committee accepted the conclusion in NICE's position statement 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of erlotinib and gefitinib. It therefore concluded that the PPRS payment mechanism was not applicable for the consideration of cost effectiveness of erlotinib and gefitinib.

4 Implementation

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

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

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

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has non-small-cell lung cancer that has progressed after chemotherapy and the healthcare professional responsible for their care thinks that erlotinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens
Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne
Vice Chair of Appraisal Committee C, Director for Adult and Older Adult Health and Wellbeing, Public Health England

Professor Kathryn Abel
Director of Centre for Women's Mental Health, University of Manchester

Dr David Black
Medical Director, NHS South Yorkshire and Bassetlaw

Mr David Chandler
Lay Member

Mrs Gail Coster
Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome
Honorary Professor, Department of Primary Care and Population Health, University College London

Professor Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell
Consultant in Public Health, Bradford Metropolitan Borough Council

Dr Alan Haycox
Reader in Health Economics, University of Liverpool Management School

Dr Janice Kohler
Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospital Trust

Ms Emily Lam
Lay Member

Dr Nigel Langford
Consultant in Clinical Pharmacology and Therapeutics and Acute Physician, Leicester Royal Infirmary

Dr Allyson Lipp
Principal Lecturer, University of South Wales

Dr Claire McKenna
Research Fellow in Health Economics, University of York

Professor Gary McVeigh
Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital

Dr Grant Maclaine

Formerly – Director, Health Economics and Outcomes Research, BD, Oxford

Dr Andrea Manca
Health Economist and Senior Research Fellow, University of York

Mr Henry Marsh
Consultant Neurosurgeon, St George's Hospital, London

Dr Suzanne Martin
Reader in Health Sciences

Dr Iain Miller
Founder and Chief Executive Officer, Health Strategies Group

Professor Stephen O'Brien
Professor of Haematology, Newcastle University

Dr Anna O'Neill
Deputy Head of Nursing and Healthcare School and Senior Clinical University Teacher, University of Glasgow

Dr Malcolm Oswald
Lay Member

Dr Alan Rigby
Academic Reader, University of Hull

Professor Peter Selby
Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Professor Matt Stevenson
Technical Director, School of Health and Related Research, University of Sheffield

Mr Cliff Snelling
Lay Member

Professor Iain Squire
Consultant Physician, University Hospitals of Leicester

Dr Paul Tappenden
Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton
Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle
Lay Member

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Martyn Burke and Carl Prescott
Technical Leads

Fay McCracken
Technical Adviser

Nicole Fisher and Lori Farrar
Project Managers

Sources of evidence considered by the Committee

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

- Greenhalgh J, Bagust A, Boland A et al. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175), October 2013.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Companies,

professional or specialist and patient or carer groups, and other consultees, were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

Companies:

- AstraZeneca
- Roche Products

Professional or specialist and patient or carer groups:

- British Thoracic Society
- National Lung Cancer Forum for Nurses
- Roy Castle Lung Cancer Foundation
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

Other consultees:

- None

Commentator organisations (without the right of appeal):

- British Thoracic Oncology Group
- Health Improvement Scotland
- National Collaborating Centre for Cancer

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on erlotinib and gefitinib by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Paul Bishop, Consultant Histopathologist, nominated by the Royal College of Pathologists – clinical expert
- Dr Yvonne Summers, Consultant Medical Oncologist, nominated by the Royal College of Physicians – clinical expert
- Dr Jesme Fox, Medical Director, nominated by the Roy Castle Lung Cancer Foundation – patient expert

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

- AstraZeneca
- Roche Products

Other sources of evidence considered by the Committee that were not included or considered in the companies submission or Assessment Group's submission:

- Morgan A, Sutton A and Wailoo A (2007). The risks and costs of febrile neutropenia in patients with non-small-cell lung cancer treated with docetaxel. NICE Decision Support Unit.

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