STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Erlotinib for the first-line treatment of EGFR-TK mutation positive non-small cell lung cancer

This report was commissioned by the NIHR HTA Programme as project number 11/08

Completed 13th December 2011

Contains in confidence data

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Erlotinib for the first-line treatment of EGFR-TK mutation positive non-small-cell lung cancer

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Date completed: 13th December 2011

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 11/08

Declared competing interests of the authors: None

Acknowledgements:
The authors are pleased to acknowledge the help of Dr Ernie Marshall who provided clinical advice and reviewed the final draft of the report.

Rider on responsibility for report:
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Order of authors. Greenhalgh J, Bagust A, Boland A, Blundell M, Beale S, Dundar Y, Dickson R, Proudlove C, Green J A, Mooney J. Erlotinib for the first-line treatment of EGFR-TK mutation positive non-small-cell lung cancer: A Single Technology Appraisal. LRiG, The University of Liverpool, 2011.

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Michaela Blundell	Critical appraisal of clinical statistical approach
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Chris Proudlove	Critical appraisal of the manufacturer's submission
Joanne Mooney	Critical appraisal of the clinical sections of the manufacturer's submission
John Green	Critical appraisal of the clinical sections of the manufacturer's submission

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

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Abbreviations

AC	Appraisal Committee
AE(s)	Adverse event(s)
BNF	British National Formulary
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CTX	chemotherapy
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EGFR M+	Epidermal growth factor receptor mutation positive
EMA	European Medicines Agency
e-MIT	Electronic Marketing Information Tool
EQ-5D	EuroQol 5D (a standardised instrument used as a measure of health outcome)
ERG	Evidence Review Group
EURTAC	European Tarceva vs Chemotherapy trial
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-L	Functional Assessment of Cancer Therapy-Lung
FAS	Full analysis set
FDA	Food and Drug Administration
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IRC	Independent Review Committee
ITT	Intention to treat
KM	Kaplan-Meier
LUCADA	Lung Cancer Data
LYG	Life year gained
MS	Manufacturer submission
MTC	Multiple treatment comparison
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-small cell lung cancer
NS	Non-squamous
OS	Overall survival
PD	Progressive disease
PR	Partial response
PFS	Progression-free survival
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SA	Sensitivity analysis
SD	Stable disease
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TKI	Tyrokinase inhibitor
vs	versus
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 Roche Ltd in support of the use of erlotinib (Tarceva®) as a first-line treatment for patients with epidermal growth factor (EGFR) tyrokinase (TK) mutation positive (M+) locally advanced or metastatic non-small cell lung cancer (NSCLC). The manufacturer's submission (MS) describes the use of erlotinib compared with doublet chemotherapy (CTX) and with gefitinib for people with previously untreated EGFR M+ locally advanced or metastatic NSCLC.

In September 2011, the European Medicines Agency (EMA) granted an extension to the existing marketing authorisation for erlotinib to include the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations.

1.2 STA process

The ERG identified very early in the process of this STA that there was a significant issue with the submission received from the manufacturer, namely:

- The manufacturer does not compare erlotinib vs pemetrexed as advised in the final scope issued by NICE;
- The incomplete mixed treatment comparison (MTC) fails to provide the appropriate links between the intervention and the comparator;
- The patient treatment pathways used in the model are not in line with current NICE guidance;
- The economic model indicates survival gain that is not demonstrated by the clinical evidence available.

The ERG's concerns were relayed to the NICE technical team. A joint ERG, NICE and manufacturer teleconference failed to result in any agreed way forward. Following discussions internally at NICE the ERG was asked to proceed with their critique of the submission. Due to the limitations identified by the ERG, the ERG was unable to formulate any clarification questions to put to the manufacturer and only a limited critique of the evidence has been possible.

1.3 Key points identified from the critique of submitted clinical-effectiveness evidence

The manufacturer does not compare erlotinib vs pemetrexed as advised in the final scope issued by NICE. This raises the following issues:

1. The manufacturer correctly states that gefitinib is the current standard of care in England and Wales for patients with EGFR M+ NSCLC due to the fact that it was recommended by NICE. However, the manufacturer does not comment on the fact that at the time of the gefitinib appraisal only immature clinical data from the IPASS trial were available to the Appraisal Committee. Nor does the manufacturer mention in the MS that the recently updated IPASS results now confirm that there is no OS gain for gefitinib vs third-generation CTX.

2. NICE's recommendation of gefitinib as a treatment for EGFR M+ NSCLC does not preclude the use of pemetrexed. Pemetrexed is the only drug that yields a statistically significant OS benefit over a third-generation CTX (gemcitabine) in patients with non-squamous lung cancer and patients who are EGFR M+ are predominantly patients with non-squamous disease. The ERG acknowledges that there is no RCT which investigates the use of pemetrexed in an EGFR M+ population and that it is uncertain whether erlotinib would be cost effective compared with pemetrexed in this patient population. However, until the matter has been fully explored firm conclusions cannot be reached.

3. The assumption that all third-generation CTX treatments are equally clinically effective for EGFR M+ patients must be carefully investigated as there is no single trial or group of trials which explore the validity of this assumption.

1.4 Key points identified from the critique of submitted cost-effectiveness evidence

The manufacturer's economic model:

1. Generates results that are uncertain in the sense that they do not provide incremental cost-effectiveness ratios (ICERs) for the full list of available treatments for patients with NSCLC who are EGFR M+;

2. Has a structure which means that in order to explore additional treatment pathways it would need to be rebuilt;

3. Yields OS gains for the first-line treatment of EGFR M+ patients with erlotinib and gefitinib that are not demonstrated by the published RCT evidence (leading to artificially low ICER estimates);

4. Fails to include the costs and benefits of second-line treatments (second-line treatments are a standard feature of lung cancer economic models).

1.5 Conclusion

As noted above, the ERG is only able to offer a limited critique of the evidence submitted. Further information and analyses are required in order to allow a fair assessment of the cost effectiveness of erlotinib as a first-line treatment for patients with EGFR M+ locally advanced or metastatic NSCLC.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

In the context section of the MS (MS, pg 38 to 45), 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,

Box 2 and Box 3. The manufacturer's interpretation of the treatment pathway is described in Figure 1 and Figure 2.

Box 1 Description of the underlying health problem

Non-small cell lung cancer (NSCLC) accounts for about 85% of the approximately 33,500 new cases of lung cancer which occur each year in England and Wales.[1, 2]

Most cases of lung cancer prove rapidly fatal, with 1 year and 5 year survival rates of around 30% and less than 10%, respectively, so that in 2007 there were 29,660 deaths from the disease in England and Wales, making it the biggest cause of cancer deaths in the country and a major public health issue.[2]

The dismal prognosis for patients with NSCLC is a reflection of the fact that most patients present with advanced disease where the efficacy of current treatments is modest. According to audit data, 67% of lung cancer patients in this country present with tumours which have either spread within the chest (Stage IIIB, locally advanced disease) or to distant organs (Stage 4, metastatic disease) to an extent where cure is not a realistic prospect.

Box 2 Current established treatment for advanced/metastatic NSCLC

For patients with Stage IIIB or Stage IV disease, the treatment recommended by NICE[3] is combination chemotherapy (CTX) with a platinum-based drug (cisplatin or carboplatin) plus a second active cytotoxic drug (gemcitabine, paclitaxel, docetaxel, vinorelbine or pemetrexed) administered with a view to extending survival by a few months whilst palliating the debilitating symptoms of advanced NSCLC (cough, pain and dyspnoea in particular). Recently, gefitinib (see below) has become an option for a subgroup of patients with NSCLC. NICE[3] recommends CTX only for patients with a performance status of 0-1; this rules out almost half of UK patients with stage IIIB/IV disease. Combined with other factors this has historically led to low treatment rates in the UK. Around half the patients who are treated achieve a reduction in their tumour burden or stabilisation of their disease following CTX and may be eligible for further maintenance treatment either with single agent CTX (NICE recommends pemetrexed[4]) or erlotinib.

The manufacturer correctly states that CTX treatments recommended for patients with advanced or metastatic NSCLC in NICE guidelines (CG121)[3] include a platinum-based drug plus gemcitabine, paclitaxel, docetaxel, vinorelbine or pemetrexed; however, the ERG notes that pemetrexed is recommended (and only in combination with cisplatin) as a first-line treatment for a specific subgroup of patients with NSCLC, those with confirmed histology of adenocarcinoma or large cell carcinoma (i.e. patients with non-squamous disease).

In relation to the maintenance setting, the manufacturer states that single agent pemetrexed or erlotinib may be used. The ERG notes that NICE recommends[4] only pemetrexed as a maintenance

treatment. The use of pemetrexed as a maintenance treatment is limited to patients who have not immediately progressed after first-line CTX and who did not receive pemetrexed as a first-line treatment.

Box 3 EGFR status and current UK treatment

Recent advances in both technology (including access) and new data have led to a more personalised approach to treating chemo-naïve NSCLC patients in turn leading to better clinical outcomes and better quality of life for the patient depending on the therapy they are receiving. Following NICE TA192[5] in 2010, testing for the epidermal growth factor (EGFR) mutation has become the standard of care in the UK. In TA192[5] NICE recommends gefitinib, an EGFR tyrokinase inhibitor (TKI) for patients who are CTX-naïve and EGFR mutation positive (M+). For those patients whose tumours are found to harbour an activating EGFR mutation (EGFR M+) an EGFR TKI (such gefitinib or erlotinib) is now utilised as a first line agent in around 95% of all patients (Kantar Health Wave 4, May 2011) with gefitinib accounting for over 90% of all first line EGFR TKI use). For patients whose tumours are found not to harbour an activating EGFR mutation (i.e. those who are EGFR wild-type (WT)) or whose tumours cannot be properly assessed for mutation status (perhaps due to lack of tissue for testing) it is standard practice to utilize a pemetrexed/cisplatin CTX doublet.[6] As the scope of this appraisal is limited to those patients with EGFR M+ tumours this EGFR WT population is not considered within the evaluation undertaken.

Erlotinib provides an alternative first-line treatment option to gefitinib for patients with EGFR M+. It is estimated that around 400 patients a year are eligible for first-line treatment with erlotinib.

The ERG questions the manufacturer's statement that EGFR testing is included in the standard care treatment package in the UK. The clinical advisors to the ERG are of the opinion that not all centres in England and Wales are able to offer EGFR testing and moreover, EGFR testing may not be routinely carried out. In a summary statement in the MS (MS, pg187), the manufacturer states that its own market research has shown that over the last 2 years EGFR mutation testing has become routine practice in the UK with over 90% of UK clinicians having access to EGFR mutation testing (Roche Market Research). Thus, there remain around 10% of centres with no access to EGFR testing.

The manufacturer states that for patients whose tumours do not harbour activating EGFR mutation it is standard practice to utilise a pemetrexed/cisplatin CTX doublet. The ERG notes that pemetrexed/cisplatin is recommended as a first-line treatment only for patients with confirmed adenocarcinoma or large cell carcinoma. Patients with other types of NSCLC will be treated with a platinum doublet of vinorelbine, gemcitabine or docetaxel or paclitaxel.

The ERG considers the manufacturer's estimate, that 400 patients would be eligible each year for first-line treatment with erlotinib, to be credible.

Treatment pathway

The manufacturer describes the proposed place of erlotinib in the treatment pathway for patients identified with EGFR M+ disease. This is replicated in Figure 1 and Figure 2.

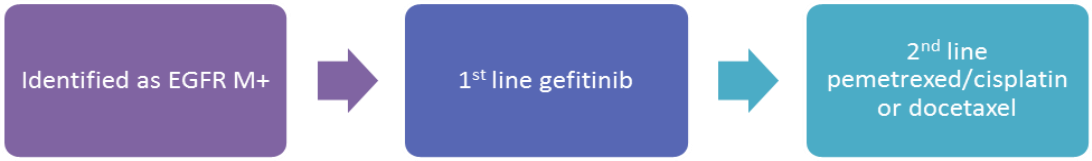

Figure 1 Current treatment pathway

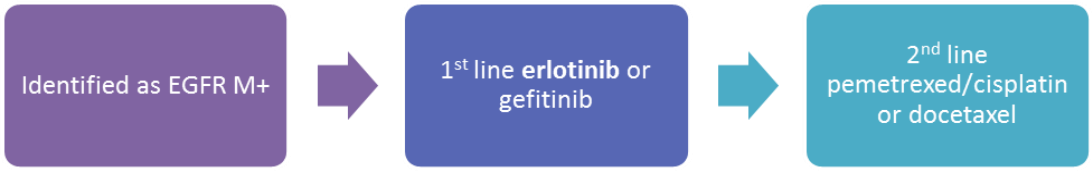

Figure 2 Proposed treatment pathway including erlotinib

The manufacturer (reflecting the opinion of its clinical advisors) maintains that patients who currently receive gefitinib as a first-line treatment receive either platinum doublet CTX (specifically pemetrexed/cisplatin) or docetaxel monotherapy upon progression. The manufacturer concludes that second-line treatment following erlotinib would be the same as that following gefitinib.

The ERG notes that the treatment pathways described in the MS do not reflect NICE clinical guidelines[3]. These guidelines[3] do not distinguish between disease subtypes (i.e. undifferentiated, squamous, non-squamous or EGFR M+). The NICE recommended second-line treatments for all patients with NSCLC are docetaxel or erlotinib; pemetrexed/cisplatin as depicted in Figure 1 and Figure 2 is not currently an option recommended by NICE. Clinical advice to the ERG is that second-line treatment after erlotinib or gefitinib is likely to be a platinum doublet (gemcitabine or vinorelbine) but not pemetrexed/cisplatin as this combination is not approved by NICE for second-line treatment of patients with NSCLC.

2.2 Critique of manufacturer's overview of health problem and current service provision

The MS provides a summary of the incidence and prognosis of NSCLC in England and Wales. With regard to the manufacturer's account of current service provision, the ERG notes that whilst the manufacturer may consider that EGFR testing is the 'standard of care' in UK clinical practice, not all centres are able to offer the test nor do all centres routinely offer the test to patients. The manufacturer's description of second-line treatments following an EGFR TKI differs from those

recommended in NICE guidelines[3] and also from our clinical expert opinion. Whether the manufacturer's description of second-line treatment options reflects UK clinical practice is therefore open to debate.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

The final scope[7] issued by NICE and the manufacturer's statement of the decision problem is described in the MS and the summary table is reproduced in Table 1.

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

	Final scope issued by NICE	**Decision problem addressed in submission**
Population	Adults with previously untreated EGFR-TK mutation positive locally advanced or metastatic non-small-cell lung cancer	As per scope
Intervention	Erlotinib	As per scope
Comparator(s)	• Gefitinib For people with non-squamous NSCLC of adenocarcinoma or large cell carcinoma histology: • Pemetrexed in combination with cisplatin or carboplatin	Gefitinib only See section 2.6. Market research indicates that an EGFR TKI (erlotinib or gefitinib) is currently used in the first line treatment of 95% of UK patients with an EGFR M+ tumour. Only around 5% of patients receive doublet CTX. Whilst pemetrexed/platinum may have been an appropriate comparator to gefitinib in TA192 the sizeable uptake in first line use of an EGFR TKI in the 12 months following the issuance of TA192 indicates that this is no longer the case. A UK patient with an EGFR M+ tumour is nearly 20 times more likely to receive an EGFR TKI than doublet CTX as a first line treatment (with that likelihood increasing rapidly in an extremely short period of time following approval of gefitinib). In addition it should be noted that in TA192 it was found that an indirect comparison of 'traditional doublet CTX' and pemetrexed/cisplatin in an EGFR M+ population was not possible due to a lack of data on the efficacy of pemetrexed/cisplatin in this group. In light of this declining relevance of pemetrexed/cisplatin in this group and the difficulty/impossibility in conducting such a comparison (as concluded in TA192) the pemetrexed based doublet CTX regimens detailed in the scope are not addressed as comparators within the submission.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life	As per scope
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 of any additional mutational testing required for this treatment should be considered in the economic analysis.	As per scope Whilst as per scope it should be noted that EGFR mutation testing is currently standard practice in the NHS. There is no additional mutational testing associated with the first line use of erlotinib and therefore no incremental cost. The ERG notes that mutation testing is not universal in the NHS
Subgroups to be considered	None	As per scope

3.1 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.[7]

The patient population in the main trial presented in the MS (EURTAC[8]), is described as patients with previously untreated stage IIIB/IV NSCLC with tumours that have EGFR exon 19 deletion or exon 21 L858R mutation.

The patients in the EURTAC[8] trial are described as Caucasian and the trial was carried out in 42 centres in European countries. The ERG notes that the major RCTs in the same clinical area have all been conducted in centres in East Asia.

3.2 Intervention

The intervention in the MS is erlotinib. This matches the intervention stated in the final scope issued by NICE.[7] Erlotinib is an orally administered inhibitor of EGFR which is over-expressed in various solid tumours including NSCLC. Erlotinib is licensed in Europe for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations. In the EURTAC[8] trial, erlotinib was given at a dose of 150mg daily until disease progression, unacceptable toxicity or death.

3.3 Comparators

Two comparators to erlotinib are described in the final scope[7] issued by NICE. Firstly, gefitinib for adults with previously untreated EGFR-TK mutation positive locally advanced or metastatic non-small-cell lung cancer. Secondly, pemetrexed in combination with cisplatin or carboplatin for those adults with previously untreated EGFR-TK mutation positive locally advanced or metastatic non-small-cell lung cancer who also have non-squamous NSCLC of adenocarcinoma or large cell carcinoma histology. (The ERG notes that pemetrexed is licensed and recommended by NICE for use as a first-line treatment only in combination with cisplatin).

Comparator 1 - gefitinib

In the EURTAC[8] trial, patients were randomised to receive either erlotinib or platinum-based CTX (docetaxel or gemcitabine). The EURTAC[8] trial did not include gefitinib as a comparator and no head to head trial exists that compares erlotinib with gefitinib. To allow such a comparison to be made the manufacturer has conducted a systematic review and mixed treatment comparison (MTC).

Comparator 2 - pemetrexed

In the MS, the manufacturer has not included pemetrexed as a comparator to erlotinib. The manufacturer justifies this approach with the following statements (MS, pg 47):

> "Market research indicates that an EGFR TKI (either erlotinib or gefitinib) is currently used in the first line treatment of 95% of UK patients with an EGFR M+ tumour. Only around 5% of patients receive doublet chemotherapy. Whilst pemetrexed/platinum may have been an appropriate comparator to gefitinib in TA192[5] the sizeable uptake in first line use of an EGFR TKI in the 12 months following the issuance of that guidance indicates that this is no longer the case. A UK patient with an EGFR M+ tumour is nearly 20 times more likely to receive an EGFR TKI than doublet chemotherapy as a first line treatment (with that likelihood increasing rapidly in an extremely short period of time following approval of gefitinib).
>
> In addition it should be noted that in TA192 it was found that an indirect comparison of 'traditional doublet chemotherapy' and pemetrexed/cisplatin in an EGFR M+ population was not possible due to a lack of data on the efficacy of pemetrexed/cisplatin in this group. In light of this declining relevance of pemetrexed/cisplatin in this group and the difficulty/impossibility in conducting such a comparison (as concluded in TA192) the pemetrexed based doublet CTX regimens detailed in the scope are not addressed as comparators within the submission."

The ERG understands the manufacturer's view that few patients appear to be treated with pemetrexed and therefore gefitinib is the key comparator of interest. However, the remit of the ERG is to assess all the clinical and economic information available. It is the view of the ERG that appropriate consideration of the decision problem requires consideration of erlotinib vs pemetrexed. The rationale underlying the ERG's position is outlined below.

The manufacturer has failed to provide a persuasive argument that pemetrexed is not a valid comparator. The manufacturer has simply stated that few patients are treated with pemetrexed and that it would be difficult or impossible to conduct a comparison of pemetrexed/cisplatin in an EGFR M+ population as there are no pemetrexed data available for the EGFR M+ population.

Pemetrexed is listed as a comparator in the final scope[7] issued by NICE. Thus the consultees at the scoping workshop considered that for people with NSCLC of adenocarcinoma or large cell carcinoma histology, pemetrexed is an appropriate comparator to erlotinib.

At the Appraisal Committee (AC) meeting for gefitinib, the AC considered the results of a MTC conducted by the manufacturer of gefitinib. The MTC included standard CTX therapy with a platinum drug and paclitaxel, docetaxel, gemcitabine or vinorelbine and pemetrexed for patients with non-squamous histology. It is stated in the guidance document (TA192[5]) that "the Committee accepted that there was uncertainty in these comparisons but concluded that it was likely that gefitinib

was no less efficacious than pemetrexed with cisplatin, and that pemetrexed in combination with cisplatin was the relevant comparator for gefitinib." The ERG considers that, as gefitinib and pemetrexed are believed to be equally efficacious, both treatments should be compared with erlotinib as stated in the final scope[7] issued by NICE in order to fully address the decision problem.

In its appraisal of gefitinib, the ERG demonstrated that pemetrexed dominated gefitinib (i.e. it was cheaper and more clinically effective). This comparison of pemetrexed with gefitinib is clearly restricted to the context of the gefitinib STA appraisal given the clinical and economic assumptions used by the manufacturer of gefitinib. It is the opinion of the ERG that erlotinib should be compared with gefitinib and pemetrexed within a single framework where consistent and transparent assumptions are made in order to fully address the decision problem set out by NICE.

Pemetrexed is the only first-line treatment for patients with non-squamous lung cancer which demonstrates a statistically significant OS gain when compared with a third generation treatment (gemcitabine).[9] Recently published updates from the IPASS[10] trial have reported that there is no overall survival (OS) gain for gefitinib vs third generation CTX treatment. A recently published meta-analysis[11] of RCTs that compared gefitinib with CTX also failed to demonstrate any OS benefit for treatment with gefitinib. This means that the efficacy gap between pemetrexed and gefitinib has grown wider in favour of pemetrexed. The ERG considers pemetrexed is a valid comparator since almost all EGFR M+ patients have non-squamous lung cancer.

The proportions of patients with non-squamous disease in the six clinical trials of EGFR TKI drugs, as cited by the manufacturer, are illustrated in Table 2.

Table 2 Proportion of patients in major trials of EGFR TKI drugs with non-squamous disease

Trial Name	Proportion of patients with non-squamous disease
IPASS[10, 12]	99.8-100%
First - SIGNAL[13]	100%
NEJGSG002 [14]	95.2-97.8%
WJTOG3405[15]	97.7-99.4%
OPTIMAL[16]	94.8%
EURTAC[8]	100%

In formulating its TA192[5] guidance for gefitinib, NICE considered a range of interventions for the treatment of EGFR M+ patients including pemetrexed; the ERG notes that NICE recommended gefitinib as an option for this population but did not exclude the use of pemetrexed for this group of patients. Not all hospitals throughout England and Wales have easy access to EGFR M+ testing. Clinical advisors to the ERG have noted that EGFR testing is not routinely performed in all hospitals. The manufacturer's own market research has demonstrated that over 90% of UK clinicians have access to EGFR mutation testing. This means that there are centres (10%) that still do not have routine access to EGFR testing. The ERG considers that it is reasonable to assume that some patients who are EGFR M+ will be treated with pemetrexed if (i) the hospital does not routinely test for EGFR (ii) delaying treatment (e.g. waiting for test results) would be detrimental to the patient's health.

In summary, the ERG is of the opinion that without appropriate consideration of pemetrexed as a comparator, the evidence presented by the manufacturer in the MS is incomplete and does not allow a full evaluation of erlotinib as set out in the decision problem.

3.4 Outcomes

The outcomes addressed in the MS are those listed in the final scope issued by NICE, namely OS, PFS, response rates, adverse events (AEs) and health-related quality of life (QoL). These outcomes are standard in this disease area.

The primary outcome of the EURTAC[8] trial was PFS, defined as the time between randomisation and the first occurrence of progressive disease (both radiological and clinical progression) or death from any cause, whichever occurred first.

The ERG notes that the OS results for EURTAC[8] are immature at both the interim and the updated analysis are presented in the MS.

3.5 Other relevant factors

In order for a patient to receive gefitinib, the EGFR mutation status of the patient must be known. It is unclear whether all patients in England and Wales will have timely access to EGFR testing.

4 CLINICAL EFFECTIVENESS

As noted in the previous section of this report, the ERG is of the opinion that the evidence presented in the MS is incomplete as it does not include pemetrexed as a comparator. In this section, the ERG provides a commentary on i) the main clinical trial (EURTAC[8]) presented in the MS in support of the efficacy of erlotinib in patients with EGFR M+ NSCLC and ii) the MTC conducted by the manufacturer to compare the clinical effectiveness of erlotinib with gefitinib.

The manufacturer has provided extensive detail in respect of two RCTs, EURTAC[8] and OPTIMAL.[16] However, the manufacturer states (MS, p58) that it considers that clinical evidence from EURTAC[8] forms the basis of the submission.

Table 3 Key clinical information in the MS

Key information	Section in the MS (page)
Description of the technology	Section A (28)
Context	2 (36)
Equity and equality	3 (46)
Statement of decision problem	4 (47)
Literature search main	5.1 (51)
Literature search indirect comparison and MTC	5.7 (123)
Search strategies	Appendix 2 (289)
Study selection	5.2 (53)
Clinical effectiveness evidence key trial:	
Trial information	5.3 (55)
Results: main	5.5 (94)
Results: subgroups	5 (101)
Results: safety	5.8.3.1(173)
Clinical effectiveness evidence meta-analysis	5.6 (114)
Clinical effectiveness evidence MTC:	
Trial information	5.7.2.1 (126)
Results: main	5.7.6 (167)
Results: safety	5.8.3.3 (182)
Results: non-RCT evidence	5.8 (170)

MTC= mixed treatment comparison

4.1 Description of manufacturer's search strategy and ERG comment on the search strategy

The aim of the literature search described in the MS was to identify evidence from RCTs on the efficacy of erlotinib in the first-line treatment of patients with activating mutations of the EGFR tyrokinase (MS, p51).

Four electronic databases were searched, Medline, Embase, Medline in Process and the Cochrane Library. The search strategy described in Appendix 2 of the MS used a filter to identify RCTs and combined drug name (erlotinib/tarceva) with disease. Search terms for electronic databases (Medline, EMBASE and CENTRAL) appropriately included a combination of free-text and index terms. In addition to the electronic searches, internal experts at Roche who were involved in the erlotinib clinical trial program were questioned; this strategy identified the EURTAC[8] trial which has yet to be published.

The search strategy is in line with the stated aim of the search and the manufacturer has carried out searches in all relevant databases. The manufacturer's search yielded 98 non-duplicate records.

4.1.1 Statement of the inclusion/exclusion criteria used in the study selection and ERG comment

Table 4 describes the inclusion and exclusion criteria presented in the MS. These appear to be appropriate to the manufacturer's stated aims.

Table 4 Key inclusion and exclusion criteria

Inclusion	Exclusion
Randomised controlled trials	Observational data, registry analyses, single arm studies, meta-analyses
Previously untreated NSCLC (metastatic) patients whose tumours harbour an activating mutation of the EGFR tyrosine kinase	Early NSCLC patients, small-cell patients, patients previously treated for their metastatic NSCLC (i.e. maintenance treatment, second and later line treatment), patients with tumours that do not contain a mutation of the EGFR tyrosine kinase or have unknown EGFR mutation status non-metastatic NSCLC
Erlotinib monotherapy	Erlotinib combination therapy, non-erlotinib therapy
Any comparator capable of informing the relative efficacy of erlotinib to gefitinib	Investigational agents
Outcomes of PFS, OS, AEs	

4.1.2 Identified studies

The manufacturer identified two RCTs, EURTAC[8] and OPTIMAL.[16] As noted previously, the manufacturer selected only the EURTAC[8] trial to form the basis of the evidence submission for the efficacy of erlotinib in patients with EGFR M+ NSCLC. The manufacturer states that the EURTAC[8] trial is the only phase III RCT to compare an EGFR TKI to standard platinum doublet chemotherapy in a Caucasian population according to EMA standards. The OPTIMAL[16] trial was conducted with patients from an East Asian background. The ERG notes that the manufacturer's inclusion and exclusion criteria do not limit the patient population to Caucasian patients only. In Section 5.6 of the

MS the manufacturer presents evidence that cautions against pooling the data from the EURTAC[8] and OPTIMAL trials. Neither EURTAC[8] nor OPTIMAL[16] compares erlotinib with gefitinib or erlotinib with pemetrexed, the comparators specified in the decision problem.

The EURTAC[8] trial formed the basis of the EMA's regulatory approval of erlotinib in this indication. Supportive evidence was provided from the OPTIMAL trial.[16] The ERG notes the EMA's concerns regarding the lack of clinical study report (CSR) available for the OPTIMAL trial.[16] The EPAR[17] published by the EMA states that the database for the trial was not designed for regulatory purposes and the data quality and Good Clinical Practice compliance could not be evaluated. For information, the key characteristics of the OPTIMAL[16] trial are described in Appendix 2 of this ERG report.

The EURTAC[8] trial is at present unpublished. All information presented in the ERG report is derived from the MS or the CSR.

4.1.3 EURTAC trial characteristics

Table 5 provides details of the EURTAC[8] trial which is a phase III RCT that compares erlotinib with platinum-based CTX, namely docetaxel or gemcitabine in CTX-naive patients (updated analysis, n=174) with stage IIIb/stage IV EGFR M+ NSCLC. Recruitment to the trial was stopped on the advice of the independent data monitoring committee (IDMC) when the results of the interim analysis where made known.

The ERG notes that EURTAC[8] does not compare erlotinib with gefitinib and none of the CTX regimens include pemetrexed.

Table 5 EURTAC trial characteristics

Trial design and number of participants	Intervention/comparator	Key inclusion/exclusion criteria	Outcomes
Multi-centre, Phase III, open-label RCT Centres in Spain, France and Italy (n=42) N= 174 CTX-naive stage IIIb/Stage IV EGFR M+ NSCLC Patients were randomised 1:1 to either erlotinib or CTX Randomisation was stratified according to i) ECOG status and ii) deletion in exon 19 vs mutation in exon 21 L858R	Intervention: Erlotinib 150mg once daily. until disease progression, unacceptable toxicity or death Comparator: Cisplatin 75 mg/m^2 i.v. Day 1 and docetaxel 75 mg/m^2 i.v. Day 1. Repeat cycles every 3 weeks or Cisplatin 75 mg/m^2 i.v. on Day 1 and gemcitabine 1250 mg/m^2 on Days 1 and 8. Repeat cycles every 3 weeks or Docetaxel 75 mg/m^2 Day 1 and carboplatin AUC = 6 Day 1, every 21days or Gemcitabine 1000 mg/m^2 Days 1 and 8 and carboplatin AUC = 5 Day 1, every 21 days Platinum doublet CTX was administered for a maximum of 4 cycles (3 months)	Inclusion: Histologic diagnosis of NSCLC, stage IV or stage IIIB with malignant pleural effusion or N3 tumours not candidates for thoracic irradiation who present exon 19 deletions or an exon 21 L858R mutation in the TK domain of EGFR (histology was performed locally) Measurable or evaluable disease Patients over 18 years ECOG <=2 Adequate bone marrow reserve, kidney and liver function Negative serum or urine pregnancy test before start (where appropriate) Patients to a contraceptive method (where appropriate) Oral swallowing capability Absence of intestinal transit problems that could alter absorption of the medication Exclusion: Pregnant, lactating, positive pregnancy test or did not undertake the test. Sexually active men and women (of childbearing age) not willing to use contraceptive methods during the study. Previous treatment with CTX for metastatic disease. The administration of neoadjuvant or adjuvant chemotherapy was allowed as long as it was completed ≥ 6 months before entering the study. Previous treatment with therapeutic agents targeting EGFR. Patients could have received radiotherapy as long as the irradiated lesion was not the only target lesion for evaluating response and as long as radiotherapy had been completed before starting study treatment (2-week period recommended). Treatment with an investigational drug agent within 3 weeks of enrolment in the study. Any known significant ophthalmologic anomaly of the ocular surface. The use of contact lenses was not recommended. Pre-existent motor or sensorial neurotoxicity grade ≥ 2 according NCI-CTC. Evidence of spinal cord compression. Incapacity to take oral medication or previous surgical procedures that affect absorption Other serious diseases or clinical conditions Absolute contraindication for steroid use. Dementia or significantly disturbed mental state that could interfere with the patient's understanding and granting of informed consent. History of another neoplasm other than carcinoma in situ of the uterine cervix, basal cell skin carcinoma treated adequately, or prostate carcinoma with a good prognosis (Gleason ≤ 6) treated radically. History of another neoplasm treated curatively and without evidence of disease in the last 5 years	Primary: Progression free survival Secondary: • Overall survival (early analysis; follow-up ongoing) • Objective tumour response rate – best overall response • Disease control • Quality of life • Safety • Tolerability

ECOG=Eastern Cooperative Oncology Group

4.1.4 EURTAC quality and validity assessment

Quality assessment and internal validity

The quality assessment of the EURTAC[8] trial conducted by the manufacturer (MS, pgs 91 to 93) and reviewed by the ERG is presented in Appendix 1. The EURTAC[8] trial is an open-label RCT in which neither clinicians nor patients were blinded to treatment. In general, the ERG considers the EURTAC[8] trial to be a well-designed trial, suitably powered to demonstrate its primary objective.

Generalisability to UK population

The comparators in the EURTAC[8] trial were platinum-based CTX, namely docetaxel and gemcitabine. These do not match either of the comparators stated in the decision problem issued by NICE[1] nor do they match the treatments in current use in UK clinical practice, i.e. gefitinib or pemetrexed/cisplatin

The ERG notes that the baseline characteristics of the patients in the EURTAC[8] trial reflect those patients in UK clinical practice who would be considered eligible for treatment with an EGFR TKI.

The patients in the EURTAC[8] trial were recruited to the trial from centres in Italy, Spain and France. The ERG considers the standards of care in these countries to be comparable to those of the UK.

The inclusion and exclusion criteria of the EURTAC[8] trial appear to be reasonable.

4.1.5 Description and critique of the manufacturer's outcome selection

The outcome measures for the EURTAC[8] trial presented in the MS are described in Table 6. 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[7] and are appropriate.

Table 6 Outcome measures used in EURTAC

Outcome	Definition and measure	Timing of assessment
Progression-free survival	The time between randomisation and the first occurrence of progressive disease (both radiological and clinical progression) or death from any cause, whichever occurred first. RECIST criteria used	Every 6 weeks
Overall survival	The time between randomisation and the date of death, irrespective of the cause of death	Not applicable
Objective response – best overall response	A patient was considered to be a responder if their best overall response was either CR or PR. Patients with a best overall response of SD, PD or missing were considered to be non-responders. Objective response analysis was performed according to the investigator's assessment of tumour response	
Disease control	defined either as response (CR, PR) or maintained disease stabilisation (SD for at least 6 weeks).	
Quality of life	The Lung Cancer Sub-Scale (LCSS) of the FACT-L questionnaire	The protocol requested that QoL assessments be completed every 3 weeks until disease progression on both treatment arms.

CR= complete response; PD= progressive disease; PR = partial response; SD= stable disease

4.1.6 Description and critique of statistical approach

The EURTAC[8] trial was an open-label study, meaning that investigators, patients and sponsor would all be aware of treatment allocations after randomisation had taken place. The primary outcome was PFS which can be a rather subjective outcome so the lack of blinding could lead to a potential assessment bias. However, the investigator assessment was backed up by an Independent Review Committee so the risk of bias should not be an issue in this trial. The ERG is however concerned by the statement in the MS that says allocation concealment was "not applicable as EURTAC[8] was an open label study" (MS, pg 92). Allocation concealment is equally as important in an open-label trial as it is in a blinded trial, the investigator should not be aware of the treatment allocation until after the patient has been randomised into the trial as prior knowledge of the treatment allocation may influence their decision to enter the patient into the trial.

Patients were randomised by means of fax to receive either erlotinib or CTX. The choice of CTX was at the discretion of the investigator and was selected based on the patients' best interests. Randomisation was stratified by ECOG performance status (0, 1 or 2) and deletion in exon19 vs mutation in exon 21 L8858R. While it is clear that efforts were made to balance treatment groups with respect to these factors, it does not appear that the manufacturer stratified by centre, which according to ICH E9[18] is advisable in a multicentre trial. Blocked randomisation with a block size of two was used but as it is unclear whether randomisation was stratified by centre, the ERG is unable to comment on the appropriateness of this method.

The planned sample size in EURTAC[8] was 174 patients and appears to be appropriate based on the following assumptions:

- Median PFS of 10 months in the erlotinib arm and of 6 months in the CTX arm, corresponding to a hazard ratio (HR) of 0.6
- Two-sided log rank test at 5% significance level for testing the hypothesis of equality of survival distribution of the parameter PFS
- Interim analysis after 65% of the PFS events had occurred in this study
- Lan-DeMets alpha-spending function with a Pocock stopping boundary
- 5% yearly dropout rate.

A two-sided log-rank test was used for testing the difference in PFS and OS between the erlotinib and CTX arms. Median and 95% confidence limits were estimated using K-M survival methodology. Plots of the Kaplan-Meier (K-M) estimates for each treatment group were also produced. The Cox proportional hazards model was used to estimate the hazard ratio (erlotinib vs CTX) and 95% confidence intervals. For the other secondary outcomes, further tests between the two treatment arms were performed, all were two-sided at a 5% significance level. All randomised patients were included in the full analysis set (FAS) analysis and presented according to the treatment they were randomised to receive (equivalent to the commonly termed intention-to-treat analysis). The primary analysis was performed on both the FAS and the per protocol set which evaluated all patients who did not violate the protocol in a major way (this was not presented in the MS but the results can be found in the CSR and are comparable to the results for the FAS). All other efficacy analyses were performed on the FAS only. All patients who received at least one dose of trial medication and had at least one safety follow-up, whether withdrawn prematurely or not, were included in the safety analysis and were analysed and presented according to the therapy they received. The ERG is satisfied with the general statistical approach employed in the trial.

An interim analysis was planned after 88 PFS events were observed across both arms. The required number of events was reached in August 2010 and the interim analysis was performed. At this time 92 events had occurred, slightly exceeding the total number of events required. After reviewing the results of the interim analysis based on the investigators' and Independent Review Committee (IRC) assessments, the IDMC decided that the study had met its primary objective and recommended that the study be closed. The ERG notes from the CSR that between the time of the interim analysis and the IDMC meeting, the number of patients recruited to the trial had increased from 154 to the trial target of 174. The effect of the IDMC's decision to close the trial at the interim analysis with regard to the follow-up and treatment of patients is unclear. The ERG notes that it has been recently demonstrated[19] that large differences in treatment effect sizes exist between trials that have been stopped early and similar trials that run their full course; this has been shown to be true regardless of the methodological quality of trials or the presence of statistical stopping rules.

Subgroup analysis: clinical effectiveness

In EURTAC, Cox-regression analyses including only treatment allocation as an explanatory variable were performed for certain subgroups of patients (i.e. univariate analyses). These analyses were conducted based upon the baseline characteristics recorded within the study and the stratification factors detailed previously.

4.2 Results

The MS presents a pre-specified interim analysis (based on 92 events in both arms) and an updated analysis (based on 111 events in both arms). The results of the interim analysis for the primary and secondary efficacy outcomes for the overall patient population in EURTAC[8] are summarised in Table 7. The results of the updated analysis are summarised in Table 8. The ERG notes that the OS data are immature at both analysis time-points. It is further noted that the EURTAC[8] trial does not compare erlotinib with any of the comparators listed in the final scope[7] issued by NICE.

The results of the interim analysis show a statistically significant benefit in favour of erlotinib for the primary endpoint of PFS in both the investigator-assessed and IRC-assessed analyses. In the investigator assessment, the median PFS in the erlotinib arm is 9.4 months compared with 5.2 months in the CTX arm ($p<0.0001$) . The risk of progression was significantly reduced by 58% (HR 0.42; [95% CI 0.27 to 0.64]) for patients in the erlotinib arm. One year after randomisation 37% of patients in the erlotinib arm compared with 12% of patients in the CTX arm were event free.

In the IRC analysis, median PFS is 10.4 months in the erlotinib arm compared to 5.4 months in the CTX arm ($p=0.0030$)

The manufacturer reports that for the initial interim analysis of the primary PFS endpoint, the K-M curves for PFS begin to separate at around 6 weeks and remain well separated over the course of the observation period

A statistically significant benefit in favour of erlotinib (investigator and IRC) is also observed for the secondary endpoint of best overall response. In reporting the outcome of disease control, the MS states that in the investigator assessment, there was no difference between the two arms. However, a statistically significant difference in favour of erlotinib was observed in the investigator assessment (71.4% vs 47.4%; $p = 0.0024$).No difference in OS between erlotinib and CTX is reported. In the opinion of the manufacturer, OS outcomes will be compromised by patients moving to post-progression treatment.

In the updated analysis, no IRC assessment was carried out. The investigator-assessed results are similar to those of the interim analysis with a statistically significant benefit in favour of erlotinib reported for the primary endpoint of PFS. The median PFS for patients in the erlotinib arm increased

to 9.7 months from 9.4 months at the interim analysis and the relative risk of having a PFS event for erlotinib-treated patients was reduced to 0.37 (95% CI: 0.25 to 0.54). One year after randomisation 40% of patients in the erlotinib arm compared with 11% of patients in the CTX arm were event free

The manufacturer reports that in the updated analysis of the primary PFS endpoint, the K-M curves for PFS also begin to separate at around 6 weeks and remain well separated over the course of the observation period.

A statistically significant benefit in favour of erlotinib is also observed for the secondary endpoint of best overall response for the erlotinib arm compared with the CTX arm (58.1% [95% CI: 47.0% to 68.7%] vs 14.9% [95% CI: 8.2% to 24.2%]$p < 0.0001$). No difference in OS between erlotinib and CTX is reported; however the ERG notes that more patients in the erlotinib arm had died (44.2% vs 35.6%)

Table 7 Key efficacy results of EURTAC (interim)

Outcome	Erlotinib (n/%)	CTX (n/%)
Median PFS (Investigator assessed)		
Patients with event	45 (58.4)	47 (61.8)
Median (months)	9.4	5.2
p-value (log-rank)	<0.0001	
HR (95% CI):		
Non-stratified	0.42 (0.27 to 0.64]	
Stratified	0.39 (0.25 to 0.61]	
Median PFS (IRC assessed)		
Patients with event	31(40.3)	30 (39.5)
Median (months)	10.4	5.4
p-value (log-rank)	<0.0030	
HR (95% CI):		
Non-stratified	0.47 (0.28 to 0.78]	
Stratified	0.55 (0.32 to 0.94]	
Overall survival		
Patients with event	27 (35.1)	27 (35.5)
Median (months)	22.9	18.8
p-value (log-rank)	0.4170	
Cox regression HR (95% CI)		
Non-stratified	0.80 (0.47 to 1.37]	
Stratified	0.88 (0.51 to 1.52]	
Best overall response (Investigator assessed)		
Responders	42 (54.5)	8 (10.5)
Non-responders	35 (45.5)	68 (89.5)
Difference in response rate [approx 95% CI, Hauck-Anderson]	44.02 (30.2 to 57.9)	
p-value (Chi-squared test)	<0.0001	
Complete response	2 (2.6)	0 (0)
Partial response	40 (51.9)	8 (10.5)
Stable disease	18 (23.4)	42 (55.3)
Progressive disease	6 (7.8)	10 (13.2)
Missing	11 (14.3)	16 (21.1)
Best overall response (IRC assessed)		
Responders	32 (41.6)	7 (9.2)
Non-responders	45 (58.4)	69(90.8)
Difference in response rate [approx 95% CI, Hauck-Anderson]	32.35 (18.8 to 45.9)	
p-value (Chi-squared test)	<0.0001	
Complete response	1 (1.3)	0 (0)
Partial response	31 (40.3)	7 (9.2)
Stable disease	23 (29.9)	29 (38.2)
Progressive disease	3 (3.9)	4 (5.3)
Missing	19 (24.7)	36 (47.4)

p-values are based on non-stratified analysis

Table 8 Key efficacy results of EURTAC(updated)

Outcome	Erlotinib (n/%)	CTX (n/%)
Median PFS (Investigator assessed)		
Patients with event	52 (60.5)	59 (67.8)
Median (months)	9.7	5.2
p-value (log-rank)	<0.0001	
HR (95% CI):	0.37 (0.25 to 0.54)	
Overall survival		
Patients with event	38 (44.2)	31 (35.6)
Median (months)	19.3	19.5
p-value (log-rank)	0.8702	
HR (95% CI)	1.04 (0.65 to 1.68)	
Best overall response (Investigator assessed)		
Responding	50 (58.1)	13 (14.9)
Non-responders	36(41.9)	74 (85.1)
Difference in response rate [approx 95% CI, Hauck-Anderson]	43.20 (29.7 to 56.7)	
p-value (Chi-squared test)	<0.0001	
Complete response	2 (2.3)	0 (0)
Partial response	48 (55.8)	13 (14.9)
Stable disease	18 (20.9)	44 (50.6)
Progressive disease	6 (7.0)	11 (12.6)
Missing	12 (14.0)	19 (21.8)

Subgroup analysis: clinical effectiveness

The results of the analyses of PFS by stratification factors were consistent with those of the FAS.

Post-progression treatments(updated analysis)

The MS reports that more patients in the CTX arm (77%) compared with the erlotinib arm (45%) received second- and further-line treatments. The manufacturer notes that this may be partly because i) more patients in the erlotinib arm were still on treatment at the cut-off for the updated analysis (due to the longer PFS compared with the CTX arm) and ii) more patients in the CTX arm compared with the erlotinib arm crossed over to receive another treatment after withdrawing from EURTAC[8] due to an AE, investigator's criterion or other reasons.

Specific post-progression treatments are recorded in the MS. In the CTX arm, 66 of the 67 patients who received post-progression treatment, received at least one treatment with a TKI (65 received erlotinib). In the erlotinib arm, anti-metabolites (mainly pemetrexed) were administered to 30 of the 39 patients (77%) who received post-progression treatment. This was the case for 13/67 (19.4%) patients in the CTX arm. It is reported in the MS that platinum-based compounds were administered to 27 of 39 patients (69%) who received a second- or further-line treatment in the erlotinib arm compared with 5 of 67 patients (7%) in the CTX arm.

Quality of life

The manufacturer appropriately used the Lung Cancer Symptom Scale[20] (LCSS) as a measure of quality of life (QoL). However, completion rates of the questionnaire were low and the data were considered by the manufacturer to be inconclusive. The results of the LCSS[20] in the EURTAC[8] trial were not submitted as part of the clinical-effectiveness evidence. The manufacturer has instead chosen to present the QoL data from the OPTIMAL[16] trial.

The QoL data were derived from 128 (83.2%) patients participating in the OPTIMAL[16] trial. Quality of life assessment was based on the Functional Assessment of Cancer Therapy–Lung (FACT–L)[21] questionnaire (in which scores range from 0 to 136, with higher scores indicating better QoL) and the Trial Outcome Index (TOI, which is the sum of the physical well-being, functional well-being, and lung-cancer subscale [LCSS] scores of FACT-L[21]). In the OPTIMAL[16] trial, patients were randomised to receive either erlotinib or gemcitabine/carboplatin. The manufacturer reports that on all the QoL scales, patients who received erlotinib experience significantly greater improvements in QoL compared with patients who received CTX. Gender, performance status and smoking history were assessed as covariates.

The ERG questions the generalisability of the QoL results. The ERG notes that the CTX regimens differed between the EURTAC[8] and OPTIMAL[16] trials. EURTAC[8] patients in the CTX arm received a platinum-based doublet therapy containing either docetaxel or gemcitabine. As noted earlier, the patients in OPTIMAL[16] were derived from a Chinese, rather than a European population. The duration of PFS (median) for patients in OPTIMAL[16] was 13.1 months in the erlotinib arm compared with 4.6 months in the CTX arm (HR=0.16; 95% CI 0.11 to 0.26). This is in contrast to the updated analysis of the EURTAC[8] trial which demonstrates median PFS in the erlotinib arm to be 9.7 months and 5.2 months in the CTX arm (HR=0.37; 95% CI 0.25 to 0.54). Differences in comparators, ethnicity of the patients and size of PFS benefit may render the generalisability of the QoL data from the OPTIMAL[16] trial open to question. As the manufacturer has argued against pooling the data from these two trials (see Section 4.3 below) it is unclear why the manufacturer is using the patient experience of QoL in the OPTIMAL[16] trial as a measure of patient experience of erlotinib vs CTX in the EURTAC trial. Further, the ERG notes that these QoL data do not indicate whether there are any differences between erlotinib and gefitinib, or between erlotinib and pemetrexed.

Safety (interim analysis)

The adverse events experienced by patients in the EURTAC[8] trial are summarised in the MS (pgs 174-6). The manufacturer's summary table is replicated in Table 9. According to the MS, the safety profile of erlotinib in the EURTAC[8] trial is consistent with that demonstrated in the first-line maintenance and relapse settings for NSCLC.

The manufacturer notes the differences in duration of treatments between the erlotinib and CTX arms of the trial; patients in the erlotinib arm were treated until progression or unacceptable toxicity (typically 9 to 10 months) whereas patients in the CTX arm received a maximum of four cycles (approximately 3 months). The manufacturer states that patients treated with erlotinib can thus continue active treatment for longer compared with CTX, but that an extended treatment period may also increase the number of reported AEs.

The majority of the reported AEs in both arms were Grade 1 or Grade 2 (432/527 events [82.0%] in CTX arm and 621/681 events [91.2%] erlotinib). Fewer patients experienced Grade 3 or 4 events in the erlotinib arm (31 patients [41.3%]) compared with the CTX arm 49 patients [66.2%]).

Similar frequencies of gastrointestinal disorders across both treatment arms are reported, (69.3% and 67.6% in the erlotinib and CTX arms, respectively); however, there were differences in the frequencies of each subtype. Diarrhoea was more commonly reported in the erlotinib arm compared with the CTX arm (57.3% vs 18.9%) whilst nausea (40.5% *vs* 22.7%), vomiting (21.6% *vs* 13.3%) and constipation (21.6% *vs* 8.0%) were more frequently reported in the CTX arm.

More skin toxicities (rash, dry skin, acne and pruritus) are reported in the erlotinib arm compared with the CTX arm (82.7% vs 23%). Fewer incidences of haematological toxicities are noted in the erlotinib arm compared with the CTX arm.

The ERG notes the greater number of incidences of dyspnoea in the erlotinib arm compared with the CTX arm (41.3% vs 25.7%).

The manufacturer reports an increased incidence of infections and infestations for patients in the erlotinib arm (49.3% *vs* 16.2% for erlotinib and CTX respectively). The manufacturer notes that this is the result of the incidence of paronychia (16%) and folliculitis (8%) which occurred only in the erlotinib arm; the manufacturer states that 'these generally represent only modest inconvenience and discomfort to patients and are not life-threatening, unlike the infections that can accompany periods of chemotherapy-induced immunosuppression.'

Table 9 Summary of adverse events with incidence of at least 10% (EURTAC)

	Erlotinib n (%)			CTX n (%)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Gastrointestinal Disorders						
Diarrhoea	43 (57.3)	3 (4.0)	-	14 (18.9)	-	-
Nausea	17 (22.7)	1 (1.3)	-	30 (40.5)	4 (5.4)	-
Vomiting	10 (13.3)	-	-	16 (21.6)	3 (4.1)	-
Constipation	6 (8.0)	-	-	16 (21.6)	-	-
Stomatitis	8(10.7)	-	-	7 (9.5)	-	-
General Disorders and Administration Site Conditions						
Asthenia	40 (53.3)	5 (6.7)	-	51 (68.9)	13 (17.6)	-
Chest Pain	13 (17.3)	1 (1.3)	-	10 (13.5)	-	-
Pyrexia	8 (10.7)	-	-	10 (13.5)	-	-
Mucosal Inflammation	13 (17.3)	1 (1.3)	-	4 (5.4)	-	-
Respiratory, Thoracic and Mediastinal Disorders						
Cough	34 (45.3)	1 (1.3)	-	26 (35.1)	-	-
Dyspnoea	31 (41.3)	6 (8.0)	-	19 (25.7)	1 (1.4)	-
Skin and Subcutaneous Tissue Disorders						
Rash	37 (49.3)	4 (5.3)	-	1 (1.4)	-	-
Alopecia	11 (14.7)	-	-	13 (17.6)	2 (2.7)	-
Dry Skin	13 (17.3)	1 (1.3)	-	2 (2.7)	-	-
Acne	9 (12.0)	-	-	-	-	-
Pruritus	8 (10.7)	-	-	1 (1.4)	-	-
Blood and Lymphatic System Disorders						
Anaemia	8 (10.7)	-	1 (1.3)	34 (45.9)	3 (4.1)	-
Neutropenia	-	-	-	27 (36.5)	11 (14.9)	5 (6.8)
Febrile Neutropenia	-	-	-	3 (4.1)	1 (1.4)	2 (2.7)
Leukopenia	2 (2.7)	-	-	10 (13.5)	4 (5.4)	-
Thrombocytopenia	1 (1.3)	-	-	9 (12.2)	4 (5.4)	5 (6.8)
Metabolism and Nutrition Disorders						
Decreased Appetite	21 (28.0)	-	-	25 (33.8)	-	-
Musculoskeletal and Connective Tissue Disorders						
Back Pain	12 (16.0)	-	-	4 (5.4)	-	-
Infections and Infestations						
Paronychia	12 (16.0)	-	-	-	-	-
Ear and Labyrinth Disorders						
Tinnitus	1 (1.3)	-	-	8 (10.8)	-	-
Eye Disorders						
Conjunctivitis	9 (12.0)	-	-	-	-	-

Multiple occurrences of the same adverse event in one individual counted only once.
Cut-off for statistical analysis: 02AUG2010

4.3 Critique of trials included in the meta-analysis and mixed treatment comparison

4.3.1 Meta-analysis

According to the Guide to the Methods of Technology Appraisal issued by NICE,[22] when more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. The manufacturer considered pooling the data from the EURTAC[8] trial with data from the OPTIMAL[16] trial. However, when the treatment effect sizes (PFS) between the two trials were compared, the

magnitude of the treatment effect was found to be inconsistent. In the EURTAC[8] trial, a PFS HR of 0.37 (95% CI: 0.25 to 0.54) was estimated with a median PFS of 9.7 months and 5.2 months for erlotinib and CTX respectively. In OPTIMAL[16] a PFS HR of 0.16 (95% CI: 0.11 to 0.26) was observed with associated median PFS values of 13.7 months for erlotinib and 4.6 months for CTX. The manufacturer examined the extent of the heterogeneity between these two studies. They conducted an indirect comparison of the erlotinib outcomes for both trials (as if they were different treatments). This resulted in a PFS HR of 0.44 which the manufacturer used to demonstrate that heterogeneity exists between the two trials. A comparison of the confidence intervals of the two estimates also showed a minimum overlap, adding further evidence of heterogeneity. The manufacturer tested the heterogeneity using RevMan software and reports that the results demonstrated a 'considerable heterogeneity between the studies (Chi^2 p-value = 0.007, I^2 value = 86%)' (MS, pg116). The identification of heterogeneity of this magnitude mitigates against a pooled analysis of the two trials.

The manufacturer investigated possible causes of heterogeneity and concluded that it was difficult to pinpoint the exact cause. Three possibilities are offered in the MS (MS, pg 112):

- *may* be due to a slightly underperforming comparator arm in OPTIMAL[16] (at least in terms of the PFS HR observed – clearly this does not explain the 4 month difference in the median PFS of patients given erlotinib in OPTIMAL[16] compared to EURTAC[8]).
- *may* be a product of differences in the ethnic mix of the patients included in each study (if people of Asian origin do indeed perform better in response to EGFR TKIs than their European counterparts)
- *may* be a product of the better compliance and more aggressive adherence to the maximum possible dose of erlotinib treatment in OPTIMAL[16] than in EURTAC.[8]

The manufacturer concluded that the EURTAC[8] trial is most relevant to clinical practice in the UK and was conducted to EMA regulatory requirements. Given these considerations the manufacturer states that the EURTAC[8] trial is 'likely to offer the best basis on which to assess the clinical and cost effectiveness of erlotinib in the first-line treatment of a Caucasian population' (MS, pg 120).

Regardless of having previously cautioned against any pooling of the EURTAC[8] and OPTIMAL[16] data, the manufacturer presents an exploratory meta-analysis of the two trials. Both random and fixed effects analyses were conducted and the manufacturer claims both produced broadly consistent and highly significant point estimates of the pooled HR of erlotinib vs doublet CTX (PFS HR = 0.25 for random effects and 0.26 for fixed effects) (MS, pg 122).

4.4 Indirect comparison and/or multiple treatment comparison

In the absence of any head to head trial data comparing erlotinib with gefitinib, the manufacturer conducted a systematic review and MTC. The search strategy used to identify randomised evidence of the efficacy of erlotinib was repeated for gefitinib (gefitinib OR IRESSA replaced erlotinib or TARCEVA). This search identified three RCTs (IPASS,[10, 12] WJT0G3405,[15] NEJGSG002[14]); a fourth RCT (First-SIGNAL[13][abstract only]) was identified following a manual search of TA192.[5] The inclusion and exclusion criteria for the MTC are described in Table 10.

Table 10 Key inclusion and exclusion criteria for the MTC

Inclusion	Exclusion
Randomised controlled trials	Observational data, registry analyses, single arm studies, meta-analyses
Previously untreated NSCLC (metastatic) patients whose tumours harbour an activating mutation of the EGFR tyrosine kinase	Early NSCLC patients, small-cell patients, patients previously treated for their metastatic NSCLC (i.e. maintenance treatment, second and later line treatment), patients with tumours that do not contain a mutation of the EGFR tyrosine kinase or have unknown EGFR mutation status non-metastatic NSCLC
Gefitinib monotherapy	Gefitinib combination therapy, non-erlotinib therapy
Any comparator capable of informing the relative efficacy of erlotinib to gefitinib	Investigational agents
Outcomes of PFS, OS, AEs	

MTC network

The manufacturer created a network of RCTs to compare the clinical effectiveness of erlotinib with gefitinib. Data were extracted and analysed for clinical efficacy (PFS, OS and best overall response). The manufacturer pooled the data from four gefitinib trials (IPASS,[10, 12] WJT0G3405,[15] NEJGSG002,[14] First-SIGNAL[13]) on the assumption that the doublet CTX arms in each of the trials are of equal efficacy. This assumption is based on a recent meta-analysis by Ku and colleagues[11] and commentary in the STA submission underpinning TA192.[5] The manufacturer has further assumed that the CTX arms of EURTAC[8] and OPTIMAL[16] can be linked to the network using doublet CTX as the anchor point. This is depicted in Figure 3. For reference, Table 11 describes the key characteristics of the RCTs for erlotinib and gefitinib. More extensive and detailed information for all the trials is presented in the MS.

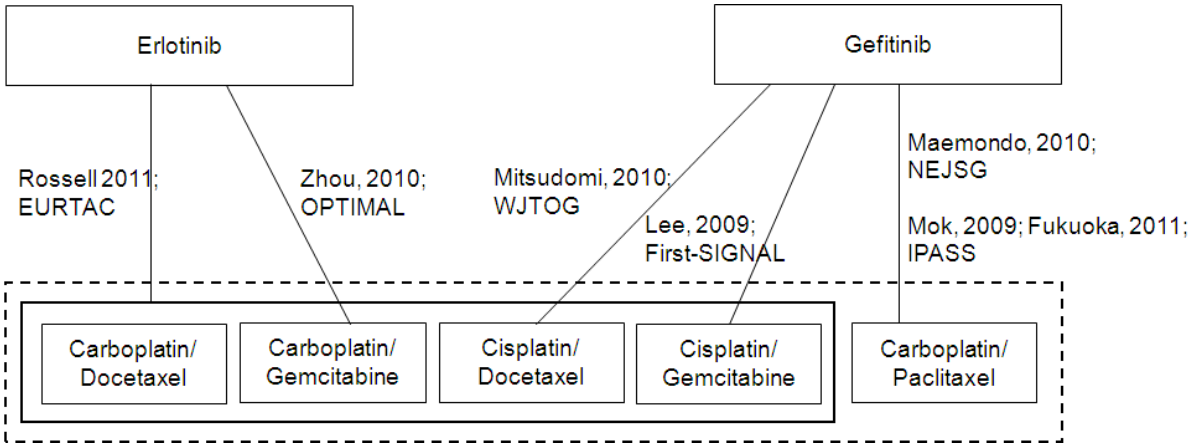

Figure 3 Network of randomised clinical trials in the manufacturer's submission

Table 11 Key characteristics of included trials

Trial Identification	Patient population	Intervention	Comparator
EURTAC[8]	European (n=174)	erlotinib	Platinum + docetaxel or gemcitabine
OPTIMAL[16]	Chinese (n=154)	erlotinib	Carboplatin + gemcitabine
IPASS[10, 12]	East Asian (*n=259, EGFR M+ only)	gefitinib	Carboplatin+ paclitaxel
WJTOG3405[15]	Japanese (n=177)	gefitinib	Cisplatin +docetaxel
NEJGSG002[14]	Japanese (n=230)	gefitinib	Carboplatin+ paclitaxel
First SIGNAL[13]	Korean (*n= 42, EGFR M+ only)	gefitinib	Cisplatin + gemcitabine

*subset of overall trial population who were EGFR M+

In the MS, the manufacturer presents a table of overall efficacy results of the gefitinib RCTs. This is replicated in Table 12.

Table 12 Summary of overall efficacy results for gefitinib RCTs

	Gefitinib	**CTX**	
	Median progression free survival		**HR (95% CI); p value**
IPASS[10, 12]	9.5 months	6.3 months	0.48 (0.36 to 0.64) *p < 0.001*
WJTOG3405[15]	9.2 months	6.3 months	0.49 (0.34 to 0.71) *p < 0.0001*
NEJGSG002[14]	10.8 months	5.4 months	0.30 (0.22 to 0.41) *p < 0.001*
First-SIGNAL[13]	8.4 months	6.7 months	0.61 (0.31 to 1.22) *p = 0.084*
	Best overall response		**Odds ratio (95% CI); p value**
IPASS[10, 12]	71.2%	47.3%	2.75 (1.65 to 4.60) p = 0.0001
WJTOG3405[15]	62.1%	32.2%	(12.6 to 47.1) p < 0.0001
NEJGSG002[14]	73.7%	30.7%	p < 0.0001
First-SIGNAL[13]	84.6%	37.5%	9.17(2.11 to 39.85) p < 0.002
	Median overall survival		**HR (95% CI); p value**
IPASS[10, 12]	21.6 months	21.9 months	1.00 (0.76 to 1.33) p = 0.990
WJTOG3405[15]	30.9 months	Not reached	n/a
NEJGSG002[14]	30.5 months	23.6 months	p = 0.31
First-SIGNAL[13]	30.6 months	26.5months	p = 0.648
Lung cancer symptoms and health-related quality of life (HRQoL)	**Patients with clinically relevant improvements in QoL during the study**		
PS, smoking history and gender as covariates	**Gefitinib**	**CTX**	**Odds ratio (95% CI); p value**
IPASS – Total FACT-L	70.2	44.5	3.01 (1.79 to 5.07) p < 0.0001
IPASS – TOI	70.2	38.3	3.96 (2.33 to 6.71) p < 0.0001
IPASS – LCSS	75.6	53.9	2.70 (1.58 to 4.62) p = 0.0003
WJTOG3405[15]	Not reported		
NEJGSG002[14]	Not reported		
First-SIGNAL[13]	Not reported		

In order to fulfil the requirements of an indirect comparison, the assumption of comparable and exchangeable treatment effects across studies needs to be met. The manufacturer has established previously that substantial heterogeneity exists between the EURTAC[8] and OPTIMAL[16] trials. The manufacturer has also assessed the similarities and differences that may exist between all other identified trials. The manufacturer concludes that ethnicity is the 'key differentiator' between the data available for erlotinib and gefitinib and therefore the only robust indirect comparison of erlotinib and gefitinib requires all patients to be from an East Asian population (i.e. EURTAC[8] data cannot be included in the indirect comparison if the results are to be robust).

However, the manufacturer then points out that the decision problem set by NICE requires an assessment of the relative effectiveness of erlotinib compared with gefitinib in a European population (MS, pg165). The manufacturer goes on to report the results of four possible indirect comparisons. All four indirect comparisons were conducted by using the values in Table 13 and applying the adjusted indirect comparison methodology developed by Bucher.[23] Whilst this methodology is valid, it is the ERG's view that it would have been preferable to use a MTC utilising the individual hazard ratios available from each of the relevant studies. The outcomes of the comparisons are described in Table 14.

The manufacturer notes that all of the results of the indirect analyses demonstrate that compared with gefitinib, erlotinib is superior (or has a trend to superiority). The manufacturer further notes that none of the analyses answers the specific question of whether erlotinib is more effective than gefitinib in a European population; however the manufacturer states that the results of the analyses provide 'the best available evidence upon which to assess the relative effectiveness of erlotinib and gefitinib in a European population'(MS, pg166).

Table 13 Summary of data used in the indirect comparisons

	PFS HR	Lower confidence limit	Upper confidence limit	Scenario
OPTIMAL	0.162	0.102	0.256	1
FE Pooling EURTAC/OPTIMAL	0.26	0.2	0.35	2
RE Pooling EURTAC/OPTIMAL	0.25	0.11	0.56	3
EURTAC	0.37	0.25	0.54	4
Ku	0.45	0.38	0.55	1,2,3,4

FE= fixed effects; RE=random effects

Table 14 Indirect comparisons

	Comparison	Indirect PFS HR erlotinib vs gefitinib
1	OPTIMAL compared with IPASS/First-SIGNAL/WJTOG3405/NEJGSG002	0.36 (0.22 to 0.59)
2	Fixed effects pooled estimate of EURTAC/OPTIMAL compared with IPASS/First-SIGNAL/WJTOG3405/NEJGSG002	0.58 (0.41 to 0.81)
3	Random effects pooled estimate of EURTAC/OPTIMAL compared with IPASS/First-SIGNAL/WJTOG3405/NEJGSG002	0.56 (0.24 to 1.28)
4	EURTAC and IPASS/First-SIGNAL/WJTOG3405/NEJGSG002	0.82 (0.54 to1.26)

No further tests of heterogeneity beyond those described for the pooling of EURTAC and OPTIMAL[16] data were undertaken by the manufacturer. The manufacturer states that in the recent appraisal of gefitinib, the ERG had recommended that the results of the key gefitinib studies be pooled and highlights that the four studies have been pooled in the published meta-analysis by Ku.[11]

The ERG notes that the results of only three studies were available at the time of the appraisal of gefitinib, IPASS,[12] First-SIGNAL[13] and NEJGSG.[14] The ERG has reviewed the methods used in the meta-analysis by Ku[11] and is satisfied that they are appropriate.

In relation to the safety and tolerability of erlotinib and gefitinib, the manufacturer states that the two treatments are broadly similar. (MS, p182).

Critique of mixed treatment comparison

In principle, the correct approach to MTC has been used by the manufacturer. However a robust MTC should include the maximum amount of relevant data and not impose external assumptions, i.e. in this case, the MTC should not restrict the inclusion of data to trials involving only EGFR M+ patients. An extended evidence network is required incorporating erlotinib, gefitinib and pemetrexed linked via RCTs to the four third-generation CTX doublets. Ideally this should be a comprehensive evidence review and should avoid assumptions of direct clinical equivalence between third-generation agents. Without these extra comparisons any resulting treatment differences between erlotinib and gefitinib are unlikely to accurately reflect those that would have resulted from a more comprehensive network comparison. While the ERG agrees that the MTC performed by the manufacturer is important, a comprehensive MTC should have been the primary approach and the restricted analysis should have been performed only as a sensitivity analysis.

One of the key assumptions underlying the manufacturer's MTC is that all third generation drugs are equally equivalent in an EGFR M+ population as demonstrated by Figure 41 in the MS. The ERG is not aware of any clinical evidence to support this assumption. In an undifferentiated NSCLC patient population evidence suggests that no significant pairwise differences exist, nonetheless there are consistent trends suggesting gemcitabine is probably the most beneficial and paclitaxel the least efficacious. Therefore in an EGFR M+ population, more careful investigation is needed since differences between third generation regimens may accumulate to influence the indirect comparisons between erlotinib and pemetrexed and gefitinib. In order to decrease heterogeneity and improve the reliability of the results, key specific data are required: individual HRs for the comparators in the EURTAC[8] trial (e.g. erlotinib vs docetaxel, erlotinib vs gemcitabine) and individual HRs from all third generation first-line trials (undifferentiated population) in order to expand the network used in the MTC. The ERG also has concerns regarding the methods used to estimate HRs in RCTs of gefitinib. The ERG is aware that K-M plots of PFS gefitinib and erlotinib have a different pattern to those applying to third generation drugs. It appears that the proportional hazards assumption may be invalid for all PFS comparisons between TKIs and standard chemotherapy, and the ERG considers that the use of conventional proportional hazards methods to estimate HRs in gefitinib and erlotinib trials compared

with any other drug is problematic; the HR results may not be accurate and should be viewed with caution.

4.4.1 Non-RCT evidence

To add further support to the evidence for the efficacy of erlotinib compared with gefitinib, the manufacturer notes the results of a published pooled analysis[24] of observational data from the outcomes of 1434 EGFR M+ patients. In the analysis, median PFS was reported as 13.2 months for patients treated with erlotinib patients, 9.8 months for patients treated with gefitinib patients and 5.9 months for patients treated with CTX. The ERG notes that the 13.2 months PFS recorded in the analysis[24] is greater than the 9.7 months reported in the EURTAC[8] trial.

4.5 Conclusions of the clinical-effectiveness section

The ERG is of the opinion that without appropriate consideration of pemetrexed as a comparator, the evidence presented in the MS is incomplete and does not allow a full evaluation of erlotinib as set out in the decision problem. Pemetrexed is the only treatment that has demonstrated a survival benefit in patients with non-squamous NSCLC and must therefore be included in as part of any assessment of clinical effectiveness of treatments for this patient population..

The ERG therefore concludes that it is inappropriate to provide the results of any further analyses for the Appraisal Committee's consideration.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by Roche in support of erlotinib 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 and (ii) a report of the manufacturer's de novo economic evaluation. Table 15 contains details of the location of key information within the MS. The manufacturer also provided an electronic version of their EXCEL-based economic model.

Table 15 Location of key economic information in the MS

Key information	Page number	Tables/figures
Details of the systematic review of the economic literature	189-192	
De novo analysis	192-196	Fig 45, Table 39
Clinical evidence used in economic evaluation	196-213	Fig 46-51, Table 40-43
Measurement and valuation of health effects	213-224	Fig 52,Table 44-45
Resource identification, measurement and valuation	225-242	Fig 53-58, Table 46-50
Methods of sensitivity analysis	243-250	Table 51-55
Results - base-case analysis	250-258	Table 56-64
Results - sensitivity analysis	258-272	Fig 59-61, Table 65-71
Validation	272	
Interpretation of economic evidence	274-276	
Assessment of factor relevant to the NHS and other parties	277-281	Table 72-74

5.1 Commentary on manufacturer's cost-effectiveness review

5.1.1 Objective of the cost-effectiveness literature review

The MS states that the objective of the literature search was to identify studies assessing the cost-effectiveness of erlotinib compared with gefitinib in the first-line treatment of EGFR M+ NSCLC. The search was also designed to evaluate whether de novo modelling was necessary in order to answer the decision problem set out in the scope.

Full details of the search strategy are included in the appendices of the MS (pg 309-311), including all the search terms, text words, subject index headings and the relationship between the search terms. The searches were conducted on 13 September 2011. Dialogue Data-Star was used to search Embase, Medline, Medline (R) In-Process and EconLit, whilst the NHS EED database was searched using the University of York's Centre for Reviews and Dissemination website. No date restrictions were in place.

The ERG considers that the search strategy used by the manufacturer was appropriate.

5.1.2 Inclusion and exclusion criteria used in study selection

The inclusion/exclusion criteria used in the study selection are presented in Table 16. The ERG considers that the inclusion criteria are incomplete as pemetrexed in combination with cisplatin has not been included as a comparator.

Table 16 Economic evaluation search inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Previously untreated NSCLC patients with an activating mutation of the EGFR tyrosine kinase	Small cell lung cancer patients, Non-lung cancer patients (i.e. mesothelioma), previously treated patients, patients without a confirmed EGFR mutation
Intervention	Erlotinib monotherapy	
Comparator	Gefitinib monotherapy	-
Outcome	Cost per QALY gained, Cost per LY gained,	-
Study design	Economic evaluations (cost effectiveness analyses, cost utility analyses, cost minimisation analyses)	RCTs, observational data, budget impact assessments

QALY=quality adjusted life year; LY= life year gained

5.1.3 Included and excluded studies

No relevant studies were identified.

5.1.4 Conclusions of the review

The manufacturer reports that as erlotinib has only recently been EMA[25] approved for use in the first-line treatment of EGFR M+ NSCLC, the lack of economic evaluations of relevance to the decision problem is expected.

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 does not appear to have undertaken any searches of the unpublished literature; which may mean that relevant unpublished studies were omitted. Further, the inclusion criteria did not allow any studies examining the cost effectiveness of pemetrexed in combination with cisplatin or carboplatin compared with erlotinib in the first-line treatment of EGFR M+ NSCLC to be included in the review.

5.2 Summary and critique of manufacturer's economic evaluation

5.2.1 NICE reference case checklist

Table 17 NICE reference case checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Partial. The model does not include pemetrexed in combination with cisplatin or carboplatin as comparators
Comparator(s)	Alternative therapies routinely used in the NHS	Partial. The model does not include pemetrexed in combination with cisplatin or carboplatin as comparators
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Partial. A time horizon of ten years is used, but second-line therapy is not modelled
Synthesis of evidence on outcomes	Systematic review	N/a – the manufacturer only uses data from the EURTAC trial
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes. The manufacturer uses values from published literature that have been used in previous STAs
Benefit valuation	Time-trade off or standard gamble	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

STA= Single Technology Appraisal

5.2.2 Model structure

Three health states are used to model disease progression. All patients enter the model in the PFS health state and in each month can either progress to a 'worse' health state (i.e. from PFS to progressed disease (PD) or from PD to Death) or remain in the same health state. The model has been developed in MS Excel and has a one month cycle length. The model structure is shown in Figure 4.

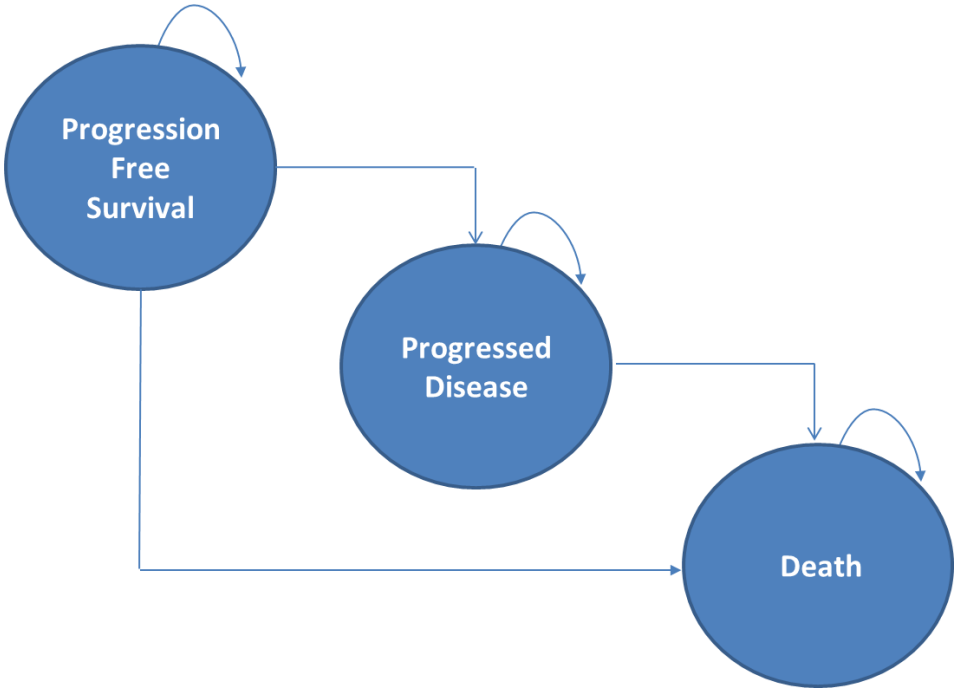

Figure 4 Schema of manufacturer's model

5.2.3 Parameters and values

Key parameters and transition probabilities used in the cost-effectiveness analysis are presented in Table 18.

Table 18 Key parameters and transition probabilities

Item	Value	95% confidence interval	Source
General parameters			
Age	63.4 years	N/A	EURTAC
Gender mix (female/male)	73.2%/26.8%	N/A	EURTAC
Transition probabilities			
Erlotinib - monthly probability of disease progression after month 16 (KM used before this time point)	0.085977	PSA of relative efficacy undertaken using indirect PFS HR confidence intervals rather than shifting of erlotinib baseline	MS Section 6.3.2
Gefitinib - monthly probability of disease progression after month 16 (indirect PFS HR adjusted KM used before this time point)	0.104567	0.0682 to 0.159 (log normal)	MS Section 6.3.2
Erlotinib and gefitinib - monthly probability of death in PFS	0.014206	-	MS Section 6.3.2
Erlotinib and gefitinib - monthly probability of death in PD	0.075719	-	MS Section 6.3.2
Indirect PFS HR of erlotinib vs gefitinib	0.82	0.54 to 1.26 (log normal)	MS Section 5.7.3

5.2.4 Population

The population considered in the economic evaluation is as per the scope[7] of this appraisal (i.e. previously untreated patients with tumours harbouring an activating mutation of the EGFR tyrosine kinase for whom erlotinib is a potential treatment option). This population is consistent with the marketing authorisation for erlotinib.

5.2.5 Interventions and comparators

In the economic evaluation conducted by the manufacturer erlotinib (maximum of one 150mg tablet per day until disease progression) is compared with gefitinib (maximum of one 250mg tablet per day until disease progression). Pemetrexed in combination with cisplatin has not been included as a comparator by the manufacturer. The ERG is, therefore, concerned that comparison of all relevant treatment options for the target population has not been undertaken by the manufacturer.

The manufacturer assumes that second-line therapy will be the same for both arms (pemetrexed/cisplatin or docetaxel) and has used this as the rationale for not modelling second-line therapy. It should be noted, however, that pemetrexed/cisplatin is not recommended by NICE as a second-line treatment for this group of patients.

5.2.6 Perspective, time horizon and discounting

The economic evaluation is undertaken from the perspective of the NHS and Personal Social Services. Outcomes are expressed in terms of life-years and quality adjusted life-years (QALYs). The time horizon is set at 10 years and, in line with the NICE Methods Guide to Technology Appraisal,[22] both costs and benefits are discounted at 3.5%.

5.2.7 Treatment effectiveness and extrapolation

The EURTAC[8] study (Caucasian patients) was utilised as the baseline in all modelling undertaken as it was assumed that this study is more representative of the outcomes expected in UK clinical practice than those from the OPTIMAL[16] study (East Asian patients).

Survival was extrapolated beyond the EURTAC[8] trial cut off for the primary analysis. The ERG notes that, at this point, recruitment appears to have been still ongoing.

The transition probabilities, along with the methods used to derive them, are summarised in Table 19. The ERG notes that the lack of gefitinib effectiveness evidence available to the manufacturer has led to a very pragmatic approach to estimating the probability of patients on gefitinib remaining in PFS.

Table 19 Transition probabilities

Comparator	Estimation method	Value	95% confidence interval	Source
Probability of remaining in progression-free survival				
Erlotinib	Derived directly from EURTAC RCT erlotinib arm. PFS curve with exponential 'tail' fitted to allow estimation of the mean time in PFS	0.085977	PSA of relative efficacy undertaken using indirect PFS HR confidence intervals rather than shifting of erlotinib baseline	MS Section 6.3.2
Gefitinib	As erlotinib but with indirect PFS HR applied	0.104567	0.0682, 0.159 (log normal)	MS Section 6.3.2
Indirect PFS HR of erlotinib vs gefitinib		0.82	0.54, 1.26 (log normal)	MS Section 5.7.3
Probability of dying in progression-free survival				
Erlotinib	Derived from EURTAC RCT erlotinib arm	0.014206	-	MS Section 6.3.2
Gefitinib	Rate assumed to be the same as for erlotinib			
Probability of disease progression				
Erlotinib and gefitinib	Defined as the residual of the above two transitions [A patient who has was previously in PFS who is no longer in PFS and has not died must have progressed]	-		
Probability of dying in progressive disease				
Erlotinib and gefitinib	Monthly probability of death in PD observed for erlotinib arm in EURTAC RCT applied to the proportion of patients in PD in each month	0.075719	-	MS Section 6.3.2
Do not die after progression (i.e. remain in progressive disease)				
Erlotinib and gefitinib	One minus the probability of death in PD. [If a patient is in PD and hasn't died he must still be in PD]			

PD=progressive disease

5.2.8 Health related quality of life

As EQ-5D was not used to measure HRQoL in EURTAC[8] or IPASS,[12] 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 study by Nafees.[26]

The ERG notes that the utility values in the Nafees[26] study 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.

The PFS utility value for erlotinib was derived by combining the Nafees[26] value with the response rate observed in EURTAC[8] and the grade of 3/4 incidence of diarrhoea and rash. Similarly, the PFS utility value for gefitinib was derived by combining the Nafees[26] value with the indirect response rate and the incidence of grade 3/4 diarrhoea and rash observed in the IPASS[12] RCT.

Utility values used in the model are presented in Table 20.

Table 20 Key model parameters: utility

State	Utility value	95% confidence interval	Source
PFS (stable disease)	0.6532	0.6096 to 0.6968	Nafees
PFS (response dummy variable)	0.0193	0.0065 to 0.0321	Nafees
Disutility of rash	-0.0325	-0.0554 to -0.0095	Nafees
Disutility of diarrhoea	-0.0468	-0.0772 to -0.0164	Nafees
PD (dummy variable disutility relative to PFS SD baseline)	-0.1798	-0.2223 to -0.1373	Nafees
Resultant erlotinib PFS	0.661	Not derived explicitly	MS section 6.4.9
Resultant gefitinib PFS	0.656	Not derived explicitly	MS section 6.4.9

5.2.9 Resources and costs

Resource use in the economic evaluation is not derived from data collected as part of the EURTAC[8] trial. A literature search was carried out which revealed no new sources of information. The resource use figures used in the model are those that have been used in previous recent NSCLC appraisals (TA227,[27] TA190[4] and TA181[6]). Values and sources of resource use in the economic evaluation are set out in **Error! Reference source not found.**and **Error! Reference source not found.**.

Table 21 Key model parameters: drug costs

Cost	Value	95% confidence interval	Source
Pharmacy costs per pack of erlotinib/gefitinib dispensed	£13	£6.63 to £19.37†	MS Section 6.5.5.2
Erlotinib drug costs	30 x 150 mg = £1631.53 30 x 100 mg: £1324.14 30 x 25mg - 50mg: £378.33 With [redacted] discount utilised in the submission: 30 x 150 mg = [redacted] 30 x 100 mg: [redacted] 30 x 25mg - 50mg: [redacted]	N/A	BNF 62 list price MS Table 6, Section 1.10
Gefitinib PAS fixed cost payment	£12,200	N/A	MS Section 6.5.5.1.2
Gefitinib PAS administration cost	£70 set up cost per pt £34 per month (ongoing)	†	MS Section 6.5.5.3
†Gamma distribution applied under assumption standard error was a quarter of base-case value			

Table 22 Key model parameters: care costs

	Included elements	Value	Source
Health states			
Monthly PFS BSC cost (including monitoring)	Supportive care plus CT assessment of response every three months	£181.46	MS Section 6.5.6
Monthly PD BSC cost	Supportive care plus CT assessment of response every three months whilst on 2nd line treatment (estimate based upon SATURN RCT in NICE TA227)	£160.06	MS Section 6.5.6
Terminal phase best supportive care	Supportive care	£2588.25	MS Section 6.5.6
Adverse events			
Rash		£116	Roche 2006 cited in Brown et al 2009 (NICE TA192 ERG report)
Diarrhoea		£867	Eli Lilly 2009 cited in Brown et al 2009 (NICE TA192 ERG report)

5.2.10 Cost-effectiveness results

The base case incremental results generated by the manufacturer's model are presented in **Error! Reference source not found.**. The incremental cost-effectiveness ratio (ICER) for the target population is £21,874 per QALY gained and £16,317 per life year gained. Disaggregated results for the target population are presented in **Error! Reference source not found.**.

Table 23 Base-case results*

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Gefitinib	£16,046	1.796	1.015					
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,874	£21,874
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

*results do not include second-line treatment costs

Table 24 Disaggregated mean costs for the base case

Unit Cost	Cost (erlotinib)	Cost (gefitinib)	Increment	Absolute increment	% absolute increment
Drug	[redacted]	£9,300	[redacted]	[redacted]	[redacted]
Pharmacy	[redacted]	£116	[redacted]	[redacted]	[redacted]
AEs	[redacted]	£36	[redacted]	[redacted]	[redacted]
PAS admin	[redacted]	£438	[redacted]	[redacted]	[redacted]
PFS BSC	[redacted]	£1,970	[redacted]	[redacted]	[redacted]
PD BSC	[redacted]	£1,711	[redacted]	[redacted]	[redacted]
Terminal BSC	[redacted]	£2,475	[redacted]	[redacted]	[redacted]
Total	[redacted]	£16,046	[redacted]	[redacted]	[redacted]
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

5.2.11 Sensitivity analyses

The manufacturer undertook a large number of one-way sensitivity analyses. A tornado diagram is included in the MS (page 266). The one-way sensitivity analysis results for the five parameters that have the largest impact on cost effectiveness are displayed in **Error! Reference source not found.**. The manufacturer also undertook four sets of scenario analyses and the results are shown in **Error! Reference source not found.**.

Box 4 Key one-way sensitivity analysis results

- Impact of patient access scheme (PAS) on the ICER: without the [redacted] discount (as confirmed in a DH letter to NICE (November 2011) the ICER is £74,300 per QALY gained
- Gefitinib PAS per patient administration costs: halving and doubling the one off and ongoing monthly costs gave ICERs of £24,204 per QALY gained and £17,213 per QALY gained respectively
- Monthly probability of disease progression after month 16 (erlotinib): ± 10% from the base case gave an ICER range of £19,232 per QALY gained to £24,800 per QALY gained
- PFS/BSC Monitoring costs: ± 95% CI from the base case gave an ICER range of £20,062 per QALY gained to £23,685 per QALY gained
- Monthly probability of disease progression after month 16 (gefitinib): ± 10% from the base case gave an ICER range of £23,915 per QALY gained to £20,471 per QALY gained

Table 25 Scenario analyses

Scenario	Baseline variable value	Range varied	Cost per QALY gained
Relative efficacy of erlotinib and gefitinib	EURTAC vs Ku et al: PFS HR for erlotinib vs gefitinib = 0.82	• OPTIMAL vs Ku et al: 0.36 • EURTAC/OPTIMAL random effects pooling vs Ku et al: 0.56 • EURTAC/OPTIMAL fixed effects pooling vs Ku et al: 0.58	£15,712 to £16,552
Proportion of patients 'activating' gefitinib PAS	EURTAC erlotinib 'time to last dose' curve 3 month value with indirect PFS HR applied (0.82)	• EURTAC erlotinib PFS curve 3 month value with indirect PFS HR applied (0.82) • IPASS gefitinib PFS curve 3 month value (95%) • 100% of patients 'activate' the PAS	[redacted] to £10,066
Point of transition from observed PFS KM curve to modelled 'tail'	After month 16	Month 5 - Month 30	£14,826 to £21,524
Point of transition from observed 'Time to last dose' erlotinib KM curve to modelled tail	After day 300	Day 150 - Day 600	£19,418 to £24,958

The sensitivity analyses show that:

- The ICER is sensitive to the relative efficacy of erlotinib and gefitinib used in the model
- The more of the observed PFS data used in the model, the lower the ICER becomes
- The model is extremely sensitive to the assumed proportion of patients for whom the gefitinib PAS payment is required.

Probabilistic sensitivity analysis (PSA) was undertaken to derive the mean ICER of erlotinib vs gefitinib in this setting. A scatter plot (incremental cost versus QALY) and a cost-effectiveness acceptability curve are included in the MS and reproduced in Figure 5 and Figure 6.

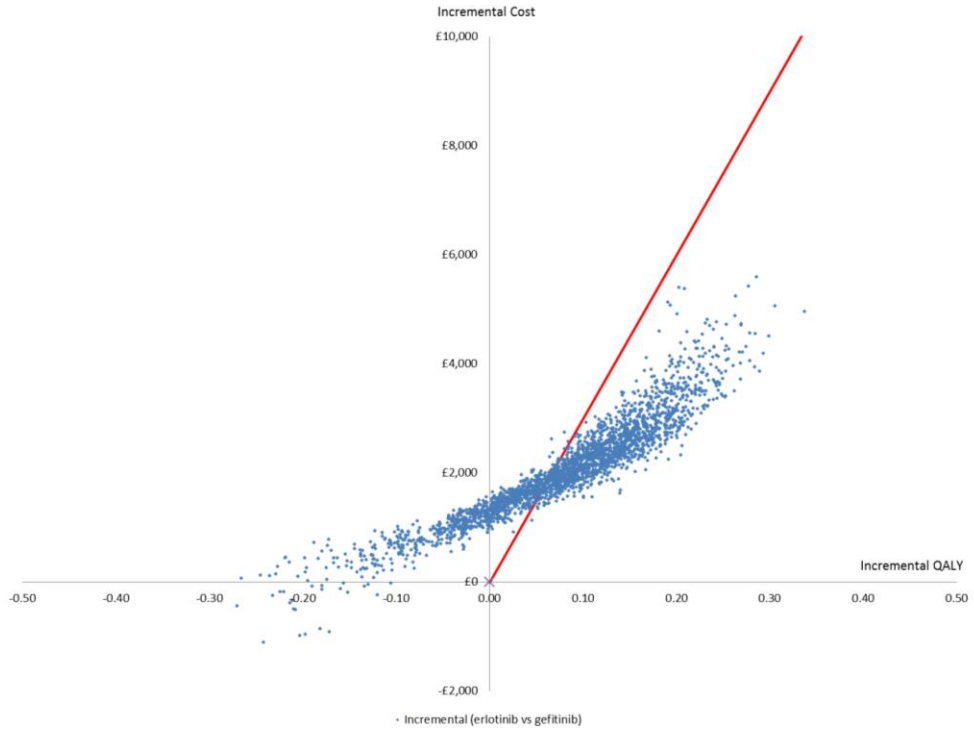

Figure 5 PSA Scatter-plot erlotinib vs gefitinib (red line = £30k/QALY)

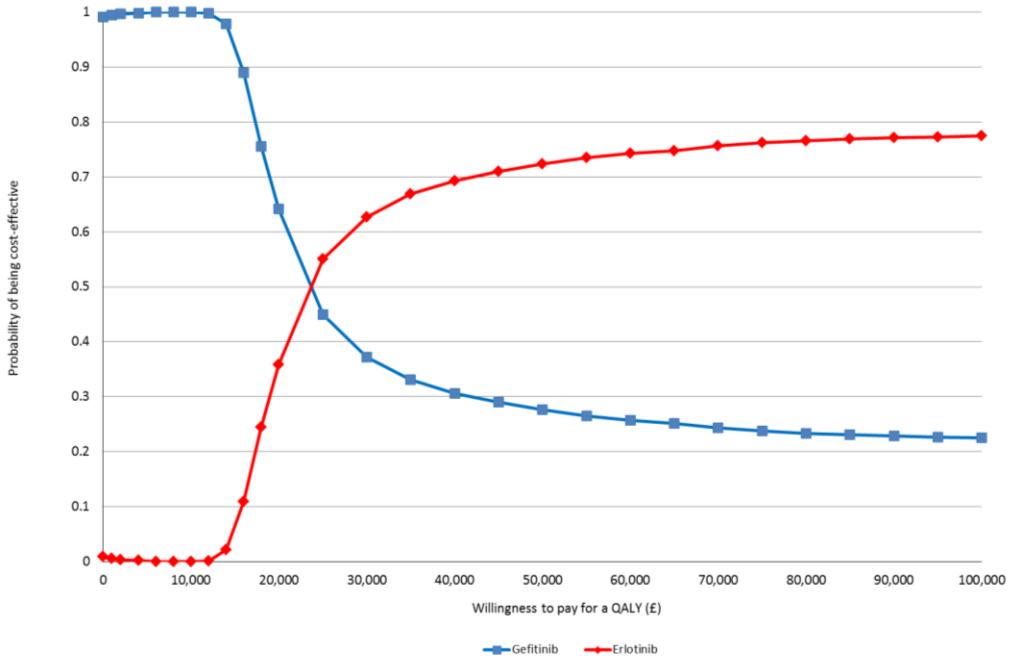

Figure 6 Cost-effectiveness acceptability curves

The manufacturer's conclusions from the PSA are summarised in Table 26.

Table 26 Conclusions from the probabilistic sensitivity analysis

	Percent of simulations in which considered cost-effective	
Threshold	**Erlotinib**	**Gefitinib**
£20,000/QALY	35.8%	64.2%
£25,000/QALY	55.04%	44.96%
£30,000/QALY	62.76%	37.24%

5.2.12 Model validation and face validity check

The MS (pg272-3) states that the model was validated by a Health Economist not directly involved in the development of the MS. This Health Economist reviewed the face validity of the model's response to changes in parameter inputs, compared the modelled erlotinib PFS survival curves with those observed in the EURTAC[8] RCT and assessed the model for logical errors.

It is reported that two errors were found, namely that (i) cost of pharmacy dispensing of erlotinib had been modelled as a monthly rather than a 30 day cost and (ii) death hazard derived from the EURTAC[8] RCT had been applied directly to the model as if it were a probability. Following the review changes were made to the model to address these issues.

5.3 Critique of manufacturer's economic model

5.3.1 Context to the appraisal

Gefitinib STA and updated evidence

The immediately relevant context to this appraisal is the NICE guidance TA192[5] issued in 2010 which recommended the use of gefitinib as an option for the first-line treatment of people with locally advanced or metastatic non-small-cell lung cancer, testing positive for EGFR-TK mutation.

In relation to the principal source of clinical evidence the Appraisal Committee noted:

> "The Committee was aware that the analysis of overall survival was an interim analysis of immature data based on 450 deaths (that is, 37% of patients having died) and that a final analysis from follow-up was due in the second quarter of 2010."

The final summary of the Appraisal Committee's deliberations on the clinical evidence was as follows:

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

The final version of the economic model used in that appraisal suggested that gefitinib yielded slightly poorer OS than pemetrexed treatment, and about 2 months OS advantage over third-generation platinum doublet regimens. The estimated OS gain (based on projective modelling) was the major component (80-90%) of the estimated QALY gain for gefitinib vs CTX doublets, whilst extended PFS contributed only 10-20%.

The final OS results from the IPASS[10] clinical trial were published in 2011, when the dataset was 78% mature. For EGFR mutation-positive patients there was no significant difference in OS between the gefitinib and third-generation CTX arms (HR = 1.00; 95% CI 0.76 to 1.33; p=0.990) – these data were not available to the Appraisal Committee at the time of the gefitinib appraisal. In addition, the ERG estimates that if pemetrexed were used instead of gefitinib, pemetrexed would yield up to 3 months additional OS over third-generation CTX.

Overall survival and crossover

Recently a meta-analysis[11] of four phase III clinical trials comparing first-line gefitinib with CTX was reported. Although confirming the important gain in PFS from use of gefitinib, the authors indicated

that none of the individual studies, or the meta-analysis, showed a statistically significant OS benefit from use of gefitinib:

> "In these studies, there was no OS benefit for upfront gefitinib over chemotherapy, quite possibly because most patients treated initially with chemotherapy received and benefited from an EGFR TKI at progression..... the lack of an OS benefit for initial gefitinib in these studies – in the overall population or even exclusively in patients with EGFR mutations – is a robust finding of this meta-analysis and is apparent across all four studies."

The suggestion that large-scale crossover of patients to gefitinib at progression might explain these findings has been reiterated by the manufacturer of erlotinib to justify similar results from the EURTAC[8] study. Clearly, on ethical grounds, it would be difficult to conduct a new trial which would avoid such crossover. However, there is a simple test which can be applied across the available study results to look for evidence of such confounding. If the suggested effect has occurred then it would be expected that there should be some evidence of a trend in hazard ratios which should tend to unity as the proportion of patients increases towards 100%. In Figure 7 the reported results of the four gefitinib RCTs[10, 12-15] and EURTAC[8] are shown plotted against the degree of crossover. This fails to show any evidence of such a trend across a range of more than 30% in crossover to gefitinib/erlotinib.

Thus, at present, there is no objective evidence available which can show any advantage in terms of extended life expectancy from use of TKIs as first-line systemic therapy, nor of the posited crossover confounding. It appears that the argument for expecting that the confirmed improvement in PFS will lead to a corresponding gain in OS has not been borne out by the validated objective evidence.

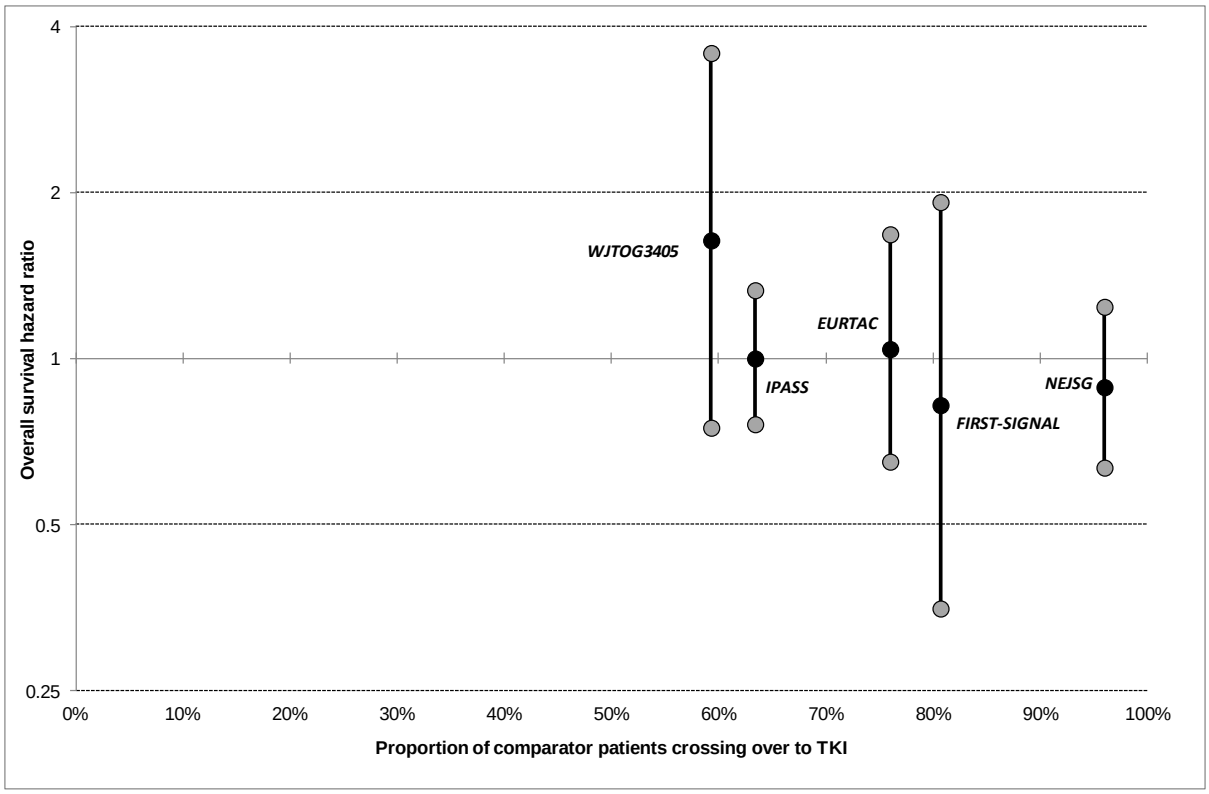

Figure 7 Overall survival hazard ratios for TKI vs chemotherapy in four gefitinib trials and EURTAC (erlotinib)

Role of pemetrexed and third generation chemotherapy

The manufacturer of erlotinib supports the omission of pemetrexed from the decision problem specified by NICE on purely pragmatic grounds, that pemetrexed with cisplatin/carboplatin is rarely used as first-line treatment in the UK. Whether or not the information presented on current usage is reliable, the need to include pemetrexed in the evaluation is strong since gefitinib was not recommended as a replacement for pemetrexed for this population but as an option alongside pemetrexed. It should also be noted that four third-generation platinum doublets (docetaxel, gemcitabine, paclitaxel and vinorelbine) remain licensed, recommended by NICE and are widely used for NSCLC patients and could also be reasonably considered as potential options for EGFR M+ patients, as they were in the initial analyses of the gefitinib appraisal. The omission of all comparators other than gefitinib has resulted in a simple model structure, and avoided a multi-way economic comparison which would most likely reduce the probability of erlotinib appearing as the most cost-effective option.

Prices paid by NHS for chemotherapy

The acquisition costs of third-generation chemotherapy agents in the gefitinib STA were based on the best BNF prices for generic products. The availability of more realistic average NHS prices from the Electronic Market Information Tool (eMit) produced by the NHS Commercial Medicines Unit indicates that the true cost of using these drugs is much lower than previously considered (varying from 20% to as little as 5% of the BNF list price for comparable product). It is likely that use of these prices as a sensitivity analysis in the gefitinib STA may have changed the status of the regimens considered, since vinorelbine appeared most cost effective in the early stages of the gefitinib appraisal. From a theoretical economic perspective there is a strong case for suggesting that the four CTX doublet regimens should also be considered alongside pemetrexed and gefitinib as valid NICE recommended options.

Implications for the decision problem

Data analyses described in the ERG report for the gefitinib STA (TA192)[5] demonstrated that pemetrexed/cisplatin yields similar or better OS for patients than gefitinib, as well as better OS than the third-generation doublet chemotherapy regimens. Appeal to market shares is not a strong argument for excluding pemetrexed from consideration in the decision problem set out by NICE. Indeed, the new and updated evidence on the clinical effectiveness of EGFR TKIs in first-line treatment of the mutation positive subgroup shows a lack of evidence to sustain the contention that the evident benefits in extended PFS will necessarily translate into OS gains. The need to conduct a comprehensive meta-analysis of the latest evidence concerning four CTX doublet regimens (now available as generic products) in order to establish the relative effectiveness of the three newer agents (pemetrexed, gefitinib and erlotinib) suggests that it may also be appropriate to include third-generation CTX agents in a full evaluation, as was undertaken for the appraisal of gefitinib.

5.3.2 Structural issues

Additional comparator(s)

The model submitted by the manufacturer of erlotinib is of a basic design, featuring only two treatments (erlotinib and gefitinib). If pemetrexed (or any other comparators) were to be added to the manufacturer's decision problem, the model would need to be restructured:

- an additional worksheet is needed to simulate each additional comparator;

- an extended evidence network is required incorporating erlotinib, gefitinib and pemetrexed linked via RCTs to the four third-generation CTX doublets. Ideally, this should be a comprehensive evidence review and should avoid assumptions of direct clinical equivalence between third-generation agents. The three primary comparators (erlotinib, gefitinib and pemetrexed) are not compared directly in trials with different individual or groups of CTX doublets, this means that apparently small

individual differences can accumulate to economically (if not statistically) important differences in effectiveness for the comparators;

- additional calibration data specific to each extra comparator are needed (e.g. acquisition costs, adverse event profiles, response rates, mortality at progression, etc.).

Second-line systemic therapy

The submitted model does not explicitly include any cost or effectiveness data relating to the choice of second-line systemic therapy. The options that the manufacturer includes in a treatment pathway are restricted to pemetrexed plus cisplatin/carboplatin or docetaxel monotherapy. The only treatments currently recommended by NICE for second-line therapy are erlotinib and docetaxel; pemetrexed was not found to be cost effective as a second-line treatment. It is argued by the manufacturer that erlotinib would not be reused in second-line after a TKI had been used initially, and that most clinicians prefer pemetrexed to docetaxel. Thus for a simple comparison of erlotinib vs gefitinib, the choice of second-line treatment is the same for all patients and the manufacturer is able to simplify the model by excluding both the costs and outcomes of second-line systemic treatments.

However, if pemetrexed (or any other comparator) is included in the decision problem as specified in the NICE scope,[7] then the inclusion of a second line of treatment is important. For patients initially receiving pemetrexed, there is a NICE approved choice between erlotinib and docetaxel, whereas for patients initially receiving erlotinib or gefitinib only docetaxel is available.

Inclusion of second-line treatments in the model will require substantial restructuring of the existing model.

Linked PFS and OS

The submitted model does not include any OS data or parameters, but relies solely on PFS data directly and through projective modelling to represent the effects of erlotinib and CTX on patient outcomes. Following disease progression all surviving patients are assumed to be subject to the same post-progression survival (PPS) experience and costs. The direct consequence of this simple structure is that most of the estimated difference in PFS between gefitinib and erlotinib is preserved via a common PPS phase, and therefore translates into a similar difference in OS.

As outlined above, there is no evidence in trials of gefitinib or erlotinib of any OS advantage over CTX attributable to TKI therapy. This issue was discussed during the gefitinib STA when a modest apparent OS gain in the immature IPASS[12] results was projected over the long-term, and the credibility of the ratio of PFS gain to OS gain was addressed. Now that the final IPASS[10] results no longer show any difference in OS between the trial arms, the presumption that a PFS gain must lead to some OS benefit appears less tenable than before.

There is some support for the alterative paradigm that PFS gain countered by reduced time in PPS, results in no change in OS; this was the conclusion reached in the appraisal of erlotinib vs docetaxel for the second-line treatment of patients with NSCLC.[28] If it is argued that first- and second- line erlotinib treatment should not be compared, then a logical problem is created:

- second-line treatments are left out of the model altogether because second-line erlotinib and docetaxel have the *same* effect on OS experience and erlotinib was priced to match docetaxel

- PFS generates extra OS in the submitted model (contrary to the trial evidence) because it is assumed that when erlotinib is used as a second-line treatment after CTX (i.e. at crossover) it *will* produce superior survival to docetaxel.

It seems that the argument favouring extra model-generated OS must be abandoned, or else second-line treatments must be included in an enhanced model – the current approach to modelling OS is logically inconsistent.

5.3.3 Conclusions

The ERG has examined the case put forward by the manufacturer to justify deviating from the scope[7] for the appraisal by limiting the evaluation to a simple comparison of erlotinib and gefitinib. The manufacturer has based their position on the views of clinical advisors and market research data which taken together claim that pemetrexed is no longer relevant. However, close examination of the latest trial evidence and careful consideration of the issues debated during the previous gefitinib STA lead the ERG to conclude that the NICE scope[7] was correct in including pemetrexed as an appropriate comparator, and furthermore that a good case can be made for also including additional third-generation CTX comparators in the appraisal.

The ERG has considered the balance of evidence relating to OS in EGFR TKI trials, and concludes that no evidence yet exists to support any significant survival advantage for gefitinib or erlotinib compared with CTX doublets in first-line systemic treatment of NSCLC with activating EGFR mutations. The importance of this observation cannot be over-estimated since both the claims for superior cost effectiveness of erlotinib over gefitinib, and of equivalence between gefitinib and pemetrexed rest predominantly on model-generated survival gain. If such OS gain proves to be illusory, then estimated ICERs will be far outside those normally considered acceptable (removing the estimated OS gain from the manufacturer's base case results increases the ICER to well over £100,000 per QALY comparing erlotinib to gefitinib (see Appendix 3, Table 29) and adjusting the model results from the gefitinib STA would indicate that pemetrexed/cisplatin is economically dominant over gefitinib).

The ERG has reviewed the manufacturer's basis for omitting second-line systemic treatments from their model. The ERG finds the evidence unconvincing since it does not accord with current NICE guidance on approved second-line treatments (pemetrexed was not approved by NICE at appraisal) and appears to involve a logical contradiction if crossover confounding is used to justify an assumption of real but concealed OS gain.

5.4 Conclusions of the cost-effectiveness section

It is the view of the ERG that the model submitted by the manufacturer does not conform sufficiently with the requirements of the NICE scope[7] to provide reliable evidence of the likely clinical effectiveness and cost effectiveness of erlotinib in first-line treatment of EGFR M+ NSCLC patients. Moreover, the current model structure is not easily modifiable by the ERG within the resources available to be able to provide such evidence for the Committee to consider.

In order to be suitable to inform the appraisal committee the ERG considers the current model would need to be substantially modified to include additional comparators, the results of an extended PFS mixed treatments comparison using a more comprehensive and robust evidence network, and the costs and health outcomes of second-line systemic therapies. In addition, the logic of the model should be modified to include meta-analysis results from available OS results for EGFR TKIs, without assuming that PFS gains automatically convert to OS gains, and a wider range of scenario analyses should be explored covering the assumptions and uncertainties identified here.

6 IMPACT ON THE ICER OF ERG ADDITIONAL ANALYSES

Not applicable.

7 END OF LIFE

Not applicable. The manufacturer did not make a case for End of Life.

8 OVERALL CONCLUSIONS

8.1 Implications for research

A major issue identified in the STA is the lack of data for the efficacy of pemetrexed as a first-line treatment for patients with EGFR M+ NSCLC. A trial that compares pemetrexed with EGFR TKIs as a first-line treatment for patients with EGFR M+ NSCLC would be informative.

A second issue identified in this STA is the difficulty in quantifying the relationship between PFS gains and any gains in OS. Systematic research that explores this relationship is required.

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10 APPENDICES

Appendix 1

Table 27 EURTAC trial quality assessment

	Manufacturer response	ERG comment
Was the method used to generate random allocations adequate?	Yes. Patients were randomised by means of fax to the Contract Research Organisation to receive either erlotinib or platinum doublet CTX who kept the randomisation list. To minimise the bias introduced by knowledge of treatment group assignment, the treatment code was not available to any person from Roche Biostatistics involved in the study prior to database closure.	The ERG agrees that the randomisation is appropriate and robust Randomisation was conducted through a computing application (ACCESS) called "randomiser". The randomisation list that supported this application was done according to the protocol using SAS statistical software.
Was allocation adequately concealed?	Not applicable as EURTAC was an open-label study	The ERG is unable to comment on whether the randomisation technique employed impacts on the concealment of allocation.
Were the care providers, participants and outcome assessors blind to treatment allocation?	No – see above for details of blinding.	As noted above, the block randomisation technique may have allowed investigators to be aware of treatment allocation. In addition, the trial was open-label with a primary endpoint of PFS. The endpoint of PFS can be considered to be subjective and open to affect by knowledge of treatment. The manufacturer provides validation of investigator-assessed PFS with an independent review of PFS. The ERG notes from the EPAR issued by the EMA that the review committee were blinded.
Was a justification for sample size provided?	Yes, based on the statistical requirement to demonstrate a predetermined treatment effect with a specified degree of statistical certainty. The sample size calculation was based on explicit assumptions about the clinical behaviour of the patient group in question and the impact of treatment	Agree
Were the groups similar at the outset of the study?	Yes. See Table 14	The baseline characteristics appear to be similar across the two arms of the trial with the exception of small differences regarding gender (more females in CTX vs erlotinib arm: 79% vs 68%) and smoking status. These differences were not considered critical by the EMA. The (small) imbalances in PS were noted by the EMA and said to be expected in subgroups
Was follow-up adequate?	Yes – analyses were event driven and conducted after sufficient events to demonstrate unequivocally the impact on highly relevant clinical end-point of PFS. At the time of analysis for the primary PFS end-point there had been 111 progression or death events across the erlotinib (52) and CTX arms (59).	The interim analysis was conducted at the pre-specified time (after 92 events had occurred). Final analysis is due when 135 events have occurred. Follwing the results of the interim analysis, the IDMC recommended trial closure. The ERG is unclear as to the impact this will have on patient follow-up
Was the design parallel group or cross-over?	The study was a parallel group design and the primary end-point (PFS) would not have been influenced by cross-over. Crossover was possible at disease progression and could have reduced the impact of the intervention on the OS	The ERG considers that any impact of cross-over would be due to artificially beneficial survival in the comparator arm. The erlotinib arm will include only the normal standard second-line effect and so would not be affected.
Imbalances in drop-outs between groups?	No	Agree
Authors measure more outcomes than reported?	No	Agree
Appropriate statistical analyses undertaken?	Yes. Manipulation of data was undertaken according to a clear plan (DRAM) finalised with expert statistician input prior to the availability of study data	Agree
Analysis included ITT?	Yes. This was the primary analysis.	Agree

Appendix 2

Table 28 Characteristics of the OPTIMAL trial

Trial design and number of participants	Intervention/comparator	Key inclusion/exclusion criteria	Outcomes
Multi-centre, Phase III, open-label RCT Centres in China N= 154 CTX-naive Stage IIIb/Stage IV EGFR M+ NSCLC Patients were randomised 1:1 to either erlotinib or CTX Randomisation was stratified according to ECOG status Deletion in exon 19 vs mutation in exon 21 L858R Histology (adenocarcinoma vs non-adenocarcinoma) Smoking status (smokers vs non-smokers)	Intervention: Erlotinib 150mg once daily. until disease progression, unacceptable toxicity or death Comparator: Platinum doublet CTX was administered for a maximum of 4 cycles (3 months) Gemcitabine 1000 mg/m^2; Day 1 and Day 8 and carboplatin AUC = 5, Day 1 every 21 days	Inclusion: Stage IIIB (cytologically confirmed with malignant pleural effusion or pericardial effusion) or histologically/ cytologically documented stage IV NSCLC or postoperatively recurrent NSCLC EGFR exon19 deletion or exon 21 L858R mutation determined by PCR-DNA direct sequencing of fresh or paraffin-embedded tumour samples Measurable or evaluable disease (RECIST criteria) Local radiotherapy permitted if completed 3 weeks prior to the first drug administration, but the lesions in the radiotherapy field were not to be included in the RECIST assessment Prior surgery was permitted if the operation was performed 4 weeks before the first drug administration Patients over 18 years ECOG <2 Life expectancy at least 12 weeks Adequate bone marrow reserve, kidney and liver function Exclusion: Pregnant, lactating, positive pregnancy test or did not undertake the test. Sexually active men and women (of childbearing age) not willing to use contraceptive methods during the study. Patients with any systemic anti-cancer therapy (e.g. cytotoxic drugs, monoclonal antibody therapy, experimental treatment, adjuvant or neoadjuvant CTX) for current or previously diagnosed NSCLC. (Post-surgical recurrent patients could be included if treatment had been discontinued for ≥ 6 months Patients with wild type EGFR Uncontrolled pericardial or pleural effusions History of cardiovascular disease: Congestive Heart Failure > NYHA grade II. Unstable angina (with symptoms at rest) or new occurrence of angina (onset within the last 3 months) or myocardial infarction in the last 6 months Brain metastases (unless metastases were controlled and did not require hormone therapy) Known infection with HIV Active serious clinical infection > CTCAE grade 2 Major operation or serious trauma within 3 weeks before the first drug administration History of non-NSCLC cancer ≥5 years prior to study treatment (patients with carcinoma in-situ of the cervix, cured basal cell carcinoma, or bladder epithelial tumour were enrolled). Mixed with small cell lung cancer Inability to take oral medication Any condition leading to malabsorption	Primary: Progression free survival Secondary: Overall survival Objective tumour response rate Time to progression Duration of response Quality of life Safety

CTCAE= common terminology criteria for adverse events

Appendix 3

Illustrative results from adjusting submitted model assuming no overall survival gain for erlotinib compared to gefitinib

The results shown in Table 29 illustrate the importance to the decision problem of the assumption, made implicitly in the submitted model, that an improved mean PFS estimate for erlotinib-treated patients compared to those treated with gefitinib automatically generates a corresponding advantage in OS.

The ERG has assumed that there is no such advantage (in line with the available reported trials of gefitinib and erlotinib), and the erlotinib estimated life-years total is therefore restricted to that obtained in the model for gefitinib. The mean time erlotinib-treated patients spend in the progressive disease state is reduced to balance the adjusted total survival, assuming that the estimated PFS advantage for erlotinib is not affected. This requires that the QALYs attributable to time spent in the progressive disease state and the corresponding BSC cost are both reduced pro-rata to the adjusted time of erlotinib patients in the PD state.

With these adjustments, the manufacturer's model indicates that the estimated ICER for the base case increases to over £127,000 per QALY gained, which reduces to more that £50,000 per QALY when the PAS price is also considered.

The ERG presents these figures only to illustrate the importance of the manufacturer's assumption of automatic OS gains when a PFS advantage is apparent from a clinical trial. The ERG does not consider that any evidence has been presented to support this hypothesis, and therefore the ERG does not endorse the use of any estimates derived from the manufacturer's model for any other purpose.

Table 29 Illustrative results from adjusting submitted model assuming no overall survival gain for erlotinib compared to gefitinib

	Base case analysis with submitted model		Base case with PAS price	Base case with no OS gain	Base case with PAS price and no OS gain
	Gefitinib	Erlotinib	Erlotinib	Erlotinib	Erlotinib
PFS life-years	0.9048	[redacted]	[redacted]	[redacted]	[redacted]
PD life-years	0.8908	[redacted]	[redacted]	[redacted]	[redacted]
Total life-years	1.7956	[redacted]	[redacted]	[redacted]	[redacted]
PFS QALYs	0.5937	[redacted]	[redacted]	[redacted]	[redacted]
PD QALYs	0.4217	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	1.0154	[redacted]	[redacted]	[redacted]	[redacted]
Incremental QALYs		[redacted]	[redacted]	[redacted]	[redacted]
Drug/admin costs	£9,854	[redacted]	[redacted]	[redacted]	[redacted]
AE costs	£36	[redacted]	[redacted]	[redacted]	[redacted]
PFS BSC costs	£1,970	[redacted]	[redacted]	[redacted]	[redacted]
PD BSC costs	£1,711	[redacted]	[redacted]	[redacted]	[redacted]
Terminal costs	£2,475	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	£16,046	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost		[redacted]	[redacted]	[redacted]	[redacted]
ICER erlotinib vs gefitinib		**£48,961**	**£21,874**	**£127,614**	**£53,081**