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

ERG Report

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Adrian Bagust carried out the critical appraisal of the manufacturer's economic model with assistance from Angela Boland. Angela Boland summarised the manufacturer's review of economic literature and described the economic model.

All authors read and commented on draft versions of the ERG report.

Table of Contents

Abbreviations:

AE(s)	Adverse event(s)
ARMS	Amplification-Refractory Mutation System
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CSR	Clinical study report
CTC	Common Terminology Criteria (for Adverse Events)
CTX	Chemotherapy
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMEA	European Medicines Agency
EQ-5D	EuroQol 5D (a standardised instrument used as a measure of health outcome)
ERG	Evidence Review Group
EU	European Union
FACT-L	Functional Assessment of Cancer Therapy-Lung
HEED	Health Economic Evaluation Database
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
INVITE	IRESSA in NSCLC versus vinorelbine investigation in the elderly
IPASS	IRESSA Pan ASian Study
IPD	Individual patient data
ITT	Intention to treat
iv	Intravenous
LCS	Lung Cancer Symptoms
LYG	Life year gained
M+	Mutation status positive
M-	Mutation status negative
MS	Manufacturer submission
MTC	Mixed-treatment comparison
NEJGSG	North East Japan Gefitinib Study Group
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-small cell lung cancer
OS	Overall survival
PAS	Patient Access Scheme
PFS	Progression free survival
PP	Per protocol
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RR	Response rate
SA	Sensitivity analysis
SAG	Scientific Advisory Group
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal

TOI	Trial outcome index
WTP	Willingness to pay

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE from AstraZeneca in support of the use of gefitinib (IRESSA) for the treatment of chemotherapy-naïve patients with non-small cell lung cancer (NSCLC) who tested positive (M+) for the epidermal growth factor receptor gene (EGFR) mutation.

The manufacturer submission (MS) describes the use of gefitinib compared with doublet chemotherapy (CTX) for people with previously untreated EGFR M+ locally advanced or metastatic NSCLC.

On 24th June 2009, the European Medicines Agency (EMEA) granted a marketing authorisation valid throughout the European Union (EU) for gefitinib to AstraZeneca. Gefitinib is indicated for the "treatment of adult patients with locally advanced or metastatic NSCLC with activating mutations of EGFR".[1]

The ERG notes that the final scope issued by NICE considers the use of gefitinib as a first-line treatment for chemotherapy-naïve patients with NSCLC who are EGFR M+, whereas the marketing authorisation awarded by the EMEA does not restrict the use of gefitinib to first-line treatment.[1]

1.2 Summary of submitted clinical effectiveness evidence

The evidence described in the MS comprises a systematic review, a description and critique of the key clinical randomised controlled trial (RCT), a meta-analysis and a mixed treatment comparison (MTC).

Direct clinical evidence

Only one RCT was identified by the manufacturer which met the inclusion criteria of the systematic review; the IRESSA Pan-ASian Study (IPASS2). IPASS was conducted in 87 centres in East Asia and is a phase III open-label RCT which compared the use of gefitinib with paclitaxel/carboplatin in 1217 clinically selected chemotherapy-naïve patients with stage

IIIB/IV pulmonary adenocarcinoma. The MS focuses on a subgroup of patients in IPASS who are EGFR M+ (n=261; 21% of the total IPASS population).

In the overall population, IPASS met its primary objective of showing the non-inferiority of gefitinib and also showed its superiority, as compared with paclitaxel/carboplatin, with respect to progression free survival (PFS) in the intention-to-treat (ITT) population (hazard ratio (HR) of 0.74 (95% CI 0.65 to 0.85; p<0.0001)).

In line with the final scope issued by NICE, a subgroup analysis of 261 patients who were EGFR M+ was presented by the manufacturer which showed that PFS was significantly longer among those who received gefitinib than among those who received paclitaxel/carboplatin (HR of 0.48, (95% CI 0.36 to 0.64; p<0.0001)).

In the subgroup of patients who were EGFR M- (n=176), PFS was significantly longer among those who received paclitaxel/carboplatin (HR with gefitinib of 2.85, (95% CI, 2.05 to 3.98; p<0.001)).

Overall survival (OS) was a secondary endpoint in IPASS, and OS estimates are based on the results of an interim analysis (37% maturity). Overall survival was similar for both groups in the overall trial population (18.6 months for gefitinib vs 17.3 months for paclitaxel/carboplatin (HR 0.91, 95% CI 0.76 to 1.10). There was no significant difference in OS between gefitinib and paclitaxel/carboplatin in EGFR M+ patients groups (HR 0.78, 95% CI 0.50 to 1.20). Median OS was 12.1 months in the gefitinib EGFR M- subgroup and was 12.6 months in the paclitaxel/carboplatin EGFR M- subgroup. P-values for OS estimates are not provided in the MS.

Significantly more patients in the gefitinib group than in the paclitaxel/carboplatin group had a clinically relevant improvement in quality of life (QoL), as assessed by scores on the Functional Assessment of Cancer Therapy – Lung[3] (FACT-L) questionnaire, (odds ratio (OR), 1.34, 95% CI, 1.06 to 1.69, p = 0.01) and by scores on the Trial Outcome Index (OR, 1.78, 95% CI, 1.40 to 2.26, p<0.001). Gefitinib was associated with fewer grade 3 or 4 adverse events (AEs).

Meta-analysis

After late identification of interim analysis data from an ongoing RCT by the manufacturer, a meta-analysis was performed using data from IPASS and the North East Japan Gefitinib Study Group (NEJGSG[4]). Combining clinical data from these two trials for EGFR M+

patients, the manufacturer was able to demonstrate significant improvement in PFS for EGFR M+ patients in the gefitinib arm compared with EGFR M+ patients in the paclitaxel/carboplatin arm (HR 0.43, 95% CI 0.34 to 0.53, p<0.00001).

Mixed treatment comparison

The manufacturer carried out a systematic review and MTC of RCTs comparing doublet CTX in chemotherapy-naïve patients with NSCLC; paclitaxel/carboplatin evidence was used as a baseline for the results. The systematic review identified 29 trials for inclusion in the network that formed the basis for the MTC of doublet CTX. The results of the MTC conducted by the manufacturer did not identify any individual doublet CTX as offering both significant clinical benefit and significantly improved tolerability over the other doublet CTX regimens assessed. The manufacturer concluded that the interplay of efficacy and tolerability in the economic evaluation would determine which type of CTX would offer best value to the NHS.

1.3 Summary of submitted cost effectiveness evidence

In the absence of UK-based economic evaluations of gefitinib for chemotherapy-naïve patients with NSCLC who are EGFR M+ (target population), the manufacturer conducted a *de novo* economic evaluation. A Markov model was developed by the manufacturer to evaluate the cost effectiveness of gefitinib compared to four different doublet CTX regimens. The clinical data used in the economic evaluation are generated from a variety of sources. The HR for PFS for gefitinib EGFR M+ patients is derived from a MA conducted by the manufacturer and the HR for OS for gefitinib EGFR M+ patients is extrapolated from IPASS. Estimates of the HRs for PFS and OS for the doublet CTX regimens are sourced indirectly from the MTC conducted by the manufacturer. Although the economic evaluation is primarily trial-based, there is also a modelling component with regard to the extrapolation of health effects as the IPASS trial is ongoing. The economic evaluation adopts a lifetime horizon for the consideration of costs and benefits and the perspective is that of the UK NHS and Personal Social Services (PSS).

The manufacturer reports an incremental cost-effectiveness ratio (ICER) of £20,744 per quality adjusted life year (QALY) gained for the target population. In addition to the main cost-effectiveness results, ICERs for selected subgroups are presented. Univariate sensitivity analysis (SA) and scenario analyses were undertaken. Probabilistic sensitivity analysis (PSA) was also conducted by the manufacturer. The PSA described in the MS illustrates that for patients who are EGFR M+, gefitinib compared with doublet CTX is not likely to be cost

effective at what would usually be considered standard levels of willingness to pay (WTP) for an additional QALY; the mean ICER for gefitinib EGFR M+ versus doublet CTX EGFR M+ is reported as £35,700 per QALY.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The clinical evidence described in the MS is derived from a high quality trial in patients with NSCLC; convincing efficacy and HRQoL evidence are presented by the manufacturer.

The trial recruited a substantial number of patients in a difficult disease area and the clinical results of IPASS offer a positive contribution to the study of personalised medicine. It is of note that the subgroup of 261 EGFR M+ patients in IPASS is by far the largest group of such patients ever studied in a RCT in NSCLC.

The manufacturer did not provide the individual patient data (IPD) requested by the ERG. However, the manufacturer did provide a great deal of information in a timely fashion in response to the ERG's other clarification requests.

1.4.2 Weaknesses

Direct clinical evidence

The main evidence cited by the manufacturer is derived from a single RCT (IPASS) which compared gefitinib with paclitaxel/carboplatin; the ERG notes that this study has only reached 37% maturity for the determination of OS. Clinical data from two other smaller trials (the NEJGSG trial and the First-SIGNAL trial[5]) comparing gefitinib with paclitaxel/carboplatin and gemcitabine/cisplatin respectively are also available.

The main focus of the MS is on the subgroup of patients (n=261) who are EGFR M+ ; this subgroup of patients cannot be considered to have been truly randomised to either gefitinib or paclitaxel/carboplatin as the randomisation process did not include stratification by biomarker type. In addition, the trial was not powered to perform this subgroup analysis.

The limited generalisability of the IPASS study to patients in England and Wales is considered a weakness of the MS. The following facts should be noted:

- None of the centres in IPASS were based in the UK; all of the patients were from East Asia

- All of the patients in IPASS had adenocarcinoma histology; in the UK patients with adenocarcinoma are estimated to make up approximately 25% of the population with NSCLC[6]

- IPASS includes patients with performance status (PS) 2; in England and Wales CTX is not recommended by NICE for patients with metastatic disease with PS 2 unless as part of a clinical trial[7]

- The demographic characteristics of patients in IPASS do not match those of the relevant population in England and Wales; in IPASS patients are predominantly female and never smokers

- In the UK, the most common first-line CTX regimen for patients with NSCLC is gemcitabine with either carboplatin or cisplatin. In IPASS, gefitinib is compared with paclitaxel/carboplatin; it has been estimated by the manufacturer that approximately only 5% of patients receive paclitaxel/carboplatin as a first-line treatment for NSCLC in England and Wales.

In summary, as IPASS is the only published relevant head-to-head RCT with sufficient data available to compare the use of gefitinib with CTX in chemotherapy-naïve patients with adenocarcinoma histology who are EGFR M+, the ERG considers the clinical evidence to support the use of gefitinib for patients with NSCLC in England and Wales to be weak.

Safety

Despite the substantial volume of published evidence available demonstrating the safety of gefitinib as a lung cancer treatment, the ERG considered that the safety evidence discussed in the MS was limited.

Meta-analysis

The ERG believes that the First-SIGNAL trial could have been appropriately included in the MA alongside IPASS and the NEJGSG trial.

Mixed treatment comparison

The MTC methods used by the manufacturer to compare paclitaxel/carboplatin with a range of doublet CTX regimens in unselected populations are appropriate. However, the ERG considers that the MTC is weak as it is reliant on the assumption that EGFR mutation status does not affect treatment outcomes if patients are receiving doublet CTX. The ERG believes this assumption is too strong as it is wholly reliant on the results of a subgroup analysis from a single RCT of patients with adenocarcinoma histology. The ERG concludes that the evidence base for the studies used in the comparison of gefitinib with doublet CTX may not be generalisable to the EGFR M+ population.

Economics

The manufacturer's economic evaluation did not compare gefitinib with docetaxel or pemetrexed; both of these CTX regimens are listed as relevant comparators in the final scope issued by NICE. This means that the decision question set out in the scope has only been partially addressed in the MS. In response to the ERG's clarification letter, the manufacturer provided an updated version of the MTC and included both docetaxel and pemetrexed as comparators. Given NICE's recent approval of pemetrexed for use in chemotherapy-naïve patients with non-squamous histology, this is appropriate.[8]

It would have been useful if the manufacturer had also updated its economic evaluation and compared the cost effectiveness of gefitinib with pemetrexed and docetaxel for EGFR M+ patients. The ERG considers that not including pemetrexed or docetaxel as comparators in the economic evaluation is a major weakness of the MS.

The ERG has identified key areas where corrections and/or adjustments to the economic model are required: CTX costs, cycles, and exposure; OS and PFS modelling; use of discounting and continuity correction methods.

During the clarification process the manufacturer was asked to provide IPD from IPASS that would allow the ERG to explore a number of weaknesses identified in the MS. The manufacturer replied that they could not share IPD but would be willing to conduct specific analyses on behalf of the ERG. A request was made to the manufacturer to conduct these analyses. The manufacturer responded that they would not able to provide the results of the requested analyses within the timeframe of the STA process.

1.4.3 Areas of uncertainty

The MS provides clinical evidence to support the use of gefitinib in EGFR M+ patients with adenocarcinoma histology only.

To date, there is no direct clinical trial data to demonstrate that use of gefitinib as a first-line treatment by EGFR M+ patients leads to improved OS compared with the use of paclitaxel/carboplatin. The final OS estimates for patients in IPASS will be available in 2010. It may be difficult for the investigators to interpret the final OS data from IPASS due to the substantial number of patients in both groups who went on to receive a variety of second-line CTX regimens.

The MS estimates, using data from a study of Spanish patients with non-squamous histology, that approximately 17% of patients with NSCLC in England and Wales will be EGFR M+.[9] However, the number of patients requiring first-line treatment for NSCLC who are EGFR M+ in England and Wales is uncertain. A recent publication has estimated this figure to be between 5 and 10% in the Western population.[10]

Before patients can be offered first-line treatment with gefitinib they must undergo EGFR mutation status testing. Currently EGFR mutation testing is not routinely available in the NHS. It is uncertain how future testing of newly diagnosed patients with NSCLC will be orchestrated within the NHS in England and Wales.

1.5 Key issues

Clinical issues

The clinical results of IPASS are not generalisable to the majority of patients with NSCLC in clinical practice in England and Wales. In particular, the clinical evidence from IPASS only supports the use of gefitinib in patients with adenocarcinoma; this means that, although not a condition of the EMEA licence, patients with adenocarcinoma histology would need to be identified prior to EGFR mutation testing. This diagnostic service is not routinely available to patients in the NHS.

Gefitinib may offer greater clinical benefit than double CTX for chemotherapy-naïve EGFR M+ patients with adenocarcinoma histology. However in order for patients in clinical practice in England and Wales to receive gefitinib treatment they will require testing for EGFR mutation status and this test may not yet be ready for general implementation across the NHS until quality standards have been fully applied. In addition the clinical validity characteristics of these tests can impact on treatment outcomes with gefitinib. In particular, a positive result for EGFR mutation status does not guarantee a good outcome as a proportion (clinical false positives) of such patients receiving gefitinib will not experience any benefit (shorter PFS) compared with current treatment with doublet CTX and may in fact be worse off by not receiving doublet CTX. The implications of using EGFR mutation tests must be carefully considered for both EGFR M+ and EGFR M- patients.

Economics issues

The results of the manufacturer's economic evaluation are predicated on the use of the EGFR mutation test (or similar) described in IPASS. This means that if a different EGFR mutation test is used and/or does not demonstrate similar analytic validity, the manufacturer's cost-effectiveness results may no longer be valid. This assessment does not relate solely to use of gefitinib, but to the specific combination of mutation testing and gefitinib treatment studied in IPASS.

Taken together, the ERG's corrections and/or adjustments to the submitted model have increased the size of the ICER for the base case population from £20,010 to over £70,000 per QALY. This suggests that the cost effectiveness of gefitinib compared to doublet CTX for chemotherapy-naïve EGFR M+ patients may be less favourable than presented by the manufacturer in the MS.

[redacted]

1.6 Critique of manufacturer's description of underlying health problem

In the context section of the MS (section 4), the manufacturer describes the key issues relating to (i) the underlying health problem and (ii) current service provision. The information is presented in the MS as described in Box 1-1, Box 1-2 and Box 1-3. These data are accurate and informative to the appraisal process.

Box 1-1 Description of underlying health problem

Lung cancer is the leading cause of cancer death worldwide and is responsible for over 33,000 deaths a year in England & Wales.[11] Non-Small Cell Lung Cancer (NSCLC) is the commonest subtype, accounting for 80% of all lung cancer cases. Despite advances in early detection most patients still present with late stage disease.

Survival rates for lung cancer are very poor. In England, for patients diagnosed between 1993 and 1995 and followed up to 2000, 21.4% of men and 21.8% of women with lung cancer were alive one year after diagnosis and less than 1% of advanced NSCLC lung cancer patients were alive after five years.[12, 13]

The majority of patients with lung cancer are diagnosed with, or relapse with incurable disease and receive palliative treatment only. For otherwise fit patients with stage III / IV NSCLC, first-line treatment consists of platinum-based combination chemotherapy followed by docetaxel chemotherapy or erlotinib, as currently recommended in NICE clinical guidelines.[12]

Box 1-2 Current established treatments for NSCLC

In the UK, NICE produced comprehensive guidelines on the management of lung cancer at the beginning of 2005. These guidelines included a recommendation that the current standard of care for the first line treatment of NSCLC is the chemotherapy doublet regimen of a platinum based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine.[12]

Doublet chemotherapy has long been established as the standard of care for the first line treatment of advanced NSCLC with improvements in overall survival demonstrated over best supportive care alone (27% reduction in the risk of death). Following the endorsement by NICE in 2005 platinum-based doublet chemotherapy has become established as the standard first-line treatment for advanced NSCLC patients with good performance status in the UK.[12] Combinations of platinum compounds with third generation compounds of gemcitabine, taxanes, vinorelbine or irinotecan have shown comparable efficacy, with differences in toxicity profiles[14-16] and the implications for clinical practice of the new technology.

There is uncertainty over what doublet regimen represents best or routine clinical practice within the UK. No national audit has been conducted within the NHS. The ACTION (**A**ssessment of **C**osts and ou**T**comes of chemotherapy **I**n an **O**bservational setting in patients with advanced **N**SCLC) study found that 67.4% of NSCLC patients in the UK received gemcitabine/carboplatin chemotherapy and this has been supported by expert opinion from within the NHS.[17]

Box 1-3 Implications for clinical practice

Testing for activating EGFR mutations is not routinely done within the NSCLC treatment pathway in the NHS. There is currently uncertainty around whether there will be regional variation in access to EGFR mutation testing in the UK. It is also currently unknown if clinicians will use clinical characteristics to pre-select NSCLC patients for EGFR mutation testing.

1.7 ERG comment on manufacturer's description of EGFR mutation testing

The MS highlights uncertainties regarding the implementation of EGFR mutation testing in the NHS. The manufacturer has adopted a 'test all' strategy to ensure that all NSCLC patients eligible for gefitinib are identified and have the opportunity to take the test. However, the ERG is concerned that the MS failed to describe adequately how EGFR mutation testing could be operationalised within the NHS. The ERG asked the manufacturer, via the clarification letter, to provide additional details of (i) the performance of currently available EGFR mutation tests and (ii) the envisaged future of EGFR mutation testing in England and Wales. The ERG is satisfied with the responses provided by the manufacturer (questions and manufacturer responses are presented in Appendix 1).

1.7.1 Other relevant information related to gefitinib in the MS

AstraZeneca proposes to make gefitinib available to the patients in the NHS through a PAS scheme and to charge the NHS a single fixed price for each patient treated with gefitinib. This fee will include the entire cost of a course of treatment of gefitinib until disease progression, irrespective of treatment duration and will be reviewed after three years in line with the Pharmaceutical Price Regulation Scheme. The ERG also notes thatAstraZeneca is currently offering EGFR mutation tests to all UK patients newly diagnosed with advanced NSCLC.[18] The service will be available until June 2010, when NICE is scheduled to publish its final guidance in relation to the use of gefitinib in the NHS.

The MS explicitly mentions four NHS centres that are currently testing for the activating EGFR mutation. The ERG contacted each of the four centres in order to elicit specific information about EGFR mutation testing. The results from the ERG's survey are available in Appendix 1. The ERG is aware that a number of pathology centres in the NHS are currently carrying out such testing, not just the four centres mentioned in the MS (Prof Cree, (2009). Personal communication, Director NETSCC (Efficacy and Mechanism Evaluations Programme)). The ERG highlights that there are a number of different types of EGFR mutation test currently in use and in development in the NHS, each with different test characteristics (sensitivity and specificity) and costs.

2 Critique of manufacturer's definition of decision problem

The final scope issued by NICE and the manufacturer's statement of the decision problem are described in the MS and the summary table is reproduced here (Table 2-1).

Table 2-1 Final scope issued by NICE and the manufacturer's statement of the decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	People with previously untreated EGFR mutation positive locally advanced or metastatic NSCLC	People with previously untreated EGFR mutation positive locally advanced or metastatic NSCLC
Intervention	Gefitinib	Gefitinib
Comparator(s)	Platinum based chemotherapy (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine Pemetrexed in combination with platinum based chemotherapy (carboplatin or cisplatin) Best supportive care	• Gemcitabine and carboplatin • Paclitaxel and carboplatin • Vinorelbine and cisplatin • Gemcitabine and cisplatin
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • health-related quality of life • adverse effects of treatment	• overall survival • progression-free survival • response rates • health-related quality of life • adverse effects of treatment
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective. Costs to the NHS associated with the testing for EGFR mutations should be included in the economic analysis	The outcome measures listed in the final scope do capture the most important health-related benefits of gefitinib Time horizon - a time horizon of 5 years will be adopted for the cost-effectiveness analysis. This is consistent with the poor prognosis of patients diagnosed with NSCLC, with fewer than 1% surviving beyond 5 years The cost of EGFR mutation testing will be included in the economic analysis
Subgroups to be considered	If evidence allows: performance status, histology, gender, and previous smoking history	If evidence allows: performance status, histology, gender, and previous smoking history

2.1 Licensed indication

The European Commission granted a marketing authorisation valid throughout the EU for gefitinib to AstraZeneca on 24 June 2009.[19] Gefitinib is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with activating mutations of EGFR.

During its deliberations, the Committee for Medicinal Products for Human Use (CHMP) consulted the Scientific Advisory Group (SAG) in Oncology to provide guidance on "…the significance of the clinical benefit observed in the context of the trials conducted in a predominantly Asian patient population with a defined genetic criteria of tumours harbouring EGFR activating mutations and the applicability of defining and treating a patient population based on their EGFR mutation status in a clinical practice".[1] A number of the key issues discussed by the SAG are covered in section four of the ERG report; the points raised are relevant to the generalisation of the clinical results from IPASS to patients in England and Wales.

2.2 Population

The manufacturer's statement of the decision problem describes the relevant patient population as people with previously untreated EGFR M+ locally advanced or metastatic NSCLC. This is in line with the final scope issued by NICE.

In the clinical section of the MS, the main evidence is derived from IPASS. In IPASS 1217 patients with adenocarcinoma were randomised to either gefitinib or paclitaxel/carboplatin at 87 centres in nine different East Asian countries. The scope does not limit the relevant patient population to those patients with adenocarcinoma only, yet IPASS only includes patients with adenocarcinoma.

As identified in the final scope, the relevant patient population for this appraisal is people with previously untreated EGFR mutation positive locally advanced or metastatic NSCLC. The ERG highlights that although "…evaluation of efficacy by baseline EGFR biomarker status was a planned exploratory objective" (MS, pg21) the randomisation process used in IPASS did not include stratification by biomarker type; nor was the trial powered to perform this subgroup analysis.

2.3 Intervention

Gefitinib is an orally active, selective EGFR tyrosine kinase inhibitor that blocks the signal pathways involved in cell proliferation; EGFR is involved in the growth and spread of cancer cells. By blocking EGFR, gefitinib helps to slow the growth and spread of the cancer. Gefitinib (250mg) is taken once daily as an oral tablet. In IPASS, patients were given gefitinib until disease progression or at the clinician's discretion.

2.4 Comparators

In IPASS, gefitinib is compared with paclitaxel/carboplatin; it has been estimated by the manufacturer that approximately 5% of patients receive paclitaxel/carboplatin as a first-line treatment for NSCLC in England and Wales.

The stated comparators in the final scope are: (i) platinum based CTX (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel, vinorelbine or pemetrexed. The manufacturer states (MS, pg76) that "…given the large number of potential comparators, a pragmatic decision was taken, in collaboration with NICE, to focus the economic evaluation on four doublet chemotherapies that were considered to be of particular relevance to the decision problem." This means that in the MS, the comparators are limited to: (i) gemcitabine/carboplatin (ii) gemcitabine/cisplatin (iii) paclitaxel/carboplatin and (iv) vinorelbine/cisplatin.

The manufacturer states (MS, pg76) that "…The decision by the Appraisal Committee to recommend pemetrexed in the first-line setting was considered to be too late to be included in any further robust analysis for this submission." The manufacturer does not therefore discuss pemetrexed as a relevant comparator to gefitinib for patients with EGFR M+ status in the economic evaluation.

The ERG did not participate in meetings where pragmatic decisions were taken regarding this appraisal (MS, pg 76). However, the ERG is concerned that docetaxel and pemetrexed have been omitted from the relevant range of comparators in the economic evaluation as both interventions are currently offered and administered as a first-line treatment to patients in England and Wales.

2.5 Outcomes

The MS identifies OS, PFS, tumour response rates, HRQoL and AEs as key outcomes, which match those within the final scope issued by NICE and are standard outcomes for research in this field. However, as IPASS is not yet complete, only an early analysis of OS, based on a small number of events (450/1217 deaths, 37% maturity) is presented by the manufacturer. Overall survival follow-up is ongoing and it is anticipated that the final analysis will be available in the second quarter of 2010.

2.6 Time frame

Patients in IPASS will be followed up until at least 944/1217 deaths have occurred. To date, published OS results from IPASS are based on 450/1217 deaths (37% maturity).

The economic model uses a lifetime model with a five-year time horizon to estimate the cost effectiveness of gefitinib in EGFR M+ patients compared to doublet CTX.

2.7 Other relevant factors

In order for a patient to receive gefitinib, the EGFR mutation status of the patient must be known. In England and Wales EGFR testing is not routinely carried out in the NHS. The ERG wishes to point out that making this service operational throughout the NHS in England and Wales in the near future will require substantial investment in both time and resources.

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach

Table 3-1 provides an outline of the key background/clinical information and its location within the MS. Its purpose is to signpost the reader to the main areas of background/clinical information within the MS.

Table 3-1 Key non-economic information in the MS

Key information	Pages in the MS
Description of technology	5-7
Statement of decision problem	7-8
Context	12-14
Equity and equality	15-16
Literature search:	
Search strategies	138-140
Study selection	16
Clinical effectiveness evidence:	
Trial information	16-24, 156-161
Results: main and subgroups (IPASS)	24-30, 33
Results: HRQoL analysis (IPASS)	31-32
Results: Safety (IPASS)	61-65, 163-167
Meta-analysis	38-42
Indirect/mixed treatment comparisons	45-61, 141-144, 169-231

3.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate

The aim of the literature search described in the MS was to identify studies which compared the intervention (gefitinib) with doublet CTX - consisting of platinum-based CTX (carboplatin or cisplatin) in combination with gemcitabine, docetaxel, paclitaxel or vinorelbine in the first-line NSCLC setting.

The search strategy described in Appendix 2 of the MS used a filter to identify RCTs and combined drug names with disease. Search terms for electronic databases (Medline, EMBASE and CENTRAL) appropriately included a combination of free-text and index terms. The search strategies did not include terms for pemetrexed despite pemetrexed being included in the final scope issued by NICE.

The manufacturer initially identified 1012 references from EMBASE, 357 from Medline and 44 from CENTRAL; after deduplication, the total number of references was 1220. Of these, three references[2, 20, 21](including two abstracts) all relating to IPASS were included in the review. A flow diagram showing how the studies were identified for potential inclusion, and detailed reasons for trial exclusions, were not provided by the manufacturer and would have been useful to make the process of study selection transparent.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate

Table 3-2 shows the inclusion and exclusion criteria presented in the MS.

Table 3-2 Inclusion and exclusion criteria

Inclusion	Exclusion
Randomised controlled trials	Second-line setting
Gefitinib monotherapy in first-line treatment of NSCLC	Third-line setting
Doublet chemotherapy comparator	Gefitinib in combination with chemotherapy
EGFR mutation subgroup analysis	
English language	

The manufacturer's inclusion and exclusion criteria appear, on the whole, to be appropriate; however the doublet CTX comparators are not explicitly stated. Gemcitabine, vinorelbine, paclitaxel, docetaxel and pemetrexed were described in the final scope issued by NICE and therefore should have been specified in the inclusion criteria of the systematic review.

3.1.3 Table of identified studies. What studies were included in the submission and what were excluded?

One trial (IPASS) was identified from the searches undertaken by the manufacturer as part of the systematic review. Table 3-3 provides details of the IPASS trial characteristics. IPASS is a phase III randomised comparison of gefitinib versus paclitaxel/carboplatin in clinically selected patients with stage IIIB/IV chemotherapy-naïve pulmonary adenocarcinoma and was set in East Asian countries only. The MS focuses on a subgroup of patients (n=261) in IPASS who are EGFR M+; this subgroup of patients only accounts for 21% of the overall IPASS population.

Although subgroup analysis by EGFR mutation status was pre-specified, randomisation was not stratified by mutation status. This means that patients within the EGFR M+ subgroup are not truly randomised to gefitinib or paclitaxel/carboplatin.

In IPASS, consent for biomarker analyses were provided by 1038 patients (85%), 683 patients (56%) provided samples and evaluable EGFR mutation data were available for 437 patients (36%). In the manufacturers' response to ERG clarification questions, it is explained that during the trial a pathology review assessed a number of factors including quality of the tissue, sufficient tissue and >100 tumour cells present. Only those that passed pathology went forward for analysis of three exploratory biomarkers (EGFR mutation, EGFR copy number by FISH, and EGFR protein expression). If EGFR mutation analysis only were being performed (not EGFR copy number or EGFR protein expression) the manufacturer explains that the threshold could have been reduced from 100 tumour cells to 50 tumour cells which would have increased the number of evaluable samples from patients in IPASS.

The inclusion and exclusion criteria for this trial are lengthy and are presented in Appendix 2.

Table 3-3 IPASS trial characteristics

Trial design and number of participants	Intervention/Comparator	Outcomes
Multi-centre, phase III, open-label RCT. 87 East Asia centres (Hong Kong, elsewhere in China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan and Thailand). Patients were randomised on a 1:1 basis. Total number randomised (n= 1217) EGFR M+ patients (n=261)	Intervention: Gefitinib 250mg/day administered orally Comparator: Paclitaxel (200 mg/m^2 of body-surface area), administered intravenously over 3 hour period on first day of cycle followed immediately by carboplatin (at a dose calculated to produce an AUC of 5.0 to 6.0 mg/ml/min), administered intravenously over a period of 15 to 60 minutes in cycles of once every 3 weeks for up to 6 cycles. Treatment continued until disease progression, unacceptable toxicity, patient/physician request to discontinue, severe protocol noncompliance, or six chemotherapy cycles were reached. The patients assigned to gefitinib whose tumour progressed were offered carboplatin/ paclitaxel; however, if the patient declined or was considered unsuitable, he/she could receive another approved therapy of the physician's choice. Following progression on paclitaxel/carboplatin, subsequent therapy was at the physician's discretion.	Primary: Progression free survival Secondary: Overall survival (early analysis; follow-up ongoing) Objective tumour response rate Health related quality of life Symptomatic improvement Safety Tolerability

RCT=randomised controlled trial

3.1.4 Details of any relevant studies that were not included in the submission

A search conducted by the ERG confirms the finding of only one relevant direct comparison trial (IPASS) that is published in full.

A randomised phase II study: 'IRESSA versus vinorelbine investigation in the elderly' (INVITE)[22] was identified by the ERG which compared gefitinib with vinorelbine in chemotherapy-naïve elderly (median age 74 years) patients with advanced NSCLC. The INVITE study also presented a limited number of results by EGFR mutation status. However vinorelbine was not given in combination with a platinum-based CTX (as stated in the scope) and therefore the ERG considers that the manufacturer's exclusion of the INVITE study is justified.

Two other trials (the NEJGSG trial and First-SIGNAL trial) were identified by the manufacturer after the systematic review was conducted; only the NEJGSG trial was included in the MA.

3.1.5 Description and critique of manufacturers approach to validity assessment

The validity assessment carried out by the manufacturer and reviewed by the ERG (Appendix 2) demonstrated that IPASS was of high quality, used robust randomisation techniques and was suitably powered to demonstrate the primary objectives of the trial for the overall population.

Internal validity

IPASS was an open-label RCT in which neither patients nor clinicians were blinded to treatment. The MS states that randomisation was via a central interactive voice response system where patients were randomised on a 1:1 ratio and randomisation was stratified by smoking status, PS, gender and treatment site. This method should have enabled adequate allocation concealment (up to the point when treatment was initially administered) and adequate randomisation across the total population.

However, the ERG notes that the clinical evidence supporting the use of gefitinib submitted by the manufacturer is primarily based on a pre-planned exploratory analysis of the EGFR M+ subgroup that was not accounted for at randomisation of patients in IPASS.

IPASS excluded patients from trial entry with known biomarker status of one or more of the following: tumour EGFR gene copy number, tumour EGFR gene mutation status and tumour EGFR protein expression without any clinical justification. This could mean that a proportion of patients otherwise suitable for treatment were excluded from the trial and may have potentially resulted in selection bias and possibly under-representation of the general population of patients.

In line with the EMEA,[1] the ERG believes the design stage and conduct of IPASS could have been improved; use of prior knowledge and regulatory guidance regarding the importance of tumour material could have been used by the manufacturer to ensure adequate mutation testing of all participants.

External validity

The generalisability of the trial to the clinical population of England and Wales who require first-line CTX for NSCLC is questionable.

None of the patients in IPASS were enrolled from the UK; 1217 patients were randomised at 87 centres in East Asia. The mean number of EGFR M+ patients per treatment site in IPASS is three. Such contextual diversity and small numbers may undermine some of the benefits of randomisation and may also cast doubt on the applicability of results to any one country.

Baseline characteristics of patients in IPASS appear to be very different from those of the first-line NSCLC population within England and Wales; patients in IPASS are predominantly female, East Asian, and non-smokers with adenocarcinoma histology. Also, the IPASS population was generally younger than the majority of patients treated in the UK and so the results from IPASS may not be replicable in England and Wales.

The decision problem addressed in the MS specified the population as people with previously untreated EGFR M+ locally advanced or metastatic NSCLC. IPASS only included patients with adenocarcinoma histology; it is thought that this group of patients may benefit more from gefitinib treatment than patients with non-adenocarcinoma histology.[23] The results from IPASS are therefore only relevant to patients with adenocarcinoma histology. In order to identify patients with adenocarcinoma histology, diagnostic testing is required which is currently not routinely carried out or consistently performed across regions within the NHS; in addition, it is not always possible to determine the exact cell type from pathology (Dr Ramani, (2009). Personal communication, Consultant Clinical Oncologist, Wirral).

The MS states that the comparator (paclitaxel/carboplatin) is used to treat a minority (5%) of chemotherapy-naïve patients with NSCLC in the UK and that gemcitabine/carboplatin is the most frequently used doublet CTX for patients with advanced NSCLC in England and Wales (MS, pg 14). For patients in the NHS, gefitinib versus gemcitabine/carboplatin would have been a more appropriate comparison. The median number of CTX cycles received by patients in the paclitaxel/carboplatin arm of IPASS was six cycles. The ERG notes that several RCTs have shown that there is no added benefit

of extending first-line, platinum-based CTX beyond four cycles (which is current practice in the UK).[24]

The trial population was clinically selected based on patient characteristics which have been shown to demonstrate improved efficacy in previous clinical trials of gefitinib, such as never smokers with adenocarcinoma histology.[23] These characteristics may not be inherent to the same extent in patients in England and Wales.

Finally, there is some debate in the published literature regarding the assumption that patients who are EGFR M+ will respond to gefitinib irrespective of ethnicity.

3.1.6 Description and critique of manufacturers outcome selection

The outcome measures presented in the MS are shown in Table 3-4. The outcome measures reported in the decision problem in the MS are standard outcomes for cancer trials and match those specified in the final scope issued by NICE and are appropriate.

Table 3-4 Outcome measures included in IPASS

Outcome	Definition and measure	Timing of assessment
Progression free survival (primary)	From the date of randomisation to disease progression or death from any cause, RECIST	N/R
Overall survival (secondary)	From the date of randomisation to death from any cause	N/A
Tumour response	RECIST criteria	Every 6 weeks until disease progression
HRQoL (clinically relevant improvement)	Clinically relevant improvement was predefined as ≥ 6-point improvement for FACT-L and TOI or ≥2-point improvement for LCS maintained for at least 21 days. FACT-L and TOI, sum of the physical and functional well-being, and lung cancer symptoms domain scores of FACT-L scores. Symptoms were assessed by LCS score.	FACT-L questionnaire was collected at randomisation, week 1, then 3-weekly until day 127, then 6-weekly until disease progression, and at discontinuation.
Safety and tolerability	National Cancer Institute Common Terminology Criteria Version 3.0.	Patients receiving treatment or within 28 days of treatment

FACT-L= Functional Assessment of Cancer Therapy-Lung; N/A=not applicable; N/R=not reported; RECIST= Response Evaluation Criteria in Solid Tumours; TOI=Trial Outcomes Index

The primary endpoint in IPASS was PFS and this was assessed from the date of randomisation to disease progression (determined by RECIST) or death from any cause. Secondary endpoints included OS, tumour response rate, HRQoL, symptomatic improvement, safety and tolerability. Overall

survival was assessed from the date of randomisation to death from any cause. Overall survival is the most reliable and preferred end-point in most oncology RCTs;[25] however the OS data presented in the MS is based only on the results of an interim analysis (450 deaths, 37% maturity) as follow-up is still ongoing.

Assessment of efficacy and safety outcomes was unblinded. Blinding is especially important when the primary outcome is PFS and is reliant on investigator assessment.[25] In response to the ERG's clarification letter, AstraZeneca provided more detail regarding the timing of the measurement of PFS. Progression free survival is defined as the time from randomisation to the first documentation of objective disease progression or death from any cause. Patients without a PFS event at the time of the primary analysis were censored at the date of their last objective tumour assessment. This includes patients lost to follow up or who have withdrawn consent. The PFS for patients without post baseline tumour assessments was censored at time zero days.

The manufacturer does attempt to reduce the potential for bias by using RECIST criteria for defining progression and using tumour measurement rather than relying only on investigator assessment of tumour response. The MS (pg24) also states that '...additional analyses that investigated evaluation time bias did not indicate any bias in favour of gefitinib.'

3.1.7 Description and critique of the statistical approach used

Generally the statistical approach employed in the trial appeared appropriate. Based on the sample size method, IPASS was adequately powered for testing for non-inferiority and also superiority between the two arms in the overall trial population. However the trial was not adequately powered for the subgroup analysis based on EGFR M+ population.

In the MS, efficacy results were presented for the ITT population but not for the per protocol (PP) population. IPASS was a non-inferiority trial and the ERG expected[26] the results for the PP population to be described in the MS as well as the ITT results. However the ERG noted that as the majority of patients received the treatment to which they were randomised, differences between the two analyses would be expected to be small for the primary endpoint. The manufacturer confirmed in their clarification response that the result of the PFS analysis in the PP population is consistent with that of the primary pre-planned analysis of PFS in the ITT patient population.

Analysis of the primary endpoint (PFS) as described in the MS (Pg21/22) used a Cox proportional hazard model in the ITT population to assess the non-inferiority of gefitinib compared to paclitaxel/carboplatin adjusting for baseline covariates. The methodology is valid if the HR in the two comparative groups on Cox regression analysis remains constant regardless of the passage of time. In

the IPASS ITT analysis it does not seem likely that this prerequisite was met as can be seen from the period hazards and temporal trend in HR for the IPASS M+ subgroup displayed by the ERG in Figure 3-1. It is difficult, therefore, to decide what confidence may be placed in the overall therapeutic results from the primary outcome of the ITT analysis, or the significance of the influence of individual covariates used in the analysis.

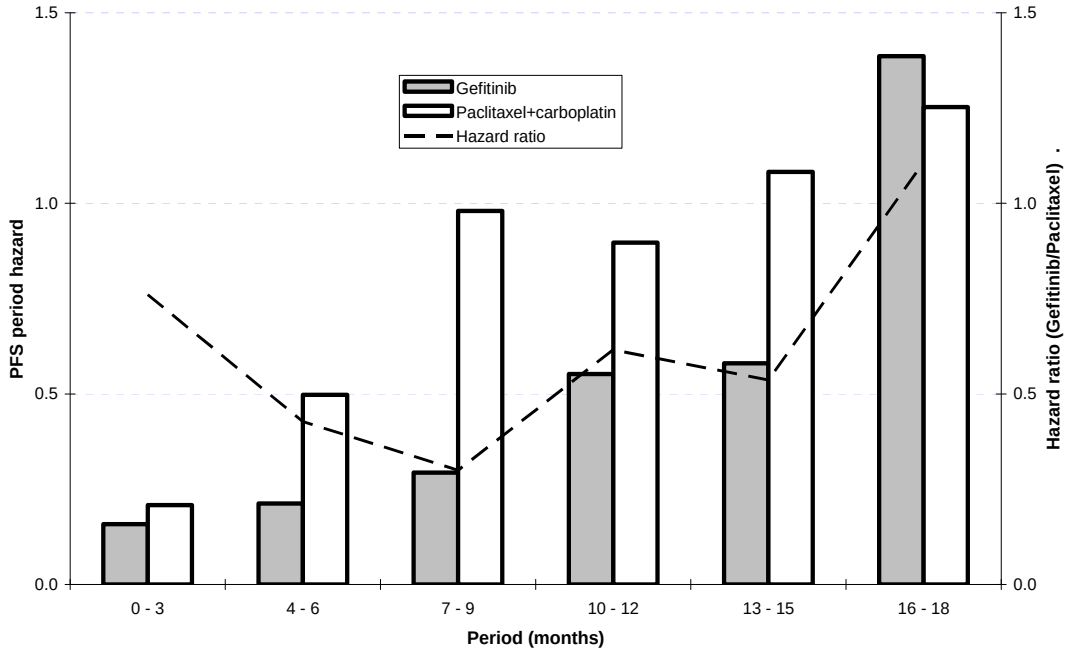

Figure 3-1 PFS period hazards and hazard ratio for IPASS M+ patients

The MS documents that OS estimates are based on the results of an interim analysis. In addition, potential confounding could have occurred due to 'cross-over' of treatment after disease progression which could also impact on the analysis of OS. Forty one percent of patients in the gefitinib arm received paclitaxel/carboplatin (39% was second line) and 13% of patients received other CTX following gefitinib. Fifty percent of the patients in the doublet CTX arm went on to receive an EGFR therapy at any point (38% gefitinib, 7% erlotinib and 6% other EGFR therapy) and 11% went on to receive other CTX. This 'cross-over' of treatment means that any benefit in OS cannot be confidently ascribed to the treatment to which patients were originally randomly assigned.

3.1.8 Summary statement

The systematic review in the MS included one published trial (IPASS) which compared gefitinib to paclitaxel/carboplatin. The search strategy was adequately reported although it did not include search terms for pemetrexed despite pemetrexed being included as a comparator in the scope. A search by the ERG confirmed that all published clinical trials (excluding the NEJSGS trial and First-SIGNAL

trial) were identified by the manufacturer. The validity of IPASS was discussed appropriately by the manufacturer. The clinical outcomes reported in IPASS are relevant outcomes as outlined in the final scope issued by NICE (OS, PFS, tumour response, HRQoL and AEs of treatment).

The main areas of concern relate to the generalisability of the clinical results from IPASS to the UK population and how EGFR testing within the NHS could become operational. In terms of statistical methodology the ERG is concerned that (i) the trial was not adequately powered for the subgroup analysis based on the EGFR M+ population, (ii) measurement of the primary outcome (PFS) may be unreliable as it was assessed without blinding and the HRs may have been inappropriately calculated using Cox proportional hazards[27] and (iii) the analysis of OS data was immature.

3.2 Summary of submitted evidence

3.2.1 Summary of results: direct evidence

The clinical effectiveness evidence in the MS is derived from a phase III multi-centre, open label RCT which compared gefitinib with paclitaxel/carboplatin. IPASS included 1217 patients (80% female) from 87 centres in East Asia (Hong Kong, elsewhere in China, Indonesia, Japan, Malaysia, the Philippines, Singapore, Taiwan and Thailand). Patients had locally advanced stage IIIB adenocarcinoma not amenable to local therapy or Stage IV (metastatic) disease with a WHO PS of 0 to 2. Patients had no prior CTX, biological or immunological therapy and were never smokers or light ex-smokers.

Demographic and baseline characteristics for IPASS are presented in Table 3-5 (MS, pg159).

Table 3-5 Demographic and baseline characteristics (ITT) in IPASS

	Gefitinib (n=609); n (%)	**Paclitaxel/Carboplatin (n=608); n (%)**
Age (Median)	57 years	57 years
Age (range)	24-84	25-84
Male	125 (20.5)	127 (20.9)
Female	484 (79.5)	481 (79.1)
Chinese	314 (51.6)	304 (50.0)
Japanese	114 (18.7)	119 (19.6)
Other East Asian	179 (29.4)	184 (30.3)
Other[a]	2 (0.3)	1 (0.2)
Never smoker	571 (93.8)	569 (93.6)
Light ex-smoker	37 (6.1)	38 (6.3)
Ex-smoker	1 (0.2)	1 (0.2)
WHO PS=0	157 (25.8)	161 (26.5)
WHO PS=1	391 (64.2)	382 (62.8)
WHO PS=2	61 (10.0)	65 (10.7)
Adenocarcinoma	581 (95.4)	591 (97.2)
Bronchocarcinoma	27 (4.4)	15 (2.5)
Unknown histology	1 (0.2)	2 (0.3)
Disease stage IIIB at entry	150 (24.6)	144 (23.7)
Disease stage metastatic at entry	459 (75.4)	463 (76.2)
Disease stage unknown at entry	0 (0)	1 (0.2)

[a]Patients belonging to East Asian ethnic groups other than Chinese and Japanese; WHO PS=World Health Organization performance status

The key evidence base for this appraisal is the subgroup of patients with EGFR M+ status which comprised 261 patients from the overall trial population. Relatively few baseline characteristics are reported by EGFR mutation status in the MS. However, in response to the ERG's clarification questions, the manufacturer provided additional information on this subgroup (Table 3-6).

Table 3-6 Demographic and baseline characteristics (EGFR M+ population) in IPASS

	Gefitinib (n=132); n (%)	**Carboplatin/Paclitaxel (n=129); n (%)**
Median age Range age	57 years 34-82	59 years 32-80
Male Female	24 (18.2) 108 (81.8)	26 (20.2) 103 (79.8)
Chinese Japanese Other East Asian[a] Other	41 (31.1) 68 (51.5) 23 (17.4) 0 (0)	35 (27.1) 61 (47.3) 33 (25.6) 0 (0)
Never smoked Light ex-smoker Ex-smoker (non-light)	124 (93.9) 7 (5.3) 1(0.8)	122 (94.6) 7(5.4) 0
WHO PS=0 WHO PS=1 WHO PS=2	30 (22.7) 89 (67.4) 13 (9.8)	39 (30.2) 83 (64.3) 7 (5.4)
Adenocarcinoma Bronchocarcinoma Unknown histology	122 (92.4) 10 (7.6) 0 (0)	125 (96.9) 4 (3.1) 0 (0)
Locally advanced disease at entry Metastatic disease at entry Disease stage unknown at entry	19 (14.8) 113 (85.6) 0 (0)	29 (22.5) 100 (77.5) 0 (0)

WHO=World Health Organization; a Patients belonging to East Asian ethnic groups other than Chinese and Japanese

Clinical efficacy

All of the trial data in the ERG report are taken directly from the MS unless otherwise stated. The results for the primary and secondary efficacy outcomes for the overall patient population in IPASS are summarised in Table 3-7.

Table 3-7 Key results of IPASS - overall population

	Gefitinib (n=609)	Paclitaxel/Carboplatin (n=608)	HR (95% CI)	OR (95% CI)	p value
Primary					
Median PFS (months)	5.7	5.8	0.74 (0.65-0.85)		<0.0001
Secondary					
Median OS (months)[a]	18.6	17.3	0.91 (0.76-1.10)		NR
Objective tumour response, n (%)	262 (43.0)	196 (32.2)		1.59 (1.25 to 2.01)	0.0001
Disease control, n (%)	444 (72.9)	482 (79.2)			

[a] interim analysis; CI=confidence interval; CR=complete response; HR=hazard ratio; OR=odds ratio; PFS=progression free survival; OS=overall survival; PR=partial response; SD=stable disease; objective tumour response = CR+PR; disease control=CR+PR+SD

Efficacy: Overall patient population in IPASS

Patients in the gefitinib arm had statistically significantly better PFS compared to patients in the paclitaxel/carboplatin arm (HR 0.74, 95% CI 0.65 to 0.85, p<0.0001), despite the lack of an apparent difference in median PFS (5.7 months for gefitinib treated patients, and 5.8 months for paclitaxel/carboplatin treated patients). The probability of being progression free favoured paclitaxel/carboplatin for the initial six months and gefitinib for the following 16 months. Twelve month PFS rates were 24.9% with gefitinib and 6.7% with paclitaxel/carboplatin.

The objective tumour response rate was significantly higher for patients in the gefitinib arm than patients in the paclitaxel/carboplatin arm (43.0% vs 32.2%, OR 1.59, 95% CI 1.25 to 2.01, p=0.0001).

Median OS was 18.6 months for patients in the gefitinib arm and 17.3 months for patients in the paclitaxel/carboplatin arm. Overall survival was similar for both groups (HR 0.91, 95% CI 0.76 to 1.10). The ERG highlights that these OS estimates are based on the results of an interim analysis (450 deaths, 37% maturity, follow-up ongoing).

Results of subgroup analysis of patients with evaluable EGFR mutation status (21% of overall population) are shown in Table 3-8.

Table 3-8 Key results of IPASS - by EGFR mutation status

	EGFR M+		EGFR M-		EGFR mutation status unknown	
	Gefitinib (n=132)	**Paclitaxel /Carboplatin (n=129)**	**Gefitinib (n=91)**	**Paclitaxel /Carboplatin (n=85)**	**Gefitinib (n=386)**	**Paclitaxel /Carboplatin (n=394)**
Primary						
Median PFS (months)	9.5	6.3	1.5	5.5	6.6	5.8
HR (95% CI)	0.48 (0.36-0.64)		2.85 (2.05-3.98)		0.68 (0.58-0.81)	
p value	<0.0001		<0.0001		<0.0001	
Secondary						
Median OS (months)	NR	19.5	12.1	12.6	18.6	16.9
HR (95% CI)	0.78 (0.50-1.20)		1.38 (0.92-2.09)		0.858 (0.677-1.089)	
Objective tumour response, n (%)	94 (71.2)	61 (47.3)	1 (1.1)	20 (23.5)	167(43.3)	115 (29.2)
Objective tumour response (OR, 95% CI)	2.75 (1.65 to 4.60)		0.04 (0.01 to 0.27)		1.88 (1.39 to 2.53)	
Disease control, n (%)	121 (91.7)	113 (87.6)	36 (39.6)	71 (83.5)	287 (74.4)	298 (75.6)
p value	0.0001		0.0013		<0.0001	

CR=complete response; HR=hazard ratio; PR=partial response; SD=stable disease; CI=confidence interval; NR=not reached; OR=odds ratio; OS=overall survival; PFS=progression free survival; objective tumour response=CR+PR; disease control=CR+PR+SD

Efficacy: EGFR M+ subgroup of patients

Patients in the gefitinib arm in the EGFR M+ subgroup had significantly longer PFS compared to EGFR M+ patients in the paclitaxel/carboplatin subgroup (HR 0.48, 95% CI 0.36 to 0.64, p<0.0001). Median PFS was 9.5 months for gefitinib EGFR M+ patients and 6.3 months for paclitaxel/carboplatin EGFR M+ patients.

The objective tumour response rate was significantly higher for the gefitinib EGFR M+ subgroup than for the paclitaxel/carboplatin EGFR M+ subgroup (71.2% vs 47.3%, OR 2.75, 95% CI 1.65 to 4.60, p=0.0001).

There was no significant difference in OS between gefitinib and paclitaxel/carboplatin in EGFR M+ patients (HR 0.78, 95% CI 0.50 to 1.20). The ERG highlights that these OS estimates are based on the results of an interim analysis (450 deaths, 37% maturity, follow-up ongoing).

Efficacy: EGFR M- subgroup of patients

Patients in the gefitinib arm in the EGFR M- subgroup had significantly shorter PFS compared to EGFR M- patients in the paclitaxel/carboplatin subgroup (HR 2.85, 95% CI 2.05 to 3.98, p<0.0001). Median PFS was 1.5 months for gefitinib EGFR M- patients and 5.5 months for paclitaxel/carboplatin EGFR M- patients.

The objective tumour response rate was significantly lower for the gefitinib EGFR M- subgroup than the paclitaxel/carboplatin EGFR M- subgroup (1.1% vs 23.5%, OR 0.04, 95% CI 0.01 to 0.27, p=0.0013).

There was no significant difference in OS between gefitinib and paclitaxel/carboplatin in EGFR M- patients (HR 1.38, 95% CI 0.92 to 2.09). However this is based on the results of an interim analysis for OS (450 deaths, 37% maturity, follow-up ongoing).

Efficacy: Unknown EGFR mutation status subgroup of patients

The results for patients with unknown mutation status were similar to those of the overall population (ITT analysis; MS, pg27).

Planned subgroup analyses

Planned subgroup analyses were conducted comparing PFS between treatments in groups defined by PS, smoking history, gender, age at randomisation and disease stage at screening. In all subgroups, PFS was statistically or numerically longer with gefitinib compared with paclitaxel/carboplatin treatment.

Health related quality of life

The HRQoL outcome in the MS was defined as clinically relevant improvement as measured using the total score and Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy – Lung (FACT-L) questionnaire.[3] The TOI is derived from sum of the physical and functional well-being, and lung cancer symptoms (LCS) domain scores of FACT-L.[3] The 'evaluable for HRQoL' population was 1151 of the 1217 ITT population which included all patients with a baseline and at least one post-baseline QoL assessment that could be evaluated.

Health related quality of life: overall IPASS trial population

Significantly more patients in the gefitinib arm had a clinically relevant improvement in HRQoL compared with patients in the paclitaxel/carboplatin arm (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 (LCS) were similar for patients in the gefitinib arm and patients in the paclitaxel/carboplatin arm (OR 1.13, 95% CI 0.90 to 1.42, p=0.3037).

Health related quality of life: EGFR M+ subgroup population

Significantly more patients in the gefitinib EGFR M+ subgroup had a clinically relevant improvement in HRQoL and disease symptoms compared with EGFR M+ patients in the paclitaxel/carboplatin arm (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 1.58-4.62, p=0.0003).

Time to worsening of HRQoL and disease related symptoms was longer in the gefitinib EGFR M+ patients compared with paclitaxel/carboplatin EGFR M+ patients (median range 11.3 to 16.6 months vs 2.9 to 3.0 months respectively).

Health related quality of life: EGFR M- subgroup population

Significantly more patients in the paclitaxel/carboplatin arm EGFR M- subgroup had a clinically relevant improvement in HRQoL and disease related symptoms compared with patients in the gefitinib EGFR M- subgroup (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 0.14-0.55, p=0.0002).

Time to worsening of HRQoL and disease related symptoms was similar or shorter in the gefitinib EGFR M- patients compared with paclitaxel/carboplatin EGFR M- patients (median of 1.4 months vs 1.4 to 4.2 months, respectively).

Safety

The ‘evaluable for safety’ population was 1196 of the 1217 ITT population which included all patients who received at least one dose of the study treatment. Table 3-9 shows patient exposure to treatment. Patients in the gefitinib arm who were identified as EGFR M+ had a median exposure to gefitinib of 8.3 months compared with a median exposure of 1.6 months for patients identified as EGFR M-. This variance in exposure to treatment may have had a significant impact on safety results; however the MS does not provide an analysis of AEs according to EGFR mutation status.

Table 3-9 Patient exposure to treatment in IPASS

	Median exposure to treatment (months)	Number (%) of patients
Gefitinib overall population	5.6	609 (50%)
Gefitinib EGFR M+	8.3	132(10.8%)
Gefitinib EGFR M-	1.6	91(7.5%)
Gefitinib unknown status	5.9	384(31.6%)
Paclitaxel/carboplatin overall population	4.1	608(50%)
Paclitaxel/carboplatin EGFR M+	4.1	129(10.6%)
Paclitaxel/carboplatin EGFR M-	4.1	85(7%)
Paclitaxel/carboplatin EGFR unknown status	4.1	375(30.8%)

Table 3-10 (MS, pg62) summarises common AEs (events that occurred in at least 10% of patients in either treatment group, either while the patients were receiving treatment or during the 28 day follow-up, and if there was at least a 5% difference between groups).

Table 3-10 Common adverse events

Adverse Events*	Gefitinib (n=607)		Paclitaxel/carboplatin (n=589)	
	All adverse events, n (%)	CTC Grade 3 /4/5, n (%)	All adverse events, n (%)	CTC Grade 3/4/5, n (%)
Rash/acne[a]	402 (66.2)	19 (3.1)	132 (22.4)	5 (0.8)
Diarrhoea	283 (46.6)	23 (3.8)	128 (21.7)	8 (1.4)
Dry skin	145 (23.9)	0 (0)	17 (2.9)	0 (0)
Anorexia[a]	133 (21.9)	9 (1.5)	251 (42.6)	16 (2.7)
Pruritus[a]	118 (19.4)	4 (0.7)	74 (12.6)	1 (0.2)
Stomatitis[a]	103 (17.0)	1 (0.2)	51 (8.7)	1 (0.2)
Asthenic conditions[a]	102 (16.8)	2 (0.3)	259 (44.0)	11 (1.9)
Nausea[a]	101 (16.6)	2 (0.3)	261 (44.3)	9 (1.5)
Paronychia	82 (13.5)	2 (0.3)	0 (0)	0 (0)
Vomiting	78 (12.9)	1 (0.2)	196 (33.3)	16 (2.7)
Constipation	73 (12.0)	0 (0)	173 (29.4)	1 (0.2)
Alopecia	67 (11.0)	0 (0)	344 (58.4)	0 (0)
Neurotoxicity[a]	66 (10.9)	2 (0.3)	412 (69.9)	29 (4.9)
Myalgia	47 (7.7)	3 (0.5)	186 (31.6)	10 (1.7)
Arthralgia	39 (6.4)	1 (0.2)	113 (19.2)	6 (1.0)
Neutropenia (Any)[b]	-	22 (3.7)	-	387 (67.1)
Febrile neutropenia	1 (0.2)	1 (0.2)	17 (2.9)	17 (2.9)
Anaemia[b]	-	13 (2.2)	-	61 (10.6)
Leucopenia[b]	-	9 (1.5)	-	202 (35.0)

*Events while on randomised treatment or during the 28-day follow-up
[a]Grouped term (sum of high-level and preferred terms)
[b]Data from laboratory reports. Worsening in laboratory value (absolute neutrophil count for neutropenia, hemoglobin for anaemia, and white blood cell count for leucopenia) from baseline to CTC grade 3-4. n=599 with gefitinib and 577 with paclitaxel/carboplatin
CTC= Common Terminology Criteria

Table 3-10 shows that rash/acne, diarrhoea, dry skin, pruritus, stomatatis and paronychia occurred more often in patients in the gefitinib arm compared with patients in the paclitaxel/carboplatin arm (at least 5% difference between groups and occurred in at least 10% of patients); it also shows that anorexia, asthenic conditions, nausea, vomiting, constipation, alopecia, neurotoxicity, myalgia, arthralgia, neutropenia (any), febrile neutropenia, anaemia and leucopenia occurred more often in patients in the paclitaxel/carboplatin arm than in patients in the gefitinib arm.

The MS reports that gefitinib was associated with fewer grade 3 or 4 AEs (28.7% versus 61.0%), fewer dose modifications due to toxicity (16.1% versus 35.2% for carboplatin and 37.5% for paclitaxel), and fewer AEs leading to discontinuation (6.9% versus 13.6%) than paclitaxel/carboplatin. In the gefitinib arm there were 3.8% of patients who experienced AEs which led to death and 2.7% of patients who had serious AEs which caused hospitalisation. In the

paclitaxel/carboplatin arm there were 13.8% of patients who experienced AEs which led to death and 13.1% of patients who had serious AEs which caused hospitalisation.

The MS reports that fewer patients in the gefitinib arm were hospitalised because of haematological AEs (four patients [0.7%] in the gefitinib arm and 18 [3.1%] in the paclitaxel/carboplatin arm). For three of the four patients in the gefitinib arm, the hospitalisations occurred after discontinuation of gefitinib treatment and whilst receiving second-line paclitaxel/carboplatin treatment. These data included hospitalisations which occurred within 28 days of the last dose.

Interstitial lung disease-type events occurred in 16 (2.6%) patients in the gefitinib arm and led to three deaths, and occurred in eight (1.4%) patients in the paclitaxel/carboplatin arm and led to one death.

The MS (pg63) reports that in general the safety profile for gefitinib by EGFR mutation status was consistent with the overall population. Some gefitinib specific AEs (such as rash) were higher in EGFR M+ patients in the gefitinib arm or lower in EGFRM- patients (such as dry eye, diarrhoea, pruritus) compared with all patients in the gefitinib arm.

The ERG notes that the safety data presented in the MS is specific only to the use of gefitinib in IPASS. However, the ERG reports that the limited data presented in the MS is consistent with the pooled safety data in the SmPC[28]: “In the pooled dataset from the ISEL, INTEREST and IPASS phase III clinical trials (2,462 IRESSA treated patients), the most frequently reported adverse drug reactions (ADRs), occurring in more than 20 % of the patients, are diarrhoea and skin reactions (including rash, acne, dry skin and pruritus). Adverse drug reactions usually occur within the first month of therapy and are generally reversible. Approximately 8 % of patients had a severe ADR (CTC grade 3 or 4). Approximately 3 % of patients stopped therapy due to an ADR. Interstitial lung disease has occurred in 1.3 % of patients, often severe (CTC grade 3 or 4). Cases with fatal outcomes have been reported”.

3.2.2 Summary of results: Meta-analysis

Meta-analysis: Description

The manufacturer identified two additional trials (First-SIGNAL trial and the NEJGSG trial) during late stage production of the MS; the ERG notes that the First-SIGNAL trial was sponsored by AstraZeneca. Both trials compared gefitinib with doublet CTX for the treatment of chemotherapy-naïve patients with predominantly adenocarcinoma histology. The manufacturer considered both trials for inclusion in a meta-analysis.

The First-SIGNAL trial compared gefitinib to gemcitabine/cisplatin in the first-line treatment of patients, never smokers, with adenocarcinoma histology. However, as the number of EGFR M+ patients was small (n=42) and the comparator was not paclitaxel/carboplatin, this study was excluded from the meta-analysis by the manufacturer.

The NEJGSG trial compared use of gefitinib to paclitaxel/carboplatin in the first-line treatment of EGFR M+ patients with NSCLC and is included within the meta-analysis. The NEJGSG trial is used in the MS as supporting evidence to IPASS and so a summary of baseline characteristics and the manufacturer's critique of this trial are provided for information in Appendix 2.

In IPASS the HR for PFS in EGFR M+ patients was reported as 0.48 (95% CI 0.36 to 0.64, p<0.0001). In NEJGSG, the HR for PFS in EGFR M+ patients was reported as 0.357 (95% CI 0.25 to 0.51, p<0.001).The meta-analysis of PFS demonstrated significant improvement in PFS for EGFR M+ patients in the gefitinib arm compared with EGFR M+ patients in the paclitaxel/carboplatin arm (HR 0.43, 95% CI 0.34 to 0.53), p<0.001). Fixed effects and random effects models demonstrated consistent results.

Table 3-11 shows the results of the meta-analyses of grade 3/4/5 AEs from IPASS and the NEJGSG trial. Significantly more patients in the gefitinib arm experienced diarrhoea (fixed effects) although this became non-significant at the 0.05 level when a random effects analysis was applied. Significantly more patients in the paclitaxel/carboplatin arm experienced anaemia and neutropenia compared with patients in the gefitinib arm.

Table 3-11 Results of the meta-analyses of grade 3/4/5 AEs from IPASS and the NEJGSG trial

Adverse Event (Grade 3/ 4/5)	Mean Odds Ratio	95% Confidence Interval		p-value	Heterogeneity Statistics
		Lower	Upper		
Anaemia					
- Fixed Effects	0.12	0.03	0.47	0.002	Chi^2=0.19, p=0.66
- Random Effects	0.13	0.03	0.49	0.003	I^2=0%
Diarrhoea					
- Fixed Effects	5.78	1.01	33.11	0.05	Chi^2=0.19, p=0.66
- Random Effects	5.55	0.95	32.36	0.06	I^2=0%
Fatigue					
- Fixed Effects	0.77	0.19	3.13	0.72	Chi^2=2.73, p=0.10
- Random Effects	0.75	0.03	16.42	0.86	I^2=63.4%
Neutropenia					
- Fixed Effects	0.01	0.00	0.03	<0.00001	Chi^2=0.04, p=0.85
- Random Effects	0.01	0.00	0.03	<0.00001	I^2=0%,
Rash					
- Fixed Effects	2.50	0.71	8.87	0.16	Chi^2=0.71, p=0.40
- Random Effects	2.26	0.61	8.37	0.22	I^2=0%,

(Odds Ratio [OR]<1 gefitinib is better than paclitaxel/carboplatin; OR>1gefitinib is worse than paclitaxel/carboplatin)

Meta-analysis: ERG critique

The manufacturer made a decision to undertake a standard meta-analysis on data from IPASS and the NEJGSG trial on the grounds that the two studies had the same comparator (paclitaxel/carboplatin); one of the reasons that the manufacturer excluded the First-SIGNAL trial from the MA was because it did not have this comparator. The results from the manufacturer's own MTC demonstrate that paclitaxel/carboplatin and gemcitabine/cisplatin are not substantially different in terms of clinical benefit and improved tolerability; the ERG believes that the First-SIGNAL trial could therefore have been appropriately included in the MA alongside the NEJGSG trial.

Furthermore, the ERG notes that the NEJGSG trial is ongoing and that only an interim analysis of PFS is available. The baseline demographic characteristics of patients in NEJGSG appear to demonstrate possible differences between groups for smoking status, adenocarcinoma histology and disease stage classification (MS, pg39) and these could have been explored further by the manufacturer. In addition, the MS (pg42) states that patients in the NEJGSG trial were similar to patients in IPASS. However there appear to be differences in baseline characteristics between IPASS patients and patients in NEJGSG; IPASS comprised younger patients (57 years vs 63 years), included a greater percentage of females (80% vs 63%), did not include current smokers (35-42% current

smokers in NEJGSG trial), included more patients with PS of 2 (10% vs 1-2%) and had more stage IIIB patients at baseline (24-25% vs 11-18%).

For the primary outcome of interest (PFS), the results from the meta-analysis are consistent with the results from IPASS. However, the ERG believes that the best evidence available to assess the clinical effectiveness of gefitinib compared to paclitaxel/carboplatin is from the head to head comparison in IPASS or from a MA which includes IPASS, NEJSGS trial and First-SIGNAL trial.

3.2.3 Summary of results: Mixed treatment comparison

Mixed treatment comparison: description

The manufacturer carried out a systematic review and MTC of RCTs comparing doublet CTX in chemotherapy-naïve patients with NSCLC; paclitaxel/carboplatin evidence was used as a baseline comparator for all MTC analyses. The systematic review identified 29 trials (original MTC: n=28; updated MTC: n=29) for inclusion in the network that formed the basis for the MTC of doublet CTX. Data were extracted and analysed for clinical efficacy (PFS, OS and objective response) and tolerability (anaemia, diarrhoea, fatigue, febrile neutropenia, nausea and vomiting) for use in the economic evaluation. The following strong assumption was made in the MTC (MS, pg46): "…the relative effect of alternative doublet CTX compared to paclitaxel/carboplatin in an unselected NSCLC population would be obtained and the relative estimates will be applied to a baseline event rate in EGFR M+ patients who received paclitaxel/carboplatin in IPASS." The results of the original MTC conducted by the manufacturer did not identify an individual doublet CTX as offering both substantial clinical benefit and most favourable tolerability over the other doublet CTX regimens assessed. The manufacturer concluded that the interplay of the different outcomes (efficacy and tolerability) in the economic evaluation would determine which type of CTX would offer best value to the NHS. However the results of the updated MTC, described in the manufacturer's clarification response, show that pemetrexed (for non-squamous patients) is much closer to gefitinib in terms of effects on PFS and OS and that pemetrexed is significantly better than the other doublet CTXs; pemetrexed is given due consideration in the economics section of the ERG report (pg99).

Via the clarification letter, the ERG asked the manufacturer to provide (i) a network diagram for each outcome of interest (PFS, OS and objective response rate) and (ii) all data points used in the MTC analyses including WinBUGS codes used for each analysis. The manufacturer responded with diagrams and tables of data, confirmed that no assumptions were made with regards to prior distributions (i.e. they were specified as uninformed or "flat" priors) and provided details of the WinBUGS codes used.

Mixed treatment comparison: ERG critique

Mixed treatment comparisons can be useful where randomised head to head comparison data are not available. For this purpose the ERG believes that the MTC methods described in the MS comparing paclitaxel/carboplatin with a range of doublet CTX regimens in unselected populations are appropriate; relevant outcomes are compared and the strength of randomisation within each study is maintained.

However, the manufacturer makes a strong assumption in order to allow comparisons of doublet CTX with gefitinib in the health economic evaluation. The manufacturer assumes that, by applying the relative effect of alternative doublet CTX compared to paclitaxel/carboplatin (as identified by the MTC) to the "baseline" event rate in EGFR M+ patients who received paclitaxel/carboplatin in IPASS, the best estimate of the effect of the alternative doublet CTX in an EGFR M+ is obtained. This assumes that the EGFR mutation status of patients has no impact on treatment outcomes if patients are receiving doublet CTX. The ERG believes this assumption is too strong as it is wholly reliant on the results of a subgroup analysis from a single RCT of patients with adenocarcinoma histology (IPASS). The ERG concludes that the evidence base for the studies used in the comparison of gefitinib with doublet CTX may not be generalisable to the EGFR M+ population.

Furthermore, the approach taken by the manufacturer for the EGFR M+ comparison can be described as a 'naive comparison' since the manufacturer is comparing treatment groups directly as though they had been randomised against each other; the ERG considers this approach to be unreliable as the benefit of randomisation within the individual trials is lost.

As part of the MTC, the manufacturer extracted unreported outcome statistics for some studies from two published meta-analysis papers.[29, 30] The ERG reviewed these two papers and discovered that different methods, including the Pamar's approach,[31] were used to estimate unreported HRs. From the ERG perspective, it is unclear why the manufacturer did not adapt the Pamar's approach[31] to estimate unreported HRs for OS and PFS for all relevant studies with reported statistics for survival outcomes. Thus, the ERG believes the results from the MTC should be carefully considered due to potential selection bias regarding the studies included in the MTC.

The MS stated that the outcomes (OS, PFS, tumour response) used in the MTC were assessed in the ITT populations of the included studies. However after cross-checking the source data, the ERG discovered that the outcome data from two included trials (Mazzanti et al[32] and Schiller et al[15]) were based on analyses that did not include all of the patients who were randomised. The ERG also noted

that the data extracted from Helbekkmo et al[33] did not come from either of the two published meta-analysis papers as cited by the manufacturer.

While baseline characteristics were well balanced between treatment arms within trials, the ERG notes that important differences were apparent across most trials in terms of varying proportions of males, number of patients with stage IV disease, ethnicity, histology type and PS. The MS did not present any SA to describe these subgroups.

As the only trials providing evidence about gefitinib compared to doublet CTX in EGFR M+ patients are IPASS (gefitinib vs paclitaxel/carboplatin), NEJGSG trial (gefitinib vs paclitaxel/carboplatin) and the First-SIGNAL trial (gefitinib vs gemcitabine/cisplatin**), the ERG is uncertain why the manufacturer did not perform an indirect comparison or MTC between gefitinib and doublet CTX in the EGFR M+ population using these three available trials.**

3.3 Summary of results

3.3.1 IPASS: Clinical results

IPASS demonstrates a statistically significant beneficial effect of gefitinib compared with paclitaxel/carboplatin on PFS in the overall trial population (HR 0.74, 95% CI 0.65 to 0.85, p<0.0001, n=1217). Median PFS was 5.7 months for gefitinib treated patients and 5.8 months for paclitaxel/carboplatin treated patients.

EGFR mutation status is associated with differential efficacy of gefitinib. Subgroup analysis in patients with EGFR M+ status (n=261) demonstrated that PFS was significantly longer in gefitinib patients compared with paclitaxel/carboplatin patients (HR 0.48; 95% CI 0.36 to 0.64, p<0.001). Median PFS was 9.5 months for gefitinib treated EGFR M+ patients and 6.3 months for paclitaxel/carboplatin treated EGFR M+ patients.

Subgroup analysis in patients with EGFR M- status (n=176) demonstrated that PFS was significantly shorter in gefitinib patients compared with paclitaxel/carboplatin patients (HR 2.85, 95% CI 2.05 to 3.98, p<0.0001). Median PFS was 1.5 months for gefitinib treated EGFR M- patients and 5.5 months for paclitaxel/carboplatin treated EGFR M- patients.

Gefitinib appears to have a better safety profile, improved HRQoL and symptom control in EGFR M+ patients compared with paclitaxel/carboplatin. The MS reports that in general the safety profile for gefitinib by EGFR mutation status was consistent with the overall population.

3.3.2 IPASS: Clinical issues

The clinical results of IPASS do not appear to be generalisable to the patient population in England and Wales.

3.3.3 Meta-analysis: results

Combining clinical data from IPASS and NEJGSG for EGFR M+ patients, the manufacturer was able to demonstrate significant improvement in PFS for EGFR M+ patients in the gefitinib arm compared with EGFR M+ patients in the paclitaxel/carboplatin arm.

3.3.4 Meta-analysis: issues

The ERG believes that the First-SIGNAL trial could also have been appropriately included in the MA alongside the NEJGSG trial.

3.3.5 Mixed treatment comparison: results

The results of the original MTC conducted by the manufacturer did not identify an individual doublet CTX as offering both substantial clinical benefit and the most favourable tolerability over the other doublet CTX regimens assessed. However the results of the updated MTC, described in the manufacturer's clarification response, show that pemetrexed (for non-squamous patients) is much closer to gefitinib in terms of effects on PFS and OS and that pemetrexed is significantly better than the other doublet CTXs.

3.3.6 Mixed treatment comparison: issues

The ERG considers that the MTC is weak as it is reliant on the very strong assumption that EGFR mutation status does not affect treatment outcomes if patients are receiving doublet CTX. The ERG critiqued the MTC on a number of methodological issues.

4 ECONOMIC EVALUATION

4.1 Introduction

This section provides a structured critique of the economic evidence submitted by AstraZeneca in support of gefitinib as a first-line treatment for patients who are EGFR M+. The two key components of the economic evidence presented in the MS are (i) a systematic review of the relevant literature (ii) a report of the manufacturer's *de novo* economic evaluation. See Table 4-1 for a summary of key information points. The manufacturer also provided an electronic version of the EXCEL-based economic model.

Table 4-1 Key information in the MS

Key information	**Pages in the MS**	**Key tables/figures in the MS**
Details of the systematic review of the economic literature	69-74	
Technology, patients, comparator, perspective and time horizon	74-76	
Framework for model-based evaluation	77-88	Fig 19-23, Table 20-22
Clinical evidence used in economic evaluation	88-89	
Measurement and valuation of health benefits	89-92	Table 23-24, Fig 24-25
Resource identification, measurement and valuation	92-99	Table 24-29
Methods of sensitivity analysis and validity assessment	99-104	Table 30-32
Results – base-case analysis	104-106	Table 33-35
Results – subgroup analysis	106-107	Table 36-38
Results – sensitivity analysis	107-112	Fig 26-28, Table 39-42
Assessment of factors relevant to the NHS and other parties	112-118	Table 43-45

4.2 Overview of manufacturer's cost-effectiveness review

The manufacturer performed an update of a systematic review originally carried out in June 2006. The objective of the systematic review was to identify cost-effectiveness analyses for the first-line treatment of NSCLC.

4.2.1 Identification and description of studies

The appendices included in the MS included full details of the (original and updated) search strategies used, including all of the search terms, text words, subject headings and the relationship between the search terms. In contrast to the clinical search strategy, gefitinib and pemetrexed were specified in the economics search strategy.

No date restrictions were in place and the actual dates that the searches were conducted were stated. The databases searched in 2009 were: Medline, EMBASE, Medline (R) In-Process, CINAHL and NHS Economic Evaluation Database. Recent conference proceedings from the American Society of Clinical Oncology, European CanCer Organisation, World Conference on Lung Cancer, American Association for Cancer Research, European Society for Medical Oncology, European Organization for Research and Treatment of Cancer-National Cancer Institute-American Association for Cancer Research and the International Society for Pharmacoeconomics and Outcomes Research were also searched. International Health Technology Assessment reports were hand-searched to April 2009.

The MS provided a study flow diagram (Figure 4-1) which showed how the papers were identified for potential inclusion in the systematic literature review

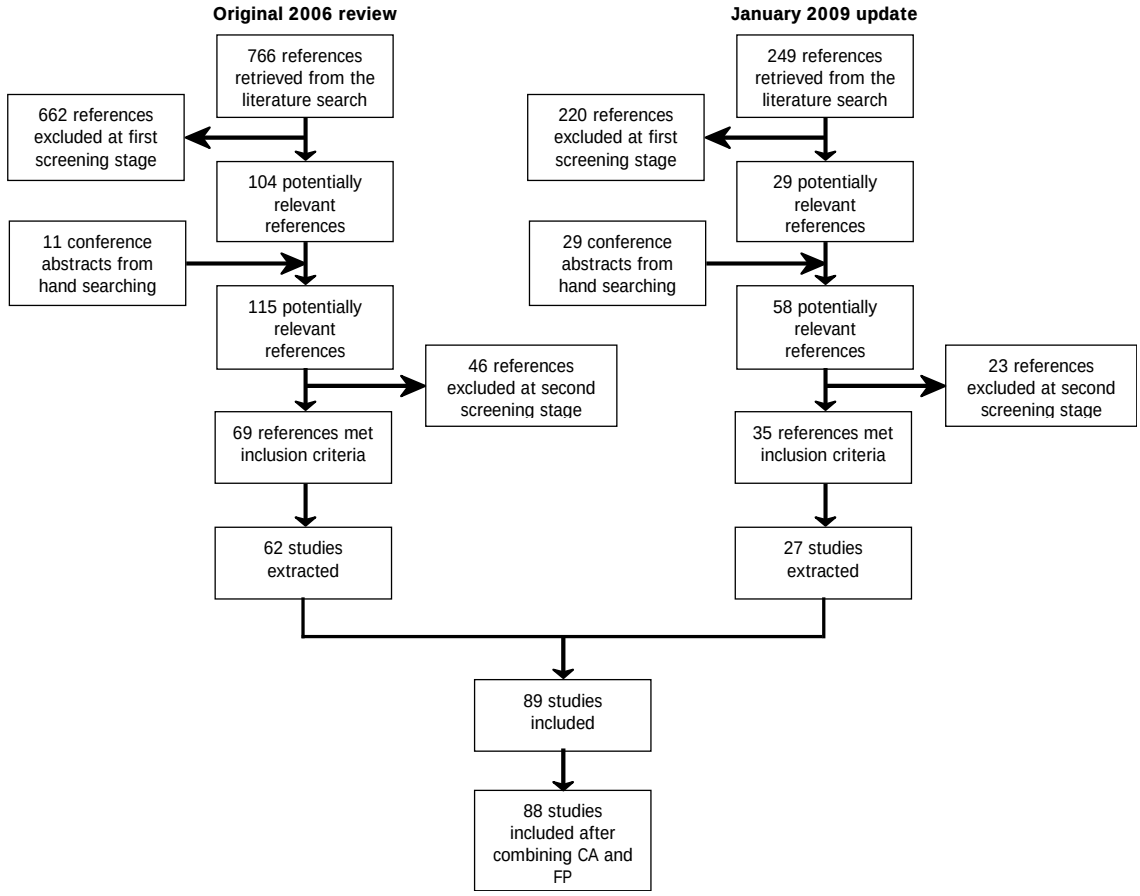

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Figure 4-1 Literature review flow diagram

Of the 1015 studies identified for potential inclusion in the review, 88 were judged to fit the inclusion criteria. The MS (pg70) states that only those studies "…of patients with IIIb/IV non small cell lung cancer who are treated with treatments currently used in clinical practice for this indication were included". The ERG is of the opinion that these inclusion criteria are somewhat vague. The MS goes

on to state that four of the 88 studies were considered "…to be of potential relevance to the decision problem outlined in the NICE scope" (MS, pg70). However, on closer inspection, the manufacturer concludes that these four papers could also be excluded from the review due to one or more of the following: (i) study evaluated second-line therapy (ii) the analytical approach was not consistent with the NICE reference case (iii) cost-effectiveness analyses were not considered generalisable to the UK. The ERG believes the manufacturer's use of inclusion/exclusion criteria to be inconsistent. However, as no studies were found by the manufacturer that evaluated the cost effectiveness of gefitinib as a first-line treatment for patients with NSCLC, the manufacturer's application of inclusion/exclusion criteria is of limited importance.

4.3 Summary and conclusions

The manufacturer's review of the published cost-effectiveness literature describing gefitinib as a first-line treatment of patients with NSCLC did not identify any relevant cost-effectiveness studies. The ERG is satisfied with the manufacturer's search strategy and is reasonably confident that the manufacturer did not miss any relevant published articles. However, the manufacturer did not appear to undertake any searches of the unpublished literature, which may mean that relevant unpublished studies were omitted. In summary, the likelihood that the manufacturer missed relevant published cost-effectiveness studies describing gefitinib is minimal.

4.4 Overview of manufacturer's economic evaluation

The purpose of the manufacturer's *de novo* of the economic evaluation is to estimate the cost effectiveness of gefitinib compared with doublet CTX in the first-line treatment of patients with NSCLC with EGFR M+ status.

4.4.1 Description of manufacturer's economic model

An Excel based 21-day Markov model was developed to examine the differences in health benefits (QALYs) and overall treatment costs between the competing interventions. Chemotherapy-naïve patients with NSCLC who have tested positive for EGFR mutations enter the model with stable disease and are then treated with either gefitinib or doublet CTX. Patients exit the model when they have died.

The base case analysis includes a comparison in which all chemotherapy-naïve patients with NSCLC are tested for their EGFR mutation status. The analysis only assesses the incremental benefits and costs in patients that are confirmed as being EGFR M+.

The structure of the manufacturer's model is shown in Figure 4-2.

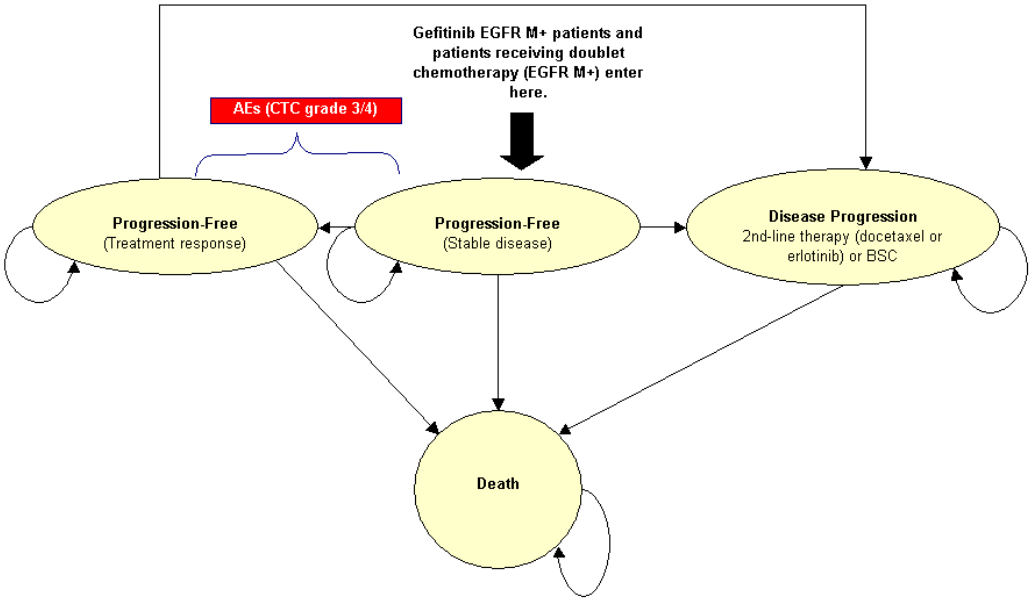


Figure 4-2 Structure of the manufacturer's model

4.5 Parameters and values

The key variables and assumptions used in the cost-effectiveness analysis are presented in Table 4-2 to Table 4-4.

Table 4-2 Key model parameters

Model Variable	Value	Source
Discount rates		
Costs	3.5%	NICE reference case[34]
Benefits	3.5%	NICE reference case[34]
Patient characteristics		
EGFR M+ (overall population)	16.6%	Rosell[9]
EGFR M+ (adenocarcinoma)	16%	Gefitinib SmPC[28]
EGFR M+ (non-adenocarcinoma)	3%	Gefitinib SmPC[28]
EGFR M+ (female)	17%	Gefitinib SmPC[28]
EGFR M+ (male)	6%	Gefitinib SmPC[28]
EGFR M+ (never smoker)	40%	Gefitinib SmPC[28]
EGFR M+ (ever smokers)	7%	Gefitinib SmPC[28]
Post-progression active treatment	61%	IPASS
Mean Body Surface Area (m^2)	1.82	ERG report[35]
GCSF use of prophylaxis of neutropenia	21.7%	IPASS

Treatment Response		
Gefitinib EGFR M+	71.2%	IPASS
Pac/carb EGFR M+	47.3%	IPASS
Gem/carb EGFR M+	43.3%	MTC (MS, section 6.6)
Vin/cis EGFR M+	49.5%	MTC (MS, section 6.6)
Gem/cis EGFR M+	50.8%	MTC (MS, section 6.6)
Hazard Ratio PFS		
Gefitinib EGFR M+	0.43	Meta-analysis (MS, section 6.5)
Gem/carb EGFR M+	1.23	MTC (MS, section 6.6)
Vin/cis EGFR M+	0.99	MTC (MS, section 6.6)
Gem/cis EGFR M+	0.92	MTC (MS, section 6.6)
Hazard Ratio OS		
Gefitinib EGFR M+	0.78	IPASS
Gem/carb EGFR M+	0.95	MTC (MS, section 6.6)
Vin/cis EGFR M+	1.08	MTC (MS, section 6.6)
Gem/cis EGFR M+	0.92	MTC (MS, section 6.6)

vin/cis= vinorelbine/cisplatin; gem/cis= gemcitabine/cisplatin; pac/carb= paclitaxel/carboplatin; gem/carb= gemcitabine/carboplatin; PFS=progression free survival; OS=overall survival; SmPC= summary of product characteristics; MTC= mixed treatment comparison; ERG= Evidence Review Group; GCSF= granulocyte colony stimulating factor

Table 4-3 Key model parameters: utility

	Value	Source
Mean utility values		
Baseline utility (stable disease no AEs)	0.6532	Nafees[36]
Treatment response (increment)	0.0193	Nafees[36]
Utility decrements		
Disease progression	-0.1798	Nafees[36]
Progression free iv therapy	-0.0425	ERG report[37]
Progression free oral therapy	-0.0139	ERG report[37]
CTC grade 3 or 4 adverse event		
Febrile neutropenia	-0.0900	Nafees[36]
Neutropenia	-0.0897	Nafees[36]
Fatigue	-0.0735	Nafees[36]
Nausea and vomiting	-0.0480	Nafees[36]
Diarrhoea	-0.0468	Nafees[36]
Hair loss (grade 2)	-0.0450	Nafees [36]
Rash	-0.0325	Nafees[36]
Anaemia	-0.0735	Eli Lilly[38]

AEs=adverse events; CTC=common terminology criteria

4.5.1 Treatment effectiveness within the MS

The treatment effectiveness data used in the manufacturer's model are taken from a variety of sources. The HR for PFS for gefitinib EGFR M+ patients is derived from the MA conducted by the manufacturer and the HR for OS for gefitinib EGFR M+ patients is taken directly from IPASS. Estimates of the HRs for PFS and OS for the doublet CTX regimens are sourced indirectly from the MTC conducted by the manufacturer. The ERG's critique of the MA and the MTC is presented in Section 4.

4.5.2 Survival

Overall survival was extrapolated beyond the IPASS trial data cut off for the primary analysis. This data cut off took place after 450/1217 deaths had occurred (37% maturity). A Weibull regression analysis of IPASS was conducted to model (costs and) outcomes beyond the IPASS trial follow-up period. Covariates in the Weibull regression model included mutation status, gender, PS (0 or 1 versus >1) and smoking status (never smoker versus smoker). The ERG is aware that estimates of OS taken directly from IPASS are based on an interim analysis only.

4.5.3 Population

Chemotherapy-naïve patients with EGFR M+ who are eligible to receive doublet CTX are included in the economic evaluation. The population in the manufacturer's economic evaluation is based on the IPASS population. The ERG highlights that the patients in IPASS are very different from chemotherapy-naïve patients with NSCLC who would be eligible for treatment in England and Wales.

4.5.4 Comparator technology

In the economic evaluation conducted by the manufacturer gefitinib is compared with doublet CTX. The manufacturer limits consideration to four different CTX combinations: paclitaxel/carboplatin; gemcitabine/cisplatin; gemcitabine/carboplatin and vinorelbine/cisplatin. The ERG notes that other doublet CTX regimens are available to chemotherapy-naïve patients with NSCLC in England and Wales and include docetaxel/cisplatin, docetaxel/carboplatin and pemetrexed/cisplatin. By not including the full range of available treatments, the ERG is concerned that comparison of all relevant treatment options for the target population has not been undertaken by the manufacturer.

4.5.5 Health related quality of life

As EQ-5D was not used to measure HRQoL in IPASS, the manufacturer undertook a review of the literature to identify relevant HRQoL data for use in the economic evaluation. The manufacturer concluded that there was an absence of relevant utility estimates and adopted utility estimates from a single UK study by Nafees.[36] The ERG notes that the utility values in the Nafees study[36] are derived

from a survey of 105 members of the general public who were asked to value health state descriptions of second-line CTX for patients with NSCLC.

Utility estimates associated with the delivery of treatment (oral versus intravenous) were not available from the study by Nafees[36] and the manufacturer used utility values as calculated in a previous ERG report[37]which looked at second-line CTX for patients with NSCLC. The use of these utility values is appropriate.

4.5.6 Resources and costs

Resource use in the economic evaluation is not derived from data collected as part of the IPASS trial; the manufacturer states that as IPASS was conducted in Asian countries, resource use would be unlikely to be generalisable to a UK setting.

Values and sources of resource use in the economic evaluation are described in Table 4-4 and include: medication, delivery of CTX, EGFR testing, patient monitoring, NHS transport service, grade 3 or 4 AE management, BSC and post-progression active treatment. The MS provides sufficient detail regarding sources of cost data used and reports that only the cost of BSC and post-progression CTX required inflation to 2007/08 prices.

The ERG notes that resource use and the costs of doublet CTX are based on a mean body surface area (BSA) of 1.82m^2 and assume a maximum of six treatment cycles of CTX.

Table 4-4 Key model parameters: costs

Costs	Value	Source
Gefitinib (single fixed payment per patient)	[redacted]	[redacted]
EGFR mutation test (per test)	[redacted]	[redacted]
Gefitinib patient monitoring (per month)	£86	Reference costs (2007/08)[39]
Drug acquisition gem/carb (per cycle)	£999	BNF (2009)[40], Medicines & Devices[41]
Drug acquisition pac/carb (per cycle)	£1,489	BNF (2009)[40]
Drug acquisition vin/cis (per cycle)	£403	BNF (2009)[40]
Drug acquisition gem/cis (per cycle)	£795	BNF (2009)[40]; Medicines & Devices[41]
Administration gem/carb (per cycle)	£307	Reference costs (2007/08)[39]
Administration pac/carb (per cycle)	£153	Reference costs (2007/08)[39]
Administration vin/cis (per cycle)	£527	Reference costs (2007/08)[39]
Administration gem/cis (per cycle)	£527	Reference costs (2007/08)[39]
Drug acquisition GCSF (per patient treated)	£1,284	BNF (2009)[40]
Grade 3 or 4 neutropenia	£92.80	ERG Addendum (2007)[42]
Grade 3 or 4 febrile neutropenia	£2,286	ERG Addendum (2007)[42]
Grade 3 or 4 fatigue	£39	Eli Lilly (2009)[38]
Grade 3 or 4 nausea and vomiting	£701	Eli Lilly (2009)[38]
Grade 3 or 4 diarrhoea	£867	Eli Lilly (2009)[38]
Grade 3 or 4 rash	£117	Roche (2006)[43]
Grade 3 or 4 anaemia	£615	Eli Lilly (2009)[38]
NHS patient transport service (per journey)	£28	Reference costs (2007/08)[39]
Best support care (per cycle)	£600	Clegg[44]
2nd line therapy followed by BSC (per cycle)	£1,022	ERG report [37]

vin/cis=vinorelbine/cisplatin; gem/cis=gemcitabine/cisplatin; pac/carb=paclitaxel/carboplatin; BNF=British National Formulary; gem/carb=gemcitabine/carboplatin; GCSF= granulocyte colony stimulating factor; ERG=Evidence Review Group; CIC=commercial in confidence

4.5.7 Perspective, time horizon and discounting

Costs are estimated from the perspective of the NHS, and outcomes are expressed as QALYs; both of which are captured over a five-year time horizon (which is assumed to be a life-time horizon). Costs and outcomes were discounted at a rate of 3.5%, in line with current NICE guidance.[34]

4.5.8 Model validation

The MS (pg103/104) listed different methods of model validation conducted by the manufacturer including:

- A health economist not working on the project, conducted internal validity checks
- An advisory panel was commissioned to critique the structure of the model, key assumptions and data inputs
- Selected clinical output generated by the model was compared to the results observed in the IPASS trial to ensure that the degree of error was acceptable.

4.5.9 Results included in the MS

Base case results

The base case pairwise incremental results generated by the manufacturer's model are presented below in Table 4-5. The ICER for the **target population** ranges from £19,402 per QALY (gefitinib versus paclitaxel/carboplatin) to £35,992 per QALY (gefitinib versus vinorelbine/cisplatin). Disaggregated results for the target population are presented in Table 4-6.

Table 4-5 Base-case results for target population

EGFR M+ population	Mean costs	Mean QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
Gefitinib	[redacted]	1.111			
Gemcitabine/carboplatin	£27,873	0.934	£3,666	0.177	£20,744
Paclitaxel/carboplatin	£27,902	0.923	£3,637	0.187	£19,402
Vinorelbine/cisplatin	£23,516	0.888	£8,023	0.223	£35,992
Gemcitabine/cisplatin	£27,401	0.966	£4,138	0.145	£28,633

ICER= incremental cost-effectiveness ratio; QALY=quality adjusted life year

Table 4-6 Disaggregated mean costs for base-case target population analysis

EGFR M+ population	Gefitinib	Gemcitabine /carboplatin	Paclitaxel /carboplatin	Vinorelbine /cisplatin	Gemcitabine /cisplatin
Pre-progression					
Drugs	[redacted]	£5,047	£7,748	£2,101	£4,158
EGFR testing	[redacted]				
Administration/ monitoring	£874	£1,738	£1,034	£2,987	£3,032
NHS transport		£283	£146	£292	£295
AE management	£58	£458	£218	£483	£350
GCSF prophylaxis		£278	£278	£278	£278
Post-progression					
Post-progression active treatment	£12,641	£14,595	£13,439	£12,634	£14,019
BSC	£4,742	£5,475	£5,040	£4,740	£5,259
Total	[redacted]	£27,873	£27,902	£23,516	£27,401
Mean # cycles	NA	5.1	5.2	5.2	5.3

AE=adverse event; GCSF=granulocyte colony stimulating factor; BSC=best supportive care;#=number

4.5.10 Subgroup analyses

The manufacturer also presented incremental pairwise results for the following subgroups: adenocarcinoma versus non-adenocarcinoma; female versus male and never smokers versus smokers. Results of the subgroup analyses are shown in Table 4-7. The ERG notes that the subgroup analyses undertaken are limited; there is no differentiation of patients in terms of efficacy (QALYs), only in terms of costs. In addition, costs are only affected by changes in the prevalence of mutation positive patients assumed to be associated with each of the subgroups identified; no supporting evidence is presented for the prevalence rates used in the subgroup analyses. In summary, the subgroup analyses undertaken by the manufacturer are incomplete.

Table 4-7 Results of subgroup analysis

	Δ Mean Costs	**Δ Mean QALYs**	**ICER (£/QALY**	**Δ Mean Costs**	**Δ Mean QALYs**	**ICER (£/QALY)**
	Adenocarcinoma			**Non-adenocarcinoma**		
Gefitinib						
Gemcitabine/carboplatin	£3,704	0.177	**£20,961**	£8,309	0.177	**£47,015**
Paclitaxel/carboplatin	£3,675	0.187	**£19,607**	£8,279	0.187	**£44,169**
Vinorelbine/cisplatin	£8,062	0.223	**£36,164**	£12,666	0.223	**£56,816**
Gemcitabine/cisplatin	£4,176	0.145	**£28,899**	£8,870	0.145	**£60,759**
	Female			**Male**		
Gefitinib						
Gemcitabine/carboplatin	£3,642	0.177	**£20,608**	£5,475	0.177	**£30,982**
Paclitaxel/carboplatin	£6,613	0.187	**£19,273**	£5,446	0.187	**£29,054**
Vinorelbine/cisplatin	£8,000	0.223	**£35,883**	£9,833	0.223	**£44,107**
Gemcitabine/cisplatin	£4,114	0.145	**£28,467**	£5,947	0.145	**£41,153**
	Never smokers			**Ever smokers**		
Gefitinib						
Gemcitabine/carboplatin	£3,067	0.177	**£17,354**	£5,070	0.177	**£28,692**
Paclitaxel/carboplatin	£3,038	0.187	**£16,206**	£5,041	0.187	**£26,895**
Vinorelbine/cisplatin	£7,425	0.223	**£33,304**	£9,428	0.223	**£42,291**
Gemcitabine/cisplatin	£3,539	0.145	**£24,488**	£5,542	0.145	**£38,352**

ICER= incremental cost-effectiveness ratio; QALY=quality adjusted life year

4.5.11 Sensitivity analyses

One-way sensitivity analysis

The manufacturer undertook a range of one-way SA. The results of the SA were not easily discernible as the manufacturer simply provided a tornado diagram without narrative (MS, pg108). The manufacturer commented that the results of the cost-effectiveness analysis were sensitive to five key parameters and these are listed in Box 4-1. The ERG notes that where the base case ICER rises to £115,888/QALY this is due to the wide CIs around the HR for OS; wide CIs reflect the fact that the data describing OS used in the economic model is very uncertain and heavily influences the size of the ICER.

Box 4-1 Five main drivers of cost-effectiveness results

- OS HR for gefitinib EGFR M+ : ± 95% CI from the base case gave an ICER range of £25,638/QALY to £115,884/QALY
- OS HR for gemcitabine/carboplatin EGFR M+ : ± 95% CI from the base case gave an ICER range of -£5,655/QALY to £24,716/QALY
- PFS HR for gemcitabine/carboplatin EGFR M+ : 95% CI from the base case gave an ICER range of £13,246/QALY to £40,313/QALY
- PFS HR for gefitinib EGFR M+ : ± 95% CI from the base case gave an ICER range of £10,386/QALY to £30,825/QALY
- Maximum number of CTX cycles : varied from 4 to 8 gave an ICER range of £12,552/QALY to £31,704/QALY

4.5.12 Scenario analysis

The manufacturer also undertook four different scenario analyses:

(i) excluding the treatment response health state in which patients responding to treatment gained a higher utility value than those with stable disease (ICER increased to £21,960/QALY)

(ii) removing the utility decrements associated with grade 3 or 4 AEs (ICER increased to £21,329/QALY)

(iii) reducing the base-case time horizon of the analysis from five years to three years (ICER decreased to £15,398/QALY) and increasing the time horizon from five years to six years (ICER increased to £21,284/QALY)

(iv) applying a 0% discount rate to costs and benefits (ICER decreased to £19,815/QALY) and applying a 6% discount rate to costs and benefits (ICER increased to £21,454/QALY).

In summary, none of the new scenarios described by the manufacturer led to any real change in the size of the ICER.

4.5.13 Probabilistic sensitivity analysis

For the PSA, a scatter plot (incremental cost versus QALYs) for EGFR M+ patients treated with gefitinib versus EGFR M+ patients treated with gemcitabine/carboplatin (Figure 4-3) is shown in the MS.

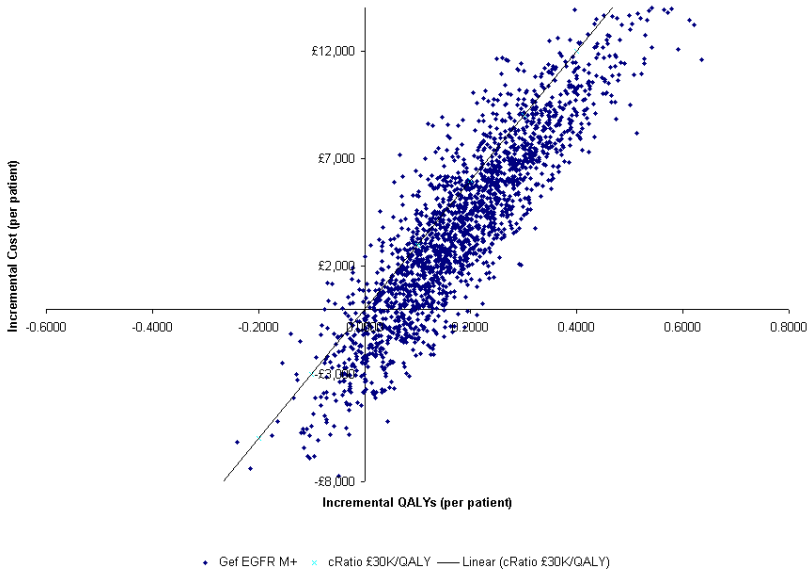


Figure 4-3 Scatterplot of gefitinib (EGFR M+) *versus* gemcitabine/carboplatin (EGFR M+)

A cost-effectiveness acceptability curve (CEAC) is included in the MS as shown in Figure 4-4. In the MS (pg111), the manufacturer concludes that with the constraints of the available clinical and utility data, vinorelbine/cisplatin, the combination with the lowest drug acquisition costs, was found to be the most cost-effective treatment for the first-line treatment of EGFR M+ patients up to a WTP threshold of £35,100/QALY. Beyond this threshold, gefitinib EGFR M+ becomes the most cost-effective treatment option. At a WTP threshold of £30,000/QALY, the probabilities of each treatment being the most cost-effective treatment option for the NHS were, in descending order, vinorelbine/cisplatin EGFR M+ (75%), gefitinib EGFR M+ (18%), gemcitabine/carboplatin EGFR M+ (4%), gemcitabine/cisplatin EGFR M+ (3%) and paclitaxel/carboplatin EGFR M+ (0%).

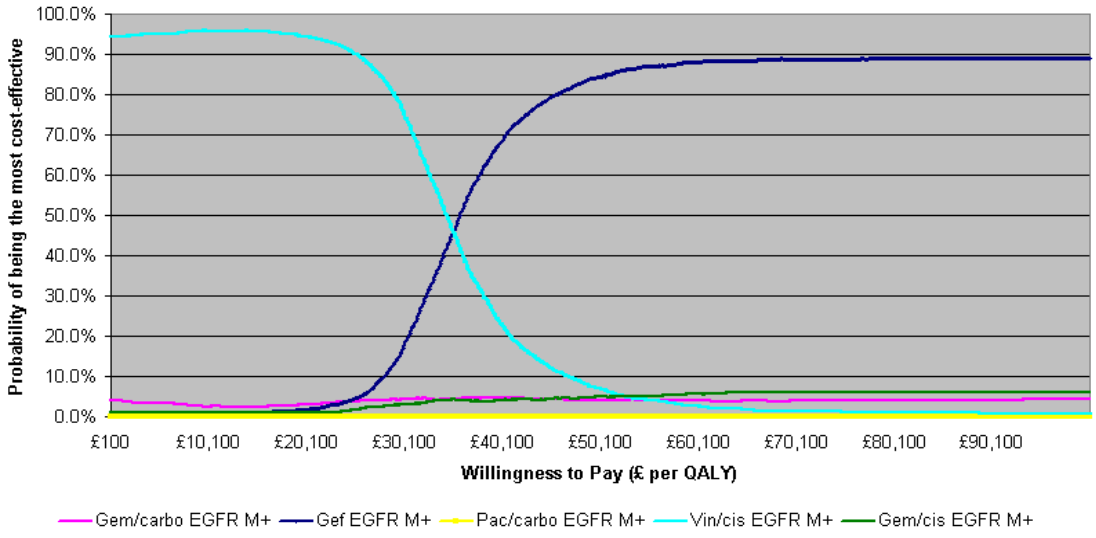


Figure 4-4 CEAC gefitinib (EGFR M+) *versus* doublet chemotherapy (EGFR M+)

4.6 Assessment of the manufacturer's model

Table 4-8 shows how closely the manufacturer's submitted economic evaluation accords with the requirements for a base-case analysis as set out in the NICE reference case checklist.[34] It is clear that the manufacturer has attempted to adhere to the NICE reference case. However, as docetaxel and pemetrexed are not included as comparators in the economic evaluation performed by the manufacturer, not all therapies routinely used in the NHS are considered. Furthermore, the source of utility values used in the economic model may not be appropriate to the decision problem.

Table 4-9 summarises the ERG's appraisal of the economic evaluation conducted by the manufacturer using the Drummond 10-point checklist.[45] The manufacturer's submitted model is limited in a number of areas including the exclusion of valid comparators and the incorrect identification and measurement of key costs and benefits. In addition, the ERG questions to what extent the clinical effectiveness of gefitinib is established for use in clinical practice in England and Wales. The ERG also highlights that the manufacturer employs differential efficacy rates for the four CTX regimens considered in the economic evaluation whilst the results of the manufacturer's own MTC demonstrate equivalent efficacy rates for the same four CTX regimens.

Table 4-8 NICE reference case checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partially – the economic evaluation does not include docetaxel or pemetrexed as comparators; both these comparators are routinely used in the NHS
Perspective costs	NHS and Personal Social Services (PSS)	The EE is carried out from the perspective of the NHS. No PSS costs are described in the MS
Perspective benefits	All health effects on individuals	Health effects to the individual are captured via QALYs
Form of economic evaluation	Cost-effectiveness analysis	Cost-effectiveness analysis
Time horizon	Sufficient to capture differences in costs and outcomes	The time horizon chosen was a lifetime horizon, which for this patient group was believed to be five years. This appears to be appropriate
Synthesis of evidence on outcomes	Systematic review	All survival data are derived (and where appropriate extrapolated) from a mix of clinical data sources: the IPASS RCT, MA (IPASS and NEJGSG) and MTC; the MA and MTC were based on systematic reviews of the literature
Outcome measure	Quality adjusted life years (QALYs)	QALYs were used which is appropriate
Health states for QALY	Described using a standardised and validated instrument	In IPASS QoL was not measured in terms of utility. After a SR conducted by the manufacturer did not identify any relevant utility values for use in the EE, the manufacturer used the utility values from the study by Nafees[36]
Benefit valuation	Time-trade off or standard gamble	The main QoL Nafees[36] study utilised standard gamble interview techniques, which is acceptable
Source of preference data for valuation of changes in HRQL	Representative sample of the public	The main QoL study Nafees[36] was based on responses from 105 members of the general public. It is not clear how representative this sample is of the UK adult population. Furthermore, the QoL study was not specifically designed to capture the QoL of patients requiring first-line CTX treatment
Discount rate	An annual rate of 3.5% on both costs and health effects	Benefits and costs have been discounted using a rate of 3.5%; the ERG recommended the use of the conventional approach in the UK (after the first year use annual discounting rather than discounting day by day from randomisation)
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Sensitivity analysis	Probabilistic sensitivity analysis (PSA)	A PSA was conducted by the manufacturer

PSS= Personal Social Services; MS=manufacturer submission; RCT=randomised controlled trial; QoL=quality of life; QALYs=quality adjusted life years; PSA=probabilistic sensitivity analysis; ERG=Evidence Review Group; EE=economic evaluation; SR=systematic review

Table 4-9 Critical appraisal checklist

Item	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Partially	The manufacturer only partially answered the decision problem set by NICE as (i) docetaxel and (ii) pemetrexed were not included as comparators
Was a comprehensive description of the competing alternatives given?	Yes	The manufacturer described the chosen comparators adequately (although two key comparators are not included)
Was the effectiveness of the programme or services established?	Partially	It is unclear to what extent treatment effectiveness is established for a UK population primarily because patients in IPASS are younger, predominantly female, non-Caucasian, mostly non-smokers, have only adenocarcinoma histology and include patients whose PS =2; in summary these patients do not represent patients eligible for treatment with gefitinib in England and Wales. The ERG has also expressed its concern regarding the methods used in the MA and in the MTC which supply the main sources of clinical effectiveness evidence; in particular the ERG questions the validity of assuming differential efficacy rates for the four doublet CTX regimens considered in the EE
Were all the important and relevant costs and consequences for each alternative identified?	Yes	The key costs and outcomes were identified. ERG proposed not to include GCSF costs as this is not used in clinical practice in NHS
Were costs and consequences measured accurately in appropriate physical units?	Not consistently	For example, the BSA value used to calculate CTX costs does not represent patients with NSCLC in the UK; cost per cycle of CTX and second-line CTX were estimated incorrectly
Were the cost and consequences valued credibly?	No	Overall survival was not adequately modelled; poor correspondence between parametric survival models and source data
Were costs and consequences adjusted for differential timing?	Partially	Costs and outcomes were discounted after one year; the ERG notes that the method of discounting did not conform to UK convention of discounting annually after the first year
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	Pairwise incremental results were presented for the base-case target population and subgroups (adenocarcinoma versus non-adenocarcinoma; females versus males; never smokers versus ever smokers)
Was allowance made for uncertainty in the estimates of costs and consequences?	No	Probabilistic SA was undertaken. Univariate SA and scenario analysis were also undertaken by the manufacturer but only limited results of the one-way SA undertaken were presented in the MS
Did the presentation and discussion of study results include all issues of concern to users?	Yes	The results are presented and discussed in detail. However, the resources and infrastructure required to implement a universal EGFR mutation test for eligible patients is not fully discussed in the MS

ERG= Evidence Review Group; MS = manufacturer submission; QALY=quality adjusted life year; SA=sensitivity analysis; PSA=probabilistic sensitivity analysis; ICER=incremental cost-effectiveness ratio; BSA=body surface area; CTX=chemotherapy; NSCLC=non small cell lung cancer; MA=meta analysis; MTC=mixed treatment comparison

4.7 Critique of approach used: Assessment of the manufacturer's economic model

4.7.1 Detailed critique of manufacturer's economic model

The decision analytic model submitted by the manufacturer is based on two parametric survival models (PFS and OS) implemented within a Markov framework. All other health states (responding to treatment, stable disease and post-progression survival) are derived from these models, and are not governed by explicit transition probabilities. Unfortunately, the model does not include any results of IPASS data analyses (such as Kaplan-Meier survival curves) so these are not compared directly with the fitted Weibull models. In addition, there is no description of the fitted models, no definitions of the variables used, and no performance/diagnostic statistics provided by which to assess the appropriateness of the model formulation.

The Excel worksheets are clearly laid out, clearly labelled and annotated appropriately. A single 'Parameters' worksheet shows all model variables set out in tabular form. For some variables, but not all, indications are given of the data sources and/or methods of derivation. A more comprehensive and systematic approach would have been helpful.

A PSA has been implemented successfully including a MTC of gefitinib and the selected CTX doublet comparators. However, no justification is provided for the selection of uncertainty distributions for individual parameters. All parameters are assumed to be independent with the exception of the Weibull model variables, though here it would have been helpful to see a correlation or covariance matrix, rather than merely the decomposition matrix.

4.7.2 Cost-effectiveness modelling in the context of diagnostic testing

Greater complexity

Modelling the cost effectiveness of a new treatment technology when a diagnostic test is required to determine eligibility for treatment introduces additional considerations to those normally addressed within a decision model. In particular it is necessary to incorporate the performance characteristics of the diagnostic test within the model structure, and then to trace the potential treatment pathways and outcome consequences for patients directed down each route. In this case the diagnostic test is binary in nature resulting in a determination that a patient either exhibits a relevant mutation, or does not.

Figure 4-5 illustrates how the adoption of diagnostic testing leads to a more complex structure for an economic evaluation in which four possible test outcomes lead to quite different consequences. A test

with high sensitivity will maximise the number of true positives (patients correctly identified as EGFR M+ status), who can expect to gain added benefit from treatment with gefitinib instead of standard CTX. Low sensitivity inflates the number of patients who are denied gefitinib treatment; gefitinib is therefore withheld from some patients who are likely to do better on gefitinib than conventional CTX (i.e. missed opportunities for health gain). If the test exhibits high specificity, most patients who would not benefit from gefitinib are correctly assigned to conventional CTX. However, with poor specificity the test will suggest wrongly that some patients are EGFR M+ status, leading to treatment with gefitinib which is no better than receiving a placebo; as a result these patients do not receive the proven benefit of conventional CTX, but do suffer the AEs associated with gefitinib. The absolute numbers of patients falling into each category also depend on the underlying prevalence of mutations in the sampled population: with a low prevalence there are fewer true positives and more false positives, and vice versa.

This last group (the false positives) are the most worrying, since it is possible for the loss of survival time and HRQoL in these (possibly few) patients receiving no effective treatment to outweigh the collective marginal gains (compared to conventional CTX) for those correctly identified for gefitinib treatment (the true positives), whilst still adding considerably to the additional costs of treatment. Thus the outcome of an economic assessment of the "test + gefitinib" strategy versus "conventional CTX without testing" strategy could hinge critically on the specificity of the diagnostic test combined with the proportion of EGFR M+ individuals within the tested population. Unfortunately, the values of both these key parameters cannot easily be determined from the evidence made available in the MS.

The role of EGFR mutation testing

There are two questions which must be addressed in order to establish a basis for using a particular diagnostic test to direct clinical treatment decisions:

1) *How well does the test correctly identify the important tumour characteristics? (Analytic validity)*

This involves determining the sensitivity and specificity of the test for identifying the target mutations in the relevant population. Pre-requisites are therefore clear definitions of the included/excluded mutations, and of the characteristics of the appropriate clinical population, as well as a framework for defining a 'gold standard' against which to judge the performance of a particular test.

2) *How well do identified target mutations predict patient outcomes? (Clinical validity)*

Clinical studies are required to relate identified mutations to the clinical outcomes likely to be influenced by test results, and to provide quantified estimates of those effects. These may be binary outcomes (e.g. response to treatment) or continuous outcomes (e.g. OS or PFS).

Combining evidence on these two issues should ideally provide the information necessary to determine the proportion of patients likely to fall within the four post-testing subgroups shown in Figure 4-5, and hence allow estimation of the treatment effects for each subgroup.

Test performance: analytic validity

The ARMS test (as used in IPASS) is designed to give rapid results and to achieve high sensitivity in detecting EGFR mutations, but only in respect of a pre-selected set of common mutations at two targeted sites commonly seen in patients with NSCLC. By contrast direct sequencing is not so constrained and is capable of identifying a wider range of possibly important mutations, but is more time consuming to carry out. Ideally, the performance of both tests should be assessed against an objective measure of the true presence/absence of each relevant mutation, and of the combined presence (M+ status) of any one of the mutations associated with differential treatment effects in the retrieved tumour tissue samples. However, no such 'gold standard' appears to exist. In a study[46] cited by the ARMS test manufacturer, the sensitivity of ARMS is compared to that of direct sequencing in a sample of 94 patients with NSCLC (including 24 with squamous cell disease). Direct sequencing was only successful in obtaining results in 83 patients, and ARMS provided results for only 91 patients. ARMS indicated mutations present in 27 cases, and direct sequencing in 13, but each identified some patients with mutations present who were not identified by the other test. The authors interpret these findings as a demonstration of the superior sensitivity of the ARMS test, but it is not clear whether some of the additional positive tests could in fact represent artefactual signals (i.e. false positives)

generated by the testing process. It appears that obtaining reliable evidence of the analytic validity (sensitivity and specificity) of either test for the detection of EGFR mutation status is not currently realistic. Expert opinion obtained by the ERG suggests that the sensitivity of the ARMS test when properly carried out may be close to 100%, and that its specificity may also be high in such circumstances (Prof Cree, (2009). Personal communication, Director NETSCC (Efficacy and Mechanism Evaluations Programme)).

Test performance: clinical validity

Some evidence has been published which considers the relationship of mutation status determined by testing to various measures of patient outcome (clinical validity). It should be noted that in the absence of a 'gold standard' test, these results may only be valid for the particular test and defined population used in each study, and should be treated with caution.

An Italian study[47] of 83 NSCLC patients treated with either erlotinib or gefitinib provides some information of the performance of direct sequencing to test for EGFR M+ status. When considered as a predictor of best response to erlotinib therapy (CR+PR), the test showed 82% sensitivity, 85% specificity and a false positive rate of 13%. However, for disease control (complete response+partial response+stable disease) sensitivity reduced to 41%, specificity remained high (89%) and the false positive rate fell to 6%. Multivariate predictive analysis for PFS and OS indicated improved survival associated with positive test results (HRs of 0.40 for PFS and 0.36 for OS).

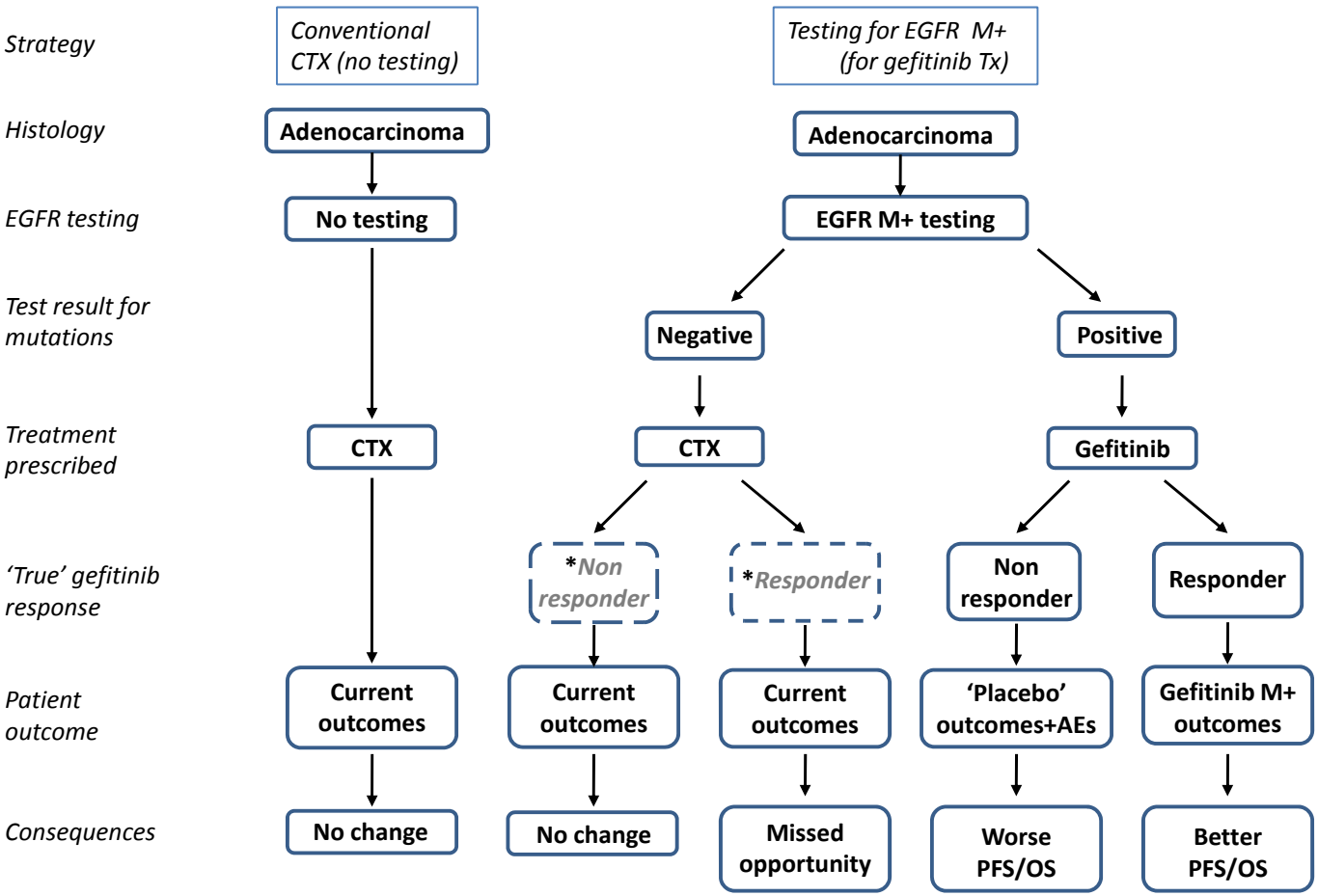
Clinical results[48] from IPASS show that only 214 (of 609) patients receiving gefitinib had both EGFR mutation status and best overall response recorded. The sensitivity of mutation status determined by the ARMS test for predicting response to gefitinib treatment was 99%, the specificity 69% and the false positive rate was 17.3%. The corresponding results for predicting disease control are: sensitivity 77%, specificity 89%, false positive rate 4.7%. No results are available for prediction of PFS and OS.

Though the Italian study[47] is smaller, it has the advantage of relating to a predominantly Caucasian population in contrast to IPASS. It is also concerning that such a small proportion of IPASS patients had useable EGFR mutation status results, calling the representative nature of this subset into question. Nonetheless the sensitivity and specificity values are not inconsistent (given the small numbers in the Italian study[47]), and the false positive rates are very similar.

The manufacturer of gefitinib was able to provide information on 65 tests carried out at six UK centres, only 7 (10.7%, [4.8-21.5%]) were positive for the presence of EGFR mutations. Only limited information has been retrieved from publications and the web-site of the test's manufacturer, relating to the pragmatic performance of ARMS test or direct sequencing to predict the patient outcomes

employed in the submitted model. Since the model is structured primarily around projections of OS and PFS, it is disappointing that the performance characteristics of the ARMS test are not available for these outcomes. Of particular interest are the projected mean survival estimates for true positive and false positive IPASS patients, since it is clear that the balance of gain and loss in these two subgroups may have an important bearing on the cost effectiveness of gefitinib compared with doublet CTX.

It is important to bear in mind that, in the absence of rating the ARMS test against a true 'gold standard' procedure, the pragmatic performance characteristics derived from IPASS can have only limited generalisability, being contingent on the precise equivalence of the testing performance achieved in a UK clinical practice population to that observed in the subset of patients tested in IPASS, both now and in the future. **Thus the results from any cost-effectiveness model of gefitinib treatment for EGFR M+ patients should not be taken to be a blanket assessment of gefitinib in isolation from the method of selecting eligible patients, but only an assessment of a specific test+gefitinib combination which may not be valid when other testing procedures are used.**



* The effect which would result if treated with gefitinib instead of CTX

Figure 4-5 Effects of diagnostic test on treatment pathways and patient outcomes

Prevalence of mutations

The manufacturer cites a single paper[9] as the basis for adopting a value of 16.6% for the prevalence of EGFR mutations in a UK patient population. However, this study is questionable on several grounds of relevance, and of research methodology:

- all patients were treated in Spanish hospitals, and therefore may not be representative of either the population, or treatment environment of UK patients

- patients were submitted for the study from 129 centres (including 29 centres volunteering to participate in addition to those randomly selected), these centres and their patients were not chosen sequentially or subject to any form of stratification, and so are likely to be affected by multiple confounding influences including pre-selection by known risk factors for EGFR M+ status (i.e. selective enrichment of the sample)

- patients were eligible if they had had up to two prior courses of CTX, and so are unlikely to be representative of patients receiving CTX for the first time

- EGFR mutation testing was not carried out using the same test kit (ARMS) used in IPASS, which is proposed for use in the UK.

For comparison, the authors of the Spanish study[9] traced only one small Italian study[49] reporting the prevalence of EGFR mutations (10% of 375 patients). In view of the high degree of uncertainty, it is appropriate that this model parameter should be the subject of a very wide SA within the manufacturer's submitted model (where it influences only the cost of gefitinib treatment).

Pre-screening by risk factors

It has been suggested that patients could be pre-screened for two known risk factors for EGFR M+ status (females and lifetime never smokers) in order to identify an 'enriched' population, excluding many patients with a low probability of benefitting from treatment with gefitinib. This would certainly increase the prevalence of EGFR M+ status, and reduce the costs of testing, but is also likely to conflict with equity standards by excluding patients from treatment on unacceptable grounds.

4.7.3 Major issues apparent from examination of the model

Time horizon and primary comparator

The MS presents a base case scenario which uses a time horizon of five years, with SA for three and six years. As a general principle a longer time horizon is always to be preferred to capture the full impact of new technology over a lifetime. The submitted base case uses gemcitabine/carboplatin as the preferred comparator, but this involves an indirect comparison via the MTC, and therefore cannot be considered as robust as the primary comparator from the clinical trial. Therefore, the detailed effects of model amendments are shown relative to a redefined base case scenario in which gefitinib is compared to paclitaxel/carboplatin over a period of six years (the longest time available within the submitted model).

Costs of first-line chemotherapy

Chemotherapy costs are presented within the submitted model for four comparator regimens as a drug cost per 21 day cycle. The authors have adopted the BSA value (1.82 m^2) used in a previous NSCLC STA,[37] but have not recognised that this was obtained from separate calculations for male and female UK patients and allows for the distribution of BSA values over a wide range. Accurate estimates may be markedly higher or lower than those presented depending on the dose of each drug required, the availability of the product in different vial sizes, and the relative pricing of such vials.

A further factor of particular concern for this STA is that the target population (EGFR M+) is likely to contain a higher proportion of female patients than the general lung cancer population. The manufacturer has estimated (IRESSA SmPC[28]; Table 6) from several clinical trials that, amongst Caucasian EGFR M+ NSCLC patients in several clinical trials, 46.7% of patients were males. Applying this figure to the available UK survey results[50] suggests that a mean BSA of 1.762 m^2 is more realistic.

The cost per cycle of (intravenous) vinorelbine assumes a dose of 30mg/m^2, but clinical advice (Dr Ramani, (2009). Personal communication, Consultant Clinical Oncologist, Wirral) suggests a dose of 25mg/m^2 is more appropriate to reduce the severity of AEs. In the submitted model, paclitaxel costs are based on a dose of 200mg/m^2 per cycle as used in IPASS, but this is contrary to the dose level specified in the Paclitaxel[51]SmPC which indicates 175mg/m^2 for treatment of patients with NSCLC.

Taking account of these various factors, the ERG has re-estimated the cost of CTX drugs for the four comparators used in the submitted model, together with two additional candidate comparators in

Table 4-10. These estimates use the latest UK prices[40] and incorporate any mandated pre-medication.

Table 4-10 Mean cost of chemotherapy drugs estimated by the manufacturer of gefitinib and by the ERG

Comparator	Model unit cost per cycle	ERG unit cost per cycle
Gemcitabine/carboplatin	£998.85	£940.39
Paclitaxel/carboplatin	£1,488.60	£838.40
Vinorelbine/cisplatin	£403.18	£346.38
Gemcitabine/cisplatin	£792.56	£820.09
Docetaxel/cisplatin	N/A	£1,081.32
Pemetrexed/cisplatin	N/A	£1,536.30

The impact of these data revisions on the cost-effectiveness results is quite modest for three of the model comparators, leading to changes in the ICER of less than £2,000 per QALY. However, the reduction in dose level and the higher proportion of female EGFR M+ patients, combined with lower BNF prices for generic paclitaxel lead to a large increase in the incremental cost per patient of gefitinib compared to paclitaxel/carboplatin of more than £18,000 per QALY gained.

Maximum number of cycles of first-line chemotherapy

The IPASS trial allowed a maximum of six cycles of first-line CTX per patient. However, the usual UK practice is to offer a maximum of four cycles. Changing this parameter in the manufacturer's model has a very large effect on the cost-effectiveness results, since it reduces the acquisition and administration costs of comparator CTX by about 29%, but has no effect on gefitinib treatment costs which are offered as a fixed price per patient irrespective of the duration of treatment. This change alone increases the base case ICER to over £32,000 per QALY for comparison with gemcitabine/carboplatin and paclitaxel/carboplatin, and to about £44,000 per QALY when gefitinib is compared to vinorelbine/cisplatin or gemcitabine/cisplatin.

However, it may be argued that reducing the number of cycles of CTX will also reduce the extent of patient benefit likely to be achieved. This issue has been debated in several recent STAs[52] without clear conclusions being reached due to lack of unambiguous evidence: manufacturers tend to argue that reduced cycles have no effect on the effectiveness of a new intervention, but do have an impact on the effectiveness of a comparator. At present the ERG is not aware of any convincing evidence which could be used as a basis for moderating the outcome gains likely to accrue from any of the

comparator regimens. The ERG sought additional information from the manufacturer in the form of a limited extract of IPD from the IPASS trial, to enable the possible relationships between the number of cycles of CTX and measures of response to treatment to be considered as a possible means of estimating downward adjustments to trial outcomes for comparators to gefitinib when the number of allowed cycles is restricted (which might have served to improve the estimated cost-effectiveness of gefitinib). The manufacturer refused this request, and subsequently failed to provide specified statistical analyses requested by the ERG in time to assist in this investigation.

Treatment exposure for comparator CTX agents

Information provided by the manufacturer in response to a request for clarification indicates that IPASS patients in the CTX arm were progressively less likely to receive paclitaxel/carboplatin, even though not yet suffering from disease progression. By contrast in the submitted model it is assumed that 100% of such patients will receive the prescribed medication up to cycle six. This has the effect of overstating the mean number of cycles of paclitaxel/carboplatin administered per patient – increasing from 4.83 in IPASS to 5.51 in the model[*]. When this difference is corrected, the cost of the comparator is reduced and the ICER for gefitinib compared to paclitaxel/carboplatin is increased from £20,010 to £25,427 per QALY gained. The same adjustment has also been applied to the other comparators (taking the fall-off of treatment exposure in the paclitaxel/carboplatin group to be broadly representative of all CTX regimens), and this leads to similar increases in the ICER.

Survival modelling and projection of overall survival and progression free survival

The results obtained with the submitted model depend upon projective modelling of OS and PFS beyond the trial period to estimate the lifetime gain in patient outcomes expected to arise from substituting gefitinib for conventional CTX as first-line CTX treatment. The model authors have adopted a two-parameter Weibull formulation for modelling both outcomes, but do not provide an objective justification for this choice, nor do they offer evidence of comparative performance of this paradigm relative to other possibilities. In order to explore this issue the ERG have digitised the Kaplan-Meier curves for EGFR M+ patients in IPASS (shown in Figures 3 and 6 of the MS), and used these to calculate the cumulative hazard for each outcome. These are shown in Figure 4-6 and Figure 4-7. The unique feature of a Weibull survival model is that the cumulative hazard of an event

[*] This represents a factual inaccuracy. The mean cycles in IPASS were 5.2. The ERG acknowledges this to be a typing error. It should read "This has the effect of overstating the mean number of cycles of paclitaxel/carboplatin administered per patient – increasing from 4.83 in IPASS to 5.239". As this was a typing error it had no effect on results.

(death or disease progression) increases exponentially over time. However, the IPASS results do not support this formulation, but instead reveal a common problem for drug trials in that there is often poor correspondence between the parametric models and the source data, particularly at the beginning and end periods of the trial.

There are several factors which may contribute to this lack of correspondence:

a) Trial inclusion/exclusion criteria frequently include direct or indirect stipulations which minimise or remove altogether the likelihood of specific events occurring in the first few weeks of the trial

b) The action of a prescribed drug takes time to achieve its full effect, partly due to the pharmacokinetic/dynamic profile of the drug, and partly due to the time required for the active agent to achieve its full effect at the target site(s). Conversely, when the period of active treatment comes to an end its effects may dissipate gradually over several weeks

c) Additional confounding is potentially introduced by the availability of subsequent courses of active CTX which may further complicate the dynamic nature of the event hazard rate following disease progression

d) There is also the possibility that the patient population is essentially heterogeneous in relation to the event risk of interest, leading to progressive survivor bias as members of one subgroup suffer death at a faster rate than other patients.

As a consequence of these influences, it is not surprising that fitting a standard parametric survival function to the full clinical trial dataset rarely produces a satisfactory correspondence to the calculated survival trajectory. Moreover, since the reliability of fit at later periods is increasingly sensitive to diminishing patient numbers, calibrating a parametric function from the full patient data may be a particularly unsatisfactory basis for projecting events beyond the trial data collection period.

The cumulative hazard plots in Figure 4-6 and Figure 4-7 reveal a two phase profile characterised by a low hazard (shallow slope) in the early period, followed by an increased hazard (steeper slope) in the long-term. This is broadly consistent with suppression of disease activity during active treatment, with resumption of a normal progression of cancer cell proliferation thereafter. This suggests an alternative approach to projective modelling. It is apparent that a simple match to the data can be obtained by fitting linear regression lines to the two phases, and since a linear hazard is equivalent to an exponential survival model, we obtain a ‘spline’ model in which two exponential models are spliced together at a time when the risk profile of patients is seen to change. In Figure 4-6 and Figure

4-7 it can be seen that this method is able to reflect the trial data accurately across the whole period of the trial.

The effect of this approach to modelling PFS is shown in Figure 4-9, and indicates that the 'spline' models are more accurate at all times than the Weibull models, which tend to overestimate PFS for both treatment arms. Although the differences between models are not so evident during the trial for OS (Figure 4-8), the differences in long-term projections is pronounced: the spline models suggest rather longer survival than the Weibull models, but with a much smaller differential between long term survival in the treatment arms.

The consequences of this re-analysis of the trial results (Table 4-11) is to reduce estimates of PFS and to increase estimates of OS, but in all cases to reduce the incremental gain attributable to gefitinib by about one month, suggestive of a reduction in modelled outcome gains of around 25% from those reported in the MS.

Table 4-11 Estimated mean projected OS and PFS using Weibull and exponential 'spline' models of IPASS EGFR M+ patients (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

The ERG sought additional information from the manufacturer in the form of a limited extract of IPD from the IPASS trial, to enable more accurate estimation of survival models to be carried out (using trial data directly, rather than via approximations obtained by digitisation). In addition this would have allowed correlations between the new model parameters to be estimated as a basis for updating the PSA facility within the manufacturer's model. The manufacturer refused this request, and subsequently failed to provide specified statistical analyses requested by the ERG in time to assist in this investigation.

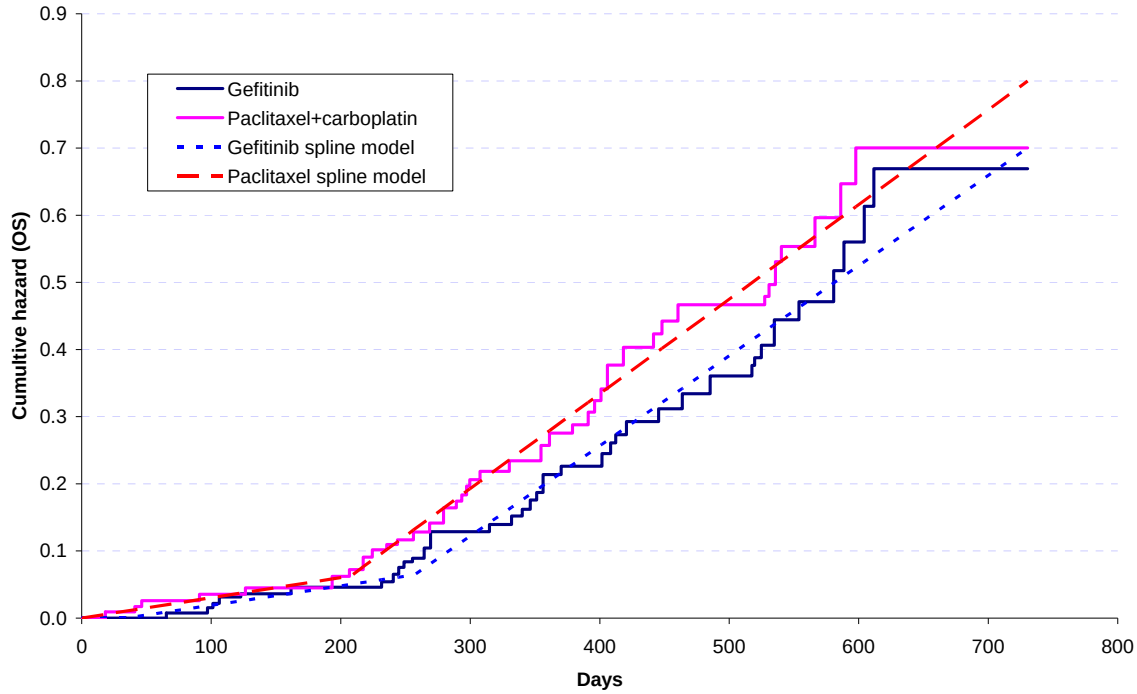


Figure 4-6 Cumulative hazard for overall survival in IPASS EGFR M+ patients

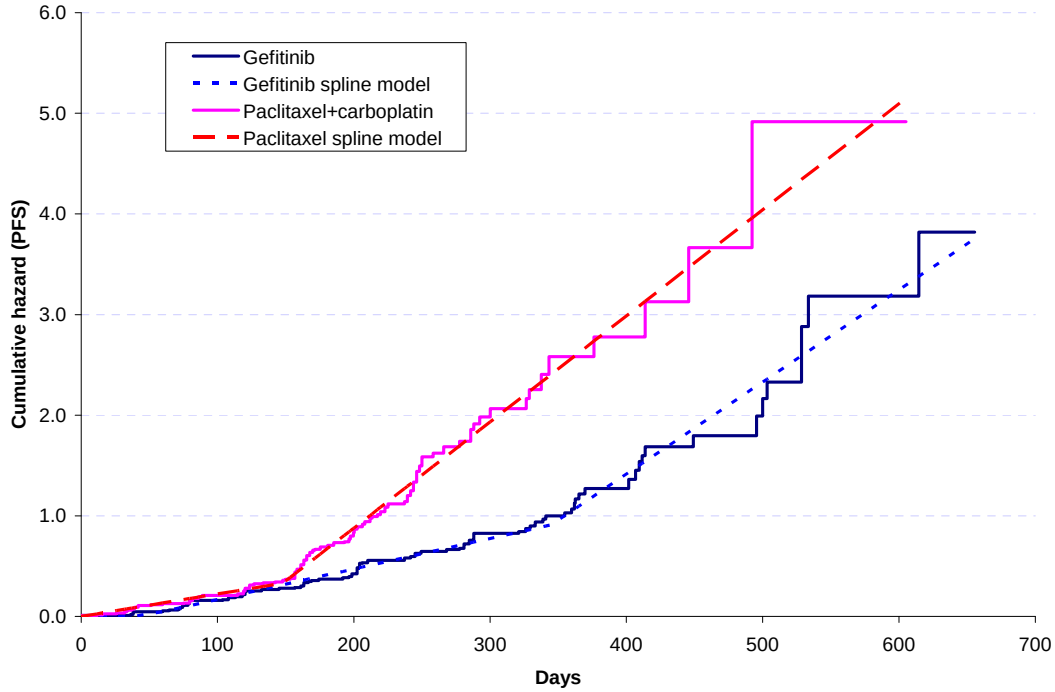


Figure 4-7 Cumulative hazard for progression free survival in IPASS EGFR M+ patients

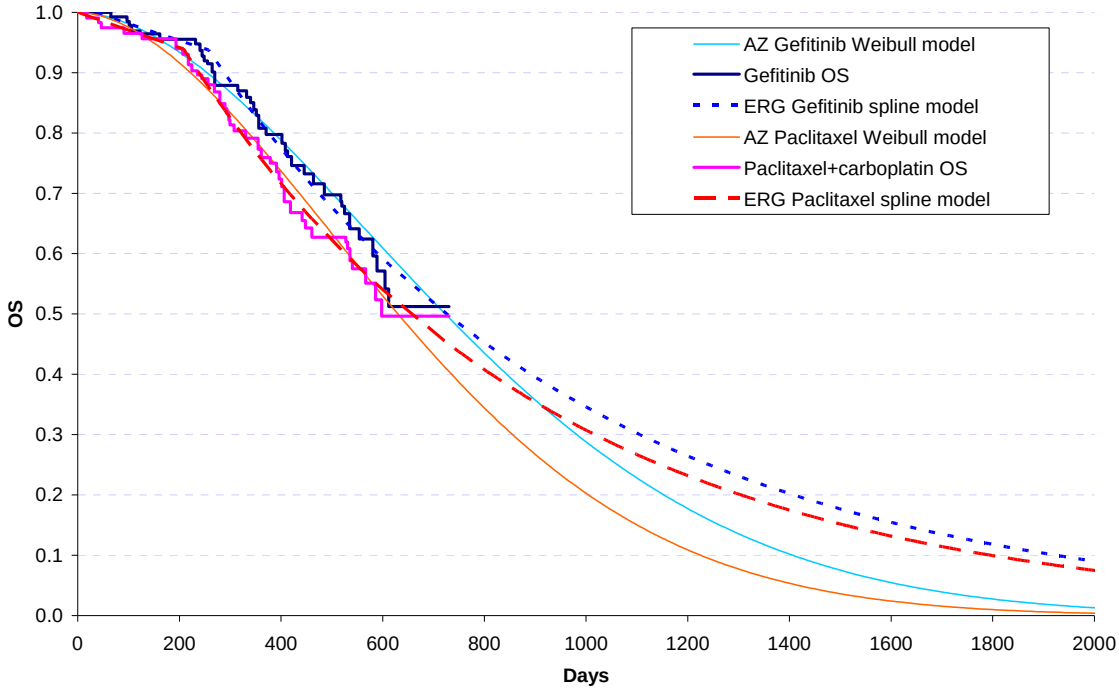


Figure 4-8 Overall survival in IPASS EGFR M+ patients

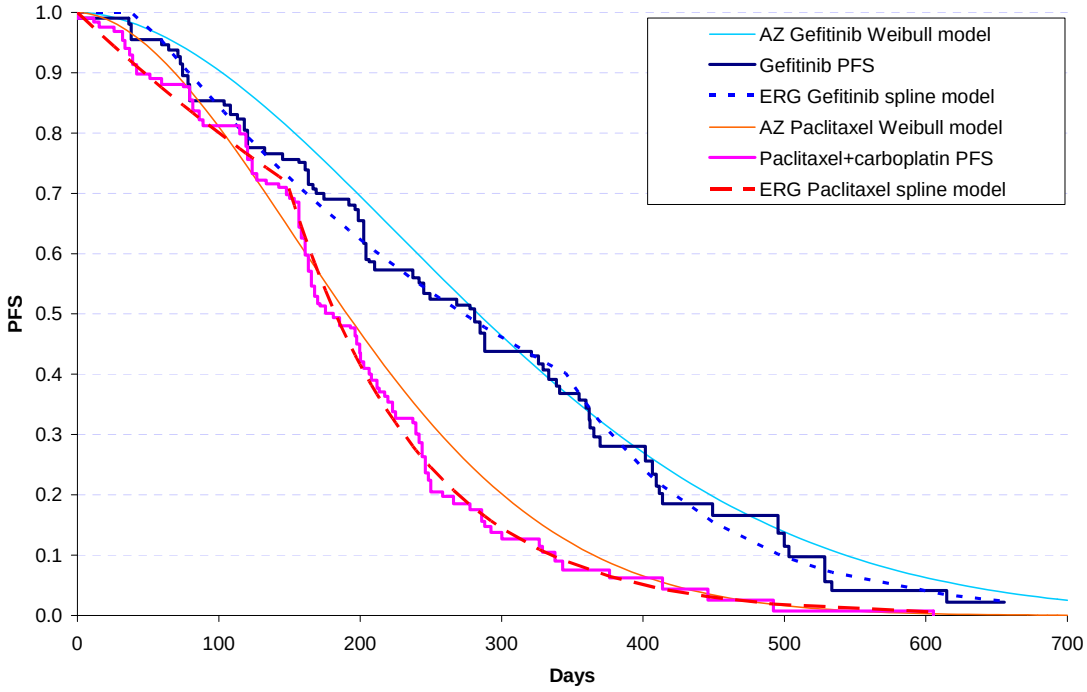


Figure 4-9 Progression free survival in IPASS EGFR M+ patients

Validity of the MTC results for economic analysis of non-trial comparators

The purpose of the MTC undertaken by the manufacturer is to allow extrapolation of key outcomes (OS, PFS, tumour response rate and AEs rates) from IPASS to other CTX regimens as comparators to gefitinib. This approach rests on strong assumptions of equivalence of the gefitinib EGFR M+ subgroup and undifferentiated NSCLC trial populations in trials of the various CTX combinations. In addition, there is also an assumption of proportionality of hazards for gefitinib relative to all comparators with respect to OS and PFS. As previously noted, the HRs within IPASS vary substantially over time calling into question the interpretation of results generated by standard analysis methods. **Since the HRs for gefitinib vs paclitaxel/carboplatin are primary drivers of patient outcomes in the submitted model, and are propagated to all comparators via the MTC results, the ERG concludes there must be a serious doubt associated with all cost-effectiveness estimates generated by the submitted model.**

4.7.4 Additional issues identified

Discounting method

Costs and outcome are discounted in the submitted model on a continuous daily basis from the time of randomisation. It is conventional in the UK to discount annually (i.e. no discounting in the first year, followed by use of a single discount factor for each successive twelve month period) to match the annual publication of price base information (e.g. NHS Reference Costs). Amending the method of discounting in this way reduces the incremental cost per patient by a small amount, and increases the incremental patient benefit slightly, so that the ICER in reduced by between £700 and £1,000 per QALY gained depending on the comparator considered.

GCSF prophylaxis

For all comparator CTX agents it is assumed that 21.7% of patients receive granulocyte colony stimulating factor prophylaxis for the prevention of neutropenia (using the proportion of IPASS paclitaxel/carboplatin patients so treated). However, this is not normal clinical practice in the UK and its omission reduces the cost of treating each patient for one of the comparators by about £278. As a result the ICER for use of gefitinib increases by between £1,200 and £1,900 per QALY gained depending on the specific comparator.

Continuity correction

A mid-cycle correction is correctly applied by the modellers when estimating the QALYs accruing in each model cycle. However, the corresponding correction is not employed when estimating the various components of cost. The requirement for such a correction varies between different comparator regimens. Drugs administered once per cycle (paclitaxel, and also docetaxel and pemetrexed) do not require adjustment as all patients who are alive and still in treatment at the start of each cycle receive a dose. By contrast, where two or more doses are required per cycle the cost must be adjusted for the number of patients dropping out of treatment during the cycle. An additional related problem has been identified in the model in that drug doses are costed as though they only relate to patients in treatment at the end of each cycle, and this must be corrected for all comparators. The combined effect of implementing these corrections is to increase the treatment costs of all comparators, and therefore to decrease the incremental cost of gefitinib therapy and improve the ICER by between £1,100 and £2,600 per QALY gained.

Misalignment of cycles

The submitted model is structured as a sequence of 21 day periods (corresponding to 21 day CTX cycles). However, these intervals do not naturally coincide with the periods chosen to define the time horizon of the analysis (3, 5 or 6 years), so that only a proportion of the costs and outcomes in the final model period should be included in the final model results. The logic used in the submitted model excludes the whole of the final period from the results, instead of allocating the correct proportion. Rectifying this error has a very minor impact on the incremental cost and the size of the estimated ICER.

Costs of second- line chemotherapy

Second-line CTX costs are entered into the model as a single cost per cycle of time following disease progression. This value was obtained by taking the total cost of care shown in the ERG report relating to the STA of erlotinib for second-line line treatment of NSCLC[37] and dividing this by the overall mean survival (9.03 months) from the same source. This approach would be satisfactory if the present model generated the same mean survival following projection, but in fact the projected times range between 14 and 17 months, so that the resulting cost estimates are considerably overstated. This is principally because the cost estimate in the earlier STA is in fact a compound of two elements: the costs of second- line CTX and its associated administration, monitoring and AE costs to which is added the lower ongoing cost of BSC after failure of second-line treatment. Only the latter element is related to duration of survival, so that if post-progression survival is greater than nine months additional unjustified CTX costs are added automatically amounting to approximately 25% greater costs than are appropriate. Correcting this problem increases the ICER for use of pemetrexed by between £1,200 and £3,500 per QALY, except if vinorelbine is the comparator when the ICER reduces slightly.

Differential outcomes for comparators

The result of the MTC carried out for both OS and PFS (Tables 8 and 9 of the MS) provides no basis for differentiating between any of the eight regimens included in the current NICE guidance, since in all cases the estimated credible interval encompasses an HR of 1.0. This suggests that all comparators should be modelled on the basis of equivalent outcome effects to those observed for use of paclitaxel/carboplatin in IPASS, rather than individual values derived from the MTC analyses. When this amendment is made to the submitted model, the ICER for gefitinib compared to gemcitabine/carboplatin is increased by £5,700 per QALY, whereas for other comparators the change is much smaller (

Table 5-2 and Table 5-3).

Response: stable disease relative proportions

The manufacturer's model allocates the number of pre-progression patients at any time between objective response to treatment and stable disease, in order to apply a utility increment (0.0193) to patients with an objective response. This allocation is based on the proportion of patients with a recorded response to treatment at any time, and this is applied without adjustment at all time periods. This approach must be considered a simplification when it is considered that patients with an objective response warranting application of a differential HRQoL benefit, may also gain from a better time to disease progression than those without evidence of response. If this effect can be confirmed it would have the consequence that a greater proportion of patients remaining in PFS would be treatment responders over time and so the utility advantage accruing from a high response rate would be underestimated.

The ERG sought additional information from the manufacturer in the form of a limited extract of IPD from the IPASS trial, to enable the ratio of patients who had recorded a response to treatment to those with at best stable disease to be estimated over time as a basis for adjusting the submitted model. The manufacturer refused this request, and subsequently failed to provide specified statistical analyses requested by the ERG in time to assist in this investigation.

In the absence of detailed analysis of IPD from IPASS it is only possible to explore the likely magnitude of such an effect on the cost-effectiveness results. An approximate calculation suggests that such an adjustment to the model might increase the incremental QALYs for gefitinib compared to paclitaxel/carboplatin by a maximum of 0.015, which would reduce the estimated ICER by less than £1,500 per QALY gained. However this finding is not sufficiently secure to be used in the ERG's preferred base case scenario.

Updated MTC

In response to a request for clarification, the manufacturer provided the results of an extended and updated MTC analysis, including pemetrexed/cisplatin and docetaxel/cisplatin as additional CTX comparators. This has no effect on the ERG's preferred base case results which are based solely on the findings of IPASS, but does lead to minor changes to the ICERs when alternative comparators are considered.

5 Additional analysis undertaken by the ERG

5.1 Introduction

This section describes the additional analysis undertaken by the ERG.

5.1.1 Additional comparators

The provision by the manufacturer of results from an enlarged and updated MTC analysis has made it possible to expand the manufacturer's model to accommodate two important additional comparators: docetaxel/cisplatin and pemetrexed/cisplatin. It is particularly interesting to consider the performance of gefitinib alongside pemetrexed, which stands out from the other drugs included in the MTC as offering significantly better outcomes than the other available CTX regimens. Results are included in the summary results tables (Table 6-2 and Table 6-3).

5.1.2 Sensitivity to EGFR M+ prevalence

As previously discussed, the prevalence of relevant EGFR mutations in the UK non-squamous NSCLC population is not known with any accuracy. This is an important variable in the estimation of cost effectiveness for two reasons:

- it determines the volume and cost of screening tests which can be expected to generate one EGFR M+ patient, and which contribute to the incremental cost of adopting a 'test+treat' policy for such patients;

- it determines the balance between true and false positives in terms of likely clinical outcomes, and so provides a basis for estimating IPASS results adjusted to UK circumstances.

The effect of prevalence on the costs of testing and its impact on the economic results is easily assessed. Varying the prevalence from the submitted value (16.6% yielding an ICER of £20,010 per QALY) between 5% and 25% generates an ICER range of £32,685 - £18,174 per QALY.

The impact of prevalence on outcomes (especially PFS and OS) is more complex and requires comparison of the outcomes reported by patient subgroups in IPASS.

The ERG sought additional information from the manufacturer in the form of a limited extract of IPD from the IPASS trial, to enable the consequences of changes to the prevalence of EGFR M+ status to be considered in more detail, with a view to improving the accuracy of SA. The manufacturer refused this request, and subsequently failed to provide specified statistical analyses requested by the ERG in time to assist in this investigation.

5.1.3 Sensitivity to adverse event costs and disutilities

It has been noted that the manufacturer's model only allows the costs and disutilities of AEs to be estimated in the first cycle (21 days) of treatment. In response to a request for clarification, the manufacturer acknowledges that it is likely that

> "applying a 21 day disutility for these adverse events may have underestimated their burden on HRQoL."

To estimate the impact of this uncertainty, the costs and effects of all AEs in the model have been doubled. In the submitted base case, this reduces the incremental cost per patient by £160, and increases the incremental QALYs slightly, so that the ICER for gefitinib compared to paclitaxel/carboplatin decreases from £20,010 to £18,845 per QALY gained.

5.1.4 Probabilistic sensitivity analysis

Although it would be instructive to perform a full PSA on the revised model, including a full set of potential comparators, this would require considerable additional time and resources to reprogramme and validate the amended procedures beyond what is currently available to the ERG. Key distributional parameters relating to HRs for OS and PFS are fixed at values which are relevant only to the manufacturer's base case, so that the PSA facility cannot currently generate accurate results when the parameter values for these variables are altered.

5.2 Summary of revised model results generated by the ERG

Table 5-1 provides a detailed set of results for the ERG base case analysis (gefitinib vs paclitaxel/carboplatin for EGFR M+ patients), indicating the individual effects of each of the amendments/corrections implemented by the ERG, together with a final revised base case results combining all the changes. The original ICER (£20,010 per QALY) is increased substantially to over £70,000 per QALY suggesting that cost effectiveness may be less favourable than presented in the MS.

Table 5-2 and Table 5-3 display similar findings for the five additional comparators including pemetrexed and docetaxel. These indicate broadly similar cost-effectiveness estimates ranging between £59,000 and £73,000 per QALY gained, except when pemetrexed/cisplatin is the comparator when it appears that gefitinib is dominated by pemetrexed (i.e. gefitinib is both more expensive and less effective than pemetrexed).

Table 5-1 Effect of corrections and amendments made by ERG to the manufacturer's model for the base case analysis (paclitaxel/carboplatin as 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 CTX costs	[redacted]	1.1110	£24,563	0.9235	£7,135	0.1874	£38,063	+£3,498	0.0000	+£18,054
Reduced cycles of CTX	[redacted]	1.1110	£25,527	0.9270	£6,170	0.1839	£33,544	+£2,420	-0.0035	+£13,535
Revise OS models	[redacted]	1.2219	£32,985	1.0834	£2,268	0.1384	£16,381	-£1,483	-0.0490	-£3,628
Revise PFS models	[redacted]	1.0923	£28,149	0.9181	£4,989	0.1741	£28,651	+£1,238	-0.0133	+£8,641
IPASS PFS HR (not MA)	[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 CTX costs	[redacted]	1.1110	£25,213	0.9235	£3,975	0.1874	£21,204	+£224	0.0000	+£1,194
CTX 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**

ICER= incremental cost effectiveness ratio; QALY=quality adjusted life year; CTX= chemotherapy; OS= overall survival; PFS= progression free survival; granulocyte colony stimulating factor; HR=hazard ratio; MA= meta-analysis

Table 5-2 Effect of corrections and amendments made by ERG to the manufacturer's model for the base case analysis (other modelled comparators) over 6 years

	Gemcitabine / carboplatin			**Vinorelbine / cisplatin**			**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 CTX costs	£4,057	0.1767	£22,956	£8,447	0.2229	£37,890	£4,077	0.1445	£28,215
Reduced cycles of CTX	£5,599	0.1735	£32,278	£9,547	0.2194	£43,512	£6,244	0.1409	£44,308
Revise OS 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 HR (not MA)	£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 CTX costs	£4,380	0.1767	£24,785	£8,085	0.2229	£36,264	£4,657	0.1445	£32,228
Common CTX outcomes	£5,114	0.1892	£27,028	£7,043	0.1896	£37,148	£5,149	0.1880	£27,394
CTX 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**

ICER= incremental cost effectiveness ratio; Inc. = incremental; QALY= quality adjusted life year; CTX= chemotherapy; PFS=progression free survival; OS= overall survival; GCSF= granulocyte colony stimulating factor; HR=hazard ratio; MA=meta-analysis

Table 5-3 Effect of corrections and amendments made by ERG to the manufacturer's model for the base case analysis (other modelled comparators) over 6 years (continuation of

Table 5-2)

	Docetaxel / cisplatin			**Pemetrexed / cisplatin**		
Model amendment	Inc. Costs	Inc. QALYs	ICER (£/QALY)	Inc. Costs	Inc. QALYs	ICER (£/QALY)
Submitted model [a]	-	-	-	-	-	-
With Revised MTC	**£4,434**	**0.1627**	**£27,252**	**-£134**	**0.0601**	**-£2,223**
Reduced cycles of CTX [b]	£6,254	0.1593	£39,263	£2,484	0.0565	£43,984
Revise OS models	£2,591	0.1013	£25,590	-£3,115	-0.0379	£82,125
Revise PFS models	£5,636	0.1494	£37,735	£1,091	0.0469	£23,271
IPASS PFS HR (not MA)	£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 CTX costs	£4,944	0.1627	£30,385	£842	0.0601	£14,004
CTX 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; Inc. = incremental; QALY= quality adjusted life year; CTX= chemotherapy; a -submitted model did not include these comparators b-submitted model did not include costs for these comparators; HR= hazard ratio; MA= meta-analysis

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

5.3 Summary of model critique

The manufacturer's submitted model is based on two parametric survival models (PFS and OS) implemented within a Markov framework using Microsoft Excel. The survival models employ a Weibull structure and are calibrated from analysis of IPASS trial data.

The assessment of this technology is more complex than the simple comparison of two treatment options presented by the manufacturer, since it involves both the specific diagnostic test employed to identify the presence of EGFR mutations and the treatment choice which follows from the test result (gefitinib or conventional CTX). It appears that the accuracy of the ARMS test to identify relevant mutations is very high (analytic validity), but the power of the test result to predict a good response to gefitinib treatment (clinical validity) is less pronounced. This suggests that the average benefits seen in IPASS for patients receiving gefitinib involve a trade-off between those who get a very good outcome (clinical 'true' positives), and those who get no benefit at all (clinical 'false' positive) but in fact are worse off since they lose the likely gain they could have expected from conventional CTX.

The extent and balance of this trade-off depends in part on the prevalence of detectable mutations in the target population as well as the characteristics of the population (both ethnicity and lifestyle). Evidence of the prevalence of mutations is scarce, and estimates vary widely in the range 5% - 25%.[10, 53] The higher the prevalence of mutations, the smaller the proportion of 'false' mutation positive patients suffering disadvantage; leading to suggestions of possible pre-screening (by known pre-disposing factors) of all candidate patients.

The ERG identified several major problems with the submitted model and the manufacturer's base case results:

- time horizon and primary comparator: This should be the longest period (six years) as the best approximation to a lifetime, comparing gefitinib to paclitaxel/carboplatin as in the IPASS trial

- CTX costing: Improved calculation methods and recent prices result in generally lower acquisition costs for treatment comparators

- the maximum number of cycles of CTX: In the IPASS trial this is six cycles, but this is not typical of UK clinical practice (four), and the model unreasonably assumes that all planned CTX cycles are delivered contrary to the trial data

- the Weibull survival models: These do not reflect the trial outcome results accurately. The ERG has proposed an improved model structure, which reduces the estimated gain from use of the gefitinib for both PFS and OS by about one month

- the manufacturer's MTC of comparator effectiveness: This depends on assumptions of proportional hazards which the IPASS trial data indicate may not be valid.

In addition the ERG identified several technical errors with the submitted model.

Wherever possible the ERG implemented corrections and/or amendments to the submitted model to address these issues, including incorporating updated MTC results provided by the manufacturer, and adding two additional comparators which were missing from the original MS.

Several important questions could not be considered in the absence of an extract of IPD from IPASS which the manufacturer refused to make available, or a set of statistical analyses requested and specified by the ERG.

Revised base case economic results were produced by the ERG, which indicate much poorer cost effectiveness for gefitinib in relation to all comparators, with re-estimated ICERs lying in the range £59,000 - £73,000 per QALY gained; exceptionally, it appears that gefitinib is dominated by pemetrexed/cisplatin therapy, being both more expensive and less effective. A threshold analysis indicates that although the manufacturer's PAS price represents a substantial discount on the NHS list price for gefitinib, it would require a substantially increased discount to be considered cost effective in relation to CTX comparators (excluding pemetrexed/cisplatin which is always preferred at any price).

6 End of life treatment criteria

6.1 Introduction

In the MS, the manufacturer did not make a case for gefitinib to be considered as an end of life medicine. However, as the ERG's suggested modifications/corrections to the manufacturer's economic model have increased the size of the manufacturer's base-case ICER, the ERG anticipates that discussion of gefitinib as an end of life treatment might prove useful to the Committee at the first Appraisal Committee meeting.

The end of life treatment criteria as stipulated by NICE has three key points:[54]

(i) treatment is indicated for patients with a short life expectancy, normally less than 24 months and;

(ii) there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional three months, compared to current NHS treatment;

(iii) treatment is licensed or otherwise indicated for small patient populations.

6.2 Application of the end of life treatment criteria

6.2.1 Patient life expectancy of less than 24 months

The ERG is of the opinion that the mean life expectancy of patients with advanced or metastatic NSCLC is likely to be less than 24 months.

6.2.2 Life extension of at least three months

The IPASS study has not yet reached maturity; only 450/1217 (37%) deaths have occurred. This means that there are no definitive OS data available for patients with EGFR M+ from this RCT. Consequently, there is insufficient evidence to indicate that the treatment offers an extension to life of at least an additional three months compared to current treatment.

6.2.3 Licensed for a small patient population

The MS estimates that, in England and Wales in 2010/11, approximately 290 newly diagnosed patients with NSCLC would be identified as being EGFR M+ (Table 6-1).

Table 6-1 Estimated size of target population in the MS

Assumptions	Number of patients	Reference
New registrations for lung cancer (England and Wales)	33,400	Cancer Research [55, 56]
80% of registrations are cases of NSCLC	26,728	NCCAC[12]
Staging available for 68% of patients	18,175	Not given
80% of patients have advanced or metastatic disease	14,540	National Lung Cancer Audit[6]
30% of patients would be eligible for chemotherapy	4,362	NCCAC [12]
Mutation status identified for 40% of patients	1,745	Based on IPASS
16.6% of patients will be EGFR TK M+	290	Rosell[9]

The ERG has the following concerns with the estimated size of the patient population:

- no reference is given for the assumption that staging will be available for 68% of patients
- the Rosell[9] study has been shown to include a number of weaknesses (ERG report, Section 5.7.2)
- the MS uses mixed data sources to estimate the size of the population.

However, the ERG highlights that despite the concerns outlined above it is very likely that gefitinib would meet NICE's criteria for a small population.

6.3 End of life treatment criteria: summary

Given the lack of OS data available to support the use of first-line gefitinib in the target population, gefitinib may not be appropriate for consideration under NICE's end of life treatment criteria.

7 Discussion

7.1 Summary of clinical effectiveness issues

The MS makes a convincing clinical case for the use of gefitinib in previously untreated patients with adenocarcinoma who are EGFR M+ based on the results of a patient subgroup analysis in IPASS. The inhibition of EGFR signalling in lung cancer is of major interest in the study of personalised medicine and IPASS makes a valuable contribution to this rapidly evolving area of scientific/medical research. Both the mutation test (ARMS) and the drug (gefitinib) used in IPASS can be considered as new health care technologies for the NHS with very little direct evidence of effectiveness. The genetic test has only been used in collaboration with AstraZeneca in a handful of NHS patients, and fully published randomised clinical evidence supporting the use of gefitinib as a first-line therapy is only available from the IPASS trial in a non-Caucasian population.

Patients are eligible for treatment with gefitinib only if they are deemed EGFR M+. In England and Wales the proportion of NSCLC patients who are likely to have EGFR M+ results is unknown. The manufacturer is currently offering EGFR M+ testing to all newly diagnosed patients with NSCLC. However the manufacturer's own experience with this test shows that data are limited; of only 65 EGFR mutation tests performed, seven tested positive for EGFR mutation. Robust evidence is not yet available to allow estimation of the prevalence of EGFR M+ in a UK population with any confidence. If resources are invested now in routine data collection, then accurate estimates of UK prevalence may be available in the future.

[redacted] However, the area of genetic testing is developing rapidly both in terms of the technology and the interpretation of specific mutations or combinations for clinical decision making. Each test has its performance characteristics (sensitivity and specificity), and associated predictive power for clinical effect in combination with a particular treatment. Thus the relevance of the evidence currently provided for the assessment of clinical effectiveness should be considered carefully.

The manufacturer supports the use of universal testing of newly diagnosed patients with NSCLC based on equity and equality grounds. The manufacturer is keen to ensure that all eligible patients are given the opportunity to receive treatment with gefitinib and therefore

does not support any pre-selection of patients before the EGFR mutation test is performed. Compared to a pre-selection strategy, a universal test strategy maximises the number of true positives in the population but simultaneously increases the number of clinical false positives (i.e. people who test positive for relevant mutations but who do not derive clinical benefit from gefitinib therapy) as more people are tested; this means that some patients will be erroneously treated with gefitinib instead of with doublet CTX. Strong circumstantial evidence from IPASS indicates that EGFR M- patients have very poor survival outcomes on gefitinib.

However, compared with a universal strategy, a pre-selection strategy offers an enriched sample of patients likely to have EGFR mutations and reduces the number of clinical false positives but at the cost of missing some EGFR M+ patients who were wrongly excluded from treatment with gefitinib because they were not tested and are therefore treated with the less clinically effective doublet CTX. The advantages and disadvantages of the two options for EGFR mutation testing must be carefully considered.

In summary, as highlighted in a recent publication[57] "...investigations should lead to the selection of a more specific subpopulation of cancer patients who benefit from therapy with EGFR inhibitors, but equally to spare those who will receive no benefit or a detrimental effect from such biological agents."

Finally, the EMEA[1] believes that the clinical evidence across trials to support the use of gefitinib in EGFR M+ patients is sufficiently convincing. The EMEA did not stipulate that a confirmatory trial exploring the use of gefitinib as a first-line treatment was required but it did request that further documented evidence of the clinical effectiveness of gefitinib be collected by the manufacturer in order to better define the level of EGFR mutation activity in Caucasian populations and further explore predictors of response.

7.2 Summary of cost effectiveness issues

The results of the economic evaluation of gefitinib in the MS are predicated on the use of the ARMS test (or similar). This means that if a different test is used to identify EGFR mutation status, for example direct sequencing, then a new estimate of cost effectiveness may be required.

A number of amendments and corrections have been made to the manufacturer's model, which taken together suggest that the use of gefitinib for patients with a positive mutation test

may not be considered conventionally cost effective compared to any of the available comparators.

A number of additional issues could not be fully explored without either an extract from the IPASS IPD, or the results of several additional data analyses requested by the ERG but not made available by the manufacturer in time to be considered in this report.

The revised and extended MTC provided by the manufacturer has allowed the ERG to consider the performance of the 'test+gefitinib' strategy against two additional CTX comparators. When combined with the other important model amendments made by the ERG (especially the alternative method of projecting PFS and OS beyond the IPASS trial period) this suggests that a short course of CTX with pemetrexed/cisplatin may be both less costly and more effective than targetted oral gefitinib for an extended period.

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7.3 Implications for research

There is a need for directly relevant evidence of clinical effectiveness for this new technology. Ideally this would involve at least one additional RCT involving a substantial proportion of Caucasian patients, preferably with a significant UK element, compared to at least one of the treatments currently recommended by NICE for first-line CTX for patients with NSCLC and would include EGFR testing of all patients.

In addition, in view of the complexity of the range of current and potential approaches to genetic testing, and the important uncertainties around the roles played by specific mutations (singly or in combination) in determining clinical benefit from gefitinib, it would be most valuable to have data from a long-term clinical registry of all UK patients treated with gefitinib and similar agents. Such a data source could provide a basis for research and audit to inform future assessments of gefitinib and similar agents together with the various genetic tests used to select patients for treatment.

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9 Appendix 1

Clarification questions and responses regarding EGFR testing in the UK

ERG question: Please provide further details of actual EGFR mutation testing currently taking place within the UK (e.g. number of tests conducted in each centre, type of test used, number/proportion of EGFR mutation positive, mutation negative, and mutation unknown patients etc).

AstraZeneca response: To date the majority of EGFR mutation testing takes place in commercial laboratories (e.g. Lab21) and multiple regional hospital laboratories (e.g. those listed on http://www.egfr-info.com/EGFR-exon/egfr-mutation-lab/).

EGFR testing	Tests performed	EGFR M+
Birmingham	23	3
Aberdeen	10	0
Leeds	4	0
Christie	4	0
Cardiff	14	2
Lab21	10	2
	65	7
EGFR mutation rate		10.7%

ERG question: Please clarify whether the ARMS test (as used in the IPASS study) is the same test as is proposed by AstraZeneca for use in UK clinical practice.

AstraZeneca response: The short-term strategy is to test patients with available methodologies that are "well-validated and robust" in line with the SmPC approved by the EMEA. This will include the EGFR29 TheraScreen kit (DxS), PCR/Sequencing and Pyrosequencing using quality processes which have been well validated within the laboratories supplying them operated by trained scientists (Quality Systems and Training Records are required, and membership of a regional quality network is advantageous). Commercial laboratories, e.g. Lab21 will provide testing using the EGFR29 TheraScreen Kit (DxS). This method is a one-step, CE marked kit, which is more sensitive than PCR/Sequencing. Please refer to A29 for details on the sensitivity of the techniques currently being used. At present, AstraZeneca is not actively seeking to advocate any one testing methodology, rather, it is seeking to optimise the number and quality of tumour samples which are suitable for EGFR Mutation testing.
Laboratories are invited to become testing facilities through the website http://www.egfr-info.com/Becoming-testing-laboratory/

ERG question: Please clarify the description of EGFR mutation testing by providing more detailed information on the infrastructure required to set up a universal and standardised method of testing in England and Wales.

AstraZeneca response: AstraZeneca is facilitating the uptake of EGFR testing in the UK. Much of this is being carried out through interactions with NHS hospital laboratory networks and through commercial laboratories. Regional quality networks are being established to monitor the quality of testing through efforts such as round-robin testing (same sample, multiple labs, testing concordance of results, followed by troubleshooting if necessary). Discussions with laboratories have indicated that a standardised methodology is not preferable, as occasionally test kits or specific reagents may become unavailable and this would result in patients not being able to access the service. Regional quality networks are the preferred way therefore, of ensuring continuity of high quality testing across the UK.

ERG question: Please outline the anticipated length of time it would take to set up a universal and standardised method of testing for EGFR mutations in England and Wales.

AstraZeneca response: Each laboratory will require 3-4 months to establish its testing service, validate its methodology and ensure that the testing methodology is robust and sensitive. An additional 2-3 months may be required to set up a whole network, however the framework for this already exists in the UK, so this second step may happen more quickly.
Where a laboratory chooses to use a commercially available kit, the set-up time may be much faster as the validation step is much more straightforward.

ERG question: Please provide details of the different types of EGFR mutation tests currently available.

AstraZeneca response: The EGFR29 TheraScreen kit, an ARMS technology, is the only EGFR mutation test available in kit form. There are many other molecular techniques available; please see http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/ for further details on the range of tests available.

- EGFR29 TheraScreen: http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/TheraScreen-Mutation-Kit/
- PCR/Sequencing: http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/egfr-Sequencing/
- Other Methods: http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/mutation-detection-methods/

ERG question: Please clarify what the associated accuracy rates of the different EGFR mutation tests are.

AstraZeneca response: EGFR29 TheraScreen quotes a sensitivity of 1% mutant DNA in normal background (given input of sufficient DNA). PCR/Sequencing is less sensitive, being able to detect 20% mutation in normal DNA background, while the other available methods are likely to be in between this range.

- Each test is heavily dependent on the quality and quantity of tumour tissue used for DNA extraction. For this reason, part of AstraZeneca's strategy is to work with pathologists to maximise the quality of the biopsy sample being taken. At present, the following issues have been identified and steps taken (including provision of information on a dedicated website) to address them.
- The type and as a consequence the **quantity** of sample obtained for the diagnosis of NSCLC is variable. Guidance:http://www.egfr-info.com/EGFR-mutation-analysis/).
- The **quality** of DNA from Formalin Fixed and Paraffin Embedded (FFPE) tissue is often poor due to the degradation that occurs during fixation. It is important to use established methods for DNA extraction to increase yield (http://www.egfr-info.com/EGFR-exon/DNA-extraction-methods/) and mutation assays that are designed against small fragments of DNA to increase assay success rates.
- Because tumours are heterogenous in nature, one way of increasing the chances of detecting a true positive result is to perform macrodissection to enrich for tumour cells prior to DNA extraction (http://www.egfr-info.com/EGFR-exon/egfr-tumour-cells/).

ERG question: Please clarify whether any of the EGFR mutation tests can use cytology rather than histology specimens.

AstraZeneca response: Currently the analysis of FFPE Biopsy/Resected Tissue is considered the "gold-standard" for mutation analysis. However, work is ongoing on surrogate tissues including cytology particularly in regions where this type of sample is used for diagnosis. The challenge is to obtain sufficient tumour cells of sufficient quality for downstream mutation analysis (http://www.egfr-info.com/EGFR-exon/egfr-mutation-future-analysis/). Although this has been demonstrated to be successful in a research setting*, at present cytology is not routinely used in clinical practice. (Once additional work has been carried out, our position will be reassessed and guidance for use of these samples may be released.)

ERG question: Please provide details on how AstraZeneca will ensure that the EGFR test proposed for use in UK clinical practice is robust. In the Summary of Product Characteristics leaflet for gefitinib, under special warnings and precautions, it states: "When assessing the EGFR mutation status of a patient, it is important that a well validated and robust methodology is chosen to avoid false negative or false positive determinations".

AstraZeneca response: AstraZeneca has launched a website (http://www.egfr-info.com/) which is aimed at both patients, healthcare professionals and importantly, molecular pathologists. This is a key part of AstraZeneca's strategy to ensure high quality, consistent testing. The website covers many areas of EGFR mutation testing including the generalised process for EGFR testing integrated with therapeutic decisions (http://www.egfr-info.com/EGFR-exon/). The key to success is to increase awareness of the need for quality samples, and quality testing using robust methodologies to ensure a robust result. Quality Systems and Training Records are required, and membership of a regional quality network is advantageous.

- Standardisation of the EGFR29 TheraScreen kit is achieved through the clear guidance on their kit insert (http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/TheraScreen-Mutation-Kit/).

- Standardisation of PCR/Sequencing and similar methods is more difficult, although aided by Quality Networks which influence laboratories to utilise best practice. In addition, AstraZeneca are providing guidance notes to kick-start best practice of EGFR mutation detection with PCR/Sequencing (Please see downloadable document on Best Practice at http://www.egfr-info.com/EGFR-exon/egfr-mutation-detection/egfr-Sequencing/). AstraZeneca is working with the Clinical Molecular Genetics Society (CMGS) to encourage this process.

Table 9-1 Responses to ERG mutation test survey of four hospitals named in MS

Question	BIRMINGHAM	WALES	MANCHESTER	MARSDEN
What EGFR TK mutation test(s) is (are) used?	We are testing the histology and cytology specimens by real time PCR using DxS kit	We are using DxS and sequence analysis, the choice depends on the required turnaround and how many samples we are able to batch. If there are only very few samples (i.e. 1 or 2) it is very expensive to us the DxS technology. However, the DxS kit is definitely more rapid than sequencing	We bi-directionally Sanger (fluorescent) sequence the entire coding sequence of EGFR exons 18, 19, 20 & 21	TheraScreen EGFR29 Mutation kit (DxS)
What is the sensitivity/specificity of the test(s)?	Test is known to be highly sensitive as with all tests performed by real time PCR; the main studies done on EGFR mutation including those recently published in N Engl J Med have been based on the DxS kit; the kit looks for the relevant mutations known to give response to Iressa including deletions in exon 19 and missense mutation at codon 858 within exon 21	The sensitivity of DxS is reported as 1%, the sensitivity of sequence is ~15-20%. However, for both we incorporate an additional step where we have the tissue samples assess by a histopathologist, we extract DNA from regions of the specimen with >40% tumour cells, therefore increasing confidence in a normal result. This would mean if there were only 40% tumour cells, we would still detect a mutation by sequence analysis	This has not been fully determined. Where applied to other genes the majority of point mutations (>95%) are detected and mutations can be detected down to an admixture level of at least 20% however the precise detection limit will depend on the sequence context of the mutation. We also do not require the material sent for analysis to have been selected for raised tumour cell content although we ask for an estimation of the tumour cell content	According to manufacturer's information the kit detects >95% of all mutations described in EGFR in NSCLC with 100% specificity –if used according to the guidelines-. In terms of limit of sensitivity, the manufacturer claims at least 1% of mutant *EGFR* alleles in a background of wild type *EGFR* alleles
How long has the testing system been in operation?	We have been working on setting up the EGFR mutation testing for 3 years, initially by direct sequencing and subsequently using the DxS kit, but we have been offering the testing as a routine test,	We've actually been performing EGFR analysis for the last 2 years as a clinical trial / research study. We have been analysing NHS clinical samples since August 2009	We have only been testing/validating for 6 weeks	Since February 2009 (9 months)

Question	BIRMINGHAM	WALES	MANCHESTER	MARSDEN
	since May 2009, after Iressa has been licensed			
How many EGFR TK M+, EGFR TK M-, and EGFR TK unknown patients have been identified?	At last review, 2 weeks ago, we had completed 60 cases and 12 showed a mutation; we have tested more cases since and could provide you with more detailed data	Since August 2009 we have analysed 12 samples, of these 10 were normal and 2 EGFR TK M+	We have identified 2 EGFR TK M- patients so far, none for the other categories	We have detected so far 15 EGFR mutants, 74 EGFR wild type and another 17 cases failed the analysis due to suboptimal sample quality
What systems, if any, have been set up to ensure that false positive and false negative determinations are minimised?	We do the EGFR testing, as all the other molecular tests we perform routinely, in a Laboratory which is CPA accredited for molecular pathology. There are therefore strict guidelines we follow for EGFR testing as for the other tests. The kit itself contains control reactions to detect false positive and false negative results	As above, false negatives are minimised by the histological confirmation that we are using the correct tissue sample and then DNA extraction only from areas which are rich in tumour cells. We then run molecular assays that will detect mutations at a level consistent with our histological selection. False positives are minimised through good laboratory practice (we are an accredited laboratory service), including separate pre-PCR and post-PCR set up areas, the running of positive and negative controls & a water blank, and all samples are checked by 2 individuals at every sample transfer step. If there are any concerns about the quality of a result as independently assessed by 2 pairs of eyes, the patient sample will be re-run	We operate to CPA accreditation standards. Any positive assay is repeated for confirmation. We aim to run known positive controls alongside analysis. These controls are being established	Unfortunately there is no EQA scheme available in the UK yet. We have used a commercially available kit that has been approved for IVD in the EU (TheraScreen EGFR29 mutation kit, DxS). This kit contains internal validation controls for >90% of the described EGFR mutations and was validated in our lab prior to use
Happy to help again?	Yes	Yes	Yes	Yes

10 Appendix 2

Table 10-1 IPASS inclusion and exclusion criteria

Inclusion criteria (main)	Exclusion criteria (main)
Provision of informed consent Male or female aged 18 years and over Histologically or cytologically confirmed NSCLC with adenocarcinoma histology (including bronchoalveolar). Note: adeno-squamous histology was not allowed. Locally advanced Stage IIIB not amenable to local therapy (eg, pleural effusion) or Stage IV (metastatic) disease. Never smokers* or light ex-smokers** .No prior chemotherapy, biological (including targeted therapies such as EGFR and VEGF inhibitors) or immunological therapy. Previous adjuvant chemotherapy was permitted if treatment was not platinum-based and was completed more than 6 months before Day 1 of study treatment. Prior surgery or radical radiotherapy had to be completed more than 6 months before Day 1. Palliative radiotherapy to a metastatic site was permitted, but palliative wide field radiotherapy to the lung had to be completed at least 4 weeks before Day 1, with no persistence of any radiotherapy-related toxicity. Measurable disease according to RECIST criteria with at least 1 measurable lesion not previously irradiated. WHO PS of 0 to 2 Willing to complete the FACT-L questionnaire.	Known severe hypersensitivity to gefitinib or any of the excipients of this product. Known severe hypersensitivity to carboplatin, paclitaxel or any of the excipients of these products. Known severe hypersensitivity to pre-medications required for treatment with carboplatin / paclitaxel doublet CTX. Newly diagnosed CNS metastases that had not yet been definitively treated with surgery and/or radiation. Patients with previously diagnosed and treated CNS metastases or spinal cord compression could be considered if they were clinically stable and had been discontinued from steroid therapy for at least 4 weeks prior to first dose of study medication. Other co-existing malignancies or malignancies diagnosed within the last 5 years (as detailed in protocol amendment 01) with the exception of basal cell carcinoma or cervical cancer in situ. Past medical history of interstitial lung disease, drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active interstitial lung disease. Pre-existing idiopathic pulmonary fibrosis evidence by computerised tomography (CT) scan at baseline. Any unresolved chronic toxicity greater than CTC AE Grade 2 from previous anticancer therapy ANC< 2.0 x 109/L (2,000/mm3), platelets <100 x 109/L (100,000/mm3) or haemoglobin <10 g/dL Serum bilirubin >1.5 x ULRR. Serum creatinine >1.5 times the ULRR or creatinine clearance less than or equal to 60 mL/min As judged by the investigator, any evidence of severe or uncontrolled systemic disease (eg, unstable or uncompensated respiratory, cardiac, hepatic or renal disease). Evidence of any other significant clinical disorder or laboratory finding that made it undesirable for the patient to participate in the study ALT or AST > 2.5 times the ULRR if no demonstrable liver metastases or greater than 5 times the ULRR in the presence of liver metastases. Pregnancy or breast-feeding. Insufficient lung function as determined by either clinical examination or an arterial oxygen tension (PaO2) of < 70 Torr. Unable to tolerate carboplatin / paclitaxel doublet CTX, as judged by the investigator. Life expectancy of <12 weeks. Concomitant use of phenytoin, carbamazepine, rifampicin, barbiturates, or St. John's Wort. Treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment Involvement in the planning and conduct of the study (applied to both AstraZeneca staff or staff at the investigational site). Previous enrolment or randomisation of treatment in the present study. Known biomarker status of 1 or more of the following: tumour EGFR gene copy number, tumour EGFR gene mutation status, tumour EGFR protein expression (as detailed in protocol amendment 01).

* defined as having smoked <100 cigarettes in their lifetime; ** defined as having ceased smoking at least 15 years before Day 1 of study treatment and having smoked 10 pack-years or fewer; AE=adverse event; ALT= alanine aminotransferase; ANC= absolute neutrophil counts; AST= aspartate aminotransferase; CNS=central nervous system; CTC=common terminology criteria; CTX=chemotherapy; FACT-L=Functional Assessment of Cancer Therapy-Lung; PS=performance status; RECIST=Response evaluation criteria in solid tumourss; ULRR= upper limit of reference range; VEGF=vascular epidermal growth factor; WHO=World Health Organization

Table 10-2 Validity assessment of the IPASS trial

Criteria for critical appraisal	Response in MS (verbatim)	ERG comment
How was allocation concealed?	Open-label: Although the study was open-label, the EGFR mutation status was not known by either the patients or the clinicians during the conduct of the study, and thus would not have affected the efficacy outcomes. It is not practical to blind an IV chemotherapy (that requires specialist administration and pre-medication) versus an oral tablet, with both drugs also having very well established and different side-effect profiles.	Even in open-label trials it is possible to blind the allocation to treatment (i.e. prior to patient receiving treatment).
What randomisation technique was used?	Centralised Registration/ Randomisation Center. Randomisation was via a central IVR telephone system to receive in a 1:1 ratio gefitinib or paclitaxel/carboplatin. The stratification factors for randomisation were smoking status; performance status; smoking status (non-smoker or ex-light smoker); gender; and centre.	Randomisation was via a central IVR telephone system and was stratified using dynamic balancing, by performance status, smoking history, sex and centre. This technique is used to produce a balance across important individual factors but not within each subtype of patient. Randomisation was not stratified by mutation status which is the focus of the MS and so mutation status is not randomly assigned across the treatment groups which could confound results.
Was a justification of the sample size provided?	The sample size goal is to conclude non-inferiority; the 95% CI for the HR had to lie entirely below the predefined non-inferiority limit of 1.2. A total of 944 progression events were needed for 80% power to conclude non-inferiority if the treatments were truly equal, with a 2-sided 5% probability (significance level) of concluding non-inferiority in error. If the CI for the HR was also below 1, then the P value would be <0.05 and superiority could be concluded from the same analysis without statistical penalty (closed test procedure). The analysis also included an evaluation of the efficacy of gefitinib compared to paclitaxel/carboplatin in pre-planned subgroups including the EGFR M+ population.	Based on the sample size method the IPASS trial would be adequately powered for testing for differences between the two arms of the trial in all patients, although it would not be adequately powered for the subgroup analysis which included the EGFR M+ population.
Was follow-up adequate?	Median follow-up (defined as time from randomisation to progression or censoring) for the primary endpoint of PFS was 5.6 months. A total of 950 progression events had occurred at this time (950/1217, 78% maturity), sufficient to meet the target of at least 944 events. At the time of data cut-off, 450 deaths had occurred (450/1217, 37% maturity). An early analysis was performed, however survival follow up will continue and the final analysis of the secondary endpoint of OS will take place when at least 944 deaths have	The primary endpoint of the trial was PFS and so follow-up is adequate for this outcome. However follow-up for OS is ongoing and final estimates may be difficult to interpret given high rates of patient cross-over.

Criteria for critical appraisal	Response in MS (verbatim)	ERG comment
	occurred.	
Were the individuals undertaking the outcomes assessment aware of allocation?	Yes - for efficacy and safety variables. No - for determination of EGFR mutation (and other biomarker) status	PFS can be subject to assessment bias and this outcome would have been made more robust if assessment had been blinded.
Was the design parallel-group or cross-over? Indicate for each cross-over trial whether a carry-over effect is likely.	Parallel group	Although the trial was parallel group, potential confounding could have occurred due to treatment cross-over after disease progression which would impact upon OS estimates. Forty one percent of patients in the gefitinib arm received paclitaxel/carboplatin (39% was second line) and 13% of patients received other CTX following gefitinib. Fifty percent of the patients in the doublet CTX arm went on to receive an EGFR at any point (38% gefitinib, 7% erlotinib and 6% other EGFR) and 11% went on to receive other CTX. This 'cross-over' of treatment means that any benefit in OS may be confidently ascribed to the treatment which patients were originally randomly assigned.
Was the RCT conducted in the UK ? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	No. This study included patients from 87 centers in China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan, and Thailand Clinical practice is similar to that in the UK at the time the study was conducted. The doublet CTX regimen used in the IPASS study is used in the UK along with other combination regimens which have demonstrated similar clinical efficacy to paclitaxel/carboplatin.	Although paclitaxel/carboplatin is used in clinical practice in the UK it is used in a minority (5-6%) of patients; the most common doublet CTX in the UK is gemcitabine plus platinum-based CTX.
How do the participants included in the RCT compare with patients who are likely to receive the intervention in the UK? Consider	IPASS was conducted in a clinically pre-selected study population recruited patients who were never or ex-light smokers with adenocarcinoma histology which showed benefit in previous gefitinib studies. From a planned subgroup analysis, IPASS showed that EGFR mutation status was driving the benefit. The patients in the RCT are a good representative sample of patients who are likely to receive doublet CTX in the UK in terms of important prognostic characteristics such as stage of disease and PS, as outlined in current clinical guidelines considered in UK	Baseline characteristics of patients in IPASS appear to be very different to those of first-line NSCLC population in the UK. Patients in IPASS are mainly younger, female, oriental, non-smokers with adenocarcinoma. Only 25% of NSCLC patients in England and Wales requiring first-line treatment have adenocarcinoma histology. Testing for EGFR M+ status is currently not ready for implementation

Criteria for critical appraisal	Response in MS (verbatim)	ERG comment
factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	clinical practice. Therefore the IPASS EGFR M+ population can be considered to be representative of the UK EGFR M+ population. The EGFR mutation is the same in all NSCLC patients regardless of ethnicity and patient characteristics and gefitinib should work the same in all EGFR M+ patients.	across the UK. Gefitinib treatment is dependent upon this test being carried out to identify EGFR M+ patients.. Results from IPASS demonstrate that patients who are EGFR M- have greater clinical benefit from paclitaxel/carboplatin than gefitinib. Therefore patients with a false positive result (from EGFR mutation testing) would not receive the best treatment.
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Gefitinib: 250mg once daily Paclitaxel (200mg/m^2)/Carboplatin (AUC 5/6) on day 1 every 3 weeks These doses are within the dosage regimens contained in the relevant UK SPCs	The dosing regimens are appropriate in the IPASS trial.
Were the study groups comparable?	Yes, demographic and baseline characteristics were well balanced between the two treatment groups and the population was representative of the advanced NSCLC population clinically selected for this study.	The treatment arms appear balanced for baseline demographic characteristics.
Were the statistical analyses used appropriate?	Yes, the analyses were pre-specified in the protocol at the start of the study and a comprehensive statistical analysis plan was prepared before database lock and analysis	Efficacy results were only presented for an ITT population and not the PP population as would be expected for a non-inferiority trial. However the majority of patients received the treatment to which they were randomised and so differences between the two analyses would be expected to be small – this was confirmed by the manufacturer who provided PP efficacy data on request.
Was an intention-to-treat analysis undertaken?	Yes	ITT was undertaken and presented.
Were there any confounding factors that may attenuate the interpretation of	Evaluation of patient scans in this open-label study did not include a BICR. Although there could be potential for some bias to be introduced in the measurement of PFS and ORR, RECIST criteria were used and tumour responses were calculated programmatically based on tumour measurements for target lesions (as opposed to	MS presents efforts to counter potential assessment bias due to not including a BICR. However confounding might have occurred due to cross-over of treatment and the fact that randomisation was not stratified by mutation status.

Criteria for critical appraisal	Response in MS (verbatim)	ERG comment
the results of the RCT(s)?	investigator assessment of tumour response) to increase the robustness of these endpoints. In addition, the clear difference in PFS efficacy results for patients with EGFR M+ status compared with those who are EGFR M- in IPASS indicates that the RECIST data are robust because the EGFR mutation status of patients was not known at the time the scans were evaluated. Further, additional analyses that investigated evaluation-time bias (differential assessment frequency between arms) did not indicate any bias in favour of gefitinib. In conclusion, given the level of superiority observed for gefitinib in IPASS, progression assessments are considered robust and not affected by bias due to lack of central radiological review in this open label study.	

BICR= blinded independent central review; CI=confidence interval; CTX=chemotherapy; HR=hazard ratio; IV=intravenous, IVR=interactive voice response; ORR=objective response rate; OS=overall survival; PFS=progression free survival; PS=performance status; RECIST=Response Evaluation Criteria in Solid Tumours

Table 10-3 Demographic and Baseline Characteristics of the NEJGSG trial

	North East Japan Gefitinib Study Group trial.	
Kobayashi 2009	**Gefitinib (n=98)**	**Paclitaxel/Carboplatin (n=100)**
Age (SD)	Mean 63.4 (7.8)	Mean 62.8 (8.7)
Gender (% male)	56 (80%)	46 (66%)
Ethnicity - Caucasian - Oriental - Other	Not reported (assumed 100% Oriental)	Not reported (assumed 100% Oriental)
- non-smoker - current smoker	64 (65.3%) 34 (34.7%)	58 (58.0%) 42 (42.0%)
PS 0 PS 1 PS 2	48 (49.0%) 49 (50.0%) 1 (1.0%)	49 (49.0%) 49 (49.0%) 2 (2.0%)
- adenocarcinoma - large cell carcinoma - adenosquamous carcinoma - squamous cell carcinoma - other	88 (89.8%) 1 (1.0%) 2 (2.0%) 3 (3.1%) 4 (4.1%)	96 (96.0%) 0 (0.0%) 1 (1.0%) 2 (2.0%) 1 (1.0%)
Stage IIIB Stage IV Stage relapse	11 (11.2%) 77 (78.6%) 10 (10.2%)	18 (18.0%) 75 (75.0%) 7 (7.0%)
EGFR mutations Exon 19 deletion L858R Others	 50(51.0%) 43 (43.9%) 5 (5.1%)	 50 (50%) 43 (43.0%) 7 (7.0%)

Table 10-4 Critical appraisal of the NEJGSG trial

10.1.1 Criteria for Critical Appraisal	North East Japan Gefitinib Study Group trial
How was allocation concealed?	Open-label
What randomisation technique was used?	Randomised 1:1 ratio, balanced for institution, sex, and stage
Was a justification of the sample size provided?	Sample size was calculated for PFS to demonstrate superiority of gefitinib vs paclitaxel/carboplatin (HR 0.69, alpha = 5%, power = 80%)
Was follow-up adequate?	Only an interim analysis of PFS is available, that was pre-specified 4 months after 200 patients had entered the trial. A subsequent analysis is planned to take place later in 2009
Were the individuals undertaking the outcomes assessment aware of allocation?	Yes
Was the design parallel-group or cross-over? Indicate for each cross-over trial whether a carry-over effect is likely.	Parallel group
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	No – the trial took place in multiple centres in Japan
How do the participants included in the RCT compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.	The trial was conducted in Japanese patients with NSCLC that were EGFR M+, were chemo-naïve, PS 0-1, aged 20-75 years
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Gefitinib: 250mg once daily Paclitaxel (200mg/m^2)/Carboplatin (AUC 6) on day 1 every 3 weeks
Were the study groups comparable?	Demographic characteristics appear to be well-balanced between groups, although slightly fewer patients were non-smokers in the doublet CTX arm compared to the gefitinib arm (58% vs 65%) but slightly more patients adenocarcinoma (96% vs 88%) and with less advanced NSCLC (stage IIIB 18% vs 11%) in the doublet chemotherapy arm compared to the gefitinib arm
Were the statistical analyses used appropriate?	No details provided
Was an intention-to-treat analysis undertaken?	No details provided
Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	No

CTX=chemotherapy; HR=hazard ratio; PFS=progression free survival