NICE National Institute for Health and Care Excellence

NICE guidance

Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer

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

1 Recommendations

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

- they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation **and**
- the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.

2 The technology

2.1 Gefitinib (Iressa, AstraZeneca) is a selective inhibitor of epidermal growth factor receptor tyrosine kinase (EGFR-TK) which blocks the signal pathways involved in cell proliferation. By blocking EGFR-TK, gefitinib helps to slow the growth and spread of the cancer. Gefitinib has a UK marketing authorisation for the treatment of adult patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating mutations of EGFR-TK.

2.2 The summary of product characteristics (SPC) states that when assessing the EGFR-TK mutation status of a patient, it is important that a well-validated and robust method is chosen to avoid false-negative and false-positive determinations. The SPC lists the following conditions that may be associated with gefitinib treatment: interstitial lung disease, hepatotoxicity and liver impairment. For full details of adverse effects and contraindications, see the SPC.

2.3 Gefitinib is administered orally as 250-mg film-coated tablets. The recommended dosage is 250 mg daily to be taken until the disease progresses or the clinician advises otherwise.

2.4 The cost for a pack of 250-mg tablets (30 tablets per pack) is £2,167.71 (excluding VAT, BNF edition 59). The manufacturer has agreed with the Department of Health a patient access scheme in which gefitinib for first-line treatment of NSCLC will be available at a single fixed cost of £12,200 per patient irrespective of the duration of treatment. The manufacturer will not invoice the NHS until the third monthly pack of gefitinib is supplied. This means that patients who need less than 3 months of treatment will not incur a charge. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

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

3.1 The manufacturer's decision problem compared gefitinib with gemcitabine and carboplatin, paclitaxel and carboplatin, vinorelbine and cisplatin, and gemcitabine and cisplatin. The decision problem defined the population as patients with locally advanced or metastatic NSCLC who are previously untreated and who test positive for an EGFR-TK mutation (EGFR-TK mutation-positive patients). Outcomes were defined as overall survival, progression-free survival, objective tumour response rates, health-related quality of life and adverse events associated with treatment. In the economic evaluation the incremental cost per quality-adjusted life year (QALY) gained was presented. A lifetime horizon was used, and costs were considered from the perspective of the NHS and personal social services (PSS).

3.2 The manufacturer's submission presented clinical effectiveness data from the Iressa Pan Asian Study (IPASS), a randomised controlled trial (RCT) set in East Asia. IPASS was a multicentre, open-label RCT in clinically selected patients older than 18 years who had the following characteristics: histologically or cytologically confirmed stage 3b (locally advanced disease such as pleural effusion not amenable to local therapy) or stage 4 (metastatic) NSCLC with adenocarcinoma histology (including bronchoalveolar carcinoma), had never smoked (or had smoked fewer than 100 cigarettes per lifetime) or had been light smokers (stopped smoking at least 15 years previously and had smoked no more than 10 pack-years), had no prior chemotherapy, biological or immunological therapy, and had a WHO performance status of 0, 1 or 2 (on a scale of 0 to 4, with low values reflecting better health).

3.3 IPASS included 1,217 patients from 87 East Asian centres. Patients were randomised to receive 250 mg of gefitinib once daily or paclitaxel (200 mg per m^2 body surface area) immediately followed by carboplatin (at a dose corresponding to an area under the curve [AUC] of concentration versus time of 5.0 to 6.0 minute.mg per ml) in 3-weekly cycles. Treatment was continued until disease progression (according to Response Evaluation Criteria in Solid Tumours

[RECIST], which used tumour measurement rather than investigator assessment), unacceptable adverse events, a patient or clinician request to discontinue, severe non-adherence to the protocol, or until six chemotherapy cycles were reached. Following disease progression, all patients in the gefitinib arm were offered treatment with paclitaxel and carboplatin; if the patient declined or the combination was considered unsuitable, the clinician chose an approved therapy. Following disease progression on paclitaxel and carboplatin treatment, choice of treatment was at the clinician's discretion.

3.4 The manufacturer's submission focused on a subgroup of 261 EGFR-TK mutation-positive patients from the overall IPASS population. This subgroup accounted for 21% of the IPASS population. Of these patients, 80.8% were women. Most patients (94.3%) had never smoked, 5.4% had been light smokers and 0.4% were ex-smokers. On a scale of 0 (good) to 4 (poor), most patients (65.9%) had a WHO performance status of 1; 26.4% had a WHO performance status of 0 and 7.7% had a WHO performance status of 2. Most patients had tumours with histology indicating adenocarcinoma (94.6%); 5.4% had histology indicating bronchocarcinoma and none had unknown histology. At study entry most patients had metastatic disease (81.6%); 18.4% had stage 3b locally advanced disease. Baseline characteristics in the subgroup were similar between both treatment arms.

3.5 The primary outcome examined in IPASS was progression-free survival, which was assessed from the date of randomisation to disease progression (determined by RECIST) or death from any cause. Secondary outcomes included overall survival, objective tumour response rate, health-related quality of life, symptomatic improvement, safety and tolerability. Estimates of overall survival in the overall population were based on an interim analysis after 450 deaths (37% of study participants), as well as modelled values reflecting median overall survival. The final analyses are due in the second quarter of 2010. Health-related quality of life was assessed by the Functional Assessment of Cancer Therapy–Lung (FACT–L) and the Trial Outcome Index (TOI), calculated from the domain scores from FACT–L representing physical and functional wellbeing, and lung cancer symptoms (LCS).

3.6 To assess the non-inferiority of gefitinib compared with paclitaxel and carboplatin, analysis of progression-free survival used a Cox proportional hazard

model adjusting for baseline covariates in the intention-to-treat population.

3.7 In the overall study population, patients randomised to receive gefitinib had a statistically significantly longer progression-free survival compared with patients randomised to receive paclitaxel and carboplatin. The hazard ratio (HR) for progression-free survival (gefitinib compared with paclitaxel and carboplatin) was 0.74 (95% confidence interval [CI] 0.65 to 0.85, p<0.0001). The objective tumour response rate was statistically significantly higher for gefitinib compared with paclitaxel and carboplatin (43.0% versus 32.2%; odds ratio [OR] 1.59, 95% CI 1.25 to 2.01, p=0.0001). The estimates of overall survival in the overall study population were similar for both groups (HR for gefitinib compared with paclitaxel and carboplatin 0.91, 95% CI 0.76 to 1.10).

3.8 In the subgroup of EGFR-TK mutation-positive patients (n=261), progression-free survival in patients randomised to receive gefitinib was statistically significantly longer than for patients randomised to receive paclitaxel and carboplatin (HR 0.48, 95% CI 0.36 to 0.64, p<0.0001). Median progression-free survival was 9.5 months for patients randomised to receive gefitinib and 6.3 months for patients randomised to receive paclitaxel and carboplatin. The objective tumour response rate was statistically significantly higher for patients randomised to receive gefitinib compared with patients randomised to receive paclitaxel and carboplatin (71.2% versus 47.3%; OR 2.75, 95% CI 1.65 to 4.60, p=0.0001). There was no statistically significant difference in the estimates of overall survival for patients randomised to receive gefitinib compared with patients randomised to receive paclitaxel and carboplatin (HR 0.78, 95% CI 0.50 to 1.20).

3.9 In the subgroup of EGFR-TK mutation-negative patients (n=176), progression-free survival in patients randomised to receive gefitinib was statistically significantly shorter than for patients randomised to receive paclitaxel and carboplatin (HR 2.85, 95% CI 2.05 to 3.98, p<0.0001). Median progression-free survival was 1.5 months for patients randomised to receive gefitinib and 5.5 months for patients randomised to receive paclitaxel and carboplatin (that is, EGFR-TK-negative patients randomised to receive gefitinib had shorter progression-free survival than patients randomised to receive conventional chemotherapy). The objective tumour response rate was statistically significantly lower with gefitinib than with paclitaxel and carboplatin (1.1% versus 23.5%; OR 0.04, 95% CI 0.01 to 0.27, p=0.0013). There was no statistically significant

difference in the estimates of overall survival for patients randomised to receive gefitinib compared with those randomised to receive paclitaxel and carboplatin (HR 1.38, 95% CI 0.92 to 2.09).

3.10 In the overall study population, statistically significantly more patients randomised to receive gefitinib experienced a clinically relevant improvement in health-related quality of life and disease symptoms, assessed by the FACT–L and TOI, than patients randomised to receive paclitaxel and carboplatin (FACT–L – OR 1.34, 95% CI 1.06 to 1.69, p=0.0148; TOI – OR 1.78, 95% CI 1.40 to 2.26, p<0.0001). Rates of symptomatic improvement were measured using the lung cancer symptoms (LCS) domain of the FACT–L and were similar for patients randomised to receive gefitinib and patients randomised receive to paclitaxel and carboplatin.

3.11 Similarly in the subgroup of EGFR-TK mutation-positive patients, statistically significantly more patients randomised to receive gefitinib experienced a clinically relevant improvement in health-related quality of life and disease symptoms than patients randomised to receive paclitaxel and carboplatin (FACT–L – OR 3.01, 95% CI 1.79 to 5.07, p<0.0001; TOI – OR 3.96, 95% CI 2.33 to 6.71, p<0.0001; LCS – OR 2.70, 95% CI 1.58 to 4.62, p=0.0003). Time to worsening of health-related quality of life and disease-related symptoms was longer for patients randomised to receive gefitinib than for patients randomised to receive paclitaxel and carboplatin (median range 11.3 to 16.6 months for gefitinib and 2.9 to 3.0 months for paclitaxel and carboplatin).

3.12 In the subgroup of EFGR-TK mutation-negative patients, statistically significantly more patients randomised to receive paclitaxel and carboplatin had a clinically relevant improvement in health-related quality of life and disease-related symptoms than patients randomised to receive gefitinib (FACT–L – OR 0.31, 95% CI 0.15 to 0.65, p=0.0021; TOI – OR 0.35, 95% CI 0.16 to 0.79, p=0.00111; LCS – OR 0.28, 95% CI 0.14 to 0.55, p=0.0002). Time to worsening of health-related quality of life and disease-related symptoms was similar or shorter for patients randomised to receive gefitinib compared with patients randomised to receive paclitaxel and carboplatin (median 1.4 months for gefitinib versus 1.4 to 4.2 months for paclitaxel and carboplatin).

3.13 The manufacturer's submission did not provide an analysis of adverse events according to EGFR-TK mutation status. The manufacturer's submission stated

that in the overall populations gefitinib was associated with fewer grade 3 or 4 adverse events than paclitaxel and carboplatin (28.7% versus 61.0%).

3.14 The manufacturer identified two additional trials (First-SIGNAL [n=42] and the North East Japan Gefitinib Study Group [NEJGSG] trial [n=198]) that compared gefitinib with chemotherapy for the treatment of chemotherapy-naive patients with predominantly adenocarcinoma histology and EGFR-TK mutations. The manufacturer considered including these studies in a meta-analysis along with data from IPASS. However, the manufacturer excluded the First-SIGNAL study on the basis that it examined only a small number of EGFR-TK mutation-positive patients (n=42) and because the comparator (gemcitabine and cisplatin) differed from IPASS. The NEJGSG trial, which compared gefitinib with paclitaxel and carboplatin, was considered suitable by the manufacturer for inclusion in the meta-analysis and used as supporting evidence for IPASS. In the NEJGSG trial, patients randomised to receive gefitinib had a statistically significant longer progression-free survival than those randomised to receive paclitaxel and carboplatin (HR 0.357, 95% CI 0.25 to 0.51, p<0.001). The meta-analysis incorporating progression-free survival from the IPASS and the NEJGSG trial demonstrated a statistically significant improvement in progression-free survival for EGFR-TK mutation-positive patients who were randomised to receive gefitinib compared with mutation-positive patients who were randomised to received paclitaxel and carboplatin (fixed effects model: HR 0.43, 95% CI 0.34 to 0.53, p<0.001).

3.15 The manufacturer carried out a systematic review and mixed-treatment comparison of RCTs comparing chemotherapy in chemotherapy-naive patients with NSCLC. The manufacturer chose paclitaxel and carboplatin as a baseline comparator for all analyses. The systematic review identified 29 trials, and 28 studies were included in the network that formed the basis for the mixed-treatment comparison. In response to a request from the ERG for clarification, the manufacturer provided an updated mixed-treatment comparison, which included treatment with pemetrexed and cisplatin as a comparator (29 studies in the updated mixed-treatment comparison). The manufacturer extracted and analysed data for clinical efficacy (progression-free survival, overall survival and objective tumour response) and tolerability (anaemia, diarrhoea, fatigue, febrile neutropenia, nausea and vomiting) for use in the economic evaluation. The manufacturer calculated the relative effect of alternative chemotherapy (other

than paclitaxel and carboplatin) compared with paclitaxel and carboplatin in an unselected population with NSCLC (that is, without regard to EGFR mutation). The manufacturer then applied the relative estimates for clinical efficacy to a baseline event rate in EGFR-TK mutation-positive patients who had been randomised to receive paclitaxel and carboplatin in IPASS.

3.16 The manufacturer used a Markov economic model to assess the cost effectiveness of gefitinib compared with chemotherapy in the first-line treatment of EGFR-TK mutation-positive patients with NSCLC. Patients entered the model with stable disease. The model had four distinct health states: response to treatment, stable disease, disease progression and death. The model had a cycle length of 21 days and a 5-year time horizon (assumed to be a lifetime horizon).

3.17 The manufacturer obtained data for effectiveness from a variety of sources. The hazard ratio for progression-free survival for EGFR-TK mutation-positive patients for gefitinib relative to paclitaxel and carboplatin was derived from the manufacturer's meta-analysis (HR 0.43) The hazard ratio for overall survival for EGFR-TK mutation-positive patients for gefitinib relative to paclitaxel and carboplatin was estimated from IPASS; estimates of hazard ratios for progression-free survival and overall survival for the chemotherapy regimens were derived from the manufacturer's mixed-treatment comparison. The manufacturer chose a Weibull model for extrapolating costs and outcomes beyond the IPASS follow-up period. Covariates in the model included: mutation status, gender, performance status (0 or 1 versus less than 1) and smoking history (never-smoker or ever-smoker).

3.18 The characteristics of the population modelled in the manufacturer's economic evaluation were based on the IPASS population, which comprised chemotherapy-naive EGFR-TK mutation-positive patients who were eligible to receive chemotherapy. The comparator technologies were paclitaxel and carboplatin, gemcitabine and cisplatin, gemcitabine and carboplatin, and vinorelbine and cisplatin.

3.19 Utility estimates in the manufacturer's model were adopted from a single UK study in which utility values were derived from a survey of 105 members of the general public who were asked to value descriptions of health states of second-line chemotherapy for patients with NSCLC. This study did not provide utility

estimates associated with the mode of delivery of treatment (oral versus intravenous), so the manufacturer used utility values previously applied in NICE's technology appraisal guidance on erlotinib for the treatment of relapsed non-small cell lung cancer, which examined second-line chemotherapy for patients with NSCLC and included utilities related to oral (erlotinib) and intravenous treatment.

3.20 Resource use in the model included: medication, delivery of chemotherapy, EGFR-TK mutation testing, patient monitoring, NHS transport service, management of grade 3 or 4 adverse events, best supportive care and active treatment after progression. Resource use was estimated from a range of secondary sources (such as references costs, BNF, previous NICE technology appraisal submissions and the ERG reports for NICE's technology appraisal guidance on erlotinib for the treatment of relapsed non-small cell lung cancer, now replaced by NICE's technology appraisal guidance on erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy). The manufacturer's model incorporated details of a patient access scheme.

3.21 In the manufacturer's base case, the incremental cost-effectiveness ratios (ICERs) for EGFR-TK mutation-positive patients ranged from £19,402 per QALY gained (gefitinib compared with paclitaxel and carboplatin) to £35,992 per QALY gained (gefitinib compared with vinorelbine and cisplatin) using a 16.6% prevalence for EGFR-TK mutation.

3.22 The manufacturer undertook a range of one-way sensitivity analyses and noted that the results of the cost-effectiveness analysis were sensitive to five key parameters: the overall survival for EGFR-TK mutation-positive patients randomised to receive gefitinib; the overall survival for EGFR-TK mutation-positive patients randomised to receive gemcitabine and carboplatin; the progression-free survival for EGFR-TK mutation-positive patients randomised to receive gemcitabine and carboplatin; the progression-free survival for EGFR-TK mutation-positive patients randomised to receive gefitinib; and the maximum number of chemotherapy cycles, which varied from four to eight.

3.23 The manufacturer also carried out a number of scenario analyses, and none led to any substantial change in the ICER. The manufacturer's probabilistic sensitivity

analysis showed that vinorelbine and cisplatin was the most cost-effective regimen for the first-line treatment of EGFR-TK mutation-positive patients up to a threshold of £35,100 per QALY gained. Beyond this threshold, gefitinib was the most cost-effective option for the first-line treatment of EGFR-TK mutation-positive patients. At a threshold of £30,000 per QALY gained the probabilities of each treatment being the most cost effective in EGFR-TK mutation-positive patients were: vinorelbine and cisplatin (75%); gefitinib (18%); gemcitabine and carboplatin (4%); gemcitabine and cisplatin (3%); and paclitaxel and carboplatin (0%).

3.24 The ERG considered that the evidence of clinical effectiveness presented in the manufacturer's submission was derived from a high-quality trial that used robust randomisation techniques and was suitably powered to demonstrate the primary objectives of the trial for the overall population. The ERG stated that the trial provided convincing evidence of the efficacy and benefits to health-related quality of life of gefitinib in EGFR-TK mutation-positive patients compared with paclitaxel and carboplatin.

3.25 The ERG highlighted several areas of concern about the clinical evidence submitted by the manufacturer. The ERG was concerned about the generalisability of the clinical results from IPASS to the UK population given the characteristics of the people in the trial (predominantly women, East Asians, non-smokers), the histological type of NSCLC (adenocarcinoma accounts for approximately 25% of the population with NSCLC in the UK), and the comparator used (it is estimated that 5% of patients in the UK receive paclitaxel and carboplatin for the first-line treatment of NSCLC).

3.26 The ERG noted that the licensed indication for gefitinib was in locally advanced or metastatic NSCLC in patients with activating mutations of EGFR-TK, and questioned the feasibility of conducting EGFR-TK mutation testing within the NHS given that this is not routinely carried out. The ERG was concerned that making the service operational throughout England and Wales may require substantial investment in time and resources.

3.27 The ERG highlighted that in IPASS the measurement of the primary outcome of progression-free survival may be unreliable because it was assessed without blinding. The ERG was also concerned that the hazard ratios for this outcome

may have been inappropriately calculated using the Cox proportional hazards method. This was because this method is valid only if the hazard ratio for the two groups being compared remains constant over time, and the ERG believed that this criterion was not met in the manufacturer's intention-to-treat analysis of IPASS. The ERG had major concerns about the immaturity of the overall survival data (that is, that relatively few deaths had occurred) because the interim analysis in the manufacturer's submission was based on 450 deaths of 1,217 participants (death of 37% of participants). The ERG highlighted that confounding may have occurred in IPASS because of crossover of treatment after disease progression. Therefore, any changes in overall survival may not result from the treatment to which trial participants were originally assigned.

3.28 The ERG highlighted that the manufacturer's meta-analysis could have appropriately included the First-SIGNAL trial because the comparator used in the First-SIGNAL trial (gemcitabine and cisplatin) was not substantially different in terms of clinical benefit and tolerability from the comparator used in IPASS. The ERG noted that an indirect comparison or mixed-treatment comparison including all three studies (IPASS, NEJGSG and First-SIGNAL) would have been more appropriate. The ERG emphasised a number of weaknesses in the manufacturer's mixed-treatment comparison, such as the extraction of unreported outcome statistics for some studies from two published meta-analyses. Different methods were used to estimate the unreported hazard ratios and this may have led to bias regarding the selection of studies included in the mixed-treatment comparison. The ERG was also concerned that the mixed-treatment comparison assumed that EGFR-TK mutation status did not affect outcomes in patients receiving chemotherapy.

3.29 The ERG noted that assessment of gefitinib is more complex than a simple comparison of two treatment options as presented in the manufacturer's submission, because it involves both a specific diagnostic test to identify the presence of EGFR-TK mutations and the consequent choice of treatment following the test result (gefitinib or chemotherapy). The accuracy (that is, analytical validity) of the amplification-refractory mutation system (ARMS) test for identifying EGFR-TK mutations is very high, but the power of the test result to predict a good response to treatment with gefitinib is lower. The ERG suggested that the average benefit for patients receiving gefitinib in IPASS involved a trade-off between those who would get a good outcome (EGFR-TK mutation-positive

patients who correctly tested positive for the mutation) and those who would get no benefit at all (EGFR-TK mutation-negative patients who tested positive for the mutation). The ERG also noted that performance characteristics of the diagnostic test should have been incorporated by the manufacturer within the model.

3.30 The ERG expressed concern that the prevalence of EGFR-TK mutations (that is, the proportion of EGFR-TK mutation-positive patients within the tested population) would determine the volume and cost of EGFR-TK tests, and that this would contribute to the incremental cost of adopting a 'test and treat' policy. The ERG highlighted that the results from the manufacturer's economic model for EGFR-TK mutation-positive patients receiving gefitinib were dependent on the prevalence of EGFR-TK mutations. The ERG noted that varying the prevalence of EGFR-TK mutations from the 16.6% stated in the manufacturer's submission (producing an ICER of £20,010 per QALY gained based on a 6-year time horizon) to between 5.0% and 25.0% produced ICERs ranging from £32,685 to £18,174 per QALY gained. The results of the economic model varied depending on the combination of a specific test (ARMS) and gefitinib treatment, and might not be valid if tests other than ARMS were used.

3.31 The ERG believed that the time horizon in the manufacturer's model should have been 6 years instead of 5 years because this more closely approximated the length of life for EGFR-TK mutation-positive patients with locally advanced or metastatic NSCLC. The ERG also highlighted that the chemotherapy costs used in the model were not accurate. The ERG made adjustments to the costs of first-line chemotherapy comparators, which had a modest impact on cost effectiveness. However, the reduction in dose level of comparator chemotherapy because of the higher proportion of female patients in the population of EGFR-TK mutation-positive patients compared with the general lung cancer population, combined with lower BNF prices for generic paclitaxel, led to an increase in the ICER of gefitinib compared with paclitaxel and carboplatin from £20,010 per QALY gained (based on the 6-year time horizon) to £38,063 per QALY gained.

3.32 The ERG was concerned that IPASS allowed a maximum of six chemotherapy cycles whereas in their view patients in the UK usually receive four cycles with up to a maximum of six allowed if their disease responds well. This adjustment to the model by the ERG increased the ICER to more than £32,000 per QALY gained when gefitinib was compared with gemcitabine and carboplatin or paclitaxel and

carboplatin, and to £44,000 per QALY gained when gefitinib was compared with vinorelbine and cisplatin or gemcitabine and cisplatin. Furthermore, the ERG noted that the economic model assumed that all patients received prescribed medication up to a maximum of six cycles and that this overestimated the mean number of cycles of chemotherapy administered per patient. When corrected, the ICER for gefitinib increased from £20,010 to £25,427 per QALY gained compared with paclitaxel and carboplatin, which was broadly representative of all chemotherapy regimens.

3.33 The ERG expressed concern about the manufacturer's method of extrapolating survival data beyond the period of IPASS. This involved a two-parameter Weibull formulation for modelling both progression-free survival and overall survival. The ERG digitised the Kaplan–Meier curves for EGFR-TK mutation-positive patients in IPASS and used these to estimate the cumulative hazard for each outcome. The ERG highlighted that in a Weibull survival model the cumulative hazard of an event increases exponentially over time, but that the results from IPASS did not support this. The ERG noted that the parametric model corresponded poorly to the IPASS data, particularly at the beginning and end of the trial. The ERG stated that it obtained a better fit to the data by fitting a linear regression line to obtain a 'spline' model (that is, in this case, two exponential models spliced together at a time when the risk profile of patients changes). The ERG stated that this method reflected the IPASS data accurately across the whole period of the study and with greater accuracy than the Weibull models, which overestimate progression-free survival for both treatment arms. The reanalysis by the ERG reduced estimates of progression-free survival and increased estimates of overall survival, but in both cases reduced the incremental gain attributable to gefitinib by approximately 1 month. This represented a reduction in modelled outcome gains of approximately 25% from those reported in the manufacturer's submission.

3.34 The ERG noted that the manufacturer's economic analysis used differential hazard ratios for the four chemotherapy regimens derived from the mixed-treatment comparison. However, the ERG felt that the four chemotherapy regimens were equally clinically effective. Furthermore, the mixed-treatment comparison depended upon the assumption of proportional hazards, and data from IPASS indicated that this may not be a valid assumption because the hazard ratios within IPASS varied over time. Because the hazard ratios for gefitinib compared with paclitaxel and carboplatin are the main factors determining

outcomes in the model and affect results for all comparators as a result of their use in the mixed-treatment comparison, the ERG expressed concern about all the estimates of cost-effectiveness generated by the manufacturer's model.

3.35 The ERG identified several technical errors in the manufacturer's model and carried out amendments and corrections to address these issues. The ERG also incorporated docetaxel and cisplatin, and pemetrexed and cisplatin (using results for pemetrexed and cisplatin from the manufacturer's updated mixed-treatment comparison) into the economic analysis.

3.36 The ERG's revised base-case analysis indicated that ICERs ranged from £59,016 to £72,908 per QALY gained depending on the comparator used. The ERG highlighted that it appeared from this analysis that gefitinib was dominated by pemetrexed and cisplatin (that is, gefitinib was both more expensive and less effective).

Revised economic analyses following consultation

3.37 Additional analyses were provided by the manufacturer in response to NICE's request for further clarification on the clinical and cost effectiveness of gefitinib presented in the appraisal consultation document. The manufacturer responded to most concerns raised by the Committee about: alternative probability distributions (models) for the extrapolation of survival data beyond the IPASS; how the models related to observational evidence on long-term survival; independent survival curves and approaches to applying the hazard ratio to incorporate other comparators (with gefitinib or paclitaxel and carboplatin as the baseline); and updated analyses to include amendments to the number and cost of chemotherapy cycles, lower first-line chemotherapy dosing in female patients, and variations in the prevalence of EGFR-TK mutations and costs for EGFR-TK mutation testing.

3.38 The manufacturer provided additional analyses examining alternative probability distributions, with consideration given to model fit to the early trial data and the shape of the curves at the tail of the distribution. The manufacturer examined five distributions – Weibull, log-normal, log-logistic, Gompertz and exponential. The models were fitted to data from IPASS (taken predominantly from EGFR-TK

mutation-positive patients) in three ways: to each treatment arm separately (stratified); to the whole population using a stratified model but in the absence of other covariates; and to the whole population using an unstratified model (which assumed proportional hazards between treatments for distributions with this property, that is, the Weibull, Gompertz and exponential models). The manufacturer evaluated the model fit using the Akaike Information Criterion (AIC) and Cox–Snell residuals. The manufacturer's analyses showed that for progression-free survival and overall survival the Weibull models consistently provided the best fit according to AIC, although the log-logistic distribution also provided a good fit to the overall survival data. The manufacturer provided evidence that the proportional hazards assumption was satisfied (that is, there was a constant ratio of the hazards between the two treatments across all points in time) and stated the 'spline' model proposed by the ERG was therefore not appropriate. The manufacturer provided, as academic in confidence, unpublished observational evidence on long-term survival of patients with NSCLC from the NEJGSG study, and published evidence, which showed that for overall survival the data supported the choice of the Weibull or log-logistic distributions.

3.39 The ERG considered that the manufacturer had provided data to address most of the Committee's concerns raised in the appraisal consultation document. However, the ERG noted that the manufacturer had not carried out sensitivity analyses to determine the robustness of the ICERs to alternative survival distributions. Furthermore, the ERG considered that there were several limitations with the manufacturer's submitted analyses because four of the requested amendments to the modelling (a mid-cycle correction, corrected costs for first- and second-line chemotherapy, and adjusted costs to take account of patient drug exposure) had not, in the ERG's view, been implemented correctly in the manufacturer's revised analyses. The ERG therefore carried out an additional analysis to adjust for this. The ERG's additional analysis resulted in ICERs for gefitinib ranging from £30,368 per QALY gained compared with six cycles of gemcitabine and carboplatin to £40,048 per QALY gained compared with four cycles of gemcitabine and carboplatin.

3.40 The ERG also adjusted the manufacturer's two-way sensitivity analyses that varied the prevalence of the EGFR-TK mutation (from 5% to 17%) and the assumed costs of EGFR-TK mutation testing (from £157.50 per test to £210.00 per test). This resulted in ICERs ranging from £27,457 to £49,323 per QALY

gained for gefitinib compared with gemcitabine and carboplatin (based on six cycles of chemotherapy). Assuming a cost of £157.50 for EGFR-TK mutation testing in line with advice from consultees and the clinical specialists resulted in ICERs ranging from £31,800 per QALY gained (with a 10% prevalence of EGFR-TK mutation) to £27,500 per QALY gained (with a 17% prevalence of EGFR-TK mutation) for gefitinib compared with gemcitabine and carboplatin (based on six cycles of chemotherapy).

3.41 Applying the ERG's corrections to the manufacturer's additional analyses also showed that, when using paclitaxel plus carboplatin as the baseline, the ICER for gefitinib compared with pemetrexed plus cisplatin was £23,615 per QALY gained for a maximum of six cycles (mean 5.4) and £64,481 per QALY gained for a maximum of five cycles (mean 4.6). When using gefitinib as the baseline, gefitinib dominated pemetrexed plus cisplatin (that is, pemetrexed plus cisplatin was both more expensive and less effective than gefitinib) regardless of whether the model assumed a maximum of five or six cycles.

3.42 The ERG identified an anomaly in the manufacturer's updated economic model relating to Kaplan–Meier estimates of survival in IPASS. However, following clarification with the manufacturer it was established that this anomaly reflected a typographical error and did not affect the manufacturer's cost-effectiveness calculations.

3.43 Full details of all the evidence are in the manufacturer's submission and the ERG report.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of gefitinib for locally advanced or metastatic NSCLC, having considered evidence on the nature of locally advanced or metastatic NSCLC and the value placed on the benefits of gefitinib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Management of locally advanced or metastatic NSCLC in UK clinical practice

4.1 The Committee discussed the clinical need of patients with locally advanced or metastatic NSCLC. It heard from the clinical specialists that the main aim of treatment is to extend progression-free and overall survival with the fewest adverse events and with the best quality of life possible for the remaining months of life.

4.2 The Committee heard from clinical specialists that up to the end of 2009 UK clinical practice was to combine gemcitabine with a platinum drug, usually cisplatin or carboplatin, but that no particular regimen of combination chemotherapy was considered more effective than another. The regimen chosen for an individual patient depended on the ease of administration and the associated adverse effects. The Committee also heard that chemotherapy with carboplatin in combination with vinorelbine or paclitaxel is not used very often because of the adverse effects associated with these agents. The clinical specialists also highlighted that following NICE's technology appraisal guidance on pemetrexed for the first-line treatment of non-small-cell lung cancer recommending pemetrexed and cisplatin for the first-line treatment of locally advanced or metastatic NSCLC, this therapy is becoming more widely used and is likely to become the standard treatment for patients with non-squamous NSCLC. The Committee accepted that current standard practice in England and Wales is platinum combination therapy, but concluded that pemetrexed plus cisplatin is the most appropriate principal comparator for the first-line treatment of non-squamous NSCLC.

4.3 The Committee was aware that the licensed indication for gefitinib is treatment of locally advanced or metastatic NSCLC in patients with activating mutations of EGFR-TK. The Committee accepted that the manufacturer's decision problem focused on EGFR-TK mutation-positive patients and therefore the subsequent discussion focused on this population only. The Committee heard from the clinical specialists that gefitinib is the first oral therapy for the first-line treatment of locally advanced or metastatic NSCLC, and that gefitinib's biological mechanism of action results in targeted therapy with fewer adverse events and improvements in health-related quality of life for EGFR-TK mutation-positive patients. The Committee agreed that treatment which is administered orally, such as gefitinib, offers an advantage because it can be taken at home, and would allow patients to carry on with normal daily activities. Furthermore, the Committee heard from the clinical specialists that targeting therapy at EGFR-TK mutation-positive patients represents an innovative approach to treatment in terms of increasing the response rate over what is normally seen in lung cancer treatment. The clinical specialists explained that, until recently, pathologists in the UK did not routinely carry out histological subtyping of NSCLC because treatment did not depend on the histological subtype. However, following NICE's technology appraisal guidance on pemetrexed for the first-line treatment of non-small-cell lung cancer recommending pemetrexed and cisplatin as a treatment option for patients with confirmed adenocarcinoma or large-cell carcinoma, it is now rapidly becoming standard practice to determine the histological subtype of NSCLC. The Committee heard from the clinical specialists that EGFR-TK mutation testing is not routinely carried out in UK clinical practice at present because it has not been needed to date. However, the clinical specialists expressed the view that the emergence of therapy targeted to EGFR-TK mutation status will lead to the introduction of testing in the NHS, and that the NHS has the capacity and expertise to undertake testing. The Committee was persuaded that the need for testing for the EGFR-TK mutation would not limit treatment and that it should be seen as analogous to testing for human epidermal growth factor receptor 2 (HER2), which has been successfully implemented in a short timeframe within the NHS.

Clinical effectiveness

4.4 The Committee considered that the clinical effectiveness evidence presented in

the manufacturer's submission was derived from a large, high-quality trial (IPASS) that used robust randomisation techniques, and was suitably powered to demonstrate the primary objectives of the trial for the overall population. However, it noted that evidence from IPASS related mainly to East-Asian women who did not smoke and who had adenocarcinoma histology. The Committee considered how this evidence would relate to the target population of EGFR-TK mutation-positive patients with locally advanced or metastatic NSCLC treated in England and Wales. It accepted advice from the clinical specialists that the efficacy of gefitinib depended on EGFR-TK mutation status and that there was no reason to assume that efficacy would differ according to gender, ethnicity, histological subtype or smoking status.

4.5 The Committee considered the results from the IPASS study presented by the manufacturer. It noted that the primary outcome of progression-free survival in IPASS was assessed by unblinded investigators. Evidence from this study showed that in EGFR-TK mutation-positive patients, gefitinib increased the median progression-free survival by 3.2 months compared with paclitaxel and carboplatin. The Committee was aware that the analysis of overall survival was an interim analysis of immature data based on 450 deaths (that is, 37% of patients having died) and that a final analysis from follow-up was due in the second quarter of 2010. The Committee noted that a longer progression-free survival may correlate with improved overall survival in NSCLC, but there was uncertainty around this. It also noted the ERG's concerns that crossover observed in IPASS may have influenced the length of overall survival observed. The Committee accepted the ERG's view that EGFR-TK mutation-positive patients who were randomised to receive gefitinib had a clinically relevant improvement in health-related quality of life and disease symptoms compared with patients randomised to receive paclitaxel and carboplatin. The Committee concluded that the evidence from IPASS demonstrated that gefitinib improved progression-free survival and health-related quality of life in EGFR-TK mutation-positive patients. By contrast, the Committee noted that for EGFR-TK mutation-negative patients gefitinib was associated with worse outcomes when compared with chemotherapy.

4.6 The Committee discussed the adverse events experienced by patients receiving treatment for locally advanced or metastatic NSCLC and noted that, in IPASS, treatment with gefitinib was associated with fewer grade 3 or 4 adverse events

than chemotherapy with paclitaxel and carboplatin. The clinical specialists confirmed that gefitinib had been shown to be well tolerated in clinical practice and that this is an important aspect of treatment with this drug. The Committee concluded that gefitinib was associated with an improved adverse effects profile compared with platinum-based chemotherapy.

4.7 The Committee noted the ERG's concerns that the manufacturer assumed a prevalence of EGFR-TK mutations of 16.6% in the UK population (representing patients with adenocarcinoma histology). The Committee heard from the clinical specialists that the prevalence of EGFR-TK mutations in patients with NSCLC may range from 5.0% to 17.0% depending on the subpopulation, and that in patients with adenocarcinoma histology the prevalence is more likely to be around 10%. This was also supported by consultees who advised that the prevalence of EGFR-TK mutations is between 10% and 15%. The Committee was therefore satisfied that the prevalence of the EGFR-TK mutation was likely to be between 10% and 15% in the target population.

4.8 The Committee noted the ERG's concerns about the accuracy and performance of the EGFR-TK mutation test and particularly the risk that patients may be wrongly identified as mutation positive and consequently receive a treatment (gefitinib) which has been shown in EGFR-TK mutation-negative patients to lead to worse outcomes than standard chemotherapy. However, the Committee heard from the clinical specialists that the EGFR-TK mutation test is qualitative rather than quantitative and shows either the presence or absence of an EGFR-TK mutation. The clinical specialists stated that it would be unlikely that patients would be wrongly identified as having a mutation when they did not have one. The Committee accepted that there was little reason to assume that patients would be incorrectly identified.

4.9 The Committee discussed the mixed-treatment comparison carried out by the manufacturer which included standard combination therapy with a platinum drug and paclitaxel, docetaxel, gemcitabine or vinorelbine. The Committee noted that this analysis supported the clinical view of similar efficacy between these treatment options, with a marginal preference for gemcitabine-containing therapy. The Committee further noted that, following feedback from NICE as part of the initial clarification process, the manufacturer included pemetrexed and cisplatin in the mixed-treatment comparison. The results of the updated mixed-

treatment comparison suggested that pemetrexed and cisplatin had a greater effect on overall survival (for patients with NSCLC of non-squamous type) than the other platinum combination therapies, that gefitinib showed similar effects in terms of overall survival to pemetrexed in combination with cisplatin, and that gefitinib showed longer progression-free survival than pemetrexed and cisplatin. The Committee accepted that there was uncertainty in these comparisons but concluded that it was likely that gefitinib was no less efficacious than pemetrexed and cisplatin, and that pemetrexed in combination with cisplatin was the relevant comparator for gefitinib.

Cost effectiveness

4.10 The Committee considered the manufacturer's economic model, and the critique and exploratory sensitivity analyses performed by the ERG. It noted that the manufacturer used a Markov economic model to evaluate the cost effectiveness of gefitinib compared with four different double chemotherapy combinations. The clinical data used were derived from a variety of sources, and although the evaluation was primarily trial-based, the manufacturer had carried out modelling to extrapolate the health effects beyond the duration of the IPASS.

4.11 The Committee noted that the manufacturer's base-case analyses incorporated a patient access scheme. It noted that the patient access scheme involved a fixed cost being charged for each patient treated with gefitinib regardless of the length of treatment. The Committee agreed that the updated scheme submitted by the manufacturer following consultation (whereby the NHS will not be invoiced until the supply of the third monthly pack of gefitinib) was probably relatively simple to administer in the NHS and that it involved less uncertainty than the original scheme. The Committee understood that the NHS would not be charged for gefitinib if patients needed two or fewer months of treatment.

4.12 The Committee discussed the incorporation of benefits to health-related quality of life and utility in the manufacturer's economic model. The Committee noted that the values of health-related quality of life derived from gefitinib's adverse event profile were included in the economic model. The Committee accepted that measurements of quality of life specific for patients with lung cancer rather than the EQ-5D were included in IPASS, because the EQ-5D is not widely used in Asia.

The Committee was aware that the manufacturer used utility estimates from a study examining second-line chemotherapy for patients with NSCLC, which had included the mode of delivery of treatment (oral versus intravenous); these estimates were also used in NICE's technology appraisal guidance on erlotinib for the treatment of non-small cell lung cancer now replaced by NICE's technology appraisal guidance on erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy. Acknowledging that patients receiving second-line treatment may have had more severe disease and slightly worse utility than patients receiving gefitinib for first-line therapy, the Committee agreed that the methods used by the manufacturer were appropriate in the absence of other data. The Committee agreed that treatment with gefitinib may reduce the amount of time spent in hospital towards the end of life, which it heard from the clinical specialists and patient experts was an important benefit for patients, and noted that this may not have been fully captured in the manufacturer's economic model. The Committee concluded that these quality-of-life benefits were an important aspect of treatment with gefitinib and that taking these into account would reduce the ICERs for gefitinib.

4.13 The Committee noted that the ICERs for gefitinib estimated in the manufacturer's original base case were between £19,400 and £36,000 per QALY gained depending on the comparator chosen, and it was aware that the ICERs depended on the manufacturer having extrapolated progression-free survival and overall survival by fitting a Weibull probability distribution. The Committee considered the four alternative probability distributions presented in the manufacturer's additional analyses following its request for further clarification in the appraisal consultation document. The Committee accepted that for progression-free survival the fitted distributions for both the stratified and unstratified models appeared similar and that the manufacturer's selection of the unstratified Weibull model was appropriate because it appeared to provide the best fit to the progression-free survival data and because it met the proportional hazards assumption (that is, a constant ratio of the hazards between the two treatments across all points in time). The Committee noted that for overall survival the tails of the stratified Weibull and log-logistic models crossed after day 930. The Committee considered the final overall survival data from the NEJGSG study, submitted in confidence by the manufacturer, and accepted the manufacturer's explanation that there was no plausible clinical reason for crossing of the survival curves. The Committee was persuaded that, for both progression-free survival

and overall survival, the unstratified Weibull distribution was appropriate for extrapolating the data beyond the duration of the IPASS because it appeared to fit the data better than other distributions and was consistent with long-term historical survival data in similar populations. The Committee considered the ERG's critique of the manufacturer's economic modelling. It was aware of the ERG's concern that there was an anomaly in the manufacturer's updated economic model relating to Kaplan–Meier estimates of survival in IPASS. However, the Committee accepted that the anomaly reflected a typographical error and did not affect the manufacturer's cost-effectiveness calculations.

4.14 In addition, the Committee was aware of concerns raised by the ERG that the costs of chemotherapy in the manufacturer's original model may not have been appropriate. The Committee heard from the ERG that EGFR-TK mutation-positive patients may differ from the general population with NSCLC and that the manufacturer's model did not take into account this variability. For example, a higher proportion of patients who test positive for the EGFR-TK mutation are women who, on average, have a smaller body surface area and a lower dosage of standard chemotherapy. The Committee acknowledged that this would reduce the cost of the comparator chemotherapy and increase the ICER of gefitinib. The Committee was also aware of the ERG's concerns that the maximum number of cycles of chemotherapy (six) assumed in the manufacturer's original model may not be appropriate. However, it accepted the views of the clinical specialists that, because of the availability of better anti-emetics and improved tolerability, there is an upward trend in the number of cycles given and that patients increasingly receive up to six cycles if their disease responds well, with five cycles being the average.

4.15 The Committee considered the manufacturer's additional analyses following its request for further clarification in the appraisal consultation document. These additional analyses incorporated amended costs for first-line chemotherapy and a sensitivity analysis varying the number of first-line chemotherapy cycles between four and six. The Committee accepted the ERG's view that four of the requested amendments to the modelling (a mid-cycle correction, corrected costs for first- and second-line chemotherapy, and adjusted costs to take account of patient drug exposure) had not been implemented correctly in the manufacturer's revised analysis. It further accepted that the ERG's additional analysis to adjust for this resulted in ICERs for gefitinib ranging from £30,400 per QALY gained

compared with six cycles of gemcitabine and carboplatin to £40,000 per QALY gained compared with four cycles of gemcitabine and carboplatin (see section 3.39).

4.16 The Committee discussed the impact of the prevalence of the EGFR-TK mutation (10% to 15% for patients with NSCLC of adenocarcinoma histology, see section 4.7) on the cost effectiveness of gefitinib. The Committee was aware that the cost of testing was linked to the prevalence of EGFR-TK mutations and the volume of tests and heard from the clinical specialists and consultees that the cost was likely to be in the region of £150. The Committee noted that, following its request for further clarification in the appraisal consultation document, the manufacturer had provided two-way sensitivity analyses, varying both the prevalence of EGFR-TK mutations and the costs of EGFR testing. The Committee further noted that applying the ERG's corrections to the manufacturer's additional analyses (see section 3.40), and assuming a cost for EGFR-TK mutation testing of £157.50 and six cycles of chemotherapy, resulted in ICERs ranging from £31,800 per QALY gained (with a 10% prevalence of EGFR-TK mutation) to £27,500 per QALY gained (with a 17% prevalence of EGFR-TK mutation) for gefitinib compared with gemcitabine plus carboplatin. The Committee concluded that varying the prevalence of EGFR-TK mutations between 10% and 15% did not dramatically alter the ICERs for gefitinib.

4.17 The Committee discussed additional analyses performed by the ERG which expanded the manufacturer's economic model to include docetaxel plus cisplatin, and pemetrexed plus cisplatin. The Committee noted that pemetrexed and cisplatin treatment was dominated by gefitinib (that is, pemetrexed and cisplatin treatment was more expensive and less effective than gefitinib) using the manufacturer's assumptions, but not when using the spline modelling and other assumptions used by the ERG. The Committee understood that this was because of different approaches used by the manufacturer and the ERG to modelling survival for the different comparators.

4.18 The Committee noted that, following its request for further clarification in the appraisal consultation document, the manufacturer had provided additional analyses comparing gefitinib with pemetrexed plus cisplatin using either paclitaxel plus carboplatin or gefitinib as the baseline (that is, the baseline rates of survival to which the hazard ratios were applied). The Committee noted that

taking into account the ERG's corrections to the manufacturer's additional analyses (see section 3.41) and using paclitaxel plus carboplatin as the baseline resulted in ICERs of £23,600 per QALY gained for a maximum of six cycles (mean 5.4 cycles) and £64,500 per QALY gained for a maximum of five cycles (mean 4.6 cycles). When using gefitinib as the baseline, gefitinib dominated pemetrexed plus cisplatin (that is, pemetrexed plus cisplatin was both more expensive and less effective than gefitinib) regardless of whether the model assumed a maximum or five or six cycles. The Committee considered that it was not possible to make a judgement about the most appropriate method for applying the hazard ratios and noted the differences in the ICERs depending on the method used. Taking into account this uncertainty, together with advice received on the variation in the number of chemotherapy cycles received by patients (see section 4.14), and the probable underestimation in the modelling of quality-of-life benefits associated with gefitinib (see section 4.12) the Committee agreed that the results of the ERG's additional analyses comparing gefitinib with pemetrexed plus cisplatin suggested, on balance, that gefitinib would be a cost-effective use of NHS resources. The Committee concluded that at the fixed price agreed under the patient access scheme, gefitinib should be recommended for the first-line treatment of locally advanced or metastatic NSCLC in EGFR-TK mutation-positive patients.

4.19 The Committee considered whether its recommendations were associated with any potential issues related to equality. The Committee was aware that selecting patients with a higher probability of being positive when testing for EGFR-TK mutations (on the basis of their gender or ethnicity) could reduce the cost to the NHS, but that this could raise issues related to equality. The Committee heard from the clinical specialists that although EGFR-TK mutation-positive patients were more likely to have certain characteristics (that is, to be Asian women who have never smoked and have tumours with adenocarcinoma histology), they would not feel comfortable limiting testing to these patients. The Committee accepted the views of the clinical specialists that testing should be carried out on all eligible patients irrespective of gender, ethnicity, and smoking status to ensure that all eligible patients who could benefit would be identified.

4.20 The Committee had initially considered whether it should follow the supplementary advice from NICE that should be taken into account when appraising treatments which may extend the life of patients with a short life

expectancy and which are licensed for indications that affect small numbers of people with incurable illnesses. However, the Committee agreed that, following the additional information submitted by the manufacturer, this consideration was no longer necessary given that the most plausible ICERs, as outlined in section 4.18, fell below the threshold normally considered to be a cost-effective use of NHS resources.

5 Implementation

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

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

5.3 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 locally advanced or metastatic non-small-cell lung cancer and the health professional responsible for their care thinks that gefitinib is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

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

Dr Amanda Adler (Chair)
Consultant Physician, Addenbrooke's Hospital, Cambridge

Professor Keith Abrams
Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong
Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson
Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Michael Boscoe
Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation

Trust

Dr Mark Chakravarty
External Relations Director – Pharmaceuticals & Personal Health, Oral Care Europe

Dr Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Ms Sally Gooch
Independent Nursing and Healthcare Consultant

Mrs Eleanor Grey
Lay member

Mr Sanjay Gupta
YPD Service Case Manager, Southwark Health and Social Care, Southwark PCT

Dr Neil Iosson
General Practitioner

Dr Rosa Legood
Lecturer, London School of Hygiene and Tropical Medicine

Mr Terence Lewis
Lay member

Dr Ruairidh Milne
Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton

Dr Rubin Minhas
General Practitioner and Clinical Director, BMJ Evidence Centre

Mr Stephen Palmer
Senior Research Fellow, Centre for Health Economics, University of York

Dr Sanjeev Patel
Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital,

Carshalton

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Mr Philip Pugh
Strategic Development Lead for Healthcare Associated Infection and Antimicrobial Resistance, Health Protection Agency

Dr Ann Richardson
Lay member

Dr Florian Alexander Ruths
Consultant Psychiatrist and Cognitive Therapist, Maudsley Hospital, London

Mr Navin Sewak
Primary Care Pharmacist, NHS Hammersmith and Fulham

Dr Lindsay Smith
General Practitioner, East Somerset Research Consortium

Mr Roderick Smith
Finance Director, West Kent Primary Care Trust

Mr Cliff Snelling
Lay member

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Andrew Stevens
Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Ms Nathalie Verin
Health Economics Manager, Boston Scientific UK and Ireland

NICE project team

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

Fay McCracken
Technical Lead

Bhash Naidoo and Zoe Charles
Technical Advisers

Jeremy Powell
Project Manager

7 Sources of evidence considered by the Committee

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

- Brown T, Boland A, Bagust A, et al. Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), November 2009

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Manufacturers, or sponsors, were also invited to make written submissions. Professional or specialist and patient or carer groups and other consultees had the opportunity to give their expert views. Manufacturers, or sponsors, professional or specialist and patient or carer groups, and other consultees, also have the opportunity to appeal against the final appraisal determination.

Manufacturer or sponsor:

- AstraZeneca

Professional or specialist and patient or carer groups:

- British Thoracic Society (Lung Cancer and Mesothelioma Working Party)
- Cancer Research UK
- Macmillan Cancer Support
- National Lung Cancer Forum for Nurses
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- Roy Castle Lung Cancer Foundation

- UK Oncology Nursing Society

Other consultees:

- Department of Health
- Kirklees Primary Care Trust
- Welsh Assembly Government

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

- British Thoracic Oncology Group
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Eli Lilly
- Medac
- NHS Quality Improvement Scotland
- Pierre Fabre
- Sanofi Aventis

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

- Professor Mike Lind, Consultant Medical Oncologist, Castle Hill Hospital, nominated by the Royal College of Physicians – clinical specialist

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

- AstraZeneca

Update information

Minor changes since publication

February 2014: Implementation section updated to clarify that gefitinib is recommended as an option for treating locally advanced or metastatic non-small-cell lung cancer.

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