NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

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

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide clarification on:

- **EGFR-TK mutation testing in the UK**
- **baseline characteristics of EGFR-TK mutation status positive (M+) patients**
- **patient adherence in IPASS**
- **treatment of patients after disease progression**
- **further details of the mixed treatment comparison.**

The manufacturer was also asked to provide:

- **individual patient data from IPASS**
- **some of the documents referenced in the manufacturer's submission (both published and unpublished).**

Licensed indication

Gefitinib (Iressa, AstraZeneca) is indicated for the treatment of locally advanced or metastatic non-small-cell lung cancer (NSCLC) with activating mutations of EGFR-TK.

Key issues for consideration

Clinical effectiveness issues

- Patients in the Iressa Pan Asian Study (IPASS) were predominantly female, East Asian, non-smokers with adenocarcinoma histology. To what extent does the Committee consider that the clinical effectiveness observed in IPASS relates to the target population in the UK with locally advanced or metastatic NSCLC?
- What is the Committee's view on implementing an EGFR-TK mutation testing system in the NHS in England and Wales?
- Does the Committee consider the manufacturer's subgroup analysis of EGFR-TK mutation status positive patients within IPASS to be appropriate?
- What is the Committee's view on the calculation of the hazard ratios using the Cox proportional hazards method?
- What is the Committee's view on the analysis of overall survival data from IPASS, given that estimates were based on the results of an interim analysis (37% maturity)?

Cost effectiveness issues

- What is the Committee's view on the use of a specific diagnostic test to identify the presence of EGFR-TK mutations and the choice of treatment being dependent on the test result?
- Does the Committee consider the manufacturer's cost-effectiveness strategy to be reasonable, taking into account the degree to which the IPASS population reflects the target UK population with locally advanced or metastatic NSCLC?
- Does the Committee consider it appropriate to use gemcitabine and carboplatin as the primary comparator in the economic evaluation?
- Does the Committee consider it reasonable to use the two-parameter Weibull formulation for modelling both progression-free survival and overall survival?

- What is the Committee's view on the manufacturer's mixed treatment comparison (and the updated analysis by the Evidence Review Group [ERG]), given that hazard ratios (HRs) for gefitinib compared with paclitaxel and carboplatin were the primary drivers of patients' outcomes in the model, and were propagated to all comparators via the results of the mixed treatment comparison?
- What is the Committee's view on the results of the ERG's amendments/corrections to the manufacturer's model?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Table 1 Decision problem for gefitinib

Population	People with previously untreated EGFR-TK mutation status positive locally advanced or metastatic non-small-cell lung cancer
Intervention	Gefitinib
Comparators	• Gemcitabine and carboplatin • Paclitaxel and carboplatin • Vinorelbine and cisplatin • Gemcitabine and cisplatin
Outcomes	• Overall survival • Progression-free survival • Objective tumour response rates • Health-related quality of life • Adverse effects of treatment
Economic evaluation	The outcome measures listed in the final scope capture the most important health-related benefits of gefitinib. A lifetime horizon of 5 years will be adopted for the cost-effectiveness analysis. This is consistent with the poor prognosis of patients diagnosed with locally advanced or metastatic non-small-cell lung cancer, with fewer than 1% surviving beyond 5 years. The cost of EGFR-TK mutation testing will be included in the economic analysis.
Subgroups	If evidence allows: performance status, histology, gender, and previous smoking history

1.2 Evidence Review Group comments

1.2.1 Population

The ERG stated that the population defined in the manufacturer's decision problem was consistent with the population defined in the final scope. However, the manufacturer's submission focused on a narrower population than that defined in the scope, that is patients with adenocarcinoma histology only, although all histology types were within the licence for gefitinib.

1.2.2 Intervention

Gefitinib is a selective EGFR-TK tyrosine kinase inhibitor that blocks the signal pathways involved in cell proliferation. By blocking EGFR-TK, gefitinib helps to slow the growth and spread of the cancer. Gefitinib is administered orally as 250-mg film-coated tablets. The recommended dose of gefitinib is 250 mg daily until disease progression or at the clinician's discretion.

1.2.3 Comparators

The manufacturer's submission stated that a pragmatic decision was taken to focus on four chemotherapy regimens that were considered to be of particular relevance to the decision problem. These regimens were gemcitabine and carboplatin, paclitaxel and carboplatin, vinorelbine and cisplatin, and gemcitabine and cisplatin. The ERG was concerned that docetaxel and pemetrexed were not considered in the manufacturer's submission because both are currently used for first-line treatment of NSCLC in UK clinical practice. The manufacturer's submission stated that the Appraisal Committee's decision to recommend pemetrexed for first-line treatment was too late to be included in a robust economic analysis, although an updated mixed treatment comparison including both docetaxel and pemetrexed as comparators was provided in response to clarification.

1.2.4 Outcomes

The ERG noted that all of the clinical outcomes identified in the decision problem were addressed in the manufacturer's submission and included overall survival, progression-free survival, tumour response rates, health-related quality of life and adverse events. However, the ERG was mindful that only an early analysis of overall survival was provided based on a small number of events (450/1217 deaths, 37% maturity) and that the final analysis would not be available until the second quarter of 2010.

1.2.5 Economic evaluation

Incremental cost per quality-adjusted life-year (QALY) gained was used as a measure of cost effectiveness, in accordance with the NICE reference case. Costs were considered from the NHS and personal social services perspective.

1.2.6 Timeframe

The manufacturer's decision problem defined the timeframe as a lifetime horizon, and stated that 5 years was chosen because it was consistent with the prognosis of patients diagnosed with locally advanced or metastatic NSCLC.

1.3 Statements from professional/patient groups and nominated experts

A patient group stated that lung cancer is the most common cause of death from cancer for both men and women in the UK. Each year 38,000 people are diagnosed with lung cancer in the UK, and NSCLC accounts for approximately 90% of all lung cancer diagnoses. The patient group noted that treatment outcomes for NSCLC are poor and only 7% of patients survive for 5 years after diagnosis, with only small improvements in long-term survival in recent years.

The patient group stated that most patients are diagnosed when NSCLC is at the advanced stage and therefore curative treatment is not an option. Furthermore, many of the symptoms of NSCLC (such as weight loss, breathlessness and cough) are very difficult to treat medically. The professional groups stated that treatment of locally advanced or metastatic NSCLC varies geographically, but typically is with platinum-based combination chemotherapy, which may include gemcitabine and carboplatin, gemcitabine and cisplatin, or vinorelbine and cisplatin. The professional groups also noted that although erloitinib and gefitinib have been available for several years, they have been used only for second-line treatment of NSCLC.

The patient group noted that there is a need for innovative approaches to improve the quality and length of patients lives. Both the professional and patient groups highlighted that gefitinib represented a new form of treatment of NSCLC and that gefitinib is given in tablet form, which would be an advantage for patients.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer's submission presented clinical effectiveness data from one main randomised clinical trial (RCT). The Iressa Pan Asian Study (IPASS) was a multicentre, open-label randomised trial in clinically selected patients with stage IIIb (locally advanced disease not amenable to local therapy such as pleural effusion) or IV (metastatic disease) chemotherapy-naïve pulmonary adenocarcinoma and was set in East Asian countries only. Patients included in the study were older than 18 years, had histologically or cytologically confirmed stage IIIb or stage IV NSCLC with adenocarcinoma histology (including bronchoalveolar carcinoma), had never smoked (fewer than 100 cigarettes lifetime) or were light ex-smokers (stopped smoking at least 15 years previously and smoked no more than 10 pack-years), had no prior chemotherapy, biological or immunological therapy, and had a WHO performance status of 0–2.

IPASS included 1217 patients from 87 East Asian centres. Patients were randomised to 250 mg of gefitinib once daily or to paclitaxel (200 mg/m^2) followed by carboplatin (at a dose calculated to produce an area under the curve [AUC] of concentration versus time of 5.0–6.0 mg/ml/minute) in cycles of once every 3 weeks. The manufacturer's submission focused on a subgroup of 261 patients from IPASS who were EGFR-TK mutation status positive and this subgroup accounted for 21% of the overall IPASS population. Patients were not stratified according to mutation status so the EFGR

mutation status positive subgroup could not be considered to be truly randomised to gefitinib or paclitaxel and carboplatin. Treatment was continued until disease progression (according to Response Evaluation Criteria in Solid Tumours [RECIST] criteria, which use tumour measurement rather than investigator assessment), unacceptable toxicity, patient or clinician request to discontinue, or severe non-adherence to the protocol, or until six chemotherapy cycles were reached. Following disease progression, all patients in the gefitinib arm of IPASS were offered treatment with paclitaxel and carboplatin; if the patient declined or the combination was considered unsuitable, an approved therapy of the clinician's choice was used. Following disease progression after treatment with paclitaxel and carboplatin, choice of treatment was at the clinician's discretion.

The subgroup of patients with EGFR-TK positive mutation status comprised 261 patients from the overall study population. Baseline characteristics were similar between both treatment arms. Of these patients, 80.8% were women. Most patients (94.3%) had never smoked, 5.4% were light ex-smokers, and 0.4% were ex-smokers. Most patients had a WHO performance status of 1 (65.9%), 26.4% had a WHO performance status of 0, and 7.7% had a WHO performance status of 2. Most patients had adenocarcinoma histology (94.6%), 5.4% had bronchocarcinoma histology and 0% had unknown histology. At study entry most patients had metastatic disease (81.6%) and 18.4% had stage IIIb locally advanced disease.

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 were based on an interim analysis after 450 deaths, with 37% data maturity and ongoing follow-up with a final analysis 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), which is a sum of the physical and functional wellbeing, and Lung Cancer Symptoms (LCS) domain.

Analysis of the primary outcome (progression-free survival) used a Cox proportional hazard model in the intention-to-treat population to assess the non-inferiority of gefitinib compared with paclitaxel and carboplatin, adjusting for baseline co-variates.

Results of IPASS

In the overall study population, patients receiving gefitinib had statistically significantly better progression-free survival compared with patients receiving paclitaxel and carboplatin. The hazard ratio (HR) for progression-free survival (gefitinib compared with chemotherapy with paclitaxel and carboplatin) was 0.74 (95% confidence interval [CI] 0.65 to 0.85, $p < 0.0001$). There was no apparent difference in median progression-free survival (5.7 months for patients receiving gefitinib and 5.8 months for patients receiving paclitaxel and carboplatin). The objective tumour response rate was statistically significantly higher for gefitinib compared with paclitaxel and carboplatin (43% and 32.3%; odds ratio [OR] 1.59, 95% CI 1.25 to 2.01, $p = 0.0001$). The estimates of overall survival were based on an interim analysis of 450 deaths. Overall survival was similar for both groups with a median of 18.6 months for patients receiving gefitinib and 17.3 months for patients receiving paclitaxel and carboplatin (HR 0.91, 95% CI 0.76 to 1.10).

The ERG stated that potential confounding could have occurred due to 'cross-over' of treatment after disease progression, which could also have had an impact on the manufacturer's analysis of overall survival. Following disease progression, 41% of patients who received gefitinib subsequently received paclitaxel and carboplatin, and 13% of patients subsequently received other chemotherapy. Of the patients receiving chemotherapy with paclitaxel and carboplatin, 50% subsequently received an EGFR-TK therapy (38% gefitinib, 7% erlotinib and 6% other EGFR-TK therapy) and 11% received other chemotherapy.

The efficacy of gefitinib was dependent on EGFR-TK mutation status. In the EGFR-TK mutation status positive subgroup (n = 261), progression-free survival in patients receiving gefitinib was statistically significantly longer than for patients receiving 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 receiving gefitinib and 6.3 months for patients receiving paclitaxel and carboplatin. The objective tumour response rate was statistically significantly higher for patients receiving gefitinib compared with patients receiving paclitaxel and carboplatin (71.2% versus 47.3% respectively; OR 2.75, 95% CI 0.36 to 0.64, p < 0.0001). There was no statistically significant difference in overall survival for patients receiving gefitinib compared with patients receiving paclitaxel and carboplatin (HR 0.78, 95% CI 0.50 to 1.20). However, as for the overall trial population, the estimates of overall survival were based on the results of an interim analysis.

In the EGFR-TK mutation status negative subgroup (n = 176), progression-free survival in patients receiving gefitinib was statistically significantly shorter than for patients receiving paclitaxel and carboplatin (HR 2.85, 95% CI 2.05 to 3.98, p < 0.0001). Median progression-free survival was 1.5 months in patients receiving gefitinib and 5.5 months for patients receiving paclitaxel and carboplatin. The objective tumour response rate was statistically significantly lower with gefitinib than with paclitaxel and carboplatin (1.1 and 23.5% respectively; OR 0.04, 95% CI 0.01 to 0.27, p = 0.0013). There was no statistically significant difference in overall survival for patients receiving gefitinib compared with those receiving paclitaxel and carboplatin (HR 1.38, 95% CI 0.92 to 2.09). Again, the estimates of overall survival were based on the results of an interim analysis.

Health-related quality of life was assessed by the FACT–L and TOI, which showed that in the overall study population statistically significantly more patients receiving gefitinib had a clinically relevant improvement in health-related quality of life and disease symptoms than patients receiving 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). Symptomatic improvement rates were measured using the Lung Cancer Symptoms (LCS) domain of the FACT–L and were similar for patients receiving gefitinib and patients receiving paclitaxel and carboplatin.

Similarly in the EGFR-TK mutation status positive subgroup, statistically significantly more patients receiving gefitinib had a clinically relevant improvement in health-related quality of life and disease symptoms than patients receiving 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 receiving gefitinib than for patients receiving paclitaxel and carboplatin (median range 11.3 to 16.6 months for gefitinib and 2.9 to 3.0 months for paclitaxel and carboplatin).

In the EFGR mutation status negative subgroup, statistically significantly more patients receiving paclitaxel and carboplatin had a clinically relevant improvement in health-related quality of life and disease-related symptoms than patients receiving 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 receiving gefitinib than for patients receiving paclitaxel and carboplatin (median range 1.4 months for gefitinib, 1.4 to 4.2 months for paclitaxel and carboplatin).

Safety was evaluated in patients who received at least one dose of the study treatment (1196 out of the 1217 intention-to-treat population). The manufacturer's submission did not provide an analysis of adverse events according to EGFR-TK mutation status. For the overall trial population, patients had a median exposure to gefitinib of 5.6 months. Patients who were EGFR-TK mutation status positive had a median exposure to gefitinib of

8.3 months compared with 1.6 months for patients who were EGFR-TK mutation status negative. The manufacturer's submission stated that gefitinib was associated with fewer grade 3 or 4 adverse events than paclitaxel and carboplatin (28.7% versus 61.0%). For patients receiving gefitinib, adverse events included: rash/acne, diarrhoea, dry skin, pruritus, stomatatis and paronychia. The most common adverse events reported with paclitaxel and carboplatin were: anorexia, asthenic conditions, nausea, vomiting, constipation, alopecia, neurotoxicity, myalgia, arthralgia, neutropenia (any), febrile neutropenia, anaemia and leucopenia. Table 4.10 of the ERG report (page 42) summarises the common adverse events. The manufacturer's submission stated that the safety profile of gefitinib according to EGFR-TK mutation status was consistent with the overall population (although compared with all patients receiving gefitinib, some adverse events such as rash were higher in patients receiving gefitinib who were EGFR-TK mutation status positive than in patients who were EGFR-TK mutation status negative). Of patients who received gefitinib, 3.8% experienced adverse events that led to death, compared with 13.8% of patients who received paclitaxel and carboplatin. Furthermore, 2.7% of patients who received gefitinib experienced serious adverse events that caused hospitalisation compared with 13.1% of those who received paclitaxel and carboplatin.

The manufacturer's submission stated that gefitinib was associated with fewer dose modifications as a result of toxicity (16.1% compared with 35.2% for carboplatin and 37.5% for paclitaxel) and fewer adverse events leading to discontinuation (6.9% compared with 13.6% for paclitaxel and carboplatin).

Manufacturer's meta-analysis

The manufacturer identified two additional trials (First-SIGNAL and NEJGSG) that compared gefitinib with chemotherapy for the treatment of chemotherapy-naïve patients with predominantly adenocarcinoma histology. These studies were considered for inclusion in the meta-analysis, but the manufacturer's submission stated that the First-SIGNAL study examined only a small number of patients with EGFR-TK positive mutations (n = 42) and the comparator was

gemcitabine and cisplatin, so the study was excluded. The NEJGSG trial compared gefitinib with paclitaxel and carboplatin in the first-line treatment of patients with NSCLC and EGFR-TK positive mutations. This study was deemed suitable for inclusion in the meta-analysis and used as supporting evidence for IPASS. The results of the NEJGSG study showed that the HR for progression-free survival was 0.357 (95% CI 0.25 to 0.51, $p < 0.001$). The meta-analysis of progression-free survival demonstrated a statistically significant improvement in progression-free survival for patients with EGFR-TK positive mutations who received gefitinib compared with patients with EGFR-TK positive mutations who received paclitaxel and carboplatin (HR 0.43, 95% CI 0.34 to 0.53, $p < 0.001$). Both fixed and random effects models demonstrated consistent results.

Statistically significantly more patients receiving gefitinib experienced diarrhoea using the fixed effects model (mean OR 0.78, 95% CI 1.01 to 33.11, $p = 0.05$), although this was not statistically significant (at the 0.05 level) when using a random effects model (OR 5.5, 95% CI 0.95 to 32.36, $p = 0.06$). Statistically significantly more patients receiving paclitaxel and carboplatin experienced anaemia (fixed effects – OR 0.12, 95% CI 0.03 to 0.47, $p = 0.002$; random effects – OR 0.13, 95% CI 0.03 to 0.49, $p = 0.003$) and neutropenia compared with patients receiving gefitinib. Table 4.11 of the ERG report (page 45) outlines the results of the meta-analysis of grade 3, 4, and 5 adverse events.

Manufacturer's mixed treatment comparison

The manufacturer carried out a systematic review and mixed treatment comparison of RCTs comparing chemotherapy in chemotherapy-naïve patients with NSCLC, with evidence on paclitaxel and carboplatin used as a baseline comparator for all analyses. The systematic review identified 29 trials for inclusion in the network that formed the basis for the mixed treatment comparison of chemotherapy (original comparison n = 28; updated comparison n = 29). Data were extracted and analysed 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's submission stated that it assumed that the relative effect of alternative chemotherapy compared with paclitaxel and carboplatin in an unselected population with NSCLC would be obtained and the relative estimates would be applied to a baseline event rate in EGFR-TK mutation status positive patients who received paclitaxel and carboplatin in IPASS. The results of the manufacturer's original mixed treatment comparison did not identify an individual chemotherapy as offering both substantial clinical benefit and favourable tolerability compared with the other chemotherapies assessed (Table 2).

Table 2 Hazard ratios for progression-free survival calculated from the mixed treatment comparison (fixed effects model) from the manufacturer's submission

		95% credible interval		Probability
Treatment	**Mean**	**Lower**	**Upper**	**'best'**
Paclitaxel/carboplatin	1.00	-- baseline treatment --		8.1%
Paclitaxel/cisplatin	1.14	0.93	1.38	0.3%
Docetaxel/carboplatin	No data	No data	No data	No data
Docetaxel/cisplatin	1.06	0.85	1.31	4.6%
Gemcitabine/carboplatin	1.23	0.68	2.06	16.6%
Gemcitabine/cisplatin	0.92	0.81	1.05	56.3%
Vinorelbine/carboplatin	No data	No data	No data	No data
Vinorelbine/cisplatin	0.99	0.80	1.21	14.2%

The manufacturer's submission stated that the interplay of the different outcomes (efficacy and tolerability) in the economic evaluation would determine which type of chemotherapy would offer best value to the NHS. In response to the request for clarification the manufacturer updated the mixed treatment comparison. The results of the updated comparison showed that pemetrexed (for patients with non-squamous histology) is more similar to gefitinib than the other chemotherapies in terms of the effect on overall survival. The results also showed that pemetrexed is associated with significantly better progression-free and overall survival than the other

chemotherapies. Pemetrexed was considered in the economics section of the ERG report (please see ERG comments on cost effectiveness in section 2.2).

2.2 Evidence Review Group comments

Clinical effectiveness

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, was suitably powered to demonstrate the primary objectives of the trial for the overall population, and was carried out in a substantial number of patients. The ERG stated that the trial provided convincing evidence of efficacy and benefits to health-related quality of life for gefitinib.

The ERG highlighted several areas of concern about the clinical evidence submitted by the manufacturer. These included:

- whether the clinical results from IPASS can be generalised to the UK population
- how EGFR-TK testing could be carried out within the NHS
- the trial did not include stratification by biomarker, so the EGFR-TK mutation status positive population cannot be considered to have been truly randomised to the different treatments
- measurement of the primary outcome of progression-free survival may be unreliable because it was assessed without blinding and the HRs may have been inappropriately calculated using the Cox proportional hazards method
- the analysis of overall survival data was immature.

The ERG considered that the clinical evidence to support the use of gefitinib for the treatment for locally advanced or metastatic NSCLC in England and Wales was weak. IPASS was not considered to be generalisable to most patients with NSCLC in England and Wales because:

- None of the patients in the study were enrolled from the UK; all patients in the study were randomised at 87 centres in East Asia. Baseline characteristics appeared to be different from those of patients with NSCLC in England and Wales. Patients in IPASS were predominantly female, East Asian, and were non-smokers with adenocarcinoma histology. The ERG noted that there was some debate in the literature about the assumption that patients who are EGFR-TK mutation status positive will respond to gefitinib irrespective of ethnicity.
- All patients in IPASS had adenocarcinoma histology, which accounts for approximately 25% of the population with NSCLC in the UK. It is thought that this group of patients may benefit more from treatment with gefitinib than patients with tumours of other histological type. The ERG noted that in order to identify patients with adenocarcinoma histology diagnostic testing is needed (prior to EGFR-TK mutation testing) and believed this diagnostic service is not routinely available, or performed consistently, across regions within the NHS.
- IPASS included patients with a performance status of 2 (less than 10%). In England and Wales NICE does not recommend chemotherapy for patients with metastatic disease with a performance status of 2 unless part of a clinical trial.
- The comparator examined in the IPASS trial was chemotherapy with paclitaxel and carboplatin. This regimen is used for first-line treatment of NSCLC in only 5% of patients in the UK. The most frequently used chemotherapy regimen for first-line treatment of NSCLC in the UK is gemcitabine and carboplatin (or occasionally cisplatin).

EGFR-TK mutation testing is not routinely carried out in the NHS in England and Wales. The ERG noted that there was uncertainty about how future testing of newly diagnosed patients with NSCLC would be orchestrated within the NHS, and that making this service operational throughout England and Wales would require substantial investment in both time and resources.

The ERG noted that the main focus of the manufacturer's submission was on the subgroup of patients who were EGFR-TK mutation status positive (261 patients from the overall trial population). The ERG stated that this subgroup could not be considered as being truly randomised to either gefitinib or paclitaxel and carboplatin because randomisation did not involve stratification by biomarker type. Furthermore, the trial was not powered to perform this subgroup analysis.

The ERG considered the manufacturer's analysis of the primary outcome (progression-free survival), which used a Cox proportional hazard model, adjusting for baseline covariates. The ERG noted that this method is valid only if the HR in the two comparative groups remains constant regardless of the passage of time. As can be seen from the period hazards and temporal trend in the HR for the EGFR-TK mutation status positive subgroup in figure 4.1 of the ERG report (page 33), this criterion was not met in the manufacturer's intention-to-treat analysis of IPASS. Therefore there was uncertainty about the results for progression-free survival and the significance of the influence of individual co-variates used in the analysis. The ERG carried out additional analysis using a 'spline' model and believed that this reflected the IPASS data accurately across the whole period of the study (further details below).

The absence of final overall survival estimates to demonstrate whether gefitinib led to improved overall survival compared with paclitaxel and carboplatin was also a major concern for the ERG. The ERG noted that overall survival is the most reliable and preferred end-point in most oncology RCTs, but that the data presented in the manufacturer's submission was an interim analysis based on only a small number of events (450/1217 deaths, 37% maturity) with follow-up ongoing.

The ERG highlighted that confounding may have occurred in IPASS because of crossover of treatment after disease progression. This meant that a substantial number of patients in both groups received a variety of second-line chemotherapy regimens. Therefore improvement in overall survival may not

be a result of the treatment to which patients were originally randomly assigned.

A meta-analysis was presented in the manufacturer's submission using data from IPASS and the NEJGSG study, both of which examined the same comparator (paclitaxel and carboplatin). The ERG believed that the First-SIGNAL trial could have been appropriately included because gemcitabine and cisplatin are not substantially different in terms of clinical benefit and tolerability. The ERG stated that it would have been more appropriate for the manufacturer to perform an indirect comparison or mixed treatment comparison between gefitinib and chemotherapy in the EGFR-TK mutation status positive population using all three studies (IPASS, NEJGSG and First-SIGNAL). The ERG noted that there were a number of other weaknesses in the manufacturer's mixed treatment comparison, such as important differences in baseline characteristics across trials in terms of the proportion of men, number of patients with stage IV disease, ethnicity, histological type and performance status. Furthermore, the manufacturer compared treatment groups directly. The ERG considered this to be unreliable because it resulted in randomisation within the individual trials being lost. As part of the mixed treatment comparison the manufacturer extracted unreported outcome statistics for some studies from two published meta-analyses. However, different methods were used to estimate unreported HRs and therefore there may have been selection bias regarding the studies included in the mixed treatment comparison. The mixed treatment comparison was also considered to be weak because of its dependence on the assumption that EGFR-TK mutation status did not affect treatment outcomes in patients receiving chemotherapy. This assumption was made because there was a lack of trial data on this sub-population. The ERG stated that this assumption was too strong because it was reliant on the results of a subgroup analysis from IPASS in patients with adenocarcinoma histology. Therefore the evidence base for the studies used in the comparison of gefitinib with chemotherapy may not be generalisable to the EGFR-TK mutation status positive population.

2.3 Statements from professional/patient groups and nominated experts

The professional groups stated that IPASS was the primary randomised trial examining the effectiveness of gefitinib versus carboplatin and paclitaxel. The professional groups noted that the population comprised East Asian patients with adenocarcinoma histology. Furthermore, the professional groups noted that gefitinib was more effective than conventional chemotherapy in patients with EGFR-TK positive mutations in terms of progression-free survival and improved quality of life.

The professional groups highlighted that performing EGFR-TK mutation analysis in a timely manner before treating patients with locally advanced or metastatic NSCLC would be a major problem. EGFR-TK mutation testing is not currently part of current UK clinical practice and the number of centres carrying out mutation testing may be limited. Furthermore it may not be possible to get sufficient samples of tumour material in some patients. There may also be a need for a histopathologist to sub-classify the NSCLC into adenocarcinoma and squamous cell carcinoma, which would require immunohistochemistry.

The patient group noted that there was anecdotal evidence to suggest that gefitinib had been effective in the treatment of NSCLC in individual patients. Both the patient and professional groups stated that gefitinib had only a few side effects (such as rash and diarrhoea), and that these were milder than the effects associated with conventional chemotherapy treatment.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's analyses incorporated a patient access scheme. Under this scheme the NHS would pay a single fixed price for each patient treated with gefitinib. This fee would include the entire cost of a course of treatment of

gefitinib until disease progression, irrespective of treatment duration. The manufacturer proposed to review the patient access scheme after 3 years, in line with the Pharmaceutical Price Regulation Scheme (PPRS).

The manufacturer carried out a Markov economic model to assess the cost effectiveness of gefitinib compared with chemotherapy in the first-line treatment of patients with NSCLC who are EGFR-TK mutation status positive. The model had four distinct health states: treatment response, 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). In the sensitivity analyses, 3- and 6-year time horizons were used.

Clinical evidence

Effectiveness data were taken from a variety of sources. The HR for progression-free survival for EGFR-TK mutation status positive patients receiving gefitinib was derived from the meta-analysis conducted by the manufacturer; the HR for overall survival for gefitinib in patients who are EGFR-TK mutation status positive receiving gefitinib was from IPASS; and estimates of the HRs for progression-free survival and overall survival for the chemotherapy regimens were derived indirectly from the manufacturer's mixed treatment comparison. A Weibull model was chosen for extrapolating costs and outcomes beyond the IPASS follow-up period (for overall survival the data cut-off took place after 450/1217 deaths had occurred; 37% maturity). Co-variates in the model included: mutation status, gender, performance status (0 or 1 versus > 1) and smoking history (never smoker or smoker).

The population in the manufacturer's economic evaluation is based on the IPASS trial population, which comprised chemotherapy-naïve patients who were EGFR-TK mutation status positive and eligible to receive chemotherapy. The comparator technologies were limited to four different chemotherapy combinations: paclitaxel and carboplatin; gemcitabine and cisplatin; gemcitabine and carboplatin; and vinorelbine and cisplatin.

Utility

The manufacturer carried out a literature review to identify relevant health-related quality of life data for use in the economic evaluation. In the manufacturer's submission utility estimates were adopted from a single UK study by Nafees et al. (2008) in which utility values were derived from a survey of 105 members of the general public who were asked to value health state descriptions of second-line chemotherapy for patients with NSCLC. This study did not provide utility estimates associated with the delivery of treatment (oral versus intravenous), so the manufacturer used utility values calculated in a previous ERG report (for NICE technology appraisal guidance 162, 'Erlotinib for the treatment of relapsed non-small cell lung cancer'), which examined second-line chemotherapy for patients with NSCLC.

Cost

Resource use in the economic model could not be derived from IPASS because the study was conducted only in Asian countries, so resource use was unlikely to be generalisable to the UK setting. Resource use in the model included: medication, delivery of chemotherapy, EGFR-TK testing, patient monitoring, NHS transport service, management of grade 3 or 4 adverse events, best supportive care and active treatment after progression. These were estimated from a range of secondary sources (such as references costs, British national formulary, previous NICE technology appraisal submissions and the ERG reports for NICE technology appraisal guidance 162).

Results

The manufacturer's analyses incorporated a patient access scheme. According to this scheme, the NHS will be charged a single fixed price of [redacted] per patient for gefitinib irrespective of the treatment duration.

[redacted]

[redacted]

The manufacturer's submission also stated that it would be likely that the cost of EGFR-TK mutation testing would decrease in future as more suppliers enter the market, biopsy techniques improve, new testing techniques become available (including the detection of the EGFR-TK mutation in patient blood samples) and economies of scale are achieved.

As outlined in Table 3 in the manufacturer's base case (which included the patient access scheme and EGFR-TK mutation test) the incremental cost-effectiveness ratios (ICERs) for the target population ranged from £19,402 per QALY gained (gefitinib versus paclitaxel and carboplatin) to £35,992 per QALY gained (gefitinib versus vinorelbine and cisplatin).

Table 3 Base case results for the manufacturer's target population

EGFR-TK mutation status positive population	Incremental costs	Incremental QALYs	ICER (£/QALY)
Gefitinib vs gemcitabine/carboplatin	£3666	0.177	£20,744
Gefitinib vs paclitaxel/carboplatin	£3637	0.187	£19,402
Gefitinib vs vinorelbine/cisplatin	£8023	0.223	£35,992
Gefitinib vs gemcitabine/cisplatin	£4138	0.145	£28,633
ICER = incremental cost-effectiveness ratio; QALY =quality adjusted life year			

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 HR for gefitinib in patients who were EGFR-TK mutation status positive; the overall survival HR for gemcitabine and carboplatin in patients who were EGFR-TK mutation status positive; the progression-free survival HR for gemcitabine and carboplatin in patients who were EGFR-TK mutation status positive; the progression-free survival HR for gefitinib in patients who were EGFR-TK mutation status positive; and the maximum number of chemotherapy cycles, which varied from four to eight.

The manufacturer also carried out a number of scenario analyses, although none led to any substantial change in the size of the ICER. The manufacturer's probabilistic sensitivity analysis showed that vinorelbine and cisplatin was the most cost-effective treatment for the first-line treatment of patients who were EGFR-TK mutation status positive up to a threshold of £35,100 per QALY gained. Beyond this threshold gefitinib was the most cost-effective treatment option for the first-line treatment of patients who were EGFR-TK mutation status positive. At a threshold of £30,000 per QALY the probabilities of each treatment being the most cost effective in patients who were EGFR-TK mutation status positive were, in descending order: vinorelbine and cisplatin (75%); gefitinib (18%); gemcitabine and carboplatin (4%); and gemcitabine and cisplatin (0%). Please see figures 27 and 28 (pages 111 and 112) in the manufacturer's submission.

3.2 Evidence Review Group comments

ERG comments on cost effectiveness

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 to identify EGFR-TK mutations is very high, but the power of the test result to predict a good response to treatment with gefitinib (that is, clinical validity) is less pronounced. The ERG noted that the sensitivity of mutation status determined by the ARMS test for predicting response to gefitinib treatment was 99%, the specificity was 69% and the false-positive rate was 17.3%.The corresponding results for predicting disease control were: sensitivity 77%, specificity 89% and false-positive rate 4.7%. This suggested that the average benefit for patients receiving gefitinib in IPASS involved a trade-off between those who would get a good outcome (people who were 'true positives', that is

people who were EGFR-TK mutation status positive and correctly tested positive for the mutation) and those who would get no benefit at all (people who were 'false positives', that is people who were EGFR-TK mutation status negative but tested positive for the mutation). Receiving treatment with gefitinib may be detrimental for patients who are 'false positive' because potential gains in survival and health-related quality of life that would have been gained from conventional chemotherapy would be lost. The ERG noted that performance characteristics of the diagnostic test should have been incorporated within the model (see figure 5.5 in the ERG report). The absolute numbers of patients falling into each category would depend on the underlying prevalence of mutations in the target population as well as the characteristics of the population (both ethnicity and lifestyle); with a low prevalence there would be fewer true positives and more false positives (and vice versa). The ERG believed that the prevalence of EGFR-TK mutations determines the volume and cost of screening tests that identify EGFR-TK mutation status positive patients, and that contribute to the incremental cost of adopting a 'test and treat' policy for such patients. The prevalence of EGFR-TK mutations also determines the balance between true and false positives in terms of likely clinical outcomes. The ERG noted that varying the prevalence of EGFR-TK mutations from that stated in the manufacturer's submission (16.6% producing an ICER of £20,010 per QALY) to between 5% and 25% produced ICERs ranging from £32,685 to £18,174 per QALY gained. The ERG highlighted that the results from the manufacturer's economic model in EGFR-TK mutation status positive patients receiving gefitinib is dependent on the prevalence of EGFR-TK mutations (that is the proportion of patients who are EGFR-TK mutation positive status within the tested population). The results of the economic model are also dependent on the combination of a specific test (ARMs) and gefitinib treatment, therefore the results from the manufacturer's analyses might not be valid if tests other than ARMs were used.

Results for subgroup analyses were also presented in the manufacturer's submission. These included: adenocarcinoma versus non-adenocarcinoma,

women versus men, and never smokers versus smokers. The ERG noted that these analyses were limited because there was differentiation only in terms of costs, not efficacy (QALYs). Furthermore, costs were affected only by changes in the prevalence of patients with mutation status positive associated with each of the subgroups; no supporting evidence was presented for the prevalence rates used in the subgroup analyses.

A number of problems with the manufacturer's economic model were identified by the ERG. These were as follows:

- time horizon and comparator selected
- costs of first-line chemotherapy
- maximum number of cycles of first-line chemotherapy
- treatment exposure to comparator chemotherapy agents
- survival modelling and projection of overall survival and progression-free survival
- validity of the results from the mixed treatment comparison for the economic analysis of non-trial comparators.

The ERG believed that the time horizon should be the longest period (6 years) because this would have been the best approximation to a lifetime. The manufacturer's economic evaluation used gemcitabine and carboplatin as the primary comparator, but the ERG noted that this involved a direct comparison from the manufacturer's mixed treatment comparison that could not be considered as robust as the primary comparator from IPASS (paclitaxel and carboplatin).

The ERG stated that chemotherapy costs in the model were not accurate. The ERG made adjustments to the costs of first-line chemotherapy comparators, which resulted in only a modest impact on cost effectiveness. However the reduction in dose level and the higher proportion of female patients who were EGFR-TK mutation status positive, combined with lower BNF prices for generic paclitaxel, led to a large increase in the incremental cost per patient of

gefitinib compared with paclitaxel and carboplatin to £18,000 per QALY gained.

IPASS allowed a maximum of six chemotherapy cycles, but the ERG believed that usual UK clinical practice allows a maximum of four chemotherapy cycles. This adjustment to the model by the ERG had a large impact on the cost-effectiveness results because it reduced the acquisition and administration costs of comparator chemotherapy by 29%, but had no effect on gefitinib treatment costs (these were a fixed price per patient irrespective of the duration of treatment). This increased the ICER to more than £32,000 per QALY 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. The ERG noted that the model unreasonably assumed that all planned chemotherapy cycles were delivered, which was contrary to the data from IPASS.

Patients in IPASS were progressively less likely to receive chemotherapy treatment even though disease progression had not occurred. The economic model assumed that all patients received prescribed medication up to cycle six. The ERG noted that this overestimated the mean number of cycles of chemotherapy administered per patient. When corrected, the cost of the comparator is reduced and the ICER for gefitinib increased (from £20,010 to £35,427 per QALY gained compared with paclitaxel and carboplatin, which was broadly representative of all chemotherapy regimens).

The manufacturer presented 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 status positive patients in IPASS and used these to calculate 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 the results from IPASS do not support this. They reveal poor correspondence between the

parametric model and the source data, particularly at the beginning and end periods of the trial (see figures 5-6 to 5-9, pages 80 to 81, in the ERG report).

The ERG stated that a simple match to the data could have been obtained by fitting a linear regression line to the two phases. A linear hazard is equivalent to an exponential survival model and a 'spline' model could be obtained in which two exponential models are spliced together at a time when the risk profile of patients changes. The ERG stated that this method reflects the IPASS data accurately across the whole period of the study and it is more accurate than the Weibull models, which overestimate progression-free survival for both treatment arms. As outlined in Table 4, the reanalysis by the ERG reduced estimates of progression-free survival and increased estimates of overall survival, but in all cases reduced the incremental gain attributable to gefitinib by approximately 1 month. This suggested a reduction in modelled outcome gains of approximately 25% from those reported in the manufacturer's submission.

Table 4 Estimated mean projected overall survival and progression-free survival using Weibull and exponential 'spline' models of EGFR-TK mutation status positive patients from IPASS (months)

	Weibull models		**Exponential 'spline' models**	
	Overall survival	Progression-free survival	Overall survival	Progression-free survival
Gefitinib	25.86	10.72	29.21	9.43
Paclitaxel/carboplatin	22.56	6.79	27.19	6.43
Survival gain	3.30	3.93	2.01	3.00

A number of sensitivity analyses were presented in the manufacturer's submission showing that the results of the cost-effectiveness analysis were sensitive to five main parameters. One of these related to the HR for overall survival in EGFR-TK mutation status positive patients receiving gefitinib. The ERG noted that where the ICER rose to £115,888 per QALY gained this was because of the extreme values used from the wide confidence intervals around the HR for overall survival. The wide confidence intervals reflect the

fact that the data describing overall survival used in the economic model were very uncertain and greatly influenced the size of the ICER.

As noted previously, the mixed treatment comparison carried out by the manufacturer allowed extrapolation of key outcomes from IPASS to other chemotherapy regimens as comparators for gefitinib. The ERG noted that the manufacturer used differential efficacy rates for the four chemotherapy regimens in the economic evaluation although the ERG felt that the results of the mixed treatment comparison presented in the manufacturer's submission demonstrated equivalent efficacy rates for the same four chemotherapy regimens. Furthermore, the mixed treatment comparison was dependent upon the assumption of proportional hazards, and data from IPASS indicated that this may not be a valid assumption because the HRs within IPASS varied over time. Therefore, because the HRs for gefitinib compared with paclitaxel and carboplatin are the primary drivers of patients' outcomes in the model, and are propagated to all comparators via the results of the mixed treatment comparison, the ERG expressed concern regarding all cost-effectiveness estimates generated by the manufacturer's model.

The ERG also identified several technical errors in the manufacturer's model and carried out amendments and corrections to address these issues. The ERG also incorporated the results of the manufacturer's updated mixed treatment comparison into the economic analysis because the omission of docetaxel and cisplatin or pemetrexed and cisplatin as comparators was considered to be a weakness of the manufacturer's submission. Results of each of the ERG's amendments or corrections are outlined in tables 5 to 7.

The ERG's revised base-case analysis indicated that ICERs ranged from £59,000 to £73,000 per QALY gained depending on the comparator used. The ERG highlighted that it appeared that gefitinib was dominated by pemetrexed and cisplatin (that is, gefitinib was both more expensive and less effective).

Table 5 Effect of corrections and amendments made by the ERG to the manufacturer's model for the base-case analysis (paclitaxel and carboplatin as the comparator) over 6 years

	Gefitinib / carboplatin		Paclitaxel / carboplatin		Incremental		ICER	Changes (from 6 year horizon base case)		
Model amendment	Costs £	QALYs	Costs £	QALYs	Costs £	QALYs	(£/QALY)	Costs £	QALYs	ICER £
Submitted base case	[redacted]	**1.1110**	**27,902**	**0.9235**	**3,637**	**0.1874**	**19,402**			
Base case with 6 year horizon	[redacted]	**1.1110**	**27,947**	**0.9235**	**3,751**	**0.1874**	**20,010**			
Amend 1st line chemotherapy costs	[redacted]	1.1110	24,563	0.9235	7,135	0.1874	38,063	+3,498	0.0000	+18,054
Reduced cycles of chemotherapy	[redacted]	1.1110	25,527	0.9270	6,170	0.1839	33,544	+2,420	−0.0035	+13,535
Revise overall survival models	[redacted]	1.2219	32,985	1.0834	2,268	0.1384	16,381	−1,483	−0.0490	−3,628
Revise progression-free survival models	[redacted]	1.0923	28,149	0.9181	4,989	0.1741	28,651	+1,238	−0.0133	+8,641
IPASS progression-free survival hazard ratio (not meta-analysis)	[redacted]	1.1020	29,947	0.9235	4,439	0.1785	24,867	+688	−0.0089	+4,857
Revise discounting method	[redacted]	1.1284	28,337	0.9378	3,680	0.1906	19,311	−71	+0.0032	−£699
Omit GCSF prophylaxis	[redacted]	1.1110	27,669	0.9235	4,029	0.1874	21,493	+278	0.0000	+1,483
Continuity correction	[redacted]	1.1110	28,426	0.9235	3,252	0.1874	17,350	−499	0.0000	−2,660
Correct misaligned cycles	[redacted]	1.1110	27,947	0.9235	3,752	0.1874	20,017	+1	0.0000	+7
Correct 2nd line chemotherapy costs	[redacted]	1.1110	25,213	0.9235	3,975	0.1874	21,204	+224	0.0000	+1,194
Chemotherapy treatment exposure	[redacted]	1.1110	26,931	0.9235	4,766	0.1874	25,427	+1,015	0.0000	+5,417
Combined effect of all changes	[redacted]	1.2223	24,574	1.0988	8,746	0.1235	70,822	+4,995	−0.0639	+50,812

GCSF = granulocyte colony stimulating factor; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year.

Table 6 Effect of corrections and amendments made by the ERG to the manufacturer's model for the base-case analysis

	Gefitinib vs gemcitabine/carboplatin			Gefitinib vs vinorelbine/cisplatin			Gefitinib vs gemcitabine/cisplatin		
Model amendment	Inc. costs £	Inc. QALYs	ICER (£/QALY)	Inc. costs £	Inc. QALYs	ICER (£/QALY)	Inc. costs £	Inc. QALYs	ICER (£/QALY)
Submitted model	**3,666**	**0.1767**	**20,744**	**8,024**	**0.2229**	**35,992**	**4,138**	**0.1445**	**28,633**
Base case with 6 year horizon	**3,761**	**0.1767**	**21,284**	**8,151**	**0.2229**	**36,562**	**4,222**	**0.1445**	**29,217**
Revised MTC	3,858	0.1824	21,151	8,149	0.2229	36,557	4,218	0.1445	29,181
Amend 1st line chemotherapy costs	4,057	0.1767	22,956	8,447	0.2229	37,890	4,077	0.1445	28,215
Reduced cycles of chemotherapy	5,599	0.1735	32,278	9,547	0.2194	43,512	6,244	0.1409	44,308
Revise overall survival models	1,985	0.1174	16,907	7,175	0.1893	37,905	2,245	0.0788	28,509
Revise PFS models	5,019	0.1630	30,788	9,299	0.2097	44,356	5,409	0.1313	41,209
IPASS PFS hazard ratio (not meta-analysis)	4,450	0.1678	26,520	8,840	0.2140	41,304	4,911	0.1356	36,219
Revise discounting method	3,674	0.1796	20,453	8,123	0.2266	35,839	4,146	0.1469	28,229
Omit GCSF prophylaxis	4,039	0.1767	22,855	8,429	0.2229	37,809	4,500	0.1445	31,141
Continuity correction	3,362	0.1767	19,024	7,891	0.2229	35,398	3,895	0.1445	26,956
Correct misaligned cycles	3,762	0.1767	21,290	8,152	0.2229	36,567	4,223	0.1445	29,223
Correct 2nd line chemotherapy costs	4,380	0.1767	24,785	8,085	0.2229	36,264	4,657	0.1445	32,228
Common chemotherapy outcomes	5,114	0.1892	27,028	7,043	0.1896	37,148	5,149	0.1880	27,394
Chemotherapy treatment exposure	4,543	0.1767	25,706	8,737	0.2229	39,189	5,067	0.1445	35,062
Combined effect of all changes	**7,554**	**0.1253**	**60,273**	**8,842**	**0.1256**	**70,390**	**7,322**	**0.1241**	**59,016**

GCSF = granulocyte colony stimulating factor; ICER = incremental cost effectiveness ratio; Inc. = incremental; PFS = progression-free survival; QALY = quality adjusted life year.

Table 7 Additional ERG analyses to determine the effect of corrections and amendments made by the ERG to the manufacturer's model for the base-case analysis (other modelled comparators) over 6 years

	Gefitinib vs docetaxel/cisplatin			Gefitinib vs pemetrexed/cisplatin		
Model amendment	Incremental. costs £	Incremental. QALYs	ICER (£/QALY)	Incremental. costs £	Incremental . QALYs	ICER (£/QALY)
Submitted model [a]	-	-	-	-	-	-
With revised MTC	**4,434**	**0.1627**	**27,252**	**−134**	**0.0601**	**−2,223**
Reduced cycles of chemotherapy [b]	6,254	0.1593	39,263	2,484	0.0565	43,984
Revise overall survival models	2,591	0.1013	25,590	−3,115	−0.0379	82,125
Revise progression-free survival models	5,636	0.1494	37,735	1,091	0.0469	23,271
IPASS progression-free survival hazard ratio (not meta-analysis)	5,123	0.1538	33,311	555	0.0512	10,838
Revise discounting method	4,356	0.1654	26,340	−264	0.0610	−4,323
Omit GCSF prophylaxis	4,712	0.1627	28,961	144	0.0601	2,402
Continuity correction	4,024	0.1627	24,728	−600	0.0601	−9,984
Correct misaligned cycles	4,435	0.1627	27,257	−134	0.0601	−2,223
Correct 2nd line chemotherapy costs	4,944	0.1627	30,385	842	0.0601	14,004
Chemotherapy treatment exposure	5,200	0.1627	31,961	958	0.0601	15,931
Combined effect of all changes	**6,285**	**0.0862**	**72,908**	**1,574**	**−0.0560**	**−28,080 (gefitinib dominated)**

GCSF = granulocyte colony stimulating factor; ICER = incremental cost effectiveness ratio; QALY= quality adjusted life year.
[a] Submitted model did not include these comparators. [b] Submitted model did not include costs for these comparators.

4 Authors

Fay McCracken (Technical Lead) and Bhash Naidoo (Technical Adviser), with input from the Lead Team (Fergus Gleeson, Stephen Palmer and Terence Lewis).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

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

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

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- AstraZeneca

II Professional/specialist, patient/carer and other groups:

- Royal College of Physicians
- Royal College of Pathologists
- Roy Castle Lung Cancer Foundation