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Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175): a systematic review and economic evaluation

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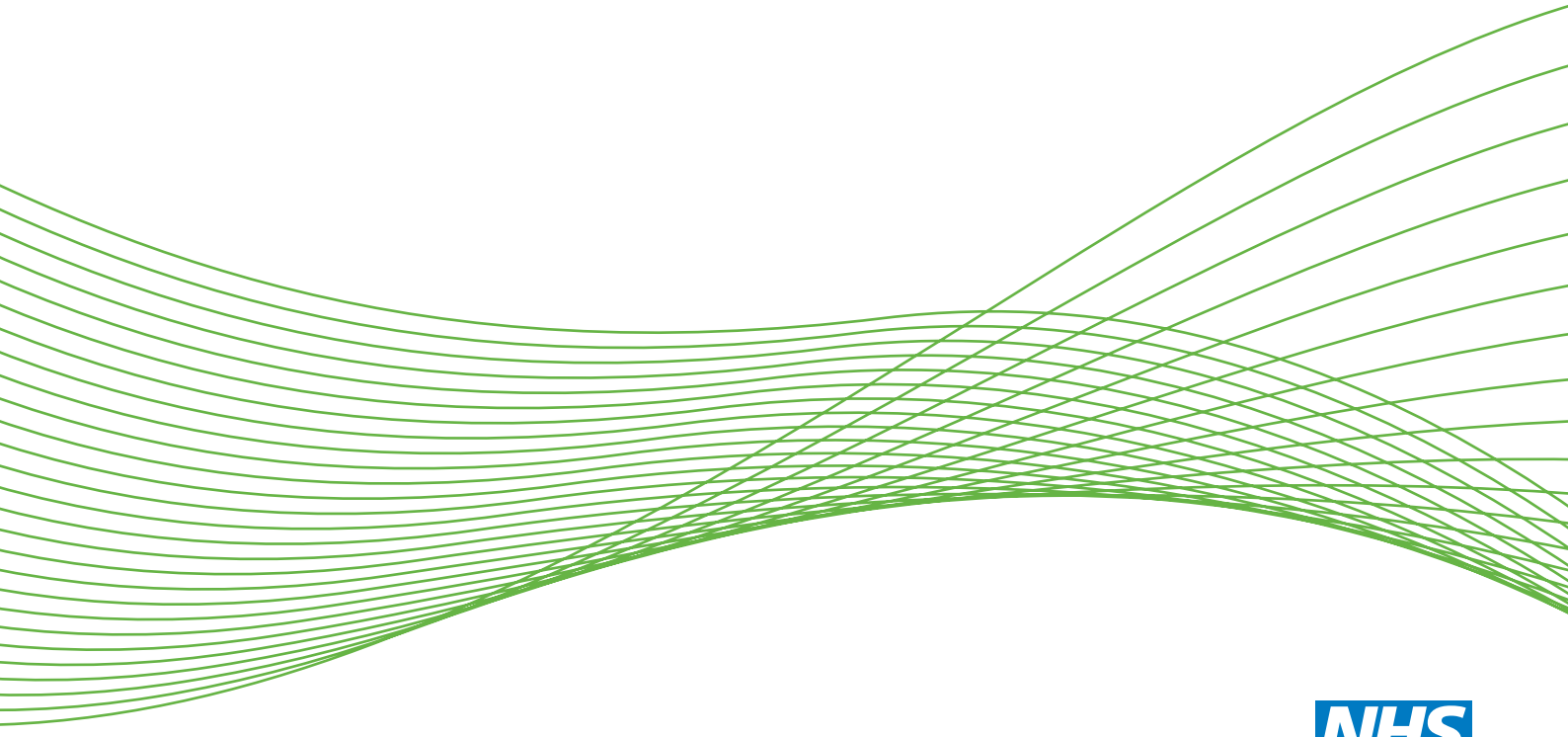

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Abstract

Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed following prior chemotherapy (review of NICE technology appraisals 162 and 175): a systematic review and economic evaluation

Janette Greenhalgh,[1]* Adrian Bagust,[1] Angela Boland,[1] Kerry Dwan,[1] Sophie Beale,[1] Juliet Hockenhull,[1] Christine Proudlove,[2] Yenal Dundar,[1] Marty Richardson,[1] Rumona Dickson,[1] Anna Mullard[3] and Ernie Marshall[3]

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Background: Lung cancer is the second most diagnosed cancer in the UK. Over 70% of lung cancers are non-small cell lung cancers (NSCLCs). Patients with stage III or IV NSCLC may be offered treatment to improve survival, disease control and quality of life. One-third of these patients receive further treatment following disease progression; these treatments are the focus of this systematic review.

Objectives: To appraise the clinical effectiveness and cost-effectiveness of erlotinib [Tarceva®, Roche (UK) Ltd] and gefitinib (IRESSA®, AstraZeneca) compared with each other, docetaxel or best supportive care (BSC) for the treatment of NSCLC after disease progression following prior chemotherapy. The effectiveness of treatment with gefitinib was considered only for patients with epidermal growth factor mutation-positive (EGFR M+) disease.

Data sources: Four electronic databases (EMBASE, MEDLINE, The Cochrane Library, PubMed) were searched for randomised controlled trials (RCTs) and economic evaluations. Manufacturers' evidence submissions to the National Institute for Health and Care Excellence were also considered.

Review methods: Outcomes for three distinct patient groups based on EGFR mutation status [EGFR M+, epidermal growth factor mutation negative (EGFR M–) and epidermal growth factor mutation status unknown (EGFR unknown)] were considered. Heterogeneity of the data precluded statistical analysis. A de novo economic model was developed to compare treatments (incremental cost per quality-adjusted life-year gained).

Results: Twelve trials were included in the review. The use of gefitinib was compared with chemotherapy ($n = 6$) or BSC ($n = 1$), and the use of erlotinib was compared with chemotherapy ($n = 3$) or BSC ($n = 1$). One trial compared the use of gefitinib with the use of erlotinib. No trials included solely EGFR M+ patients; all data were derived from retrospective subgroup analyses from six RCTs [Kim ST, Uhm JE, Lee J, Sun JM, Sohn I, Kim SW, *et al.* Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. *Lung Cancer* 2012;**75**:82–8, V-15-32, Tarceva In Treatment of Advanced NSCLC (TITAN), BR.21, IRESSA Survival Evaluation in Lung cancer (ISEL) and IRESSA NSCLC Trial Evaluating REsponse and Survival versus Taxotere (INTEREST)]. These limited data precluded conclusions regarding the clinical effectiveness of any treatment for EGFR M+ patients. For EGFR

M– patients, data were derived from the TArceva Italian Lung Optimization tRial (TAILOR) trial and Docetaxel and Erlotinib Lung Cancer Trial (DELTA). Retrospective data were also derived from subgroup analyses of BR.21, Kim *et al.*, TITAN, INTEREST and ISEL. The only statistically significant reported results were for progression-free survival (PFS) for TAILOR and DELTA, and favoured docetaxel over erlotinib [TAILOR hazard ratio (HR) 1.39, 95% confidence interval (CI) 1.06 to 1.82; DELTA HR 1.44, 95% CI 1.08 to 1.92]. In EGFR unknown patients, nine trials (INTEREST, IRESSA as Second-line Therapy in Advanced NSCLC – KoreA, Li, Second-line Indication of Gefitinib in NSCLC, V-15-32, ISEL, DELTA, TITAN and BR.21) reported overall survival data and only one (BR.21) reported a statistically significant result favouring the use of erlotinib over BSC (HR 0.7, 95% CI 0.58 to 0.85). For PFS, BR.21 favoured the use of erlotinib when compared with BSC (HR 0.61, 95% CI 0.51 to 0.74) and the use of gefitinib was favoured when compared with BSC (HR 0.82, 95% CI 0.73 to 0.92) in ISEL. Limitations in the clinical data precluded assessment of cost-effectiveness of treatments for an EGFR M+ population by the Assessment Group (AG). The AG's economic model suggested that for the EGFR M– population, the use of erlotinib was not cost-effective compared with the use of docetaxel and compared with BSC. For EGFR unknown patients, the use of erlotinib was not cost-effective when compared with BSC.

Conclusions/future work: The lack of clinical data available for distinct patient populations limited the conclusions of the assessment. Future trials should distinguish between patients with EGFR M+ and EGFR M– disease.

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List of abbreviations

AC	Appraisal Committee
AE	adverse event
AG	Assessment Group
BNF	*British National Formulary*
BSC	best supportive care
CI	confidence interval
DELTA	Docetaxel and Erlotinib Lung Cancer Trial
ECOG	Eastern Cooperative Oncology Group
EE	economic evaluation
EGFR	epidermal growth factor receptor
EGFR M–	epidermal growth factor mutation negative
EGFR M+	epidermal growth factor mutation positive
EGFR unknown	epidermal growth factor mutation status unknown
eMit	electronic market information tool
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
FN	febrile neutropenia
HR	hazard ratio
HRG	health research group
ICER	incremental cost-effectiveness ratio
INTEREST	IRESSA NSCLC Trial Evaluating REsponse and Survival versus Taxotere
ISEL	IRESSA Survival Evaluation in Lung cancer
ISTANA	IRESSA as Second-line Therapy in Advanced NSCLC – KoreA
ITT	intention to treat
i.v.	intravenous
KPS	Karnofsky Performance Status scale
LY	life-year
NICE	National Institute for Health and Care Excellence
NSCLC	non-small cell lung cancer
OS	overall survival
PD	progressed disease
PFS	progression-free survival
PPS	post-progression survival
PS	performance status
PSA	probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	response rate
SIGN	Second-line Indication of Gefitinib in NSCLC
SPC	summary of product characteristics
TAILOR	TArceva Italian Lung Optimization tRial
TITAN	Tarceva In Treatment of Advanced NSCLC
TKI	tyrosine kinase inhibitor
WHO	World Health Organization

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence data removed and replaced by the statement 'commercial-in-confidence information removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Lung cancer is the second most common cancer in the UK, and in 2010 42,000 people in the UK were diagnosed with the disease. Over 75% of lung cancers are of a specific kind called non-small cell lung cancer (NSCLC). People with incurable NSCLC may be given treatment to control symptoms and improve quality of life. When initial treatments are no longer effective, patients who are well enough may receive a follow-on treatment. We considered the benefits and costs of two follow-on drug treatments, erlotinib [Tarceva®, Roche (UK) Ltd] and gefitinib (IRESSA®, AstraZeneca). We looked for evidence comparing these drugs with each other and with other current treatments (the drug docetaxel and supportive care). In this systematic review we identified 12 trials; seven compared the use of gefitinib with the use of docetaxel or supportive care, four compared the use of erlotinib with the use of docetaxel or supportive care and one trial compared the use of erlotinib with the use of gefitinib. We considered the evidence for three groups of people with NSCLC: people who tested positive for the epidermal growth factor receptor (EGFR) mutation, people who tested negative for the EGFR mutation and people who have not been tested or for whom the results of EGFR testing are unknown. For patients with the EGFR mutation, there was limited evidence and we could not determine the best treatment. For patients without the EGFR mutation, we found that the drug docetaxel had more benefits and lower costs than erlotinib, and that docetaxel also offered value for money to the NHS. For patients whose EGFR status is unknown, we found the use of erlotinib to be more effective than supportive care, but erlotinib did not offer value for money to the NHS.

Scientific summary

Background

Lung cancer is the most common cancer worldwide and is the second most diagnosed cancer in the UK after breast cancer (12.9% of all cancer cases). It is also the most common cause of death in the UK. In 2010, 42,000 people in the UK were diagnosed with lung cancer and there were 35,000 registered deaths from lung cancer. The majority of cases (80%) are diagnosed in people over 60 years of age. The treatment options for patients with non-small cell lung cancer (NSCLC) depend on the stage of disease, disease histology, epidermal growth factor receptor (EGFR) mutation status, performance status, comorbidities and patient preferences. Patients with stage III or IV disease, good performance status and for whom curative treatment is not an option, may be initially offered chemotherapy to improve survival, disease control and quality of life. A proportion of this group of patients (33%) will go on to receive further chemotherapy treatment following disease progression after first-line therapy. It is this patient group that is of relevance to this appraisal. Two oral anticancer treatments, used within their licensed indications are the focus of this review: erlotinib [Tarceva®, Roche (UK) Ltd] and gefitinib (IRESSA®, AstraZeneca). Both are EGFR tyrokinase inhibitors that block the signal pathways involved in cell proliferation.

Objectives

The remit of this review is to appraise the clinical effectiveness and cost-effectiveness of erlotinib and gefitinib within their licensed indications for the treatment of NSCLC after disease progression following prior chemotherapy [review of National Institute for Health and Care Excellence (NICE) technology appraisals TA162 and TA175].

Methods

Four electronic databases were searched for randomised controlled trials (RCTs) and economic evaluations (EEs). Studies that compared the use of erlotinib or gefitinib with each other or with the use of docetaxel or best supportive care (BSC) were considered. Patients with NSCLC whose disease had progressed following prior chemotherapy were included. Outcomes for clinical effectiveness included overall survival (OS), progression-free survival (PFS), response rate (RR) and adverse events (AEs). Cost-effectiveness outcomes included incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained. Two reviewers independently screened all titles and/or abstracts including EEs, applied inclusion criteria to relevant publications and quality assessed the included (clinical) studies. The results of the data extraction and (clinical) quality assessment are summarised as a narrative description. No meta-analysis or network meta-analyses were undertaken.

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Results of the literature review

Clinical effectiveness

Twelve trials were identified for inclusion in this review, only one of which (BR.21) was included in the previous review of erlotinib (NICE TA162). Seven trials compared the use of gefitinib with chemotherapy or BSC, four trials compared the use of erlotinib with chemotherapy or BSC, and one trial compared the use of gefitinib with the use of erlotinib.

No trials were identified that were conducted in a population of solely EGFR mutation-positive (EGFR M+) patients. EGFR mutation data were derived retrospectively from six subgroup analyses of RCTs that included patients of unknown EGFR mutation status at the time of randomisation for OS, PFS and RR. Seven trials reported subgroup data describing EGFR mutation-negative (EGFR M–) patients; however, only one trial [TArceva Italian Lung Optimization tRial (TAILOR)] was conducted in a population of solely EGFR M– patients. Ten studies presented quantitative data describing the EGFR unknown population; the results of the Bhatnagar *et al.* trial (Bhatnagar AR, Singh DP, Sharma R, Kumbhaj P. Docetaxel versus gefitinib in patients with locally advanced or metastatic NSCLC pretreated with platinum-based chemotherapy. *J Thorac Oncol* 2012;**3**:S159) and the Docetaxel and Erlotinib Lung Cancer Trial (DELTA) were described in an abstract in narrative format only.

Epidermal growth factor mutation positive

No trials were identified that were conducted in a population of solely EGFR M+ patients. Limited EGFR mutation status data were derived retrospectively from relatively small subgroup analyses from RCTs that included patients of unknown EGFR mutation status at the time of randomisation. Four studies reported OS outcomes, none of which was statistically significantly different for any of the comparisons described. Four studies reported PFS but only one trial, IRESSA NSCLC Trial Evaluating REsponse and Survival versus Taxotere (INTEREST), showed a statistically significant improvement for any comparison considered; the results favoured gefitinib over docetaxel.

Epidermal growth factor mutation negative

Key clinical data were derived from the results of TAILOR and DELTA. However, EGFR mutation status data were also derived retrospectively from subgroup analyses carried out in the BR.21, Tarceva In Treatment of Advanced NSCLC, INTEREST and IRESSA Survival Evaluation in Lung cancer (ISEL) trials and the study by Kim *et al.* (Kim ST, Uhm JE, Lee J, Sun JM, Sohn I, Kim SW, *et al.* Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small cell lung cancer who failed previous chemotherapy. *Lung Cancer* 2012;**75**:82–8). The only statistically significant differences identified for any treatment were in the comparison of erlotinib with docetaxel; in both TAILOR and DELTA, PFS improved in patients in the docetaxel arm.

Epidermal growth factor mutation unknown

Clinical data were available from 10 trials in populations in which EGFR mutation status was not a factor in the recruitment process, or in which overall trial results were presented (with the exception of TAILOR, in which only EGFR M– patients were recruited). The only statistically significant OS benefit for any treatment was reported in BR.21. However, this finding was based on an adjusted rather than an unadjusted analysis of the data (favouring erlotinib over placebo). Only one of the four trials (IRESSA as Second-line Therapy in Advanced NSCLC – KoreA) reported a statistically significant PFS benefit for the comparison of gefitinib with docetaxel favouring gefitinib, although this was based on 90% confidence intervals. For the comparison of gefitinib with BSC, gefitinib was reported to have a statistically significant benefit (ISEL), and in BR.21 a statistically significant PFS benefit of erlotinib was reported (in an adjusted analysis) when compared with a placebo.

Cost-effectiveness

Eleven studies containing economics information were identified. However, the Assessment Group (AG) concluded that the results of the systematic review were of limited value to decision-makers in the UK NHS. This is a result of (1) relatively recent changes in the price of docetaxel and (2) the increased significance of EGFR mutation testing for patients with NSCLC.

Manufacturer's submissions (economics)

Neither of the manufacturers submitted a review of cost-effectiveness literature. Only Roche (UK) Ltd, the manufacturer of erlotinib, submitted economics evidence. Roche (UK) Ltd's base-case analysis compared the use of erlotinib with BSC in patients whose EGFR mutation status is unknown and who are unsuitable for docetaxel or who have previously received docetaxel. In a separate subgroup analysis, Roche (UK) Ltd also considered the use of erlotinib compared with BSC for patients with EGFR M– tumours. The AG provides a summary and critique of the EE that is presented in Roche (UK) Ltd's submission.

Summary of the Assessment Group's cost-effectiveness results

To allow all therapy options for the post-progression treatment of patients with NSCLC to be compared using a consistent framework, the AG developed a de novo cost-effectiveness model. Costs and outcomes were assessed from the perspective of the UK NHS and Personal Social Services. Wider indirect costs and benefits (e.g. loss of productivity, value of informal care and impact on utility of patients' family) were not considered.

Relevant patient populations

Three distinct populations were modelled as follows:

1. previously treated adult patients with locally advanced or metastatic NSCLC and who exhibit EGFR-activating mutations (referred to as the EGFR M+ population)
2. previously treated adult patients with locally advanced or metastatic NSCLC and who do not exhibit EGFR-activating mutations (referred to as the EGFR M– population)
3. previously treated adult patients with locally advanced or metastatic NSCLC and for whom EGFR mutation status is unknown or indeterminate (referred to as the EGFR unknown population).

Epidermal growth factor mutation-positive population

In the absence of any relevant clinical trial evidence in the EGFR M+ population, the AG concluded that there was no reliable basis on which to assess the clinical effectiveness or cost-effectiveness of available treatments for this patient population.

Epidermal growth factor mutation-negative population

Using data from TAILOR for patients who are EGFR M–, in the AG's comparison of erlotinib with docetaxel, erlotinib was found to be dominated by docetaxel, yielding a reduced mean survival and fewer QALYs while also involving a greater net cost of treatment. A univariate sensitivity analysis indicated that the use of generic docetaxel in place of the branded product is the major factor in establishing docetaxel as the preferred option. The incidence rate of febrile neutropenia (FN) has a larger influence on the estimated incremental cost-effectiveness ratio (ICER) than other model parameters, but for none of model parameters is the known parameter uncertainty sufficient to alter the conclusion that erlotinib is dominated by docetaxel in the EGFR M– population. The only model input which could alter this conclusion is the incidence rate of FN in docetaxel-treated patients. The probabilistic sensitivity analysis (PSA) strongly indicated that erlotinib is less cost-effective than docetaxel. The AG's estimated ICER when comparing erlotinib with docetaxel is –£5112 per QALY gained.

Using subgroup data from the BR.21 trial for patients who are EGFR M–, the AG's comparison of erlotinib with BSC yielded an ICER of £54,687 per QALY gained, which is above the range normally considered cost-effective. The results of univariate sensitivity analyses indicated that these results are most affected by projective survival model parameters (especially for the OS model), utility model parameters and the incidence of key AEs. Examination of the PSA scatterplot and the cost-effectiveness acceptability curves indicated strong general confidence that erlotinib exhibits a high ICER when compared with BSC in this subgroup (0% of simulations favour erlotinib at a willingness-to-pay threshold of £30,000 per QALY gained and 12% favour it at a threshold of £50,000 per QALY gained).

Epidermal growth factor mutation status unknown population

Using data from the BR.21 trial for patients whose EGFR status is unknown, the AG's comparison of erlotinib with BSC yielded an ICER of £61,132 per QALY gained, which is well beyond the range normally considered cost-effective. The results of univariate sensitivity analyses indicated that these results were unaffected by uncertainty in almost all model parameters. The only exceptions were the intercept parameter value in the Nafees *et al.* (Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non-small-cell lung cancer. *Health Qual Life Outcom* 2008;**6**:84) utility model (i.e. the baseline NSCLC population utility value in patients with stable disease) and the incidence of FN when docetaxel was used. Examination of the PSA scatterplot and the cost-effectiveness acceptability curves indicated strong

general confidence that erlotinib is not more cost-effective than BSC in this population (0% of simulations favour erlotinib at a willingness-to-pay threshold of £30,000 per QALY gained).

Discussion

Strengths and limitations of the analyses

A key strength of this review is that it has brought together all the available evidence relevant to the clinical effectiveness and cost-effectiveness of erlotinib and gefitinib in patients who have progressed following prior chemotherapy. The review has also highlighted the importance of EGFR mutation status for the selection of effective treatments for patients with NSCLC. In addition, the AG's cost-effectiveness analyses have incorporated the most up-to-date cost and benefit information available (i.e. the off-patent price of docetaxel and clinical results from TAILOR) and, therefore, offer relevant economic evidence to inform decision-making in this complex clinical area.

The main limitation of the assessment is the lack of clinical data available for distinct patient populations. The gaps in the evidence base have precluded the assessment of clinical effectiveness and cost-effectiveness of relevant treatments. Specifically, the AG was unable to carry out an EE of treatments for patients with EGFR M+ tumours.

Uncertainties

The results of the recent TAILOR trial demonstrate that docetaxel has a statistically significant PFS benefit when compared with erlotinib in a European EGFR M– population. However, it is not yet certain whether or not the reported PFS benefit seen in an Italian population would be achieved by NHS patients in England and Wales.

The cost-effectiveness analyses rely on the QALY values modelled from data obtained from a sample of the general population; however, these values do not directly reflect patient experience or patients' preference for the mode of treatment (oral vs. intravenous treatments). This is most important in the comparison of docetaxel with erlotinib. The AG carried out a sensitivity analysis to assess the effect of applying the maximum possible patient health utility increment (bonus) on the estimated ICER. This extreme sensitivity analysis indicates that any realistic assessment of utility advantage due to oral therapy is very unlikely to have more than a minor impact on the size of the estimated ICER.

Conclusions

Implications for service provision

The largest group of patients to whom the results of this appraisal apply is the EGFR M– patient population. The results of the AG's cost-effectiveness analysis comparing erlotinib with docetaxel in patients whose disease has progressed favour the use of docetaxel. Switching from an oral therapy (erlotinib) to an intravenous therapy (docetaxel) would have substantial implications for service provision for both patients and staff in the UK NHS.

Suggested research priorities

It is suggested that any future trials in this area should distinguish between patients who have EGFR M+ and EGFR M– disease. To date, the evidence base supporting the use of post-progression treatments following prior chemotherapy for patients with activating EGFR mutations is weak and is not sufficiently robust to inform decision-making.

Funding

The National Institute for Health Research Health Technology Assessment programme.

Chapter 1 Background

Description of health problem

Lung cancer is the most common cancer worldwide (approximately 1.61 million new cases were diagnosed in 2008) and is the second most diagnosed cancer in the UK after breast cancer (12.9% of all cancer cases).[1] It is also the most common cause of death in the UK.[1] In 2010, 42,000 people in the UK were diagnosed with lung cancer and there were 35,000 registered deaths from lung cancer.[1] The majority of cases (80%) are diagnosed in people aged over 60 years.[1]

Survival rates from lung cancer are low because the majority (66%) of cases are diagnosed at a late stage when a cure is not possible.[2] Other modifying factors for survival from lung cancer include smoking status, general health, sex, race and cancer treatment.[2] Incidence rates for lung cancer differ between men and women; for men, rates have decreased by more than 45% since the late 1970s, while incidence rates for women are still increasing.[1] The Royal College of Physicians reports that survival rates from lung cancer have increased in the last 40 years.[3] However, the outlook for patients in the UK remains poor with a 1-year survival rate of 27% for women and 30% for men. At 5 years, survival in men and women is 7% and 9% respectively.[3]

Table 1 illustrates recent statistics for lung cancer survival. The table is taken from Cancer Research UK's leaflet *Cancer Statistics – Key Facts*.[1]

The majority (86%) of lung cancers are caused by smoking and 3% by passive smoking. Other risk factors include family history, exposure to radon, air pollution and exposure to asbestos.[1]

The symptoms of lung cancer may include cough, shortness of breath, coughing up phlegm with signs of blood, loss of appetite, fatigue, weight loss, and recurrent or persistent chest infection. Symptoms associated with more advanced disease include hoarseness, difficulty in swallowing, finger clubbing, swelling of the face, swelling of the neck, chest pain and shoulder pain.[4]

TABLE 1 Lung cancer statistics table

Lung cancer statistics	Males	Females	Persons	Country	Year[a]
Number of new cases per year	23,175	18,851	42,026	UK	2010
Incidence rate per 100,000 population[b]	58.0	39.7	47.8	UK	
Number of deaths per year	19,410	15,449	34,859	UK	2010
Mortality rate per 100,000[b]	47.9	31.3	38.6	UK	
1-year survival rate[c]	29.4%	33.0%	31.0%	England	2005–9
5-year survival rate[c]	7.8%	9.3%	9.0%		
10-year survival rate[c]	4.9%	5.9%	5.3	England and Wales	2007 (predicted)

a Latest statistics available.
b European age standardised.
c Adults diagnosed.
Reproduced with permission from Cancer Research UK, www.cancerresearchuk.org/cancer-info/cancerstats/keyfacts/lung-cancer/ (accessed September 2013).

Around 72% (approximately 20,000) of lung cancers are non-small cell lung cancers (NSCLC), which can be further classified into three histological subtypes of large-cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma.[5]

Since the introduction of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) into clinical practice in the UK, people with non-squamous NSCLC may be further differentiated as having either EGFR-activating mutation-positive (EGFR M+) or -negative (EGFR M–) status, the latter is otherwise known as the wild type. In the UK, approximately 10% of NSCLC tumours are EGFR M+.[2] Confirmation of histological and EGFR mutation status are key drivers of treatment decisions.

Diagnosis and staging

Diagnosis

Guidelines produced by the National Institute for Health and Care Excellence (NICE; CG121[6]) recommend that urgent referral for chest radiography should be made when a patient presents with haemoptysis or any unexplained or persistent (lasting more than 3 weeks) symptoms, as detailed previously. If chest radiography or chest computed tomography indicates lung cancer, the patient should be urgently referred to a chest physician who will choose the most appropriate investigations for diagnosis and staging. Within the diagnostic process key issues to be addressed include histology, EGFR mutation status, disease staging, performance status (PS) and comorbid disease.

Staging

The TNM classification of malignant tumours staging system (Union for International Cancer Control[7]) is used to classify the size and degree of spread of NSCLC tumours. The TNM classification indicates the appropriate type of treatment (curative or palliative) and prognosis. In the TNM system, the T describes the size of the primary tumour, N describes the involvement of lymph nodes and M describes the presence of metastases. These categories can be classified further into stages. The TNM system is now in its seventh edition, having been updated in 2010. *Table 2* describes the TNM staging system and illustrates the differences between the sixth and seventh editions. *Table 3* describes the surgical stage groupings. Patients of interest to this appraisal are those with stage IIIB or stage IV disease, often described as patients with locally advanced or metastatic disease.

TABLE 2 TNM staging of NSCLC seventh edition compared with sixth edition

Sixth edition	Seventh edition	
TNM stage	TNM stage	Descriptor
T1	T1a	Maximum dimension ≤ 2 cm
	T1b	Maximum dimension 2–3 cm
T2	T2a	Maximum dimension 3–5 cm
	T2b	Maximum dimension > 5–7 cm
	T3	Maximum dimension > 7 cm
T4	T3	Additional nodule in same lobe
M1	T4	Additional nodule in ipsilateral different lobe
M1	M1a	Additional nodules in contralateral lung or ipsilateral pleural effusion
M1	M1b	Distant metastases

M, metastasis; T, tumour.

TABLE 3 Stage groupings in seventh TNM classification

Stage	T	N	M
0	T1a	N0	M0
IA	T1a, T1b	N0	M0
IB	T2a	N0	M0
IIA	T1a, T1b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
IIB	T2b	N1	M0
	T3	N0	M0
IIIA	T1, T2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
IIIB	T4	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1a, M1b

M, metastasis; N, node; T, tumour.

Performance status

The measure of PS indicates the degree of a patient's general well-being. The PS rating may be used when determining fitness for treatment, need for dose adjustment and a patient's supportive care needs. The three main PS scales are the World Health Organization (WHO) PS scale,[8] the Eastern Cooperative Oncology Group (ECOG) PS scale[9] and the Karnofsky PS (KPS) scale.[10] The WHO PS scale is most commonly used in UK clinical practice and is described in *Table 4*. A WHO rating of 0 indicates that a patient is completely able to look after him/herself and a rating of 4 indicates that a patient requires substantial support.

TABLE 4 The WHO PS criteria

Scale	WHO criteria
0	Patient is fully active and more or less the same as before illness
1	Patient is unable to carry out heavy physical work, but can do anything else
2	Patient is up and about more than half the day; able to look after him/herself, but not well enough to work
3	Patient is in bed or sitting in a chair for more than half the day; needs some help to look after him/herself
4	Patient is in bed all the time and needs a lot of looking after

Treatment options

The treatment options for patients with NSCLC depend on the stage of disease, disease histology, EGFR mutation status, PS, comorbidities and patient preferences. For patients with early-stage disease (stages I–II and some stage III) curative surgical resection or radiotherapy may be an option, providing the patient is medically fit.[6] A combination of radiotherapy and chemotherapy may also be an option for patients with stage I–III disease. Patients with stage III or IV disease, good PS and for whom curative treatment is not an option may initially be offered chemotherapy to improve survival, disease control and quality of life (QoL).[6] A proportion of this group of patients (33%) go on to receive further chemotherapy treatment following disease progression after first-line therapy. It is this patient group that is of relevance to this appraisal.

Epidemiology

The National Lung Cancer Audit

The National Lung Cancer Audit is part of a wider programme of national audit run by the Information Centre for Health and Social Care. The audit uses the LUngCAncerDAta database, a database that was originally developed by the Royal College of Physicians in the late 1990s. The data set use key data to describe the demographics, stage, presentation and management of patients with mesothelioma or lung cancer in England and Wales. The National Lung Cancer Audit report is published annually.

The current audit (published in 2012) reports data for patients diagnosed with lung cancer or mesothelioma first seen in 2011.[11,12] The summary report states that it represents almost all cases of lung cancer presenting to secondary care in this year. In England and Wales there were 27,649 cases of NSCLC and, of these, 19,155 were histologically confirmed. This represents a histological diagnosis rate of 70%, with the national histological diagnosis rate for all types of lung cancer reported to be 77% for all lung cancers. Of the patients diagnosed with NSCLC, approximately 57% had stage IIIB or stage IV disease. More males than females were diagnosed (15,471 compared with 12,178, respectively). There were 6698 patients with stage IIIB/IV disease who had a PS score of 0 or 1 and, of these, 55.2% received chemotherapy. Median survival for all cancer cases was 185 days (interquartile range 57–309 days) from diagnosis date. Our clinical advisors tell us that, in UK clinical practice, 25% of patients with a PS score of 0 or 1 receive second-line chemotherapy and approximately 5–15% of patients with a PS score of 2 receive second-line treatment.

Impact of lung cancer

The annual cost of lung cancer to the UK economy is estimated at £2.4B. Half of the cost of lung cancer is a result of premature deaths and time off work. Health-care costs account for a further 35%, while an additional 16% is attributable to unpaid care provided by friends and family. According to Cancer Research UK,[13] each lung cancer patient is thought to cost the UK health-care system £9071 every year.

In addition to the burden of illness and effects of treatment, living with lung cancer will impact on finances, work and employment, emotional well-being and relationships with friends and family.[14]

Relevant national guidelines, including National Service Frameworks

Clinical guidelines published by NICE (NICE CG121[6]) provide recommendations for good practice in the diagnosis and treatment of lung cancer in England and Wales. In addition, NICE has published a quality standard (NICE QS17[15]) that defines best practice for the care of people with lung cancer. The QS17[15] states that people with stage IIIB or IV NSCLC and eligible PS scores should be offered systemic therapy (first and second line) in accordance with NICE guidance that is tailored to the pathological subtype of the tumour and individual predictive factors.[16]

There are a number of NICE guidance documents that are relevant to this appraisal. These are described in *Table 5*.

TABLE 5 Relevant NICE documents

NICE clinical guideline/guidance	Patient group (histology/EGFR status)	Recommended treatment
First line		
CG121[6] – The diagnosis and treatment of lung cancer	All patients with NSCLC of good PS score (WHO rating 0 or 1 or Karnofsky score of 80–100)	Platinum-doublet docetaxel, gemcitabine, vinorelbine or paclitaxel. Or single agent if unable to tolerate platinum therapy
TA192[17] – Gefitinib for the first-line treatment of locally advanced or metastatic NSCLC	EGFR M+ only	Gefitinib if provided at agreed PAS price
TA258[18] – Erlotinib for the first-line treatment of locally advanced or metastatic EGFR M+ NSCLC	EGFR M+ only	Erlotinib if provided at the agreed PAS price
TA181[19] – Pemetrexed for the first-line treatment of NSCLC	Confirmed adenocarcinoma or large cell (non-squamous) only	Pemetrexed + cisplatin
Maintenance following first line		
TA190[20] – Pemetrexed for the maintenance treatment of NSCLC	Non-squamous (adenocarcinoma or large cell) without disease progression after first-line platinum chemotherapy with gemcitabine, paclitaxel or docetaxel	Pemetrexed
Second line		
CG121[6] – The diagnosis and treatment of lung cancer	All NSCLC	Docetaxel monotherapy
TA162[21] – Erlotinib for the treatment of NSCLC	All NSCLC	Erlotinib if provided at an overall treatment cost equal to that of docetaxel. It is not recommended in patients for whom docetaxel is unsuitable or contraindicated
TA175[22] – Gefitinib for the treatment of locally advanced or metastatic NSCLC	EGFR M+ only	Gefitinib. NICE was unable to recommend the use in the NHS of gefitinib for the second-line treatment of locally advanced or metastatic NSCLC because no evidence submission was received from the manufacturer or sponsor of the technology
TA124[23] – Pemetrexed for the treatment of NSCLC	All NSCLC	Not recommended

PAS, patient access scheme.

First-line treatment options

The first-line chemotherapy treatment options recommended by NICE[16] include platinum-based (cisplatin or carboplatin) doublet chemotherapy with docetaxel, gemcitabine, paclitaxel or vinorelbine. Pemetrexed (Alimta®, Eli Lilly & Co Ltd) plus cisplatin is an option for patients with predominantly non-squamous NSCLC. Single agents erlotinib [Tarceva®, Roche (UK) Ltd] or gefitinib (IRESSA®, AstraZeneca) are options for patients with locally advanced or metastatic EGFR M+ NSCLC.[16]

Maintenance treatment options

Maintenance treatment has recently become an option for a limited group of patients. Pemetrexed as a single-agent maintenance treatment is an option for patients with locally advanced or metastatic non-squamous lung disease whose disease has not progressed following first-line chemotherapy treatment with a platinum-based doublet containing gemcitabine, paclitaxel or docetaxel.[16] NICE guidance for the use of pemetrexed as a single-agent maintenance treatment as an option for patients with locally advanced or metastatic non-squamous lung disease whose disease has not progressed following first-line chemotherapy treatment with pemetrexed plus cisplatin is currently under development.

Second-line treatment options

Current NICE recommendations for second-line treatment of NSCLC include docetaxel monotherapy or erlotinib monotherapy. Erlotinib is not recommended for the second-line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (that is, in patients who are intolerant to docetaxel or in whom docetaxel is contraindicated) or for third-line treatment after docetaxel therapy.[16]

Recommendation by NICE was not possible for the use of gefitinib as a second-line treatment option for patients in England and Wales, as the single technology appraisal process (2009) was terminated because no evidence submission was received from the manufacturer or sponsor of the technology.[16]

Pemetrexed as a second-line treatment for locally advanced or metastatic NSCLC was not recommended by NICE.

Variation in services and/or uncertainty about best practice

Histological diagnosis

The National Lung Cancer Audit[11] reports an overall histological diagnosis rate of 77% for all lung cancers. For NSCLC, the rate appears to be 70%. This means that the histological status of their disease is not tested in 30% of patients with NSCLC. Our clinical advisors tell us that some patients are too ill for treatment and thus do not undergo histological diagnosis.

Epidermal growth factor mutation testing

In clinical practice, EGFR mutation status is mostly ascertained at the same time as histological status for patients considered likely to be EGFR M+. However, clinical advice (Dr Ernie Marshall, The Clatterbridge Centre NHS Foundation Trust, Liverpool, 2013, personal communication) to the Assessment Group (AG) suggests that the EGFR testing pathway is not uniform across England and Wales. Our clinical advisors tell us that EGFR mutation testing rates are improving annually.

In the UK NHS, most patients with NSCLC have an EGFR mutation test prior to being treated for the first time, and clinicians tell us very few people need to have an EGFR mutation test before second-line treatment. The AG acknowledges that the significance of EGFR mutation status has only recently been clarified and EGFR mutation status is now increasingly being considered in the design of lung cancer trials (e.g. prospective recruitment of EGFR M+ or EGFR M– patient populations; EGFR mutation status as a stratification factor).

Description of technology under assessment

Two oral anticancer treatments, used within their licensed indications, are the focus of this review: erlotinib and gefitinib. Both are EGFR-TKIs that block the signal pathways involved in cell proliferation. The summaries of product characteristics (SPCs) for erlotinib and gefitinib are available from the Electronic Medicines Compendium.[24]

Erlotinib

Erlotinib is available as film-coated tablets in 25 mg, 100 mg or 150 mg. The recommended daily dose of erlotinib is 150 mg taken at least 1 hour after food. No guidance as to duration of treatment is given. Erlotinib is licensed in the UK for the treatment of NSCLC and metastatic pancreatic cancer. The latter indication is not relevant to this review.

In the setting of NSCLC, erlotinib is licensed for use with three patient populations. In the first-line setting, erlotinib is licensed for the treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations. The SPC[25] stipulates that, prior to initiation of erlotinib therapy, people with chemotherapy-naive NSCLC should undergo EGFR mutation testing using a well-validated and robust methodology.

In the post-first-line maintenance setting, erlotinib is licensed as monotherapy for people with locally advanced or metastatic NSCLC whose disease is stable following four cycles of standard platinum-based first-line chemotherapy.

In the second-line setting, erlotinib is licensed for patients with locally advanced or metastatic NSCLC following failure of at least one prior chemotherapy.

Gefitinib

Gefitinib is available as a 250-mg film-coated tablet. The recommended dose of gefitinib is one 250-mg tablet daily. No guidance as to duration of treatment is given. It is licensed in the UK for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR-activating mutations. The licence places no restriction on where in the treatment pathway gefitinib is used. As was noted for erlotinib, the SPC[26] for gefitinib stipulates that a well-validated and robust methodology is used to determine EGFR mutation status before therapy.

The *Special warnings and precautions for use* section of the SPC[26] notes that an increased incidence of interstitial lung disease has been observed in epidemiological studies of gefitinib. Periodic liver function testing is also recommended for patients treated with gefitinib. The AG is aware that in 2003 the Food and Drug Administration (FDA) in the USA approved the use of gefitinib as a second-line treatment for patients who are refractory to platinum-based chemotherapy or docetaxel. The approval was made under the FDA's accelerated approval regulations that allow the conditional approval of medicines based on surrogate outcomes, in this case tumour response rate (RR). The manufacturer was then required to provide the FDA with data on survival outcomes. The manufacturer has been unable to provide any data that show a positive benefit of gefitinib for survival and, consequently, the FDA (with the agreement of AstraZeneca) removed the licence for gefitinib use in the USA.[27]

Current usage in the NHS

The manufacturer of erlotinib [Roche (UK) Ltd] states in its evidence submission to NICE that 70% of patients who receive second-line treatment receive erlotinib.[28]

The manufacturer of gefitinib (AstraZeneca) presented in its evidence submission to NICE the number of patients receiving first-line treatment with gefitinib only. These patients are not relevant to this appraisal.

The pack costs of erlotinib and gefitinib are shown in *Table 6*. The costs of erlotinib to the NHS are subject to a further (confidential) discount under the patient access scheme.

TABLE 6 Drug pack cost

Drug	Pack size and cost
Erlotinib	150 mg, 30-tablet pack = £1631.53. BNF list price[29] September 2013
Gefitinib	250 mg, 30-tablet pack = £2167.71. BNF list price[29] September 2013. NHS-discounted price available of £12,200 per patient receiving treatment beyond 60 days

BNF, *British National Formulary*.

Chapter 2 Definition of the decision problem

Decision problem

The remit of this appraisal is to review and update (if necessary) the clinical effectiveness and cost-effectiveness evidence base described in NICE TA162[21] and NICE TA175.[22] The key elements of the decision problem are described in *Table 7*.

The AG notes that treatments given at first line will impact on treatments available to patients at disease progression. It is unlikely that any patient would be re-treated at second line with the same agent. This means that patients with EGFR M+ tumours treated at first line with a TKI (erlotinib or gefitinib) would not be treated with a TKI following disease progression.

The AG further notes that the eligible patient population for second-line erlotinib or gefitinib is small as the majority of people with EGFR M+ tumours will be diagnosed and treated with a first-line TKI, rendering them ineligible for a TKI at second line.

TABLE 7 Decision problem

Interventions	Erlotinib Gefitinib
Patient population	Adults with locally advanced or metastatic NSCLC that has progressed following prior chemotherapy[a]
Comparators	Erlotinib and gefitinib to be compared with each other and with: • docetaxel • best supportive care
Outcomes	• Overall survival • Progression-free survival • RRs • Adverse effects of treatment • HRQoL
Economic analysis	The reference case stipulates that: • the cost-effectiveness of treatments should be expressed in terms of incremental cost per QALY • the time horizon for estimating clinical effectiveness and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared • costs will be considered from a NHS and Personal Social Services perspective
Other considerations	• Guidance will only be issued in accordance with the marketing authorisations • If the evidence allows, subgroups such as those defined by histology (squamous/non-squamous) and EGFR mutation status • The appraisal should consider the implications of mutation testing • The availability of any patient access schemes for the interventions and comparators should be taken into account in the analysis

HRQoL, health-related quality of life; QALY, quality-adjusted life-year.
a The AG assumes that prior chemotherapy refers to both to cytotoxic chemotherapy and targeted therapy.

Overall aims and objectives of assessment

The remit of this review is to appraise the clinical effectiveness and cost-effectiveness of erlotinib and gefitinib within their licensed indications for the treatment of NSCLC that has progressed following prior chemotherapy (review of NICE technology appraisals TA162[21] and TA175[22]).

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing effectiveness

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Search strategies

In addition to searching the two manufacturers' submissions for relevant references, the following databases were searched for studies of erlotinib and gefitinib:

- EMBASE (via OvidSP), from 1974 to 26 April 2013
- MEDLINE (via OvidSP), from 1946 to 26 April 2013
- The Cochrane Library, from inception to 28 April 2013
- PubMed, from January 2010 to 28 April 2013.

The results were entered into an EndNote X5 (Thomas Reuters, CA, USA) library and the references were de-duplicated. Full details of the search strategies are presented in *Appendix 1*.

The reference lists of included trials were searched for relevant trials. Information on trials in progress was sought from oncology conference databases (American Society for Clinical Oncology and the European Society for Medical Oncology), and the ClinicalTrials.gov website was searched for ongoing trials. In addition, advice was sought from the two clinical advisors to the review and the three clinical peer reviewers.

Inclusion and exclusion criteria

Two reviewers, JG and JH, independently screened all titles and abstracts identified via searching and obtained full-paper manuscripts that were considered relevant by either reviewer (stage 1). The relevance of each study was assessed (JG and JH) according to the criteria set out in this section (stage 2). Studies that did not meet the criteria were excluded and their bibliographic details were listed alongside reasons for their exclusion. Any discrepancies were resolved by consensus and, where necessary, a third reviewer was consulted.

Study design

Only randomised controlled trials (RCTs) were included in the assessment of clinical effectiveness.

Interventions and comparators

The effectiveness of two EGFR-TKIs, erlotinib and gefitinib, within their licensed indications were assessed. Studies that compared the use of erlotinib or gefitinib with the use of docetaxel or best supportive care (BSC), or, where appropriate, with each other, were included in the review. Trials in which erlotinib was combined with other active treatments were excluded from the review.

Patient populations

Adults with locally advanced or metastatic NSCLC that has progressed following prior chemotherapy treatment were included.

Outcomes

Data on any of the following outcomes were included in the assessment of clinical effectiveness: overall survival (OS), progression-free survival (PFS), RRs, adverse events (AEs) and health-related quality of life. For the assessment of cost-effectiveness, outcomes included incremental cost per life-year (LY) gained and incremental cost per quality-adjusted life-year (QALY) gained.

Data extraction strategy

Data relating to both study design and quality were extracted by two reviewers (JG and KD) into a Microsoft Excel® spreadsheet (Microsoft Corporation, Redmond, WA, USA). Two reviewers cross-checked each other's data extraction and where multiple publications of the same study were identified, data were extracted and it was reported as a single study.

Quality assessment strategy

The quality of clinical effectiveness studies was assessed independently by two reviewers (JG and KD) in accordance with the Centre for Reviews and Dissemination at York University's suggested criteria.[30] All relevant information is tabulated and summarised within the text of the report. Full details and results of the quality assessment strategy for clinical effectiveness studies are reported in *Appendix 2*.

Methods of data synthesis

The results of the clinical data extraction and clinical study quality assessment are summarised in structured tables and as a narrative description. For patients who have progressed following prior treatment, the decision problem of interest to this review is made up of the following comparisons: the effectiveness of erlotinib and gefitinib in a population of patients with EGFR M+ tumours, the effectiveness of erlotinib and gefitinib in a population of patients with EGFR M– tumours and the effectiveness of erlotinib and gefitinib in an EGFR unknown population (i.e. whose EGFR mutation status is unknown at the time of randomisation).

Results

Quantity and quality of research available

A total of 1563 titles and abstracts were screened for inclusion in the review of clinical effectiveness and cost-effectiveness evidence. Overall, 12 relevant RCTs were identified. The process of study selection is shown in *Figure 1*.

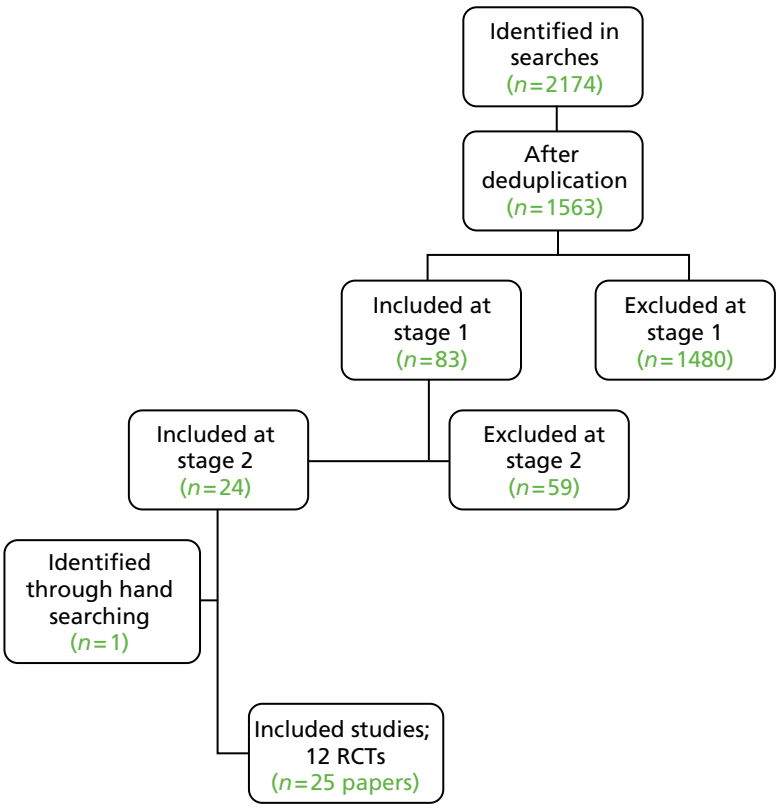

FIGURE 1 Study selection process.

Clinical effectiveness (randomised controlled trials)

A total of 12 RCTs (one of which was discussed in NICE TA162,[21] namely BR.21[31]) were reported in 25 publications and met the criteria for inclusion into the review. The reference cited in the text refers to the primary report, and subsequent publications describing outcomes of the trials are listed by trial in *Appendix 3*. The AG did not find any relevant publications that were not identified by the manufacturers.

The identified trials are summarised in *Table 8*. A full list of publications that were excluded from the review following the application of the inclusion criteria is presented in *Appendix 4*. The AG also identified and assessed the quality of existing systematic reviews in order to cross-check for the identification of

TABLE 8 Summary of included trials

Trial	Design	Intervention	Comparator	Patient population (EGFR M+, EGFR M– or EGFR unknown)	Retrospective EGFR subgroup data available
Gefitinib vs. erlotinib					
Kim *et al.*[32]	Open-label, non-comparative randomised Phase II trial	Gefitinib	Erlotinib	EGFR M+ and two out of three factors associated with EGFR mutations	Yes
Gefitinib vs. docetaxel					
Bhatnagar *et al.*[33]	RCT	Gefitinib	Docetaxel	EGFR unknown	No
INTEREST[34]	Open-label Phase III RCT	Gefitinib	Docetaxel	EGFR unknown	Yes
ISTANA[35]	Open-label Phase III RCT	Gefitinib	Docetaxel	EGFR unknown	No
Li *et al.*[36]	RCT	Gefitinib	Docetaxel	EGFR unknown	No
SIGN[37]	Open-label Phase II RCT	Gefitinib	Docetaxel	EGFR unknown	No
V-15-32[38]	Open-label Phase III RCT	Gefitinib	Docetaxel	EGFR unknown	Yes
Gefitinib vs. placebo					
ISEL[39]	Placebo-controlled Phase III RCT	Gefitinib + BSC	Placebo + BSC	EGFR unknown	Yes
Erlotinib vs. docetaxel					
DELTA[40]	Open-label Phase III RCT	Erlotinib	Docetaxel	EGFR M+ and EGFR M–	Yes
TAILOR[41]	Open-label Phase III RCT	Erlotinib	Docetaxel	EGFR M– only	Yes
Erlotinib vs. docetaxel/pemetrexed					
TITAN[42]	Open-label Phase III RCT	Erlotinib	Docetaxel or pemetrexed	EGFR unknown	Yes
Erlotinib vs. placebo					
BR.21[31]	Placebo-controlled Phase III RCT	Erlotinib	Placebo	EGFR unknown	Yes

DELTA, Docetaxel and Erlotinib Lung Cancer Trial; INTEREST, IRESSA NSCLC Trial Evaluating REsponse and Survival versus Taxotere; ISTANA, IRESSA as Second-line Therapy in Advanced NSCLC – KoreA; ISEL, IRESSA Survival Evaluation in Lung cancer; SIGN, Second-line Indication of Gefitinib in NSCLC; TAILOR, TArceva Italian Lung Optimization tRial; TITAN, Tarceva In Treatment of Advanced NSCLC.

additional studies as well as to gain an understanding of the issues related to the combining of data in this complex clinical area. A summary and critique of relevant systematic reviews is presented in *Appendix 5*.

As EGFR mutation status is a key factor in this review, it is noted in *Table 8* whether or not a patient's EGFR mutation status was determined before randomisation and used as the basis for inclusion in the trial. For those trials that did not select patients based on EGFR mutation status, the final column of the table indicates whether or not any retrospective analyses of the data were conducted. It should be noted that, where retrospective EGFR subgroup analyses are available, the data are limited.

Two of the included trials, Bhatnagar *et al.*[33] and the Docetaxel and Erlotinib Lung Cancer Trial (DELTA),[40] were only reported as conference abstracts and, therefore, limited information is available to describe these studies. The final results of the TArceva Italian Lung Optimization tRial (TAILOR)[41] were published after our searches were completed; however, we have included these results in the review.

Gefitinib trials ($n = 7$)

Gefitinib was compared with docetaxel in six trials of patients of unknown EGFR status at the time of randomisation.[33–38] A single trial[39] compared gefitinib with placebo in an EGFR unknown population.

Erlotinib trials ($n = 4$)

Two trials[40,41] compared erlotinib with docetaxel. DELTA[40] was designed to allow the assessment of treatment outcomes in EGFR M– and EGFR M+ patient populations. TAILOR[41] included only patients who were known to be EGFR M–. One trial[42] compared erlotinib with chemotherapy in patients whose EGFR status was unknown at the time of randomisation; the chemotherapy regimen was either docetaxel or pemetrexed depending on the treating physician's choice. In the BR.21 trial,[31] erlotinib was compared with a placebo in a population whose EGFR mutation status was unknown.

Gefitinib versus erlotinib ($n = 1$)

Gefitinib was compared with erlotinib in one trial[32] in patients who were EGFR M+ or who were likely to be EGFR M+.

Quality assessment of the included randomised controlled trials

The results of the quality assessment exercise are presented in *Appendix 2*. Overall, the trials were considered to be of reasonable methodological quality.

Randomisation

Of the 10 trials reported in published papers, four[32,35,36,38] did not state the methods used to randomise patients into the trial and whether or not the allocation method precluded prediction of participant assignment. One trial[35] reported partial details of the randomisation method used, but stated that the treatment allocation was conducted centrally. All trials reported the number of patients randomised into the trial. Of the two trials reported in conference abstracts,[33,40] only DELTA[40] described the randomisation method used in the trial. Neither study reported details of allocation concealment.

Comparability across groups

All of the published trials reported the key characteristics of the participants and, with the exception of the Tarceva In Treatment of Advanced NSCLC (TITAN) trial,[42] showed comparability across trial arms. The Kim *et al.*[32] trial was considered to be unclear on this criterion – in the trial, a 'historical control' was used to ascertain the efficacy of the two interventions (rather than comparing both arms) and no details are presented for the historical control group. The erlotinib and gefitinib arms of the Kim *et al.*[32] trial appear to be well balanced. In TAILOR,[41] differences in the numbers of smokers and never-smokers, and the numbers of patients with adenocarcinoma histology were noted. In the conference abstracts (Bhatnagar *et al.*[33] and DELTA[40]) details of comparability were not presented.

Eligibility and co-interventions

All published trials specified eligibility criteria for entry into the trial. Three trials [IRESSA NSCLC Trial Evaluating REsponse and Survival versus Taxotere (INTEREST),[34] Li *et al.*[36] and Second-line Indication of Gefitinib in NSCLC (SIGN)[37]] reported the use of co-medications that may have had an effect on trial outcomes. In all cases these were corticosteroids and/or antiemetics administered as premedications prior to intravenous (i.v.) chemotherapy. It is likely that the remaining trials also used these premedications but did not report this use in the publication. In the conference abstracts, limited details of inclusion criteria were reported and neither of the abstracts noted the use of comedications.[33,40]

Blinding

The reporting of blinding procedures across the 10 published trials was poor. Two of the 10 published trials were placebo controlled[31,39] and were stated as being 'double blind.' It is clear from the IRESSA Survival Evaluation in Lung cancer (ISEL)[39] trial that both patients and investigators were blinded as to treatment allocation, although it is unclear whether the investigators were treatment administrators or outcome assessors, or both. We have assumed that, in the BR.21 trial,[31] the patients, administrators and outcome assessors were blinded to treatment allocation, although this is not explicitly stated. Neither ISEL[39] nor BR.21[31] reported any testing of the blinding procedures.

The remaining eight published trials were open label. In trials in which the interventions in the trial arms are very different (e.g. i.v. infusion vs. orally administered), it is not always possible to blind patients or administrators to the treatments received. It should be possible, however, to employ procedures whereby outcome assessment is conducted in a blinded fashion or where unblinded assessment is verified by independent blinded assessment. Few details of any blinding procedures were reported in the publications of the included trials. It is noted in TAILOR[41] that two independent radiologists, masked to treatment assignment, carried out post-hoc reviews of all the scans of responding patients, and in V-15-32[38] the primary overall RR results that were based on investigator judgement were generally consistent with those obtained from independent response evaluation committee assessment. However, it is unknown whether or not any of the remaining trials employed similar blinding protocols.

Both of the trials[33,40] reported as conference abstracts appear to be open label and neither of the trials report details of any blinding procedures used.[40,41]

Patient withdrawals

The 10 trials reported as published papers all appear to have included more than 80% of randomised patients in the final analysis. Reasons for patient dropouts were clearly reported. However, this aspect of the trials is not reported in the two conference abstracts.[33,41]

Intention-to-treat analysis

All but one of the trials (Li *et al.*[36]) reported in the published papers state that an intention-to-treat (ITT) analysis was conducted. However, this aspect of the trials is not reported in the two conference abstracts.[33,40]

Outcomes

None of the trials appeared to have reported fewer outcomes than were proposed in the methods section of the published paper, although the two trials reported as conference abstracts cannot be assessed on this criterion.[33,40]

In addition, the AG highlights the following aspects of the included studies that have not been discussed within the remit of the quality assessment exercise:

- TITAN[42] – the trial was terminated early because of slow recruitment.
- Kim *et al.*[32] – the trial used a historical control (no details were provided) to assess the relative clinical effectiveness of erlotinib and gefitinib.

- TAILOR[41] – several protocol changes were made to TAILOR, including a change of primary end point.
- SIGN[37] – the trial was not powered to formally test outcomes.
- INTEREST[34] and V-15-32[38] were non-inferiority trials.

Trial characteristics

The characteristics of the included trials are presented in *Table 9*. All of the trials were published between 2005 and 2013. Five trials were conducted internationally, one exclusively in multiple centres in Italy (TAILOR[41]) and six in Asian countries: South Korea, India, the People's Republic of China and Japan [IRESSA as Second-line Therapy in Advanced NSCLC – KoreA (ISTANA)[35] and Kim *et al.*,[32] Bhatnagar *et al.*,[33] Li *et al.*,[36] DELTA[40] and V-15-32,[38] respectively]. Of the trials conducted in Asia, three were multicentred.[35,38,40] With the exception of the Li *et al.*[36] trial, all trial results were published in English. The Li *et al.*[36] paper was translated from Mandarin Chinese to English by a translation service contracted by the AG. The number of randomised patients ranged from 30[33] to 1692.[39] Inclusion and exclusion criteria used in the included studies are shown in *Appendix 6*.

Two of the trials were Phase II,[32,37] while ISTANA,[35] ISEL,[39] DELTA,[40] TAILOR,[41] TITAN,[42] V-15-32,[38] INTEREST[34] and BR.21[31] were all Phase III trials. The phase of the Bhatnagar *et al.*[33] and Li *et al.*[36] trials is unknown. Seven of the trials were funded solely, or in part, by pharmaceutical companies,[31,34,35,37–39,42] three were funded by research grants[32,40,41] and the funding source for two trials[33,36] is not known.

The dosage of erlotinib and gefitinib was consistent with the recommended licensed dose (150 mg or 250 mg, respectively) across the trials in which those treatments were used. Of the nine trials in which docetaxel was a comparator,[33–38,40–42] seven trials[33–37,41,42] treated patients with 75 mg/m^2 every 3 weeks and two trials[38,40] treated patients with 60 mg/m^2 every 3 weeks, this being the standard dose used in Japan. Median follow-up (when reported) ranged between 7.2 months[39] and 33 months.[41] Information regarding post-progression treatments was not reported in four trials.[33,36,37,40]

Patient characteristics

Patient characteristics are presented in *Table 10*. Details of individual trial inclusion and exclusion criteria are presented in *Appendix 6*. The median patient age (when reported) ranged between 49 and 61 years. With the exception of the Kim *et al.*[32] trial, the majority of patients were male (when reported). With the exception of the Li *et al.*[36] trial, the majority of patients were considered to have stage IV disease (when reported). The main histological type across trials was adenocarcinoma; however, the ratio of adenocarcinoma to other histological subtypes varied. For example, approximately 90% of patients in the Kim *et al.*[32] trial and 77% in V-15-32[38] had adenocarcinoma, while lower rates were reported in BR.21[31] and TITAN[42] (both approximately 50%). In the main, the majority of patients had received a single prior chemotherapy treatment; however, in ISEL[39] and BR.21[31] approximately half of the patients had received two previous chemotherapy treatments.

In terms of PS, the majority of patients were assessed to have an ECOG score of 0 or 1 or a WHO score of 0 or 1.[32,34,35,38,41] Up to one-third of patients in the TITAN,[42] ISEL[39] and SIGN[37] trials were considered to have a PS score of 2 (ECOG or WHO). The patients in the Li *et al.*[36] trial were KPS scores of 70 or greater, and the two conference abstracts (Bhatnagar *et al.*[33] and DELTA[40]) report that patients had ECOG scores of 0 to 2.

The trial populations included in TAILOR[41] and the Kim *et al.*[32] trial were tested for EGFR mutation status before entry into the trial. In the TAILOR[41] trial, only those who were EGFR M– were randomised. The patients recruited to the Kim *et al.*[32] trial were those who were EGFR M+ or who had two out of three factors associated with EGFR mutations (female, never-smoker and adenocarcinoma histology). DELTA[40] included patients who were EGFR M–, but it is unclear if EGFR status was ascertained at the time of randomisation.

TABLE 9 Key trial characteristics

Trial	Type of trial	Intervention	Comparator	Number patients	Location	Median follow-up	Trial support	Treatment crossover
Gefitinib vs. erlotinib								
Kim *et al.* 2012[32]	Open-label, non-comparative randomised Phase II	Gefitinib 250 mg daily	Erlotinib 150 mg daily	$N = 96$; gefitinib, $n = 48$; erlotinib $n = 48$	South Korea	16.3 months	IN-SUMG Foundation for Medical Research	At the discretion of each physician
Gefitinib vs. docetaxel								
[a]Bhatnagar *et al.* 2012[33]	RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m^2 every 3 weeks	$N = 30$	India	2 years	NS	NS
INTEREST 2008[34]	Open-label Phase III non-inferiority RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m^2 every 3 weeks	$N = 1466$; gefitinib, $n = 733$; docetaxel, $n = 733$	Europe, Asia and the Americas	7.6 months	AstraZeneca	Gefitinib arm: $n = 28$ (4%) EGFR-TKI; $n = 225$ (31%) docetaxel; $n = 112$ (15%) other chemotherapy Docetaxel arm: $n = 4$ (1%) docetaxel; $n = 268$ (37%) EGFR-TKI; $n = 74$ (10%) other chemotherapy
ISTANA 2010[35]	Open-label Phase III RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m^2 every 3 weeks	$N = 161$; gefitinib, $n = 82$; docetaxel, $n = 79$	Korea	13 months	AstraZeneca	Gefitinib arm: 24.7% received no further systemic chemotherapy apart from further EGFR-TKIs (2.5% gefitinib/erlotinib), 22.2% received no treatment, 29.6% received docetaxel and 44.4% received other chemotherapy Docetaxel arm: 67.1% received an EGFR-TKI and 6.6% received other chemotherapy
Li *et al.* 2010[36]	RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m^2 every 3 weeks	$N = 98$; gefitinib, $n = 50$; docetaxel, $n = 48$	People's Republic of China	NS	NS	NS

continued

TABLE 9 Key trial characteristics (*continued*)

Trial	Type of trial	Intervention	Comparator	Number patients	Location	Median follow-up	Trial support	Treatment crossover
SIGN 2006[37]	Open-label Phase II RCT	Gefitinib 250 mg daily	Docetaxel 75 mg/m^2 every 3 weeks	$N = 141$; gefitinib, $n = 68$; docetaxel, $n = 73$	Europe, South America and the Middle East	9.2 months (gefitinib), 9.4 months (docetaxel)	AstraZeneca	NS
V-15-32 2008[38]	Open-label Phase III non-inferiority RCT	Gefitinib 250 mg daily	Docetaxel 60 mg/m^2 every 3 weeks	$N = 490$; gefitinib, $n = 245$; docetaxel, $n = 244$[b]	Japan	21 months	AstraZeneca	Crossover was greater than initially expected, and differences in the number and types of patients who received these post-study treatments complicated interpretation of survival results
Gefitinib vs. placebo								
ISEL 2005[39]	Placebo-controlled double-blind Phase III RCT	Gefitinib 250 mg daily	Placebo + BSC	$N = 1692$; gefitinib, $n = 1129$; placebo, $n = 563$	Europe, Asia, Central and South America, Australia and Canada	7.2 months	AstraZeneca	Placebo arm: 3% received gefitinib. All subsequent treatments for NSCLC were well balanced between the treatment groups. The protocol allowed for up to 15% crossover to gefitinib
Erlotinib vs. docetaxel								
[a]DELTA 2013[40]	Open-label Phase III RCT	Erlotinib 150 mg daily	Docetaxel 60 mg/m^2 every 3 weeks	$N = 301$; erlotinib, $n = 150$; docetaxel, $n = 151$	Japan	NS	Japanese National Hospital Organization	NS
TAILOR 2013[41]	Open-label Phase III RCT	Erlotinib 150 mg daily	Docetaxel 75 mg/m^2	$N = 222$; erlotinib, $n = 112$; docetaxel, $n = 110$	Italy	33 months	Italian Agency for Drug Administration	No crossover allowed Erlotinib arm: seven participants crossed over Docetaxel arm: four participants crossed over. Third-line treatment with pemetrexed/GEM/VIN

Trial	Type of trial	Intervention	Comparator	Number patients	Location	Median follow-up	Trial support	Treatment crossover
Erlotinib vs. docetaxel/pemetrexed								
TITAN 2012[42]	Open-label Phase III RCT	Erlotinib 150 mg daily	Docetaxel or pemetrexed dosing at discretion of the investigator	$N = 424$; erlotinib, $n = 203$; chemotherapy, $n = 221$	International	Erlotinib: 27.9 months, docetaxel/ pemetrexed: 24.8 months	Hoffmann F – La Roche, Basel, Switzerland	Erlotinib arm: 25% antimetabolites, 23% docetaxel or PAX Chemotherapy arm: 12% antimetabolites, 23% TKIs, 5% switch to docetaxel, 7% switch to pemetrexed
Erlotinib vs. placebo								
BR.21 2005[31]	Placebo-controlled Phase III RCT	Erlotinib 150 mg daily	Placebo	$N = 731$; erlotinib, $n = 488$; placebo, $n = 243$	International	NS	Supported in part by a grant from OSI Pharmaceuticals	Erlotinib arm: 8 (1.6%) Placebo arm: 18 (7.4%) received other EGFR inhibitors after study medication discontinued

GEM, gemcitabine; NS, not stated; PAX, paclitaxel; VIN, vinorelbine.
a Abstract only.
b One person was excluded from the docetaxel group after randomisation for a good clinical practice violation.

TABLE 10 Key patient characteristics

Trial	Median age, years (range)	% male	Stage IIIB (%)	Stage IV (%)	Histology, adenocarinoma/ squamous (%)	Previous treatment	PS	Ethnicity	Smoking status (%)
Gefitinib vs. erlotinib									
Kim *et al.* 2012[32]	60 (37–83)	14.6	14.6	72.9	Adenocarinoma, 91.7; squamous, 6.3	Placebo treatment = 96.9%	ECOG score of: • 1, 85.4% • 2, 14.6%	Korean[a]	Current/former, 8.3; never, 91.7
	56 (32–81)	14.6	10.4	70.8	Adenocarinoma, 89.6; squamous, 6.3	Placebo treatment = 100%	ECOG score of: • 1, 85.4% • 2, 14.6%	Korean[a]	Current/former, 4.2; never, 95.8
Gefitinib vs. docetaxel									
[b]Bhatnagar *et al.* 2012[33]	NR	NR	NR	NR	NR	NR	ECOG score of 0 to 2	Indian[a]	NR
	NR	NR	NR	NR	NR	NR	ECOG score of 0 to 2	Indian[a]	NR
INTEREST 2008[34]	61 (27–84)	63.6	At diagnosis: 25	At diagnosis: 52.9	Adenocarinoma, 53.9; squamous, 25.2	1 = 84.4%; 2 = 15.3%; 3 = 0.3%	WHO score of: • 0, 29.7% • 1, 58.4% • 2, 11.7%	White, 75%; Asian, 21%; black, 1.4%; other, 2.6%	Ever, 79.8; never, 20.2
	60 (20–84)	66.6	At diagnosis: 28.8	At diagnosis: 52.3	Adenocarinoma, 54.8; squamous, 24	1 = 83.2%; 2 = 16.8%; 3 = 0	WHO score of: • 0, 24.7% • 1, 63.2% • 2, 11.5%	White, 73.7%; Asian, 23.1%; black, 1.6%; other, 1.6%	Ever, 79.6; never, 20.5

Trial	Median age, years (range)	% male	Stage IIIB (%)	Stage IV (%)	Histology, adenocarinoma/ squamous (%)	Previous treatment	PS	Ethnicity	Smoking status (%)
ISTANA 2010[35]	57 (21–74)	67.1	13.4 (LA)	86 (Met)	Adenocarinoma, 65.9; squamous, 20.7	1 (placebo-doublet)	WHO score of: • 0, 2.4% • 1, 90.2% • 2, 7.3%	Korean and East Asian	Ex, 62.2; regular, 1.2; never, 36.6
	58 (20–73)	57	17.7	82.3	Adenocarinoma, 69.6; squamous, 13.9	1 (placebo-doublet)	WHO score of: • 0, 3.8% • 1, 89.9% • 2, 6.3%	Korean and East Asian	Ex, 54.4; regular, 0; never, 45.6
Li *et al.* 2010[36]	50.7	60	58	42	Adenocarinoma, 56; squamous, 44	CIS + GEM/VIN; or GEM/VIN monotherapy	KPS score of ≥ 70	Chinese	NR
	48.2	60	60	40	Adenocarinoma, 56; squamous, 44	CIS + GEM/VIN; or GEM/VIN monotherapy	KPS score of ≥ 70	Chinese	NR
SIGN 2006[37]	63 (34–85)	69	NR	60	NR	1 = 97.1%	WHO score of: • 0, 19.1% • 1, 44.1% • 2, 36.8%	Caucasian 41.2%; Hispanic 48.5%; oriental 4.4%; other 5.9%	Yes, 67.6; no, 26.5; unknown, 5.9
	59.5 (29–83)	51	NR	56	NR	1 = 98.6%	WHO score of: • 0, 15.1% • 1, 56.2% • 2, 28.8%	Caucasian, 43.8%; black, 2.7%; Hispanic, 39.7%; oriental, 5.5%; other, 8.2%	Yes, 67.1; no, 24.7; unknown, 8.2
V-15-32[38]	≤ 64 = 56.3%; ≥ 65 = 43.7%	61.6	19.2	64.9	Adenocarinoma, 78.4; squamous, 15.1	1: 86.5%; 2: 13.5%	WHO score of: • 0, 34.7% • 1, 60.8% • 2, 4.5%	Japanese[a]	Ever, 71; never, 29
	≤ 64: 55.3%; ≥ 65: 44.7%	61.9	20.5	61.5	Adenocarinoma, 77; Squamous 16.8	1: 82.4%; 2: 17.2%	WHO score of: • 0, 38.1% • 1, 57.8% • 2, 4.1%	Japanese[a]	Ever, 64.3; never, 35.7

continued

TABLE 10 Key patient characteristics (*continued*)

Trial	Median age, years (range)	% male	Stage IIIB (%)	Stage IV (%)	Histology, adenocarinoma/ squamous (%)	Previous treatment	PS	Ethnicity	Smoking status (%)
Gefitinib vs. placebo									
ISEL 2005[39]	62 (28–90)	67	21 (LA)	79 (Met)	Adenocarinoma, 45; squamous, 35	0 = 1 person; 1 = 49%; 2 = 50%; ≥ 3 = 1%	WHO score of: • 0, 12% • 1, 53% • 2, 29% • ≥ 3, 5%	White, 75%; Asian, 21%; black, 1%; other, 4%	Habitual, 17; occasional, 1; ex, 60; never, 22
	61 (31–87)	67	20 (LA)	80 (Met)	Adenocarinoma, 45; squamous, 33	0 = 1 person; 1 = 49%; 2 = 50%; ≥ 3 = 1%	WHO score of: • 0, 12% • 1, 56% • 2, 26% • ≥ 3, 5%	White, 77%; Asian, 19%; black, 1%; other, 4%	Habitual, 16; occasional, 1; ex, 60; never, 22
Erlotinib vs. docetaxel									
[b]DELTA 2013[40]	NR	NR	NR	NR	NR	NR	ECOG score of 0 to 2	Japanese[a]	NR
	NR	NR	NR	NR	NR	NR	ECOG score of 0 to 2	Japanese[a]	NR
TAILOR 2013[41]	66 (40–81)	71	NR	NR	Adenocarinoma, 63; squamous, 28	1 = 92%	ECOG score of: • 0, 48% • 1, 44% • 2, 8%	White, 99%; Asian, 1%	Current/former, 83; never, 17
	67 (35–83)	66	NR	NR	Adenocarinoma, 75; squamous, 21	1 = 93%	ECOG score of: • 0, 48% • 1, 45% • 2, 6%	White, 99%; Asian, 1%	Current/former, 73; never, 27

Trial	Median age, years (range)	% male	Stage IIIB (%)	Stage IV (%)	Histology, adenocarinoma/ squamous (%)	Previous treatment	PS	Ethnicity	Smoking status (%)
Erlotinib vs. docetaxel/pemetrexed									
TITAN 2012[42]	59 (36–80)	79	20	80	Adenocarinoma, 47; squamous, 38	Placebo–doublet: PAX/GEM/docetaxel/VIN	ECOG score of: • 0, 14% • 1, 67% • 2, 19%	Caucasian, 85%; Asian, 14%; other, 1%	Present, 56; past, 29; never, 15
	59 (22–79)	72	23	77	Adenocarinoma, 52; squamous, 35	Placebo–doublet: PAX/GEM/docetaxel/VIN	ECOG score of: • 0, 10% • 1, 69% • 2, 21%	Caucasian, 86%; Asian,12%; other, 2%	Present, 51; past, 29; never, 20
Erlotinib vs. placebo									
BR.21 2005[31]	62 (34–87)	64.5	NR	NR	Adenocarinoma, 50.4; squamous, 29.5	1 = 50.6%; ≥ 2 = 49.4%	ECOG score of: • 0, 13.1% • 1, 52.5% • 2, 25.8% • 3, 8.6%	Asian, 12.9%; other, 87.1%	Current/ever, 73.4; unknown, 5.3; never, 21.3
	59 (32–89)	65.8	NR	NR	Adenocarinoma, 49; squamous, 32.1	1 = 50.2%; ≥ 2 = 49.8%	ECOG score of: • 0, 14% • 1, 54.3% • 2, 23% • 3, 8.6%	Asian, 12.2%; other, 87.8%	Current/ever, 77; unknown, 5.8; never, 17.3

CIS, cisplatin; GEM, gemcitabine; LA, locally advanced; Met, metastatic; NR, not reported; PAX, paclitaxel; VIN, vinorelbine.
a Assumed from reported area of recruitment area.
b Abstract only.

Six,[32,33,35,36,38,40] of the 12 trials were conducted in East Asia and, therefore, exclusively included patients of East Asian ethnicity. With the exception of SIGN,[37] the patients in the remaining trials were predominantly white/Caucasian. When reported, the percentage of never-smokers ranged across the trials from approximately 17%[42] to 94%.[32]

Assessment of effectiveness

The AG's assessment of effectiveness is based on the following patient groups:

1. previously treated adult patients with locally advanced or metastatic NSCLC and who exhibit EGFR-activating mutations (referred to as EGFR M+ population)
2. previously treated adult patients with locally advanced or metastatic NSCLC and who do not exhibit EGFR-activating mutations (referred to as EGFR M– population)
3. previously treated adult patients with locally advanced or metastatic NSCLC and for whom EGFR mutation status is unknown or indeterminate (referred to as EGFR unknown population).

Epidermal growth factor mutation-positive population

Six trials reported subgroup data on EGFR M+ patients. Kim *et al.*,[32] V-15-32[38] and TITAN[42] reported subgroup data in the main paper. BR.21,[31,43] ISEL[39,44] and INTEREST[34,45] reported subgroup data in a separate publication.

Overall survival

Four trials reported OS, one trial reported only the number of events[39,44] and three presented hazard ratios (HRs).[31,34,42] The HRs were not statistically significant for any of the comparisons described. *Table 11* summarises the results.

Progression-free survival

Four trials reported limited data for PFS (*Table 12*). Kim *et al.*[32] reported median PFS and ISEL[39] reported the number of events in each arm. TITAN[42] found no statistically significant difference between erlotinib and docetaxel/pemetrexed. Only INTEREST[34] found a statistically significant difference in PFS favouring gefitinib [HR 0.16, 95% confidence interval (CI) 0.05 to 0.49].

TABLE 11 Epidermal growth factor mutation positive: OS

Study name	% of deaths in intervention arm (number of events/ number randomised)	% of deaths in control arm (number of events/ number randomised)	Median OS (months)	HR (95% CI)	*p*-value
Gefitinib vs. docetaxel					
INTEREST[34]	72.73 (32/44 over both arms)		14.2 vs. 16.6	0.83 (0.41 to 1.67)	0.60
Gefitinib vs. BSC					
ISEL[39]	33.33 (7/21)	0.60 (3/5)	NR	NR	NR
Erlotinib vs. docetaxel/pemetrexed					
TITAN[42]	NR	NR	19.3 vs. NR	1.19 (0.12 to 11.49)	0.88
Erlotinib vs. BSC					
BR.21[31]	NR	NR	10.9 vs. 8.3	0.55 (0.25 to 1.19)	0.12

CI, confidence interval; NR, not reported.

TABLE 12 Epidermal growth factor mutation positive: PFS

Study name	% of patients who progressed in intervention arm (number of events/ number randomised)	% of patients who progressed in control arm (number of events/ number randomised)	Median PFS (months)	HR (95% CI)	*p*-value
Gefitinib vs. docetaxel					
INTEREST[34]	NR	NR	7.0 vs. 4.1	0.16 (0.05 to 0.49)	0.001
Gefitinib vs. BSC					
ISEL[39]	52.38 (11/21)	0.80 (4/5)	NR	NR	NR
Gefitinib vs. erlotinib					
Kim *et al.*[32]	NR	NR	11.9 over both arms	NR	NR
Erlotinib vs. docetaxel/pemetrexed					
TITAN[42]	NR	NR	NR	0.71 (0.13 to 3.97)	NR

NR, not reported.

Response rate

Five trials reported data on RR (*Table 13*). The three trials that presented data separately by treatment[32,34,38] found that gefitinib appears to be favoured compared with docetaxel or erlotinib. However, patient numbers in the trials are small, and only one study[34] presented a *p*-value of 0.04 to indicate that the difference between gefitinib and docetaxel was statistically significant. Two studies[31,39] presented RRs for gefitinib versus BSC and erlotinib versus BSC of 37.50%[39] and 26.67% respectively.[31]

TABLE 13 Epidermal growth factor mutation positive: RR

Study name	RR in intervention arm (%) (number responded/ number randomised)	RR in control arm (%) (number responded/ number randomised)	Overall RR (%) (number responded/ number randomised)	*p*-value
Gefitinib vs. docetaxel				
INTEREST[34]	42.11 (8/19)	21.05 (4/19)	NR	0.04
V-15-32[38]	66.67 (6/9)	45.45 (5/11)	NR	NR
Gefitinib vs. BSC				
[a]ISEL[39]	NR	NR	37.50 (6/16)	NR
Gefitinib vs. erlotinib				
Kim *et al.*[32]	66.70 (NR)	62.50 (NR)	76.47 (13/17)	NR
Erlotinib vs. BSC				
BR.21[31]	NR	NR	26.67 (4/15)	0.035

NR, not reported.
a ISEL reported objective RR.

Epidermal growth factor mutation-negative population

Five trials reported subgroup data on EGFR M– patients.[31,32,34,37,42] The DELTA trial included patients with and without activating mutations and whose EGFR status was known prior to their randomisation into the trial. TAILOR[41] included only patients who were known to be EGFR M–.

Trials of gefitinib are included here for completeness only.

Overall survival

Six trials reported data for OS, although ISEL[39] reported only the number of events in each trial arm (*Table 14*). The other five trials[31,34,40–42] reported HRs; however, these were not statistically significant for any of the comparisons described.

Progression-free survival

Six trials reported PFS (*Table 15*),[32,34,39–42] although ISEL[39] reported only the number of events in each treatment group and Kim *et al.*[32] reported PFS for EGFR M– patients overall rather than for each treatment group separately. Two trials reported HRs that were not statistically significant.[34,42] In two other trials,[40,41] PFS was statistically significantly greater in the docetaxel arm than in the erlotinib arm [HR 1.39, 95% CI 1.06 to 1.82 (unadjusted), and HR 1.44, 95% CI 1.08 to 1.92 (adjusted)].

Response rate

Five trials reported data on RR (*Table 16*). Only one trial[34] reported a *p*-value ($p = 0.37$) indicating that there was no statistically significant difference between the groups. One other trial[41] reported a *p*-value ($p = 0.003$) indicating that there was a statistically significant difference in RR, favouring docetaxel.

TABLE 14 Epidermal growth factor mutation negative: OS

Study name	% of deaths in intervention arm (number of events/ number randomised)	% of deaths in control arm (number of events/ number randomised)	Median OS (months)	HR (95% CI)	*p*-value
Gefitinib vs. docetaxel					
INTEREST[34]	84.98 (215/253 over both arms)		6.4 vs. 6.0	1.02 (0.78 to 1.33)	0.91
Gefitinib vs. BSC					
ISEL[39]	70.45 (93/132)	64.91 (37/57)	NR	NR	NR
Erlotinib vs. docetaxel					
TAILOR[41]	NR	NR	5.4 vs. 8.2	1.37 (1.00 to 1.89) (adjusted) 1.28 (0.95 to 1.96) (unadjusted)	0.05 0.10
DELTA[40]	NR	NR	9.0 vs. 9.2	0.98 (0.69 to 1.39)	0.914
Erlotinib vs. docetaxel/pemetrexed					
TITAN[42]	NR	NR	6.6 vs. 4.4	0.85 (0.59 to 1.22)	0.37
Erlotinib vs. BSC					
BR.21[31]	NR	NR	7.9 vs. 3.3	0.74 (0.52 to 1.05)	0.09

NR, not reported

TABLE 15 Epidermal growth factor mutation negative: PFS

Study name	% of deaths in intervention arm (number of events/ number randomised)	% of deaths in control arm (number of events/ number randomised)	Median PFS (months)	HR (95% CI)	*p*-value
Gefitinib vs. docetaxel					
INTEREST[34]	NR	NR	1.7 vs. 2.6	1.24 (0.94 to 1.64)	0.14
Gefitinib vs. BSC					
ISEL[39]	84.09 (111/132)	85.96 (49/57)	NR	NR	NR
Gefitinib vs. erlotinib					
Kim *et al.*[32]	NR	NR	2.8 months overall	NR	NR
Erlotinib vs. docetaxel					
TAILOR[41]	NR	NR	2.4 vs. 2.9	1.41 (1.05 to 1.89) (adjusted); 1.39 (1.06 to 1.82) (unadjusted)	0.02; 0.01
DELTA[40]	NR	NR	1.3 vs. 2.9	1.44 (1.08 to 1.92)	0.013
Erlotinib vs. docetaxel/pemetrexed					
TITAN[42]	90.67 (68/75)	79.73 (59/74)	NR	1.25 (0.88 to 1.78)	0.20

NR, not reported.

TABLE 16 Epidermal growth factor mutation negative: RR

Study name	RR in intervention arm (%) (number responded/ number randomised)	RR in control arm (%) (number responded/ number randomised)	Overall RR (%) (number responded/ number randomised)	*p*-value
Gefitinib vs. docetaxel				
INTEREST[34]	6.60 (7/106)	9.76 (12/123)	NR	0.37
Gefitinib vs. BSC				
[a]ISEL[39]	NR	NR	2.59 (3/116)	NR
Gefitinib vs. erlotinib				
Kim *et al.*[32]	NR	NR	25.00 (8/32)	NR
Erlotinib vs. docetaxel				
TAILOR[41]	3 (3/100)	15.46 (15/97)	NR	0.003
Erlotinib vs. BSC				
BR.21[31]	NR	NR	6.93 (7/101)	NR

NR, not reported.
a ISEL reported objective RR.

Overall population: epidermal growth factor mutation status unknown

Four trials[33,35–37] considered the overall population without distinguishing between patients' EGFR mutation status. There are no data available from the Bhatnagar *et al.*[33] study as this study is published as an abstract only; the AG contacted the authors and asked for additional study data, but no reply was received.

Eight trials reported data for the overall population and also performed subgroup analyses based on EGFR mutation status.[31,32,34,35,37–39,42] TAILOR[41] reported overall population data which comprised EGFR M– patient data only.

Overall survival

Eight trials reported data on OS for the overall population (*Table 17*).[31,34–40,42] Five trials[34–38] compared gefitinib with docetaxel. A median survival of 7.1 months for gefitinib and 6.9 months for docetaxel were the only data available from Li *et al.*[36] The other four trials presented HRs, but no statistically significant differences between the interventions were noted.

No statistically significant difference in survival was reported between gefitinib and BSC,[39] between erlotinib and docetaxel[40] or between erlotinib and docetaxel/pemetrexed.[42]

BR.21[31] found a statistically significant difference in OS, favouring erlotinib over BSC (HR 0.7.0, 95% CI 0.58 to 0.85). However, the authors presented only adjusted analyses, no details were presented describing the unadjusted analyses.

TABLE 17 Epidermal growth factor mutation status unknown: OS

Study name	% of deaths in intervention arm (number of events/ number randomised)	% of deaths in control arm (number of events/ number randomised)	Median OS (months)	HR (95% CI)	*p*-value
Gefitinib vs. docetaxel					
INTEREST[34]	82.02 (593/723)	81.13 (576/710)	7.6 vs. 8	PP: 1.02 (0.91 to 1.15)	0.47
				ITT: 1.015 (0.901 to 1.143)	NS
ISTANA[35]	81.71 (67/82)	74.68 (59/79)	14.1 vs. 12.2	0.87 (0.61 to 1.24)	0.437
Li *et al.*[36]	NR	NR	7.1 vs. 6.9	NR	NR
SIGN[37]	NR	NR	7.5 vs. 7.1	0.97 (0.61 to 1.52)	0.88
V-15-32[38]	63.67 (156/245)	61.48 (150/244)	11.5 vs. 14	1.12 (0.89 to 1.40)	0.33
Gefitinib vs. BSC					
ISEL[39]	NR	NR	5.6 vs. 5.1	0.89 (0.77 to 1.02)	0.087
Erlotinib vs. docetaxel					
DELTA[40]	NR	NR	14.8 vs. 12.2	0.91 (0.68 to 1.22)	0.527
Erlotinib vs. docetaxel/pemetrexed					
[a]TITAN[42]	NR	NR	5.3 vs. 5.5	0.96 (0.78 to 1.19)	0.73
Erlotinib vs. BSC					
BR.21[31]	77.46 (378/488)	86.01 (209/243)	6.7 vs. 4.7	0.70 (0.58 to 0.85)	< 0.001

NR, not reported; NS, not stated; PP, per protocol.
a Without the 30 patients with squamous cell carcinoma who received pemetrexed (HR 0.93; 95% CI 0.75 to 1.17, $p = 0.544$).

Progression-free survival

Nine trials reported data for PFS (*Table 18*). Four studies compared gefitinib with docetaxel.[34,35,37,38] In ISTANA,[35] PFS was statistically significantly longer in the gefitinib arm than in the docetaxel arm (HR 0.729, 90% CI 0.533 to 0.988); however, if using a 95% CI as was planned in the published paper, the CI would range from 0.51 to 1.05 and the difference in PFS is no longer statistically significant. The other three trials[34,37,38] found no statistically significant differences in PFS between the groups.

Neither TITAN[42] nor DELTA[40] found any statistically significant differences between erlotinib and docetaxel/pemetrexed or between erlotinib and docetaxel. In BR.21[31] a statistically significant difference in PFS favouring erlotinib compared with BSC was reported (HR 0.61, 95% CI 0.51 to 0.74); the authors of BR.21[31] presented the results of adjusted analyses only. ISEL[39] found a statistically significant difference in PFS favouring gefitinib compared with BSC (HR 0.82; 95% CI 0.73 to 0.92); the authors only presented adjusted analyses. The only data that were available from the head-to-head comparison of gefitinib compared with erlotinib was a median PFS of 4.9 versus 3.1 months.[32]

TABLE 18 Epidermal growth factor mutation status unknown: PFS

Study name	% of deaths in intervention arm (number of events/ number randomised)	% of deaths in control arm (number of events/ number randomised)	Median PFS (months)	HR (95% CI)	*p*-value
Gefitinib vs. docetaxel					
INTEREST[34]	82.02 (593/723)	76.62 (544/710)	2.2 vs. 2.7	1.04 (0.93 to 1.18)	NR
ISTANA[35]	74.39 (61/82)	74.68 (59/79)	3.3 vs. 3.4	0.729[a] (0.533 to 0.988) (unadjusted)	0.0441
				0.634[a] (0.459 to 0.875) (adjusted)	0.0134
SIGN[37]	NR	NR	3.0 vs. 3.4	0.94 (0.64 to 1.39)	0.76
V-15-32[38]	90.00 (180/200)	84.49 (158/187)	2.0 vs. 2.0	0.90 (0.72 to 1.12)	0.335
Gefitinib vs. BSC					
ISEL[39]	NR	NR	3.0 vs. 2.6	0.82 (0.73 to 0.92)	0.0006
Gefitinib vs. erlotinib					
Kim *et al.*[32]	NR	NR	4.9 vs. 3.1	NR	NR
Erlotinib vs. docetaxel					
DELTA[40]	NR	NR	2.0 vs. 3.2	1.22 (0.97 to 1.55)	0.092
Erlotinib vs. docetaxel/pemetrexed					
TITAN[42]	92.61 (188/203)	83.26 (184/221)	6.3 weeks vs. 8.6 weeks	1.19 (0.97 to 1.46)	0.089
Erlotinib vs. BSC					
BR.21[31]	92.21 (450/488)	95.47 (232/243)	2.2 vs. 1.8	0.61 (0.51 to 0.74)	< 0.001

NR, not reported.
a 90% CI used.

Response rate

Nine trials reported data for RR (*Table 19*). Five of these compared gefitinib with docetaxel; the RR in the gefitinib arm ranged from 9.10% to 28.10% and the RR in the docetaxel arm ranged from 7.60% to 18.75%. INTEREST[34] and V-15-32[38] both reported odds ratios, although only V-15-32[38] found a statistically significant difference between the two groups favouring gefitinib over docetaxel. In addition, one trial found a statistically significant difference in RR favouring gefitinib when compared with BSC.[39]

Meta-analysis and network meta-analysis

Meta-analysis can be used to integrate the results of multiple trials which directly compare one specific treatment with another to produce an overall estimate of treatment effect size. Network meta-analysis can be used to compare effect sizes of treatments which have not previously been directly compared in a RCT using a common treatment comparator. After careful consideration of the clinical evidence available, the AG concluded that it would be inappropriate to use meta-analysis or network meta-analysis to investigate the treatment effects of erlotinib or gefitinib. The AG has identified several clinical and methodological weaknesses in the available clinical data which preclude use of quantitative synthesis methods.

First, the major weakness is the lack of available clinical data describing the key patient populations. There are no reliable OS or PFS data available for the comparison of erlotinib or gefitinib with any comparator in patients who are EGFR M+ and who have been previously treated. The AG agrees with the manufacturer of gefitinib, which states in its manufacturer's submission that 'All options for meta-analysis (direct, indirect and multiple treatment comparison) have been explored, however, all options were limited by heterogeneity in important clinical factors and ultimately such analyses were deemed more likely to increase rather than reduce uncertainty'.[46]

TABLE 19 Epidermal growth factor mutation status unknown: RR

Study name	RR in intervention arm (%) (number responded/ number randomised)	RR in control arm (%) (number responded/ number randomised)	Overall RR: odds ratio (95% CI)	*p*-value
Gefitinib vs. docetaxel				
INTEREST[34]	9.10 (NR)	7.60 (NR)	1.22 (0.82 to 1.84)	0.33
ISTANA[35]	28.10 (NR)	7.60 (NR)	NR	NR
Li *et al.*[36]	22.44 (11/49)	18.75 (9/48)	NR	NR
SIGN[37]	13.24 (9/68)	13.70 (10/73)	NR	NR
V-15-32[38]	22.50 (45/200)	12.80 (24/187)	2.14 (1.21 to 3.78)	0.009
Gefitinib vs. BSC				
[a]ISEL[39]	8.00 (77/959)	1.00 (6/480)	7.28 (3.10 to 16.90)	< 0.0001
Gefitinib vs. erlotinib				
Kim *et al.*[32]	47.92 (23/48)	39.58 (19/48)	NR	NR
Erlotinib vs. docetaxel/pemetrexed				
TITAN[42]	7.88 (16/203)	6.33 (14/221)	NR	NR
Erlotinib vs. BSC				
BR.21[31]	8.90 (NR)	Less than 1 (NR)	NR	NR

NR, not reported.
a ISEL reported objective RR.

For the EGFR M– population, median OS and PFS data are available from four trials.[31,34,40,41] As DELTA[40] is made up of Japanese patients for whom there no patient characteristics data are available, the AG could not include the results from this trial in a network meta-analysis. The AG does not consider that INTEREST,[34] BR.21[31] and TAILOR[41] include patient populations that are sufficiently similar to be included in a network meta-analysis. To illustrate: both TAILOR[41] and INTEREST[34] included a higher proportion of patients (93% and 89%, respectively) with PS score 0 or 1 than BR.21[31] (70%); TAILOR[41] and INTEREST[34] included mainly patients who had received only one prior chemotherapy (92% and 84%, respectively) whereas this applied to only 50% of participants in BR.21[31] (50%); and TAILOR[41] has a higher rate of adenocarcinoma patients (70%) than either INTEREST[34] (54%) or BR.21[31] (50%).

There are survival data available from eight trials that included patients whose EGFR mutation status was unknown at the time of analysis, that is the trials included both EGFR M+ and EGFR M– status patients.[31,34–39,42] A higher proportion of patients in the ISEL[39] trial (50%) than in the other trials had received more than one prior treatment, although it is difficult to know exactly how many prior treatments patients in Li *et al.*[36] and ISTANA[35] had undergone. It is therefore uncertain whether or not the patients in ISEL[39] are sufficiently similar to those in the other trials. In three trials ethnicity is a key differentiator (ISTANA,[35] South Korean patients; Li *et al.*,[36] Chinese patients; V-15-32,[38] Japanese patients) and the AG considers that including all Asian trials in a network meta-analysis may not yield relevant results for a non-Asian population. The remaining two trials[31,42] compared erlotinib with BSC and pemetrexed and/or docetaxel. The AG considers that the patients in TITAN[42] are different from the patients in BR.21,[31] as in TITAN[42] 100% of patients had received a single prior chemotherapy while in BR.21[31] 50% of patients had received two or more prior chemotherapies. In addition, outcome data were not reported separately for docetaxel- and pemetrexed-treated patients in TITAN,[42] and the AG notes that it has not been proved that docetaxel and pemetrexed are clinically equivalent when used in this patient population. For the assessment of PFS, data are available from eight trials;[31,34,35,37–40,42] no HR was reported in Kim *et al.*[32] The arguments outlined above for three trials[35,38,39] for the assessment of OS are valid again here. Further, the Kim *et al.*[32] trial is made up of Korean patients and the AG would not include this trial in a network meta-analysis designed to inform treatment pathways for patients in England and Wales. The arguments against using data from TITAN[42] and BR.21[31] in a network meta-analysis are valid again here for the assessment of PFS.

In addition to the lack of comparable clinical data available from the included trials, the AG also considers that a number of the trials used statistical methods that prohibit inclusion of the trial results in a network meta-analysis. To this end, the AG examined the methods of analyses and investigated the suitability of the Cox proportional hazards models employed; details are provided in *Table 20*. Specifically, for the EGFR unknown populations, the Kaplan–Meier plot crosses for six trials.[34,35,37–39,42] This is a sufficient condition to reject proportionality and means that the assumption behind the Cox proportional hazards model is violated, rendering the HR difficult to interpret. Crossing of Kaplan–Meier curves may be expected for small trials with few events. However, four of these trials are large with sample sizes ranging from 424 to 1692.[34,38,39,42] In addition, the AG has previously stated[2] that Kaplan–Meier plots of PFS for erlotinib and gefitinib have a different pattern to those relating to third-generation drugs in first-line studies, and it appears that Kaplan–Meier plots of PFS for several second-line trials exhibit similar differences in patterns. The proportional hazards assumption may therefore be invalid for all PFS comparisons between TKIs and standard chemotherapy. The AG considers that the use of conventional (Cox) proportional hazards methods to estimate HRs in trials of erlotinib and gefitinib compared with any other drug is problematic and that the HR results may not be accurate and should be viewed with caution. The AG concludes that conducting a network meta-analysis using data from these trials may produce unreliable results.

Finally, the AG notes that some trials report unadjusted and adjusted analyses, whereas others report only unadjusted or only adjusted analyses. This may be a form of selective reporting; for example, one set of outcomes is reported rather than the other so as to maximise the apparent effectiveness of one of the interventions. It is not sensible to combine adjusted and unadjusted results, as they may not be directly comparable. In particular, the unadjusted estimate from a Cox proportional hazards model is attenuated towards the null value, so heterogeneity is likely to be introduced when adjusted and unadjusted results

TABLE 20 Summary of analysis methods of included studies

Trial	Adjusted/unadjusted analysis presented	Cox proportional hazards model suitable	Statistical analysis
Gefitinib vs. docetaxel			
INTEREST[34]	Unadjusted for OS	K-M plot crosses for OS	'We used an unadjusted Cox proportional hazards model to estimate the overall survival HR and CI in the per-protocol population'[35]
	Adjusted and per-protocol for PFS	No K-M plot for PFS	To estimate the OS HR and CI in the per-protocol population, an unadjusted Cox proportional hazards model was used to estimate the HR for PFS in the evaluable-for-response population (patients in the per-protocol population with unidimensional disease according to RECIST) a Cox proportional hazards model with adjustment for sex, racial origin, histology, PS, smoking history, previous regimens, previous platinum and previous paclitaxel was used
ISTANA[35]	Unadjusted and adjusted presented for OS and PFS	K-M plot crosses for OS and PFS	To compare the treatment groups, an unadjusted Cox proportional hazards model was used to analyse PFS and OS (two-sided test at the 5% significance level, 95% CI). Supportive analyses using a Cox proportional hazards model were conducted with adjustment for gender, histology, smoking history, stage and performance status were also conducted
SIGN[37]	Adjusted for OS and PFS	K-M plot crosses for OS and PFS	'Overall and progression-free survival were analysed using a proportional hazards model that allowed for the effect of treatment and the covariates above (PS, sex and smoking history)'[38]
Li *et al.*[36]	NR	Yes	No details presented
V-15-32[38]	Unadjusted and adjusted presented (PFS-reported population)	K-M plot crosses for OS and PFS	Supportive analyses in the per-protocol population were conducted using a Cox regression model with covariate adjustment for sex, PS, tumour type, smoking history, number of prior chemotherapy regimens, age at random assignment, time from diagnosis to random assignment and best response to prior chemotherapy
Bhatnagar *et al.*[33]	NR	NR	Abstract only
Gefitinib vs. BSC			
ISEL[39]	Adjusted for OS. Unclear for PFS	K-M plot crosses for OS and time to treatment failure near to the top of the plot	A stratified log-rank test was used in the primary analysis of survival. The stratification factors were: sex, histology, PS, smoking history, number of previous regimens and reason for previous chemotherapy failure. A Cox's regression analysis was also conducted as a supportive analysis. This used a covariate adjustment for the same factors as the log-rank test

TABLE 20 Summary of analysis methods of included studies (*continued*)

Trial	Adjusted/unadjusted analysis presented	Cox proportional hazards model suitable	Statistical analysis
Gefitinib vs. erlotinib			
Kim *et al.*[32]	Unadjusted PFS. No OS	Yes	'A univariate analysis revealed that adenocarcinoma and activating EGFR mutation status were significant factors associated with longer PFS. A multivariate analysis revealed that adenocarcinoma histology was the only independent predictor affecting prolongation of PFS'[32]
Erlotinib vs. docetaxel			
TAILOR[41]	Unadjusted and adjusted reported for OS and PFS	Yes. Schoenfeld residuals considered	'Time-to-event data were analysed by the K-M method. Cox proportional hazards model was used to adjust the treatment effect for histology, smoking habit'[41]
TITAN[42]	Unadjusted for both OS and PFS	K-M plot crosses towards the tail for PFS. K-M plot crosses in the middle for OS	Adjusted analyses included in appendices but primary are unadjusted
DELTA[40]	NR	NR	Abstract only
Erlotinib vs. BSC			
BR.21[31]	Yes	Yes	In order to adjust for treatment effect and to identify prognostic factors for PFS and OS, exploratory forward stepwise regression analyses using the Cox model were conducted. Covariates explored included EGFR expression, stratification factors (except centre), sex, age, race or ethnic group, prior radiotherapy, histological subtype of cancer and smoking status

K-M, Kaplan–Meier; NR, not reported; PR, partial response.

are combined again, rendering results from a network meta-analysis difficult to interpret. For the EGFR unknown results, three trials report adjusted analyses only for OS[31,32,39] and four only for PFS.[31,34,37,39] In BR.21,[31] erlotinib is statistically significantly more effective than BSC in terms of both OS and PFS, and in ISEL[39] gefitinib is statistically significantly more effective than BSC.

In summary, the AG considers that because of the clinical and statistical weaknesses identified in the available clinical data, it would be inappropriate to carry out any meta-analysis or network meta-analysis to assess treatment effects of erlotinib or gefitinib in any patient population after progression following chemotherapy.

Quality of life

Quality of life data are presented in 10 trials for the overall EGFR unknown population and are summarised in *Table 21*. QoL data from TAILOR[41] and DELTA[40] are not yet available.

Gefitinib

Six trials compared gefitinib and docetaxel. The results of four of these studies favoured gefitinib,[33,34,36,38] although no data were available from Bhatnagar *et al.*[33] to confirm their conclusions. Two studies found no statistically significant differences between gefitinib and docetaxel.[35,37] One trial compared gefitinib to BSC,[39] and changes in QoL were similar in the two groups. In the comparison of erlotinib and gefitinib[32] no statistically significant difference in QoL was noted.

TABLE 21 Summary of QoL results

Trial	Number of respondents	Measurement tool	Author summary
Gefitinib vs. docetaxel			
INTEREST[34]	Gefitinib, $n = 490$; docetaxel, $n = 476$	FACT-L every 3 weeks until treatment discontinuation	Significantly more patients had sustained a clinically relevant improvement in QoL with gefitinib than with docetaxel
ISTANA[35]	Gefitinib, $n = 68$; docetaxel, $n = 66$	FACT-L every 3 weeks	Similar proportions of patients in each treatment group experienced an improvement
SIGN[37]	Gefitinib, $n = 85\%$; docetaxel, $n = 87\%$	FACT-L every 3 weeks until treatment discontinuation	Mean FACT-L score change from baseline to end point were similar for both groups
Li *et al.*[36]	NR	The improvements of symptoms and QoL were focused on the observation of cough, shortness of breath, chest tightness, fatigue and KPS scores	The improvement rate of symptoms and QoL for the patients in the gefitinib group was higher than that in the docetaxel group, resulting in a significant difference in the two groups
V-15-32[38]	Gefitinib, $n = 185$; docetaxel, $n = 173$	FACT-L questionnaire at baseline and every 4 weeks during study treatment until week 12	Gefitinib showed statistically significant benefits compared with docetaxel in QoL improvement rates but there were no significant differences between treatments in lung cancer symptoms improvement rates
Bhatnagar *et al.*[33]	NR	NR	Improvement in QoL for gefitinib patients
Gefitinib vs. BSC			
ISEL[39]	Paper states that about 85% of patients completed the FACT-L	FACT-L questionnaire every 4 weeks	In the overall population, changes in QoL were similar in the gefitinib and BSC groups
Gefitinib vs. erlotinib			
Kim *et al.*[32]	NR	EORTC QLQ-C30-Version 3.0	There was no significant difference in QoL between the two arms
Erlotinib vs. docetaxel			
TAILOR[41]	NR	NR	NR
TITAN[42]	Completion rates were around 90% at the baseline visit and remained above 80%	FACT-L, version 4 at baseline, every 3 weeks until week 48, and every 12 weeks thereafter until disease progression or the end of the study	There was no statistically significant difference in the time to symptom progression (or time to deterioration) in QoL in the two treatment groups
DELTA[40]	NR	NR	NR
Erlotinib vs. BSC			
BR.21[31]	Compliance was 87% at baseline and more than 70% during treatment	QLQ-C30 every 4 weeks	Significant improvement in global QoL for erlotinib patients compared with BSC

EORTC, European organisation for research and treatment of cancer; FACT-L, Functional Assessment of Cancer Therapy-Lung; NR, not reported; QLQ, Quality of Life Questionnaire.

Erlotinib

Erlotinib was found to significantly improve QoL in comparison with BSC.[31] No statistically significant difference in QoL was reported between erlotinib and docetaxel in TITAN.[42]

Incidence of grade 3 or 4 adverse events

In 9 of the 12 studies,[31,32,34,35,37–39,41,42] grade 3 and 4 AEs were presented for the overall population only (*Table 22*). In the remaining three trials, only limited AE data are reported; DELTA[40] and the Bhatnagar *et al.*[33] trial are reported in abstract format only and therefore do not describe AEs, and the investigators in the Li *et al.*[36] trial did not provide detailed AE data.

TABLE 22 Incidence of grade 3 and 4 AEs

Study	BSC % (*n*/*N*)	Docetaxel % (*n*/*N*)	Erlotinib % (*n*/*N*)	Gefitinib % (*n*/*N*)
Fatigue				
TITAN[42]	NA	0.45 (0.5/111.8)	0 (0/196)	NA
SIGN[37]	NA	4.23 (3/71)	NA	5.88 (4/68)
INTEREST[34]	NA	8.95 (64/715)	NA	4.39 (32/729)
Kim *et al.*[32]	NA	NA	0 (0/48)	0 (0/48)
ISTANA[35]	NA	3.95 (3/76)	NA	1.23 (1/81)
V-15-32[38]	NA	2.51 (6/239)	NA	0.41 (1/244)
BR.21[31]	23.14 (56/242)	NA	18.97 (92/485)	NA
ISEL[39]	2.67 (15/562)	NA	NA	3.20 (36/1126)
TAILOR[41]	NA	9.62 (10/104)	5.61 (6/107)	NA
Diarrhoea				
TITAN[42]	NA	0 (0/111.8)	2.55 (5/196)	NA
SIGN[37]	NA	4.23 (3/71)	NA	2.94 (2/68)
INTEREST[34]	NA	3.08 (22/715)	NA	2.47 (18/729)
Kim *et al.*[32]	NA	NA	0 (0/48)	0 (0/48)
ISTANA[35]	NA	0 (0/76)	NA	1.23 (1/81)
V-15-32[38]	NA	0.84 (2/239)	NA	2.05 (5/244)
BR.21[31]	0.62 (1.5/242)	NA	5.77 (28/485)	NA
ISEL[39]	0.89 (5/562)	NA	NA	2.75 (31/1126)
TAILOR[41]	NA	1.92 (2/104)	2.80 (3/107)	NA
FN				
TITAN[42]	NA	0.89 (1/111.8)	0 (0/196)	NA
SIGN[37]	NA	2.82 (2/71)	NA	0 (0/68)
INTEREST[34]	NA	10.07 (72/715)	NA	1.23 (9/729)
Kim *et al.*[32]	NA	NA	0 (0/48)	0 (0/48)
ISTANA[35]	NA	0 (0/76)	NA	0 (0/81)
V-15-32[38]	NA	7.11 (17/239)	NA	0.82 (2/244)
BR.21[31]	0 (0/242)	NA	0 (0/485)	NA
ISEL[39]	0 (0/562)	NA	NA	0 (0/1126)
TAILOR[41]	NA	3.85 (4/104)	0 (0/107)	NA

continued

TABLE 22 Incidence of grade 3 and 4 AEs (*continued*)

Study	BSC % (*n*/*N*)	Docetaxel % (*n*/*N*)	Erlotinib % (*n*/*N*)	Gefitinib % (*n*/*N*)
Hair loss				
TITAN[42]	NA	0.45 (0.5/111.8)	0 (0/196)	NA
SIGN[37]	NA	0 (0/71)	NA	0 (0/68)
INTEREST[34]	NA	0 (0/715)	NA	0 (0/729)
Kim *et al.*[32]	NA	NA	0 (0/48)	0 (0/48)
ISTANA[35]	NA	0 (0/76)	NA	0 (0/81)
V-15-32[38]	NA	0 (0/239)	NA	0 (0/244)
BR.21[31]	0 (0/242)	NA	0 (0/485)	NA
ISEL[39]	0 (0/562)	NA	NA	0 (0/1126)
TAILOR[41]	NA	14.42 (15/104)	0 (0/107)	NA
Nausea/vomiting				
TITAN[42]	NA	0.45 (0.5/111.8)	0.51 (1/196)	NA
SIGN[37]	NA	2.82 (2/71)	NA	2.94 (2/68)
INTEREST[34]	NA	2.38 (17/715)	NA	0.96 (7/729)
Kim *et al.*[32]	NA	NA	0 (0/48)	0 (0/48)
ISTANA[35]	NA	0 (0/76)	NA	0 (0/81)
V-15-32[38]	NA	5.02 (12/239)	NA	3.69 (9/244)
BR.21[31]	2.69 (6.5/242)	NA	5.98 (29/485)	NA
ISEL[39]	0.71 (4/562)	NA	NA	1.95 (22/1126)
TAILOR[41]	NA	2.88 (3/104)	0.93 (1/107)	NA
Neutropenia				
TITAN[42]	NA	0.89 (1/111.8)	0 (0/196)	NA
SIGN[37]	NA	40.85 (29/71)	NA	1.47 (1/68)
INTEREST[34]	NA	56.78 (406/715)	NA	2.06 (15/729)
Kim *et al.*[32]	NA	NA	0 (0/48)	0 (0/48)
ISTANA[35]	NA	0 (0/76)	NA	0 (0/81)
V-15-32[38]	NA	73.64 (176/239)	NA	8.20 (20/244)
BR.21[31]	0 (0/242)	NA	0 (0/485)	NA
ISEL[39]	0 (0/562)	NA	NA	0 (0/1126)
TAILOR[41]	NA	20.19 (21/104)	0 (0/107)	NA
Rash				
TITAN[42]	NA	0 (0/111.8)	4.59 (9/196)	NA
SIGN[37]	NA	2.82 (2/71)	NA	2.94 (2/68)
INTEREST[34]	NA	0.56 (4/715)	NA	2.06 (15/729)
Kim *et al.*[32]	NA	NA	10.42 (5/48)	2.08 (1/48)
ISTANA[35]	NA	1.32 (1/76)	NA	6.17 (5/81)
V-15-32[38]	NA	0.42 (1/239)	NA	0.41 (1/244)
BR.21[31]	0 (0/242)	NA	9.07 (44/485)	NA
ISEL[39]	0.18 (1/562)	NA	NA	1.60 (18/1126)
TAILOR[41]	NA	0 (0/104)	14.02 (15/107)	NA

FN, febrile neutropenia; NA, not applicable.

Each study reported AEs in different ways. ISEL[39] reported AEs that occurred in more than 5% of either treatment group or with a difference of at least 3% between treatment groups. TITAN[42] reported those that occurred in at least 2% of patients in either group. V-15-32[38] reported the most common AEs, which were considered to be those that occurred in more than 10% of the study population or that occurred with more than a 5% difference between treatments. Two studies[34,37] reported AEs that occurred in more than 10% in either group. ISTANA[35] reported the most common AEs, which were considered to be those occurring in at least 10% of patients in either treatment group. Three studies[31,32,41] simply reported AEs, and it was unclear if the data presented by the authors included all of the AEs that occurred during the trial.

In the Bhatnagar *et al.*[33] trial it was reported that gefitinib had a more favourable tolerability profile than docetaxel. In DELTA,[40] patients in the erlotinib arm experienced more rash and leucopenia than patients in the docetaxel arm. In the Li *et al.* trial[37] the incidence of rash was higher in the gefitinib group than in the docetaxel group ($p = 0.0296$) but the incidence of other side effects was similar in both groups.

The AG considers that the AEs reported appear to be consistent with the information available for erlotinib, gefitinib and docetaxel in the SPCs.[24]

Summary of clinical results

Epidermal growth factor mutation-positive population

- No trials were identified that were conducted in a population of solely EGFR M+ patients. Limited EGFR mutation status data were retrospectively derived from relatively small subgroup analyses of RCTs that included patients of unknown EGFR mutation status at the time of randomisation.
- Four studies reported OS outcomes,[31,34,39,42] none of which was statistically significantly different for any of the comparisons described.
- Five studies reported PFS,[31,32,34,39,42] but only one trial[36] found a statistically significant improvement for any comparison considered, and the results favoured gefitinib over docetaxel.

Epidermal growth factor mutation-negative population

- Key data were derived from results of TAILOR[41] and DELTA[40] trials.
- EGFR mutation status data were retrospectively derived from subgroup analyses in BR.21,[31,43] Kim *et al.*,[32] TITAN,[42] INTEREST,[34,45] and ISEL.[39,44]
- OS outcome: no statistically significant differences were noted for OS for either erlotinib or gefitinib compared with any treatment.
- PFS outcome: TAILOR[41] and DELTA[40] reported a statistically significant benefit of docetaxel compared with erlotinib. No statistically significant PFS benefit was reported from subgroup data.
- RR: patients in the docetaxel arm of TAILOR[41] had statistically significantly higher RRs than patients in the erlotinib arm.

Epidermal growth factor mutation unknown: overall population

- Data were available from 11 trials[31–41] carried out in populations in which EGFR mutation status was not a factor in the recruitment process (or in which overall trial results were presented).
- OS outcome: the only statistically significant OS benefit for any treatment was reported in BR.21[31] (erlotinib vs. placebo). However, this finding was based on an adjusted rather than an unadjusted analysis of the data.

- PFS outcome:
  - Gefitinib versus docetaxel – only one of the four trials (ISTANA[35]) reported a statistically significant benefit of gefitinib.
  - Gefitinib versus BSC – gefitinib was reported to have a statistically significant benefit.[39]
  - Erlotinib versus placebo (BR.21[31]) – a statistically significant PFS benefit of erlotinib was reported (in an adjusted analysis).
- RR: of the trials reporting RRs,[31,32,34–39,41] two noted significant differences in favour of gefitinib when compared with docetaxel[38] and BSC.[39]

Meta-analysis and network meta-analysis

For clinical and methodological reasons, no meta-analysis or network meta-analysis was conducted by the AG.

Quality of life

Where reported, the QoL data were derived from the EGFR unknown patients (overall population, i.e. the data are not specific to the EGFR mutation status of patients). All of the 12 trials included in this review measured QoL. However, the QoL outcomes from TAILOR[41] and DELTA[40] are not yet available.

Adverse events

Adverse events were reported for the overall population, that is the data are not specific to the EGFR mutation status of patients, with the exception of TAILOR.[41] Details of the AEs reported in Bhatnagar *et al.*,[33] Li *et al.*[36] and DELTA[40] were limited. The AG considers that the AEs reported, despite inconsistencies across trials, appear to be consistent with the information available for erlotinib, gefitinib and docetaxel in the SPCs.[24]

Discussion of clinical results

Erlotinib

Clinical evidence supporting the previously published NICE guidance TA162[21] (erlotinib for the treatment of NSCLC) issued in 2008 was based on the results of a single RCT, the BR.21[31] trial, that compared erlotinib with placebo. At the time of the appraisal of erlotinib in NICE TA162,[21] no direct evidence comparing erlotinib with docetaxel was available and, in the evidence submission to NICE, the manufacturer of erlotinib presented an indirect treatment comparison in which docetaxel was compared with BSC and pemetrexed. The Appraisal Committee (AC) did not consider the indirect treatment comparison to be robust and concluded that it was difficult to reach a decision as to the effectiveness of erlotinib compared with docetaxel. NICE guidance (TA162[21]) states that erlotinib is recommended, within its licensed indication, as an alternative to docetaxel as a second-line treatment option for patients with NSCLC only on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, AEs and monitoring costs) equal to that of docetaxel. The patient access scheme was then superseded to a simple discount patient access scheme following the publication of NICE TA227.[47] The price of erlotinib relevant to the NHS now is that of the list price minus the simple discount, as noted in the latest version of NICE TA162.[21]

Since the publication of NICE TA162,[21] three developments are worthy of note. First, the results of one RCT comparing erlotinib with chemotherapy (TITAN[42]) in a population of patients with unknown EGFR status have been published. The chemotherapy comparator was docetaxel or pemetrexed according to the treating physician's choice. Pemetrexed is licensed as a second-line treatment but is not recommended by NICE and therefore was not listed as a comparator in the decision problem for this appraisal. No statistically significant differences between erlotinib and chemotherapy were reported. The authors of the published paper[42] note that the choice of either docetaxel or pemetrexed was at the treating physician's

discretion and treatments were, therefore, not randomised. In addition, pemetrexed and docetaxel were not always available in all centres. For these reasons, the trial investigators published only outcomes for chemotherapy (i.e. aggregated), as the results of efficacy of erlotinib versus docetaxel and erlotinib versus pemetrexed were considered unreliable.

Second, the patent for docetaxel has expired. Docetaxel is now available generically at a considerably reduced price (less than 10% of its previous list price).[48] To date, NICE has not issued any statement suggesting that this lower price of docetaxel necessitates any change to the recommendations set out in NICE TA162.[21]

Third, clinical practice has also changed since the publication of NICE TA162,[21] with the identification of EGFR mutation status as a prognostic factor. Erlotinib is an EGFR-TKI and is licensed as a first-line treatment for patients with EGFR M+ tumours and as a second-line treatment for locally advanced or metastatic NSCLC regardless of EGFR mutation status. As noted previously, the majority of patients in clinical practice in England and Wales have their tumours histologically tested at diagnosis and prior to first-line treatment. Patients who are likely to have EGFR M+ tumours are also tested for activating mutations. Patients who test positive for EGFR-activating mutations are treated at first line with a TKI (either erlotinib or gefitinib), while those who are EGFR M– are treated with third-generation platinum-doublet chemotherapy or monotherapy. On progression, EGFR M+ patients are not re-treated with an EGFR-TKI and therefore receive docetaxel in line with current NICE guidance.[21] The AG is aware that some patients in the NHS are given platinum-doublet chemotherapy after first-line EGFR-TKI; however, this treatment pathway is not standard UK clinical practice. Patients who are EGFR M– are offered erlotinib or docetaxel. In summary, increased significance of EGFR mutation status in lung cancer treatment raises questions about how to treat both EGFR M+ and EGFR M– patients.

Two recent trials (TAILOR[41] and DELTA[40]) were both designed to compare the effectiveness of erlotinib versus docetaxel in EGFR M– patients. The results of TAILOR[41] are reported in a published paper, while the results of DELTA[40] are presently available only as a conference abstract from the American Society for Clinical Oncology in 2013. Since TAILOR[41] provides key data on the effectiveness of erlotinib compared with docetaxel in the EGFR M– population, further consideration of the trial and its relevance to clinical practice in England and Wales is warranted here.

TAILOR[41] was conducted in 52 hospitals in Italy and randomised patients to receive erlotinib ($n = 112$) or docetaxel ($n = 110$). While OS was not statistically significantly different between the two arms, there was a statistically significant benefit of docetaxel over erlotinib for PFS. The QoL data are not yet available.

TAILOR[41] has attracted a number of criticisms. First, the primary objective of the trial was changed at the first planned interim analysis. According to the published paper,[41] the trial was initially designed to assess the effects of docetaxel and erlotinib according to the biomarkers of EGFR amplification and protein expression, and *KRAS* mutations. When, after masked efficacy analysis, these biomarkers were found to have no effect, the independent monitoring and safety committee recommended that the primary objective of the trial be changed to a comparison of efficacy between erlotinib and docetaxel with a primary end point of OS.

Second, TAILOR[41] employed two regimens of docetaxel administration, either 75 mg/m^2 every 3 weeks or weekly infusions of 35 mg/m^2. The AG notes that this latter regimen would not be used in clinical practice in England and Wales.

Third, the fitness of the patients in TAILOR[41] is an important consideration. The patient population consisted of a majority of patients with an ECOG PS score of 0 or 1 and only 7% with a PS score of 2. This is unlikely to reflect patients in the NHS, in which a higher proportion of PS 2 patients would be treated in routine clinical practice. The AG is aware that PS is a prognostic factor in NSCLC and poorer PS is linked to poorer outcomes. However, the AG notes that the patient population in TAILOR[41] may reflect

future populations of patients seen in clinical practice in England and Wales as treatment for NSCLC continues to evolve. In modern clinical practice, patients are diagnosed earlier and treated more aggressively than in the past, which means that future patients may be fitter at second line than those currently receiving second-line treatments in England and Wales.

Fourth, there are differences in other important prognostic factors between the treatment arms of TAILOR.[41] There are differences in patient characteristics (docetaxel vs. erlotinib): never-smokers (27% vs. 17%), squamous cell (21% vs. 28%) and adenocarcinoma (75.55% vs. 63.00%). All of these differences have been identified as possible modifiers of trial outcome in favour of docetaxel.[48]

In its submission to NICE, the manufacturer of erlotinib has questioned the low rates of haematological toxicity in the docetaxel arm of TAILOR[41] [febrile neutropenia (FN) grade 3 or 4 = 4%, neutropenia grade 3 or 4 = 21%] in comparison with the INTEREST[34] trial (FN grade 3 or 4 = 10%, neutropenia grade 3 or 4 = 58%) and the JMEI[49] trial (FN grade 3 or 4 = 13%, neutropenia grade 3 or 4 = 40%). The manufacturer questions whether or not these low rates are related to the fitter patient population or the use of weekly treatment schedules. The AG considers that there may be another explanation, the increased clinical awareness of docetaxel-related AEs. Docetaxel has been used in the NHS for many years and it is likely that these related AEs are currently better managed and/or more frequently avoided than in the past.

In summary, it is open to debate how far TAILOR[41] reflects clinical practice in England and Wales and, therefore, whether or not the trial results are likely to be mirrored in a UK clinical population. TAILOR[41] is a large, high-quality RCT in a population of patients who do not have activating EGFR mutations. The trial is very relevant to patients in the UK, as it compares two lung cancer treatments that are currently recommended by NICE for the post-progression treatment of patients with NSCLC.

The specific details of DELTA[40] are as yet unavailable and so it is not possible to assess how far the Japan-based trial reflects clinical practice in England and Wales.

Gefitinib

In 2009, NICE was unable to recommend the use of gefitinib in the NHS for the second-line treatment of locally advanced or metastatic NSCLC because no evidence submission was received from the manufacturer or sponsor of the technology.[22]

The marketing authorisation for gefitinib granted by the European Medicines Agency[50] was based on the results of the first-line IRESSA Pan-Asia Study[51] trial and second-line INTEREST[34] trial. Supporting trials included ISEL,[39] SIGN,[37] V-15-32[38] and ISTANA.[35] The European Medicines Agency's European Public Assessment Report[52] reports that concerns were raised by the scientific advisory group about the data submitted by AstraZeneca (London, UK) in support of the licensing application for gefitinib. In particular, the advisory group noted a large number of missing data with respect to EGFR mutation status and considered that this aspect should have been controlled for by the design and conduct of the clinical studies. In this respect, the clinical studies presented were considered by the European Medicines Agency[52] to be inadequate. Three new trials of gefitinib have been published since 2009, which was when the European Medicines Agency[52] considered the application. The three trials were conducted in small populations of patients, Kim *et al.*[33] (vs. erlotinib), Li *et al.*[36] (vs. docetaxel) and Bhatnagar *et al.*[33] (vs. docetaxel), and the new data they provide are not sufficiently robust to permit recommendation of a change in clinical practice.

The AG notes, as does the manufacturer of gefitinib, that in clinical practice in England and Wales patients with EGFR M+ NSCLC should be diagnosed and treated appropriately (with a TKI) at first line. As noted above, patients who go on to second-line treatment will not be re-treated with the same therapy. It is likely, therefore, that the number of patients treated with gefitinib after progression will be limited to a very small minority who were not treated with a TKI at first line, perhaps as a result of lack of diagnostic facilities.

Meta-analysis and network meta-analysis

In view of the paucity of relevant data, the AG was unable to conduct either a meta-analysis or network meta-analysis in respect of the efficacy of treatments for patients with known EGFR M+, EGFR M– or EGFR unknown NSCLC.

The majority of the clinical evidence lies with the trials that included patients with NSCLC who were of unknown mutation status. Unfortunately, a number of issues precluded any comparison of the available data for patients with NSCLC of unknown mutation status, the issues were both clinical (differences in patient populations) and methodological (adjusted vs. unadjusted outcome data, Cox proportional hazards violations). However, even if the comparison could have been carried out, given the increased significance of EGFR mutation testing, its relevance to the current decision problem and to modern clinical practice is questionable.

From the 12 included RCTs, the most reliable evidence is from a study of the EGFR M– population. For this group of patients, the results of TAILOR[41] demonstrate that there is a statistically significant benefit of docetaxel over erlotinib for PFS; however, there is no statistically significant OS benefit demonstrated in this trial.

Chapter 4 Assessment of cost-effectiveness

This chapter presents a review of the published cost-effectiveness literature describing the use of erlotinib and gefitinib as treatments for patients with NSCLC who have progressed following prior chemotherapy. The AG notes that neither of the manufacturers included a cost-effectiveness review as part of its manufacturer's submission. The AG also provides a critique of the economic model (erlotinib vs. BSC) submitted by Roche (UK) Ltd. The AG notes that AstraZeneca did not submit an economic model as part of their evidence supporting the use of gefitinib.

Systematic review of existing cost-effectiveness evidence

Methods of cost-effectiveness review

Full details of the main search strategy conducted by the AG and the proposed methods for selecting clinical and economic evidence are presented in detail in *Chapter 3*, *Methods for reviewing effectiveness*. The AG did not use specific economics-related search terms in the main strategy, as all of the potential references were scanned for references containing economic evidence. For the selection of cost-effectiveness evidence, AB and SB independently screened all economics-related titles/abstracts identified via searching and obtained full-paper manuscripts of all relevant references. The relevance of each study was then assessed (by AB and SB) according to the specific inclusion and exclusion criteria shown in *Table 23*. Data were extracted (AB and SB) and summarised in structured tables and as a narrative description.

In the NHS in England and Wales (and in countries elsewhere in the world), docetaxel is commonly used to treat patients with NSCLC who have progressed after chemotherapy and is, therefore, described as a relevant comparator to erlotinib and gefitinib in published economic evaluations (EEs). Recently, the price of docetaxel has fallen[29] substantially as a result of the expiry of the manufacturer's patent. The AG discussed whether or not to exclude papers that presented data using the higher docetaxel price. The AG decided to include these papers but to highlight in the discussion section that the results of EEs that only include docetaxel at its higher price are of limited relevance to this appraisal.

Until recently, patients who required post-progression treatment for NSCLC were treated as a homogeneous group. However, clinical practice is now changing and there is growing awareness that a patient's EGFR mutation status can affect treatment outcomes. With this in mind, the AG discussed excluding papers that did not consider how EGFR mutation status can affect patient outcomes and the treatment options available. However, on reflection, the AG decided not to exclude these papers but to highlight in the discussion that the results of EEs that only include patients with EGFR unknown status should be treated with caution.

TABLE 23 Inclusion criteria for economic papers

Criteria	Inclusion	Exclusion
Intervention	Erlotinib or gefitinib	–
Study design	Full EE	Methodological, editorial, commentary, cost analysis, etc.
Type of paper	Full paper	Abstract

Quantity of included evidence

From the main search, the AG identified 44 potentially relevant economic papers for inclusion in the review of economic evidence. Of these, 16 papers were considered for inclusion after stage 1 screening. Of these 16 papers, 10 were then excluded from the review and six were included in the review at stage 2. The reasons for excluding 10 papers are listed in *Table 24*.

From the systematic review by Bongers *et al.*,[54] a further four papers were identified for inclusion in the AG's review. This finding alerted the AG to the fact that the main search had not picked up all of the relevant published economic studies available. The AG then carried out further searching using a combination of the following broad search terms to identify papers in MEDLINE and The Cochrane Library: erlotinib, gefitinib, lung cancer and cost. This additional generic search identified one more relevant paper by Vergnenegre *et al.*[63]

In summary, the AG considered 11 papers to be eligible for inclusion in the review and these are listed in *Table 25*.

TABLE 24 Reasons for excluding papers from review at stage 2

Reference	Reason for exclusion
Bongers[53]	Abstract
Bongers[54]	Systematic review[a]
Borget[55]	Focus is on a 'strategy' not an individual drug
Capri[56]	Not a full EE
Cuileanu[57]	Abstract
Horgan[58]	No outcome data
Horgan[59]	Cost–consequence analysis – not a full EE
Laurendeau[60]	Abstract
Nguyen[61]	Abstract
Thongsprasert[62]	Abstract – full-text study included in review

a All relevant studies identified in this systematic review are included in the AG's review.

TABLE 25 Papers included in AG's review of cost-effectiveness evidence

Reference	Title
Araujo[64]	An economic analysis of erlotinib, docetaxel or pemetrexed and best supportive care as second- or third-line treatment of non-small cell lung cancer
Asukai[65]	Cost-effectiveness analysis of pemetrexed versus docetaxel in the second-line treatment of non-small cell lung cancer in Spain: results for the non-squamous histology population
Bradbury[66]	Economic analysis: randomised placebo-controlled clinical trial of erlotinib in advanced non-small cell lung cancer
Holmes[67]	A cost-effectiveness analysis of docetaxel in the second-line treatment of non-small cell lung cancer
Thongsprasert[68]	Cost–utility and budget impact analyses of gefitinib in second-line treatment for advanced non-small cell lung cancer from a Thai payer perspective
Cromwell[69]	Erlotinib or docetaxel for second-line treatment of non-small cell lung cancer
Cromwell[70]	Erlotinib or best supportive care for third-line treatment of advanced non-small cell lung cancer: a real-world cost-effectiveness analysis
Lewis[71]	Cost-effectiveness of erlotinib versus docetaxel for second-line treatment of advanced non-small cell lung cancer in the United Kingdom
Leighl[72]	Economic analysis of the TAX317 trial: docetaxel versus best supportive care as second-line therapy of advanced non-small cell lung cancer
Carlson[73]	Comparative clinical and economic outcomes of treatments for refractory non-small cell lung cancer (NSCLC)
Vergnenegre[63]	Cost-effectiveness of second-line chemotherapy for non-small cell lung cancer

Quality of included evidence

The AG made the decision not to quality assess the papers included in the review of cost-effectiveness evidence. This decision was made because none of the 11 studies is directly relevant to UK health-care decision-making as they do not use the off-patent price of docetaxel. Additionally, none of the studies consider the confirmed EGFR mutation status of the patient when assessing post-progression treatments.

Cost-effectiveness review: results

Relevant data were extracted from the 11 eligible papers (*Table 26*). These papers were published between 2002 and 2013; seven papers[63,65,66,68–71] were published from 2010 onwards. All of the papers described full EEs using cost minimisation analysis ($n = 1$[64]), cost-effectiveness analysis ($n = 6$[65,67,69,70,72]) and/or cost–utility analysis ($n = 6$[63–65,68,71,73]) techniques. All but one study[70] used cost per QALY gained or cost per LY gained as the measure of cost-effectiveness. The results of six studies[64,65,67,68,71,73] were derived from use of an economic model: one study[63] conducted an economic analysis alongside a RCT and the remaining four studies[66,69,70,72] conducted retrospective reviews of costs and/or benefits. Four studies[66,69,70,72] were carried out from a Canadian NHS perspective, two[67,71] from that of the UK NHS perspective, one[73] from the US perspective, three[63–65] from a European perspective and one[68] from a Thai payer perspective. None of the studies had a time horizon of longer than 3 years. The authors of two studies[69,70] had not received any financial support from the pharmaceutical industry.

TABLE 26 Study characteristics of EE

Study	Method of EE	Measure of cost-effectiveness	Study design/model	Year published	Perspective	Time horizon	Discounting	Funding body
Araujo[64]	CMA and CUA	Cost per LY gained, cost per QALY gained	Markov-type model	2008	Portuguese NHS	24 months with the option to consider 36 months	5% for costs and benefits	Pharma
Asukai[65]	CEA and CUA	Cost per LY gained, cost per QALY gained	Markov model	2010	Spanish health-care system	36 months (lifetime)	3% for costs and benefits	Pharma
Bradbury[66]	CEA	Cost per LY gained	Retrospective analysis of direct medical costs AND published clinical trial data	2010	Canadian public health-care system	Maximum of 18 months	No discounting applied (few patients remained on study post-12 months)	Pharma
Holmes[67]	CEA	Cost per LY gained	Decision-analytic model	2004	UK NHS	2 years	Discounting was not applied	Pharma
Thongprasert[68]	CUA	Cost per QALY gained	Markov model	2012	(Thai) Comptroller General's Department, Ministry of Finance for the Civil Servant Medical Benefit Scheme	2 years	3%	Pharma
Cromwell[69]	CEA	Cost per unit change in OS, cost per unit change in PFS	Retrospective review of medical records (costs and outcomes) of patients who had received treatment	2011	British Columbia Health Care System	Data were collected between September 2005 and March 2008 (31 months)	N/A	Public
Cromwell[70]	CEA	Cost per QALY gained	Retrospective review of medical records (costs and outcomes) of patients who had received treatment vs. historical controls	2012	British Columbia Health Care System	Controls: April 2002 and March 2004 (2 years) Intervention: April 2004 and November 2006 (32 months)	N/A	Public

Study	Method of EE	Measure of cost-effectiveness	Study design/model	Year published	Perspective	Time horizon	Discounting	Funding body
Lewis[71]	CUA	Cost per QALY gained	Heath-state transition model	2010	UK NHS	2 years	3.5% was applied for year 2 of the analysis	Pharma
Leighl[72]	CEA	Cost per QALY gained	Retrospective economic analysis of a clinical trial	2002	Canada's public health-care system	Less than 1 year	Discounting was not applied as median duration of survival < 12 months in both arms	Public and pharma
Carlson[73]	CUA	Cost per QALY gained	Decision-analytic model	2008	US-payer perspective	2 years	Costs and benefits were discounted at 3%	Pharma
Vergnenegre[63]	CUA	Cost per LY gained, cost per QALY gained	Economic analysis alongside a RCT	2011	French-payer perspective	34 months	3% discount rate used for costs	Pharma

CEA, cost effectiveness analysis; CMA, cost minimisation analysis; CUA, cost–utility analysis; N/A, not applicable.

The 19 comparisons described in the 11 economic studies included one or more of the following interventions: erlotinib, docetaxel, pemetrexed and BSC. The most common comparison was erlotinib versus docetaxel ($n = 5$[64,68,69,71,73]). Other comparisons were erlotinib versus BSC ($n = 3$[64,66,70]), pemetrexed versus docetaxel ($n = 4$[63,65,68,73]), docetaxel versus BSC ($n = 3$[63,67,72]), erlotinib versus pemetrexed ($n = 2$[64,73]), pemetrexed versus BSC ($n = 1$[63]) and gefitinib versus docetaxel ($n = 1$[68]). The populations described in the EEs appeared to have similar patient characteristics, namely previously treated stage III–IV patients with advanced NSCLC. The clinical data used in the EEs were derived mainly from relevant published RCT data: TAX317[74] (docetaxel vs. BSC), JMEI[49] (pemetrexed vs. docetaxel), BR.21[31] (erlotinib vs. placebo) and INTEREST[34] (gefitinib vs. docetaxel). The source of the clinical data described in two studies was patient medical records. The paper by Nafees *et al.*[75] provided the source of the QALY values in two papers.[63,73]

The outcome data (e.g. QALY values and LYs gained) used in the evaluations were variable as a result of the assumptions employed (*Table 27*). To illustrate, the average total QALY value accrued over the time horizon of the models associated with each of the drugs used in the studies range was as follows: erlotinib (0.174[68] to 0.420[75]), docetaxel (0.160[68] to 0.420[73]), pemetrexed (0.171[68] to 0.520[65]). In addition, the AG notes that Araujo *et al.*[64] assume that erlotinib, docetaxel and pemetrexed yield equivalent LYs (0.77 years), Thongprasert *et al.*[68] assume that the gain in LYs is equivalent when comparing docetaxel and pemetrexed (0.97 years) and when comparing erlotinib and gefitinib (0.96 years), and Carlson *et al.*[73] assume that the gain in LYs for erlotinib, docetaxel and pemetrexed is equivalent (0.77 years).

Cost data were mainly derived from relevant national sources of published cost information (*Table 28*), for example Spanish reference database (BOT database of pharmaceutical prices),[65] Portuguese ministerial dispatch report,[64] Ontario Case Costing Acute Inpatient Database[69] and *British National Formulary* (BNF).[67] Costs were typically categorised as drug, drug administration and/or monitoring and treatment of AEs. The publication year differed by no more than 3 years from the base-cost year used in the studies.

The costs estimated and employed in the EEs differ because of the assumptions made by the authors. For example, total costs per patient for erlotinib range from CA$16,487 to CA$35,708.[69] In Vergnenegre *et al.*,[63] the costs of BSC are assumed to equal zero while in Leighl *et al.*[72] the average cost of care in the BSC group was CA$6935.04. Costs and benefits were discounted at a 3%, 3.5% or a 5% discount rate, although some studies[69,71,72] did not use discounting despite estimating costs and benefits over a time period greater than 12 months.

Despite variations in the methods employed and reporting of results across the studies, five of the six studies that assessed erlotinib compared with chemotherapy or BSC favoured erlotinib;[64,66,70,71,72] the authors of the remaining study[69] concluded that erlotinib and docetaxel were equal in terms of costs and benefits. Two studies[67,72] comparing docetaxel versus BSC concluded that docetaxel was cost-effective. In another study[68] gefitinib was preferred to docetaxel, and, of the two studies comparing pemetrexed versus docetaxel, one study favoured docetaxel[63] and the other favoured pemetrexed.[65]

TABLE 27 Clinical inputs, data sources and total benefits

Study	Comparison (intervention vs. comparator)	Characteristics of population	Details of prior treatments	Clinical outcomes	Clinical data source	Total benefits
Araujo[64]	Erlotinib vs. BSC Erlotinib vs. docetaxel Erlotinib vs. pemetrexed	Advanced or metastatic NSCLC, stage IIIA, IIIB or IV (hypothetical cohort)	Failed at least one prior treatment	Median OS, mean OS, PFS	NICE TAX317[73] (docetaxel vs. BSC) JMEI[49] (pemetrexed vs. docetaxel) BR.21[30] (erlotinib vs. placebo)	QALYs: erlotinib = 0.250, BSC = 0.186, docetaxel = 0.225, pemetrexed = 0.241 LY gained: erlotinib = 0.77, BSC = 0.62, docetaxel = 0.77, pemetrexed = 0.77
Asukai[65]	Pemetrexed vs. docetaxel	Stage IIIB or IV patients with NSCLC with predominantly non-squamous histology	Previously undergone a course of chemotherapy	Median OS, PFS and tumour response	Post-hoc retrospective subgroup analysis of the JMEI[49] trial (pemetrexed vs. docetaxel)	QALYs: pemetrexed = 0.52, docetaxel = 0.42, difference = 0.1 LY gained: pemetrexed = 1.03, docetaxel = 0.89, difference = 0.14
Bradbury[66]	Erlotinib vs. placebo	Advanced NSCLC	Previously treated	Median OS and mean OS	BR.21[30] (erlotinib vs. placebo)	Median OS: erlotinib = 6.7 months, placebo = 4.7 months, HR = 0.70, $p < 0.001$, difference = 2.0 months (0.16 years) Mean OS: erlotinib = 9.0 months, placebo = 7.4 months, HR = not reported, difference = 1.6 months (0.13 years)
Holmes[67]	Docetaxel vs. BSC	Second-line treatment of NSCLC	Prior treatment with a platinum containing chemotherapy regime (no taxanes)	Mean OS calculated using an AUC analysis	NICE TAX317[73] (docetaxel vs. BSC)	LY gained: docetaxel = 8.89 months, BSC = 5.16 months, difference = 3.82 months (0.32 years)

continued

TABLE 27 Clinical inputs, data sources and total benefits (*continued*)

Study	Comparison (intervention vs. comparator)	Characteristics of population	Details of prior treatments	Clinical outcomes	Clinical data source	Total benefits
Thongprasert[68]	Gefitinib vs. docetaxel	Advanced NSCLC patients with stage III–IV (hypothetical cohort – based on INTEREST trial)	After one or two previous platinum-based chemotherapy regimens	OS and PFS – assumed erlotinib and gefitinib had the same mean OS/PFS	INTEREST[34] (gefitinib vs. docetaxel) – data used for gefitinib/erlotinib and docetaxel	OS (years): docetaxel = 0.97, gefitinib = 0.96, erlotinib = 0.96, pemetrexed = 0.97. Difference gefitinib vs. docetaxel = 0.013, difference erlotinib vs. docetaxel = 0.013, difference pemetrexed vs. docetaxel = 0
	Erlotinib vs. docetaxel Pemetrexed vs. docetaxel				JMEI[49] (pemetrexed vs. docetaxel) – data used for pemetrexed	QALYs: docetaxel = 0.160, gefitinib = 0.174, erlotinib = 0.174, pemetrexed = 0.171. Difference gefitinib vs. docetaxel = 0.014, difference erlotinib vs. docetaxel = 0.014, difference pemetrexed vs. docetaxel = 0.011
Cromwell[70]	Erlotinib vs. docetaxel	Stage IIIb/IV advanced NSCLC	Previously treated patients	Mean and median OS and PFS and 1-year OS	British Columbia Cancer Agency medical records[68]	Mean OS (95% CI): erlotinib = 311 days (264 to 344 days), docetaxel = 310 days (248 to 333 days), difference = 1 day
				AUC analysis		Mean PFS (95% CI): erlotinib = 64 days (61 to 66 days), docetaxel = 75 (43 to 77 days), difference = –11 days 1-year OS: erlotinib = 36%, docetaxel = 32.4%
Cromwell[71]	Erlotinib vs. BSC	Stage IIIb/IV advanced NSCLC	Patients who had progressed after second-line treatment	Mean and median OS	British Columbia Cancer Agency medical records[68]	Mean OS (95% CI): erlotinib = 291 days (233 to 349 days), BSC = 181 days (141 to 222 days), difference = 110 days
				PTD and 1-year OS		Mean PTD days (95% CI): erlotinib = 195 days (148 to 242 days), BSC = 105 days (82 to 129 days), difference = 90 days
				AUC analysis		1 year OS: erlotinib = 36%, docetaxel = 32.4%

Study	Comparison (intervention vs. comparator)	Characteristics of population	Details of prior treatments	Clinical outcomes	Clinical data source	Total benefits
Lewis[71]	Erlotinib vs. docetaxel	Stage III/IV patients with advanced NSCLC	One or more prior chemotherapy treatments	Mean OS	NICE TAX317[73] (docetaxel vs. BSC)	QALY progression free health state: erlotinib = 0.150, docetaxel = 0.104
				Mean PFS	BR.21[30] (erlotinib vs. placebo) EQ-5D scores (general population – visual analogue method)	QALY progression free health state: erlotinib = 0.088, docetaxel = 0.102
				Utility scores		Total QALY: erlotinib = 0.238, docetaxel = 0.206, difference = 0.032
Leighl[72]	Docetaxel vs. BSC	Stage IIIB or IV patients with advanced NSCLC	Previously treated with cisplatin-based chemotherapy	Mean OS. Survival data analysed using log-rank test	NICE TAX317[73] (docetaxel vs. BSC)	Mean OS months (95% CI): docetaxel = 9.10 (7.51 to 10.69), BSC = 7.11 (5.60 to 8.62), $p = 0.07$
Carlson[73]	Erlotinib vs. docetaxel	> 60-year-old patients with advanced stage III–IV NSCLC	Failed at least one platinum-based chemotherapy	Mean PFS and mean OS	BR.21[30] (erlotinib vs. placebo)	Mean OS: erlotinib, docetaxel, pemetrexed = 0.75 years
	Erlotinib vs. pemetrexed			Assumed PFS and OS were the same for all three drugs	NICE TAX317[73] (docetaxel vs. BSC)	Mean PFS: erlotinib, docetaxel, pemetrexed = 0.34 years
					TAX 320 (docetaxel vs. BSC)	
	Pemetrexed vs. docetaxel			AE rates and utility scores	JMEI[49] (pemetrexed vs. docetaxel)	QALY: erlotinib = 0.42, docetaxel = 0.41, pemetrexed = 0.41
					Published literature and Nafees EQ-5D study[74]	
Vergnenegre[63]	Docetaxel vs. BSC	Patients with stage IIIB or IV NSCLC	Failed after first-line cisplatin-based chemotherapy	Median PFS and median OS	Le Groupe Français de Pneum Cancérologie 2005–6 study[61]	Objective RRs: docetaxel = 10.7%, pemetrexed = 12.0%
	Pemetrexed vs. BSC			Objective RR	Nafees EQ-5D study[74]	Median PFS: docetaxel = 2.8 months, pemetrexed = 2.5 months
	Docetaxel vs. pemetrexed			Utility scores		Median OS: docetaxel = 8 months, pemetrexed = 6.4 months
						QALY: docetaxel = 0.42, pemetrexed = 0.41

AUC, area under the curve; EQ-5D, European Quality of Life-5 Dimensions; PTD, progression-to-death.

TABLE 28 Cost inputs, data sources total costs

Study	Types of costs	Cost data sources	Cost year/currency	Costs
Araujo[64]	Chemotherapy drugs, AEs, medical consultations, laboratory costs, complementary exams, concomitant medications, procedures and hospital stays	Grupos de Diagnosticos Homogeneos (ministerial dispatch no. 110-A/2007), hospital analytical accounting reports, Infarmed, Institute of IT and Financial Management (IGIF) database. Cost of erlotinib was supplied by Roche (UK) Ltd and the cost of pemetrexed was estimated through the price supplied by two hospital pharmacies. Cost of docetaxel was taken from the IGIF database	Prices obtained from 2006 and 2007 data were updated to 2008 prices using an annual inflation rate of approximately 3%/EUR	Total cost per patient: erlotinib = €26,478, BSC = €16,112, docetaxel = €29,262, pemetrexed = €32,762
Asukai[65]	Chemotherapy (drug and administration), AE treatment, BSC and one-off terminal/palliative care	Spanish reference database BOT was used for medication prices. Hospital treatment costs and laboratory tests were sourced from the Oblikue and Costs/Base de datos de costes sanitarios (SOIKOS) databases. Other costs were obtained from two IMS Health reports	2007/EUR	Total cost per patient: pemetrexed = €34,677, docetaxel = €32,343
Bradbury[66]	Chemotherapy treatment, diagnostic tests, outpatient visits, concomitant medications, management of treatment-related toxicity, hospitalisations, radiation therapy and red-blood-cell transfusions	Costs were obtained from PPS Pharma Publication, Ontario Case Costing Acute Inpatient Database, individual patient trial data and Canadian Blood Service	2007/CA$	Mean cost per patient: erlotinib = CA$16,487, placebo = CA$4184
Holmes[67]	Docetaxel, drug administration and co-drug. Cost offsets (mean additional costs in the BSC group for radiotherapy and morphine use) and toxicity treatment costs were included in a sensitivity analysis	BNF and Unit Costs of Health and Social Care	2000–01/GBP	Mean net cost per patient: docetaxel = £4432, BSC = £0.00
Thongprasert[68]	Direct medical costs: drug acquisition costs, drug administration and monitoring, and AE management	Drug and Medical Supply Information Center, standard cost list for health technology assessment, prices of Services of Health Facilities under the Ministry of Public Health (HITAP)	2010 – converted to US$ using exchange rate of 30.28 THB = 1US$ (Bank of Thailand website)/THB	Total cost per patient: docetaxel = US$6483, gefitinib = US$6237, erlotinib = US$8229, pemetrexed = US$9092

Study	Types of costs	Cost data sources	Cost year/currency	Costs
Cromwell[69]	CTX drugs, radiation therapy, physician appointments, diagnostic tests and hospital admission	Drug costs from PPS Pharma Publication, hospital costs per diem from the Ontario Case Costing Acute Inpatient Database, transfusion costs from Canadian Blood Services, other costs from medical opinion and trial database	2009/CA$	Mean overall cost/patient (range): erlotinib = CA$35,708 (CA$32,241–CA$39,174), docetaxel = CA$32,817 (CA$27,940–CA$37,693), difference = CA$2891
Cromwell[70]	CTX drugs, radiation therapy, physician appointments, diagnostic tests and hospital admission	Provincial Medical Services Plan, provincial PharmaCare plan, home and community care and hospital-specific mean case costs	2009/CA$	Mean overall cost/patient (range): erlotinib = CA$34,326 (CA$6569–CA$99,370); BSC = CA$23,224 (CA$1095–CA$78,775)
Lewis[71]	Monthly medical resource utilisation, treatment-related AEs and drug administration costs for three health states were agreed upon by a panel of lung cancer clinicians	Unit costs from BNF (2006) and PSSRU (2008)	2009/GBP	Lifetime per patient costs: erlotinib = £13,730, docetaxel = £13,956
Leighl[72]	Outpatients assessments, chemotherapy administration, hospitalisation, radiation therapy, community-based nursing and supportive care, and miscellaneous items	Costs derived from trial data, hospital medical records as well as other facilities at which care was received. All physician services were based on the 1999 Ontario Health Insurance Plan fee schedule	Canadian dollars/1999	Average cost per patient arm in NICE TAX317: docetaxel (75 mg/m^2) = CA$17,738.96 BSC = CA$6935.04
Carlson[73]	Drug utilisation, drug administration, hospital inpatient admission, outpatient appointments AE treatments	Wholesale drug acquisition costs from First Data Bank I online database, medical services from CMS physicians fee schedule and inpatient prospective payment system, disease progression from a Kaiser Permanente study	2007/US$	Total cost (US$): erlotinib = $36,977, docetaxel = $39,104, pemetrexed = $43,795
Vergnenegre[63]	CTX drugs, drug administration, supportive treatment, hospitalisation for any reason, outpatient follow-up attendance, medical transport and grade 3 or 4 AE management costs	Costs were derived from national tariffs for diagnosis-related groups and national fees for ambulatory care, provided by French Ministry of Health and the national health insurer. Drug administration, follow-up and AE costs are an average of 2006, 2007 and 2008 tariffs	2009/EUR	Total cost: docetaxel = €13,714 ± €7387, pemetrexed = €16,802 ± €7852. Authors compared docetaxel with BSC and pemetrexed with BSC, and assumed costs and benefits of BSC were equal to zero

CTX, chemotherapy; IMS, Intercontinental Marketing Services; IT, information technology; PPS, Pharma Professional Services; PSSRU, Personal Social Services Research Unit.

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Cost-effectiveness review: discussion of study methods and results

It is clear from the methods and results reported in the published cost-effectiveness literature that the conclusions drawn are very dependent on the assumptions made by the investigators and the data sources employed in the EEs (*Table 29*). These differ from evaluation to evaluation. Each EE must therefore be judged on its own merits and any attempt to make summary statements about different comparisons in terms of cost-effectiveness is meaningless.

Of the 19 comparisons considered in the 11 published studies, 13 included docetaxel as a comparator. The AG notes that the patent on docetaxel has expired and docetaxel is now available in its generic form at a cost that is less than 10% of its previous list price.[29] The AG therefore considers that the incremental cost-effectiveness ratios (ICERs) estimated in these 13 comparisons are now of limited value to decision-makers in the UK NHS. Of the six remaining comparisons, three included pemetrexed as a comparator [pemetrexed vs. BSC ($n = 1$[63]) and pemetrexed vs. erlotinib ($n = 2$[64,73])]. Again, the AG considers that the results of these studies cannot be used directly to inform decision-making in the UK as pemetrexed is not recommended by NICE for the second-line treatment of patients with NSCLC in the UK NHS. The remaining three studies[64,66,69] focused on the comparison of erlotinib with BSC. However, as none of the studies report ICERs for an EGFR M+ or EGFR M– patient population, the AG considers that the estimated ICERs are useful only when making treatment decisions for patients whose EGFR status is unknown, as the EGFR mutation status of this patient group can influence treatment choices. In addition, the AG is of the opinion that, although BSC is a valid comparator for a small population of patients with NSCLC, docetaxel is a more appropriate comparison for patients in the UK NHS.

TABLE 29 Cost-effectiveness results, sensitivity analysis and conclusions

Study	Cost-effectiveness results	Sensitivity analysis	Conclusions
Araujo[64]	Cost/QALY gained: erlotinib vs. BSC = €161,742, erlotinib vs. docetaxel = erlotinib dominates, erlotinib vs. pemetrexed = erlotinib dominates Cost/LY gained = erlotinib vs. BSC = €70,424, erlotinib vs. docetaxel = erlotinib reduces costs, erlotinib vs. pemetrexed = erlotinib reduces costs	Sensitivity analyses undertaken generate results similar to the base case	Use of erlotinib instead of docetaxel or pemetrexed could contribute to annual savings for the Portuguese NHS and a gain in QALYs
Asukai[65]	Cost/QALY gained: pemetrexed vs. docetaxel = €23,967 Cost/LY gained: pemetrexed vs. docetaxel = €17,225	Model is most sensitive to variation in OS. The PSA results show that pemetrexed has a 62% likelihood of having a QALY below €30,000 and a 77% likelihood of having a cost per LY gained below €30,000	In the Spanish setting, pemetrexed for the second-line treatment of patients with NSCLC other than predominantly squamous cell histology is indicated as a cost-effective chemotherapy option compared with the standard docetaxel, based on its superior OS benefit and toxicity profile
Bradbury[66]	Cost/LY gained: erlotinib vs. placebo = CA$94,638 Subgroup analyses: cost/LY gained (never-smokers) = CA$39,487, cost/LY gained (high EGFR gene copy number) = CA$33,353	Magnitude of the survival benefit was the main influence on the size of the ICER Subgroup analyses revealed that erlotinib may be more cost-effective in never-smokers or patients with high EGFR gene copy number	Authors conclude that erlotinib for patients with previously treated advanced NSCLC is marginally cost-effective and that the use of molecular predictors of benefit for targeted agents may help identify more or less cost-effective subgroups for treatment

TABLE 29 Cost-effectiveness results, sensitivity analysis and conclusions (*continued*)

Study	Cost-effectiveness results	Sensitivity analysis	Conclusions
Holmes[67]	Cost/LY gained: docetaxel vs. BSC = £13,863	Sensitivity analysis showed that the number of treatment cycles per patient had most influence on the cost/LY gained	Authors conclude that docetaxel 75 mg/m^2 in 3-weekly cycles is a cost-effective second-line treatment from the perspective of the UK NHS for pre-treated NSCLC in terms of survival gains made for a reasonable increase in costs
Thongprasert[68]	Cost/QALY gained: gefitinib vs. docetaxel = gefitinib dominates, erlotinib vs. docetaxel = US$124,703, pemetrexed vs. docetaxel = US$237,150	Sensitivity analyses showed that varying docetaxel cost and the duration of docetaxel treatment had the greatest effect on cost-effectiveness	Authors conclude that gefitinib is a dominant cost-saving strategy compared with docetaxel for the second-line treatment of advanced NSCLC from the Thai payer perspective
Cromwell[69]	Costs and benefits were not significantly different between the two groups, it was not possible to calculate a meaningful ICER	Univariate SA could not be performed as SA results in either a numerator or a denominator of zero	Erlotinib = docetaxel in terms of costs and benefits. Choice of treatment should depend on patient preferences
Cromwell[70]	Cost per LY gained: erlotinib vs. BSC = CA$36,838, incremental mean OS = 110 days, incremental mean cost = CA$11,102	Univariate SA (from varying total treatment costs) yielded ICERs ranging from CA$21,300/LY gained to CA$51,700/LY gained. Other parameters varied included mean drug cost/patient and hospital cost/patient	Analyses suggest that erlotinib may be an effective and cost-effective third-line treatment for advanced NSCLC compared with BSC
Lewis[71]	Cost per QALY gained: erlotinib vs. docetaxel = –£7106, net monetary benefit = £1181, incremental benefit = 0.032, incremental cost = –£226	Sensitivity analyses showed the robustness of the baseline analysis, i.e. that erlotinib was cost-effective compared with docetaxel	From a health-economics perspective, for the treatment of patients with relapsed stage III–IV in the UK, erlotinib has advantages over docetaxel
Leighl[72]	Cost per LY gained: docetaxel (75 mg/m^2) vs. BSC = CA$31,776	In univariate SA, cost-effectiveness ratios were most sensitive to changes in survival ranging from CA$18,374 to CA$117,434 with 20% variation in survival at recommended (75 mg/m^2) dose	Authors concluded that the estimated cost per LY gained is within an acceptable range of health-care expenditures
Carlson[73]	Cost per QALY gained: erlotinib vs. docetaxel = erlotinib dominates, erlotinib vs. pemetrexed = erlotinib dominates, pemetrexed vs. docetaxel = US$1,743,359	Estimates of treatment duration were among the most influential parameters in the SA, others were time in PFS, drug costs and values of some health-state utilities. In the PSA, erlotinib was cost-saving in 65% and 87% of the simulations compared with docetaxel and pemetrexed, respectively	Results of the study suggest that erlotinib in the treatment of refractory NSCLC in the USA is less costly than alternative treatments and may lead to a slight improvement in QALYs
Vergnenegre[63]	Cost per QALY gained: docetaxel vs. BSC = €32,652, pemetrexed vs. BSC = €40,980 Cost per LY gained: docetaxel vs. BSC = €15,545, pemetrexed vs. BSC = €22,798	SA showed that the price of pemetrexed would need to fall by 30% to balance the cost per QALY values in each arm	Second-line treatment for NSCLC is more cost-effective with docetaxel than with pemetrexed. Both strategies have acceptable cost-effectiveness ratios compared with commonly used and reimbursed regimes for advanced NSCLC

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; SA, sensitivity analysis.

The AG concludes that the results of the systematic review are of limited value to decision-makers in the UK NHS. This is a result of (1) relatively recent changes in the price of docetaxel and (2) the increased significance of EGFR mutation testing for patients with NSCLC. The AG does not summarise or draw conclusions from any other manufacturer's submission used in previous NICE appraisals of erlotinib and/or gefitinib as these submissions were written at a time when it was not possible to take into account these aforementioned changes. The AG anticipates that future EEs in this complex clinical area will make use of the most up-to-date clinical effectiveness and cost data available.

Critique of the economic analyses submitted by manufacturers

The manufacturer of gefitinib (AstraZeneca) did not include any cost-effectiveness analyses in its submission. The objective of its manufacturer's submission was to demonstrate the clinical benefit of gefitinib therapy in EGFR M+ patients with NSCLC following prior chemotherapy.

The manufacturer of erlotinib [Roche (UK) Ltd] states in its manufacturer's submission that it does '. . . not believe it is possible to demonstrate [that] erlotinib is cost-effective compared to docetaxel following the availability of generic docetaxel at less than 10% of the list price of docetaxel in NICE TA162'.[28] The manufacturer's base-case analysis therefore compares erlotinib and BSC in patients whose EGFR mutation status is unknown and who are unsuitable for docetaxel or who have previously received docetaxel. In a separate subgroup analysis, the manufacturer considers erlotinib versus BSC for patients with EGFR M– tumours. The AG provides a summary and critique of the EE presented in the manufacturer's submission submitted by Roche (UK) Ltd.

The AG notes that the manufacturer of erlotinib [Roche (UK) Ltd] has not compared the cost-effectiveness of erlotinib with gefitinib. In the UK NHS, patients who have EGFR M+ tumours are likely to have received either erlotinib or gefitinib as a first-line treatment and it is, therefore, unlikely that this group of patients would be re-treated with a EGFR-TKI as part of second-line treatment. The manufacturer, therefore, has not carried out an EE for this group of patients. Furthermore, as gefitinib does not have a licence for patients who have EGFR M– tumours, the manufacturer has not carried out an EE comparing erlotinib with gefitinib for this patient population.

Review of Roche (UK) Ltd economic model: erlotinib versus best supportive care

The ERG assessed the economic model submitted by Roche using NICE's reference case checklist (*Table 30*).

Overview of submitted manufacturer's submission

The manufacturer developed a de novo economic model using data from the BR.21[31] trial. In the base-case analysis, the manufacturer compares erlotinib versus BSC using ITT data from the BR.21[31] trial. In a separate subgroup analysis, the manufacturer compares erlotinib versus BSC in an EGFR M– patient population only, this patient group was identified retrospectively.[43]

The developed model is a partitioned survival model with three health states (a structure that has been used in many previous NICE oncology technology appraisals, including TA162,[21] TA227[47] and TA295[76]). The model projects PFS and OS independently with the proportion of patients in the progressed health state over time being the proportion of patients alive but not in the PFS health state.

The model structure is shown in *Figure 2*. All patients enter the model in the PFS health state and in each month can either progress to a worse health state [i.e. from PFS to progressed disease (PD) or from PD to death] or remain in the same health state. The model has been developed in Microsoft Excel and has a 1-week cycle length.

TABLE 30 National Institute for Health and Care Excellence reference case checklist

NICE reference case requirements	Reference case	Does the de novo EE match the reference case?
Defining the decision problem	The scope developed by NICE	Partial. Docetaxel was not considered. The manufacturer stated that they do not believe it would be possible to demonstrate that erlotinib is cost-effective compared with docetaxel following the availability of generic docetaxel. No comparison with gefitinib
Comparators	Therapies routinely used in the NHS, including technologies currently regarded as best practice	
Perspective on costs	NHS and Personal Social Services	Yes
Perspective on outcomes	All health effects on individuals	Yes
Type of EE	Cost-effectiveness analysis	Yes
Synthesis of evidence on outcomes	Based on a systematic review	N/A – only evidence from BR.21[31] was used
Measure of health benefits	QALYs	Yes
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of general public	No. Source of preference data not specified
Discount rate	An annual rate of 3.5% on both costs and QALYs	Yes
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes

HRQoL, health-related quality of life; N/A, not applicable.

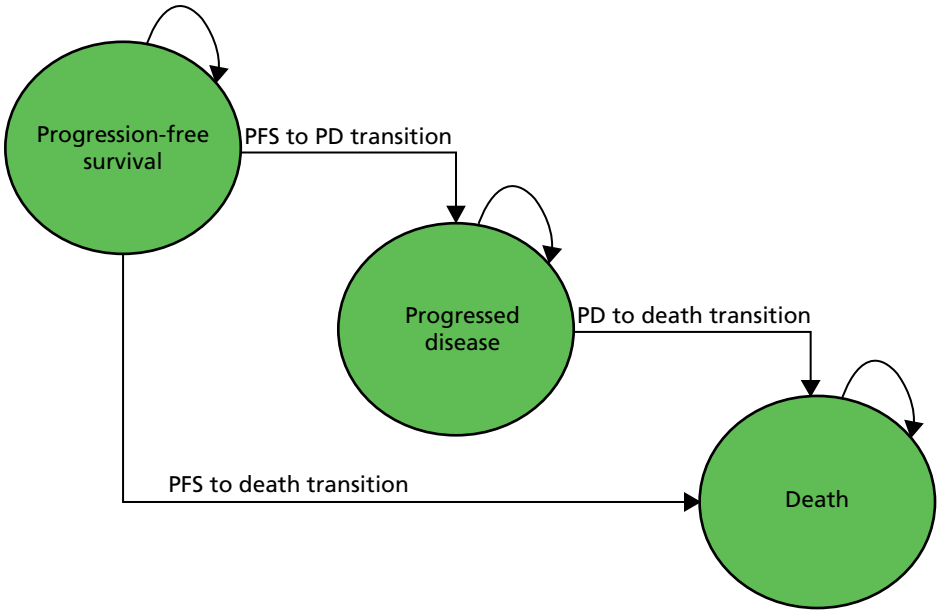

FIGURE 2 Schema of manufacturer's model. PD, progressed disease.

Population

The population was assumed to be the same as that recruited to the BR.21[31] trial, that is patients 18 years of age or older with an ECOG PS score of between 0 and 3 and who had documented pathological evidence of NSCLC. Patients in this trial had to have received one or two regimens of combination chemotherapy and not be eligible for further chemotherapy. The only baseline population characteristic used in the model was age (61.4 years in both arms).

Interventions and comparators

The manufacturer believes that, following the availability of generic docetaxel at less than 10% of the previous list price, it is not possible to demonstrate that erlotinib is cost-effective when compared with docetaxel. The manufacturer has, therefore, only presented an analysis comparing erlotinib (maximum of one 150-mg tablet per day until disease progression) with BSC. In addition, the AG notes that the manufacturer did not compare the cost-effectiveness of erlotinib with gefitinib.

Perspective, time horizon and discounting

The EE is undertaken from the perspective of the NHS and Personal Social Services Research Unit (PSSRU). Outcomes are expressed in terms of LYs gained and QALYs gained. The time horizon is set at 6 years and, in line with the NICE *Guide to the Methods Technology Appraisal*,[77] both costs and benefits are discounted at 3.5%.

Treatment effectiveness and extrapolation

Data from BR.21[32] were used to estimate PFS and OS.

Progression-free survival

No extrapolation of PFS data was required as, by 18 months, all patients on BSC had progressed and only two patients using erlotinib remained free of progression. These two patients were assumed to have progressed at the next cycle.

Overall survival

Cumulative hazards were calculated and plotted for both arms. A linear trend was observed for both arms indicating that, although different, the rate of death in each arm remained constant over time. Based on factors including visual inspection and small patient numbers, week 70 and week 78 were chosen as the time points at which extrapolation should begin for erlotinib and BSC, respectively.

Health-related quality of life

The manufacturer extracted utility values from the published appraisal of crizotinib for the treatment of previously treated NSCLC associated with a lymphoma kinase fusion gene (NICE TA296[78]). The manufacturer selected and applied the pooled chemotherapy (pemetrexed or docetaxel) values to both the erlotinib and BSC arms of the model. The manufacturer considers this to be a conservative assumption, as QoL data from BR.21[31] showed that erlotinib improved QoL as regards time to deterioration of key symptoms of cough, dyspnoea and pain compared with BSC.

The manufacturer notes that the patient population in PROFILE 1007[79] (described in TA296[78]) is anaplastic lymphoma kinase positive and that the utility values from this population are relatively high for patients with NSCLC. Furthermore, the patient group in PROFILE 1007[79] was younger and less fit than those patients enrolled in the BR.21[31] trial.

The source of the utility values used in the model is presented in *Table 31*.

TABLE 31 Key model parameters: utility

State	Utility value	Standard error	Source
PFS	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	TA296[78]
PD	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	TA296[78]

Commercial-in-confidence information has been removed.

Resources and costs

Erlotinib acquisition costs

The model assumes that erlotinib is dispensed in packs of 30 tablets (150 mg) every 4 weeks. The cost calculation takes into account the treatment duration by using data taken from BR.21[31] (mean duration = 9.57 weeks). In BR.21[31] 19% of patients had some form of dose reduction; the effect of this is assessed in a sensitivity analysis. The cost used in the model includes the simple confidential discount agreed during TA162[21] and TA258[18] (*Table 32*).

Supportive care costs

The supportive care resources described in the manufacturer's submission are in line with those used in TA162,[21] which were elicited from an expert panel and updated using NHS Reference Costs (2011/12),[82] PSSRU (2011),[81] BNF (2012)[48] and the electronic market information tool (eMit).[83] It is noted that the supportive care costs applied to the PD health state are considerably higher than those employed in recent appraisals of advanced NSCLC because in this model the high-cost end-of-life phase is not shown as a separate element.

These costs, which are displayed in *Table 33*, have been applied in the model at each weekly cycle.

Adverse events

Adverse event rates were taken from BR.21[31] and only those AEs for which the cumulative percentage across both arms was greater than 5% were included in the manufacturer's model. The assumed costs for treating each AE were based on resource use elicited from an expert panel and previously used in NICE TA162.[21] Costs were taken from NHS Reference Costs (2011/12),[82] PSSRU (2012),[84] BNF (2012)[48] and eMit[83] and are displayed in *Table 34*.

TABLE 32 Erlotinib costs

Cost	Value	95% CI	Source
Pharmacy costs per pack of erlotinib dispensed	£18.20 (12 minutes of pharmacy time at £91/hour)	£9.28 to £27.12[a]	Millar,[80] PSSRU,[81] manufacturer's submission section 4.5[28]
Erlotinib drug costs	30 tablets × 150 mg = £1631.53,[b] 30 tablets × 100 mg: £1324.14,[b] 30 tablets × 25–50 mg: £378.33[b]	N/A	BNF, September 2013[29] list price, manufacturer's submission table 12, section 4.5[28]

N/A, not applicable.
a Gamma distribution applied under assumption standard error was a quarter of base-case value.
b Costs to the NHS are subject to a further (confidential) discount under the patient access scheme.

TABLE 33 Supportive care costs

Supportive care costs	Included elements (per month)		Value (weekly)
	Visits and hospitalisation	Tests, procedures and medications	
PFS BSC cost (including monitoring)	Hospital stay episode (2.5% points)	Blood count (all points × 0.75)	£84.67
	Cancer nurse (20% points × one visit)	Palliative radiotherapy (12.5% points × 1)	
	Palliative care nurse (30% points × one visit)	Computed tomography (30% points × 0.75)	
	Palliative care physician (7.5% points × one visit)	Radiography (all points × 0.75)	
	OP attendance (0.75 visits)	Biochemistry (all points × 0.75)	
	GP visit (10% points × one visit)		
PD BSC cost	Hospital stay episode (30% points)	Blood count (all points × 1)	£220.34
		Palliative radiotherapy (20% points × 1)	
	Cancer nurse (10% points × one visit)	Computed tomography (5% points × 0.75)	
		Radiography (30% points × 0.75)	
	Palliative care nurse (20% points × one visit)	Biochemistry (all points × 0.75)	
		Home oxygen (20% points × 1)	
	Palliative care physician (80% points × two visits)	Steroids (dexamethasone) (50% points 0.5 mg × 160)	
		Non-steroidal anti-inflammatory drugs (aspirin) (30% points 200 mg × 60)	
	OP attendance (one visit)	Morphine (75% of patients 60 mg × 7)	
	GP visit (28% points × one visit)	Bisphosphonate (ibandronic acid) (7.5% points 5 mg × 28)	

GP, general practitioner; OP, outpatient.

TABLE 34 Adverse event costs

AE	Included elements	Value
Rash	Outpatient attendance, oral tetracycline	£275.36
Anorexia	Dietitian, steroids (dexamethasone)	£76.85
Nausea and vomiting	Hospital stay, outpatient attendance, GP visit, Macmillan nurse, domperidone, steroids (dethamethasone), blood count, biochemistry	£387.59
Diarrhoea	Hospital stay, outpatient attendance, GP visit, loperamide, stool culture	£584.81
Infection	Hospital stay, emergency room, blood count	£1813.65
Fatigue	GP visit, Macmillan nurse	£4.29

GP, general practitioner.

Cost-effectiveness results

The base-case incremental results generated by the manufacturer's model are presented in *Table 35*. The ICER for the comparison of erlotinib with BSC in patients with NSCLC whose EGFR mutation status is unknown and who have progressed after prior chemotherapy treatment, is £51,036 per QALY gained and £35,593 per LY gained. Disaggregated costs for the target population are presented in *Table 36*.

Sensitivity analyses

The manufacturer carried out a large number of one-way sensitivity analyses. A tornado diagram is included in the manufacturer's submission (figure 27, page 67). The one-way sensitivity analysis results for the five changes that have the largest impact on cost-effectiveness are displayed in *Table 37*.

Probabilistic sensitivity analysis (PSA) was undertaken (5000 iterations of the model) by the manufacturer. A scatterplot (incremental cost vs. QALY) and a cost-effectiveness acceptability curve are included in the manufacturer's submission (p. 70) and reproduced in *Figures 3* and *4*.

TABLE 35 Base-case results

Technologies	Total costs (£)	Total LY gained	Total QALYs	Incremental costs (£)	Incremental LY gained	Incremental QALYs	ICER per QALY gained (£)
BSC	5993	0.656	0.432	–	–	–	–
Erlotinib	13,522	0.867	0.579	7529	0.212	0.148	51,036

TABLE 36 Disaggregated mean costs for the base-case analysis

Element	Cost (£)		Increment (£)	Absolute increment (£)	Absolute increment (%)
	Erlotinib	BSC			
Drug	Commercial-in-confidence information has been removed	0	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Pharmacy	Commercial-in-confidence information has been removed	0	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
AEs	Commercial-in-confidence information has been removed	113	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
PFS BSC	Commercial-in-confidence information has been removed	1020	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
PD BSC	Commercial-in-confidence information has been removed	4860	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Total	13,522	5993	7529	7529	100

Commercial-in-confidence information has been removed.

TABLE 37 Key one-way sensitivity analysis results

Change from base case	Lower ICER estimate (difference from base-case ICER)	Higher ICER estimate (difference from base-case ICER)
Use of the Nafees[75] utility values for PFS and PD	–	£61,317
Variation (±20%) from the base case of PFS utility	£44,900 (–£6136)	£59,116 (£8080)
Erlotinib dose reduction in 19% of patients and PFS cost reduction by 50%	£44,121 (–£6915)	–
Reduction of PFS costs (–50%) for the erlotinib arm	£45,565 (–£5471)	–
Variation (±20%) from the base case of PD utility	£47,997 (–£3039)	£54,487 (£3451)

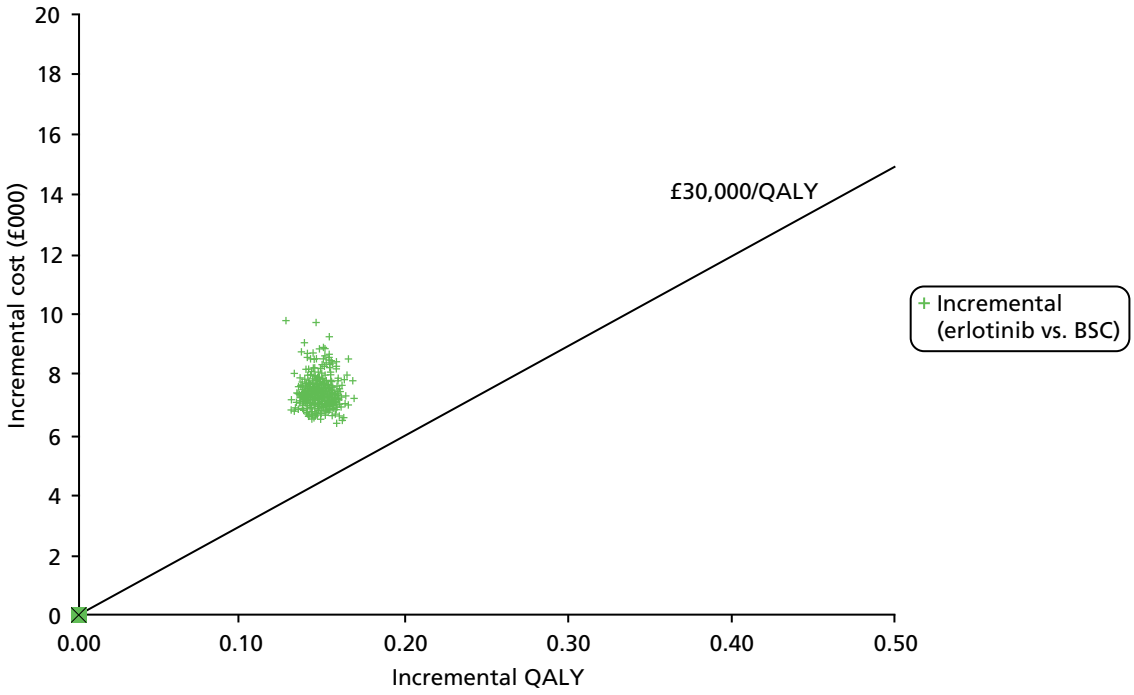

FIGURE 3 Probabilistic sensitivity analysis scatterplot erlotinib vs. BSC (diagonal line = £30,000 per QALY gained).

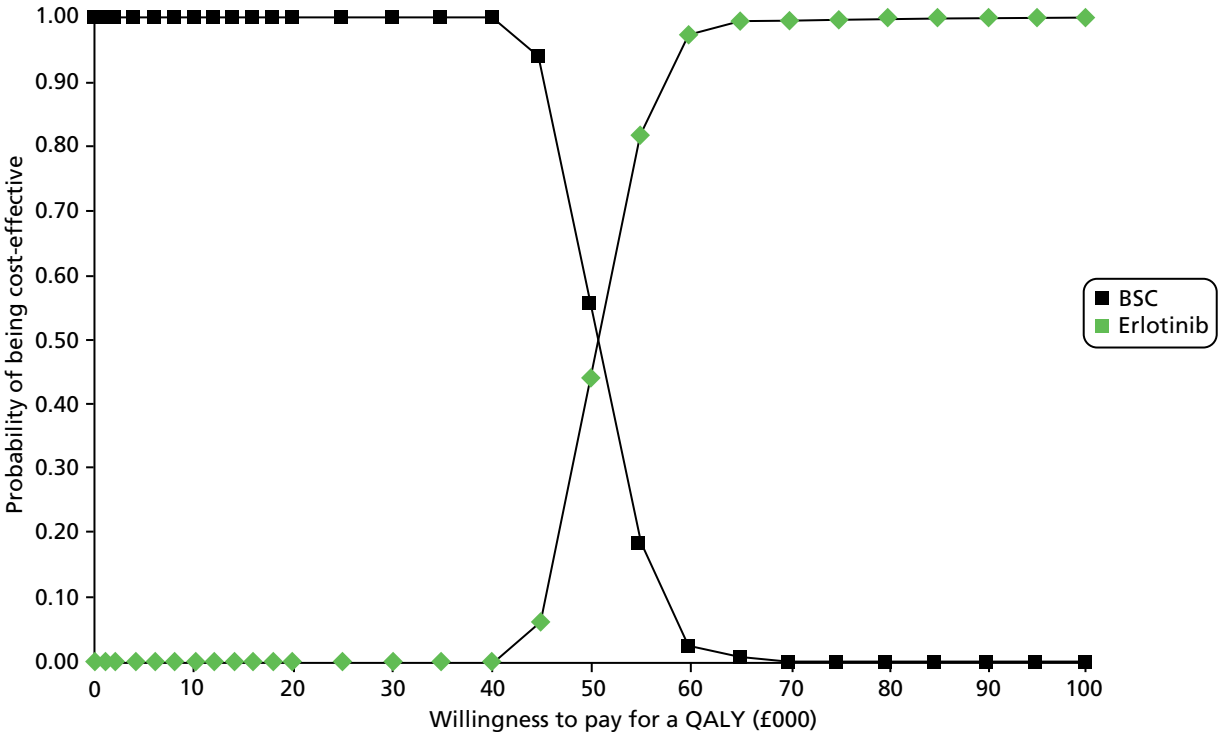

FIGURE 4 Cost-effectiveness acceptability curve.

The results of the PSA are displayed in *Table 38*. The PSA ICER is estimated to be £50,825 per QALY gained, which is only £211 less than the base-case deterministic ICER of £51,036 per QALY gained.

The PSA results show that there is a 0% probability that erlotinib is cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained. However, at a threshold of £60,000 per QALY gained there is a 40% probability that erlotinib is cost-effective, and at a threshold of £65,000 per QALY gained erlotinib is cost-effective in approximately 76% of all scenarios.

TABLE 38 Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY gained (£)	Difference from base-case ICER (£)
BSC	5775	0.431	–	–	–	–
Erlotinib	13,265	0.578	7490	0.147	50,825	–211

Subgroup analysis

The manufacturer undertook a separate subgroup analysis for the EGFR M– population of the BR.21[31] trial using data from the publication by Zhu *et al.*[43] The ICER for this group was £58,579 per QALY gained, a value which is approximately 14% higher than the base-case ICER. The QALY gain comes entirely from the PFS health state. The manufacturer advises that the results from this analysis, which are displayed in *Table 39*, should be interpreted with caution because of the limitations of the available data.

Critique of the submitted model

The AG notes that, as well as not analysing the cost-effectiveness of erlotinib compared with docetaxel, the manufacturer did not carry out an analysis of the cost-effectiveness of erlotinib compared with gefitinib. This critique therefore focuses on the manufacturer's analysis of the cost-effectiveness of erlotinib compared with BSC that is presented in the manufacturer's submission. A detailed examination of model formulae and calculations has not been carried out.

The economic model submitted by the manufacturer was of a structure used in many previous oncology technology appraisals. The presented evaluation was based on data from one RCT (BR.21[31]). This trial recruited a population of patients with NSCLC and of unknown EGFR status; however, treatment pathways have evolved and currently patients who have EGFR M+ disease would not generally be given a EGFR-TKI as a second-line treatment, as they would already have received a TKI as a first-line therapy.

The manufacturer carried out a wide range of sensitivity analyses. The biggest impact on the size of the cost per QALY ICER (an increase of £10,281) resulted when utility values from Nafees *et al.*[75] replaced values from PROFILE 1007[79] in the manufacturer's base-case analysis.

The AG has several concerns about the use of PROFILE 1007[79] values in the base-case analysis, namely:

- These values have not been published, peer reviewed or validated.
- There is no information on the coverage of patients within the trial completing the survey (i.e. at which time point and at which stage of treatment) so no assessment can be made of the potential for bias in any overall averages obtained.
- The crude averages incorporate the effects of treatment-related AEs, which relate to another treatment given to younger but less fit patients with a different type of NSCLC.

In the manufacturer's economic model, the social tariff algorithm used to calculate European Quality of Life-5 Dimensions (EQ-5D) scores is unknown. As the predominant data source in the PROFILE 1007[79] trial is the USA, it would not be surprising if the US tariff, which gives consistently higher scores than the UK tariff, had been used.

Figure 5 shows the relationship between health state scores using UK and US tariffs. When this conversion is applied to the PROFILE 1007[79] utility scores, the PFS average (US tariff) changes. The Nafees *et al.*[75] model gives 0.653 for stable disease PFS and 0.673 for responder PFS. Similarly, the PD average US tariff utility changes and compares closely with the Nafees *et al.*[75] PD utility.

TABLE 39 Epidermal growth factor mutation-negative results

Technologies	Total costs (£)	Total LY gained	Total QALYs	Incremental costs (£)	Incremental LY gained	Incremental QALYs	ICER per QALY gained (£)
BSC	6362	0.682	0.447	–	–	–	–
Erlotinib	13,853	0.850	0.574	7490	0.168	0.128	58,579

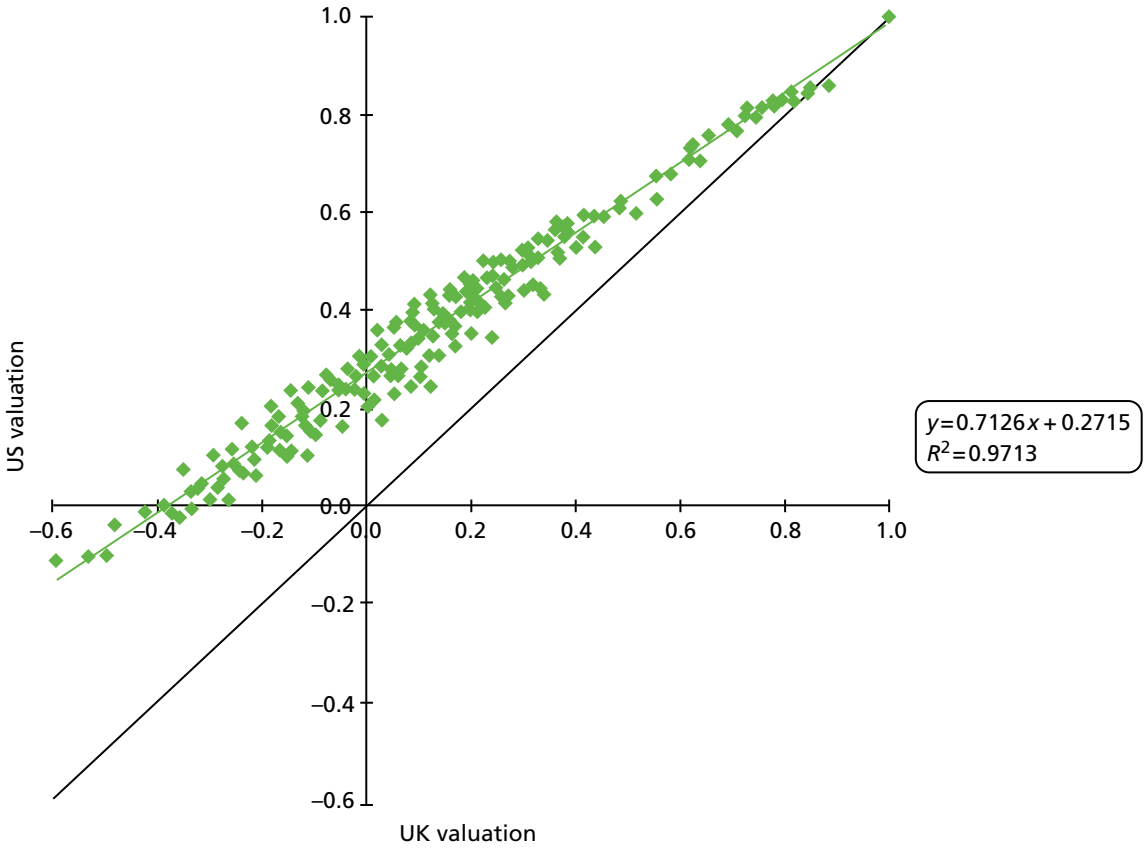

FIGURE 5 Relationship between health-state scores using UK and US tariffs.

One further point which, in this case, is likely to have only a minor impact on the size of the cost per QALY ICER relates to the cost of a hospital pharmacist's time, which is used to estimate erlotinib administration costs. A value of £91 per hour (PSSRU 2011[81]) has been used in the model but the most up-to-date value is £67 (PSSRU 2012[84]).

In view of these issues, and to allow all therapy options to be compared using a consistent framework, the AG has developed a de novo cost-effectiveness model.

Assessment Group de novo economic model

This section describes the de novo cost-effectiveness model developed by the AG.

Methods

Assessment perspective

Costs and outcomes are assessed from the perspective of the UK NHS and PSSRU. Wider indirect costs and benefits (e.g. loss of productivity, value of informal care and impact on utility of patient's family) are not considered.

Relevant patient populations

Three distinct populations are modelled as follows:

1. Previously treated adult patients with locally advanced or metastatic NSCLC and who exhibit EGFR-activating mutations (referred to as 'EGFR M+ population')
2. Previously treated adult patients with locally advanced or metastatic NSCLC and who do not exhibit EGFR-activating mutations (referred to as 'EGFR M– population')
3. Previously treated adult patients with locally advanced or metastatic NSCLC and for whom EGFR mutation status is unknown or indeterminate (referred to as 'EGFR unknown population')

Treatment options to be evaluated

Four pharmaceutical products are currently licenced for use in these populations:

- Erlotinib and docetaxel may be used for treating patients in all three populations.
- Gefitinib may be used only for patients with disease that exhibits EGFR-activating mutations.
- Pemetrexed may be used only for patients with predominantly non-squamous disease following platinum-doublet chemotherapy as a first-line treatment. Pemetrexed was appraised as a second-line treatment for patients with NSCLC but not approved by NICE, and it is not within the scope of the current reappraisal.

Additionally, it is generally considered that a patient is unlikely to be re-treated with the same agent that was used as a first-line therapy. This constraint should, therefore, be considered as a limiting consideration when interpreting the cost-effectiveness results in each of the above populations.

Time horizon

A lifetime perspective is taken in the model, which projects all patient events and costs to a maximum of 5 years, at which time it is assumed that all patients will have died.

Mid-cycle correction

Treatment costs (drug and administration) are costed according to the number of patients progression free on the expected date of administration (when treatment is subject to specific cycle length) and to the date when a new pack of medication would be required for oral treatments. All other costs and QALYs estimates are based on PFS/OS mid-cycle corrected data, with the exception of terminal-care costs and QALYs, to which a more complex correction was applied to reflect costs and utilities in the 2 weeks prior to death.

Discount rates (costs and benefits)

In the base-case analysis both costs and outcomes are discounted at 3.5% per annum in line with NICE guidance.[78] Sensitivity analyses are reported for discount rates of 0% and 6%.

Model design

The decision model (*Figure 6*) is conceptually straightforward, involving two health states prior to death (progression free after second-line chemotherapy, post progression). Therapy is treated as an extended event, given over several cycles (usually of 3 weeks' duration). However, orally administered treatments (erlotinib and gefitinib) are given continuously until the disease progresses, and treatment is assumed to be coterminous with the duration of the PFS state.

Disease progression after second-line therapy is treated as an event, resulting in one of two transitions, either to a period of post-progression survival (PPS), which eventually results in death, or to immediate death. Further lines of therapy are possible but are not modelled explicitly, as the proportion of patients receiving subsequent active treatments is small in the UK. Instead, additional resources and utility effects are included in the post-progression health state to represent average usage.

The model is implemented as a Microsoft Excel workbook, using macro-programming to perform PSA to assess the relative probabilities of cost-effectiveness between the available second-line treatments.

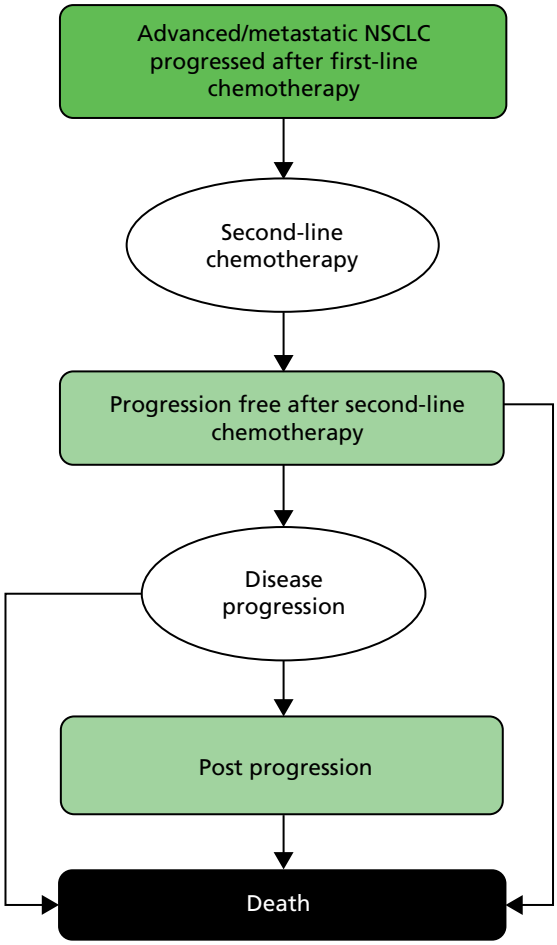

FIGURE 6 Conceptual model of second-/third-line decision model, indicating health states (rectangles), events/procedures (ovals) and transitions (arrows).

Ideally, the model should be driven by evidence from clinical trials relating to each of the model's health states: the duration of PFS when patients receive second-line treatment and the duration of PPS when patients receive only BSC. Unfortunately, the only outcomes routinely reported for clinical trials are PFS and OS. Thus the model can only be populated indirectly by inferring the probable experience of patients in the intermediate states. This leads to potentially serious difficulties and inconsistencies in model implementation. In particular, the normal practice of treating PFS and OS as independent variables is naive, since PFS is a major component of OS. Not recognising this easily leads to situations where deriving an estimate for PPS by subtracting estimated PFS from estimated OS leads to erroneous negative values at some point during the simulation period. The modeller has to exercise great care at every stage of model development, calibration and use so as to guard against producing nonsensical results.

Synthesis of outcome data: progression-free survival and overall survival

Epidermal growth factor mutation-positive population

No clinical trials have been identified which compare second-line treatments in a population of only patients with EGFR-activating mutations.

Epidermal growth factor mutation-negative population

Clinical effectiveness data for this patient group are restricted to TAILOR,[41] which compares erlotinib with docetaxel. Published Kaplan–Meier survival curves were digitised by the AG to provide source data for projecting the full cohort experience until death. Both PFS and OS curves exhibited forms inconsistent with the standard parametric functions routinely featured in commercially available statistical software.

All such functions assume that a single continuous disease and treatment process is in effect throughout the duration of the trial, resulting in gradual smooth changes in event risk and survival outcomes from randomisation until the outcome event (progression/death for PFS or death for OS). The Kaplan–Meier curves from TAILOR[41] show clearly that this assumption is invalid, with quite different behaviour exhibited over different periods of the trial in both patient groups.

The natural history of untreated advanced/metastatic lung cancer is generally straightforward, involving a high but constant risk of disease progression and death within a short time period (usually best represented as a Poisson process, i.e. an exponential survival function). However, when short-term interventions are applied to patients, the normal disease dynamic is distorted, typically into three time periods: an initiation period (prior to treatments achieving full efficacy), an efficacious period (when different treatments may show divergent risk of progression/death) and a loss of efficacy period (when the natural course of progressive disease is reasserted).

Examination by the AG of the cumulative hazard plots for the trial data indicated that a three-phase spline model (with two 'knot' points) closely represents the published trial results and outperforms any of the standard parametric functions conventionally employed. In the first phase, event risks are very similar in both trial arms. In the second phase, patients in both trial arms are subject to increased risk of an event (progression or death) and at different levels of risk corresponding to differential treatment efficacy, so that the survival curves diverge. In the final phase, event risks reduce substantially in both arms. In addition, the transitions between phases appear to occur at the same time from randomisation in both treatment arms. The event risk within each phase was found to conform closely to a constant (equivalent to an exponential survival function) in both treatment arms. The main structural difference between statistical models for the two treatments occurs in the final phase. For PFS the event risk remains higher in the erlotinib arm, suggesting that PFS outcomes continue to diverge indefinitely, whereas in the OS comparison the long-term mortality risk stabilises at the same level once all patients have suffered disease progression, thus suggesting that for the remainder of patients' lifetimes survival prognosis is unrelated to previous treatments.

Figures 7 and *8* demonstrate the correspondence between TAILOR[42] data and the AG's projective models. The calibrated models were only used to project PFS and OS during and beyond the third phase to maximise the use of the unadjusted trial data. In all cases projection was commenced at the same value of the estimated remaining PFS or OS to avoid introducing bias from projecting different proportions of

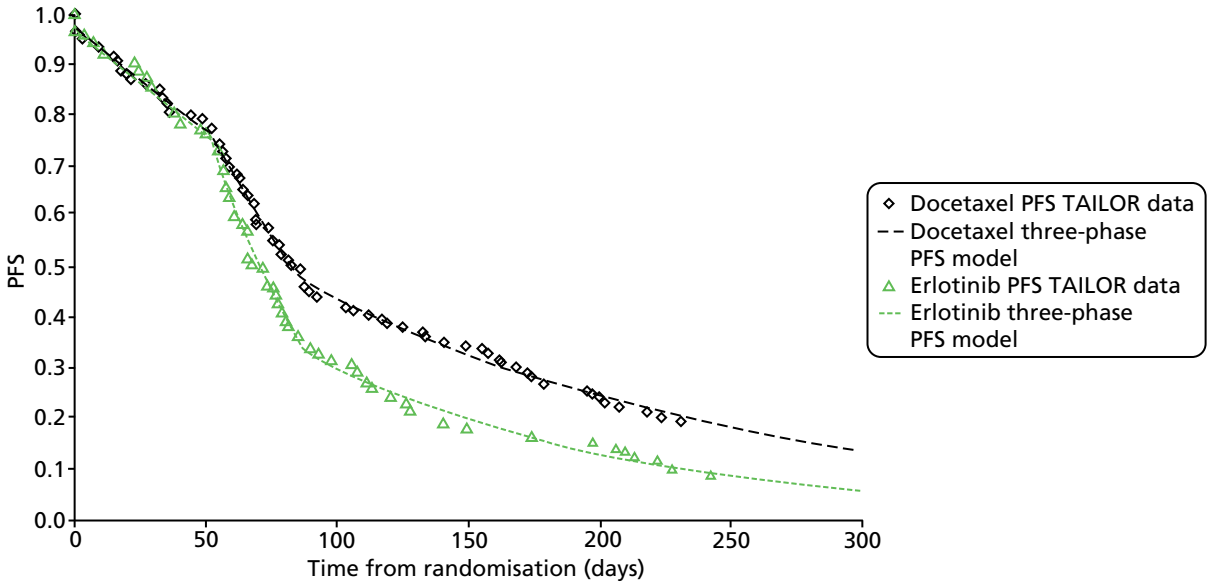

FIGURE 7 Three-phase projective spline models fitted to PFS data from TAILOR.[42]

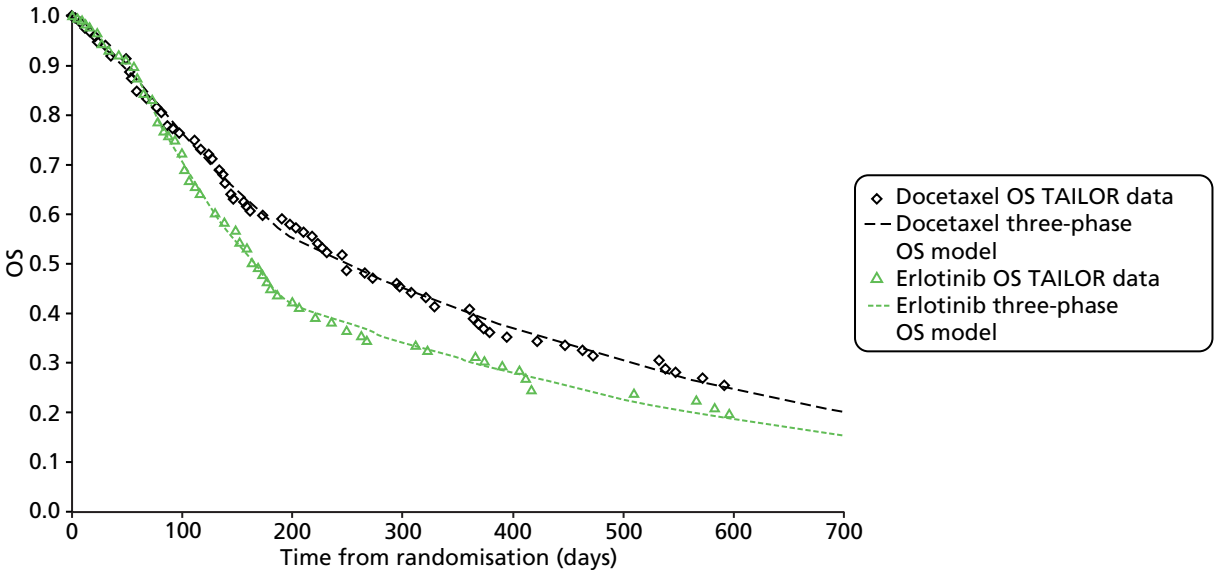

FIGURE 8 Three-phase projective spline models fitted to OS data from TAILOR.

patient experience subject to different degrees of modelling error. For PFS projection began at the point when 30% of patients were estimated to be event-free and for OS projection began at 41%. Details of the AG's model parameters, estimates and standard errors are provided in *Appendix 7*.

Epidermal growth factor mutation status unknown population

Clinical effectiveness data for this patient group are restricted to the BR.21[31] trial. The manufacturer's model included detailed Kaplan–Meier analysis data, which provided the source data for projecting the full cohort experience until death. Both PFS and OS curves exhibited similar forms to those observed in TAILOR.[41] Therefore, a similar three-phase spline model (with two 'knot' points) was employed for analysis of the BR.21[31] data. The transitions between phases ('knot' points) in the two trial arms occur at different points between the first two phases but at a common time point between phases 2 and 3. The event risk within each phase was found to conform closely to a constant (equivalent to an exponential survival function) in both treatment arms. In both OS and PFS models the long-term event risk (phase 3) exhibits the same hazard rate in both arms of the trial.

In these circumstances a simplified model formulation could be focused on the final long-term period (phase 3), recognising that accurate Kaplan–Meier data are available into the final period and should be applied directly, which limits the need for projection of missing data to a short final period. A single exponential long-term model was calibrated for a single hazard parameter, and separate constant parameters for each treatment arm which together correspond to the separation between the survival curves at the second 'knot' point (296 days).

Figures 9 and *10* show the correspondence between the trial data and the late-stage projective models. These calibrated models were only used to project PFS and OS during and beyond the third phase to maximise the use of the unadjusted trial data. In all cases projection was commenced at the same value of the estimated remaining PFS or OS to avoid introducing bias from projecting different proportions of patient experience subject to different degrees of modelling error. For PFS projection began at the point when 5% of patients were estimated to be event-free and for OS at 25%. Details of the model parameters, estimates and standard errors are provided in *Appendix 7*.

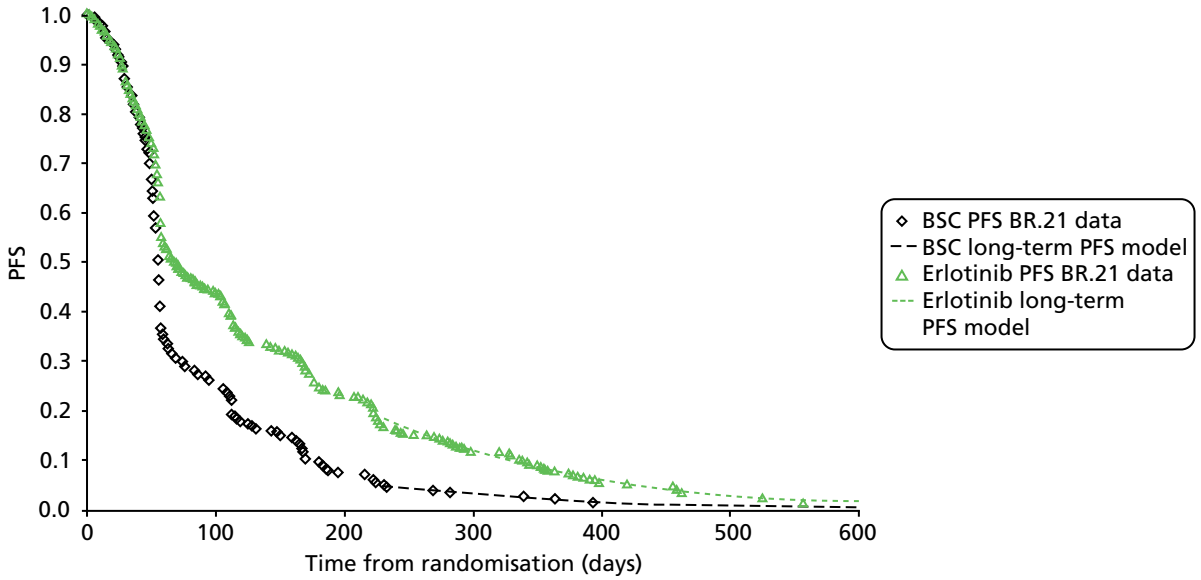

FIGURE 9 Long-term projective models fitted to PFS data from the BR.21 trial.[31]

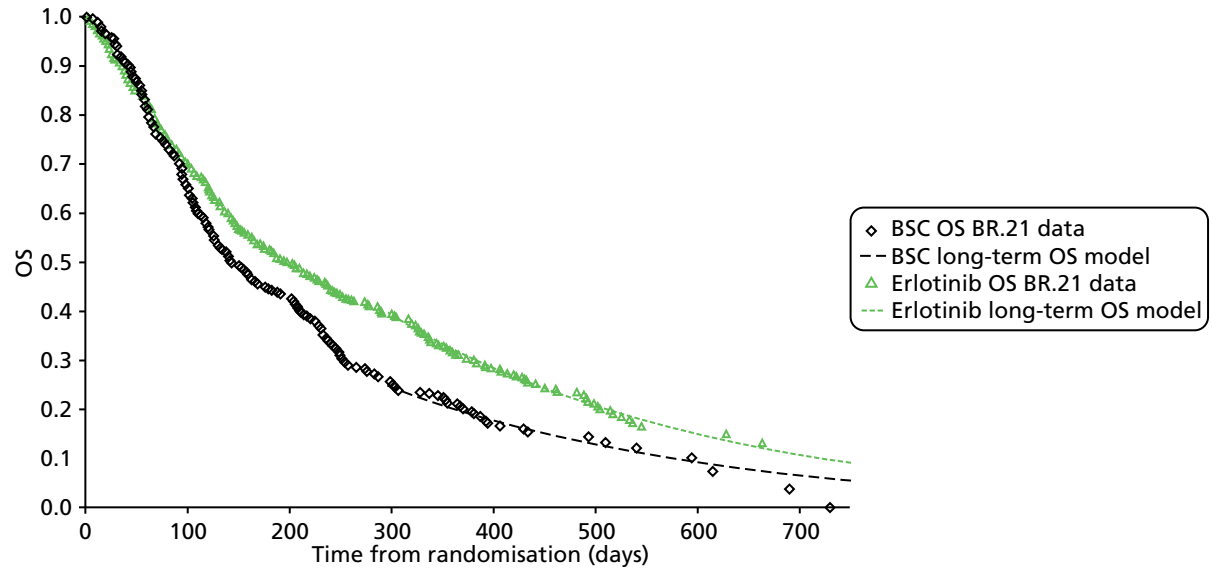

FIGURE 10 Long-term projective models fitted to OS data from the BR.21 trial.[31]

Synthesis of outcome data: RRs to second-line chemotherapy

The Nafees *et al.*[75] multivariate utility model (which is used in the AG model) includes two levels of response to therapy as predictive variables: 'responder' (either complete or partial response) and 'stable disease' (neither response nor disease progression). Estimates for these variables were obtained by pooling reported responses described in published clinical trials relevant to each population: 15 trials[31,34,37–39,42,49,54,74,85–91] involving patients undifferentiated by mutation status and only one trial each for the EGFR M+ population[32] and the EGFR M– population.[41] The Kim *et al.* trial[32] included 35% of patients with confirmed EGFR M+ status and also patients with a high probability of EGFR-activating mutations on the basis of other patient characteristics. The parameter values obtained are shown in *Table 40*.

TABLE 40 Pooled RRs (%) for second-line chemotherapy

Patient population and treatment	Responders (%)		Stable disease (%)	
	Mean	95% CI	Mean	95% CI
EGFR M+ population				
Erlotinib	39.6	26.4 to 53.6	27.1	15.6 to 40.4
Gefitinib	47.9	34.1 to 61.9	30.2	27.8 to 32.6
EGFR M– population				
Docetaxel	15.5	9.0 to 23.3	28.9	20.3 to 38.2
Erlotinib	3.0	0.6 to 7.1	23.0	15.3 to 31.7
EGFR unknown population				
BSC/placebo	1.2	0.5 to 2.1	30.8	26.8 to 35.0
Docetaxel	8.5	7.2 to 9.9	36.2	33.1 to 39.3
Erlotinib	8.7	6.8 to 10.7	29.8	26.6 to 33.0

Synthesis of outcome data: adverse events

The costs and disutilities of treatment-related AEs are limited in the model to seven major categories, (using the results of a multivariate model by Nafees *et al.*[75] described in detail in *Health valuation estimation*): diarrhoea, fatigue, FN, hair loss, nausea/vomiting, neutropenia and skin rash.

The reported incidences of grade 3 and 4 AEs in all published second-line chemotherapy trials were pooled to obtain estimates of the proportion of patients suffering each event during treatment. No attempt was made to carry out a more sophisticated meta-analysis as reporting of AEs was often incomplete and lacking consistency. *Table 41* details the incidence rates obtained for each second-line chemotherapy agent.

These values were used to model treatments in the EGFR M+ population (where no relevant clinical trial has been undertaken) and in the EGFR unknown population. For the EGFR M– population, the AE incidence rates reported in TAILOR[41] have been used directly, as shown in *Table 42*.

TABLE 41 Pooled grade 3 and 4 AE incidence rates (%) for second-line chemotherapy

AE incidence rates	Diarrhoea	Fatigue	FN	Hair loss	Nausea/ vomiting	Neutropenia	Skin rash
BSC/placebo							
Mean (%)	0.7	11.0	0.0	0.0	1.8	0.0	0.1
95% CI	0.3 to 1.4	9.0 to 13.1	0.0 to 0.2	0.0 to 0.2	1.1 to 2.8	0.0 to 0.2	0.0 to 0.4
Docetaxel							
Mean (%)	2.1	7.4	7.6	1.1	2.9	46.7	0.5
95% CI	1.5 to 2.9	6.2 to 8.6	6.4 to 8.8	0.6 to 1.6	2.1 to 3.7	44.4 to 48.9	0.3 to 0.9
Gefitinib							
Mean (%)	2.3	2.9	0.4	0.0	1.6	1.4	1.7
95% CI	1.7 to 2.9	2.3 to 3.6	0.2 to 0.7	0.0 to 0.1	1.1 to 2.1	1.0 to 1.9	1.2 to 2.3
Erlotinib							
Mean (%)	3.7	9.9	0.0	0.0	3.4	0.0	8.1
95% CI	2.6 to 4.9	8.1 to 11.8	0.0 to 0.2	0.0 to 0.2	2.4 to 4.6	0.0 to 0.2	6.5 to 9.9

TABLE 42 Grade 3 and 4 AE incidence rates (%) for second-line chemotherapy in an EGFR M– population (TAILOR)

Treatment arm	Diarrhoea	Fatigue	FN	Hair loss	Nausea/ vomiting	Neutropenia	Skin rash
Docetaxel							
Mean (%)	1.9	9.6	6.35[a]	14.4	2.9	20.2	0.0
95% CI	0.2 to 5.3	4.8 to 15.9	1.8 to 13.5	8.4 to 21.8	0.6 to 6.8	13.1 to 28.4	0.0 to 2.4
Erlotinib							
Mean (%)	2.8	5.6	0.0	0.0	0.9	0.0	14.0
95% CI	0.6 to 6.7	2.1 to 10.7	0.0 to 2.4	0.0 to 2.4	0.0 to 3.4	0.0 to 2.4	8.1 to 21.2

a Rates are for patients treated on a 3-weekly cycle.

Active treatment cost estimation

Second-line active treatment doses for docetaxel were calculated individually on the basis of the patient's body surface area. Calculations are carried out separately for males and females, and a weighted average cost is obtained using the relative proportions of recorded deaths[91] from malignant neoplasm of trachea, bronchus and lung in England and Wales in 2012 (55.2% males, 44.8% females).

Two sources are available as options to provide unit costs relating to the purchase of drugs: the list prices of erlotinib, gefitinib, docetaxel (generic) and dexamethasone shown in the BNF[29] (July 2013), and the prices reported in eMit[83] produced by the Commercial Medicines Unit of the Department of Health for docetaxel and dexamethasone. The eMit provides estimated mean product prices for generic medicines drawn from information from about 95% of NHS trusts. For both erlotinib and gefitinib, patient access schemes prices have been agreed with the Department of Health and are shown in *Table 43*, which summarises the unit cost data employed in the estimation of chemotherapy acquisition costs.

TABLE 43 Unit acquisition costs for chemotherapy agents

		BNF price[29] (£)	eMit price[84] (£)
Product	Vial content	Mean	Mean
Docetaxel[a]	20 mg	138.33	7.93
	80 mg	454.53	32.40
	140 mg	900.00	39.13
Gefitinib[b]	Per patient	12,200	12,200
Erlotinib	30 × 150 mg	1631.53	1631.53
	NHS discount	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Dexamethasone[a]	50 × 2 mg	6.96	1.80

a Best generic price used.
b Patient access scheme price per patient applies only to patients receiving treatment beyond 60 days.
Commercial-in-confidence information has been removed.

Docetaxel costs are estimated per 21-day cycle (including the costs of required co-medication). The oral medications (erlotinib and gefitinib) are costed on the basis of whole-pack costs incurred whenever previous supplies are exhausted. As part-used packs cannot be reused when treatment is discontinued, some wastage is unavoidable. The AG's base-case analysis is carried out using the eMit[83] prices for docetaxel and co-medication, with BNF[29] prices used in a sensitivity analysis. Where a discounted price for a patented drug is available across the whole NHS, the appropriate discount is applied in all analyses. The estimated drug cost per cycle to the NHS of each second-line treatment is shown in *Table 44*.

It is assumed that treatment continues until disease progression or death. Time-to-off-treatment data for erlotinib from the BR.21[31] trial were analysed and compared with PFS data but were not found to be statistically significantly different.

The unit costs employed for chemotherapy administration, based on NHS Reference Costs 2011/12,[82] are shown in *Table 45*. On clinical advice, docetaxel is assumed always to be administered in a day-case setting and oral medication packs are issued as part of a nurse-led outpatient visit.

Health state cost estimation

Costs have been estimated relating to patient monitoring and supportive care in three health states: in PFS (either during or following second-line treatment), post progression when no active treatment is received and for terminal care (assumed to last, on average, for 14 days).

In PFS patients are expected to receive regular consultant-led outpatient consultations and periodic diagnostic tests (chest radiography, computed tomography and electrocardiogram). During PPS patients are assumed to have been discharged to community-based supportive care where care is provided by the patient's general practitioner (in surgery or at home) and community nursing staff. In the terminal phase, care is likely to be more intensive, with the package varying by the chosen setting.

TABLE 44 Estimated acquisition cost per cycle of chemotherapy

Second-line treatment	Estimated cost – BNF 66 prices[29] (£)		Estimated cost – eMit prices[84] (£)	
	Per cycle	Per patient	Per cycle	Per patient
Docetaxel	922.81[a]	N/A	44.88[a]	N/A
Erlotinib	Commercial-in-confidence information has been removed[b]	N/A	Commercial-in-confidence information has been removed[b]	N/A
Gefitinib	N/A	12,200	N/A	12,200

N/A not applicable.
a 3-week cycle for docetaxel.
b 4-week cycle for erlotinib.
Commercial-in-confidence information has been removed.

TABLE 45 Unit costs of chemotherapy administration

Treatment setting	HRG code	Description	Mean (£)	Standard error[a] (£)
Day-case unit	SB12Z	Simple parenteral chemotherapy at first attendance	203.16	7.47
Day-case unit	SB15Z	Subsequent doses of chemotherapy	283.89	10.14
Outpatient visit	NCLFUSFF 370	Medical oncology	106.00	10.60[a]

HRG, health resource group.
a 10% of mean assumed.

Table 46 details the mean volumes of each resource assumed and *Table 47* summarises the unit costs used with the relevant sources. More detailed information describing cost assumptions is presented in the publication by Brown *et al.*[2]

Adverse event cost estimation

The costs of treating grade 3 and 4 AEs of second-line therapy are spread over 12 weeks (four cycles) and estimated using NHS Reference Costs for 2011/12,[82] as follows:

Diarrhoea

It is assumed that a typical patient will have two hospital admissions during second-line treatment, corresponding to health research group (HRG) code FZ48C (malignant general abdominal disorders of length of stay 1 day or less) as a non-elective short-stay episode, each costing £525.38.

Fatigue

It is assumed that a typical patient will have one hospital admission during second-line treatment, corresponding to HRG code WA17X (other admissions related to neoplasms with intermediate complicating conditions) as a non-elective long-stay episode of 5 to 7 days costing £2233.40.

TABLE 46 Estimated health-care resource use per patient for disease monitoring and supportive care in PFS, PPS and during the terminal phase

Resource	PFS	PPS	Terminal care	Source
Outpatient visit	9.61 pa	–	–	Big Lung Trial[92]
Chest radiography	6.79 pa	–	–	Big Lung Trial[92]
CT (chest)	0.62 pa	–	–	Big Lung Trial[92]
CT (other)	0.36 pa	–	–	Big Lung Trial[92]
ECG	1.04 pa	–	–	Big Lung Trial[92]
Hospital/hospice episode	–	–	8.93 days	Average stay for non-elective long-stay IP episode plus average IP excess days for HRG DZ17 A – NHS Reference Costs 2011/12[82]
Community nurse visit	26 visits (20 minutes) pa	52 visits (20 minutes) pa	28 hours (2 hours per day)	Appendix 1 of NICE Guideline CG81,[93] Marie Curie report[94]
Clinical nurse specialist	12 hours contact time pa	52 hours contact time pa	–	Appendix 1 of NICE Guideline CG81[93]
GP surgery	12 consultations pa	–	–	Appendix 1 of NICE Guideline CG81[93]
GP home visit	–	26 visits pa	7 visits (alternate days)	Marie Curie report[94]
Therapist visit	–	26 hours pa	–	Appendix 1 of NICE Guideline CG81[93]
Macmillan nurse	–	–	50 hours	Marie Curie report[94]
Drugs/equipment	–	–	As required	Marie Curie report[94]
Location of terminal care	–	–	Hospital 55.8%, hospice 16.9%, home 27.3%	Office for National Statistics death registration summary tables 5.2 and 12[91]

CT, computed tomography; ECG, electrocardiogram; GP, general practitioner; HRG, health resource group; pa, per annum; IP, inpatient.

TABLE 47 Unit costs of disease monitoring and supportive care

Resource	Unit cost (£)	Source
Outpatient follow-up visit	£113.17	NHS Reference Costs 2011–12, HRG code CLFUSFF 800 – clinical oncology[82]
Chest radiography	£30.26	NHS Reference Costs 2011/12, code DAPF – direct access plain film[82]
CT (chest)	£124.99	NHS Reference Costs 2011–12, HRG code RA12Z (2 areas with contrast)[82]
CT (other)	£134.57	NHS Reference Costs 2011–12, HRG code RA13Z (3 areas with contrast)[82]
ECG	£60.73	NHS Reference Costs 2011/12, code EA47Z – direct access ECG[82]
Community nurse	£70.00 per hour	PSSRU *Unit Costs of Health and Social Care 2012*, page 175, cost per hour spent on home visits (including qualification)[84]
Clinical nurse specialist	£91.00 per contact hour	PSSRU *Unit Costs of Health and Social Care 2012*, page 181, cost per contact hour (including qualification)[84]
GP surgery visit	£43.00	PSSRU *Unit Costs of Health and Social Care 2012*, page 183, cost per surgery visit (11.7 minutes, including direct care staff)[84]
GP home visit	£110.00	PSSRU *Unit Costs of Health and Social Care 2012*, page 183, cost per home visit (23.4 minutes, including travel time)[84]
Therapist	£44.00	PSSRU *Unit Costs of Health and Social Care 2012*, page 194, cost per hour (including training)[84]
Terminal care inpatient care	£2716.53 + 0.84 excess days at £232.90 per day	NHS Reference Costs 2011/12, code DZ17 A (respiratory neoplasms with major complicating conditions) non-elective inpatient (long stay – episode/excess days)[83]
Terminal care in hospice	25% increase on hospital inpatient care	Assumption
Macmillan nurse	66.7% of community nurse cost	Assumption
Drugs and equipment	£500	Marie Curie report,[94] figure of £240 increased for inflation

CT, computed tomography; ECG, electrocardiogram; GP, general practitioner; HRG, health resource group; pa, per annum.

Febrile neutropenia

The NICE Decision Support Unit report on the cost of FN[95] has been updated for current NHS Reference Costs.[83] This assumes 1.4 episodes per patient during the second-line treatment. The estimated cost per patient is £7066.63.

Hair loss

It is assumed that there are no hospital episodes related to this AE and no direct costs are incurred.

Nausea/vomiting

It is assumed that a typical patient will have two hospital admissions during second-line treatment, corresponding to HRG code FZ48C (malignant general abdominal disorders of length of stay 1 day or less) as a non-elective short-stay episode, each costing £525.38.

Neutropenia (non-febrile)

It is assumed that 10% of patients will experience two episodes of neutropenia requiring hospital treatment during second-line treatment. The cost per episode is £866.61 and is estimated from the weighted average of mean costs for HRG codes WA02W (disorders of immunity without human immunodeficiency virus/acquired immune deficiency syndrome with complicating condition) and PA48A (blood cell disorders with complicating condition) across non-elective long and short-stay episodes, and day-case admissions.

Skin rash

It is assumed that a typical patient will have one additional outpatient consultation for this condition during second-line treatment. A weighted-average NHS reference cost of £109.77 is used, based on codes 370 (Medical oncology) and 800 (Clinical oncology), for both consultant-led and non-consultant-led visits.

Health valuation estimation

Ideally, the utility of patients with NSCLC should be informed by data obtained directly from the relevant patient population relating to their perceived condition at all phases of the treatment pathway covered by the economic model. Unfortunately, this is practically and ethically impractical for patients suffering advanced disease with severe symptoms (arising from either the natural course of the disease or related to treatments received) and who have generally very limited remaining life expectancy. Few clinical trials have attempted to collect patient health utility data, and RRs are generally poor as few patients continue to complete questionnaires as their condition worsens. We identified, via a comprehensive literature search, very few studies describing relevant utility data for use in our model.

An observation study conducted in the Netherlands[96] between 1999 and 2002 attempted to obtain such data (using the EQ-5D instrument) from patients with NSCLC treated between 2004 and 2007 and surviving to 2008. Unfortunately, this patient sample is not representative of the populations considered in the AG's model (patients with locally advanced and/or metastatic NSCLC), since only 44% of patients had received any chemotherapy, only 41% had stage III/IV disease and only 14% had local/regional or metastatic recurrent disease at the time of the survey. Clearly the results of the observation study are dominated by patients who were diagnosed at an early stage and had successful surgery, thus potentially biasing numeric estimates of utility towards higher values.

One clinical trial with relevant data compared two radiotherapy regimens for poor-prognosis patients with NSCLC in 13 Dutch radiotherapy centres.[97] Patients completed EQ-5D questionnaires initially weekly, and then 2-weekly until death, enabling EQ-5D utility scores to be estimated. Responses were obtained on 83% of occasions, allowing the temporal trend in patient utility to be characterised. Some data from the published results have been used in the AG's model.

The only alternative to direct measurement of patient symptoms for estimating utility is via a structured sample of the general public valuing a set of typical patient scenarios, representing the range of likely conditions experienced by patients with NSCLC during their remaining lifetime. Two such recent studies have been identified. Doyle *et al.*[98] recruited 101 volunteers from the general public in the London area, who were asked to value six typical health states experienced by advanced NSCLC patients, using the standard gamble method. This allowed estimation of a mean utility value for patients with stable disease on treatment, as well as the incremental effect of response to treatment and also the incremental disutility of three common symptoms (cough, dyspnoea and pain). Although promising, this study provides only limited results which are insufficient to populate all the health states and important AEs which are required to populate the current model.

The utility scheme which has been adopted for use in the AG's model is that described in a paper published in 2008 by Nafees *et al.*[75] This also uses the standard gamble method and employed 100 volunteers from the UK general population. In this case a more extensive set of scenarios were used (17 specific disease health states plus two anchor states), developed with the help of a panel of oncologists and designed

specifically to address a range of the most common severe AEs experienced by advanced NSCLC patients undergoing second-line treatment for metastatic cancer. A mixed-model analysis yielded simultaneous utility estimates for three health states (responding to treatment, stable disease and progressive disease) together with incremental disutility values for seven common serious grade 3 and 4 AEs – diarrhoea, fatigue, FN, hair loss (alopecia), nausea/vomiting, neutropenia and rash. The range of AEs in the Nafees *et al.*[75] model is sufficient to cover all the major problems experienced with current treatments.

Applying the treatment-specific AE incidence rates (see *Tables 41* and *42*) and treatment RRs (see *Table 40*) to the Nafees *et al.*[75] utility model yields a full set of health-state utilities for each treatment option as shown in *Table 48*. The utility for the terminal period (last 2 weeks of life) was obtained by use of results reported for average EQ-5D scores relative to the time prior to death (figure 3 in the van den Hout *et al.* 2006 study[97] of palliative radiotherapy in patients with NSCLC).

Modelling assumptions

Following disease progression it is assumed that subsequent experience of health care (and associated health and social costs) and QoL is broadly equivalent for all patients and are independent of previous treatments received.

No explicit disutility adjustment is included to reflect differences in patient preferences and experience of i.v. therapy versus oral therapy versus BSC, beyond that implicit in differences in AE incidence rates.

Sensitivity analysis

For each modelled scenario, univariate sensitivity analysis was performed for all model parameters using lower and upper CIs, and these are reported in the form of a torpedo diagram indicating the 20 variables most influential on the size of the deterministic ICER. In addition, a PSA was carried out and through a probabilistic ICER, a scatterplot of replication incremental costs and QALYs and cost-effectiveness acceptability curves.

Beta distributions are employed in both univariate sensitivity analyses and PSA for parameters involving proportions (RRs, AE rates, sex mix, place of death and proportion of PFS which are fatal). For all other parameters, normal distributions are used.

The manufacturer of erlotinib proposed in their submission an exploratory analysis comparing erlotinib with BSC in a subgroup[43] of BR.21[31] trial patients. The AG has, therefore, applied data for this subgroup to their model as a further sensitivity analysis.

TABLE 48 Estimated health-related utility values using Nafees' model

Second-line therapy	PFS	PPS (> 2 weeks prior to death)	Terminal period (2 weeks)
EGFR M– population (TAILOR trial[41])			
Docetaxel	0.6225	0.4734	0.2488
Erlotinib	0.6450	0.4734	0.2488
EGFR M– population (wild-type subgroup of BR.21 trial[31]) and EGFR unknown population (BR.21 trial[31])			
Erlotinib	0.6351	0.4734	0.2488
BSC	0.6353	0.4734	0.2488

Results

Epidermal growth factor mutation-positive population

In the absence of any relevant clinical trial evidence in this population there is no reliable basis on which to assess the cost-effectiveness of available treatments.

The AG has considered carefully the evidence submitted by the manufacturer of gefitinib, but it concludes that the information made available to the AG in the manufacturer's submission does not allow any formal decision modelling to be undertaken. This is because, at the very least, compatible PFS data and treatment RRs would be required in addition to OS estimates to allow a decision model to be populated.

Epidermal growth factor mutation-negative population

Erlotinib versus docetaxel

Deterministic results from the main EGFR M– model based on data from TAILOR[41] are summarised in *Table 49*. It should be noted that the rate of FN and the estimation of its costs were a key point of debate during the assessment process (see *Appendix 8*). Several iterations of the cost-effectiveness results for the EGFR M– patient population were produced in response to particular needs; the results presented in *Table 49* are those presented at the NICE final AC meeting. The calculations are based on a rate of FN of 6.35%. This figure is derived from the subgroup of patients in TAILOR[41] who received 3-weekly treatments of docetaxel (the treatment regime used in clinical practice in England and Wales).

Erlotinib is dominated by docetaxel in the EGFR M– population, yielding a reduced mean survival and fewer QALYs while also involving a greater net cost of treatment. Univariate sensitivity analysis (*Figure 11*) for the deterministic base case indicates that the use of generic docetaxel in place of the branded product is the major factor in establishing docetaxel as the preferred option. The incidence rate of FN has a larger influence on the estimated ICER than other model parameters, but for none of model parameters is the known parameter uncertainty sufficient to alter the conclusion that erlotinib is dominated by docetaxel in the EGFR M– population. The only model input which could alter this conclusion is the incidence rate of FN in docetaxel-treated patients; this is considered in *Appendix 8*.

A PSA (*Figure 12*) and the cost-effectiveness acceptability curve (*Figure 13*) yield a similar result: an estimated ICER of –£7709 per QALY gained, indicating that for any cost-effectiveness threshold greater than £0 per QALY there is a probability greater than 99% that erlotinib is less cost-effective than docetaxel.

TABLE 49 Base-case deterministic cost-effectiveness results erlotinib vs. docetaxel second-line treatment in the EGFR M– population using evidence from TAILOR[41]

Cost-effectiveness result	Docetaxel		Erlotinib		Incremental	
Survival (mean)	**Years**	**Months**	**Years**	**Months**	**Years**	**Months**
PFS	0.409	4.91	0.287	3.45	0.122	1.46
PPS	0.731	8.77	0.641	7.70	0.089	1.07
Terminal	0.038	0.46	0.038	0.46	0.000	0.00
OS	1.178	14.13	0.967	11.60	0.211	2.53
QALYs	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**
PFS	0.2537	0.2526	0.1853	0.1850	0.0684	0.0676
PPS	0.3459	0.3311	0.3036	0.2920	0.0423	0.0392
Terminal	0.0095	0.0092	0.0095	0.0093	0.0000	0.0001
OS	0.6091	0.5930	0.4984	0.4863	–0.1107	–0.1067
Costs	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**
2L Tx acquisition	£342	£340	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
2L administration	£2314	£2305	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
2L Tx AEs	£585	£585	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
PFS BSC	£1531	£1524	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
PPS BSC	£5148	£4928	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Terminal care	£3917	£3820	–	–	–	–
Total costs	£13,837	£13,504	£14,302.08	£14,049.00	£465	£545
ICER						
Cost per QALY gained	–£5112 (discounted) for erlotinib vs. docetaxel (dominated)					
Net benefit						
£ per patient (£30,000 per QALY)	–£3746 per patient for erlotinib vs. docetaxel (dominated)					

2L, seocnd line; Tx, treatment.
Commercial-in-confidence information has been removed.

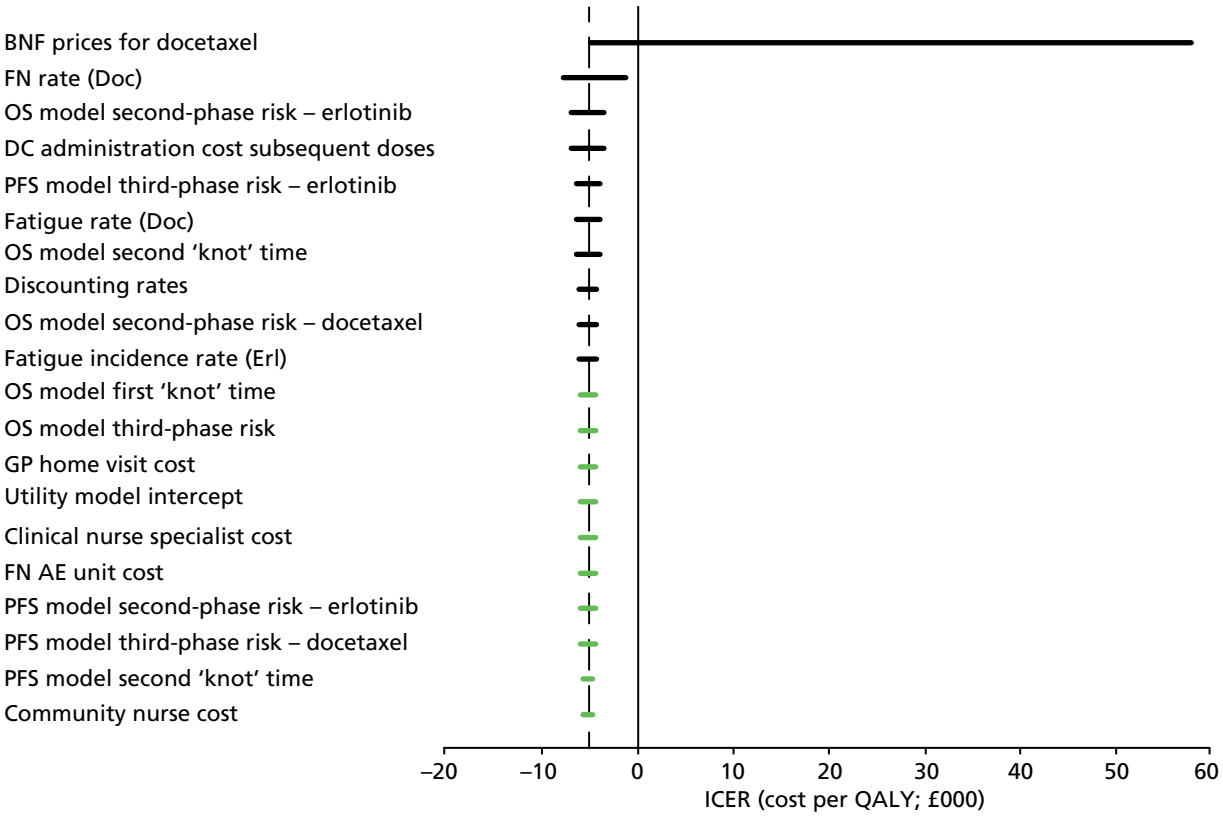

FIGURE 11 Univariate sensitivity analysis: erlotinib vs. docetaxel second-line treatment in the EGFR M– population from TAILOR – 20 most influential parameters. DC, day case; Doc, docetaxel; Erl, erlotinib; GP, general practitioner.

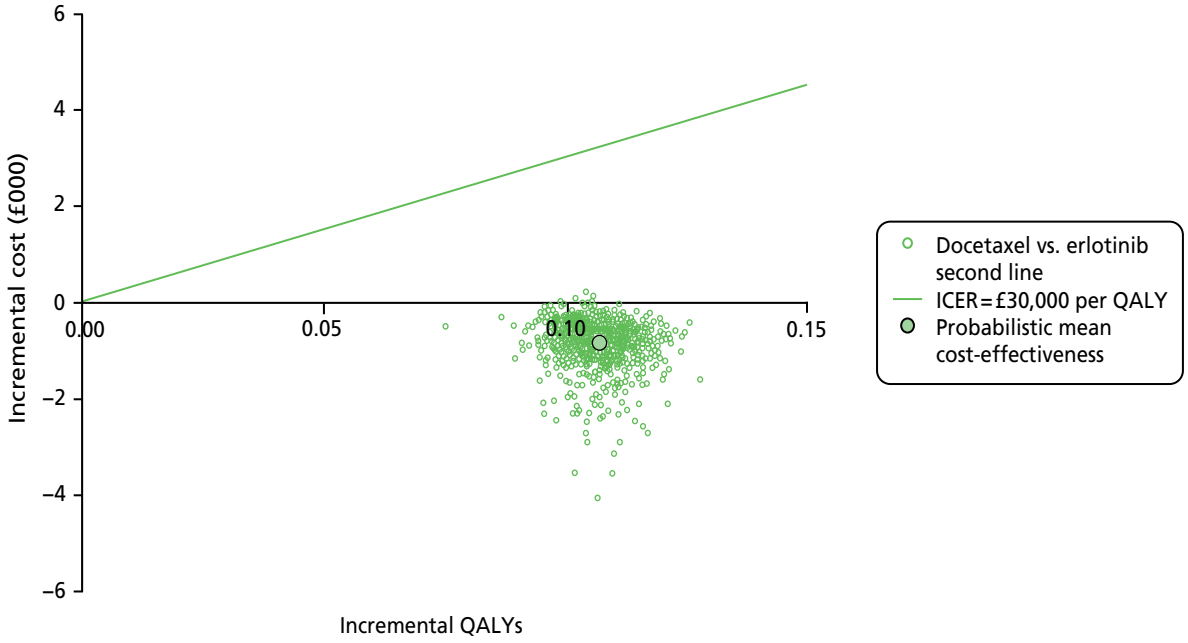

FIGURE 12 Probabilistic sensitivity analysis: scatterplot of the base-case analysis for erlotinib vs. docetaxel second-line treatment in the EGFR M– population using evidence from TAILOR.[41]

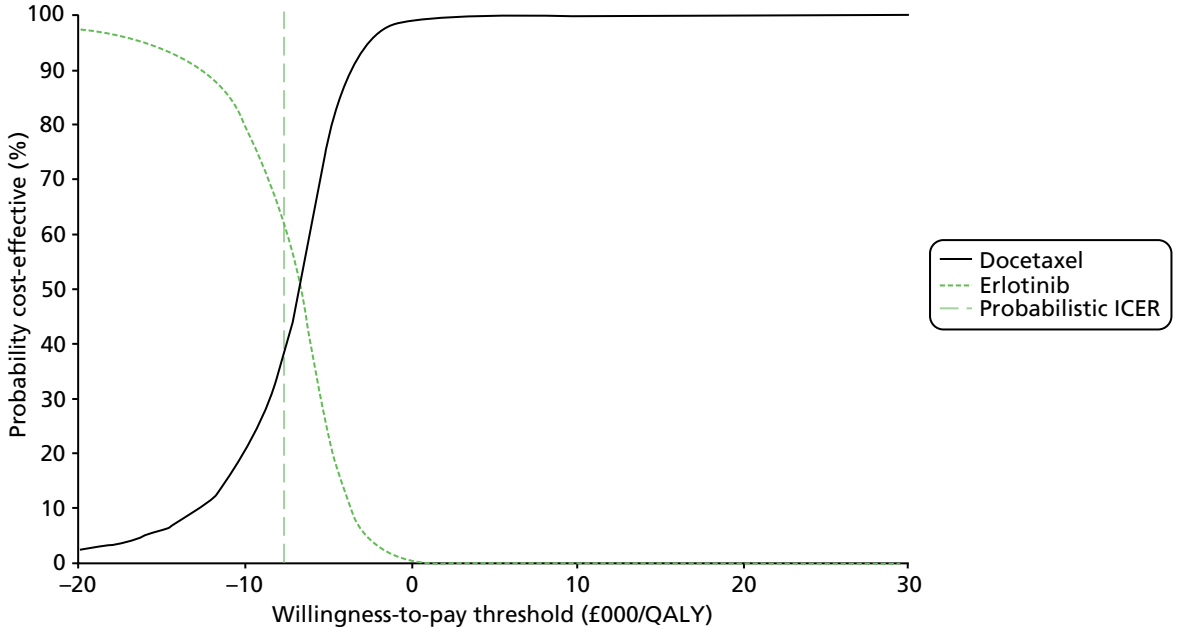

FIGURE 13 Cost-effectiveness acceptability curves for the comparison of erlotinib vs. docetaxel second-line treatment in the EGFR M– population using evidence from TAILOR.[41]

Erlotinib versus best supportive care

The manufacturer of erlotinib submitted a sensitivity analysis of its main economic analysis of the population of unknown EGFR status (see next section), using survival data from a post-hoc reanalysis[42] of the results of the BR.21[31] trial. This analysis restricts attention to those patients who were confirmed not to have EGFR-activating mutations, that is only EGFR M– (or EGFR wild-type) disease. Inevitably the source data[43] are less reliable than the main ITT analysis of BR.21[31] results because of the risk of imbalance in baseline patient characteristics and the reduced sample size.

In order to replicate this sensitivity analysis, the AG has carried out a similar exercise using the same outcome data applied to the AG model structure. *Figures 14* and *15* show the trajectories fitted to the trial data to populate the decision model.

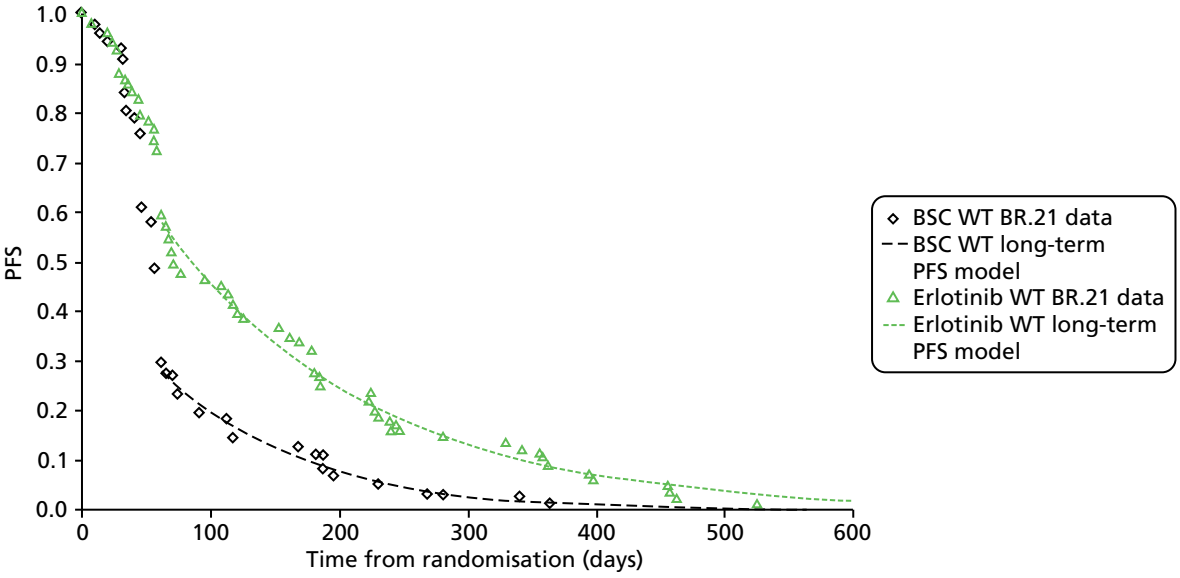

FIGURE 14 Projective models fitted to PFS data from the EGFR M– subgroup of the BR.21[31] trial. WT, wild type.

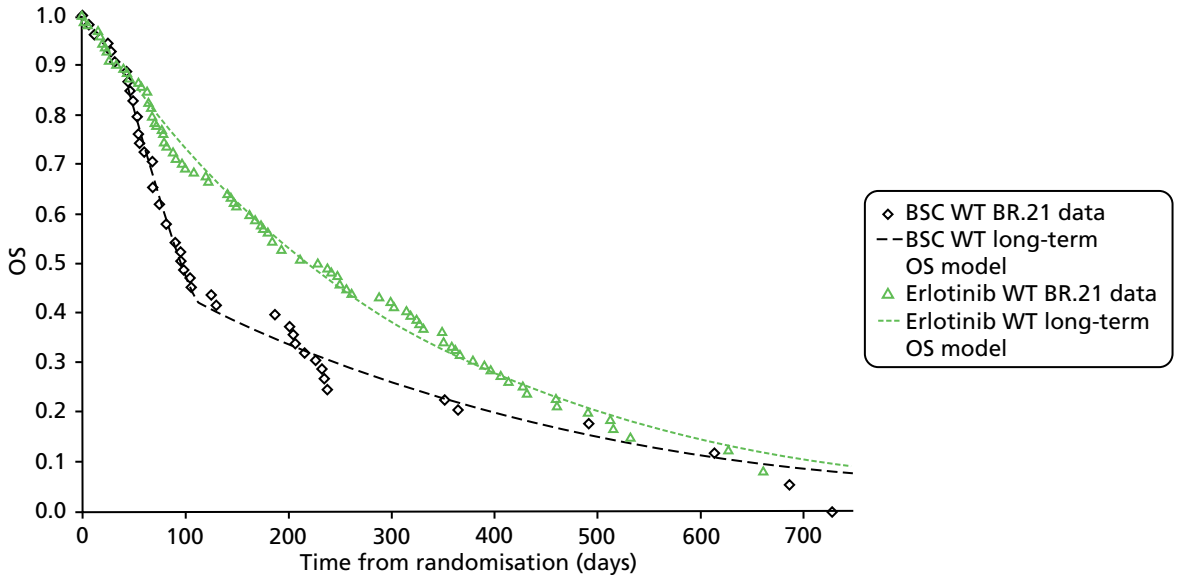

FIGURE 15 Projective models fitted to OS data from the EGFR M– subgroup of the BR.21[31] trial. WT, wild type.

Deterministic results from the EGFR M– model based on subgroup EGFR M– data[43] from the BR.21[31] trial are summarised in *Table 50*. The estimated mean OS advantage of using erlotinib rather than BSC is 2.2 months, all of which occurs prior to disease progression. The corresponding gain in mean discounted QALYs is 0.116 per patient. The estimated ICER of £54,686.73 per QALY gained is above the range normally considered cost-effective. The results of univariate sensitivity analyses are summarised in *Figure 16*, indicating that these results are most affected by projective survival model parameters (especially for the OS model), utility model parameters and the incidence of key AEs.

Probabilistic sensitivity analysis incorporating uncertainty in all model parameters indicates a slightly lower estimated ICER of £54,184 per QALY gained. Examination of the PSA scatterplot (*Figure 17*) and the cost-effectiveness acceptability curves (*Figure 18*) indicate strong general confidence that erlotinib exhibits a high ICER when compared with BSC in this subgroup (0% of simulations favour erlotinib at a willingness-to-pay threshold of £30,000 per QALY gained, and 12% at £50,000 per QALY gained).

TABLE 50 Base-case deterministic cost-effectiveness results for erlotinib vs. BSC second-line treatment in the EGFR M– population (EGFR M– subgroup from the BR.21 trial[31])

Cost-effectiveness result	BSC		Erlotinib		Incremental (erlotinib vs. BSC)	
Survival (mean)	**Years**	**Months**	**Years**	**Months**	**Years**	**Months**
PFS	0.223	2.670	0.407	4.884	0.184	2.213
PPS	0.416	4.987	0.415	4.976	–0.001	–0.011
Terminal	0.038	0.452	0.038	0.453	0.000	0.001
OS	0.676	8.109	0.859	10.313	0.184	2.204
QALYs	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**
PFS	0.1414	0.1413	0.2585	0.2575	0.1171	0.1163
PPS	0.1967	0.1911	0.1963	0.1911	–0.0005	0.0001
Terminal	0.0094	0.0093	0.0094	0.0093	0.0001	0.0000
OS	0.3475	0.3416	0.4641	0.4579	0.1167	0.1163
Costs	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**
2L Tx acquisition	£0.00	£0.00	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
2L administration	£0.00	£0.00	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
2L Tx AEs	£533.70	£533.31	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
PFS BSC	£827.93	£827.33	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
PPS BSC	£2961.94	£2878.02	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Terminal care	£3882.90	£3836.73	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
ICER						
Total costs	£8206.46	£8075.39	£14,596.93	£14,436.92	£6390.47	£6361.53
Cost per QALY gained	£54,686.73 for erlotinib vs. BSC					

2L, second line; Tx, treatment.
Commercial-in-confidence information has been removed.

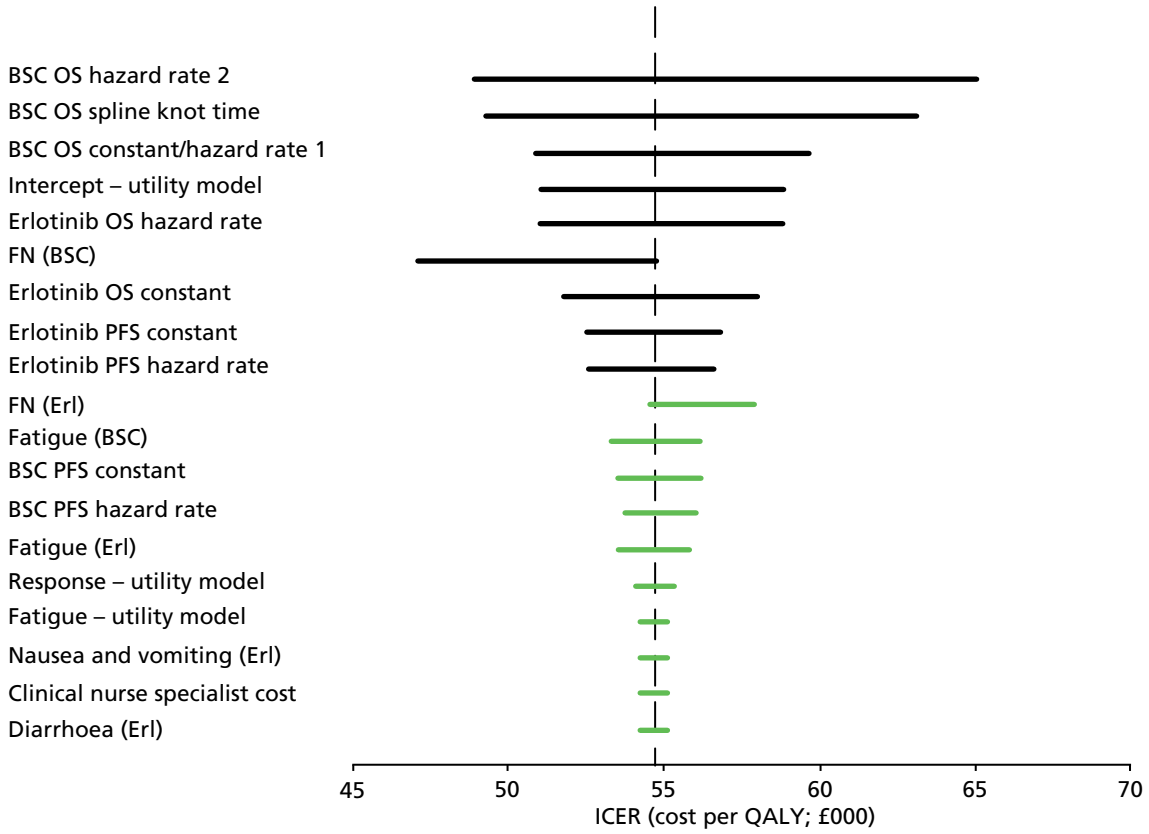

FIGURE 16 Univariate sensitivity analysis: erlotinib vs. BSC second-line treatment in the EGFR M– population subgroup of the BR.21[31] trial – 20 most influential parameters. Erl, erlotinib.

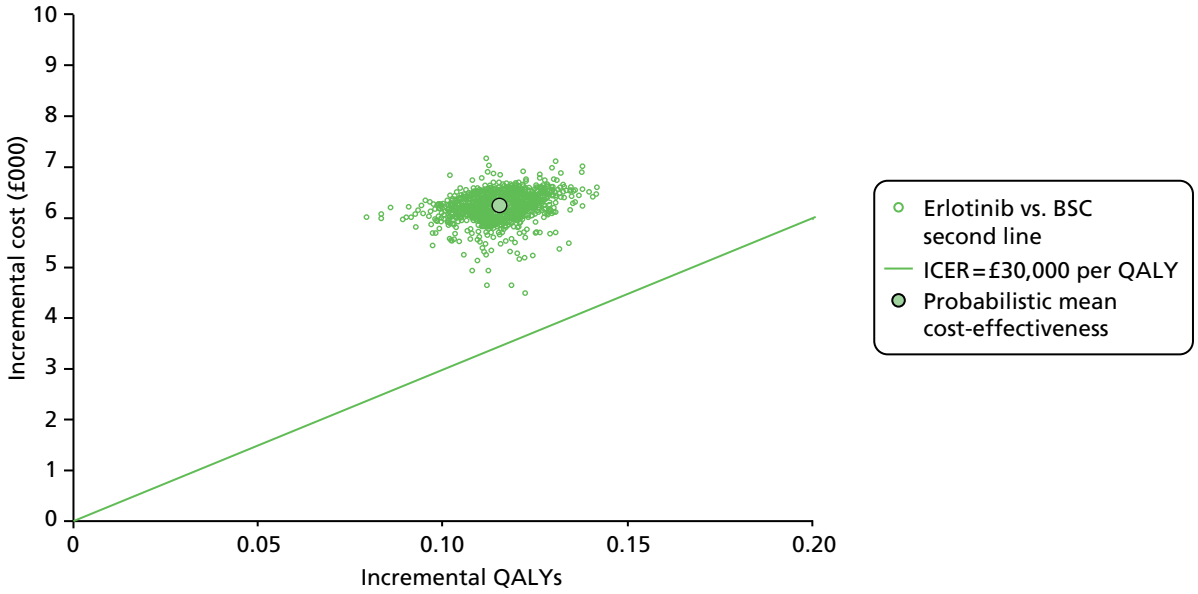

FIGURE 17 Probabilistic sensitivity analysis: scatterplot of the base-case cost-effectiveness analysis for erlotinib vs. BSC second-line treatment in the EGFR M– subgroup of the BR.21[31] trial.

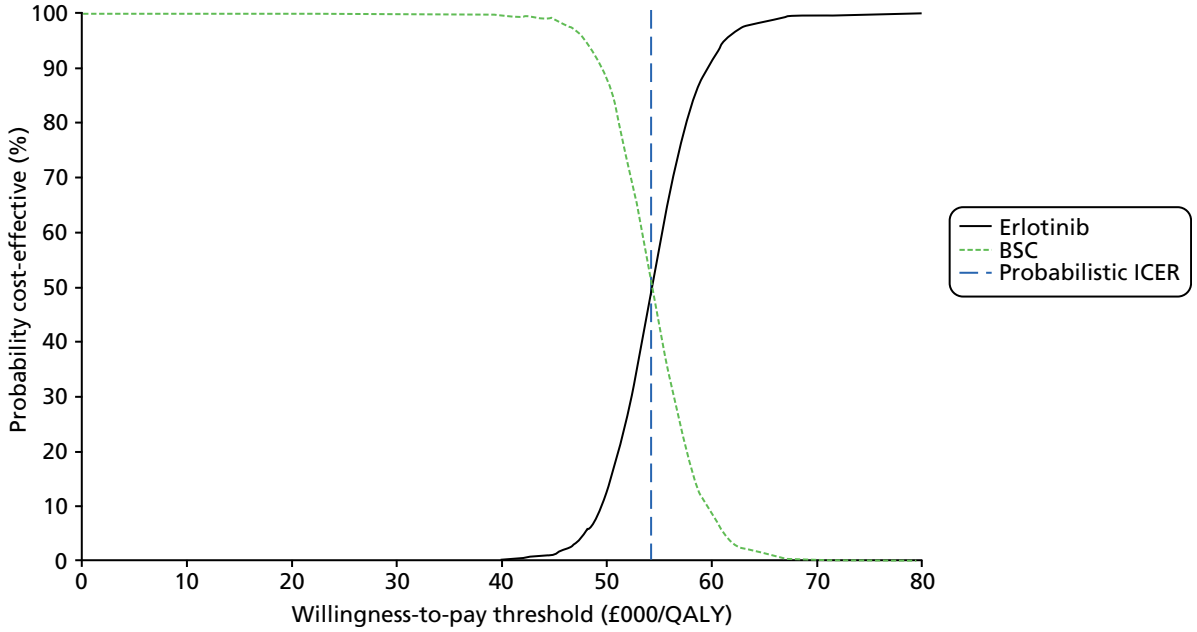

FIGURE 18 Cost-effectiveness acceptability curves for the comparison of erlotinib vs. BSC second-line treatment in the EGFR M– subgroup from the BR.21[31] trial.

Epidermal growth factor mutation status unknown population

Deterministic results from the EGFR status unknown model based on data from the BR.21[31] trial are summarised in *Table 51*. The estimated survival advantage of using erlotinib rather than BSC is 2.1 months, of which 1.7 months is prior to disease progression. The corresponding gain in mean discounted QALYs is 0.103 per patient. The overall incremental cost per patient is higher for erlotinib use (£6314 discounted), primarily because of the acquisition cost of erlotinib (£5677 discounted). The estimated ICER of £61,132 per QALY gained is well beyond the range normally considered cost-effective. The results of univariate sensitivity analyses are summarised in *Figure 19*, indicating that these results are unaffected by uncertainty in almost all model parameters. The only exceptions are the intercept parameter value in the Nafees *et al.*[75] utility model (i.e. the baseline NSCLC population utility value in patients with stable disease) and the incidence of FN when docetaxel is used.

Probabilistic sensitivity analysis incorporating uncertainty in all model parameters indicates a slightly lower estimated ICER of £59,973 per QALY gained. Examination of the PSA scatterplot (*Figure 20*), and the cost-effectiveness acceptability curves (*Figure 21*) indicate strong general confidence that erlotinib is not more cost-effective than BSC in this population (0% of simulations favour erlotinib at a willingness-to-pay threshold of £30,000 per QALY gained).

TABLE 51 Base-case deterministic cost-effectiveness results for erlotinib vs. BSC second-line treatment in the EGFR unknown population using evidence from BR.21[31] trial

Cost-effectiveness result	BSC		Erlotinib		Incremental (erlotinib vs. BSC)	
Survival (mean)	**Years**	**Months**	**Years**	**Months**	**Years**	**Months**
PFS	0.235	2.815	0.374	4.490	0.140	1.675
PPS	0.403	4.831	0.439	5.267	0.036	0.435
Terminal	0.038	0.458	0.038	0.454	0.000	–0.004
OS	0.675	8.104	0.851	10.211	0.176	2.106
QALYs	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**
PFS	0.1490	0.1488	0.2376	0.2369	0.0886	0.0881
PPS	0.1906	0.1869	0.2077	0.2023	0.0171	0.0153
Terminal	0.0095	0.0094	0.0094	0.0093	–0.0001	–0.0001
OS	0.3491	0.3452	0.4548	0.4484	0.1057	0.1033
Costs	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**	**Undiscounted**	**Discounted**
2L Tx acquisition	£0.00	£0.00	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
2L administration	£0.00	£0.00	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
2L Tx AEs	£562.53	£561.77	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
PFS BSC	£873.25	£872.06	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
PPS BSC	£2853.14	£2798.84	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Terminal care	£3938.22	£3900.12	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed	Commercial-in-confidence information has been removed
Total costs	£8227.15	£8132.79	£14,610.64	£14,446.38	£6383.49	£6313.59
ICER						
Cost per QALY gained	£61,161.81 for erlotinib vs. BSC					

2L, second line; Tx, treatment.
Commercial-in-confidence information has been removed.

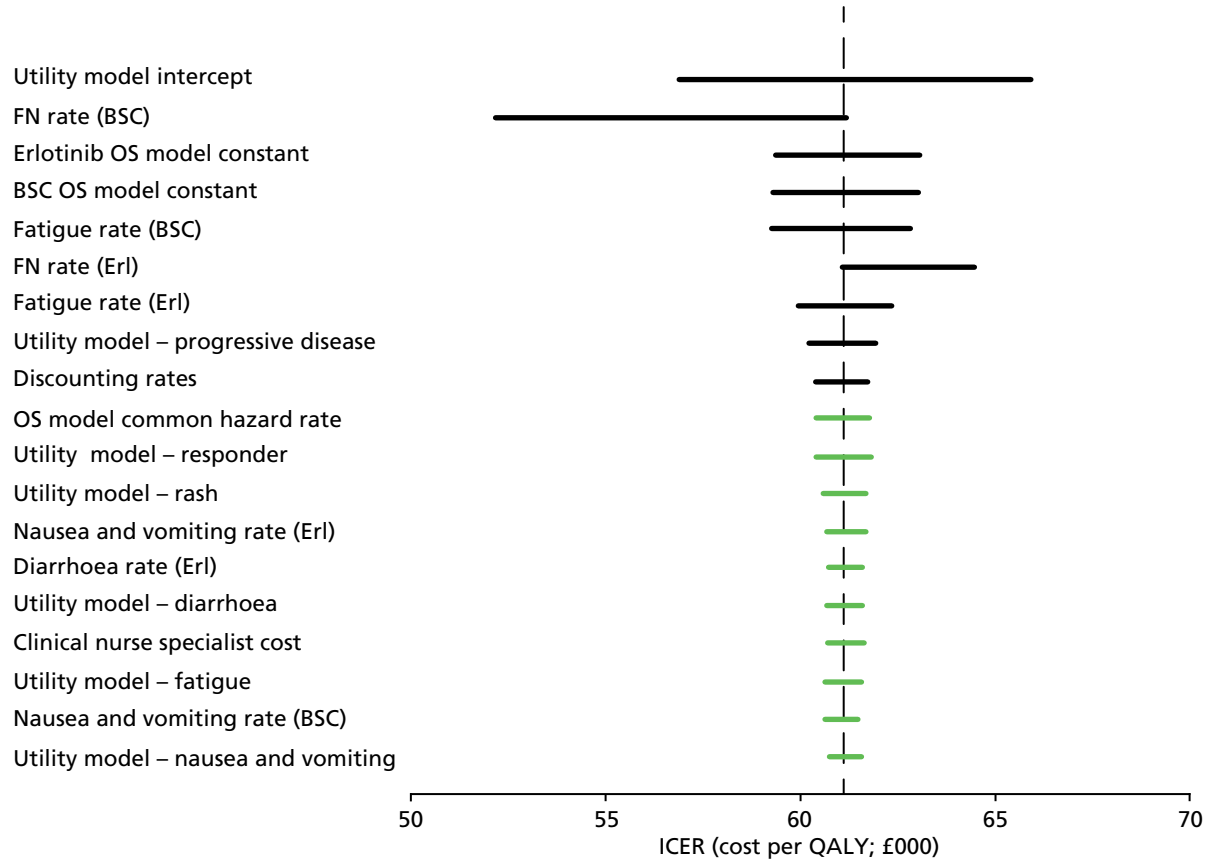

FIGURE 19 Univariate sensitivity analysis: erlotinib vs. BSC second-line treatment in the EGFR unknown subgroup of the BR.21[31] trial – 20 most influential parameters. Erl, erlotinib.

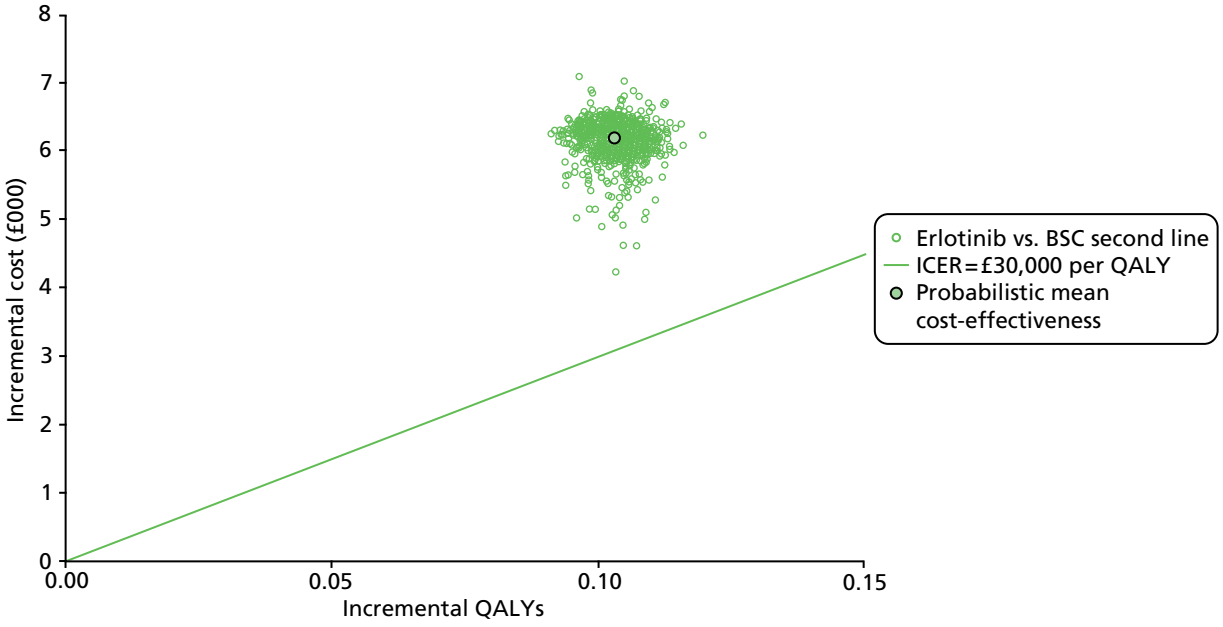

FIGURE 20 Probabilistic sensitivity analysis: scatterplot of the base-case cost-effectiveness analysis for erlotinib vs. BSC second-line treatment in the EGFR unknown population from the BR.21[31] trial.

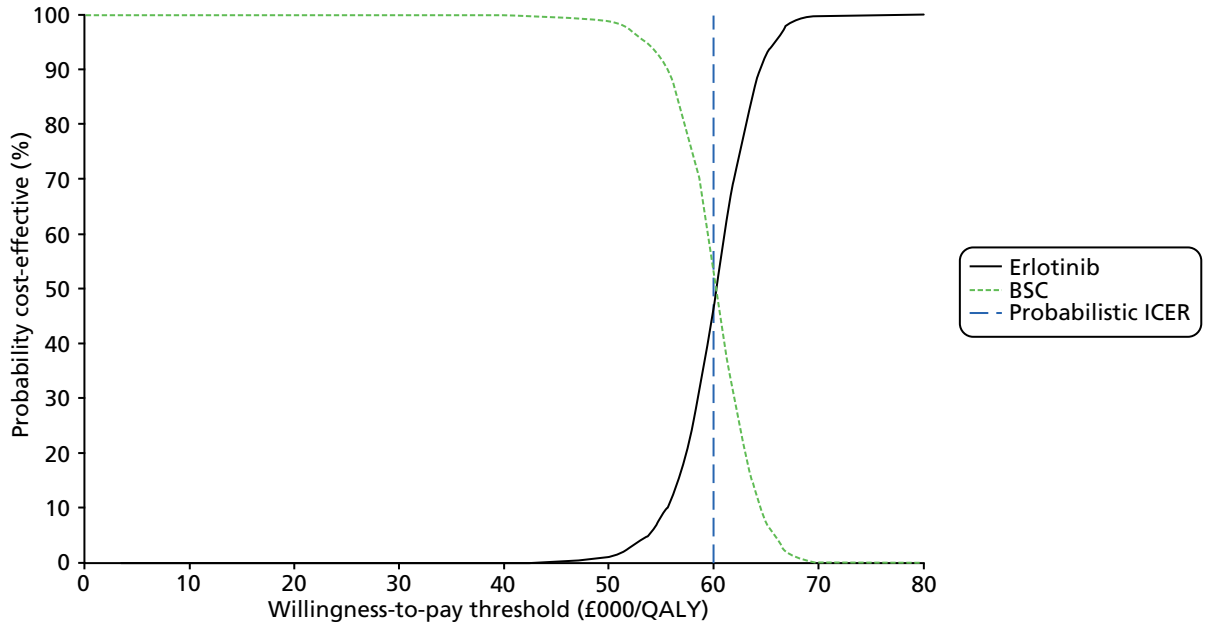

FIGURE 21 Cost-effectiveness acceptability curves for the base case for erlotinib vs. BSC second-line treatment of NSCLC in the EGFR unknown population using results from the BR.21[31] trial.

Summary and discussion of Assessment Group model results

The very weak evidence base for comparative second-line treatments, especially in subgroups defined by EGFR-TKI activating mutation status, has severely restricted the AG's ability to assess the relative cost-effectiveness of all potential treatments and comparators indicated in appraisal scope.

In the absence of reliable RCT data comparing second-line treatments in a population with confirmed EGFR-activating mutations, no cost-effectiveness analysis could be undertaken. This is a serious information deficit that urgently requires remedy. In particular, this problem prevents any consideration of gefitinib as a potential post-progression treatment, as gefitinib is licensed for use only in patients with activating mutations. The AG is aware that current treatments for patients who have EGFR M+ disease are evolving and include the use of platinum-doublet chemotherapy after progression following EGFR-TKI treatments; however, no robust data are available for use in this appraisal.

TAILOR[41] comparing the effectiveness of docetaxel monotherapy and erlotinib is the only RCT with data currently available in a population with confirmed disease and lacking EGFR-activating mutations. Cost-effectiveness analysis using data from this trial indicates that erlotinib is dominated by docetaxel in the EGFR M– population yielding a reduced mean survival and fewer QALYs while involving a greater net cost of treatment. When additional studies are published for the EGFR M– population, it will become clearer whether this result is confirmed or brought into question.

A significant survival benefit for docetaxel may be translated into good cost-effectiveness over erlotinib (erlotinib is dominated by docetaxel, ICER = –£5112 per QALY gained), on the basis that generic docetaxel is priced at the level corresponding to that currently paid by the NHS. If published list prices are substituted, docetaxel looks much less attractive.

A subgroup analysis of the BR.21[31] trial comparing erlotinib with BSC in those patients without EGFR-activating mutations confirms that erlotinib generates survival advantages, but at high cost, so that the estimated ICER is high for the EGFR M– population (£54,687 per QALY gained).

In the case of patients who are eligible for second-line therapy but for whom definitive determination of EGFR mutation status is not available for any reason, cost-effectiveness analysis based on the whole of the BR.21[31] trial cohort also yields a high ICER value for the EGFR unknown population (£61,132 per QALY gained).

Thus, on the basis of the clinical-effectiveness data currently useable for economic analysis, it does not appear that second-line erlotinib for NSCLC is an attractive option in the EFGR M– or EGFR unknown populations, and at present there are no sources of effectiveness data on which to base an assessment of erlotinib compared with any other option in those patients with confirmed EGFR-activating mutations. The absence of suitable head-to-head trials in the era of EGFR mutation testing is therefore the main limitation on the economic analyses that could be carried out by the AG.

The analyses described here do not take into account the issue of patient experience and preferences in the delivery of second-line treatment, in particular, that oral therapy is widely preferred by patients and clinicians to treatments delivered intravenously. This affects only the comparison made between erlotinib and docetaxel in the EGFR M– population. One possible approach to dealing with this concern is to include an additional utility increment applied only to erlotinib in the analysis to represent the reduction in pain, anxiety and disruption to everyday activities from switching to an oral treatment. There is no objective way to measure such an effect at present. However, a sensitivity analysis can be carried out by assessing the effect of the maximum possible patient health utility increment on the estimated ICER. This is achieved by setting the additional increment at the level which corresponds to returning a patient to the average QoL experienced in the general population at the equivalent mean age (utility about 0.8). This requires raising the EQ-5D score by 0.155, which reduces the incremental loss of QALYs slightly but leaves erlotinib still dominated by docetaxel. This extreme sensitivity analysis indicates that any realistic assessment of utility advantage due to oral therapy is very unlikely to alter the relative cost-effectiveness of erlotinib and docetaxel in the EGFR M– population.

Assessment of factors relevant to the NHS and other parties

This review has highlighted that a key development since TA162[21] in 2009 has been the expiration of the patent for docetaxel. This means that generic versions of docetaxel are now available in England and Wales at a substantially reduced cost to the NHS. In TA162,[21] NICE recommends the use of docetaxel and erlotinib as second-line treatments for patients with NSCLC. Erlotinib is currently recommended only on the basis that it is provided by the manufacturer at an overall treatment cost equal to that of docetaxel. Docetaxel is now available at 10% of its original list price. Clearly, this reduced price of docetaxel has resource implications that are relevant to the NHS, NICE and the manufacturer of erlotinib. In particular, the results of the AG's cost-effectiveness analysis comparing erlotinib with docetaxel show that docetaxel is more cost-effective than erlotinib in an EGFR M– patient population.

Recent advances in lung cancer diagnosis and treatments have revealed that expected clinical benefit from available lung cancer treatments can be positively or negatively affected by a patient's EGFR mutation status. The AG therefore considers it imperative that EGFR mutation tests are routinely available for all NSCLC patients at the time of diagnosis, prior to treatment. The NHS is making every effort to offer timely EGFR mutation tests to patients with NSCLC across England and Wales, however clinical expert opinion is that EGFR mutation tests are not currently routinely available in all centres because of the unavailability of testing facilities and inconclusive results.

In patient populations in which docetaxel is preferred to erlotinib from a cost-effectiveness perspective, there are concerns that this represents a backwards step in patient treatment options. Docetaxel is administered as an i.v. infusion, which means that patients are required to attend hospital as a day-case to receive this treatment. Replacing erlotinib (oral therapy) with docetaxel (i.v. therapy) has major implications not only for NHS resource use and staff, but also in terms of patient preference.

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness results

Epidermal growth factor mutation-positive population

No trials were identified that were conducted in a population of solely EGFR M+ patients. The EGFR M+ data for this population were retrospectively derived from subgroup analyses of RCTs that included patients of unknown EGFR mutation status at the time of randomisation.[31,32,34,38,39,42] The outcome data described in these analyses are based on small patient numbers. The outcomes reported are diverse and, in many cases, are limited by poor reporting and lack of statistical power.

Epidermal growth factor mutation-negative population

The clinical effectiveness data available for the EGFR M– population were derived from a RCT that randomised only EGFR M– patients[41] and a RCT that was designed to assess clinical outcomes in an EGFR M– population.[40] In addition, EGFR mutation status data were retrospectively derived from BR.21,[31] Kim *et al.*,[32] TITAN,[42] INTEREST[34] and ISEL;[39] however, the subgroup data suffered from the same limitations described previously for the EGFR M+ population. The AG is aware that gefitinib is not licensed for patients with EGFR M– and so the INTEREST[34] and ISEL[39] trials are included in this group for completeness only. No statistically significant differences were noted for OS for either erlotinib or gefitinib compared with any treatment. For PFS, a statistically significant benefit of docetaxel compared with erlotinib was noted in both TAILOR[41] and DELTA.[40] The RR in TAILOR[41] was statistically significantly greater for the docetaxel arm of the trial than for the erlotinib arm.

Epidermal growth factor mutation status unknown: overall population

The overall population is made up of trial populations in which EGFR mutation status was not a factor in the recruitment process (or where overall trial results were presented). The data from 11 trials were included in this assessment (TAILOR[41] reported only EGFR M– population data). For OS, only BR.21[31] reported a statistically significant benefit of any treatment (favouring erlotinib compared with placebo); however, the AG notes that this finding was based on an adjusted rather than an unadjusted analysis of the data.

For PFS, when gefitinib was compared with docetaxel, only one of the four trials (ISTANA[35]) reported a statistically significant benefit for gefitinib (using 90% CI). When compared with BSC, gefitinib was reported to have a statistically significant benefit in the ISEL[39] trial. When erlotinib was compared with placebo in BR.21,[31] a statistically significant PFS benefit of erlotinib was reported (in an adjusted analysis). The head-to-head comparison of erlotinib and gefitinib[32] did not report HRs for the PFS.

The AG was unable to compare data from any of the trials for any patient population or treatment via meta-analysis or network meta-analysis.

Cost-effectiveness results

The AG developed a de novo economic model for the specific purpose of this Multiple Technology Appraisal and carried out several cost-effectiveness analyses.

For the EGFR M+ population, the AG was not able to carry out a cost-effectiveness analysis of available treatments, as there is an absence of relevant direct clinical trial evidence in this patient population.

For the EGFR M– population, the AG compared docetaxel with erlotinib using data from TAILOR.[41] In this comparison erlotinib was dominated by docetaxel, yielding a reduced mean survival and fewer QALYs while also involving a greater net cost of treatment. Docetaxel yielded a survival advantage over erlotinib of 2.5 months. The overall treatment cost of docetaxel was £545 lower than the cost of erlotinib. The AG estimated the size of the erlotinib versus docetaxel ICER to be –£5112 per QALY gained. However, if published list prices are used instead of eMit prices, the ICER for docetaxel versus erlotinib increases to over £57,000 per QALY gained, with a probabilistic ICER of nearly £70,000 per QALY gained.

For the EGFR M– population, the AG also compared erlotinib versus BSC in a sensitivity analysis using data from the post-hoc reanalysis of BR.21[43] described in the manufacturer's submission submitted by Roche (UK) Ltd. In this comparison, erlotinib yielded a survival advantage over BSC of 2.2 months, with an incremental QALY gain of 0.116. The overall treatment cost of erlotinib was £6362 higher than the cost of BSC. The AG estimated the size of the erlotinib versus BSC ICER to be £54,687 per QALY gained. This ICER is above the range normally accepted to be cost-effective. PSA incorporating uncertainty in all model parameters indicates a slightly lower ICER of £54,984 per QALY gained.

For the EGFR unknown population, the AG compared erlotinib and BSC using data from the BR.21[31] trial. In this comparison, erlotinib yielded a survival advantage of 2.1 months, with an incremental QALY gain of 0.103. The overall treatment cost of erlotinib was £6312 higher than the cost of BSC. The AG estimated the size of the erlotinib versus BSC ICER to be £61,132 per QALY gained. This ICER is outside the range normally accepted to be cost-effective. PSA incorporating uncertainty in all model parameters indicates a slightly lower ICER of £59,973 per QALY gained.

Strengths and limitations of the assessment

A key strength of this review is that it has brought together all the available evidence relevant to the clinical effectiveness and cost-effectiveness of erlotinib and gefitinib in patients who have disease progression following prior chemotherapy. From a clinical perspective, this has enabled the AG to identify the substantial gaps in the current evidence base and to offer pertinent research recommendations. The findings of the review have also highlighted the importance of EGFR mutation status for the selection of effective treatments for patients with NSCLC. From a health economics perspective, a key strength of the review is that the current price of docetaxel has been used in the EEs carried out by the AG when appropriate. To date, there are no published cost-effectiveness analyses that have used this off-patent price of docetaxel to compare second-line treatments for patients with NSCLC. Consequently, no speculation regarding the implications of this lower price of docetaxel for the NHS is required as the AG is able to provide the AC with up-to-date and relevant cost-effectiveness information. Finally, the AG has attempted to consider the implicit benefit associated with the use of an oral therapy rather than an i.v. therapy by including an additional utility increment applied only to erlotinib in the extreme sensitivity analysis to represent the reduction in pain, anxiety and disruption to everyday activities from switching to an oral treatment. However, this failed to reverse the dominance of docetaxel over erlotinib in the EGFR M– population.

The main limitation of the assessment is the lack of clinical data available for distinct patient populations. Clearly, the gaps in the evidence base have precluded the assessment of clinical effectiveness and cost-effectiveness of relevant treatments. Specifically, the AG was unable to carry out an EE of treatments for patients with EGFR M+ tumours. A second limitation is that the evidence that is available to support the second-line use of erlotinib, gefitinib and docetaxel is mainly derived from trials that include patients whose EGFR mutation status was unknown at the time of randomisation. A final limitation is that the cost-effectiveness analyses rely on the QALY values modelled from data obtained from a sample of the general population, as highlighted by the AG, these values do not reflect directly patient experience or patients' preference for the mode of treatment (oral vs. i.v. treatments).

Uncertainties

The results of the recent TAILOR[41] trial demonstrate that docetaxel has a statistically significant PFS benefit when compared with erlotinib in a European EGFR M– population. However, a number of criticisms have been levelled at TAILOR,[41] and it is as yet uncertain whether or not the reported PFS benefit seen in an Italian population would be achieved by patients in clinical practice in England and Wales.

There is much debate about the true rate of FN in patients treated with docetaxel in the UK NHS. The AG considered this issue in depth and the results can be seen in *Appendix 8*.

Other relevant factors

There is a clear and well-expressed argument in the manufacturer's submission submitted by Roche (UK) Ltd that some clinicians are not in favour of a move from oral erlotinib to i.v. docetaxel for patients with NSCLC. In the manufacturer's submission Roche (UK) Ltd states that 'restricting funding of erlotinib on the basis of this re-review would represent a substantial backwards step in the treatment of advanced NSCLC, worsen the poor survival of people with relapsed lung cancer in the UK and remove the only treatment option available to many in this patient group. It would also have a significant impact upon the future treatment options available for UK NSCLC patients (given the fact that a significant number of technologies currently in development are designed to be combined with erlotinib)'.[28] It is not within the remit of the AG to address these concerns. The AG has instead focused on providing a systematic review of the clinical effectiveness and cost-effectiveness evidence available, and has carried out robust, relevant cost-effectiveness analyses based on its own de novo economic model.

Chapter 6 Conclusions

Implications for service provision

The largest group of patients to whom the results of this appraisal apply is the EGFR M– patient population. The results of the AG's cost-effectiveness analysis comparing erlotinib and docetaxel in patients who have disease progression favour the use of docetaxel. Switching from an oral therapy (erlotinib) to an i.v. therapy (docetaxel) would have substantial implications for service provision for both patients and staff in the UK NHS.

Suggested research priorities

It is suggested that any future trials in this area should distinguish between patients who have EGFR M+ and EGFR M– status. To date, the evidence base supporting the use of post-progression treatments for patients with activating EGFR mutations is weak and not sufficiently robust to inform decision-making.

Even when there is a wealth of evidence available (e.g. EGFR unknown status), it is not possible to compare the results of different RCTs using quantitative methods, as the included trial populations are often very diverse. To facilitate treatment comparisons, future trials in this area must be designed to ensure that only patients who best represent patients in clinical practice are included in the trials (e.g. in terms of histology, PS, smoking status and previous treatments).

There has been recent clinician interest in the role of second-line platinum-doublet chemotherapy in EGFR M+ patients as well as manufacturer interest in the use of gefitinib post chemotherapy in the same group of patients, and both of these research areas should be investigated. It would also be valuable to research further the issues associated with re-challenge (re-challenge with EGFR-TKIs in EGFR M+ patients and re-challenge with chemotherapy in EGFR M– patients and EGFR unknown patients) after treatment failure.

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Declared competing interests of the reviewers

Dr Paula Scullin has received hospitality, sponsorship to attend meetings and speaker fees from Roche (UK) Ltd and AstraZeneca. Dr Clive Mulatero has received remuneration from Roche (UK) Ltd and AstraZeneca for consultancy, attending symposia, organising education and speaker fees. He has also received research funding from both manufacturers.

Contributions of authors

Janette Greenhalgh was project lead and reviewed the clinical evidence.

Adrian Bagust undertook critical appraisal of manufacturers' economic model and development of de novo economic model.

Angela Boland supported the review process (clinical and economics).

Kerry Dwan undertook clinical quality assessment, data extraction and was a statistical advisor.

Sophie Beale undertook economic quality assessment and data extraction.

Juliet Hockenhull undertook literature selection and data management.

Christine Proudlove was the pharmacological advisor.

Yenal Dundar undertook literature searching.

Marty Richardson undertook data extraction and was a statistical advisor.

Rumona Dickson supported the review process.

Anna Mullard was a clinical advisor.

Ernie Marshall was a clinical advisor.

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

Data sharing statement

All available data can be obtained from the corresponding author.

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109. 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. *Br J Cancer* 2004;**91**:1996–2004. http://dx.doi.org/10.1038/sj.bjc.6602241

110. Lilenbaum R, Rubin M, Samuel J, Boros L, Chidiac T, Seigel L, *et al.* A randomized phase II trial of two schedules of docetaxel in elderly or poor performance status patients with advanced non-small-cell lung cancer. *J Thorac Oncol* 2007;**2**:306–11. http://dx.doi.org/10.1097/01.JTO.0000263713.38826.8e

111. 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. *Ann Oncol* 2005;**16**:294–9. http://dx.doi.org/10.1093/annonc/mdi053

112. Quoix 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/m^2) as second-line monotherapy for non-small-cell lung cancer. *Ann Oncol* 2004;**15**:38–44. http://dx.doi.org/10.1093/annonc/mdh005

113. Ramlau R, Gorbunova V, Ciuleanu TE, Novello S, Ozguroglu M, Goksel T, *et al.* Aflibercept and docetaxel versus docetaxel alone after platinum failure in patients with advanced or metastatic non-small-cell lung cancer: a randomized, controlled phase III trial. *J Clin Oncol* 2012;**30**:3640–7. http://dx.doi.org/10.1200/JCO.2012.42.6932

114. Schuette W, Nagel S, Blankenburg T, Lautenschlaeger C, Hans K, Schmidt EW, *et al.* Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. *J Clin Oncol* 2005;**23**:8389–95. http://dx.doi.org/10.1200/JCO.2005.02.3739

115. Wachters FM, Groen HJ, Biesma B, Schramel FM, 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. *Br J Cancer* 2005;**92**:15–20. http://dx.doi.org/10.1038/sj.bjc.6602268

116. Royal College of Physicians (RCP). *Professional Organisation Statement. Multiple Technology Appraisal: Erlotinib and Gefitinib for Treating Non-Small Cell Lung Cancer that has Progressed Following Prior Chemotherapy (Review of NICE Technology Appraisals 162 and 175) [ID620]*. London: RCP; 2013.

117. Sharma A, Lo A, Mukherji D, Burcombe R, Sevitt T, Taylor H, *et al.* An analysis of rate of admissions to an inpatient facility across 3 trusts in relation to the delivery of docetaxel chemotherapy in non small cell lung cancer (NSCLC). *Lung Cancer* 2009;**63**(Suppl. 1):S6. http://dx.doi.org/10.1016/S0169-5002(09)70018-2

Appendix 1 Literature search strategies

MEDLINE (via OvidSP)

URL: http://ovidsp.tx.ovid.com/sp–3.15.1b/

Date range searched: 1946 to 26 April 2013.

Date searched: 26 April 2013.

Search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. randomly.ab.
6. trial.ab.
7. or/1-6
8. (animals not (humans and animals)).sh.
9. 7 not 8
10. exp Carcinoma, Non-Small-Cell Lung/ or nsclc.ti,ab.
11. (non-small or non small or nonsmall).ti,ab.
12. (lung or pulmonary or bronchus or bronchogenic or bronchial or bronchoalveolar or alveolar).ti,ab.
13. (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chrondosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis or tumour$ or tumor$ or metast$).ti,ab.
14. 10 or (and/11-13)
15. (erlotinib or tarceva or "osi 774").ti,ab.
16. (gefitinib or iressa or ZD 1839).ti,ab.
17. 15 or 16
18. 9 and 14 and 17
19. limit 18 to English language

EMBASE (via OvidSP)

URL: http://ovidsp.tx.ovid.com/sp–3.15.1b/

Date range searched: 1974 to 26 April 2013.

Date searched: 26 April 2013.

Search strategy

1. Randomized Controlled Trial/
2. Randomization/
3. Single blind procedure/
4. Double blind procedure/
5. Double blind procedure/
6. Crossover procedure/

7. Randomi?ed controlled trial$.tw.
8. random$.ti,ab.
9. placebo.ti,ab.
10. or/1-9
11. animal/ not (animal/ and human/)
12. 10 not 11
13. exp lung non small cell cancer/ or nsclc.ti,ab.
14. (non-small or non small or nonsmall).ti,ab.
15. (lung or pulmonary or bronchus or bronchogenic or bronchial or bronchoalveolar or alveolar).ti,ab.
16. (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chrondosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis or tumour$ or tumor$ or metast$).ti,ab.
17. 13 or (and/14-16)
18. exp erlotinib/
19. (erlotinib or tarceva or "osi 774").ti,ab.
20. exp gefitinib/
21. (gefitinib or iressa or ZD 1839).ti,ab.
22. or/18-21
23. 12 and 17 and 22
24. limit 23 to English language

The Cochrane Library

URL: http://onlinelibrary.wiley.com/cochranelibrary/search/

Date range searched: inception to 28 April 2013.

Date searched: 28 April 2013.

Search strategy

#1. MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees

#2. "non-small-cell lung cancer":ti,ab,kw (word variations have been searched)

#3. erlotinib or tarceva:ti,ab,kw (word variations have been searched)

#4. gefitinib or iressa:ti,ab,kw (word variations have been searched)

#5. #1 or #2

#6. #3 or #4

#7. #5 and #6

PubMed

URL: www.ncbi.nlm.nih.gov/pubmed

Date range searched: January 2010 to 28 April 2013.

Date searched: 28 April 2013.

Search strategy

((erlotinib or tarceva or gefitinib or iressa)) AND lung cancer

Filters

Clinical trial, publication date from 2010/01/01 to 2013, humans, English

Search detail

((“erlotinib”[Supplementary Concept] OR “erlotinib”[All Fields]) OR (“erlotinib”[Supplementary Concept] OR “erlotinib”[All Fields] OR “tarceva”[All Fields]) OR (“gefitinib”[Supplementary Concept] OR “gefitinib”[All Fields]) OR (“gefitinib”[Supplementary Concept] OR “gefitinib”[All Fields] OR “iressa”[All Fields])) AND (“lung neoplasms”[MeSH Terms] OR (“lung”[All Fields] AND “neoplasms”[All Fields]) OR “lung neoplasms”[All Fields] OR (“lung”[All Fields] AND “cancer”[All Fields]) OR “lung cancer”[All Fields]) AND (Clinical Trial[ptyp] AND (“2010/01/01”[PDAT] : “2013/12/31”[PDAT]) AND “humans”[MeSH Terms] AND English[lang])

Appendix 2 Quality assessment of included studies

TABLE 52 Quality assessment of included studies

	Randomisation			Baseline comparability				Blinding				Withdrawals			
Trial	Truly random	Allocation concealment	Number stated	Presented	Achieved	Eligibility criteria specified	Co-interventions identified	Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated	ITT	Other outcomes
[a]Bhatnagar *et al.* 2012[33]	NS	NS	✓	✗	NS	✓✗	NS	NS	NS	NS	NS	NS	NS	NS	Unclear
BR.21 2005[31]	✓	✓	✓	✓	✓	✓	NS	✓[b]	✓[b]	✓	NS	✓	✓	✓	✗
[a]DELTA 2013[40]	✓	NS	✓	✗	NS	✓	NS	NS	NS	✗	NA	NS	NS	NS	Unclear
INTEREST 2008[34]	✓	✓	✓	✓	✓	✓	✓	NS	✗	✗	NA	✓	✓	✓	✗
ISEL 2005[39]	✓	✓	✓	✓	✓	✓	NS	NS	✓	✓	NS	✓	✓	✓	✗
ISTANA 2010[35]	NS	NS	✓	✓	✓	✓	NS	NS	✗	✗	NA	✓	✓	✓	✗
[c]Kim 2012[32]	NS	NS	✓	Unclear	Unclear	✓	NS	NS	✗	✗	NA	✓	NA	Unclear	✗
Li *et al.* 2010[36]	NS	NS	✓	✓	✓	✓	✓	NS	NS	NS	NS	✓	NS	NS	✗
SIGN 2006[37]	Unclear	✓	✓	✓	✓	✓	✓	✗	✗	✗	NA	✓	✓	✓	✗
TAILOR 2013[41]	✓	✓	✓	✓	✓✗[d]	✓	NS	✓✗[e]	✗	✗	NA	✓	✓	✓	✗
TITAN 2012[42]	✓	✓	✓	✓	✓✗	✓	NS	✗	✗	✗	NA	✓	✓	✓	✗
V-15-32 2008[38]	NS	NS	✓	✓	✓	✓	NS	✓✗[f]	✗	✗	NA	✓	✓	✓	✗

NA, not applicable; NS, not stated; ✓, yes; ✓✗, partially; ✗, no.

a Abstract only.

b Assumed from 'double-blind'.

c No details presented for historical control group.

d Differences between groups for smokers and non-smokers, and adenocarcinoma.

e Two independent radiologists, masked to treatment assignment, did post-hoc reviews of all the scans of responding patients.

f Primary overall RR results that were based on investigator judgement were generally consistent with those obtained from independent response evaluation committee assessment.

Appendix 3 Table of included studies and associated publications

TABLE 53 Table of included studies and associated publications

Trial	Associated publications
Bhatnagar *et al*.[33]	Bhatnagar AR, Singh DP, Sharma R, Kumbhaj P. Docetaxel versus gefitinib in patients with locally advanced or metastatic NSCLC pretreated with platinum-based chemotherapy. *J Thorac Oncol* 2012;**3**:S159
BR.21[31]	Shepherd FA, Pereira JR, Ciuleanu T, Eng HT, Hirsh V, Thongprasert S, *et al*. Erlotinib in previously treated non-small-cell lung cancer. *New Engl J Med* 2005;**353**:123–32
	Bezjak A, Shepherd F, Tu D, Clark G, Santabarbara P, Pater J, *et al.* Symptom response in non-small-cell lung cancer (NSCLC) patients (pts) treated with erlotinib: quality of life analysis of the NCIC CTG BR.21 trial. *J Clin Oncol: ASCO Annual Meeting Proceedings* 2005;**23**:625
	Bezjak A, Tu D, Seymour L, Clark G, Trajkovic A, Zukin M, *et al*. Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol* 2006;**24**:3831–7
	Zhu CQ, Da Cunha Santos G, Ding K, Sakurada A, Cutz JC, Liu N, *et al.* Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada clinical trials group study BR.21. *J Clin Oncol* 2008;**26**:4268–75
DELTA[40]	Okano Y, Ando M, Asami K, Fukuda M, Nakagawa H, Ibata H, *et al.* Randomized phase III trial of erlotinib (E) versus docetaxel (D) as second- or third-line therapy in patients with advanced non-small-cell lung cancer (NSCLC) who have wild-type or mutant epidermal growth factor receptor (EGFR): Docetaxel and Erlotinib Lung Cancer Trial (DELTA). *J Clin Oncol: ASCO Annual Meeting Proceedings* 2013;**31**:8006
INTEREST[34]	Kim ES, Hirsh V, Mok T, Socinski MA, Gervais R, Wu YL, *et al*. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008;**372:**1809–18
	Douillard JY, Shepherd FA, Hirsh V, Mok T, Socinski MA, Gervais R, *et al*. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. *J Clin Oncol* 2010;**28**:744–52
ISEL[39]	Chang A, Parikh P, Thongprasert S, Tan EH, Perng RP, Ganzon D, *et al.* Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small-cell lung cancer: subset analysis from the ISEL study. *J Thorac Oncol* 2006;**1**:847–55
	Thatcher N, Chang A, Parikh P, Pereira JR, Ciuleanu T, Von Pawel J, *et al.* Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (IRESSA Survival Evaluation in Lung cancer). *Lancet* 2005;**366**:1527–37
	Hirsch FR, Varella-Garcia M, Bunn Jr PA, Franklin WA, Dziadziuszko R, Thatcher N, *et al*. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol* 2006;**24**:5034–42
ISTANA[35]	Lee D, Kim S, Park K, Kim J, Lee J, Shin S, *et al.* A randomized open-label study of gefitinib versus docetaxel in patients with advanced/metastatic non-small-cell lung cancer (NSCLC) who have previously received platinum-based chemotherapy [abstract no. 8025]. *J Clin Oncol: ASCO Annual Meeting Proceedings* 2008;**26**:430
	Lee DH, Park K, Kim JH, Lee JS, Shin SW, Kang JH, *et al.* Randomized Phase III trial of gefitinib versus docetaxel in non-small-cell lung cancer patients who have previously received platinum-based chemotherapy. *Clin Cancer Res* 2010;**16**:1307–14

continued

TABLE 53 Table of included studies and associated publications (*continued*)

Trial	Associated publications
Kim *et al.*[32]	Kim ST, Uhm JE, Lee J, Sun JM, Sohn I, Kim SW, *et al.* Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small-cell lung cancer who failed previous chemotherapy. *Lung Cancer* 2012;**75**:82–8
	Ahn J, Kim S, Ahn M, Lee J, Uhm J, Sun J, *et al.* Randomized phase II study of gefitinib versus erlotinib in patients with advanced non-small-cell lung cancer who failed previous chemotherapy. *J Clin Oncol* 2010;**28**:7551
Li *et al.*[36]	Li H, Wang X, Hua F. [Second-line treatment with gefitinib or docetaxel for advanced non-small-cell lung cancer]. *Chin J Clin Oncol* 2010;**37**:16–18
SIGN[37]	Cufer T, Vrdoljak E. Results from a Phase II, open-label, randomized study (SIGN) comparing gefitinib with docetaxel as second-line therapy in patients with advanced (stage IIIb or IV) non-small-cell lung cancer [abstract]. *J Clin Oncol: ASCO Annual Meeting Proceedings* 2005;**23**:629
	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. *Anti-Cancer Drugs* 2006;**17**:401–9
TAILOR[41]	Farina G, Longo F, Martelli O, Pavese I, Mancuso A, Moscetti L, *et al.* Rationale for treatment and study design of tailor: a randomized phase III trial of second-line erlotinib versus docetaxel in the treatment of patients affected by advanced non-small-cell lung cancer with the absence of epidermal growth factor receptor mutations. *Clin Lung Cancer* 2011;**12**:138–41
	Garassino MC, Martelli O, Bettini A, Floriani I, Copreni E, Lauricella C, *et al.* TAILOR: a phase III trial comparing erlotinib with docetaxel as the second-line treatment of NSCLC patients with wild-type (wt) EGFR. *J Clin Oncol* 2012;**30**
	Garassino MC, Marabese M, Broggini M, Lauricella C, Floriani I, Martelli O, *et al.* Effect of tumor-specific KRAS mutational status on impact of anti-EGFR therapy in non-small-cell lung cancer (NSCLC). *J Clin Oncol* 2010;**1**:7564
	[a]Garassino MC, Martelli O, Broggini M, Farina G, Veronese S, Rulli E, *et al*. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. *Lancet Oncol* 2013;**14**:981–8
TITAN[42]	Ciuleanu T, Stelmakh L, Cicens S, Gonzlez EE. Efficacy and safety of erlotinib versus chemotherapy in second-line advanced non-small-cell lung cancer (NSCLC) with poor prognosis: the phase III TITAN study. *Lung Cancer* 2011;**71**:S44
	Ciuleanu T, Stelmakh L, Cicenas S, Miliauskas S, Grigorescu AC, Hillenbach C, *et al*. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. *Lancet Oncol* 2012;**13**:300–8
V-15-32[38]	Maruyama R, Nishiwaki Y, Tamura T, Yamamoto N, Tsuboi M, Nakagawa K, *et al.* Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. *J Clin Oncol* 2008;**26**:4244–52
	Sekine I, Ichinose Y, Nishiwaki Y, Yamamoto N, Tsuboi M, Nakagawa K, *et al*. Quality of life and disease-related symptoms in previously treated Japanese patients with non-small-cell lung cancer: results of a randomized phase III study (V-15-32) of gefitinib versus docetaxel. *Ann Oncol* 2009;**20**:1483–8

a Paper published after searches were completed.

Appendix 4 Table of excluded publications with rationale

TABLE 54 Table of excluded studies

Full reference	Reason for exclusion
Abstracts of the Chicago Multidisciplinary Symposium in Thoracic Oncology. 6–8 September 2012, Chicago, IL, USA. *J Thorac Oncol* 2012;**7**(Suppl. 4):S203–340	Not a RCT
Addison CL, Ding K, Zhao H, Le Maitre A, Goss GD, Seymour L, *et al.* Plasma transforming growth factor alpha and amphiregulin protein levels in NCIC Clinical Trials Group BR.21. *J Clin Oncol* 2010;**28**:5247–56	Subgroup analysis
Aparisi F, Sanchez A, Giner V, Munoz J, Esquerdo G, Garde J, *et al.* A multi-center, open, randomized, phase II study to investigate the sequential administration of docetaxel and intermittent erlotinib versus erlotinib as a second-line therapy for advanced non-small-cell lung cancer (NSCLC). *Eur J Cancer* 2011;**47**:S630	No relevant comparator
Aprile G, Belvedere O, Puglisi F. From the podium to the patient: bringing the 2008 ASCO meeting to the clinic. *Anti-Cancer Drugs* 2008;**19**:941–56	Meeting report
Asahina H, Oizumi S, Inoue A, Kinoshita I, Ishida T, Fujita Y, *et al.* Phase II study of gefitinib readministration in patients with advanced non-small-cell lung cancer and previous response to gefitinib. *Oncology* 2010;**79**:423–9	Not a RCT
Augustovski F, Pichon Riviere A, Alcaraz A, Bardach A, Ferrante D, Garcia Marti S, *et al. Erlotinib for the Management of Advanced Lung Cancer*. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS); 2005	Not a RCT
Augustovski F, Pichon Riviere A, Alcaraz A, Bardach A, Ferrante D, Garcia Marti S, *et al. Gefitinib for Advanced Lung Cancer Treatment*. Buenos Aires: Institute for Clinical Effectiveness and Health Policy (IECS); 2005	Review
Bezjak A. Erlotinib improves symptoms as well as survival in NSCLC. *Oncol Rep* 2005;(Fall):99–100	Review
Canadian Coordinating Office for Health Technology Assessment. *Gefitinib for Advanced or Metastatic Non-Small-Cell Lung Cancer*. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2004	Review
Canadian Coordinating Office for Health Technology Assessment. Gefitinib. *Gefitinib for Inoperable or Recurrent Non-Small-Cell Lung Cancer*. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2004	Review
Cella D, Herbst RS, Lynch TJ, Prager D, Belani CP, Schiller JH, *et al*. Clinically meaningful improvement in symptoms and quality of life for patients with non-small-cell lung cancer receiving gefitinib in a randomized controlled trial. *J Clin Oncol* 2005;**23**:2946–54	No relevant comparator
Danish Centre for Evaluation and Health Technology Assessment. *Health Technology Assessment of Erlotinib (Tarceva) for Palliative Treatment of Non-Small-Cell Lung Cancer – Accelerated Assessment*. Copenhagen: Danish Centre for Evaluation and Health Technology Assessment (DACEHTA); 2005	Review
Danish Centre for Evaluation and Health Technology Assessment. *IRESSA for Non-Small-Cell Lung Cancer – Early Warningon New Health Technology*. Copenhagen: Danish Centre for Evaluation and Health Technology Assessment (DACEHTA); 2002	Non-English abstract
Douillard JY, Giaccone G, Horai T, Noda K, Vansteenkiste JF, Takata I, *et al.* Improvement in disease-related symptoms and quality of life in patients with advanced non-small-cell lung cancer (NSCLC) treated with ZD1839 ('IRESSA') (IDEAL 1). *Proc Am Soc Clin Oncol* 2002;**21**:299a, abstract 1195	No relevant comparator
Erlotinib: new drug. Non small-cell lung cancer: like gefitinib, no established advantage. *Prescrire Int* 2006;**15**:86–9	Review

continued

TABLE 54 Table of excluded studies (*continued*)

Full reference	Reason for exclusion
Fehrenbacher L, O'Neill V, Belani CP, Bonomi P, Hart L, Melnyk O, *et al.* A phase II, multicenter, randomized clinical trial to evaluate the efficacy and safety of bevacizumab in combination with either chemotherapy (docetaxel or pemetrexed) or erlotinib hydrochloride compared with chemotherapy alone for treatment of recurrent or refractory non-small-cell lung cancer. *J Clin Oncol: ASCO Annual Meeting Proceedings* 2006;**24**:7062	Not for licensed indication
Feld R, Sridhar SS, Shepherd FA, Mackay JA, Evans WK. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small-cell lung cancer: a systematic review. *J Thorac Oncol* 2006;**1**:367–76	Review
Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, *et al.* Final results from a phase II trial of ZD1839 ('IRESSA') for patients with advanced non-small-cell lung cancer (IDEAL 1). *J Clin Oncol: Proceed Am Soc Clin Oncol* 2002;**21**:298a, abstract 1188	No relevant comparator
Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, *et al.* Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol* 2003;**21**:2237–46.	No relevant comparator
Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, *et al*. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2003;**21**:2237–46. [Erratum published in *J Clin Oncol* 2004;**22**:4863]	Erratum
Gefitinib: a second look. Non-small cell lung cancer: still very disappointing. *Prescrire Int* 2009;**18**:145–7	Review
Gefitinib: Disappointing. *Prescrire Int* 2006;**15**:88	Review
Gridelli C, Rossi A, Venturino P, de Marinis F. Treatment, rationale, and study design of TALISMAN study: a randomized phase II open-label study of second-line erlotinib versus intermittent erlotinib dosing with docetaxel in the treatment of former-smoker men affected by recurrent squamous non-small-cell lung cancer. *Clin Lung Cancer* 2011;**12**:70–3	No relevant comparator
Gridelli C, Rossi A, Venturino P, de Marinis F. Treatment, rationale, and study design of TALISMAN study: a randomized phase II open-label study of second-line erlotinib versus intermittent erlotinib dosing with docetaxel in the treatment of former-smoker men affected by recurrent squamous non-small-cell lung cancer. *Clin Lung Cancer* 2011;**12**:258	No relevant comparator
Hirsch FR, Dziadziuszko R, Thatcher N, Mann H, Watkins C, Parums DV, *et al.* Epidermal growth factor receptor immunohistochemistry: comparison of antibodies and cutoff points to predict benefit from gefitinib in a phase 3 placebo-controlled study in advanced non-small-cell lung cancer. *Cancer* 2008;**12**:1114–21	Not relevant patient population
Hong J, Kyung SY, Lee SP, Park JW, Jung SH, Lee JI, *et al.* Pemetrexed versus gefitinib versus erlotinib in previously treated patients with non-small-cell lung cancer. *Korean J Intern Med* 2010;**25**:294–300	Not a RCT
Johnson DH, Arteaga CL. Gefitinib in recurrent non-small-cell lung cancer: an IDEAL trial? *J Clin Oncol* 2003;**21**:2227–9	Editorial
Kris MG, Natale RB, Herbst RS, Lynch TJ Jr, Prager D, Belani CP, *et al.* Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 2003;**290**:2149–58	No relevant comparator
Kris MG, Natale RB, Herbst RS, Lynch TJ, Prager D, Belani CP, *et al.* A phase II trial of ZD1839 ('IRESSA') in advanced non-small-cell lung cancer (NSCLC) patients who had failed platinum- and docetaxel-based regimens (IDEAL 2) [abstract]. *Proc Am Soc Clin Oncol* 2002;**21**:292a, abstract 1166	No relevant comparator
Leki R, Kawahara M, Watanabe H, Takada Y, Mori K, Yana T, *et al.* The impact of response evaluation committee in a phase III study (V-15-32) of gefitinib versus docetaxel in Japanese patients with non-small-cell lung cancer [Abstract No. 298P]. *Ann Oncol* 2009;**19**(Suppl. 8):109–10	No relevant outcome

TABLE 54 Table of excluded studies (*continued*)

Full reference	Reason for exclusion
Leki R, Kawahara M, Watanabe H, Takada Y, Mori K, Yana T, *et al.* The impact of response evaluation committee in a phase III study (V-15-32) of gefitinib versus docetaxel in Japanese patients with non-small-cell lung cancer. *Ann Oncol* 2008;**19**:viii109–viii10	No relevant outcome
Liu G, Cheng D, Ding K, Maitre A, Liu N, Patel D, *et al.* Pharmacogenetic analysis of BR.21, a placebo-controlled randomized phase III clinical trial of erlotinib in advanced non-small-cell lung cancer. *J Thorac Oncol* 2012;**7**:316–22	No relevant outcome
Liu G, Cheng D, Le Maitre A, Liu N, Chen Z, Seymour L, *et al.* EGFR and ABCG2 polymorphisms as prognostic and predictive markers in the NCIC CTG BR.21 trial of single-agent erlotinib in advanced non-small-cell lung cancer (NSCLC). *J Clin Oncol* 2010;**28**:7538	No relevant outcome
Liu G, Cheng D, Le Maitre A, Liu N, Chen Z, Seymour L, *et al.* Genetic polymorphisms as prognostic/predictive biomarkers of single-agent erlotinib therapy in NCIC-CTG BR.21 non-small-cell lung cancer (NSCLC) trial. *Pharmacoepidemiol Drug Safety* 2010;**19**:S207	No relevant outcome
Manegold C, Gatzemeier U, Kaukel E. Results from a randomised, double blind phase II trial of ZD1839 (IRESSA) as 2nd/3rd-line monotherapy in advanced non small cell lung cancer (NSCLC) (IDEAL 1). *J Cancer Res Clin Oncol* 2002;**128**(Suppl. 1):S45	No relevant comparator
Morere JF, Brechot JM, Westeel V, Gounant V, Lebeau B, Vaylet F, *et al.* Randomized phase II trial of gefitinib or gemcitabine or docetaxel chemotherapy in patients with advanced non-small-cell lung cancer and a performance status of 2 or 3 (IFCT-0301 study). *Lung Cancer* 2010;**70**:301–7	First-line treatment
Murphy M, Stordal B. Erlotinib or gefitinib for the treatment of relapsed platinum pretreated non-small-cell lung cancer and ovarian cancer: a systematic review (structured abstract). *Drug Resist Updates* 2011;**14**:177–90	Review
Natale RB, Skarin A, Maddox AM, Hammond LA, Thomas R, Gandara DR, *et al.* Improvement in symptoms and quality of life for advanced non-small-cell lung cancer patients receiving ZD1839 ('IRESSA') in IDEAL 2 [abstract]. *Proc Am Soc Clin Oncol* 2002;**21**:292a, abstract 1167	No relevant comparator
National Horizon Scanning Centre. *Erlotinib (Tarceva) for Non Small Cell Lung Cancer – Advanced or Metastatic, Maintenance after First-Line Therapy and Second Line (in Combination with Bevacizumab): Horizon Scanning Technology Briefing*. Birmingham: National Horizon Scanning Centre (NHSC); 2009	Not a RCT
National Institute for Health and Care Excellence (NICE). *Erlotinib for the Treatment of Non-Small-Cell Lung Cancer (Structured Abstract)*. London: NICE; 2008.	Not a RCT
National Institute for Health and Care Excellence (NICE). *Gefitinib for the Second-Line Treatment of Locally Advanced or Metastatic Non-Small-Cell Lung Cancer (Terminated Appraisal)*. London: NICE; 2009	Not a RCT
National Horizon Scanning Centre. IRESSA for NSCLC – horizon scanning review. Birmingham: National Horizon Scanning Centre (NHSC); 2002	Review
Niho S. [V15-32 and INTEREST]. *Japan J Lung Cancer* 2009;**49**:944–9	Report
Nishiwaki Y, Yano S, Tamura T, Nakagawa K, Kudoh S, Horai T, *et al.* [Subset analysis of data in the Japanese patients with NSCLC from IDEAL 1 study on gefitinib.] *Gan To Kagaku Ryoho* 2004;**31**:567–73	No relevant comparator
Park K, Goto K. A review of the benefit-risk profile of gefitinib in Asian patients with advanced non-small-cell lung cancer. *Curr Med Res Opin* 2006;**22**:561–73	Review
Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, *et al.* Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small-cell lung cancer patients harboring either exon 19 or 21 mutation. *Lung Cancer* 2012;**77**:556–60	Not a RCT
Reinmuth N, Thomas M. An approach to personalized medicine: the BATTLE trial. *Clin Investig* 2011;**1**:699–705	No relevant comparator
Robinson DM, Keating GM, Perry CM. Erlotinib. *Am J Cancer* 2005;**4**:247–52	Review

continued

TABLE 54 Table of excluded studies (*continued*)

Full reference	Reason for exclusion
Roman PS, Leon L, Slawomir WP. Cutaneous toxicity secondary to erlotinib therapy in patients with non-small-cell lung cancer in the NCIC CTG BR.21 study: time course and correlation with survival. *J Clin Oncol* 2012;**30**:7573	No relevant outcome
Rosell R, Bastus R, Olaverri A, Anton I, Blanco R, Domine M, *et al.* Customized chemotherapy based on BRCA1 mRNA expression and EGFR mutations in lung adenocarcinoma. *Ann Oncol* 2008;**19**:viii93	Not a RCT
Rossi D, Dennetta D, Ugolini M, Catalano V, Alessandroni P, Giordani P, *et al.* Activity and safety of erlotinib as second- and third-line treatment in elderly patients with advanced non-small-cell lung cancer: a phase II trial. *Target Oncol* 2010;**5**:231–5	Not a RCT
Sequist LV, Muzikansky A, Engelman JA. A new BATTLE in the evolving war on cancer. *Cancer Discov* 2011;**1**:14–16	Review
Sim EHA, Yang IA, Fong K, Wood-Baker R, Bowman R. Gefitinib for advanced non-small-cell lung cancer. *Cochrane Database Syst Rev* 2007;**4**:CD006847	Protocol
Sorlini C, Barni S, Petrelli F, Novello S, De Marinis F, De Pas TM, *et al.* PROSE: randomized proteomic stratified phase III study of second line erlotinib versus chemotherapy in patients with inoperable non-small-cell lung cancer (NSCLC). *J Clin Oncol* 2011;**1**	Not relevant comparator
[Tyrosine kinase inhibitor erlotinib (Tarceva) improves survival of patients with multiple previous treatments]. *Krankenpfl J* 2004;**42**:158	Non-English
Wheatley-Price P, Ding K, Seymour L, Clark GM, Shepherd FA. Erlotinib for advanced non-small-cell lung cancer in the elderly: an analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR.21. *J Clin Oncol* 2008;**26**:2350–7	Subgroup analysis
Xu B, Lee D, Ranganathan A. Highlights from: The 2009 Annual Meeting of the American Society of Clinical Oncology. *Clin Lung Cancer* 2009;**10**:217–22	Review
Yamamoto N, Nishiwaki Y, Negoro S, Jiang H, Itoh Y, Saijo N, *et al.* Disease control as a predictor of survival with gefitinib and docetaxel in a phase III study (V-15-32) in advanced non-small-cell lung cancer patients. *J Thorac Oncol* 2010;**5**:1042–7	No relevant outcome
Zielinski SL, Travis K. Randomized trial of gefitinib for advanced lung cancer closed early. *J Natl Cancer Inst* 2005;**97**:712	Not relevant patient population

Appendix 5 Systematic reviews

Quality appraisal of identified reviews

Six systematic reviews were identified. Two were reported as conference abstracts[99,100] and a third[101] was a Chinese language publication with an English abstract and data extraction tables in English. These three reviews did not lend themselves well to the quality assessment exercise. In the three full-text publications the reporting quality was high. These reviews, however, pooled data from the included trials. The AG considers this pooling to be inappropriate.

TABLE 55 Quality appraisal of identified systematic reviews

Quality criterion	[a]Bianic *et al.* (2011)[99]	[b]Guo *et al.* (2011)[101]	Hawkins *et al.* (2008)[102]	Jiang *et al.* (2011)[103]	[a]Kris *et al.* (2009)[100]	Petrelli *et al.* 2012[104]
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	✓	✓	✓	✓	✓	✓
Was the search strategy adequate and appropriate?	NS	✓	✓	✓✗[c]	NS	✓
Were preventative steps taken to minimise bias and errors in the study selection process?	NS	NS	✓	NS	NS	NS
Were appropriate criteria used to assess the quality of the primary studies?	NS	✓	✓	✓	NS	✗
Were preventative steps taken to minimise bias and errors in the QA process?	NS	NS	NS	NS	NS	NS
Were preventative steps taken to minimise bias and errors in the data extraction process?	NS	✓	✓	✓	NS	NS
Were adequate details presented for each of the primary studies?	✗	✓	✓	✓	✗	✓
Were appropriate methods used for data synthesis? Were differences between studies assessed? Were the studies pooled, and if so was it appropriate and meaningful to do so?	NS	Unclear	✗[d]	✗[d]	Unclear	✗[d]
Do the authors' conclusions accurately reflect the evidence that was reviewed?	Unclear from abstract	Unclear from abstract	✓✗[d]	✗[d]	Unclear from abstract	✗[d]

NS, not stated; QA, quality appraisal; ✓, yes; ✓✗, partially; ✗, no.
a Abstract data only.
b Chinese language with English abstract.
c Only the PubMed and CENTRAL databases were searched.
d AG does not agree that studies should be pooled. Conclusions of review concur with procedures but AG is of the opinion that the meta-analysis is flawed.

Table of identified systematic reviews: summary

TABLE 56 Table of identified studies

Review	Title	Patient population	Stated purpose and studies included	Main conclusions
[a]Bianic (2011)[99]	Network meta-analysis of second and third-line treatments on overall response and overall survival in patients with metastatic non-small-cell lung cancer	Metastatic NSCLC who have progressed after first-line treatment	To perform a network meta-analysis of recommended second/third-line treatments for overall response and survival in metastatic NSCLC. Included seven RCTs: JMEI, TAX317, V-15-32, INTEREST, ISTANA, ISEL and BR.21	Evidence for second/third-line treatment effects on response is stronger than evidence for survival. The exceptions are targeted therapies – this class is likely to be the most promising source for badly needed new therapies
Guo (2011)[101]	Gefitinib for non-small-cell lung cancer: a meta-analysis	First- and second-line NSCLC	To evaluate the clinical efficacy and safety of gefitinib for NSCLC. Meta-analysis of 13 RCTs	Gefitinib shows more superiority for NSCLC and its clinical application is worthy to be advocated
Hawkins (2008)[102]	Time to broaden our horizons, the case for network meta-analysis within relapsed non-small-cell lung cancer (NSCLC)	Locally advanced/metastatic NSCLC who have progressed after first-line treatment	Network meta-analysis of six RCTs including SIGN, JMEI, TAX317, BR.21, INTEREST and ISEL	The analysis of the limited network suggested that docetaxel is more effective than erlotinib, whereas the analysis of the extended network suggested the opposite
Jiang (2011)[103]	Gefitinib versus docetaxel in previously treated advanced non-small-cell lung cancer: a meta-analysis of randomized controlled trials	Previously treated NSCLC	To compare the efficacy, QoL, symptom improvement and toxicities of gefitinib with docetaxel in previously treated advanced NSCLC. Analysis of four RCTs: ISTANA, V-15-32, INTEREST and SIGN	Although similar for OS and PFS, gefitinib showed an advantage over docetaxel in terms of objective RR, QoL and tolerability. Therefore, gefitinib is an important and valid treatment option for previously treated advanced NSCLC patients
[a]Kris (2009)[100]	Response and progression-free survival in 1006 patients with known EGFR mutation status in Phase III randomized trials of gefitinib in individuals with non-small-cell lung cancer	NSCLC	Phase III trials of gefitinib monotherapy, focusing on patients with known EGFR mutation status	These results justify pre-treatment determination of EGFR mutation status at the time of diagnosis to select therapy with higher response and improved PFS
Petrelli (2012)[104]	Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated nonsmall-cell lung cancer: a meta-analysis of 13 randomized trials	Previously treated or untreated EGFR M+ NSCLC	Phase II or III RCTs of gefitinib or erlotinib compared with chemotherapy, BSC or placebo. Included first-line trials and INTEREST, BR.21, ISEL and V-15-32	Selecting patients with NSCLC for EGFR mutations and offering them an EGFR-TKI results in a better RR and progression-delaying effect than does standard chemotherapy. The performance appears similar in second-line settings in which the chance of obtaining a response is 63% higher with EGFR-TKIs

a Conference abstract.

Appendix 6 Data abstraction tables

TABLE 57 Key inclusion and exclusion criteria of included trials

Trial	Key inclusion criteria	Key exclusion criteria
[a]Bhatnagar 2012[33]	• Locally advanced/metastatic NSCLC previously treated with cisplatin-based chemotherapy • Progressive/recurrent disease • ECOG score of 0–2	• NS
BR.21 2005[31]	• ≥ 18 years • ECOG score of 0–3 • One or two previous regimens of combination chemotherapy • Ineligible for further chemotherapy • ≥ 21 days after chemotherapy (14 days after vinca alkaloids or gemcitabine) and 7 days after radiation • Adequate haematological and biochemical values	• Prior breast cancer, melanoma, or hypernephroma • Other malignant diseases (except basal-cell skin cancers) within 5 years • Symptomatic brain metastases
[a]DELTA 2013[40]	• Stage IIIB or IV (America Joint Committee on Cancer version 6) • Previously treated with one or two chemotherapy regimens including at least one platinum agent • Evaluable or measurable disease • ECOG score of 0–2	• NS
INTEREST 2008[34]	• ≥ 18 years • Locally advanced or metastatic NSCLC • At least one previous platinum-based chemotherapy regimen (1 to 2 regimens allowed) • WHO score of 0–2 • Measurable or non-measurable disease by RECIST • No previous EGFR-TKI • Adequate hepatic function	• NS
ISEL 2005[39]	• > 18 years • Locally advanced or metastatic NSCLC • One or two previous chemotherapy regimens • Refractory to, or intolerant of, latest chemotherapy regimen • At least one previous platinum-based chemotherapy regimen • WHO score of 0–2 (PS score of 3 if PS not because of comorbidity) • ≥ 8 weeks life expectancy	• > 2 previous chemotherapy regimens • Chemotherapy within the previous 14/21 days (single/(combination) • New CNS metastases • Unresolved toxicities from previous therapy • Coexisting malignant disease • Inadequate bone marrow, renal or hepatic function • Severe/uncontrolled systemic disease • Interstitial lung disease • Pregnancy or breastfeeding
ISTANA 2010[35]	• > 18 years • Stage IIIB or IV NSCLC • One previous platinum-doublet chemotherapy • WHO score of 0–2 • Measurable disease (RECIST) • Adequate bone marrow, renal and hepatic function	• Previous docetaxel or any other EGFR-targeted treatment • Clinically active interstitial lung disease • Newly diagnosed CNS metastases • Unresolved toxicity from previous anticancer therapy

continued

TABLE 57 Key inclusion and exclusion criteria of included trials (*continued*)

Trial	Key inclusion criteria	Key exclusion criteria
Kim 2012[32]	• Stage IIIB or IV NSCLC • Failure of first-line chemotherapy • Adequate organ function • ≥ 1 measurable lesion • ≥ 18 years • WHO PS score of 0–2 • ≥ 12 weeks life expectancy • activating EGFR mutation or 2 out of 3 factors: female, adeno histology, never-smoker	• Gastrointestinal illness • Previous treatment with EGFR inhibitors • Radiation therapy within 4 weeks
Li *et al*. 2010[36]	• Advanced NSCLC failed first-line CTX	• NR
SIGN 2006[37]	• Stage IIIB or IV progression after first-line chemotherapy • ≥ 18 years • WHO PS score of 0–2 • ≥ 12 weeks life expectancy symptomatic (LCS ≥ 24) • Capable of understanding FACT-L questionnaire	• Previous taxane • Any chemotherapy within 30 days • Cerebral metastasis • Interstitial lung disease • Other malignancies, (except basal cell carcinoma or cervical cancer in situ) • Unresolved toxicity from previous therapy • Laboratory values outside requested limits • Psychiatric disorder that may affect completion of the FACT-L questionnaire
TAILOR 2013[41]	• (Wild type) EGFR M– NSCLC • Previously treated with a first-line platinum-based regimen • No previous taxanes • No previous EGFR drugs • ECOG score of > 2 • Adequate vital functions	• NR
TITAN 2012[42]	• Patients with disease progression during first-line treatment in Sequential Tarceva in Unresectable NSCLC (SATURN) trial • Recurrent or metastatic NSCLC • ECOG PS score of 0–2 • ≥ 18 years adequate renal, hepatic and haematological function	• Previous EGFR-directed drugs or drugs directed at pemetrexed molecular targets • Previous chemotherapy or systemic anti-neoplastic therapy other than the permitted platinum-based regimens • Uncontrolled or untreated brain metastasis • Other malignancies within 5 years (except carcinoma in situ)
V-15-32 2008[38]	• ≥ 20 years • Stage IIIB to IV • Prior treatment with one or two chemotherapy (1 platinum-based) • ≥ 3 months life expectancy • WHO PS score of 0–2 disease-measurable disease by RECIST • (6 months after study initiation patients without measurable lesions eligible)	• Treatment within 4 weeks of enrolment prior treatment with docetaxel or anti-EGFR therapy • Other coexisting malignancies • Unresolved chronic toxicity from previous anticancer therapy • Severe/uncontrolled systemic diseases • CNS metastases • History/concurrent interstitial lung disease

CNS, central nervous system; CTX, chemotherapy; FACT-L, Functional Assessment of Cancer Therapy-Lung; LCS, lung-cancer subscale; NR, not reported; NS, not stated; RECIST, response evaluation criteria in solid tumours.
a Based on conference abstract.

Appendix 7 Details of probabilistic sensitivity analysis: survival model parameters

All survival parameters are assumed to be drawn from normal distributions. Please note that the following terms and their abbreviations have been used in *Tables 58–67*.

TABLE 58 Terms used in *Appendix 7*

Term	Abbreviation
Zero time hazard	S0
First spline knot	S1
Second spline knot	S2
Hazard rate – phase 1	R1
Hazard rate – phase 2 (erlotinib)	R2E
Hazard rate – phase 2 (docetaxel)	R2D
Hazard rate – phase 3	R3
Hazard rate – phase 3 (erlotinib)	R3E
Hazard rate – phase 3 (docetaxel)	R3D
BSC intercept	B
Erlotinib intercept	E
Common hazard rate	R
BSC phase 1 intercept	A
BSC phase 1 hazard rate	BSCR1
Spline knot time	S
BSC phase 2 hazard rate	BSCR2

TABLE 59a The TAILOR trial: OS model

Parameters (monthly)	Estimate	Standard error	Lower 95% CI	Upper 95% CI
S1	1.95859	0.09800	1.76442	2.15277
S2	6.46245	0.14348	6.17816	6.74675
R1	0.06972	0.00226	0.06525	0.07420
R2E	0.16142	0.00342	0.15465	0.16820
R2D	0.10000	0.00177	0.09651	0.10350
R3	0.06118	0.00136	0.05849	0.06388

TABLE 59b The TAILOR trial: OS model

Correlation	S1	S2	R1	R2E	R2D	R3
S1	1	–0.295	0.608	0.699	0.171	0.040
S2	–	1	0.008	–0.635	–0.434	–0.461
R1	–	–	1	0.080	–0.436	0.057
R2E	–	–	–	1	0.551	0.061
R2D	–	–	–	–	1	–0.218
R3	–	–	–	–	–	1

TABLE 60a The TAILOR trial: PFS model

Parameters (monthly)	Estimate	Standard error	Lower 95% CI	Upper 95% CI
S0	0.02216	0.00424	0.01384	0.03048
S1	1.71743	0.01793	1.68229	1.75257
S2	2.88616	0.03963	2.80848	2.96385
R1	0.14308	0.00466	0.13395	0.15222
R2E	0.71455	0.01608	0.68303	0.74607
R2D	0.42007	0.00939	0.40167	0.43848
R3E	0.25035	0.01025	0.23025	0.27044
R3D	0.17527	0.00497	0.16554	0.18501

TABLE 60b The TAILOR trial: PFS model

Correlation	S0	S1	S2	R1	R2E	R2D	R3E	R3D
S0	1	–0.283	–0.003	–0.817	–0.050	0.117	0.017	–0.028
S1	–	1	–0.259	0.560	0.673	0.305	–0.039	0.066
S2	–	–	1	0.006	–0.552	–0.500	–0.451	–0.426
R1	–	–	–	1	0.100	–0.232	–0.033	0.056
R2E	–	–	–	–	1	0.541	–0.098	0.167
R2D	–	–	–	–	–	1	0.147	–0.250
R3E	–	–	–	–	–	–	1	0.212
R3D	–	–	–	–	–	–	–	1

TABLE 61a The BR.21 trial: time to off-treatment

Parameters (weekly)	Estimate	Standard error	Lower 95% CI	Upper 95% CI
Intercept	0.30686	0.01474	0.27724	0.33648
Hazard rate	0.04167	0.00036	0.04094	0.04240

TABLE 61b The BR.21 trial: time to off-treatment

Correlation	Intercept	Hazard rate
Intercept	1	–0.878
Hazard rate	–	1

TABLE 62a The BR.21 trial (intention to treat): OS model

Parameters (daily)	Estimate	Standard error	Lower 95% CI	Upper 95% CI
B	0.42445	0.02050	0.38371	0.46519
E	–0.02941	0.02048	–0.07011	0.01128
R	0.00320	0.00005	0.00311	0.00330

TABLE 62b The BR.21 trial (intention to treat): OS model

Correlation	B	E	R
B	1	0.909	–0.935
E	–	1	–0.972
R	–	–	1

TABLE 63a The BR.21 trial (intention to treat): PFS model

Parameters (daily)	Estimate	Standard error	Lower 95% CI	Upper 95% CI
B	1.46083	0.05163	1.35702	1.56464
E	0.14557	0.05047	0.04409	0.24705
R	0.00664	0.00015	0.00634	0.00694

TABLE 63b The BR.21 trial (intention to treat): PFS model

Correlation	B	E	R
B	1	0.811	–0.829
E		1	–0.979
R			1

TABLE 64a The BR.21 trial (wild type): erlotinib OS model

Parameters (monthly)	Estimate	Standard error	Lower 95% CI	Upper 95% CI
Erlotinib intercept	–0.00978	0.01237	–0.03449	0.01494
Erlotinib hazard rate	0.09791	0.00137	0.09517	0.10065

TABLE 64b The BR.21 trial (wild type): erlotinib OS model

Correlation	Intercept	Hazard rate
Intercept	1	–0.856
Hazard rate	–	1

TABLE 65a The BR.21 trial (wild type): BSC OS model

Parameters (monthly)	Estimate	Standard error	Lower 95% CI	Upper 95% CI
A	–0.30146	0.05571	–0.41539	–0.18752
BSCR1	0.31157	0.02270	0.26515	0.35799
S	3.75313	0.19346	3.35747	4.14880
BSCR2	0.07890	0.00414	0.07043	0.08737

TABLE 65b The BR.21 trial (wild type): BSC OS model

Correlation	A	R1	S	R2
A	1	–0.957	0.574	0.000
BSCR1	–	1	–0.708	0.000
S	–	–	1	–0.466
BSCR2	–	–	–	1

TABLE 66a The BR.21 trial (wild type): erlotinib PFS model

Parameters (daily)	Estimate	Standard error	Lower 95% CI	Upper 95% CI
Erlotinib intercept	0.15445	0.03923	0.07480	0.23410
Erlotinib hazard rate	0.00623	0.00016	0.00590	0.00655

TABLE 66b The BR.21 trial (wild type): erlotinib PFS model

Correlation	Intercept	Hazard rate
Intercept	1	–0.882
Hazard rate		1

TABLE 67a The BR.21 trial (wild type): BSC PFS model

Parameters (daily)	Estimate	Standard error	Lower 95% CI	Upper 95% CI
BSC intercept	0.65426	0.08620	0.47053	0.83798
BSC hazard rate	0.00959	0.00043	0.00867	0.01051

TABLE 67b The BR.21 trial (wild type): BSC PFS model

Correlation	Intercept	Hazard rate
Intercept	1	–0.885
Hazard rate	–	1

Appendix 8 Rates of febrile neutropenia associated with treatment with docetaxel

See addendum 1 and addendum 2 of the AG report.[105]

Evidence from published trials

Several approaches can be taken to estimate of the proportion of patients treated with docetaxel monotherapy who will experience one or more episodes of grade 3 or 4 FN as a result of treatment. A total of eight different estimated incidence rates were identified as follows.

Assessment Group base case (TAILOR)[41]

Four patients in TAILOR[41] were reported to have experienced grade 3 or 4 FN in the docetaxel arm, all of whom were in the subgroup of 63 patients treated every 3 weeks with high-dose docetaxel (75mg/m^2 body surface area). This corresponds to an incidence rate of 6.35% (95% CI 1.79% to 13.50%) and relates to the dose and frequency of docetaxel administration most commonly used in the UK.

Decision Support Unit Report[94]

During the first appraisal of erlotinib versus docetaxel in second-line chemotherapy for NSCLC (NICE TA162[21]) the Decision Support Unit was asked to investigate the incidence of FN and its associated treatment costs. They conducted a meta-analysis of reported trials and estimated the incidence as 5.95% (95% CI 5.30% to 7.70%).

TAILOR trial[41] (all patients)

If no distinction is made between high dose (3-weekly) and low dose (weekly docetaxel 35mg/m^2 body surface area), the FN incidence rate is 3.85% (95% CI 1.07% to 8.28%).

Other trials (pre-epidermal growth factor testing)

Data from 17 randomised clinical trials,[34,37,41,42,49,64,74,85,106–115] which included 3-weekly high-dose docetaxel monotherapy as one treatment arm, were combined to provide a weighted average incidence rate. It was not possible to carry out a formal meta-analysis because of the diversity of comparators, populations and settings of these trials. The weighted average estimate is 7.3% (95% CI 6.3% to 8.3%). Heterogeneity testing of trial incidence values identified that two of the larger trials[34,49] exhibited significantly higher incidence rates than the remaining 15 trials. Therefore, two weighted average values were selected for sensitivity testing, 10.8% (95% CI 8.9% to 12.8%) and 5.0% (95% CI 4.0% to 6.2%), corresponding to these distinct data subsets. The maximum estimated incidence among all 17 trials, 12.7% (95% CI 9.0% to 16.8%) was also selected for exemplification in the decision model.

Extreme sensitivity analysis

In order to explore the impact of a very high incidence rate, the value of the greatest upper confidence limit of any of these 17 trial arms was selected – 25%.

Comment on Royal College of Physicians suggested incidence rates

In the Royal College of Physicians submission document to NICE it is stated that:

'In clinical practice, admission rates for neutropaenic sepsis and treatment complications are 25–50% with docetaxel compared to < 5% with erlotinib'.[116]

Unfortunately no supporting evidence was cited for this statement. Subsequently, the Royal College of Physicians responded to the Appraisal Consultation Document citing a conference abstract by Sharma[117] of an observational study of admissions in three NHS trusts to support a figure of 41%. The abstract shows that 41% is the total number of hospital admissions in second-line docetaxel treatment (9 out of 22 admissions), whereas only four of these were a result of neutropenic sepsis (i.e. 18%). In addition, it should be noted that admission rates are necessarily higher than incidence rates, as the Decision Support Unit estimated that affected patients require an average of 1.4 admissions per patient. Using this factor to adjust admission rates to incidence rates, the best estimate from the Sharma[117] study is an incidence rate of 13.0% (95% CI 2.7% to 29.5%). The small numbers involved and the wide CI (which encompasses all of the eight estimates listed above) indicates that these data add nothing useful to the consideration of FN incidence rates.

Sensitivity analysis for febrile neutropenia incidence

Table 68 summarises the cost-effectiveness results for the AG-revised base case and the seven alternative FN scenarios described previously. In all cases erlotinib is not cost-effective compared with docetaxel, because the cost and utility effect of varying FN incidence is not sufficient to counteract the estimated survival advantage of docetaxel. The incremental cost is zero for a FN rate of 16.2% (equal cost, but QALY gain for docetaxel). The ICER for erlotinib versus docetaxel only exceeds £30,000 cost savings per QALY lost for docetaxel FN incidence rates above 63%.

Table 69 provides an overview of the three estimated AG base-case ICERs made available to the AC during this appraisal.

TABLE 68 Sensitivity analysis of AG-revised base-case scenario, with alternative assumed values of the incidence rate of grade 3 and 4 FN during second-line docetaxel 3-weekly monotherapy

		Erlotinib		Docetaxel		Incremental		ICER
Scenario	FN incidence (%)	Total cost	Total QALYs	Total cost	Total QALYs	Cost	QALYs	£/QALY
AG-revised base case	6.35	£14,049	0.4863	£13,504	0.5930	£545	–0.1067	–£5112 (dominated)
Decision Support Unit estimate	5.95	£14,049	0.4863	£13,482	0.5931	£567	–0.1067	–£5312 (dominated)
TAILOR trial[41] (all patients)	3.85	£14,049	0.4863	£13,365	0.5939	£684	–0.1076	–£6353 (dominated)
Weighted average (all trials)	7.26	£14,049	0.4863	£13,554	0.5926	£495	–0.1063	–£4654 (dominated)
Weighted average (2 high-incidence trials)	10.80	£14,049	0.4863	£13,749	0.5913	£300	–0.1050	–£2854 (dominated)
Weighted average (15 low-incidence trials)	5.03	£14,049	0.4863	£13,431	0.5934	£618	–0.1072	–£5768 (dominated)
Maximum trial	12.68	£14,049	0.4863	£13,853	0.5906	£196	–0.1044	–£1876 (dominated)

TABLE 69 Estimated base-case cost-effectiveness estimates of erlotinib vs. docetaxel for the EGFR M– population provided by the AG during the appraisal

Amendment	Incremental cost	Incremental QALYs	Deterministic ICER	Probabilistic ICER
AG report estimate	–£1653	–0.1076	£15,359/QALY	£12,719/QALY
Amended for FN incidence rate (6.35%) (addendum 1)	–£3311	–0.1076	£31,039/QALY	£28,328/QALY
Amended for FN incidence rate and corrected FN cost calculation (addendum 2)	£545	–0.1076	–£5112/QALY (dominated)	–£7709/QALY (dominated)

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