Erlotinib for the treatment of relapsed non-small cell lung cancer

ERG Report

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Abbreviations:

AE	Adverse events
ASC	Active supportive care
ASCO	American Society of Clinical Oncology
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost effectiveness acceptability curve
CR	Complete response
CRD	Centre for Reviews and Dissemination
ECOG	Eastern Clinical Oncology Group
EGFR	Epidermal growth factor receptor
EMEA	European Medicines Evaluation Agency
ERG	Evidence review group
EU	European Union
HER1	Epidermal growth factor receptor
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
NICE	National Institute for Health and Clinical Excellence
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression-free survival
PPS	Post-progression survival
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SA	Sensitivity analysis
SMC	Scottish Medicines Consortium
STA	Single technology appraisal
TNM	TNM (tumour, nodule, metastasis) classification of malignant tumours
TTF	Time to treatment failure
TTP	Time to disease progression or death
VAS	Visual analogue score
WHO	World Health Organisation
WTP	Willingness to pay

Definition of terms:

Complete response	Disappearance of all measurable and evaluable disease
Duration of response	Time from first objective status assessment of CR/PR to the first time disease progression is documented.
Overall survival*	Time from randomisation to death from any cause.
Partial response	More than or equal to 50% decrease in the sum of products of perpendicular diameters of all measurable lesions
Progressive disease	50% increase in the sum of products of all measurable lesions, or worsening of evaluable disease, or appearance of any new lesions
Progression free survival*	Time from randomisation to the first observation of disease progression or death from any cause.
Response rate*	Proportion of patients meeting the criteria for CR or PR
Stable disease	Not qualifying for complete response, partial response or progressive disease
Time to disease progression	The time from the date of randomization to the first date of documented disease progression and was censored at the date of death for patients who died without documented disease progression or the date of the last follow-up visit for patients who were still alive and who had not progressed
Time to treatment failure	The time from randomization to the date of progression of disease, discontinuation of treatment, or death due to any cause and was censored at the date of the last follow-up visit for patients who did not discontinue, who were still alive, and who did not have disease progression

* Definitions taken from Roche submission. The remaining definitions were taken from the JMEI trial[1] as they were not available in the company submission or BR21 trial and are therefore assumed to be approximate.

1 EXECUTIVE SUMMARY

1.1 Scope

This report presents the results of the assessment of the company evidence submission regarding the use of erlotinib for the second-line treatment of patients with locally advanced or metastatic (stage III/IV) non-small cell lung cancer (NSCLC). The report includes an assessment of both the clinical and cost-effectiveness evidence submitted by the company (Roche Products Limited).

1.2 Summary of submitted clinical effectiveness evidence

The submitted clinical evidence includes one randomised, placebo-controlled, double-blind trial (BR21)[2] that investigates the effect of erlotinib within its licensed indication (of treatment of relapsed NSCLC) versus placebo. The BR21 trial demonstrates that erlotinib significantly increases median overall survival by 42.5% compared with placebo (6.7 months versus 4.7 months, respectively; $P<0.001$, hazard ratio, 0.70). Progression-free survival (PFS) is significantly longer in the erlotinib arm when compared to placebo (2.2 months versus 1.8 months, respectively; $P<0.001$, hazard ratio, 0.61), and the overall response rate is significantly higher (8.9% versus 0.9%, $P<0.001$).

The majority of patients in the BR21 trial experienced non-haematological drug-related adverse effects (AEs). The most commonly reported adverse events attributed to erlotinib were rash (76%) and diarrhoea (55%); leading to a dose reduction in 12% and 5% of patients, respectively.

Currently there are no trials which directly compare erlotinib with any other second-line chemotherapy agent. For the purposes of indirect comparison, the submission provides a narrative discussion of data from 11 randomised controlled trials (RCTs) investigating the use of docetaxel at a dose of 75 mg/m^2.

The company extracted detailed data from two of the 11 trials involving docetaxel; docetaxel versus best supportive care (TAX317[3]) and docetaxel versus pemetrexed (JMEI[1]). In these trials, docetaxel showed similar efficacy levels to erlotinib as reported in the BR21 trial. Median overall survival was 7.5 months (docetaxel, TAX317), 7.9 months, (docetaxel, JMEI) and 6.7 months (erlotinib, BR21). Median

progression-free survival was reported as 2.9 months (docetaxel, JMEI) and 2.2 months (erlotinib, BR21) and overall response rates were reported as 8.9% (docetaxel, JMEI) and 8.8% (erlotinib, BR21).

Analyses of TAX317 and JMEI in relation to the BR21 study demonstrated the lower rates of haematological toxicities experienced by patients receiving erlotinib, compared with docetaxel, particularly incidences of febrile neutropenia.

The submission therefore concludes that erlotinib has similar clinical efficacy levels to docetaxel but fewer serious haematological adverse events.

When interpreting the results of BR21, a number of issues relating to the patient population must be considered. For example, the BR21 patient population is younger than that expected to present in UK clinical practice; almost half of the trial participants received erlotinib as third-line chemotherapy, third-line chemotherapy in the UK is rare. Furthermore, a large number of participants in the BR21 trial had an ECOG PS of 2-3; typically patients receiving chemotherapy in UK clinical practice have a PS of 0-1. For these reasons it is difficult to compare the results of BR21 with TAX317 and JMEI or to current UK clinical practice.

1.3 Summary of submitted cost-effectiveness evidence

The economic model submitted in support of the company submission is a basic three state model comparing erlotinib with docetaxel, furnished with clinical data from TAX317 and the BR21 trial. The company report an incremental cost effectiveness ratio (ICER) of £-2,941 per QALY for erlotinib compared to docetaxel, with a 68% probability that erlotinib is cost-effective at a willingness to pay (WTP) of £30,000 per QALY gained. After adjustment for the double-counting of half-cycle correction, the company model yields a corrected ICER of £-1,764.

However, a number of key assumptions and parameters in the model do not seem to be clinically and/or economically justified, particularly in terms of costs. For example, the company underestimates the acquisition cost of erlotinib and overestimates the acquisition cost of docetaxel. Once these assumptions are adjusted to reflect more realistic estimates, the ICER increases to £52,098 per QALY, with a 44% probability that erlotinib is cost effective at a WTP of £30,000.

In terms of health outcomes, a further issue is the use of visual analogue scores (VAS) from the Oxford Outcomes study; the scores were not adjusted to zero for death and conflict with the tariff values calculated using responses from the same sample of healthy volunteers. Re-analysis of the model rescaling the VAS PFS utility scores to ensure death has zero utility, further increased the ICER (£68,673 per QALY). Similarly, re-analysis using tariff PFS utility values lead to an ICER well above the WTP threshold of £30,000 (£31,261 per QALY).

Joint exploration of uncertainty in the cost of docetaxel and the degree of variation in dosing introduced by clinical judgement yields a range of ICER estimates between £41,943 and £70,418 per QALY gained.

There is also a large amount of unquantifiable uncertainty in the model, relating to adverse events, post-progression survival and PFS health state costs, and the length of PFS. These areas of ambiguity could potentially further increase the ICER and may even result in docetaxel dominating erlotinib.

2 BACKGROUND

2.1 Introduction

The purpose of this single technology appraisal is to assess the use of erlotinib for the treatment of relapsed non-small cell lung cancer.

Erlotinib (*Tarceva*®) is an orally active inhibitor of epidermal growth factor receptor/human epidermal growth factor receptor 1 (EGFR/HER1) tyrosine kinase inhibitor. EGFR/HER1 is implicated in essential biological processes of malignancy and is expressed in a high proportion of NSCLCs. In non-clinical models, inhibition of EGFR tyrosine kinase results in cell stasis and/or death.[4]

The specified scope for this single technology appraisal is for treatment with erlotinib compared to current standards of care in second-line advanced non-small cell lung cancer (NSCLC). At present only docetaxel is recommended for such patients, and therefore the company submission rightly presents a case for the replacement of docetaxel by erlotinib as second-line chemotherapy in NSCLC patients for whom the former is currently considered appropriate.

2.2 Epidemiology

Lung cancer is the most common cause of cancer-related death in men, and the second most common cause of cancer-related death after breast cancer in women.[5] In 2002, 37,700 patients were newly diagnosed with lung cancer in the UK accounting for one in seven new cancer cases, with an incidence of about 62-65 per 100,000 population; the incidence of NSCLC is approximately 52 per 100,000 population.[6] Lung cancer is rarely diagnosed in people under 40 years of age, but the incidence rises steeply with age thereafter, peaking in people aged 75 to 84 years.[6]

In the 1950s the male to female ratio for lung cancer cases was 6:1; the ratio is now 3:2 and this is considered to reflect changes in smoking behaviour.[6] There is a strong association between incidence and mortality rates and levels of deprivation.[6]

2.3 Types of lung cancer

There are four main histological classifications of lung cancer; squamous cell carcinoma, adenocarcinoma, large cell carcinoma and small cell carcinoma. Because

the behaviour and management of the first three are very similar, they are often grouped together as non-small cell lung cancer (NSCLC). Around 70-80% of lung cancers are NSCLC.[6] Squamous cell carcinomas, adenocarcinomas and large cell carcinomas account for approximately 35%, 15% and 10% respectively of all lung cancers.[6] The remainder are small cell lung cancers, which have a distinct natural history and management, and are not addressed in this report.

2.4 Staging of NSCLC

NSCLC is classified according to the TNM classification of malignant tumours staging system (TNM). In this system, T refers to the size of the tumour and its spread, N to the number of lymph nodes involved and M to the presence of metastases (Table 2-1). The TNM system can be categorised further into stages I-IV (Table 2-2).

Table 2-1 A simplified TNM staging classification system for NSCLC

Primary tumour (T)	
T0	No evidence of primary tumour
T1	Small tumour < 3 cm across
T2	Tumour is > 3 cm or involves main bronchus or invades the visceral pleura.
T3	Tumour of any size that directly invades: chest wall, diaphragm, mediastinal pleura or pericardium
T4	Tumour of any size that invades: mediastinum, heart, great vessels, trachea, oesophagus, or with malignant pleural effusion or pericardial effusion
Regional lymph nodes (N)	
N0	No cancer in any lymph nodes (cancer is localised)
N1	Cancer to lymph nodes nearest affected lung
N2	Cancer in the mediastinal lymph nodes on the same side of affected lung
N3	Cancer in the lymph nodes on the opposite side from the affected lung
Distant metastasis (M)	
M0	No distant metastasis
M1	Cancer spread to another lobe of the lung or another part of the body

Source: Mason (2005)[7]

Table 2-2 Stage grouping by TNM subset

	Tumour				
Nodes		**T1**	**T2**	**T3**	**T4**
	N0	IA	IB	IIB	IIIB
	N1	IIA	IIB	IIIA	IIIB
	N2	IIIA	IIIA	IIIA	IIIB
	N3	IIIB	IIIB	IIIB	IIIB
Metastases	M1 = Stage IV				

Source: NICE (2005) [8]; Shaded areas indicate diseases states where chemotherapy is recommended

2.5 Aims of treatment

Patients with NSCLC have a number of treatment options depending upon the stage of disease. A proportion of patients in the early stages (I - II, and some stage III) are candidates for surgical resection, provided they have no medical complications and adequate lung function.[8] However, a minority of patients are diagnosed at this early stage. Approximately 75% of newly diagnosed patients have advanced NSCLC (stage III or IV) of whom two-thirds have advanced metastatic (stage IV) disease. Chemotherapy is recommended for some patients with non-resectable stage III or IV NSCLC (shaded in Table 2-2) provided they have a good performance status (PS).

Performance status can be measured on a number of scales. Guidance from the National Institute for Health and Clinical Excellence (NICE) recommends chemotherapy for some patients with stage III or IV NSCLC with a good performance status score of 0 or 1 on the World Health Organisation (WHO) performance status scale, or of 80 to 100 on the Karnofsky Performance Scale.[8] A number of clinical trials use the Eastern Cooperative Oncology Group (ECOG) performance scale. The WHO and ECOG scales are very similar in design and purpose (see Table 2-3).

Stage III and IV NSCLC are generally not considered to be curable, with five year survival rates of less than 1%.[5] Chemotherapy can be useful in improving patients' quality of life and may offer a modest survival benefit.

Patients with NSCLC should also receive active supportive care (ASC); often referred to as best supportive care (BSC). ASC can be given in conjunction with a

chemotherapy regimen, or independently for patients who are intolerant to, or whose performance status contraindicates chemotherapy. The composition of ASC varies widely but is generally aimed at alleviating the symptoms of cancer and the adverse effects of chemotherapy regimens.

Table 2-3 WHO/ ECOG performance status scale

Score	WHO/ ECOG performance status[8, 9]
0	Asymptomatic
1	Symptomatic, fully ambulatory
2	Symptomatic, in bed < 50% of the day
3	Symptomatic, in bed > 50% of the day but not bedridden
4	Bedridden
5	Dead

2.6 Current treatment options

2.6.1 Clinical guidance in England and Wales

First-line treatment, as recommended by NICE, states that chemotherapy should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug, either carboplatin or cisplatin.[8] Single agent chemotherapy with a third-generation drug can be offered to patients who cannot tolerate a platinum combination. Evidence suggests that combination therapy increases median survival by approximately nine weeks compared to ASC. The optimal duration of therapy has not been identified; the typical median number of cycles delivered in recent randomised trials is three to four. [8]

For patients who relapse after first-line treatment, NICE recommends consideration of docetaxel monotherapy as second-line treatment.[8]

There is currently no defined third-line agent for patients who fail to respond to, or relapse after, first- and second-line treatment. ASC alone will probably be the only option for the majority of patients.

2.6.2 Licensed agents

Three drugs have valid European Union marketing authorisations (EMEAs) for the second-line treatment of NSCLC. In 1995, docetaxel (Taxotere®) was licensed for "*the treatment of patients with locally advanced or metastatic non-small cell lung*

cancer after failure of prior chemotherapy". The licensing submission for docetaxel was supported by a phase III study comparing docetaxel with BSC

In 2004, pemetrexed (Alimta®) received a licence for use "*as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy"*. The licensing submission for pemetrexed was supported by a phase III study comparing pemetrexed and docetaxel.[1]

In 2005, erlotinib (Tarceva®) was licensed *"for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen"*. The licensing submission for erlotinib was supported by a phase III study comparing erlotinib with placebo.[2]

2.6.3 Clinical guidance in other countries

Erlotinib has been reviewed by the Scottish Medicines Consortium (SMC), firstly in November 2005, when the advice given was that erlotinib was "not recommended for use in NHS Scotland…..as the economic case has not been demonstrated".[10] This advice was modified in May 2006 after the company resubmitted its application.[11] The current advice from the SMC is that "erlotinib is restricted to use in patients who would otherwise be eligible for treatment with docetaxel. No economic case has been made for those whose performance status would make them ineligible to receive docetaxel".

Other guidelines such as the US National Comprehensive Cancer Network Practice guidelines in NSCLC state that docetaxel, pemetrexed and erlotinib are all established second-line agents.[12]

The Pharmaceutical Benefits Advisory Committee, Australian Department of Health, when assessing erlotinib "rejected the submission because equivalent effectiveness with docetaxel had not been demonstrated and there was uncertain cost-effectiveness in comparison with BSC. The PBAC considered that any re-submission should also present a comparison with pemetrexed".[13]

2.6.4 Number of patients treated

Evidence relating to the number of NSCLC patients receiving chemotherapy in England and Wales is scarce and contradictory. In 2001 NICE estimated that of the 26,400 patients diagnosed with NSCLC, 15% would be potential candidates for

chemotherapy; patient numbers receiving chemotherapy were reported to vary from 1,320 to 5,280.[4] When estimating the cost impact of its 2005 guidance on the treatment of lung cancer, NICE used an upper estimate of 30% as the proportion of patients with NSCLC who might potentially receive first-line chemotherapy.[14] It is estimated that a smaller proportion, possibly one third to one half of those receiving first-line therapy, will be suitable for second-line treatment.[15, 16]

In contrast, the Royal College of Physicians estimates that over 16,000 (49%) NSCLC patients a year are eligible for chemotherapy.[5, 14]

One of the reasons for these differences and the increasing use of chemotherapy could be the growing evidence for the benefits of its use as an adjuvant following surgery and in combination with radical radiotherapy.[5] An assessment of the benefits of adjuvant chemotherapy is not discussed in this appraisal.

2.7 Critique of company background

The company evidence submission provides a generally accurate and thorough discussion of the background to the disease of lung cancer and its treatments. However, the following points are worthy of note.

2.7.1 Scope of the company submission

There are likely to be some second-line patients with stage III/IV NSCLC whose condition precludes them from receiving intravenous chemotherapy (e.g. docetaxel) and who therefore receive only ASC. These patients could be considered for treatment with erlotinib as it is a less demanding oral regimen. Unfortunately, Roche Products Ltd. have chosen not to submit evidence in support of erlotinib as a second-line treatment for this sub-group, and therefore the ERG is precluded from considering the cost-effectiveness of this option.

2.7.2 Comparators

The submission claims that docetaxel is the only relevant comparator for this appraisal. The reasons given are that docetaxel is the only second-line treatment of NSCLC endorsed by NICE guidance for this group of patients and is the only active treatment in regular clinical use for this disease. Pemetrexed is therefore dismissed as a relevant comparator as it is claimed to be infrequently used in England and Wales

(company submission: page 6). Pemetrexed has not yet been reviewed by NICE for the treatment of second-line NSCLC but is currently being assessed as a single technology appraisal.[17]

The company submission also states that the Scottish Medicines Consortium specifically recommends that pemetrexed is not to be used in this indication. While this is correct in essence, the SMC append this statement with the following caveat "the holder of the marketing authorisation has not made a submission to SMC regarding this product in the indication. As a result we cannot recommend its use within NHS Scotland".[18] In summary, there is no SMC recommendation regarding pemetrexed for the second-line treatment of NSCLC because the company has not yet submitted an application for consideration.

2.7.3 Subgroups

The submission states that although examination of sub-populations from the key clinical trial has led to various hypotheses about how patients may benefit from erlotinib, at present there is no robust evidence identifying particular groups of patients who will not benefit from erlotinib.[19] As such, no pre-treatment investigations are required to select patients for therapy; patient eligibility is defined solely by progression after prior chemotherapy. While this is correct, the Summary of Product Characteristics for erlotinib state that "no survival benefit or other clinically relevant effects of treatment have been demonstrated in EGFR-negative tumours".[4] This statement reflects a concern about efficacy and EGFR status that was raised during the licensing process.[20]

3 CLINICAL EFFECTIVENESS

The company submission includes three systematic reviews. The company attempts to determine the clinical effectiveness of erlotinib versus placebo, the clinical effectiveness of docetaxel versus erlotinib (indirect comparison) and the cost effectiveness of erlotinib versus docetaxel. The two clinical effectiveness reviews are presented here.

3.1 Critique of clinical systematic reviews

Key aspects of the methodological quality of the company's review of the clinical literature was assessed based on an accepted quality assessment tool[21] and the results are summarised in Table 3-1.

Table 3-1 Quality assessment of the two clinical effectiveness reviews

Quality assessment checklist item	Yes/No
Did the review address a clearly focused research question?	✔
Was the search strategy adequate? (i.e. did the reviewers identify all relevant studies?)	✔/✖
Are the inclusion/exclusion criteria specified?	✔
Did the review include the right type of studies?	✔
Is there a statement of completeness from the company?	✖
Did the reviewers assess the quality of the included studies?	✔/✖
Was the method of data extraction reported?	✖
Were appropriate measures of outcomes used?	✔
If the results of the studies have been combined, was it reasonable to do so?	NA
Are appropriate sub-group analyses presented?	✔
Are the main results of the review reported? (e.g. numerical results included with the CIs)	✔
Are issues of generalisability addressed?	✔

✓=yes, ✓/X=partially, X=no, NA=Not applicable

3.1.1 Search strategy

Appropriate databases and conference proceedings were searched. Search terms for electronic databases included a combination of free-text and index terms combined with drug names used as free-text terms. We were unable to reproduce these searches as sufficient detail (e.g. specific search strategies used for each database and the numbers of references retrieved for each search) was not provided in the submission.

In addition to these searches, it is stated that the study report from the key licensing study for erlotinib, BR21, obtained from the Roche Regulatory Affairs Department, was used as a further data source.

The search strategy conducted by the ERG confirms the finding of only one relevant direct comparison trial. However, the indirect comparison search conducted by the ERG identified a further RCT, investigating the use of docetaxel given every three weeks compared with a weekly schedule administered as a second-line therapy in 125 patients with advanced NSCLC.[22]

3.1.2 Inclusion and exclusion criteria

Details of inclusion and exclusion criteria are provided in Table 3-2 and are considered appropriate and complete.

3.1.3 Application of inclusion criteria

Application of inclusion criteria (e.g. the number of reviewers involved in the process and whether this was done independently) was not defined in the submission.

Flow diagrams and tables of included trials are presented in the submission for both reviews. For searches of trials which include direct comparisons of erlotinib, the inclusion criteria were applied to 14 publications. A total of five publications describing one RCT were included in the review. For searches of studies relevant to the indirect comparison of erlotinib and docetaxel, 48 publications were identified and 24 were included in the company submission. Appendix 3 (Tables 10 and 11) in the submission outlines the characteristics of the included 11 trials as compared to erlotinib in the BR21 trial. These covered data from four phase II trials and seven phase III trials.

Table 3-2 Scope of the literature review

	Clinical effectiveness	
	Direct comparison	**Indirect comparison**
Population	Adults with incurable stage III/IV non-small cell lung cancer who had failed at least one prior cytotoxic chemotherapy regimen	
Intervention	Erlotinib	Docetaxel
Comparators	Any	Any
Outcomes	• Overall survival • Progression-free survival • Overall survival rates (partial and complete) • Duration of response • Toxic effects • Quality of life	Not specified
Study design	Randomised controlled trials (RCTs)	
Inclusion criteria	• Main focus of non-small cell lung cancer • Clinical trial data publications • Studies in previously treated patients	• Docetaxel had to be the major focus • NSCLC had to be a major focus • Clinical trial data • Previously treated patients • Phase II studies involving more than 50 patients allocated to docetaxel at a dose of 75 mg/m^2 every three weeks • Phase III studies using 75 mg/m^2 of docetaxel in one study arm
Exclusion criteria	• Clinical trials in first-line use in chemotherapy naïve patients • Reviews • Animal studies or in vitro research work	• Clinical trials in first-line use in chemotherapy naïve patients • Reviews • Animal studies or in vitro research work
Included studies	• 1 study	• 11 studies

3.1.4 Quality assessment

Direct comparison

The company submission did not include a formal quality assessment, or discuss the methodological limitations of the one included trial (BR21). However, the submission provides information concerning certain aspects of the methodological quality of the included trial including the randomisation procedure and the adequacy of follow up.

As the randomisation process was performed centrally, it is likely that allocation concealment was adequate. Baseline characteristics were generally comparable in each treatment arm.

The nature of blinding was not explicitly reported in the submission or in the published paper; but, as this was a double-blind trial, it is likely that both participants and investigators were kept blind to treatment assignment. No information on blinding

of the outcome assessors was provided. However, due to the large proportion of patients in the erlotinib arm who developed a rash, blinding may well have been compromised as it may have been apparent to both participants and investigators who had been randomised to the erlotinib arm of the trial. This might be irrelevant for the measurement of the primary endpoint (overall survival) but needs to be considered when analysing key secondary outcomes (progression-free survival, objective response and quality of life).

Indirect comparison

The company submission did not provide any quality assessment of the studies included in the indirect comparison of erlotinib versus docetaxel.

3.1.5 Data extraction

Details of the data extraction process (e.g. number of reviewers and whether data were extracted independently) were not provided in the submission.

3.2 Direct comparison: erlotinib versus placebo

One international, multi-centre, phase III, randomised, placebo-controlled, double-blind single-agent trial involving 731 patients was included in the review. Between August 2001 and January 2003, patients were randomly assigned in a 2:1 ratio and given erlotinib at a dose of 150 mg daily or placebo. Twenty-two patients (12 assigned to erlotinib and 10 to placebo), not eligible for inclusion in the trial, were included in the efficacy analyses. A total of 727 patients (485 assigned to erlotinib and 242 to placebo) were included in the safety analyses. Results from this trial were reported in two peer-reviewed journal articles, two conference abstracts, and one study report. A detailed summary of this trial is provided in the submission.

Data presented in this report have been extracted from both the submission and the primary published, peer-reviewed clinical paper.[2] Additional information was also provided by the company in clarification of questions raised by the ERG.

3.2.1 Trial characteristics

Study characteristics are summarised in Table 3-3.

Table 3-3 Study characteristics

Study name	Interventions drug & dose, N	Study enrolment	Study design	Outcomes	Location & centres	Inclusion criteria	Exclusion criteria	Follow-up
BR21[2]	Erlotinib (150 mg/m^2) n=488 Placebo n=243	August 2001 – January 2003	RCT Phase III	Primary outcomes: overall survival Secondary outcomes: progression-free survival, overall response rate (complete and partial), duration of response, toxicity Qualtiy of life (Qol)	International (17 countries), multi-centre (86 sites) The study was not conducted in the UK	All of the following: patients ≥18 years with ECOG[a] performance status 0,1,2 and 3, documented pathological evidence of NSCLC, one or two prior chemotherapy (not be eligible for further chemotherapy), recovery from any toxic effects of prior, therapy adequate haematologic and biochemical values	One or more of the following: patients with prior breast cancer, melanoma, hypernephroma, other malignant diseases (except basal-cell skin cancer) within the preceding 5 years, symptomatic brain metastases, clinically significant cardiac disease within one year, ventricular arrhythmias requiring medication, clinically significant ophthalmologic or gastrointestinal abnormalities. Pregnant or lactating females, prior treatment with EGFR inhibitors of any kind, serious active infection or other serious underlying medical condition that would impair the ability of the patient to receive protocol therapy	No median follow-up reported. 582/731(79.6 %) patients were followed until death

a ECOG=Eastern Cooperative Oncology Group

3.2.2 Participant characteristics

Patients included in the trial were stratified by treatment centre, performance status, best response to previous chemotherapy, number of prior regimens and exposure to prior platinum therapy. Therefore, as would be expected patient groups were comparable at baseline.

Patient demographics were similar in both groups. Overall, 64.5% of patients in the erlotinib arm, and 65.8% patients in the placebo arm were male, with a median age of 62 years in the erlotinib arm, and 59 years in the placebo arm. The majority of patients were either current or ex-smokers (erlotinib:73%, placebo:77%) and over half of the patients (erlotinib:52.5%, placebo:54.3%) had an ECOG performance status of one. About half of the patients in the erlotinib arm had received one prior chemotherapy regimen (51%) and half had received two prior regimens (49%). Ninety-two percent of patients in both arms had a platinum-based prior chemotherapy. In the erlotinib arm, the best response to prior chemotherapy included complete or partial response for 38%, stable disease for 34% and progressive disease for 28% of patients.

A lack of biopsy material meant that EFGR status could only be assessed in 33% (erlotinib: 31%, placebo:35%) of these patients, 15.2% in each arm were EGFR negative and 16.0% and 20.2% were EGFR positive in the erlotinib and placebo arms respectively.

There are several related concerns regarding the study population. Firstly, the median age of the study population was 61.4 years, which is likely to be younger than those presenting with NSCLC in UK clinical practice. The company justify this anomaly by citing a recent audit which found that the majority of patients receiving second-line therapy were under 65.[23] Furthermore, the company undertook multivariate analyses which did not identify age as a significant predictor of response to erlotinib. However, this low age may reflect the exclusion criteria applied in the trial. For example, patients with cardiac disease and any other underlying disease were excluded from the trial. Therefore the trial population is likely to be unrepresentative of the general population of NSCLC patients. The need for exclusion of these individuals from the trial is not reflected in the licence indication.

Despite this arguably healthier patient population, the BR21 trial population included a large number of patients with ECOG PS 2-3. In England and Wales, patients with PS 2 are usually only recommended for chemotherapy as part of a clinical trial; patients with PS 3 are not usually recommended for chemotherapy as they are considered too unwell for any chemotherapy products.[8] Multivariate analyses included in the submission showed that poor PS was associated with a poorer response to erlotinib. Once again the company believe this will only bias the analysis in favour of docetaxel, as the docetaxel trials utilised in the economic analyses did not include patients with PS 3.

A further disparity between the trial population and the UK clinical practice population is that a proportion of BR21 patients received erlotinib (49%) as a third-line treatment. However, third-line therapy for NSCLC in the UK is rare.[19] The company state the difference in number of prior chemotherapies between trials (if significant) will only bias the analysis in favour of docetaxel as the docetaxel trials used to inform the economic analyses did not include third-line patients.

Also, the trial was conducted in 86 centres in 17 countries worldwide. None of the trial centres was located in the United Kingdom. The submission argues that the management of NSCLC in the UK is similar to that of other industrialised countries and therefore the results of BR21 would be applicable to the UK population.

The final concern regarding the trial population is the proportion of patients who were EGFR negative. Identifying and pre-selecting patients most likely to respond to EGFR/HER1-targeted agents, such as erlotinib, may be a key factor in using these agents cost effectively. In the BR21 trial of erlotinib, EGFR status was determined in about a third of patients at study baseline.[2] Information on the status of an additional 104 patients was submitted to the EU licensing authority, giving them EGFR results for 45% of study subjects[20]. Analysis within this subgroup did not establish efficacy as measured by overall survival, progression-free survival or tumour response in patients with EGFR-negative status. The licensing authority considered that for a compound targeting EGFR-signalling, solid evidence should be available showing that the compound is active in EGFR-negative tumours and the issue was referred to the European Medicines Evaluation Agency Scientific Advisory Group for Oncology. This group concluded that there is no pharmacological reason for using erlotinib in EGFR-negative patients and that EGFR status should be known and taken into

account when deciding which patients should receive erlotinib.[20] While this advice was not incorporated into the licence because the evidence was not robust, if it were to be followed, patients being considered for erlotinib therapy would have their EGFR status determined, and this would have attendant cost and service implications

3.2.3 Comparator

In BR21 erlotinib is compared to placebo. A key issue surrounding this trial is the BSC component of treatment given to patients whilst on therapy and on placebo. Details of BSC are not provided therefore it is not possible to determine if the components of care were the same in both of the arms of the trial.

3.2.4 Clinical results

The key results of trial BR21 are presented in Table 3-4.

Table 3-4 Key results of study BR21

	Measure	Erlotinib (n=488)		Placebo (n=243)	
Overall survival	*Median* overall survival (months) (95%CI)	6.7 (5.5-7.8)		4.7 (4.1-6.3)	
	Adjusted HR	0.70; (95% CI, 0.58-0.85; *P*<0.001)			
	Mean overall survival (months)	9.5		Not reported	
	One year overall survival%	31.2		21.5	
Progression-free survival	*Median* PFS (months)	2.2		1.8	
	Adjusted HR	0.61 (95% CI, 0.51-0.74; *P*<0.001)			
	Mean PFS (months)	4.41		2.76	
Response rate	Response	**N**	**% (95% CI)**	**N**	**% (95% CI)**
	CR	4	0.9	1	0.5
	PR	34	8	1	0.5
	SD	150	35.1	56	26.5
	Overall Response Rate (CR+PR)	38	8.9 (6.4, 12.0)	2	0.9 (0.1, 3.4)
	PD	164	38.4	121	57.3
	Inevaluable or not applicable	75	17.6	32	15.2

PFS: Progression-free survival; HR: Hazard ratio; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease

Overall survival

At the time of the analysis, 378 deaths had occurred in the erlotinib arm and 209 in the placebo arm. The submission does not specify as to whether these deaths were cancer related.

The median overall survival (OS) for patients treated with erlotinib was 6.7 months compared to 4.7 months for those on placebo (P<0.001). At one year, 31% of the patients taking erlotinib were still alive compared to 22% of those taking the placebo.

The BR21 trial protocol was amended three times. Most significantly, the company revised their sample size calculation in order to detect a 33% (initially 50%) improvement in median overall survival (hazard ratio 0.75, initially 0.67) with erlotinib, using a two-sided 5% level test of significance and 90% power, assuming a median survival of 4 months for the placebo arm.

Progression-free survival

The median progression-free survival was statistically significantly longer in the erlotinib group: 2.2 months compared to 1.8 months in the placebo group (P<0.001).

The submission also reports the mean PFS from the BR21 trial as 4.41 months for erlotinib and 2.76 months for placebo, although it is not clear whether this is "last event time" or "last observed time". It is stated in the submission that the Kaplan-Meier PFS curves show that they do not separate until almost half of the patients have responded in both the erlotinib and placebo arms. This indicates that a large number of patients progress early, with little impact on their PFS, but that those patients who benefit from treatment do so to a marked degree, therefore explaining the difference between the median and mean PFS.

Response rates

In the erlotinib arm, the rates of complete response and partial response were 0.9% and 8.0%, respectively (median duration, 7.9 months); in the placebo arm, the rate of complete response was 0.5% and the rate of partial response was also 0.5% (P<0.001). Stable disease was reported as 35.1% for the erlotinib arm and 26.5% for the placebo arm. The overall response rate was reported as 8.9 (95% CI, 6.4-12.0) in the erlotinib arm and 0.9 (95% CI, 0.1-3.4) in the placebo arm.

In the intention to treat (ITT) population, the disease control rate (i.e. the rate of complete or partial responses and stable disease) in the patients treated with erlotinib was 44%; of the remaining patients, 38.4% had progressive disease, and progression was not confirmed in 17.6%. [2]

In the placebo arm there were two patients who had a positive response reported, one with a complete response and one with a partial response. Use of palliative radiotherapy is not described in the submission; what these patients were responding to is therefore unclear and may highlight the subjective nature of measuring response. If there is a placebo effect causing clinically reported responses then adequate blinding is imperative. In BR21, tumour response on progression was assessed by independent radiologists only for the first 330 patients. This means that for the majority of patients in the trial (n=401) no central radiology review was performed. Given the 2:1 randomisation in favour of erlotinib, blinding of local investigators may have been compromised by the identification of erlotinib patients presenting with rash; hence bias may have been introduced inadvertently.

Quality of life

The BR21 trial used the EORTC QLQ-C30 and the QLQ-LC13 questionnaires to assess a number of quality of life (QOL) parameters.

Patients treated with erlotinib demonstrated improved or stable QoL responses for a number of QoL domains (pain, dyspnea, and cough) compared to patients treated with placebo (see Table 3-5). However, in terms of diarrhoea, and sore mouth, the QoL responses of the erlotinib patients were notably inferior to the placebo patients. It was therefore not possible to determine whether erlotinib lead to a global improvement in QoL compared to placebo.

Table 3-5 Quality of life response analyses

Domain/item	Erlotinib		Placebo	
	Improved/ stable	Worse	Improved/ Stable	Worse
	N (%)		N (%)	
Global	Academic in Confidence	Academic in Confidence	Academic in Confidence	Academic in Confidence
Pain	Academic in Confidence	Academic in Confidence	Academic in Confidence	Academic in Confidence
Dyspnea	Academic in Confidence	Academic in Confidence	Academic in Confidence	Academic in Confidence
Diarrhoea	Academic in Confidence	Academic in Confidence	Academic in Confidence	Academic in Confidence
Cough	Academic in Confidence	Academic in Confidence	Academic in Confidence	Academic in Confidence
Sore mouth	Academic in Confidence	Academic in Confidence	Academic in Confidence	Academic in Confidence

Analyses by subgroups

Both univariate and multivariate analyses of the hazard ratios for death were conducted and reported in the submission. In the multivariate analyses, factors that were significantly associated with survival included performance status (ECOG), best response to prior therapy, exposure to prior platinum, smoking status, histology, weight loss in previous six months and time from initial diagnosis to randomisation. The factors that were not associated with survival included the number of prior regimens, prior exposure to taxanes, geographical region, EFGR status, gender or age.

Adverse events

The rates of haematological and non-haematological adverse events are shown in Table 3-6 and Table 3-7. Only a few patients experienced haematological toxicities; 3% experienced anaemia and 1% experienced thrombocytopenia. No patients experienced neutropenia or febrile neutropenia.

The most commonly reported toxic effects associated with erlotinib were non-haematological in nature (Table 3-7). These included rash (76%) and diarrhoea (55%). The toxic effects in the erlotinib group were generally mild to moderate, with 9% of patients suffering grade 3/4 rash and 6% of patients suffering grade 3/4 diarrhoea (0% and <1% in the placebo arm, respectively). Of these, rash led to a dose reduction in 12% of patients, and diarrhoea in 5% of patients.

Whilst all grades of infection were reported more frequently in the erlotinib arm (34% versus 21%, P=<0.001) grade 3 to 4 infection was reported more frequently in the placebo arm (2% versus 5%, P=0.03).

Overall, 5% of patients discontinued erlotinib because of toxic effects compared to 2% of placebo patients.

Table 3-6 Haematological toxicities reported after treatment with erlotinib

Effect	Neutropenia	Anaemia	Thrombocytopenia	Febrile neutropenia
% of patients affected	0	3	1	0

Table 3-7 Non-haematological toxicities reported after treatment with erlotinib or placebo

Toxic effect	Erlotinib		Placebo		P values	
	all	*% Grade 3-4*	*All*	*% Grade 3-4*	*All p=*	*grades p=*
Rash	76	9	17	0	<0.001	<0.001
Anorexia	69	9	56	5	<0.001	0.06
Nausea	40	3	34	<1	0.12	0.07
Vomiting	25	3	23	2	0.52	0.45
Stomatitis	19	<1	3	0	<0.001	0.31
Diarrhoea	55	6	19	<1	<0.001	<0.001
Dehydration	7	4	6	3	0.64	0.67
Ocular toxic effect	28	1	9	<1	<0.001	0.67
Fatigue	79	19	74	23	0.22	0.33
Infection	34	2	21	5	<0.001	0.03
Pulmonary fibrosis	3	<1	3	0	1	1
Pneumonitis or pulmonary infiltrates	3	<1	3	<1	0.64	1
Death from pneumonitis	1		1		1	
Reason for dose reduction						
Any toxic effect	19		2		<0.001	
Diarrhoea	5		0		<0.001	
Rash	12		0		<0.001	
Conjunctivitis	1		0		0.19	
Vomiting	1		0		0.55	
Stomatitis	<1		0		1	
Reason for treatment interruption						
Any toxic effect	27		5		<0.001	
Diarrhoea	6		<1			
Rash	14		0		<0.001	
Conjunctivitis	1		0		0.19	
Vomiting	2		<1		0.11	
Stomatitis	<1		<1		1	
Treatment discontinued because of any toxic effect	5		2		0.02	

N.B All data extracted from the published paper[2]

3.3 Indirect comparison: erlotinib versus docetaxel

As there are no trials directly comparing erlotinib with other chemotherapy regimens, the submission included (and narratively discussed) further clinical evidence involving the use of docetaxel as monotherapy for the treatment of relapsed NSCLC. Using this evidence, the submission indirectly compares the clinical efficacy of erlotinib with docetaxel. However, the lead investigator from the BR21 trial (erlotinib versus placebo) and TAX317 (docetaxel versus BSC), who was also involved in JMEI (pemetrexed versus docetaxel), explicitly states in a peer reviewed publication "it is inappropriate to compare the results of BR21, TAX317 and JMEI since their patient populations differed considerably."[13]

3.3.1 Trial characteristics

Characteristics of the included trials are provided in Table 10 in the submission. Of the 11 trials, only one compared docetaxel with BSC (TAX317). Four trials compared different doses of docetaxel, two compared docetaxel with docetaxel plus irinotecan and one trial compared docetaxel with a higher dose of docetaxel ($100mg/m^2$) or vinorelbine. The remaining three trials compared docetaxel with gefitinib, pemetrexed (JMEI) and oral topotecan.

Seven trials stated they were not blinded, and four did not mention blinding. The number of trial participants ranged in size from 108 to 829 patients. The number of patients receiving docetaxel ($75mg/m^2$) ranged from 55 to 415 patients.

Different primary end points were reported in the 11 trials including the following: median survival (n=2), one-year-survival (n=2), response rates (n=2), non-inferiority of survival rates (n=2), time to treatment failure (n=1), quality of life at three weeks (n=1) and descriptive statistics (n=1).

3.3.2 Patient characteristics

Patients from the BR21 study are similar to the patients in the docetaxel trials for all but two characteristics; performance status and the number of prior chemotherapy regimens (Table 11 in the submission).

The BR21 was the only trial to allow patients with PS 3 (9%) to be included in the study population and therefore the percentage of patients with higher levels of PS is greater in BR21 than in any of the docetaxel trials. Given that none of the docetaxel

trials included patients with PS 3, it is therefore inappropriate to indirectly compare these patient groups.

The proportion of patients with only one prior chemotherapy regimen was much lower in BR21 (51%) than any of the docetaxel trials (80%-100%) and the proportion with two prior regimens was considerably higher (49% compared to 0-12.7%). The exception amongst the docetaxel trials was trial TAX320.[24] This trial reported 74% of patients had received one or two prior chemotherapy regimens and 26% of patients had received three prior regimens. For the reasons outlined above, it is therefore inappropriate to indirectly compare these patient groups.

3.3.3 Clinical results

The company submission provides summary tables for the 11 indirect comparison trials showing key trial outcomes and adverse events, including weighted averages. Although the submission calculates these weighted averages, they fail to incorporate this information into their analyses of clinical and cost effectiveness.

Due to differences in patient populations, the ERG believes that it is inappropriate to compare the results of the 11 trials and therefore feels it is superfluous to include a discussion of these trials here. For reference, copies of the tables are provided in Appendix 1.

In the economic evaluation section of the company submission, the company focus on clinical data from TAX317 and, where necessary, supplement their analyses with clinical data from the JMEI trial. Therefore, the ERG also concentrates on the clinical data from TAX317 and JMEI in conjunction with the data from BR21.

Patients in the docetaxel arms of TAX317 and JMEI demonstrated similar efficacy levels to erlotinib patients in the BR21 trial (Table 3-8). Median overall survival of 7.5 months, 7.9 months and 6.7 months was reported in TAX317, JMEI and BR21 respectively. Median PFS was reported as 2.9 months by JMEI and 2.2 months in the BR21 trial and overall response rates were reported as 8.8 months and 8.9 months by JMEI and BR21 respectively. The submission concludes that the clinical efficacy results of erlotinib are equivalent to that of docetaxel.

Table 3-8 Key outcomes for trials BR21, TAX317 and JMEI

Measure	Erlotinib (BR21)[2] (n=488)	Docetaxel (TAX317)[3] (n=55)	Docetaxel (JMEI)[1] (n=288)
Median overall survival (months)	6.7	7.5	7.9
Mean overall survival (months)	9.5	8.89[a]	NS
Median progression-free survival (months)	2.2	NS	2.9
Mean progression-free survival (months)	4.41	NS	NS
Response rate (%)	OR=8.9; PR =8	OR=NS; PR =5.5	OR=8.8; PR=NS
One year overall survival (%)	31.2	37	29.7

NS: not stated; OR: overall response; PR: partial response

Analyses of TAX317 and JMEI in relation to the BR21 study demonstrated the lower rates of haematological toxicities experienced by patients receiving erlotinib, compared with docetaxel, particularly incidences of febrile neutropenia. The incidences of febrile neutropenia resulted in 37 patients (13.4%) in the JMEI trial being hospitalised on 43 occasions and 52 patients (19.2%) needing treatment with G-CSF. There were no hospitalisations for febrile neutropenia in the BR21 trial. There were five treatment related deaths (2%) in the JMEI trial and two (<1%) in the BR21 trial.

Non-haematological toxicities such as mucositis, fluid retention, neuropathy, alopecia rash/dermatological conditions, diarrhoea and conjunctivitis were reported in all trials. Whilst most were more commonly reported in the docetaxel trial patients, the patients in the BR21 trial reported greater incidences of rash/dermatological conditions, diarrhoea and conjunctivitis.

The company submission therefore concludes that erlotinib has similar clinical efficacy levels to docetaxel but fewer serious haematological adverse events.

3.4 Summary of clinical evidence

3.4.1 Clinical results

Direct comparison: erlotinib versus placebo

- Compared to placebo, erlotinib increased median overall survival by 42.5%, median PFS by 22.2%, overall response rate from 0.9% to 8.9% and duration of response from 3.7 months to 7.9 months
- Patients treated with erlotinib reported significant improvements in symptoms including dyspnoea, pain and cough
- Although very few patients experienced haematological toxicity the majority did experience non-haematological toxicity, e.g. rash (76%) and diarrhoea (55%)
- In the erlotinib group, 19% of patients required a dose reduction because of drug-related toxic effects compared to 2% of patients in the placebo group. In addition, the percentage of patients discontinuing erlotinib due to drug-related toxic effects was 5% compared to 2% in the placebo arm.

Indirect comparison: erlotinib versus docetaxel

- Patient populations in the trials were dissimilar
- Median overall survival of 7.5 months, 7.9 months and 6.7 months was reported in TAX317, JMEI and BR21 respectively
- Median PFS was reported as 2.9 months and 2.2 months in JMEI and BR21 respectively; overall response rates were reported as 8.8 months and 8.9 months in JMEI and BR21 respectively
- Haematological toxicities were more frequently experienced in patients receiving docetaxel than patients receiving erlotinib
- Non-haematological toxicities were reported by all trials although diarrhoea, conjunctivitis and rash/dermatological conditions were reported more frequently by patients treated with erlotinib.

3.4.2 Clinical issues

Direct comparison: erlotinib versus placebo

- The average age of the BR21 trial population is younger than expected in the UK clinical practice but may represent the appropriate treatment population
- A proportion of the BR21 trial population (49%) received erlotinib as a third line treatment. Third-line therapy for NSCLC in the UK is rare
- 31% of patients included in BR21 had an ECOG PS of 2-3
- The proportion of patients (76%) in the erlotinib arm experiencing a rash may have compromised the blinding of the trial and raises questions about bias in the care and clinical assessment of patients.

Indirect comparison: erlotinib versus docetaxel

- The company indirectly compare erlotinib with docetaxel citing 11 docetaxel studies. However, these trials may not be comparable owing to a number of factors
- The company calculate weighted averages for adverse events. However, they do not appear to use them in their analysis of clinical and cost effectiveness.

4 COST EFFECTIVENESS

4.1 Summary of published cost-effectiveness studies identified in the submission

4.1.1 Identification and description of studies

The submission did not fully describe the details of the electronic search strategy. The ERG was therefore unable to replicate the electronic searches undertaken by the company. However, key terms used and databases searched were described. The number of papers initially found and the number of papers excluded from the review were not reported.

Stated inclusion criteria were:

- **Date of publication**

  Studies published after January 1st 1996 were included.

- **Language of publication**

  Only studies published in English or where English translations were available were included in the systematic review.

- **Type of study and outcome**

  Studies were included if they described an economic evaluation quantifying both costs and benefits.

- **Intervention**

  Studies that examined the second-line treatment of NSCLC with docetaxel or erlotinib were included. However due to lack of data, studies that evaluated the use of docetaxel in first-line were also included as well as some general costing studies on lung cancer.

- **Subjects**

  Studies examining patients with lung cancer were included. No restrictions were placed on the age or gender of patients included in the analysis. Economic evaluations conducted on patients with different levels of disease severity were also included if they assessed cost-effectiveness in a subgroup of patients with early disease.

Using these inclusion criteria, the company identified 10 studies for inclusion in the review. However, by including the criterion "some general costing studies on lung cancer" the company's inclusion criteria becomes disorderly. Under the heading "type of study and outcome", studies are to be included if they describe both costs and benefits. To then allow general costing studies on lung cancer to be included only

serves to confuse eligibility as the type of costing/economic study to be included in the review becomes undefined. It is not then possible to determine whether or not all relevant studies are included in the review, as there are many studies which could be considered relevant under the title "general costing studies on lung cancer".

4.1.2 Data extraction

The company extracted data from the 10 papers included in the review including the aim of the study, the study results, and relevance to decision making in England and Wales. This data extraction is simplistic and does not provide sufficient detail for a comprehensive comparison of studies without obtaining the original references. As there is no commentary to the table of 10 studies, it is difficult to interpret the results of the studies.

The 10 studies from which data have been extracted are heterogeneous in terms of treatment (first-line and second-line treatments), type of evaluation (full economic evaluations and partial economic evaluations) and type of study (empirical cost effectiveness study, review of cost-effectiveness studies). Only two of the included studies appear to be full economic evaluations which are relevant to the UK NHS (Clegg[25], Holmes 2004[26]). Both of these studies assess the cost-effectiveness of docetaxel versus BSC.

As none of the papers compared erlotinib with docetaxel, these studies are not directly comparable with the economic evaluation presented in the company submission.

4.1.3 Quality assessment

The submission states that descriptions of any shortcomings in the included papers will be reported. However, it is not clear from the data extraction table if this has been carried out. No formal quality assessment of the included papers is reported.

4.1.4 Summary and conclusions

The economic literature review did not identify any studies which compared the use of erlotinib versus docetaxel for the second-line treatment of NSCLC. Two economic studies which compared docetaxel with BSC were identified. The data extraction of the economic literature undertaken by the company is lacking in depth, and no quality assessment of the included studies is provided. However, given the fact that these

studies do not compare the same healthcare technologies as the company's own economic evaluation, this is disappointing but of limited importance.

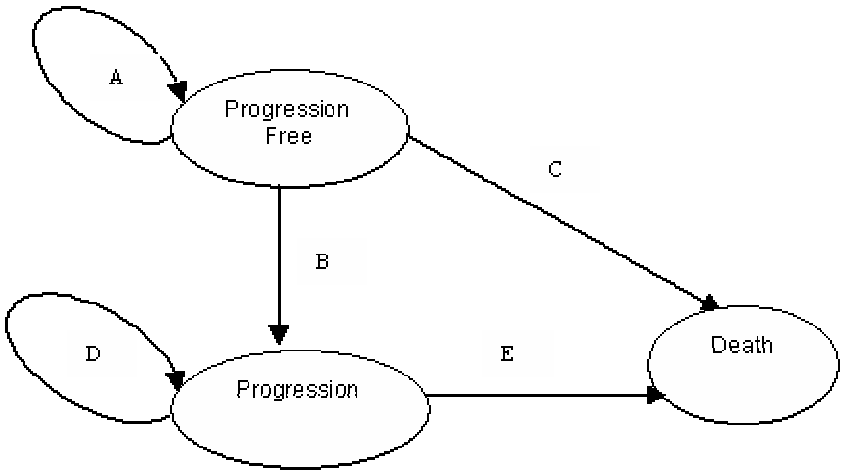
4.2 Overview of company economic evaluation

4.2.1 Description and critique of company model

The model is a three-state health state transition model, (see Figure 4-1) with the health states being defined as: progression-free survival (PFS); post-progression survival (PPS); and death, which is an absorbing state.

Patients begin in the PFS state and at the end of each cycle (cycle length 1 month) can either stay within this health state or move to the PPS health state or death state. Once in the PPS health state patients either move to the death state or continue in the progressed health state. But once in the PPS health state they cannot return to PFS.

Figure 4-1 Structure of the company model (adapted from company submission)



A number of parameters are used in the model (see Table 4-1).

Table 4-1 Model variables

Model Variable	Value	Source
Patient Survival		
Erlotinib overall survival (OS)	9.03 months	BR21 – Roche data on file
Docetaxel OS	9.03 months	BR21 – Roche data on file
Erlotinib progression-free survival (PFS)	4.11 months	BR21 (treatment duration)
Docetaxel PFS	3.33 months	Adapted from Holmes et al (treatment duration)
Erlotinib post-progression survival (PPS)	4.92 months	Calculated
Docetaxel PPS	5.56 months	Calculated
Costs		
Erlotinib	£54.38 per day	British National Formulary (BNF)
Docetaxel	£1,023 per cycle	BNF
PFS	£327 per month	Expert panel (resource use); schedule of reference costs and PSSRU (unit costs)
PPS	£988 per month	Expert panel (resource use); schedule of reference costs, BNF and PSSRU 2004 (unit costs)
Docetaxel drug administration	£202 per month	Expert panel (resource use); not stated (unit costs)
Cost per episode of rash	£117	Expert panel (resource use); schedule of reference costs and BNF (unit costs)
Cost per episode of anorexia	£119	Expert panel (resource use); schedule of reference costs and BNF (unit costs)
Cost per episode of diarrhoea	£237	Expert panel (resource use); schedule of reference costs, BNF and PSSRU 2004 (unit costs)
Cost per episode of nausea	£240	Expert panel (resource use); schedule of reference costs, BNF and PSSRU 2004 (unit costs)
Cost per episode of infection	£1227*	Expert panel (resource use); schedule of reference costs (unit costs)
Cost per episode of stomatitis	£188	Expert panel (resource use); schedule of reference costs (unit costs)
Cost per episode of neutropenia	£375	Expert panel (resource use) and schedule of reference costs and BNF (unit costs)
Cost per episode of fatigue	£19	Expert panel (resource use); schedule of reference costs and BNF (unit costs)
Cost per episode of neuropathy	£18	Expert panel (resource use); schedule of reference costs and PSSRU 2004 (unit costs)
Utilities		
PFS (oral therapy)	Academic in Confidence	Oxford Outcomes Study
PFS (IV therapy)	Academic in Confidence	Oxford Outcomes Study
PPS	Academic in Confidence	Oxford Outcomes Study
Rash	Academic in Confidence	Oxford Outcomes Study
Diarrhoea	Academic in Confidence	Oxford Outcomes Study
Fatigue	Equal to PFS	Not stated
Anorexia	Equal to PFS	Not stated
Neutropenia (grade 4)	Academic in Confidence	Oxford Outcomes Study
Febrile neutropenia	Academic in Confidence	Oxford Outcomes Study
Nausea	Academic in Confidence	Oxford Outcomes Study
Infection	Equal to PFS	Not stated

Stomatitis	Academic in Confidence	Oxford Outcomes Study
Neuropathy	Academic in Confidence	Oxford Outcomes Study

* High cost is due to 100% of patients requiring hospitalisation, and 50% requiring an emergency room visit

4.2.2 Population

The patient ITT populations from the BR21 and TAX317 trials, are assumed to be comparable. The age range in the two trials is very similar (median age between 59 and 62), although young for the target UK population. The proportion of males is approximately 65% in both trials. The main difference between the two trials is the proportion of patients on third-line therapy. In the BR21 trial 50% of patients had failed on two or more regimens, whilst in the TAX317 trial only 24% had been unsuccessful with two or more regimens. The company feel that this may bias the analysis but only in favour of docetaxel. In addition, the BR21 trial included patients with an ECOG PS 3, whilst TAX 317 did not include PS 3 patients.

4.2.3 Perspective and time horizon

An NHS perspective is adopted, in accordance with NICE guidelines. The time horizon is two years, even though all patients in the TAX317 trial had already died by that time, which is in part explained by the small patient numbers in the trial (n = 55). The company believe that this will bias the indirect analysis in favour of docetaxel as 15% of patients in the erlotinib arm of the BR21 trial (n = 488) were still alive beyond the two year cut-off. The company argue that this is a conservative approach as, by excluding these patients from the analysis, the full health benefits of erlotinib are not realised.

4.2.4 Comparator

Docetaxel was chosen as the main comparator. The data for docetaxel was obtained from the TAX317 trial, and indirectly compared with the erlotinib arm of the BR21 trial. Where data were unavailable from this trial, data from JMEI were used. Pemetrexed is also considered in comparison to erlotinib but only in the sensitivity analysis. TAX317 is not the largest trial involving docetaxel, nor the most recent; hence the heavy reliance on this small trial does not seem justified.

4.2.5 Survival

Overall survival (OS) for both docetaxel and erlotinib was assumed to be equivalent based on the mean overall survival (time to last observation) for erlotinib from the BR21 trial (9.03 months). At first sight this assumption appears reasonable as figures for mean OS are presented for erlotinib and docetaxel at two years (9.03 and 8.89, respectively), suggesting a small advantage for erlotinib. However, close re-examination of the Kaplan-Meier plot for docetaxel 75mg (TAX317) by the ERG leads to an estimated mean survival of 9.47 months, which closely matches the estimate of 9.48 months calculated by the investigators and reported by Leighl. [27] At the same time point (19.3 months) the equivalent restricted mean survival (by AUC) for erlotinib is 8.59 months. If instead exponential survival curves are fitted to the Kaplan-Meier plots and projected to death, the estimated mean survival times are 11.2 months for docetaxel and 9.9 months for erlotinib. It is therefore far from clear that the assumption of survival equivalence is in fact conservative. This suspicion is reinforced by the reported median overall survival results: 7.5 months for docetaxel 75mg versus 6.7 months for erlotinib.

In the model, docetaxel PFS was based on the estimate of mean treatment duration during the TAX317 trial (3.33 months), as data on docetaxel *mean* PFS was not available directly. This was compared to the mean PFS for erlotinib, estimated as 4.11 months (based on the proxy measure of mean treatment duration from the BR21 trial).

However, data on docetaxel median time to progression (TTP, which is virtually equivalent to PFS) was available from TAX317, but was not mentioned in the submission. Unsurprisingly the median PFS (using TTP as a proxy) for docetaxel is greater than the median PFS for erlotinib (2.5 months versus 2.2 months). Furthermore, the JMEI trial estimates the median PFS of docetaxel as 2.9 months, which is greater than the 2.2 months reported for erlotinib.

Once again, whilst it is appropriate to use means in economic analyses, the median should have been discussed especially since a poor proxy measure for PFS was used in its place. Furthermore, upon examination of the median PFS, it could be argued that docetaxel and erlotinib are at best equivalent, and that, based on the clinical data, docetaxel may be superior. In summary, the company's supposition that erlotinib is

superior to docetaxel in terms of PFS seems overly generous. It is based on a proxy measure which is inherently flawed, and reverses the conclusion that might reasonably be drawn from the available clinical data.

4.2.6 Health benefits and utilities

Health benefits within the model were assessed using the quality adjusted life year (QALY). Utility values were taken from a quality of life study (Oxford Outcomes Study) in which an EQ-5D VAS dataset had been obtained for 154 patients (see Table 4-1 for a list of utilities used in the model). It is worth noting that the assumption that fatigue, anorexia and infection have equal utility to PFS is not based on the Oxford Outcomes Study, nor is the source for this assumption provided. Furthermore there appears to be some disparity between the derivation of utility values for these adverse events and the corresponding resource utilisation. For example infection is not associated with any loss of utility, however in terms of resource usage 100% of patients experiencing this side effect are hospitalised. One would argue that side-effects serious enough in nature to warrant hospitalisation would surely impact upon a patient's utility. Similarly, patients who experienced fatigue did not suffer any loss of utility; however 20% of patients are assumed to require transportation. Once again the two do not appear to be consistent.

4.2.7 Resources and costs

A number of costs were included in the model, split into cost of PFS, cost of progression, and cost of the most common side-effects (see Table 4-1) for a brief summary of costs, for more detail see submission Tables 25 to 36.

4.2.8 Discounting

Health benefits and costs were discounted at 3.5% in line with current NICE guidance.[28]

4.2.9 Results

The model provided by the company as part of their submission was found to contain an error and did not appear to incorporate a half-cycle correction as described in the modelling methodology. The company therefore submitted an amended model. The results of this altered model are shown in Table 4-2. In terms of cost per QALY

erlotinib appears to dominate docetaxel, in that it is both more effective and less costly.

Table 4-2 Cost-effectiveness results from company amended model

	Erlotinib	Docetaxel	Incremental
COST RESULTS			
Total Drug costs	£6,796	£4,931	£1,865
Total cost of PFS	£1,501	£1,247	£254
Total cost of PPS	£4,739	£5,490	-£751
Total drug administration costs	£0	£971	-£971
Total adverse event costs	£140	£672	-£533
Total Direct Cost	**£13,175**	**£13,312**	**-£136**
EFFECTIVENESS RESULTS			
LYG Progression-free survival	0.34	0.28	0.07
LYG Progression	0.40	0.47	-0.07
QALY Progression-free survival	0.181	0.121	0.044
QALY Progression	0.087	0.100	-0.014
Total LYG	0.75	0.75	0.0
Total QALYs	**0.268**	**0.222**	**0.046**
ICER			
Cost per additional QALY			**-£2,941**

4.2.10 Sensitivity analysis

Univariate sensitivity analysis (SA) and probabilistic sensitivity analysis (PSA) were conducted by the company using the new amended model, see Table 4-3 and Figure 4-2 and Figure 4-3.

As can be seen from the univariate SA (Table 4-3), the model is most sensitive to variations in survival (overall and PFS), the cost of docetaxel administration, and the cost of progressed health state. However, none of the assumptions increased the incremental cost effectiveness ratio (ICER) above £30,000.

In terms of the PSA the cost effectiveness acceptability curve (CEAC) shown in Figure 4-2 demonstrates that erlotinib is cost-effective in 68% of scenarios at a WTP threshold of £30,000. The scatter plot of PSA results shown in Figure 4-3 illustrates that the ICER is tending towards the origin, with little variation.

Figure 4-2 Cost-effectiveness acceptability curve from company amended model

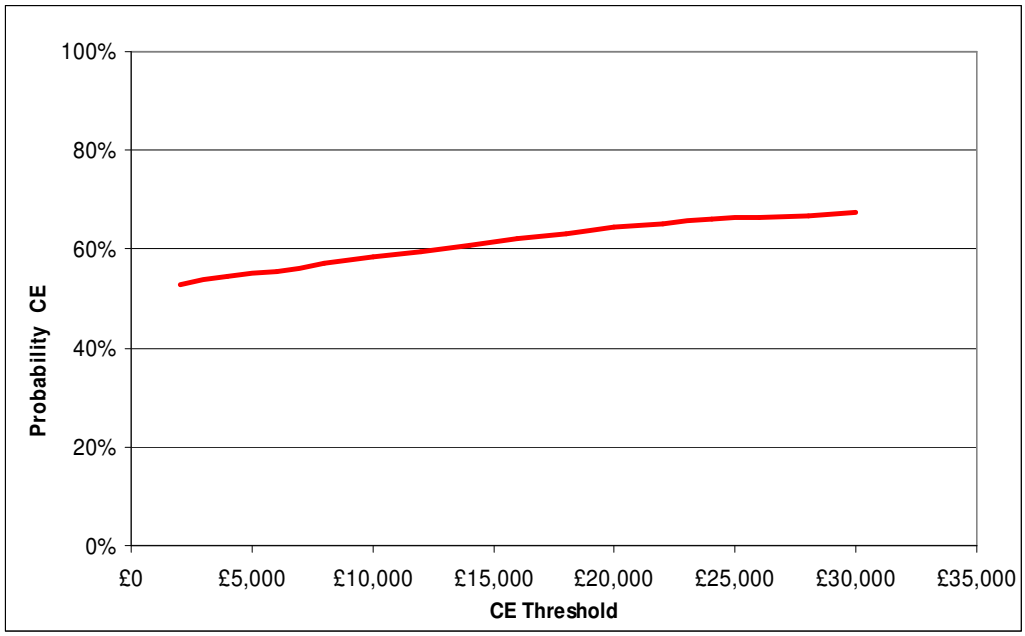


Figure 4-3 Cost-effectiveness plane from company amended model

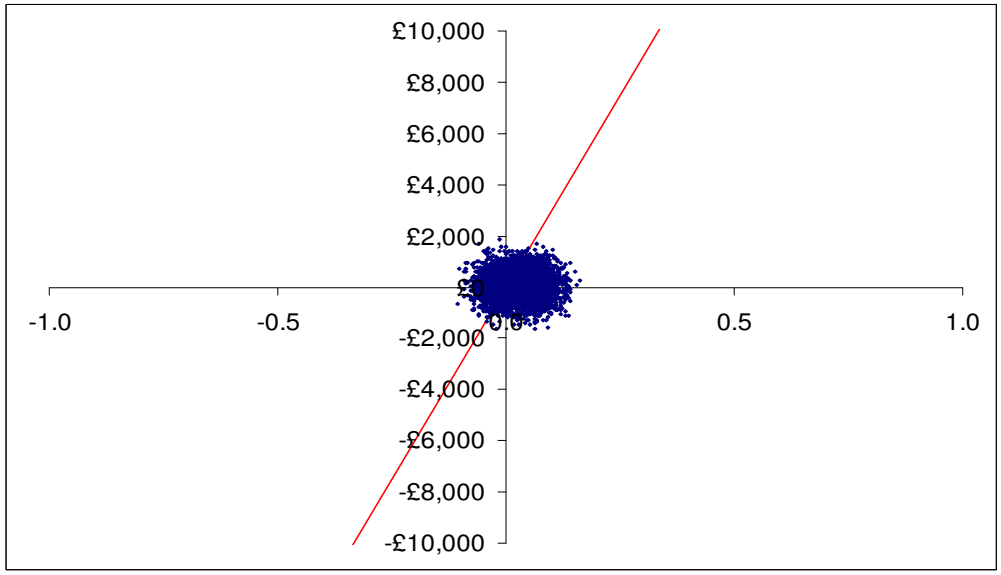


Table 4-3 Sensitivity analyses for cost-effectiveness results from company amended model

Variables	Assumptions	Result (Cost per QALY)
Base case		**Erlotinib Dominant (-£2,941)**
Equivalent overall survival and PFS (based mean BR21 results)	9.03 months (OS) 4.41 months (PFS)	£8,328
Equivalent utility score for progression-free survival	0.450	Erlotinib dominant
Equivalent treatment duration	125 days	Erlotinib dominant
No adverse event utilities included	n/a	Erlotinib dominant
Cost of febrile neutropenia:		
Expert panel estimate	£1,664	Erlotinib dominant
Bhalla et al (2004) publication	£3,852	Erlotinib dominant
Cost of docetaxel drug administration		
Low	-50% (£101)	£7,465
High	+50%(£303)	Erlotinib dominant
Cost of PFS health state		
Low	-50% (£163.42)	Erlotinib dominant
High	+50% (£490.26)	Erlotinib dominant
Cost of progressed health state		
Low	-50%(£494)	£5,176
High	+50% (£1483)	Erlotinib dominant
Utility score for progression-free survival		
Low	-20% (0.34)	Erlotinib dominant
High	+20% (0.50)	Erlotinib dominant
Utility score for progression		
Low	-20% (0.17)	Erlotinib dominant
High	+20% (0.26)	Erlotinib dominant
Febrile neutropenia rate (docetaxel)		
Low	0%	£176
High	13%	Erlotinib dominant

4.2.11 Model validation reported within the submission

The company provided a simple spreadsheet table which reproduces the model results quite closely and demonstrates face validity for the technical implementation of the main model assumptions. This provides reassurance that no serious formula errors have gone undetected, but does not address any issues relating to the assumptions made or the parameter values used in the submitted model.

4.2.12 Budget impact analysis

The company submission estimates the five year budget impact of introducing erlotinib for second-line therapy, assuming a staggered uptake of erlotinib. In year one, assuming 25% of patients receive erlotinib and 75% receive docetaxel, the budget impact is in the region £0.5 million, rising to £1.8 million in year five assuming 80% of patients receive erlotinib and just 20% receive docetaxel.

4.3 Corrections and adjustments to company model

In this section we consider several aspects of the submitted models where other assumptions and/or parameters values appear to be justified. In each case the source of our proposed alternative is described, and the magnitude of difference estimated. We then recalculate the cost-utility ratios taking account of all of the quantifiable changes, and present the revised results in tabular and graphical form.

4.3.1 Model versions

The original submitted model was replaced by an updated version dated 23/06/2006 which contained two amendments:

- a formula correction in the calculation of the mean time spent in the PFS state;
- application of a 'half-cycle correction' for the calculation of costs and outcomes.

The results of this amended model are reported above in Table 4-2.

Unfortunately, a 'half-cycle correction' had already been incorporated in the model via the attribution of proportions of mean progression-free survival to specific cycles. Thus the amended logic introduced had the effect of 'double-counting' the intended effect, leading to slightly erroneous results. The ERG has remedied this error by using a version with only the first of these two changes implemented. The revised results are shown below in Table 4-4 and form the basis for all subsequent alterations.

Table 4-4 Cost-effectiveness results from Roche model, corrected as described above

	Erlotinib	Docetaxel	Incremental
COST RESULTS			
Total Drug costs	£6,796	£4,931	£1,865
Total cost of PFS	£1,340	£1,085	£254
Total cost of PPS	£4,800	£5,561	-£761
Total drug administration costs	£0	£971	-£971
Total adverse event costs	£129	£570	-£441
Total Direct Cost	**£13,064**	**£13,118**	**-£54**
EFFECTIVENESS RESULTS			
Progression-free survival	0.34	0.28	0.07
Progressed Survival	0.40	0.47	-0.07
QALY Progression-free survival	0.150	0.106	0.044
QALY Progressed	0.088	0.102	-0.014
Total Life Years	0.75	0.75	0.0
Total QALYs	**0.238**	**0.207**	**0.030**
ICER			
Cost per additional QALY			**-£1,764**

4.3.2 Resources and costs

Drug acquisition: erlotinib

The company model assumes patients receive an average of 125 days treatment, priced at £54.37 per tablet. This calculation assumes that there is no drug wastage. However, the drug is prescribed in 30-tablet blister packs, so that any unused tablets at the end of treatment will be discarded. Based on the rate of discontinuation in each 4 week period from randomisation implied by the Kaplan-Meier statistics for PFS on which the model is based, we estimate that each patient will be prescribed an average of 4.39 packs of erlotinib tablets costing £7,164. This compares with the estimate of £6,796 in the company's submission, which therefore underestimates the acquisition cost by £368 per patient due to unaccounted wastage of 5.1%.

Drug acquisition: docetaxel

In the case of docetaxel, the authors of the company's model employ a misleading simplification when estimating the amount of docetaxel required. They have assumed the same average usage of the drug for every patient, irrespective of physical characteristics. In fact, dosing is calculated individually according to a patient's body-surface area (at 75mg/m^2). To exemplify the impact of realistic dose calculation we have assumed a normal distribution of body surface area (BSA) among patients with a mean of 1.83m^2 and standard deviation of 0.21. This is consistent with results of a large Australian survey of chemotherapy patients reported in 2004.[32] From this we estimate that on average patients will use 1.44 large vials (80mg) and 1.63 small vials (20mg) per cycle of treatment; this contrasts with the Roche assumption of 1 large and 3 small vials per cycle. This more realistic assessment results in the docetaxel acquisition cost (including the small cost of pre and post-administration steroids) increasing from £4,931 per patient (£1,023 per cycle) used in the company model to £5,022 per patient (£1042 per cycle), a difference of £91 per patient. Note that there is no assumption here of any vial sharing between patients treated at the same time; were this to be factored in as well, the estimated docetaxel cost would be reduced.

Drug administration and monitoring costs

The submission assumes that docetaxel treatment is given in an outpatient setting (costing £125 per 3 weekly cycle). The model adds costs for a further outpatient visit

every two months for 'additional check-ups' with associated full blood count (FBC), biochemistry tests and X-ray. These are in addition to the regular outpatient visits given to all patients remaining free of disease progression (i.e. while on therapy), and do not relate to drug-related adverse events which are accounted for separately (see below). On this basis a patient receiving docetaxel would be attending the outpatient department every 11 days on average, compared to about every 6 weeks when on erlotinib. The size of this discrepancy appears excessive. There is plenty of scope within such a busy schedule to allow 'doubling-up' of functions between regular visits, and visits for drug administration. Our clinical advice is that the extra 'check-up' visits are unnecessary and not normal practice. In addition, there is good reason to expect the cost of minor diagnostic tests to be accounted within the unit cost of an outpatient visit, and so should not be shown separately. The main difference in costs attributable to administration of chemotherapy is the more frequent visits required by the 21 day treatment cycle for docetaxel. We have therefore adjusted costs to reflect routine 4-weekly visits for erlotinib patients, and 3-weekly visits for docetaxel patients (costed at £125 covering both drug administration and monitoring). However, we consider that a proportion of docetaxel patients may require help with transportation to and from chemotherapy sessions, and have included costs for (say) 50% of journeys using the average cost of NHS patient transport service (£49 per journey - PSSRU 2005).

Overall the estimated cost of administration and patient monitoring during treatment/PFS is then estimated to be £473 per patient receiving erlotinib and £839 per patient on docetaxel. This compares to equivalent totals in the company model of £639 per patient on erlotinib and £517 per patient on docetaxel.

Adverse event costs

Adverse event costs in the company model are only estimated for Grade3/4 events. In each case a profile of typical resource use additional to normal care was assessed by five clinical experts. In no instance was trial or routine data employed for this purpose. All such costs are assigned in the model to the first month, with the exception of nausea which is considered continuous on therapy. Analysis of the main contributors to month one adverse event costs is as shown in Table 4-5. Thus the claimed savings from reduced adverse events with erlotinib are almost exclusively determined by the extra effects of neutropenia associated with docetaxel.

Table 4-5 Main contributors to month one adverse event costs

Component	Docetaxel	Erlotinib	Difference	
Neutropenia Grade 3	£35.87	£0.00	£35.87	6.7%
Neutropenia Grade 4	£311.77	£0.00	£311.77	58.2%
Febrile neutropenia	£144.25	£0.00	£144.25	26.9%
Infection	£140.40	£56.12	£84.29	15.7%
Others	£15.90	£56.58	-£40.68	-7.6%
Total	£648.19	£112.70	£535.50	100.0%

Of particular concern is the assumption that 20% of patients suffering Grade 4 non-febrile neutropenia without infection will be hospitalised. Comparison with information from another cancer study (confidential IPD seen by ERG) suggests that only about 7% of episodes result in hospital admission and then of very short duration. One clinical advisor reports such patients would not be hospitalised without evidence of fever. We use a lower hospitalisation rate of 10%, and adopt the reduced short-stay APC NHS tariff charge (£888.80 for HRG S07). This reduces the overall average cost of adverse events in the docetaxel arm from £648 to £374 per patient.

Regular outpatient visit costs

In the company model, the NHS reference cost for Palliative Medicine (£115) is used for routine outpatient visits throughout patients' treatment. In fact patients may be treated in a variety of specialty clinics depending on local circumstances and patient needs, including General Medicine, Medical and Clinical Oncology, Respiratory Medicine and Pain Management all of which are more generally available in the NHS than Palliative Medicine. We have therefore calculated a weighted average cost, based on national treatment volumes in England and Wales, of £106.59 in place of the Roche figure of £115. The net effect of this change is relatively minor.

4.3.3 Outcomes

Oxford Outcomes Study

The detailed results provided in the Oxford Outcomes Study, used as the primary source for model utility variables, raise a number of issues which warrant careful consideration.

The EuroQol EQ-5D instrument includes two mechanisms from which a score may be derived. Respondent assessments on the five dimensions of health-related quality of

life (each taking one of three levels) can be used to calculate a time-trade-off utility measure, where the parameters in the formula should reflect the preferences of a cross-section of the general population. This score (known as the 'tariff' score) is the primary EQ-5D utility measure. Alongside this is a simple visual analogue 'thermometer' scale (from 0 'worst possible' to 100 'best possible') on which respondents indicate their overall assessment of general health.

Although the respondent panel for the Oxford Outcomes Study completed both parts of the questionnaire, the model authors chose to use only the VAS scores as a (pseudo) measure of utility, though no explanation is given for this decision. In theory the VAS should not be used in this way since it violates a principal assumption of utility measures, in that it does not naturally identify zero as the value of death, nor allow for the possibility of states valued as 'worse than death'. This failing is well illustrated in this case by the mean VAS score attributed by the panel to death: (Academic in Confidence). If we wish to use the VAS scores as pseudo-utilities it would be necessary to map them onto a scale with a zero value at death. Using a simple linear transformation we can obtain revised scores, which may then be compared more meaningfully with those calculated for the EuroQol 'tariff' (Table 4-6). In general the rank order of rated states should be broadly similar between the two scales, and this is often used as a test of internal consistency.

Table 4-6 Comparison of rescaled VAS scores and EuroQol 'tariff' utility estimates from the Oxford Outcomes Study

Health state	Mean VAS scores		Mean tariff scores	Difference VAS-Tariff
	Original	Rescaled		
Stable disease on no therapy	Academic in Confidence	Academic in Confidence	Academic in Confidence	-0.0084
Stable disease on oral therapy	Academic in Confidence	Academic in Confidence	Academic in Confidence	-0.0226
Stable disease on IV therapy	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.0035
Initial response to therapy	Academic in Confidence	Academic in Confidence	Academic in Confidence	-0.0486
Recently progressed disease	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.3703
Near death	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.5152
Stable disease plus neutropenia	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.1341
Stable disease plus febrile neutropenia	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.5178

Stable disease plus diarrhoea	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.1671
Stable disease plus nausea	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.1320
Stable disease plus stomatitis	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.2351
Stable disease plus neuropathy	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.1470
Stable disease plus rash	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.0207
Dead	Academic in Confidence	Academic in Confidence	Academic in Confidence	0.0000

For those health states with the least detrimental features (i.e. stable disease with no severe complications), the two sets of values are quite well matched. However, very large discrepancies appear for all but one of the adverse events, and also for patients with progressive disease or near to death.

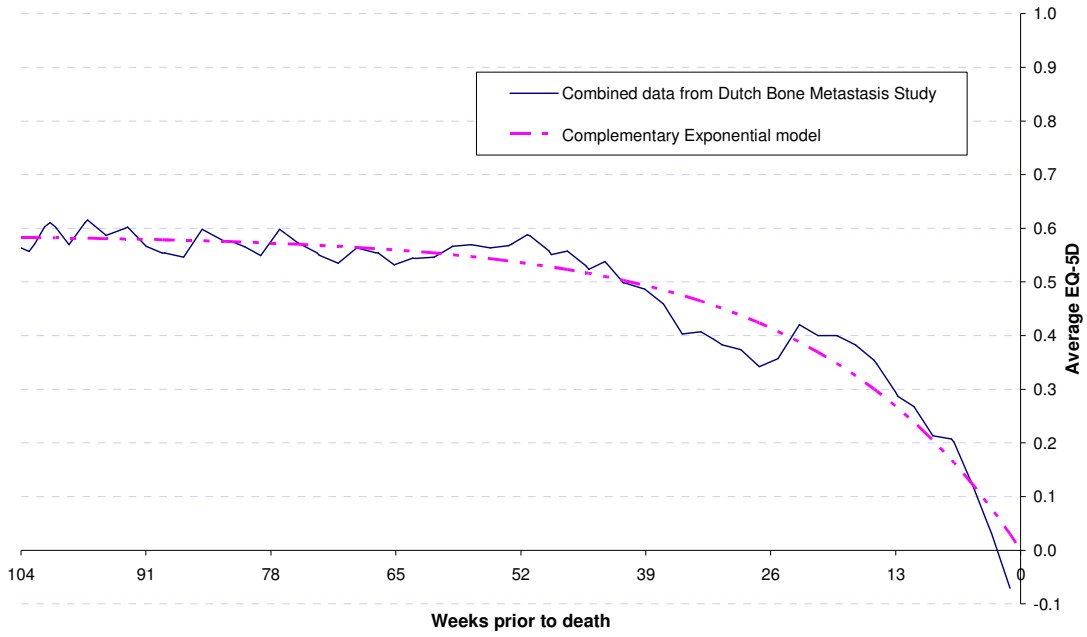
These evident problems prompt discussion of the appropriateness of employing self-selected members of the general public to make judgements about extreme states of dysfunction and discomfort which most will never have experienced, or observed in those close to them. Equally it may be that the scenarios presented for comparison by the respondents were framed in a manner which tended to solicit more extreme responses to the five dimensional questions than to an overall 'gut-feeling' assessment. However the discordance may have arisen, it calls into question the validity of both sets of scores as a basis for judging meaningful changes in health-related utility.

Verifying utility values

There are few published studies providing information to validate the assumed utility values assigned to patient states in the company model. The most significant element in the estimation of outcome gain is the estimated utility for the post-progression state which continues until death. One useful paper has been traced which relates to the Dutch Bone Metastasis Study[33] in which patients suffering from a range of late stage solid tumours (25% lung cancer) with bone metastases were offered one of two regimens of palliative radiotherapy. The authors provide a profile of average EQ-5D utility scores obtained from patients by the time of observation relative to the end of life. This shows an accelerating decline in utility over the course of the last year of life (Figure 4-4). We found that a complementary exponential time series model,

assuming a value of zero at death, fitted these data closely and the result is shown superimposed on the trial data.

Figure 4-4 Dutch Bone Metastasis Study EQ-5D utility results with the ERG time series model



The functional form of the utility model calls into question a basic assumption of the company model: that both costs and outcomes of patients assigned to a health state in the model are constant (i.e. independent of time). In fact it appears that the average utility value for a patient for a period preceding their death will vary depending on how long they remain in that state. This focuses attention on a basic problem with the company model in that it presumes that disease progression is a meaningful defining point for both resource use and patient experience. In reality, disease progression is frequently a deduction made from clinical test results, which may precede significant clinical changes by some considerable time.

To test the credibility of the utility values in the company model we have calculated the average utility scores we would expect before and after progression in each arm of the economic evaluation (Table 4-7). This requires the use of a realistic utility value for a similar population in stable condition: for this we have used the mean EQ-5D score for 193 UK patients from the ACTION study[34] - 0.64. Although the values obtained are broadly comparable, they are more favourable to erlotinib prior to disease progression and favour docetaxel after progression.

Table 4-7 Comparison of company and the ERG estimated average utility scores

	Erlotinib		Docetaxel	
State	**The ERG model**	**Submission**	**The ERG model**	**Submission**
PFS	0.466	Academic in Confidence	0.412	Academic in Confidence
PPS	0.236	Academic in Confidence	0.261	Academic in Confidence

These estimates involve no amendment to the assumed disutility from intravenous administration of chemotherapy, nor to the magnitude of disutilities associated with specific adverse events. On this basis the revised estimate for the probable gain in quality-adjusted life years in shown in Table 4-8. This has the effect of reducing the likely benefit by 40% from the estimate used in the base case submission.

Table 4-8 Revised estimate of QALY gains, assuming the ERG model for PPS utility values

	Erlotinib	Docetaxel	Increment
PFS QALYs (submission)	0.1501	0.1057	
PPS QALYs (submission)	0.0878	0.1017	
Total (submission)	**0.2379**	**0.2074**	**0.0304**
PFS QALYs (The ERG)	0.1591	0.1139	
PPS QALYs (The ERG)	0.0953	0.1224	
Total QALYs (PPS adjusted)	**0.2544**	**0.2362**	**0.0182**

4.3.4 Cost-utility results

Applying all the alterations and adjustments described above to the company model produces the results shown in Table 4-9, with much higher incremental cost per patient from substitution of docetaxel by erlotinib, and substantially reduced benefits. As a consequence the previously advantageous cost-effectiveness ratio has been dramatically changed to one which far exceeds normally acceptable values. This extreme sensitivity is due to the very small value of incremental benefit, which renders the ICER highly unstable to small changes. What is clear from this analysis is that there are significant additional costs associated with substitution of docetaxel by erlotinib, but the net benefits measured in terms of the conventional utility values are very small. Thus adoption of erlotinib would need to be justified on grounds outwith the factors included in the model (for example, patient preference for oral self-

medication and service pressures to limit or reduce demand for hospital administered chemotherapy).

Table 4-9 Cost-effectiveness summary table updated for identified corrections and amendments to the company model

	Erlotinib	Docetaxel	Increment
Costs per Patient			
Drug acquisition	£7,164	£5,022	£2,142
Drug admin and monitoring	£473	£839	-£365
Adverse event treatment	£113	£374	-£261
Other pre-progression care	£1,034	£859	£175
Post-progression care	£4,699	£5,444	-£745
Total cost	**£13,482**	**£12,536**	**£946**
Outcomes per Patient			
Overall mean survival (months)	9.03	9.03	0.00
PFS (months)	4.11	3.33	0.78
PPS (months)	4.92	5.70	-0.78
PFS QALYs	0.1591	0.1139	0.0452
PPS QALYs	0.0953	0.1224	-0.0271
Total QALYs	**0.2544**	**0.2362**	**0.0182**
Incremental cost per QALY			**£52,098**

It is not possible to carry out a fully revised probabilistic sensitivity analysis (PSA) as it would be necessary to redesign several aspects of the model. In additional there are several aspects of the PSA implementation which are questionable (in particular the use of arbitrary distributions and parameter values for variable uncertainty, the assumption of independence between all parameter estimates, and the lack of important causal links in the model logic). Instead we have made very simple average adjustments to both the net incremental cost per patient and the net incremental QALY gain in the original PSA replications to reassess the impact of likely changes to the cost-acceptability curve (Figure 4-5) and the distribution of uncertainty on the cost-effectiveness plane (Figure 4-6).

Figure 4-5 Modified cost-acceptability curve using company PSA results adjusted for average incremental cost and outcome alterations

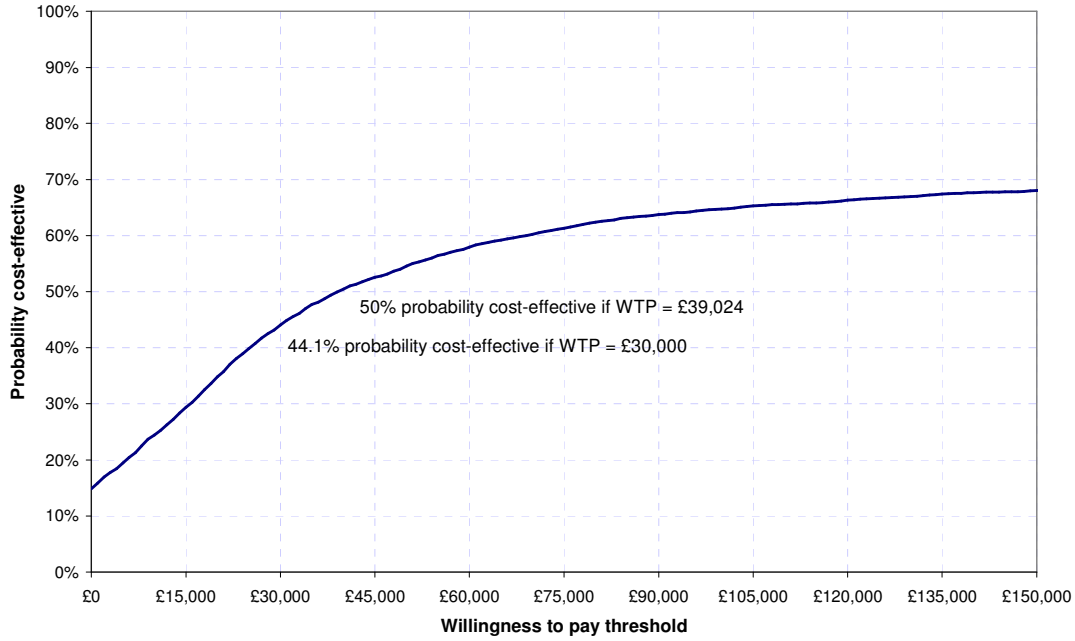
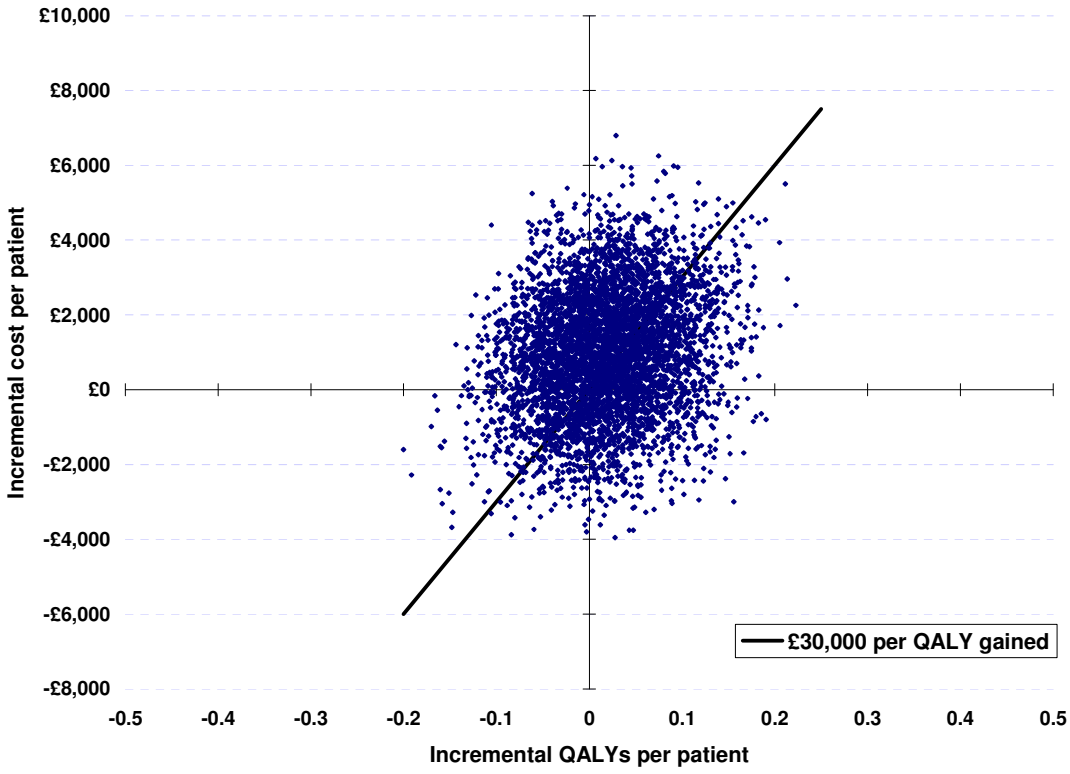


Figure 4-6 Modified cost-effectiveness uncertainty scatter plot using company PSA results adjusted for average incremental cost and outcome alterations



Sensitivity analysis for pre-progression utilities

We may further test the stability of these results by considering different approaches to estimating adverse event outcome effects in the pre-progression period (which we have not previously altered in our adjustments to the company model). By substituting two different sets of parameter values in the company model, alternate estimates of benefit can be obtained. These are summarised in Table 4-10 for use of the rescaled VAS scores, and the Tariff scores reported in the Oxford Outcomes Study report. As expected, the narrower range of utility scores in the rescaled VAS serves to reduce the apparent benefit due to erlotinib, and conversely the wider range in the tariff scores increases it. Nonetheless, the estimated incremental cost per QALY ratios remain well above acceptable levels.

Table 4-10 Sensitivity analyses - alternative methods to estimate utility in pre-progression period

	Erlotinib	Docetaxel	Increment
Using rescaled VAS values in PFS			
PFS QALYs (rescaled VAS)	0.1292	0.0883	0.0409
PPS QALYs (The ERG estimate)	0.0953	0.1224	-0.0271
Total QALYs	0.2245	0.2107	0.0138
Incremental cost per QALY			**£68,673**
Using Tariff values in PFS			
PFS QALYs (Tariff)	0.1337	0.0763	0.0573
PPS QALYs (The ERG estimate)	0.0953	0.1224	-0.0271
Total QALYs	0.2289	0.1987	0.0303
Incremental cost per QALY			**£31,261**

Sensitivity analysis for docetaxel dosing assumptions

The estimation of docetaxel dosing costs described in section 4.3.3, may be questioned on two grounds:

- that the assumed mean body surface area (BSA) is too high, and that patients may have suffered significant weight loss since their first course of chemotherapy;

- that our calculations imply an overly precise application of the standard formula, which may not be necessary in clinical practice.

Unfortunately, it is not normal practice in published trials to report BSA (or patient height and weight from which BSA may be estimated) so it is difficult to find additional sources to validate the Australian survey findings we have used (mean BSA = 1.833). One additional study has been identified which reported details of 283 patients undergoing chemotherapy for solid tumours in the Netherlands[35] (61% male, 30% NSCLC), and recorded a mean BSA of 1.86 (SD 0.19) thus providing some confirmation of the basis for our calculations.

Dooley [34] discusses the clinical impact of dose rounding and concludes "that dose rounding to within 5% of calculated dose would not have any significant clinical effect on either response or toxicity. This, of course, is a practical judgement and has not been tested in a controlled manner."

We consider the joint effect of these two factors on the cost of docetaxel, and on the cost-effectiveness of erlotinib in Table 4-11. It is apparent that these uncertainties in the calculation of drug costs are not sufficient to lead to acceptable cost-effectiveness ratios. It should also be noted that in this case, the adoption of a lower mean BSA (which is more likely to be the case due to weight loss) has the effect of *increasing* the cost-effectiveness ratio.

Table 4-11 Sensitivity analyses - costing docetaxel for lower mean BSA and dose rounding

	Cost per patient of Docetaxel	ICER (per QALY)
The ERG Base Case (BSA = 1.833, no rounding)	**£5,022**	**£52,098**
BSA = 1.75, no rounding	£4,861	£60,965
BSA = 1.75, dose rounding = -5%	£4,689	£70,418
BSA = 1.75, dose rounding = +5%	£5,037	£51,230
BSA = 1.833, dose rounding = -5%	£4,857	£61,144
BSA = 1.833, dose rounding = +5%	£5,206	£41,943

Sensitivity analysis for limited chemotherapy cycles

The corrected model assumes that docetaxel patients receive a mean of 4.82 cycles of treatment, and pemetrexed patients receive treatment for the equivalent of 6.27 21-day cycles. This is compatible with the assumed difference in PFS between the treatments, which governs the duration of chemotherapy in the model. Clinical advice is that chemotherapy for docetaxel is generally limited in UK to no more than 4 cycles

per patient, and presumably a similar limitation would be expected in the case of erlotinib. In the absence of detailed data on dosing patterns for both drugs it is not possible to employ precise estimates for these parameters, nor to adjust outcomes for the likely consequences on outcomes of such restrictions. However, the structure of the model does allow us to explore the cost consequences of cycle limitation, assuming no deterioration in outcome gains - a conservative position. Because the submitted model assumes that all the benefits arise from better PFS with erlotinib (and not from extended survival) the only option for reducing therapy duration whilst maintaining outcome gains is to reduce the mean PFS by the same amount in both treatments. We therefore assume that mean PFS is shorter in both arms by 1 month, and PPS is increased by the same amount. The net result of these changes is very modest, so that the incremental cost per patient of erlotinib reduces from £946 to £939 and the cost-utility ratio reduces from £52,098 to £51,703 per QALY gained.

4.3.5 Unquantifiable uncertainty

There are other issues where assumptions made in the company model give rise to concern, but for which it is not possible to quantify the extent of associated error or bias, without access to other data.

Adverse events

There is a curious note on the table of event probabilities for adverse events which seems to imply that the model does not allow patients to suffer multiple adverse events. If this is so, it is a severe and unrealistic constraint, since individual patients frequently suffer multiple events either concurrently (for example rash with diarrhoea) or serially.

Pre-progression and post-progression health state costs

The resources assumed to be incurred each month for patients before and after disease progression were exclusively determined by five clinical experts without use of any observational data. The main elements contributing to the increase in such costs post-progression are shown in Table 4-12.

Table 4-12 Main elements of monthly post-progression costs per patient

Component	Cost per month	Proportion
Hospital episodes	£547.97	55.4%
Health professionals	£331.54	33.5%
Medications	£39.46	4.0%
Tests	£69.83	7.1%
Total	£988.80	100.0%

Clearly hospital episodes constitute the dominant component in these estimates. It seems disappointing that no attempt has been made to sample routine hospital records and statistics to validate the expert opinion in this respect.

Progression-free survival

The issue raised in section 4.2.5 about the validity of the claims to equivalence in OS and to improved PFS with erlotinib is of profound importance to the economic evaluation of erlotinib. If either of these assertions proves to be untenable then most of the modest outcome gains claimed for erlotinib will disappear, other than the very small short-term quality of life benefits associated with oral administration and reduced adverse events. In the context of important increases in drug acquisition costs, this would mean that erlotinib could not be considered cost-effective, and might in fact be dominated by docetaxel (more expensive and less effective).

4.4 Summary of cost-effectiveness evidence

4.4.1 Economic evaluation results

Base case: company

- The company report an ICER of -£2,941 per QALY for erlotinib compared to docetaxel (i.e. erlotinib dominates docetaxel), with a 68% probability that erlotinib is cost-effective at a WTP of £30,000 per QALY gained.

- After adjustment for the double-counting of half-cycle correction, the company model yields a corrected ICER of -£1,764.

Base case: ERG

- A number of key assumptions and parameters in the model do not seem to be clinically and / or economically justified, particularly in terms of costs. Once these assumptions are adjusted to more realistic estimates, the ICER increases to £52,098 per QALY, with a 44% probability that erlotinib is cost-effective at a WTP threshold of £30,000 per QALY gained.

4.4.2 Economic issues

- Inappropriate use of VAS scores from Oxford Outcomes Study. Re-analysis of the model rescaling the VAS PFS utility scores to ensure death has zero utility, only further increased the ICER (£68,673 per QALY). Similarly, re-analysis using tariff PFS utility values led to an ICER slightly above the WTP threshold of £30,000 (£31,261 per QALY).

- Joint exploration of uncertainty in the cost of docetaxel and the degree of variation in dosing introduced by clinical judgement yields a range of ICER estimates between £41,943 and £70,418 per QALY gained.

- Limiting the number of treatment cycles per patient has very little effect on costs and cost effectiveness, due to the nature of the model used, and the absence of any survival gain.

- There is also a large amount of unquantifiable uncertainty in the model, relating to adverse events, PPS and PFS health state costs, and the length of PFS. These areas of ambiguity could potentially further increase the ICER and may even result in docetaxel dominating erlotinib.

5 DISCUSSION

The company submission presents a case for the replacement of docetaxel by erlotinib as second-line chemotherapy for NSCLC patients with advanced or metastatic disease. However, there is a proportion of NSCLC patients whose poor health status precludes them from receiving docetaxel; for these patients best supportive care is currently the only treatment option available. It may be argued that some of these patients could be considered for erlotinib instead of docetaxel as it is a less demanding oral regimen. Unfortunately, Roche Products Ltd. have chosen not to submit evidence in support of erlotinib as a second-line treatment for this sub-group of patients, and therefore the ERG are precluded from considering the cost-effectiveness of this option.

The company make a case for the effectiveness of erlotinib based on equivalent clinical efficacy compared (indirectly) to docetaxel, together with a superior side-effect profile, particularly in terms of haematological adverse events. This assumption is applied to the economic analysis with the additional caveat that erlotinib offers longer progression-free survival compared to docetaxel with an associated benefit in terms of increased utility and lower costs. The resulting incremental cost effectiveness ratio is in the region of -£3,000 for erlotinib compared to docetaxel with a 68% probability that erlotinib is cost-effective at a willingness to pay of more than £30,000. However, there are a number of clinical and economic issues which call into question the validity of these claims, and the credibility of the model results.

A major limitation in the submission is the reliance on the BR21 trial (currently the only available erlotinib study) which compares erlotinib with placebo, rather than an accepted chemotherapy regimen. As a consequence, the company submission is forced to compare erlotinib and docetaxel indirectly; such comparisons have inherent difficulties and are subject to biases (due to unmeasured or unreported factors). This weakness of indirect comparisons is further compounded by differences in the patient populations; (1) between the BR21 trial and clinical practice, and (2) between the BR21 trial and the key docetaxel trial utilised by the company in the economic analysis (TAX317).

In order to inform the economic analysis an indirect comparison of erlotinib and docetaxel was undertaken by the company employing data from TAX317, and, where

data were not available, from JMEI. TAX317 is not the largest trial involving docetaxel, nor the most recent; hence the heavy reliance on this small trial does not seem justified. Further to this, there are a number of differences between the patient population in the BR21 trial and the TAX317 study, of which the most important are the number of prior chemotherapy regimens and the performance status of patients.

In addition, the best supportive care component of treatment given to patients within the BR21 and TAX317 needs to be discussed. The BSC component of treatment may not be comparable between the trials, which could potentially inflate a treatment response in one of the trials unjustifiably. This confounding issue was not discussed in the submission, but should have been considered when undertaking an indirect comparison.

Consideration of these issues highlights the serious limitations within the indirect comparison analysis undertaken by the company. Data from such analyses must therefore be viewed with caution. The ERG agrees with the statement made by Shepherd[29], clinical investigator in BR21, TAX317 and JMEI, that "it is inappropriate to compare the results of BR21, TAX317 and JMEI trials since their patient populations differ considerably." In their submitted evaluation of cost-effectiveness, the company relies upon the results generated by a three-state health state transition model, which was populated with clinical data from the BR21 study and the TAX317 trial. However a number of issues challenge the validity of the model results.

Firstly, the estimation of resource use and costs is inconsistent and often biases the analysis in favour of erlotinib. For example, the company submission underestimates the acquisition cost of erlotinib and overestimates the acquisition cost of docetaxel.

Secondly, the assumption that mean overall survival is equivalent between erlotinib and docetaxel is not unequivocally demonstrated but relies on an indirect comparison between BR21 and the small underpowered TAX317 study. Furthermore, re-analysis of the Kaplan Meier survival curves suggests that docetaxel may offer a survival advantage compared with erlotinib, which is also supported by data on median overall survival. This view is endorsed by the Australian Department of Health who reported that an indirect comparison of erlotinib versus docetaxel "…favoured docetaxel such that a statistically significant survival advantage for docetaxel could not be excluded".[13]

Thirdly, the case for a progression-free survival benefit in patients treated with erlotinib compared with docetaxel is also based on an indirect comparison of BR21 and TAX317, and furthermore relies on the proxy measure of mean treatment duration. Using the proxy measure of median time to progression, estimates of progression-free survival appear to be greater for docetaxel patients than for erlotinib patients. Hence, it could be argued that in terms of progression-free survival docetaxel and erlotinib should be considered clinically equivalent at best. The company do not discuss this in their submission.

Fourthly, the use of the Oxford Outcomes Study in order to generate utility estimates for the various health states in the model is inherently flawed. The reliance on visual analogue scores which had not been scaled to reflect death as having zero utility, and which differed somewhat from the tariff scores obtained from the same population, raises doubts over the utility advantage generated by the model. Furthermore the assumptions that utility values assigned to patient health states are constant and independent of time does not seem realistic.

Finally, the inability within the model for patients to suffer more than one adverse event (other than nausea), either serially or at the same time does not seem realistic.

The ERG attempted to rectify several of these limitations, generating much higher incremental cost effectiveness ratios than those generated in the submission (in excess of £52,000). This extreme sensitivity is due to the very small value of incremental benefit, which renders the ICER highly unstable to small changes.

There is still a large amount of unquantifiable uncertainty, however at the current price it is unlikely that erlotinib could be considered to be cost-effective compared with docetaxel at a willingness to pay of £30,000. There may even be the potential for docetaxel to dominate erlotinib (i.e. be more effective yet less expensive). This means that adoption of erlotinib would need to be justified on grounds outwith the factors included in the model (for example, patient preference for oral self-medication and service pressures to limit or reduce demand for hospital administered chemotherapy).

5.1 Implications for future research

Given the limitations of the indirect analysis undertaken by the company and their subsequent economic modelling exercise there is a need for a head-to-head trial comparing erlotinib with docetaxel. The results of the Hoffman-La Roche sponsored TITAN study directly comparing erlotinib with docetaxel or pemetrexed as second-line treatment for NSCLC patients are eagerly awaited.

Future work is also necessary in order to undertake a comprehensive comparison between all relevant treatment strategies for the second-line treatment of stage IIIb/IV NSCLC patients. A full systematic review and meta-analysis of trials assessing all relevant chemotherapy options and best supportive care could inform such a comparison.

Finally, there is a paucity of data describing chemotherapy up-take in England and Wales. Coordinated data collection of current chemotherapy statistics, including the number of patients eligible for treatment, the number of patients receiving first-line and second-line chemotherapy and the types of chemotherapy delivered, is essential if the true budget impact of new treatments is to be estimated.

6 REFERENCES

1. Hanna N, Shepherd FA, Fossella FV, Pereira JR, Demarinis F, Von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. Journal of Clinical Oncology 2004;22(9):1589-1597.
2. Shepherd FA, Pereira JR, Ciuleanu T, Eng HT, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. New England Journal of Medicine 2005;353(2):123-132.
3. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy.[see comment]. Journal of Clinical Oncology 2000;18(10):2095-103.
4. Roche Products Ltd. Summary of Product Characteristics. Tarceva 25mg, 100mg and 150 mg film coated tablets; 2006 22.03.2006.
5. National Collaborating Centre for Acute Care. The diagnosis and treatment of lung cancer. Methods, evidence and guidance. 2005 [cited 02.2005]; Available from: www.rcseng.ac.uk
6. Cancer Research UK. Cancer facts and figures. 2006 [cited 06.2006]; Available from: http://www.cancerresearchuk.org/
7. Mason P. Lung cancer - the disease and non-drug treatment. Hosp. Pharm. 2005;12:129-135.
8. NICE. The diagnosis and treatment of lung cancer: Clinical guideline 24. 2005 [cited 02.2005]; Available from: http://www.nice.org.uk/page.aspx?o=cg024niceguideline
9. Food and Drug Administration. Oncology Tools. 2006 [cited 2006]; Available from: www.fda.gov/cder/cancer/perstatframe.htm
10. Scottish Medicines Consortium. Erlotinib 25, 100 and 150 mg film-coated tablets. No. (220/05). . In; 2005.
11. Scottish Medicines Consortium. Resubmission. Erlotinib 25, 100 and 150 mg film-coated tablets. No. (220/05). In; 2006.
12. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. 2006 [cited 06.2006]; version 2.2006:[Available from: www.nccn.org/professionals/physician_gls/PDF/nscl.pdf
13. Australian Department of Health. Public summary document for erlotinib. 2006 [cited 2006]; Available from: http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-erlotinib-mar06
14. NICE. Lung cancer. National cost impact report. In; 2005.
15. EMEA. Alimta® European Public Assessment Report (EPAR); 2006 09.02.2006.
16. London Cancer New Drugs Group. Erlotinib (Tarceva®) in non-small cell lung cancer; 2006 March 2006.
17. NICE. Lung cancer (non-small cell) - pemetrexed, single technology appraisal. 2006 [cited 26.06.2006]; Available from: www.nice.org.uk/page.aspxVo=305340
18. Scottish Medicines Consortium. Pemetrexed (Alimta). No. (268/06). Indication, non-small cell lung cancer after prior chemotherapy. Statement of Advice. In; 2006.

19. Roche Products Ltd. Tarceva® (erlotinib) NICE STA Submission. Achieving clinical excellence in the treatment of relapsed non-small cell cancer. Welwyn Garden City: Roche Products Limited; 2006.
20. EMEA. Tarceva®. European Public Assessment Report (EPAR) 2005 03.11.2005.
21. The University of Sheffield School of Health and Related Research. Critical Appraisal of Secondary Research, MSc Health Informatics, Unit Five. 2006 [cited; Available from: http://www.shef.ac.uk/scharr/ir/mschi/unit5/3appraising.htm#casr
22. Gervais R, Ducolone A, Breton JL, Braun D, Lebeau B, Vaylet F, et al. Phase II randomised trial comparing docetaxel given every 3 weeks with weekly schedule as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC). Annals of Oncology 2005;16(1):90-6.
23. Peake MD, Thompson S, Lowe D, Pearson MG. Ageism in the management of lung cancer. Age Ageing 2003;32(2):171-7.
24. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. Journal of Clinical Oncology 2000;18(12):2354-2362.
25. Clegg A, Scott D, Sidhu M, Hewitson P, Waugh N. A rapid and systematic review of the clinical and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small cell lung cancer: a systematic review. Health Technol. Assess. 2001;5(32).
26. Holmes J, Dunlop D, Hemmett L, Sharplin P, Bose U. A cost-effectiveness analysis of docetaxel in the second-line treatment of non-small cell lung cancer. Pharmacoeconomics 2004;22(9):581-589.
27. Leighl NB, Shepherd FA, Kwong R, Burkes RL, Feld R, Goodwin PJ. Economic analysis of the TAX 317 trial: Docetaxel versus best supportive care as second-line therapy of advanced non-small cell lung cancer. Journal of Clinical Oncology 2002;20(5):1344-1352.
28. NICE. Guide to the methods of technology appraisal. London: National Institute for Health and Clinical Excellence; 2004 April 2004.
29. Shepherd F, Seymour L. Erlotinib in Lung Cancer - correspondence. New England Journal of Medicine 2005;353(16):1740-1741.
30. Camps C, Massuti B, Jimenez A, Maestu I, Garcia Gomez R, Isla D, et al. Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: A Spanish Lung Cancer Group trial. Annals of Oncology 2006;17(3):467-472.
31. Cufer T, Vrdoljak E, Gaafar R, Erensoy I, Pemberton K. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer. Anticancer Drugs 2006;17(4):401-9.
32. Gridelli C, Gallo C, Di Maio M, Barletta E, Illiano A, Maione P, et al. A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study. British Journal of Cancer 2004;91(12):1996-2004.
33. Pectasides D, Pectasides M, Farmakis D, Kostopoulou V, Nikolaou M, Gaglia A, et al. Comparison of docetaxel and docetaxel-irinotecan combination as second-line chemotherapy in advanced non-small-cell lung cancer: A randomized phase II trial. Annals of Oncology 2005;16(2):294-299.

34. Quiox E, Lebeau B, Depierre A, Ducolone A, Moro-Sibilot D, Milleron B, et al. Randomised, multicentre phase II study assessing two doses of docetaxel (75 or 100 mg/m²) as second-line monotherapy for non-small-cell lung cancer. Annals of Oncology 2004;15(1):38-44.
35. Schuette W, Nagel S, Blankenburg T, Lautenschlaeger C, Hans K, Schmidt E-W, et al. Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. Journal of Clinical Oncology 2005;23(33):8389-95.
36. Wachters FM, Groen HJM, Biesma B, Schramel F, Postmus PE, Stigt JA, et al. A randomised phase II trial of docetaxel vs docetaxel and irinotecan in patients with stage IIIb-IV non-small-cell lung cancer who failed first-line treatment. British Journal of Cancer 2005;92(1):15-20.

7 APPENDICES

Appendix 1: Erlotinib versus docetaxel clinical outcomes

Summary tables for the 11 indirect comparison trials showing key trial outcomes and adverse events, including weighted averages are shown in Table 7-1 and Table 7-2.

Table 7-1 Efficacy outcomes in studies utilising docetaxel 75 mg/m^2 or erlotinib 150 mg/day as treatment for relapsed NSCLC

Trial	Response rate % (95% CI)	Stable disease rate % (95% CI)	Median overall survival months (95% CI)*	1-year survival % (95% CI)	Median PFS weeks (95% CI)**	Median TTP weeks (95% CI)**
Docetaxel						
SLCG[30]	OR=[a]9.3 (4.3, 14.3)	34.1	6.6 (5.5, 7.7)	27 (18.9, 35.1)	NS	10.8
SIGN[31]	13.7	NS	7.1	NS	13.6	NS
TAX317[3]	PR= [a] 5.5	47.3	7.5	37	NS	NS
TAX320[24]	PR=6.7 (3.1, 13.1)	36.0	5.7	32 (23,40)		8.5 (6.7-11)
DISTAL 01[32]	PR=2.7	NS	7.25 (5.25-9.36)	21	NS	NS
JMEI[1]	8.8	46.4	7.9	29.7	11.6	14
Pectasides[33]	PR= [a] 14 (5.5, 22)	35 (23, 46)	6.4 (0.1-21.2) [a]	34.0	NS	19.2
Quoix [34]	OR = [a] 8.6 3.7 [a]	37.1 40 [a]	4.7 (3.8-5.9)	NS	NS	6 (5.2-8.0)
Study 387	5	36	7.68 (6.9, 8.5)	28.7 (24.3, 33.0)	NS	13.1 (12.3, 15.6)
Schuette[35]	OR=12.6	37.9	6.3 (4.68, 7.84)	26.9	NS	13.6
Wachters[36]	16 (6-26)%	45	8.00 (6.25-10.00)	26 (+/- 6% SE)	18 (16-21)	NS
Erlotinib						
BR21[2]	8.9 (6.4-12.0)	35.1	6.67 (5.52, 7.79)	31.2	9.71 [b] (8.43-12.43)	9.71 [c] (12.3, 15.6)

CI: confidence interval; NS: not stated; NA: not applicable; PFS: progression-free survival
* Converted to months where appropriate using 1 month = 4 weeks
** Converted to weeks, where appropriate, using 1 month = 4 weeks
[a] As reported in the original paper
[b] Reported as 2.2 months i.e. 8.8 weeks in both the paper and the submission text
[c] Not reported in the paper and reported as 9.71 in the submission text

Table 7-2 Reported toxicity of docetaxel 75 mg/m^2 and erlotinib

Severe (Grade 3) and life-threatening (Grade 4) haematological toxicity - % of patients				
Study	Neutropenia	Anaemia	Thrombocytopenia	Febrile neutropenia
Docetaxel				
SLCG[30]	9.3	2.3	0	7.8
SIGN[31]	46	1.5	0	3.2
TAX317[3]	67	5.5	0	1.8
TAX320[24]	54 (Grade IV only)	0 (Grade IV only)	2	8
DISTAL 01[32]	19	3	1	5
JMEI[1]	40.2	4.3	0.4	12.7
Pectasides[33]	43	12	6	5
Quoix [34]	44	12	3.3	6.7
Study 387	60	10	7	5
Schuette[35]	20.6	5.9	0	2
Wachters[36]	43 (Granulocytes)	0	0	5
Weighted Average	**42.9**	**5.9**	**2.7**	**6.6**
Erlotinib				
BR21[2]	0	3	1	0

Non-haematological toxicities with any grade (Grade 3 or 4) - % of patients							
Study	Mucositis	Fluid retention	Neuropathy	Alopecia	Rash/derm-atological	Diarrhoea	Conjunctivitis
Docetaxel							
SLCG[30]	22.5 (1.6)	NS	33.3 (0.8)	62	9.3 (0)	17.8 (0.8)	NS
SIGN[31]	15.5 (1.4)	NS	14.1 (2.8)	11.3	9.9 (2.8)	40.8 (4.2)	NS
TAX317[3]	25.5 (1.8)	12.7 (0)	34.5 (3.6)	NS	NS	36.4 (1.8)	NS
TAX320[24]	NS (2)	NS (1)	NS (1)	NS	NS	NS (2)	NS
DISTAL 01[32]	17 (1)	NS	24 (1)	37	9 (1)	21 (3)	NS
JMEI[1]	17.4 (1.1)	8.3 (0)	15.9 (1.1)	37.7	0.7	24.3 (2.5)	NS
Pectasides[33]	NS (4)	NS (3)	NS (2)	85	NS (2)	NS (3)	NS
Quoix [34]	NS	NS (0)	NS (1.1)	NS (2.2)**	NS	NS (1.1)	NS
Study 387	NS	NS	26 (3)	35	NS	18 (3)	NS
Schuette[35]	NS	NS	NS	NS	NS	NS	NS
Wachters[36]	16 (0)	NS	34 (0)	56	9 (0)	29 (2)***	NS
Weighted Average*	**17.6 (1.5)**	**18.0 (0.5)**	**15.4 (1.8)**	**41.3 (NA)**	**9.3 (1.10)**	**22.8 (2.4)**	**NS**
Erlotinib							
BR21[2]	17 (<1)^	0 (0)	0 (0)	0	75 (8)***	54 (6)***	24 (<1)^

NA: not applicable; NS: not stated in publication.
* Weighted average = sum (% reported in study x number of pts treated in study)/ sum of recruits to all studies
**Authors state this percentage Grade III/IV unclear how severe/life-threatening alopecia defined
*** Less than 1% Grade IV
^ No grade IV