MTA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

This report was commissioned by the NIHR HTA Programme as project number 12/49/01

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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1 DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report.

AC	Appraisal Committee
AE	adverse event
AG	Assessment Group
ASCO	American Society for Clinical Oncology
BNF	British National Formulary
BSC	best supportive care
CRD	Centre for Reviews and Dissemination
CRUK	Cancer Research UK
ECOG	Eastern Cooperative Oncology Group
EGFR M-	epidermal growth factor mutation negative
EGFR M+	epidermal growth factor mutation positive
EGFR-unknown	epidermal growth factor mutation status unknown
EMA	European Medicines Agency
eMIT	electronic market information tool
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
ERL	Erlotinib
FACT-L	Functional Assessment of Cancer Therapy – Lung Questionnaire
GEF	gefitinib
GEM	gemcitabine
HR	hazard ratio
HRQoL	health-related quality of life
i.v.	intravenous
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
KPS	Karnofsky Performance Scale
LUCADA	National Lung Cancer Data Audit
LY	life year
NLCA	National Lung Cancer Audit
NLCAD	National Lung Cancer Audit Data
NICE	National Institute for Health and Care Excellence
ORR	overall response rate
OS	overall survival
PAX	paclitaxel
PEM	pemetrexed
PFS	progression-free survival
PSA	probabilistic sensitivity analysis
QALY	quality adjusted life year
RCP	Royal College of Physicians
RCT	randomised controlled trial
TKI	tyrosine kinase inhibitor
VIN	vinorelbine
WHO	World Health Organisation
WT EGFR	(wild type) epidermal growth factor mutation negative
WTP	willingness to pay

2 EXECUTIVE SUMMARY

2.1 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 (EGFR) mutation status, performance status (PS), co-morbidities and patient preferences. Patients with stage III or IV disease, good PS and for whom curative treatment is not an option may be initially offered chemotherapy to improve survival, disease control and quality of life (QoL). A proportion of this latter 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 respective licensed indications are the focus of this review: erlotinib (Tarceva®, Roche Ltd) and gefitinib (Iressa®, AstraZeneca). Both are epidermal growth factor tyrokinase inhibitors (EGFR-TKI) that block the signal pathways involved in cell proliferation.

2.2 Objectives

The remit of this review is to appraise the clinical and cost effectiveness of erlotinib and gefitinib within their licensed indications for the treatment of NSCLC after progression following prior chemotherapy (review of NICE technology appraisals TA162 and TA175).

2.3 Methods

Four electronic databases were searched for randomised controlled trials (RCTs) and economic evaluations (EEs). Studies that compared erlotinib or gefitinib with each other or with 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 years (LY) gained and incremental cost per quality adjusted life year (QALY) gained. Two reviewers independently screened all titles and/or abstracts including economic evaluations, 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 in structured tables and as a narrative description. No meta-analysis or network meta-analyses were undertaken.

2.4 Results of the literature review

Clinical effectiveness

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

No trials were identified that were conducted in a population of solely 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 M- patients; however, only one 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 and DELTA trials were described in an abstract in narrative format only.

EGFR M+

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 were statistically significantly different for any of the comparisons described. Four studies reported PFS, but only one trial (INTEREST) showed a statistically significant improvement for any comparison considered; the results favoured gefitinib over docetaxel.

EGFR M-

Key clinical data were derived from the results of the TAILOR and DELTA trials. However, EGFR mutation status data were also derived retrospectively from subgroup analyses of BR.21, KIM, TITAN, INTEREST and ISEL. The only statistically significant differences identified for any treatment was in the comparison of erlotinib vs docetaxel; in both the TAILOR and DELTA trials patients in the docetaxel arm had improved PFS.

EGFR-unknown

Clinical data were available from ten trials in populations in which EGFR mutation status was not a factor in the recruitment process, or where overall trial results were presented (with the exception of TAILOR where 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 (ISTANA) reported a statistically significant PFS benefit for the comparison of gefitinib vs docetaxel,

favouring gefitinib although this was based on 90% confidence limits. For the comparison of gefitinib vs 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 placebo.

Cost-effectiveness

Eleven studies containing economics information were identified. However, the Assessment Group concluded that the results of the systematic review were of limited value to decision-makers in the UK NHS. This is due to relatively recent changes in (i) the price of docetaxel and (ii) 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 submitted economics evidence. Roche's base-case analysis compared erlotinib vs 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 also considered erlotinib vs BSC for patients with EGFR M- tumours. The AG provides a summary and critique of the economic evaluation that is presented in Roche's submission.

2.5 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 "EGFR M+ population")

2) Previously treated adult patients with locally advanced or metastatic NSCLC and who do <u>not</u> 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")

EGFR M+ 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 or cost effectiveness of available treatments for this patient population.

EGFR M- population

Using data from the TAILOR trial for patients who are EGFR M-, the AG's comparison of docetaxel vs erlotinib yielded an incremental cost-effectiveness ratio (ICER) of £15,359 per QALYgained which is well within the range normally considered to be cost effective. The results of univariate sensitivity analyses indicated that this result is unaffected by uncertainty in almost all model parameters. The only exceptions were the price used for docetaxel (the base-case analysis applies the electronic Market Information Tool [eMIT] average NHS price which is much lower than the British National Formulary (BNF) list price), and the incidence of febrile neutropenia when docetaxel was used. Examination of the probabilistic sensitivity analysis (PSA) scatterplot and the cost-effectiveness acceptability curves indicated strong general confidence that docetaxel is more cost effective than erlotinib in this population (75% of simulations favoured docetaxel at a willingness to pay threshold of £20,000 per QALY gained, and 91% at £30,000 per QALY gained).

Using subgroup data from the BR.21 trial for patients who are EGFR M-, the AG's comparison of erlotinib vs 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% at £50,000 per QALY gained).

EGFR-unknown population

Using data from the BR.21 trial for patients who are EGFR-unknown, the AG's comparison of erlotinib vs 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 utility model (i.e. the baseline NSCLC population utility value in patients with stable disease), and the incidence of febrile neutropenia 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).

2.6 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 and cost effectiveness of gefitinib and erlotinib 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 the TAILOR trial) 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 and cost effectiveness of relevant treatments. Specifically, the AG was unable to carry out an economic evaluation 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 the reported PFS benefit seen in an Italian population would be achieved by NHS patients in in England and Wales.

The results of the manufacturer's post-hoc analysis of clinical data from the control arm of the IPASS trial are relevant to the decision problem. However, these findings, and others, require careful and detailed validation in a robustly designed RCT before they can be used to inform decision-making in this complex clinical area.

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 i.v. treatments). This is most important in the comparison of docetaxel vs 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 increased the size of the estimated ICER (docetaxel vs erlotinib) in the EGFR M- population from £15,359 to £26,176 per QALY gained. This result is within the range normally considered cost effective. 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.

2.7 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 docetaxel vs erlotinib in patients who's disease has progressed 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- 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.

3 BACKGROUND

3.1 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.[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.[3] Incidence rates for lung cancer differ between men and women; for men, rates have decreased by more than 45% since the late 1970s, whilst incidence rates for women are still increasing.[1] The Royal College of Physicians (RCP) reports that mortality rates from lung cancer have improved in the last 40 years.[4] 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 five years, survival in men and women is 7% and 9% respectively.[4]

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

Table 1 Cancer survival statistics

	Males	Females	Total
Number of new cases per year UK 2010	23,175	18,851	42,026
Rate per 100,000 population*	58.0	39.7	47.8
Number of deaths per year UK 2010	19,410	15,449	34,859
Mortality rate per 100,000*	47.9	31.3	38.6
1-year survival rate – adults diagnosed between 2005 and 2009 England	29.4%	33.0%	31.0%
5-year survival rate – adults diagnosed between 2005 and 2009 England	7.8%	9.3%	9.0%
10-year survival rate – adults diagnosed 2007 England and Wales (predicted)	4.9%	5.9%	5.3

*Age standardised to the European population

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.[5]

Around 72% (approximately 20,000) of lung cancers are non-small cell lung cancers (NSCLC), which can be further classified into three histological sub-types of large-cell undifferentiated carcinoma, squamous cell carcinoma and adenocarcinoma.[6]

Since the introduction of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) into clinical practice in the UK, people with non-squamous NSCLC may be further differentiated as having either epidermal growth factor receptor (EGFR) activating mutation positive (M+) or negative (M-) status, the latter is otherwise known as wild type (WT EGFR). 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.

3.1.1 Diagnosis and staging

Diagnosis

Guidelines (CG121[7]) produced by the National Institute for Health and Care Excellence (NICE) recommend that urgent referral for a chest X-ray should be made when a patient presents with haemoptysis or any unexplained or persistent (lasting more than 3 weeks) symptoms as detailed previously. If a chest X-ray or chest computed tomography (CT) scan 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 co-morbid disease.

Staging

The TNM staging system (UICC[8]) 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 6th and 7th 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 7th edition compared with 6th edition

6th edition	7th edition	
TNM stage	**TNM stage**	**Descriptor**
T1	T1a T1b	Maximum dimension ≤2 cm Maximum dimension 2 – 3 cm
T2	T2a T2b T3	Maximum dimension 3 – 5 cm Maximum dimension >5 – 7 cm 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
M1	M1a	Ipsilateral pleural effusion

T=tumour; M=metastasis

Table 3 Stage groupings in 7th TNM classification

Stage	T	N	M
Stage 0	T1a	N0	M0
Stage IA	T1a, b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a, b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1,2	N2	M0
	T3	N1, N2	M0
	T4	N0, N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1a, b

T=tumour; N=node; M=metastasis

3.1.2 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 comprise the World Health Organisation (WHO[9]) PS scale, The Eastern Cooperative Oncology Group (ECOG[10]) PS scale and the Karnofsky PS Scale (KPS[11]). 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 themselves and a rating of 4 indicates that a patient requires substantial support.

Table 4 WHO performance status 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

3.2 Treatment options

The treatment options for patients with NSCLC depend on the stage of disease, disease histology, EGFR mutation status, PS, co-morbidities 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.[7] A combination of radiotherapy and chemotherapy may also be an option for patients with stages I-III disease. Patients with stage III or IV disease, good PS and for whom curative treatment is not an option may be initially offered chemotherapy to improve survival, disease control and quality of life (QoL).[7] A proportion of this latter 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.

3.2.1 Epidemiology

The National Lung Cancer Audit

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

The current audit (published in 2012) reports data for patients diagnosed with lung cancer or mesothelioma first seen in 2011.[12,13] 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; 19,155 of these 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% were stage IIIB or stage IV. More males than females were diagnosed (15,471 compared to 12,178). There were 6,698 patients with stage IIIB/IV who had a PS of 0 or 1 and of these 55.2% received chemotherapy. Median survival for all cancer cases was 185 days (interquartile range 57-309) from diagnosis date.

Our clinical advisors tell us that in UK clinical practice 25% of PS 0-1 patients receive second-line chemotherapy and approximately 5% to 15% of PS 2 patients receive second-line treatment.

Impact of lung cancer

The annual cost of lung cancer to the UK economy is estimated at £2.4 billion. Half of the cost of lung cancer is due to premature deaths and time off work. Healthcare costs account for a further 35% whilst an additional 16% is attributable to unpaid care provided by friends and family. According to Cancer Research UK (CRUK),[14] each lung cancer patient is thought to cost the UK healthcare system £9,071 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.[15]

3.2.2 Relevant national guidelines, including National Service Frameworks

The National Institute for Health and Care Excellence has published a clinical guideline (CG121[7]) that provides recommendations for good practice in the diagnosis and treatment of lung cancer in England and Wales. In addition, NICE has published a quality standard (QS17[16]) that defines best practice for the care of people with lung cancer. The QS17[16] states that people with stage IIIB or IV NSCLC and eligible PS 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.[17]

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

First-line treatment options

The first-line chemotherapy treatment options recommended by NICE[17] include platinum-based (cisplatin or carboplatin) doublet chemotherapy with docetaxel, gemcitabine, paclitaxel or vinorelbine. Pemetrexed plus cisplatin is an option for patients with predominantly non-squamous NSCLC. Single agents gefitinib (Iressa®) or erlotinib (Tarceva®) are options for patients with locally advanced or metastatic EGFR M+ NSCLC.[17]

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.[17] 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, where there is intolerance of or contraindications to docetaxel) or for third-line treatment after docetaxel therapy.[17]

NICE was unable to recommend 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.[17]

NICE did not recommend pemetrexed as a second-line treatment for locally advanced or metastatic NSCLC.

Table 5 Relevant NICE documents

NICE clinical guideline/guidance	Patient group (histology/EGFR status)	Recommended treatment
First-line		
CG121[7] The diagnosis and treatment of lung cancer	All patients with NSCLC of good performance status (WHO 0 or 1 or Karnofsky score of 80 to 100)	Platinum doublet docetaxel, gemcitabine, vinorelbine or paclitaxel. Or single agent if unable to tolerate platinum therapy
TA192[18] Gefitinib for the first-line treatment of locally advanced or metastatic NSCLC	EGFR M+ only	Gefitinib if provided at agreed PAS price
TA258[19] 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[20] Pemetrexed for the first-line treatment of NSCLC	Confirmed adenocarcinoma or large cell (non-squamous) only	Pemetrexed+cisplatin
Maintenance following first-line		
TA190[21] Pemetrexed for the maintenance treatment of NSCLC	Non-squamous (adenocarcinoma or large cell) without disease progression after 1st line platinum chemotherapy with gemcitabine, paclitaxel or docetaxel	Pemetrexed
Second-line		
CG121[7] The diagnosis and treatment of lung cancer	All NSCLC	Docetaxel monotherapy
TA162[22] 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[23] 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[24] Pemetrexed for the treatment of NSCLC	All NSCLC	Not recommended

3.2.3 Variation in services and/or uncertainty about best practice

Histological diagnosis

The NLCA[12] reports an overall histological diagnosis rate of 77% for all lung cancers. For NSCLC, the rate appears to be 70%. This means that 30% of patients with NSCLC are not tested for the histological status of their disease. Our clinical advisors tell us that some patients are too ill for treatment and so are not tested for histology.

EGFR 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 (EM, 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 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).

3.3 Description of technology under assessment

Two oral anticancer treatments, used within their respective licensed indications are the focus of this review: erlotinib (Tarceva®, Roche Ltd) and gefitinib (Iressa®, Astra Zeneca). Both are EGFR-TKI that block the signal pathways involved in cell proliferation. The Summary of Product Characteristics (SPC) for erlotinib and gefitinib are available from the Electronic Medicines Compendium (eMC[25]).

3.3.1 Erlotinib

Erlotinib is available as film coated tablets 25mg, 100mg or 150mg. The recommended daily dose of erlotinib is 150mg taken at least one 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[26] stipulates that prior to initiation of erlotinib therapy, people with chemotherapy-naïve NSCLC should undergo EGFR mutation testing using a well-validated and robust methodology.

In the post-first-line maintenance setting, erlotinib is licensed as a 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.

3.3.2 Gefitinib

Gefitinib is available as a 250mg film-coated tablet. The recommended dose of gefitinib is one 250mg 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[27] 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[27] notes that increased incidents of interstitial lung disease have 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. 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.[28]

3.3.3 Current usage in the NHS

The manufacturer of erlotinib (Roche) states in its evidence submission to NICE that 70% of patients who receive second-line treatment receive erlotinib (MS, p4).

The manufacturer of gefitinib (AstraZeneca) states in its evidence submission to NICE that [redacted] This number refers to first-line treatment only and is not relevant to this appraisal.

The pack costs of erlotinib and gefitinib and their PAS are shown in Table 6.

Table 6 Drug pack cost

Cost of erlotinib	[redacted]
Cost of gefitinib	250 mg, 30-tab pack = £2167.71 British National Formulary list price September 2013 NHS discounted price available of £12,200 per patient receiving treatment beyond 60 days

4 DEFINITION OF THE DECISION PROBLEM

4.1 Decision problem

The remit of this appraisal is to review and update (if necessary) the clinical and cost-effectiveness evidence base described in TA162[29] and TA175.[23] The key elements of the decision problem are described in Table 7.

Table 7 Decision problem

Interventions	Erlotinib
	Gefitinib
Patient population	Adults with locally advanced or metastatic NSCLC that has progressed following prior chemotherapy*
Comparators	Erlotinib and gefitinib to be compared with each other and with: • docetaxel • best supportive care
Outcomes	• overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life
Economic analysis	The reference case stipulates that: • the cost effectiveness of treatments should be expressed in terms of incremental cost per quality adjusted life year • the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective
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

*The AG assumes that prior chemotherapy refers to both to cytotoxic chemotherapy and targeted therapy

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, (gefitinib or erlotinib) 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 since 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.

4.2 Overall aims and objectives of assessment

The remit of this review is to appraise the clinical 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[29] and TA175[23]).

5 ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

5.1.1 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 (Ovid) 1974 to 2013 April week 3
- Medline (Ovid) 1946 to 2013 April 26
- The Cochrane Library to 2013 April 28
- PUBMED 2013 January 2010 to 2013 April 28

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.

5.1.2 Inclusion and exclusion criteria

Two reviewers JG/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/JH) according to the criteria set out below (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 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 erlotinib or gefitinib with 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

Patients with locally advanced or metastatic NSCLC that has progressed following prior cancer 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), response rates, AEs, health related quality of life (HRQoL). 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.

5.1.3 Data extraction strategy

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

5.1.4 Quality assessment strategy

The quality of clinical-effectiveness studies was assessed independently by two reviewers (JG/KD) according 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.

5.1.5 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).

5.2 Results

5.2.1 Quantity and quality of research available

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

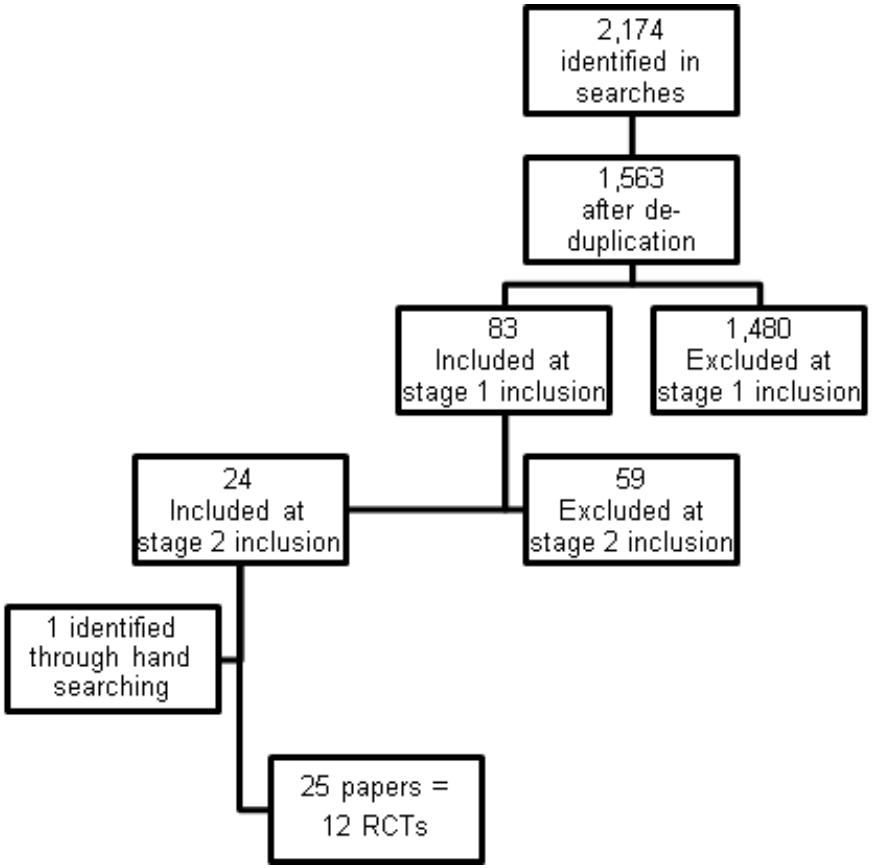

Figure 1 Study selection process

5.2.2 Clinical effectiveness (RCTs)

A total of 12 RCTs (one of which was discussed in TA162[29] 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 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.

Since 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 any retrospective analyses of the data were conducted. It should be noted that where the retrospective EGFR subgroup analyses are available the data are limited.

Two of the included trials Bhatnagar[32] and DELTA[33] were reported as conference abstracts only and therefore limited information is available to describe these studies. The final results of the TAILOR [34] trial 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 who were EGFR-unknown at the time of randomisation (Bhatnagar,[32] INTEREST,[35] ISTANA,[36] LI,[37] SIGN,[38] V-15-32[39]). A single trial (ISEL[40]) compared gefitinib with placebo in an EGFR-unknown population.

Erlotinib trials (n=4)

Two trials (DELTA[33] and TAILOR[34]) compared erlotinib with docetaxel. The DELTA[33] trial was designed to allow the assessment of treatment outcomes in EGFR M- and EGFR M+ patient populations. The TAILOR[34] trial included only patients who were known to be EGFR M-. One trial (TITAN[41]) compared erlotinib with chemotherapy in patients who were EGFR-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[31] trial erlotinib was compared with placebo in an EGFR-unknown population.

Gefitinib vs erlotinib (n=1)

Gefitinib was compared with erlotinib in one trial (KIM[42]) in patients who were EGFR M+ or who were likely to be EGFR M+.

Table 8 Summary of included trials

Trial	Design	Intervention	Comparator	Patient population (EGFR M+ or EGFR M- or EGFR-unknown)	Retrospective EGFR subgroup data available
GEF vs ERL					
Kim	Open-label, non-comparative randomised phase II trial	GEF	ERL	EGFR M+ and two out of three factors associated with EGFR mutations	Y
GEF vs DOC					
Bhatnagar	RCT	GEF	DOC	EGFR-unknown	N
INTEREST	Open-label phase III RCT	GEF	DOC	EGFR-unknown	Y
ISTANA	Open-label phase III RCT	GEF	DOC	EGFR-unknown	N
LI	RCT	GEF	DOC	EGFR-unknown	N
SIGN	Open-label phase II RCT	GEF	DOC	EGFR-unknown	N
V-15-32	Open-label phase III RCT	GEF	DOC	EGFR-unknown	Y
GEF vs PLA					
ISEL	Placebo-controlled phase III RCT	GEF+BSC	PLA+BSC	EGFR-unknown	Y
ERL vs DOC					
DELTA	Open-label phase III RCT	ERL	DOC	EGFR M+ and EGFR M-	Y
TAILOR	Open-label phase III RCT	ERL	DOC	EGFR M- only	Y
ERL vs DOC/PEM					
TITAN	Open-label phase III RCT	ERL	DOC or PEM	EGFR-unknown	Y
ERL vs PLA					
BR.21 2005	Placebo-controlled phase III RCT	ERL	PLA	EGFR-unknown	Y

BSC=best supportive care, PLA=placebo

Quality assessment of the included RCTs

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 ten trials reported in published papers, four (ISTANA,[36] KIM,[42] LI,[37] V-15-32[39]) did not state the methods used to randomise patients into the trial or whether the allocation method precluded prediction of participant assignment. One trial (SIGN[38]) 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 (DELTA[33] and Bhatnagar[32]), only the DELTA[33] trial 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 TITAN,[41] showed comparability across trial arms. The KIM[42] 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 gefitinib and erlotinib arms of the KIM[42] trial appear to be well-balanced. In the TAILOR[34] trial differences in the numbers of smokers and never-smokers and numbers of patients with adenocarcinoma histology were noted. In the conference abstracts (Bhatnagar[32] and DELTA[33]) details of comparability were not presented.

Eligibility and co-interventions: All published trials specified eligibility criteria for entry into the trial. Three trials (INTEREST,[35] LI[37] and SIGN[38]) reported the use of co-medications that may have had an effect on trial outcomes. In all cases these were corticosteroids and/or anti-emetics administered as pre-medications prior to i.v. chemotherapy. It is likely that the remaining trials also used these pre-medications 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 co-medications.[32,33]

Blinding: The reporting of blinding procedures across the ten published trials was poor. Two of the ten published trials were placebo-controlled (BR.21[31] and ISEL[40]) and were stated as being 'double-blind.' It is clear from the ISEL[40] 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. In the BR.21[31] trial, we have assumed that the patients, administrators and outcome assessors were blinded to treatment allocation although this is not explicitly stated. Neither ISEL[40] nor BR.21[31] reported any testing of the blinding procedures.

The remaining eight published trials were open-label. In trials where 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 as 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 the TAILOR[34] trial 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[39] the primary overall response rate results that were based on investigator judgment were generally consistent with those obtained from independent response evaluation committee assessment. However, it is unknown whether any of the remaining trials employed similar blinding protocols.

Both of the trials[32,33] reported as conference abstracts appear to be open label and neither of the trials report details of any blinding procedures used.[33,34]

Patient withdrawals: The ten 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.[32,33]

Intention-to-treat analysis: All but one of the trials (LI[37]) 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.[32,33]

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.[32,33]

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[41] – the trial was terminated early due to slow recruitment
- KIM[42] – the trial used a historical control (no details provided) to assess the relative effectiveness of erlotinib and gefitinib
- TAILOR[34] – several protocol changes were made to the TAILOR trial, including a change of primary endpoint
- SIGN[38] – the trial was not powered to formally test outcomes
- ISTANA[36] and V-15-32[39] 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 multi-centres in Italy (TAILOR[34]) and six in Asian countries, Korea, South Korea, India, China and Japan (ISTANA[36] KIM,[42] Bhatnagar,[32] LI,[37] DELTA,[33] V-15-32[39]). Of the trials conducted in Asia, three were multi-centred (DELTA,[33] ISTANA,[36] V-15-32[39]). With the exception of the LI[37] trial, all trial results were published in English. The LI[37] paper was translated from Mandarin Chinese to English by a translation service contracted by the AG. The number of randomised patients ranged from 30 (Bhatnagar[32]) to 1692 (ISEL[40]). Inclusion and exclusion criteria used in the included studies are shown in Appendix 6.

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

The dosage of erlotinib and gefitinib was consistent with the recommended licensed dose (150mg or 250mg respectively) across the trials in which those treatments were used. In the nine trials in which docetaxel was a comparator (Bhatnagar,[32] INTEREST,[35] ISTANA,[36] LI,[37] SIGN,[38] V-15-32,[39] DELTA,[33] TAILOR,[34] TITAN[41]), seven trials (Bhatnagar,[32] INTEREST,[35] ISTANA,[36] LI,[37] SIGN,[38] TAILOR,[34] TITAN[41]) treated patients with 75mg m^2 every 3 weeks and two trials (DELTA[33] and V-15-32[39]) treated patients with 60mg m^2 every 3 weeks, the latter being the standard dose used in Japan. The dose of docetaxel in the TITAN[41] trial was at the treating physician's discretion. Median follow-up (where reported) ranged between 7.2 months (ISEL[40]) and 33 months (TAILOR[34]). Information regarding post-progression treatments was not reported in four trials (Bhatnagar,[32] DELTA,[33] LI,[37] SIGN,[38]).

Patient characteristics

Patient characteristics are presented in *=assumed from reported area of recruitment area; [a]=abstract only

GEM=gemcitabine, DOC=docetaxel, PAX=paclitaxel, VIN= vinorelbine; PEM=pemetrexed

Table 10. Details of individual trial inclusion and exclusion criteria are presented in Appendix 6. The median patient age (where reported) ranged between 49 and 61 years. With the exception of the KIM[42] trial, the majority of patients were male (where reported). With the exception of the LI[37] trial, the majority of patients were considered to have stage IV disease (where 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[42] trial and 77% in V-15-32[39] had adenocarcinoma, whilst lower rates were reported in BR.21[31] and TITAN[41] (both approximately 50%). In the main, the majority of patients had received a single prior chemotherapy, however in ISEL[40] 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 be of ECOG 0 or 1 or WHO 0 or 1.[34-36,39,42] Up to one third of patients in the TITAN,[41] ISEL[40] and SIGN[38] trials were considered to be of PS 2 (ECOG or WHO). The patients in the LI[37] trial were KPS of 70 or greater and the two conference abstracts (Bhatnagar[32] and DELTA[33]) report that patients were of ECOG 0 to 2.

The trial populations included in the TAILOR[34] and KIM[42] trials were tested for EGFR mutation status before entry into the trial. Patients randomised to TAILOR[34] were those who were EGFR M- only. The patients recruited to the KIM[42] 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). The DELTA[33] trial included patients who were EGFR M- but it is unclear if EGFR status was ascertained at the time of randomisation.

Six (KIM,[42] Bhatnagar,[32] DELTA,[33] ISTANA,[36] LI,[37] V-15-32[39]) of the 12 trials were conducted in East Asia and therefore included exclusively patients of East Asian ethnicity. With the exception of SIGN,[38] the patients in the remaining trials were predominantly white/Caucasian. Where reported, the percentage of never-smokers ranged across the trials from approximately 17% (TITAN[41]) to 94% (KIM[42]).

Table 9 Key trial characteristics

Trial	Intervention	Comparator	Number patients	Location	Median follow-up	Trial support	Treatment cross-over
GEF vs ERL							
Kim 2012 Open-label, non-comparative randomised phase II	GEF 250mg daily	ERL 150mg daily	96 GEF=48 ERL= 48	South Korea	16.3 months	IN-SUMG Foundation for Medical Research	At the discretion of each physician
GEF vs DOC							
Bhatnagar 2012[a] RCT	GEF 250mg daily	DOC 75mg m^2 every 3 weeks	30	India	2 years	NS	NS
INTEREST 2008 Open-label phase III non-inferiority RCT	GEF 250mg daily	DOC 75mg/m^2 every 3 weeks	1466 GEF=733 DOC=733	Europe, Asia, Americas	7.6 months	AstraZeneca	*GEF arm* n=28 (4%) EGFR-TKI n=225 (31%) DOC n= 112 (15%) other chemotherapy *DOC arm* n=4 (1%) DOC n=268 (37%) EGFR -TKI n=74 (10%) other chemotherapy
ISTANA 2010 Open-label phase III RCT	GEF 250mg daily	DOC 75mg m^2 every 3 weeks	161 GEF=82 DOC=79	Korea	13 months	AstraZeneca	*GEF arm* 24.7% received no further systemic chemotherapy apart from further EGFR TKI (2.5% GEF/ERL) 22.2% received no treatment, 29.6% received DOC and 44.4% received other chemotherapy *DOC arm* 67.1% received an EGFR -TKI, and 6.6% received other chemotherapy
LI 2010 RCT	GEF 250mg daily	DOC 75mg m^2 every 3 weeks	98 GEF= 50 DOC= 48	China	NS	NS	NS
SIGN 2006 Open-label phase II RCT	GEF 250mg daily	DOC 75mg m^2 every 3 weeks	141 GEF= 68 DOC= 73	Europe, South America, Middle East	9.2 months (GEF) 9.4 months (DOC)	AstraZeneca	NS
V-15-32 2008	GEF 250mg daily	DOC 60mg m^2 every 3 weeks	490 GEF=245 DOC=244	Japan	21 months	AstraZeneca	Cross-over was greater than initially expected, and differences in the number and types of patients who received these post-study treatments complicated

Trial	Intervention	Comparator	Number patients	Location	Median follow-up	Trial support	Treatment cross-over
							interpretation of survival results
GEF vs PLA							
ISEL 2005 Placebo-controlled double-blind phase III RCT	GEF 250mg daily	PLA+BSC	1692 GEF=1129 PLA= 563	Europe, Asia, Central and South America, Australia, Canada.	7.2 months	AstraZeneca	*Placebo arm* 3% received GEF. All subsequent treatments for NSCLC well balanced between the treatment groups. The protocol allowed for up to 15% crossover to GEF.
ERL vs DOC							
DELTA 2013[a] Open-label phase III RCT	ERL 150mg daily	DOC 60mg m^2 every 3 weeks	301 ERL = 150 DOC= 151	Japan	NS	Japanese National Hospital Organization	NS
TAILOR 2013 Open-label phase III RCT	ERL 150mg daily	DOC 75mg m^2	222 ERL=112 DOC=110	Italy	33 months	Italian Agency for Drug Administration	No cross-over allowed. *ERL arm* 7 pts crossed over *DOC arm* 4 pts crossed over 3rd- line treatment with PEM/GEM/VIN
ERL vs DOC/PEM							
TITAN 2012 Open-label phase III RCT	ERL 150mg daily	DOC or PEM dosing at discretion of investigator	424 ERL=203 Chemotherapy=221	International	ERL: 27.9 months DOC/PEM: 24.8 months	F Hoffmann-La Roche, Basel, Switzerland	*ERL arm* 25% anti-metabolites 23% DOC or PAC *CTX arm* 12% anti-metabolites 23% TKI 5% switch to DOC 7% switch to PEM
ERL vs PLA							
BR.21 2005 Placebo-controlled phase III RCT	ERL 150mg daily	PLA	731 ERL=488 PLA = 243	International	NS	Supported in part by a grant from OSI Pharmaceuticals	*ERL arm* 8 (1.6 %) *Placebo arm* 18 (7.4 %) received other EGFR inhibitors after study medication discontinued

*=assumed from reported area of recruitment area; [a]=abstract only
GEM=gemcitabine, DOC=docetaxel, PAX=paclitaxel, VIN= vinorelbine; PEM=pemetrexed

Table 10 Key patient characteristics

Trial	Median age (yrs) (range)	% Male	Stage IIIB	Stage IV	Histology: Adeno/Squamous	Previous treatment	Performance status	Ethnicity	Smoking status
GEF vs ERL									
Kim 2012	60 (37 to 83)	14.6%	14.6%	72.9%	Adeno: 91.7% Squamous: 6.3%	PLAT=96.9%	ECOG 1: 85.4% 2: 14.6%	Korean*	Current/Former: 8.3% Never: 91.7%
	56 (32 to 81)	14.6%	10.4%	70.8%	Adeno: 89.6% Squamous: 6.3%	PLAT=100%	ECOG 1: 85.4% 2: 14.6%	Korean*	Current/Former: 4.2% Never: 95.8%
GEF vs DOC									
Bhatnagar 2012[a]	NR	NR	NR	NR	NR	NR	ECOG 0 to 2	Indian*	NR
	NR	NR	NR	NR	NR	NR	ECOG 0 to 2	Indian*	NR
INTEREST 2008	61 (27 to 84)	63.6%	At diagnosis: 25%	At diagnosis: 52.9%	Adeno: 53.9% Squamous:25.2%	1=84.4% 2=15.3% 3=0.3%	WHO 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 to 84)	66.6%	At diagnosis: 28.8%	At diagnosis: 52.3%	Adeno: 54.8% Squamous:24%	1=83.2% 2=16.8% 3=0	WHO 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%
ISTANA 2010	57 (21 to 74)	67.1%	13.4% (LA)	86% (Met)	Adeno: 65.9% Squamous: 20.7%	1 (PLAT doublet)	WHO 0: 2.4% 1: 90.2% 2: 7.3%	Korean and East Asian	Ex: 62.2% Regular:1.2% Never: 36.6%
	58 (20 to 73)	57%	17.7%	82.3%	Adeno: 69.6% Squamous: 13.9%	1 (PLAT doublet)	WHO 0: 3.8% 1: 89.9% 2: 6.3%	Korean and East Asian	Ex: 54.4% Regular: 0 Never: 45.6%
LI 2010	50.7	60%	58%	42%	Adeno: 56% Squamous: 44%	CIS+GEM/VIN Or GEM/VIN monotherapy	KPS≥70	Chinese	NR
	48.2	60%	60%	40%	Adeno: 56%	CIs+GEM/VIN	KPS≥70	Chinese	NR

Trial	Median age (yrs) (range)	% Male	Stage IIIB	Stage IV	Histology: Adeno/Squamous	Previous treatment	Performance status	Ethnicity	Smoking status
					Squamous: 44%	Or GEM/VIN monotherapy			
SIGN 2006	63 (34 to 85)	69	NR	60%	NR	1=97.1%	WHO 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 to 83)	51	NR	56%	NR	1= 98.6%	WHO 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	≤64=56.3% ≥65= 43.7%	61.6	19.2%	64.9%	Adeno: 78.4% Squamous: 15.1%	1: 86.5% 2: 13.5%	WHO 0: 34.7% 1: 60.8% 2: 4.5%	Japanese*	Ever: 71% Never: 29%
	≤64: 55.3% ≥65: 44.7%	61.9	20.5%	61.5	Adeno: 77% Squamous 16.8%	1: 82.4% 2: 17.2%	WHO 0: 38.1% 1: 57.8% 2: 4.1%	Japanese*	Ever: 64.3% Never: 35.7%
GEF vs PLA									
ISEL 2005	62 (28 to 90)	67	21% (LA)	79% (Met)	Adeno :45% Squamous: 35%	0 = 1 1 = 49% 2 = 50% ≥3 = 1%	WHO 0:12% 1: 53% 2: 29% ≥5%	White: 75% Asian: 21% Black: 1% Other: 4%	Habitual: 17% Occasional: 1% Ex: 60% Never: 22%
	61 (31 to 87)	67	20% (LA)	80% (Met)	Adeno: 45%, Squamous: 33%	0 = 1 1 = 49% 2 = 50% ≥3 = 1%	WHO 0: 12% 1: 56% 2: 26% ≥3: 5%	White: 77% Asian: 19% Black: 1% Other: 4%	Habitual: 16% Occasional: 1% Ex: 60% Never: 22%
ERL vs DOC									
DELTA 2013[a]	NR	NR	NR	NR	NR	NR	ECOG: 0 to 2	Japanese*	NR
	NR	NR	NR	NR	NR	NR	ECOG: 0 to 2	Japanese*	NR

Trial	Median age (yrs) (range)	% Male	Stage IIIB	Stage IV	Histology: Adeno/Squamous	Previous treatment	Performance status	Ethnicity	Smoking status
TAILOR 2013	66 (40 to 81)	71	NR	NR	Adeno: 63% Squamous: 28%	1=92%	ECOG 0: 48% 1: 44% 2: 8%	White: 99% Asian: 1%	Current/Former: 83% Never:17%
	67 (35 to 83)	66	NR	NR	Adeno:75% Squamous: 21%	1=93%	ECOG 0: 48% 1: 45% 2: 6%	White: 99% Asian: 1%	Current/Former: 73% Never: 27%
ERL vs DOC/PEM									
TITAN 2012	59 (36 to 80)	79	20%	80%	Adeno:47% Squamous: 38%	PLA-doublet: PAX/GEM/DOC/VIN	ECOG 0: 14% 1: 67% 2: 19%	Caucasian: 85% Asian: 14% Other: 1%	Present: 56% Past: 29% Never: 15%
	59 (22 to 79)	72	23%	77%	Adeno: 52% Squamous: 35%	PLA-doublet: PAX/GEM/ DOC/VIN	ECOG 0: 10% 1: 69% 2: 21%	Caucasian:86% Asian:12% Other: 2%	Present: 51% Past: 29% Never: 20%
ERL vs PLA									
BR.21 2005	62 (34 to 87)	64.5	NR	NR	Adeno: 50.4% Squamous: 29.5%	1 = 50.6 % ≥2 = 49.4%	ECOG 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 to 89)	65.8	NR	NR	Adeno: 49 Squamous: 32.1	1 = 50.2% ≥2 = 49.8%	ECOG 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%

*=assumed from reported area of recruitment area; [a]=abstract only
Adeno=adenocarcinoma, GEM=gemcitabine, DOC=docetaxel, PAX=paclitaxel, VIN= vinorelbine

5.2.3 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")

EGFR M+ population

Six trials reported subgroup data on EGFR M+ patients. KIM,[42] V-15-32[39] and TITAN,[41] reported subgroup data in the main paper. BR.21,[31,43] ISEL[40,44] and INTEREST,[35,45] reported subgroup data in a separate publication.

Overall survival

Four trials reported OS, one trial only reported the number of events (ISEL[40,44]) and three presented hazard ratios (HRs) (INTEREST,[35,45] TITAN,[41] BR.21[31,43]). The HRs were not statistically significant for any of the comparisons described. Table 11 summarises the results.

Table 11 EGFR M+ overall survival

Study name	% of deaths (number of events/number randomised)	% of deaths (number of events/number randomised)	Median OS (months)	Hazard ratio (95% CI)	*p-value*
GEF vs DOC					
INTEREST	72.73 (32/44 over both arms)		14.2 vs 16.6	0.83 (0.41 to 1.67)	0.60
GEF vs BSC					
ISEL	33.33 (7/21)	0.60 (3/5)	NR	NR	NR
ERL vs DOC/PEM					
TITAN	NR	NR	19.3 vs NR	1.19 (0.12 to 11.49)	0.88
ERL vs BSC					
BR.21	NR	NR	10.9 vs 8.3	0.55 (0.25 to 1.19)	0.12

CI=confidence interval; NR=not reported

The AG noted that, in the MS, AstraZeneca presented evidence of an exploratory post-hoc analysis of patients from a first-line trial of gefitinib compared with paclitaxel and carboplatin (IPASS[46,47]). The analysis considered the EGFR M+ subgroup from the chemotherapy arm of the trial and compared OS for those who did with those who did not receive post-progression TKI treatment. The AG's

exploratory analysis of these OS results (described in Section 6.3.1 of this report) concluded that the data suggest longer mean OS than normally reported in trials of either EGFR-TKI treatment or chemotherapy, with an apparent gain of more than [redacted] associated with second-line EGFR-TKI following prior chemotherapy.

Progression-free survival

Four trials reported limited data for PFS (Table 12). KIM[42] reported median PFS and ISEL[40,44] reported the number of events in each arm. TITAN[41] found no statistically significant difference between erlotinib and docetaxel/pemetrexed. Only INTEREST[35,45] found a statistically significant difference in PFS favouring gefitinib (HR 0.1;6 95% CI: 0.05 to 0.49).

Table 12 EGFR M+ progression-free survival

Study name	**% of patients who progressed (number of events/number randomised)**	**% of patients who progressed (number of events/number randomised)**	**Median PFS (months)**	**Hazard ratio (95% CI)**	***p-value***
GEF vs DOC					
INTEREST	NR	NR	7 vs 4.1	0.16 (0.05 to 0.49)	0.001
GEF vs BSC					
ISEL	52.38 (11/21)	0.80 (4/5)	NR	NR	NR
GEF vs ERL					
KIM	NR	NR	11.9 over both arms	NR	NR
ERL vs DOC/PEM					
TITAN	NR	NR	NR	0.71 (0.13 to 3.97)	NR

CI=confidence interval; NR=not reported

Response rate

Five trials reported data on response rate (Table 13). Of the three trials that presented data separately by treatment (INTEREST,[35,45] V-15-32,[39] KIM[42]) gefitinib appears to be favoured compared to docetaxel or erlotinib. However, patient numbers in the trials are small and only one study (INTEREST[30,37]) presented a p-value of 0.04 to indicate that the difference between gefitinib and docetaxel was statistically significant. Two studies (ISEL,[40,44] BR.21[31,43]) presented response rates for gefitinib vs BSC and erlotinib vs BSC of 37.50% and 26.67% respectively.

Table 13 EGFR M+ response rate

Study name	Response rate in intervention arm (%) (number responded/number randomised)	Response rate in control arm (%) (number responded/number randomised)	Overall response rate (%) (number responded/number randomised)	*p-value*
GEF vs DOC				
INTEREST	42.11 (8/19)	21.05 (4/19)	NR	0.04
V-15-32	66.67 (6/9)	45.45 (5/11)	NR	NR
GEF vs BSC				
ISEL*	NR	NR	37.50 (6/16)	NR
GEF vs ERL				
KIM	66.70 (NR)	62.50 (NR)	76.47 (13/17)	NR
ERL vs BSC				
BR.21	NR	NR	26.67 (4/15)	0.035

NR=not reported;*ISEL reported objective response rate

EGFR M- population

Five trials reported subgroup data on EGFR M- patients (KIM,[42] INTEREST,[35,45] TITAN,[41] BR.21,[31,43] ISEL[40,44]). The DELTA[33] trial included patients with and without activating mutations and who's EGFR status was known prior to their randomisation into the trial. The TAILOR[34] trial 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[40,44] only reported the number of events in each trial arm (Table 14). The other five trials (INTEREST,[35,45] TAILOR,[34] DELTA,[33] TITAN,[41] BR.21[31,43]) reported HRs, however, these were not statistically significant for any of the comparisons described.

Table 14 EGFR M- overall survival

Study name	% of deaths (number of events/number randomised)	% of deaths (number of events/number randomised)	Median OS (months)	Hazard ratio (95% CI)	*p-value*
GEF vs DOC					
INTEREST	84.98 (215/253 over both arms)		6.4 vs 6.0	1.02 (0.78 to 1.33)	0.91
GEF vs BSC					
ISEL	70.45 (93/132)	64.91 (37/57)	NR	NR	NR
ERL vs DOC					
TAILOR	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	NR	NR	9.0 vs 9.2	0.98 (0.69 to 1.39)	0.914
ERL vs DOC/PEM					
TITAN	NR	NR	6.6 vs 4.4	0.85 (0.59 to 1.22)	0.37
ERL vs BSC					
BR.21	NR	NR	7.9 vs 3.3	0.74 (0.52 to 1.05)	0.09

CI=confidence interval; NR=not reported

Progression-free survival

Six trials reported PFS (

Table 15), although ISEL[40,44] only reported the number of events in each treatment group and KIM[42] reported PFS for EGFR M- patients overall rather than for each treatment group separately. Two trials reported HRs that were not statistically significant (INTEREST,[35,45] TITAN[41]). Two other trials (TAILOR,[34] DELTA[33]) reported statistically significantly longer PFS for docetaxel compared to erlotinib (HR 1.39; 95% CI: 1.06 to 1.82 [unadjusted] and HR 1.44; 95% CI 1.08 to 1.92).

Table 15 EGFR M- progression-free survival

Study name	% of deaths (number of events/number randomised)	% of deaths (number of events/number randomised)	Median PFS (months)	Hazard ratio (95% CI)	*p-value*
GEF vs DOC					
INTEREST	NR	NR	1.7 vs 2.6	1.24 (0.94 to 1.64)	0.14
GEF vs BSC					
ISEL	84.09 (111/132)	85.96 (49/57)	NR	NR	NR
GEF vs ERL					
KIM	NR	NR	2.8 months overall	NR	NR
ERL vs DOC					
TAILOR	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	NR	NR	1.3 vs 2.9	1.44 (1.08 to 1.92)	0.013
ERL vs DOC/PEM					
TITAN	90.67 (68/75)	79.73 (59/74)	NR	1.25 (0.88 to 1.78)	0.20

CI=confidence interval; NR=not reported

Response rate

Five trials reported data on response rate (Table 16). Only one trial (INTEREST[35,45]) reported a p-value (p=0.37) indicating that there was no statistically significant difference between the groups. One other trial (TAILOR[34]) reported a p-value (p=0.003) indicating that there was a statistically significant difference in response rate, favouring docetaxel.

Table 16 EGFR M- response rate

Study name	Response rate in intervention arm (%) (number responded/number randomised)	Response rate in control arm (%) (number responded/number randomised)	Overall response rate (%) (number responded/number randomised)	*p-value*
GEF vs DOC				
INTEREST	6.60 (7/106)	9.76 (12/123)	NR	0.37
GEF vs BSC				
ISEL*	NR	NR	2.59 (3/116)	NR
GEF vs ERL				
KIM	NR	NR	25.00 (8/32)	NR
ERL vs DOC				
TAILOR	3 (3/100)	15.46 (15/97)	NR	0.003
ERL vs BSC				
BR.21	NR	NR	6.93 (7/101)	NR

NR=not reported; *ISEL reported objective response rate

Overall population: EGFR-unknown

Four trials considered the overall population without distinguishing between patients' EGFR mutation status (ISTANA,[36] SIGN,[38] LI,[37] Bhatnagar[32]). There are no data available from the Bhatnagar[32] 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 (INTEREST,[35,45] ISTANA,[36] V-15-32,[39] ISEL,[40,44] KIM,[42] TITAN,[41] BR.21,[31,43] DELTA[33]). The TAILOR[34] trial 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). Five trials compared gefitinib to docetaxel (INTEREST,[42] ISTANA,[36] LI,[37] SIGN,[38] V-15-32[39]). A median survival of 7.1 months for gefitinib and 6.9 months for docetaxel were the only data available from LI.[37] 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 (ISEL[40]) erlotinib and docetaxel (DELTA[33]) or between erlotinib and docetaxel/pemetrexed (TITAN[41]).

BR.21[31] found a statistically significant difference in OS, favouring erlotinib over BSC (HR 0.7, 95% CI: 0.58 to 0.85). However, the authors only presented adjusted analyses, no details were presented describing the unadjusted analyses.

Table 17: EGFR-unknown overall survival

Study name	% of deaths (number of events/number randomised)	% of deaths (number of events/number randomised)	Median OS (months)	Hazard ratio (95% CI)	*p-value*
GEF vs DOC					
INTEREST	82.02 (593/723)	81.13 (576/710)	7.6 vs 8	1.02 (0.91 to 1.15) (PP) 1.015 (0.901 to 1.143) (ITT)	0.47 NS
ISTANA	81.71 (67/82)	74.68 (59/79)	14.1 vs 12.2	0.87 (0.61 to 1.24)	0.4370
LI	NR	NR	7.1 vs 6.9	NR	NR
SIGN	NR	NR	7.5 vs 7.1	0.97 (0.61 to 1.52)	0.88
V-15-32	63.67 (156/245)	61.48 (150/244)	11.5 vs 14	1.12 (0.89 to 1.4)	0.33
GEF vs BSC					
ISEL	NR	NR	5.6 vs 5.1	0.89 (0.77 to 1.02)	0.087
ERL vs DOC					
DELTA	NR	NR	14.8 vs 12.2	0.91 (0.68 to 1.22)	0.527
ERL vs DOC/PEM					
TITAN**	NR	NR	5.3 vs 5.5	0.96 (0.78 to 1.19)	0.73
ERL vs BSC					
BR.21	77.46 (378/488)	86.01 (209/243)	6.7 vs 4.7	0.7 (0.58 to 0.85)	<0.001

CI=confidence interval; NR=not reported; PP=per protocol; ITT=intention-to-treat; NS=not stated
** Without the 30 patients with squamous cell carcinoma who received PEM (HR= 0.93; CI=0.75 to 1.17, p=0.544)

Progression-free survival

Nine trials reported data for PFS (Table 18). Four studies compared gefitinib to docetaxel (INTEREST,[35] ISTANA,[36] SIGN,[38] V-15-32[39]). ISTANA[36] found that PFS was statistically significantly longer for gefitinib compared to docetaxel (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 found no statistically significant differences in PFS between the groups.

Neither TITAN[41] nor DELTA[33] 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 to 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[40] found a statistically significant difference in PFS favouring gefitinib compared to 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 to erlotinib was a median PFS of 4.9 vs 3.1 months (KIM[42]).

Table 18: EGFR-unknown progression-free survival

Study name	% of deaths (number of events/number randomised)	% of deaths (number of events/number randomised)	Median PFS (months)	Hazard ratio (95% CI)	*p-value*
GEF vs DOC					
INTEREST	82.02 (593/723)	76.62 (544/710)	2.2 vs 2.7	1.04 (0.93 to 1.18)	NR
ISTANA	74.39 (61/82)	74.68 (59/79)	3.3 vs 3.4	0.729* (0.533 to 0.988) (unadjusted) 0.634* (0.459 to 0.875) (adjusted)	0.0441 0.0134
SIGN	NR	NR	3 vs 3.4	0.94 (0.64 to 1.39)	0.76
V-15-32 2008	90.00 (180/200)	84.49 (158/187)	2 vs 2	0.9 (0.72 to 1.12)	0.335
GEF vs BSC					
ISEL	NR	NR	3.0 vs 2.6	0.82 (0.73 to 0.92)	0.0006
GEF vs ERL					
KIM	NR	NR	4.9 vs 3.1	NR	NR
ERL vs DOC					
DELTA	NR	NR	2.0 vs 3.2	1.22 (0.97 to 1.55)	0.092
ERL vs DOC/PEM					
TITAN	92.61 (188/203)	83.26 (184/221)	6.3 weeks vs 8.6 weeks	1.19 (0.97 to 1.46)	0.089
ERL vs BSC					
BR.21	92.21 (450/488)	95.47 (232/243)	2.2 vs 1.8	0.61 (0.51 to 0.74)	<0.001

CI=confidence interval; NR=not reported; *90% CI used

Response rate

Nine trials reported data for response rate (Table 19). Five of these compared gefitinib to docetaxel, the response rate in the gefitinib arm ranged from 9.10% to 28.10% and in the docetaxel arm the response rate ranged from 7.60% to 18.75%. INTEREST[35] and V-15-32[39] both reported odds ratios although only V-15-32[39] found a statistically significant difference between the two groups favouring gefitinib when compared to docetaxel. In addition, one trial found a statistically significant difference in response rate favouring gefitinib when compared to BSC (ISEL[40]).

Table 19: EGFR-unknown response rate

Study name	Response rate in intervention arm (%) (number responded/number randomised)	Response rate in control arm (%) (number responded/number randomised)	Overall response rate: odds ratio (95% CI)	*p-value*
GEF vs DOC				
INTEREST	9.10 (NR)	7.60 (NR)	1.22 (0.82 to1.84)	0.33
ISTANA	28.10 (NR)	7.60 (NR)	NR	NR
LI	22.44 (11/49)	18.75 (9/48)	NR	NR
SIGN	13.24 (9/68)	13.70 (10/73)	NR	NR
V-15-32	22.50 (45/200)	12.80 (24/187)	2.14 (1.21 to 3.78)	0.009
GEF vs BSC				
ISEL*	8 (77/959)	1 (6/480)	7.28 (3.1 to 16.9)	<0.0001
GEF vs ERL				
KIM	47.92 (23/48)	39.58 (19/48)	NR	NR
ERL vs DOC/PEM				
TITAN	7.88 (16/203)	6.33 (14/221)	NR	NR
ERL vs BSC				
BR.21	8.90 (NR)	less than 1 (NR)	NR	NR

CI=confidence interval; NR=not reported; *ISEL reported objective response rate

Meta-analysis and network meta-analysis

Meta-analysis can be used to integrate the results of multiple trials which directly compare one specific treatment to 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 gefitinib or erlotinib with any comparator in patients who are EGFR M+ and who have been previously treated. The AG agrees with the manufacturer of gefitinib who states that "All options for meta-analysis (direct, indirect and MTC) 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" (AstraZeneca MS, pg7).

For the EGFR M- population, median OS and PFS data are available from four trials (DELTA,[33] INTEREST,[35] BR.21[31] and TAILOR[34]). As the DELTA[33] trial is made up of Japanese patients for whom there are no patient characteristics data available, the AG could not include the results from this trial in a network meta-analysis. The AG does not consider that INTEREST,[35] BR.21[31] and TAILOR[34] include patient populations that are sufficiently similar to be included in a network meta-analysis. To illustrate: both TAILOR[34] (93%) and INTEREST[35] (89%) have high rates of patients with PS 0 or 1 when compared to BR.21[31] (70%), TAILOR[34] (92%) and INTEREST[35] (84%) include mainly patients who have received only one prior chemotherapy compared with BR.21[31] (50%), TAILOR[34] (70%) has a higher rate of adenocarcinoma patients than either INTEREST[35] (54%) or BR.21[31] (50%).

There are survival data available from eight trials that include patients whose EGFR mutation status was unknown at the time of analysis, i.e. the trials included both EGFR M+ and EGFR M- status patients (INTEREST,[35] ISTANA,[36] LI,[37] SIGN,[38] V-15-32,[39] ISEL,[40] TITAN,[41] BR.21[31]). A higher proportion of patients in the ISEL[40] trial (50%) had received more than one prior treatment compared with the other trials, although it is difficult to know exactly how many prior treatments patients in LI[37] and ISTANA[36] had had. It is therefore uncertain whether the patients in ISEL[40] are sufficiently similar to those in the other trials. In three trials ethnicity is a key differentiator (ISTANA[36] – Korean patients, LI[37] – Chinese patients, V-15-32[39] – 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 (TITAN[41] and BR.21[31]) compare erlotinib with BSC and pemetrexed and/or docetaxel. The AG considers that the patients in TITAN[41] are different from the patients in BR.21[31] as in TITAN[41] 100% of patients had received a single prior chemotherapy whilst in BR.21[31] 50% of patients had received two or more prior chemotherapies. In addition, there are no separate outcome data reported for docetaxel and pemetrexed patients in TITAN,[41] the AG notes that it is not proven that docetaxel and pemetrexed are clinically equivalent when used in this patient population. For the assessment of PFS, there are data available from eight trials (INTEREST,[35] ISTANA,[36] SIGN,[38] V-15-32,[39] ISEL,[40] DELTA,[33] TITAN,[41] BR.21[31]); no HR was reported in KIM.[42] The arguments outlined above for three trials (ISEL,[40] ISTANA,[36] V-15-32[39]) for the assessment of OS are valid again here. Further, the KIM[42] 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[41] 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 (INTEREST,[35] ISTANA,[36] SIGN,[38] V-15-32,[39] TITAN,[41] ISEL[40]). 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 and sample sizes range from 424 to 1692 (INTEREST,[35] V-15-32,[39] TITAN,[41] ISEL[40]). Also, the AG has previously stated[2] that Kaplan-Meier plots of PFS for gefitinib and erlotinib 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 gefitinib and erlotinib 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, e.g. 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 are combined again rendering results from a network meta-analysis difficult to interpret. For the EGFR-unknown results, three trials only report adjusted analyses for OS (SIGN,[38] BR.21,[31] ISEL[40]) and four for PFS (SIGN,[38] BR.21,[31] ISEL,[40] INTEREST[35]). In BR.21[31] erlotinib is statistically significantly more effective than BSC for both OS and PFS, and in ISEL[40] gefitinib is statistically significantly more effective than BSC.

In summary, the AG considers that due to 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.

Table 20 Summary of analysis methods of included studies

Trial	Adjusted/ unadjusted analysis presented	Cox proportional hazards model suitable	Statistical analysis
GEF vs DOC			
INTEREST	Unadjusted for OS Adjusted and per-protocol for PFS	KM plot crosses for OS No KM plot for PFS	"We used an unadjusted Cox proportional hazards model to estimate the overall survival HR and CI in the per-protocol population" A Cox proportional hazards model with adjustment for the effects of sex, racial origin, histology, performance status, smoking history, previous regimens, previous platinum, and previous paclitaxel was used to estimate the HR for progression-free survival in the evaluable-for-response population (patients in the per-protocol population with unidimensional disease according to RECIST)."
ISTANA	Unadjusted and adjusted presented Unadjusted used for OS Unadjusted used for PFS	KM plot crosses for OS and PFS	"An unadjusted Cox proportional hazards model was used to analyse progression-free survival and overall survival (two-sided test at the 5% significance level, 95% CI) to compare the treatment groups. Supportive analyses using a Cox proportional hazards model adjusting for gender, histology, smoking history, stage, and performance status were also done."
SIGN	Adjusted for OS and PFS	KM 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)."
LI	NR	Yes	No details presented
V-15-32	Unadjusted and adjusted presented (PFS reported population)	KM plot crosses for OS and PFS	"Robustness of the primary conclusion was assessed by supportive analyses in the per-protocol population and by using a Cox regression model with covariate adjustment for sex (male vs female), PS (0 or 1 v 2), tumour type (adenocarcinoma vs other), smoking history (ever vs never), number of prior chemotherapy regimens (1 vs 2), age at random assignment (< 65 years vs >65 years), time from diagnosis to random assignment (<6 vs 6 to 12 vs >12 months), and best response to prior chemotherapy (CR/PR v stable disease [SD] v progressive disease not assessable/ unknown)."
Bhatnagar	NR	NR	Abstract only
GEF vs BSC			
ISEL	Adjusted for OS Unclear for PFS	KM plot crosses for OS and time to treatment failure near to the top of the plot	"The primary analysis of survival used a stratified log-rank test. The strata were histology, smoking history, reason for previous chemotherapy failure, number of previous regimens, PS, and sex. As defined in the protocol, a supportive Cox's regression analysis was also done, with covariate adjustment for the same factors as the log-rank test."
GEF vs ERL			
KIM	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."
ERL vs DOC			
TAILOR	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."
TITAN	Unadjusted for both OS and PFS	KM plot crosses towards the tail for PFS. KM plot crosses in the middle for OS	Adjusted analyses included in appendices but primary are unadjusted.
DELTA	NR	NR	Abstract only

Trial	Adjusted/ unadjusted analysis presented	Cox proportional hazards model suitable	Statistical analysis
ERL vs BSC			
BR.21	Yes	Yes	"Exploratory forward stepwise regression analyses with the use of the Cox model were performed to adjust for treatment effect and to identify prognostic factors for progression-free survival and overall survival. Candidate covariates included EGFR expression, stratification factors (except centre), sex, age (60 years or less vs more than 60 years), race or ethnic group (Asian vs others), prior radiotherapy (yes vs no), histologic subtype of cancer (adenocarcinoma vs others), and smoking status (smoker vs non-smoker vs unknown)." "In the Cox regression analysis, erlotinib remained associated with longer survival (P=0.002), as did Asian origin (P=0.01), adenocarcinoma on histologic examination (P=0.004), and never having smoked (P=0.048 vs current or past smoking)."

PS=performance status; KM=Kaplan-Meier; HR=hazard ratio; CI=confidence interval; CR=complete response; PR=partial response; SD=stable disease

Quality of life

Quality of life (QoL) data are presented in ten trials for the overall EGFR-unknown population and are summarised in Table 21. Quality of life data from the TAILOR[34] and DELTA[33] trials are not yet available.

Gefitinib

Six trials compared gefitinib to docetaxel. The results of four of these studies favoured gefitinib (INTEREST,[35] LI,[37] V-15-32,[39] Bhatnagar[32]), although no data were available from Bhatnagar[32] to confirm their conclusions. Two studies found no statistically significant differences between gefitinib and docetaxel (ISTANA,[36] SIGN[38]). One trial compared gefitinib to BSC (ISEL[40]) and changes in QoL were similar in the two groups. In the comparison of gefitinib and erlotinib (KIM[42]) no statistically significant difference in QoL was noted.

Erlotinib

Erlotinib was found to significantly improve QoL in comparison to BSC (BR.21[31]). No statistically significant difference in QoL was reported between erlotinib and docetaxel in TITAN.[41]

Table 21 Summary of quality of life results

Trial	Number of respondents	Measurement tool	Author summary
GEF vs DOC			
INTEREST	GEF=490 DOC=476	Functional Assessment of Cancer Therapy-Lung (FACT-L) every 3 weeks until treatment discontinuation	Significantly more patients had sustained a clinically relevant improvement in QoL with GEF than with DOC
ISTANA	GEF=68 DOC=66	Functional Assessment of Cancer Therapy Lung (FACT-L) every 3 weeks	Similar proportions of patients in each treatment group experienced an improvement
SIGN	GEF=85% DOC= 87%	Functional Assessment of Cancer Therapy-Lung (FACT-L) every 3 weeks until treatment discontinuation	Mean FACT-L score change from baseline to endpoint were similar for both groups
LI	NR	The improvements of symptoms and quality of life 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 GEF group was higher than that in the DOC group, resulting in a significant difference in the two groups
V-15-32	GEF=185 DOC=173	FACT-L questionnaire at baseline and every 4 weeks during study treatment until week 12.	GEFshowed statistically significant benefits compared with DOC in QoL improvement rates but there were no significant differences between treatments in LCS improvement rates
Bhatnagar	NR	NR	Improvement in QoL for GEF patients.
GEF vs BSC			
ISEL	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 GEF and BSC groups.
GEF vs ERL			
KIM	NR	QLQ-C30-Version 3.0	There was no significant difference in QOL between the two arms.
ERL vs DOC			
TAILOR	NR		NR
TITAN	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	NR		NR
ERL vs BSC			
BR.21	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 to BSC

Incidence of grade 3/4 adverse events

In 9 of the 12 studies, grade 3/4 AEs were presented for the overall population only (Table 22). In the remaining three trials only limited AE data are reported; the DELTA[33] trial and the Bhatnagar[32] trial are reported in abstract format only and therefore do not describe AEs and the investigators in the LI[37] trial did not provide detailed AE data.

Each study reported AEs in different ways. ISEL[40] reported AEs that occurred in more than 5% of either treatment group or with a difference of at least 3% between treatment groups. TITAN[41] reported those that occurred in at least 2% of patients in either group. V-15-32[39] reported the most common AEs, these were considered to be those that occurred in more than 10% of the study population or occurred with more than a 5% difference between treatments. Two studies (SIGN,[38] INTEREST[35]) reported AEs that occurred in more than 10% in either group. ISTANA[36] reported the most common AEs, these were considered to be those occurring in at least 10% of patients in either treatment group. Three studies (BR.21,[31] TAILOR,[34] KIM[42]) 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[32] trial it was reported that gefitinib had a more favourable tolerability profile than docetaxel. In the DELTA trial, patients in the erlotinib arm compared with patients in the docetaxel arm experienced more rash and leukopenia. In the LI trial the incidence of rash was higher in the gefitinib group compared to docetaxel (p=0.0296) and that other side effects were similar for the patients 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.[25]

Table 22: Incidence of grade 3/4 adverse events

Study	BSC % (n/N)	DOC % (n/N)	ERL % (n/N)	GEF % (n/N)
Fatigue				
TITAN	NA	0.45 (0.5/111.8)	0 (0/196)	NA
SIGN	NA	4.23 (3/71)	NA	5.88 (4/68)
INTEREST	NA	8.95 (64/715)	NA	4.39 (32/729)
KIM	NA	NA	0 (0/48)	0 (0/48)
ISTANA	NA	3.95 (3/76)	NA	1.23 (1/81)
V-15-32	NA	2.51 (6/239)	NA	0.41 (1/244)
BR.21	23.14 (56/242)	NA	18.97 (92/485)	NA
ISEL	2.67 (15/562)	NA	NA	3.20 (36/1126)
TAILOR	NA	9.62 (10/104)	5.61 (6/107)	NA
Diarrhoea				
TITAN	NA	0 (0/111.8)	2.55 (5/196)	NA
SIGN	NA	4.23 (3/71)	NA	2.94 (2/68)
INTEREST	NA	3.08 (22/715)	NA	2.47 (18/729)
KIM	NA	NA	0 (0/48)	0 (0/48)
ISTANA	NA	0 (0/76)	NA	1.23 (1/81)
V-15-32	NA	0.84 (2/239)	NA	2.05 (5/244)
BR.21	0.62 (1.5/242)	NA	5.77 (28/485)	NA
ISEL	0.89 (5/562)	NA	NA	2.75 (31/1126)
TAILOR	NA	1.92 (2/104)	2.80 (3/107)	NA
Febrile neutropenia				
TITAN	NA	0.89 (1/111.8)	0 (0/196)	NA
SIGN	NA	2.82 (2/71)	NA	0 (0/68)
INTEREST	NA	10.07 (72/715)	NA	1.23 (9/729)
KIM	NA	NA	0 (0/48)	0 (0/48)
ISTANA	NA	0 (0/76)	NA	0 (0/81)
V-15-32	NA	7.11 (17/239)	NA	0.82 (2/244)
BR.21	0 (0/242)	NA	0 (0/485)	NA
ISEL	0 (0/562)	NA	NA	0 (0/1126)
TAILOR	NA	3.85 (4/104)	0 (0/107)	NA
Hairloss				
TITAN	NA	0.45 (0.5/111.8)	0 (0/196)	NA
SIGN	NA	0 (0/71)	NA	0 (0/68)
INTEREST	NA	0 (0/715)	NA	0 (0/729)
KIM	NA	NA	0 (0/48)	0 (0/48)
ISTANA	NA	0 (0/76)	NA	0 (0/81)

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

5.3 Summary of clinical results

EGFR M+ 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
- Five studies reported OS outcomes, none of which were statistically significantly different for any of the comparisons described
- Four studies reported PFS, only one trial (INTEREST[37,44]) showed a statistically significant improvement for any comparison considered, the results favoured gefitinib over docetaxel
- The AG's exploratory analysis of the OS results presented by the manufacturer of post-progression TKI use in the control arm of the IPASS[46,47] trial noted greater OS than is normally reported in trials of either EGFR-TKI treatment or chemotherapy

EGFR M- population

- Key data were derived from results of TAILOR[34] trial and DELTA[33]
- EGFR mutation status data were retrospectively derived from subgroup analyses of BR.21,[31,43] KIM,[42] TITAN,[41] INTEREST[35,45] and ISEL[40,44]
- OS outcome: no statistically significant differences noted for OS for either erlotinib or gefitinib compared to any treatment
- PFS outcome: TAILOR[34] and DELTA[33] reported a statistically significant benefit of docetaxel compared with erlotinib. No statistically significant PFS benefit was reported from subgroup data
- Response rate: patients in the docetaxel arm of the TAILOR[34] trial had statistically significantly higher response rates compared with patients in the erlotinib arm

EGFR-unknown: overall population

- Data were available from 11 trials in populations in which EGFR mutation status was not a factor in the recruitment process (or where 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 vs docetaxel, only one of the four trials (ISTANA[36]) reported a statistically significant benefit of gefitinib
  - Gefitinib vs BSC, gefitinib was reported to have a statistically significant benefit (ISEL[40])

- Erlotinib vs placebo (BR.21[31]), a statistically significant PFS benefit of erlotinib was reported (in an adjusted analysis)
- Response rate: of the trials reporting response rates, two noted significant differences in favour of gefitinib when compared with docetaxel (V-15-32[39]) and BSC (ISEL[40]).

Meta-analysis and network meta-analysis

For clinical and methodological reasons, no meta-analysis or network meta-analysis were 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 the TAILOR[34] trial and the DELTA[33] trial are not yet available.

Adverse events

Adverse events were reported for the overall population, i.e. the data are not specific to the EGFR mutation status of patients with the exception of the TAILOR[34] trial. Details of the AEs reported in Bhatnagar,[32] LI[37] and DELTA[33] 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.[25]

5.4 Discussion of clinical results

Erlotinib

Clinical evidence supporting the previously published NICE guidance TA162[29] (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 TA162,[29] 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[29]) 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 PAS was then superseded to a simple discount PAS following the publication of NICE TA227.[48] 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 TA162.[22]

Since the publication of TA162,[29] three developments are worthy of note. First, the results of one RCT comparing erlotinib with chemotherapy (TITAN[41]) 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[41] 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 efficacy of erlotinib vs docetaxel and erlotinib vs 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).[49] To date, NICE has not issued any statement suggesting that this lower price of docetaxel necessitates any change to the recommendations set out in TA162.[29]

Third, clinical practice has also changed since the publication of TA162[29] 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), whilst 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.[29] The AG is aware that some patients in the UK 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[34] and DELTA[33]) were both designed to compare the effectiveness of erlotinib vs docetaxel in EGFR M- patients. The results of the TAILOR[34] trial are reported in a

published paper, whilst the results of the DELTA[33] trial are presently only available as a conference abstract from ASCO in 2013. Since the TAILOR[34] trial 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.

The TAILOR[34] trial was conducted in 52 hospitals in Italy and randomised patients to receive erlotinib (n=112) or docetaxel (n=110). Whilst 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.

The TAILOR[34] trial 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,[34] 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 endpoint of OS.

Second, the TAILOR[34] trial employed two regimens of docetaxel administration, either 75mg/m^2 every 3 weeks or weekly infusions of 35mg/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 the TAILOR[34] trial is an important consideration. The patient population consisted of a majority of patients who were ECOG PS 0 or 1, only 7% were of PS 2. This is unlikely to reflect patients in the UK NHS where 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 the TAILOR[34] trial 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 patients in the future may be fitter at second-line than those currently treated with second-line treatments in England and Wales.

Fourth, there are differences in other important prognostic factors between the treatment arms of the TAILOR[34] trial. 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%). All of these differences have been identified as possible modifiers of trial outcome in favour of docetaxel.[50]

In their submission to NICE, the manufacturer of erlotinib has questioned the low rates of haematological toxicity in the docetaxel arm of the TAILOR[34] trial (febrile neutropenia grade 3/4 = 4%, neutropenia grade 3/4 = 21%) in comparison with the INTEREST[35] trial (febrile neutropenia grade 3/4 = 10%, neutropenia grade 3/4 = 58%) and the JMEI[51] trial (febrile neutropenia grade 3/4 = 13%, neutropenia grade 3/4 = 40%). The manufacturer questions whether 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 i.e. increased clinical awareness of docetaxel-related AEs. Docetaxel has been used in the NHS for many years and it is likely that these AEs are currently better managed and/or more frequently avoided than in the past.

In summary, it is open to debate as to how far the TAILOR[34] trial reflects clinical practice in England and Wales and therefore whether the trial results are likely to be mirrored in a UK clinical population. The TAILOR[34] trial 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 the DELTA[33] trial 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.[23]

The marketing authorisation for gefitinib granted by the EMA[52] was based on the results of the first-line IPASS[47] trial and second-line INTEREST[35] trial. Supporting trials included ISEL,[40] SIGN,[38] V-15-32[39] and ISTANA.[36] The EMA's EPAR[53] reports that concerns were raised by the scientific advisory group about the data submitted by AstraZeneca in support of the licensing application for gefitinib. In particular, the advisory group noted a large amount of missing data with respect to EGFR mutation status and considered that this 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 EMA[53] to be inadequate. Three new trials of gefitinib have been published since 2009 which was the date when the EMA[53] considered the application. The three trials were conducted in small populations of patients, KIM[42] (vs erlotinib), LI [37](vs docetaxel) and Bhatnagar[32] (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 number who were not treated with a TKI at first-line, perhaps due to 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 the TAILOR[34] trial 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.

6 ASSESSMENT OF COST EFFECTIVENESS

This section 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 their MS. The AG also provides a critique of the economic model (erlotinib vs BSC) submitted by Roche. The AG notes that AstraZeneca did not submit an economic model as part of their evidence supporting the use of gefitinib.

6.1 Systematic review of existing cost-effectiveness evidence

6.1.1 Methods of cost-effectiveness review

Full details of the main search strategy conducted by the AG and the proposed methods for selecting clinic and economics evidence are presented in detail in Section 5. 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/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 (AB/SB) according to the specific inclusion and exclusion criteria shown in Table 23. Data were extracted (AB/SB) and summarised in structured tables and as a narrative description.

Table 23 Inclusion criteria for economic papers

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

In the NHS in England and Wales (and 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. Recently, the price of docetaxel has fallen[54] substantially due to the expiry of the manufacturer's patent. The AG discussed whether 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 economic evaluations 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 economic evaluations that only include patients with EGFR-unknown status should be treated with caution.

6.1.2 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, ten papers were then excluded from the review and six papers were included in the review at stage 2. The reasons for excluding ten papers are listed in Table 24.

Table 24 Reasons for excluding papers from review at stage 2

Reference	Reason for exclusion
Bongers (2011[55])	Abstract
Bongers (2012[56])	Systematic review*
Borget[57]	Focus is on a "strategy" not an individual drug
Capri[58]	Not a full economic evaluation
Cuileanu[59]	Abstract
Horgan[60]	No outcome data
Horgan[61]	Cost consequence analysis – not a full economic evaluation
Laurendeau[62]	Abstract
Nguyen[63]	Abstract
Thongsprasert[64]	Abstract – full-text (2012) included in review

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

From the systematic review by Bongers et al,[56] 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.[65]

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

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

Reference	Title
Araujo[66]	An economic analysis of erlotinib, docetaxel or pemetrexed and best supportive care as second or third line treatment of non-small cell lung cancer
Asuki[67]	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[68]	Economic analysis: randomised placebo-controlled clinical trial of erlotinib in advanced non-small cell lung cancer
Holmes[69]	A cost-effectiveness analysis of docetaxel in the second-line treatment of non-small cell lung cancer
Thongsprasert[70]	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[71]	Erlotinib or docetaxel for second-line treatment of non-small cell lung cancer
Cromwell[72]	Erlotinib or best supportive care for third-line treatment of advanced non-small cell lung cancer: a real-world cost-effectiveness analysis
Lewis[73]	Cost-effectiveness of erlotinib versus docetaxel for second-line treatment of advanced non-small cell lung cancer in the United Kingdom
Leighl[74]	Economic analysis of the TAX317 trial: docetaxel versus best supportive care as second-line therapy of advanced non-small cell lung cancer
Carlson[75]	Comparative clinical and economic outcomes of treatments for refractory non-small cell lung cancer (NSCLC)
Vergnenegre[65]	Cost-effectiveness of second-line chemotherapy for non-small cell lung cancer

6.1.3 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 are 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.

6.1.4 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[65,67,68,70-73] were published from 2010 onwards. All of the papers described full economic evaluations using either cost-minimisation analysis (n=1[66]), cost-effectiveness analysis (n=6[67-69,71,72,74] and/or cost-utility analysis (n=6[65-67,70,73,75]) techniques. All but one study[71] used cost per QALY gained or cost per LY gained as the measure(s) of cost effectiveness. The results of six studies[66,67,69,70,73,75] were derived from use of an economic model, one study[65] conducted an economic analysis alongside an RCT and the remaining four studies[68,71,72,74] conducted retrospective reviews of costs and/or benefits. Four studies[68,71,72,74] were carried out from a Canadian NHS perspective, two[69,73] from that of the UK NHS, one[75] from the US perspective, three[65-67] from a European perspective and one[70] from a Thai payer perspective. None of the studies had a time horizon of longer than 3 years. The authors of two studies[71,72] had not received any financial support from the pharmaceutical industry.

The 19 comparisons described in the 11 economic studies included either one or more of the following interventions: erlotinib, docetaxel, pemetrexed and BSC. The most common comparison was erlotinib vs docetaxel (n=5[66,70,71,73,75]). Other comparisons were: erlotinib vs BSC (n=3[66,68,72]), pemetrexed vs docetaxel (n=4[65,67,70,75]), docetaxel vs BSC (n=3[65,69,74]), erlotinib vs pemetrexed (n=2[66,75]), pemetrexed vs BSC (n=1[65]) and gefitinib vs docetaxel (n=1[70]). The populations described in the economic evaluations appeared to have similar patient characteristics, namely previously treated stage III-IV patients with advanced NSCLC. The clinical data used in the economic evaluations were derived mainly from relevant published RCT data: TAX317[76] (docetaxel vs BSC), JMEI[51] (pemetrexed vs docetaxel), BR.21[31] (erlotinib vs placebo) and INTEREST[35] (gefitinib vs docetaxel). The source of the clinical data described in two studies was patient medical records. The paper by Nafees et al[77] provided the source of the QALY values in two papers.[65,75]

The outcome data (e.g. QALY values and LYs gained) used in the evaluations were variable due to 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 as follows: erlotinib (0.174[78] to 0.420[75]), docetaxel (0.160[78] to 0.420[75]), pemetrexed (0.171[78] to 0.520[67]). In addition, the AG notes that Araujo et al[66] assume that erlotinib, docetaxel and pemetrexed yield equivalent LYs (0.77 years), Thongprasert et al[70] assume the gain in LYs is equivalent when comparing docetaxel vs pemetrexed (0.97 years) and when comparing gefitinib vs erlotinib (0.96 years), and Carlson et al[75] 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) e.g., Spanish Reference database (BOT),[67] Portuguese ministerial dispatch report,[66] Ontario Case Costing Acute Inpatient Database[71] and British National Formulary.[69] 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 economic evaluations differ due to the assumptions made by the authors. For example, total costs per patient for erlotinib range from Can$16,487[68] to Can$35,708.[71] In Vergnenegre et al,[65] the costs of BSC are assumed to equal zero whilst in Leighl et al[74] the average cost of care in the BSC group was Can$6935.04. Costs and benefits were discounted at a 3%, 3.5% or a 5% discount rate, although some studies[71,72,74] 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 to chemotherapy or BSC favoured erlotinib,[66,68,72,73,75] the authors of the remaining study[71] concluded that erlotinib and docetaxel were equal in terms of costs

and benefits. Two studies[69,74] comparing docetaxel vs BSC concluded that docetaxel was cost effective. In another study[70] gefitinib was preferred to docetaxel, and in the two studies comparing pemetrexed vs docetaxel, one study favoured docetaxel[65] and the other favoured pemetrexed.[67]

Table 26 Study characteristics of economic evaluation

Study	Method of economic evaluation	Measure of cost effectiveness	Study design/model	Year published	Perspective	Time horizon	Discounting	Funding body
Araujo[66]	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
Asuki[67]	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[68]	CEA	Cost per LYG	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[69]	CEA	Cost per LY gained	Decision-analytic model	2004	UK NHS	2 years	Discounting was not applied	Pharma
Thongprasert[70]	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[71]	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 Colombia Health Care System	Data were collected between Sept 2005 and March 2008 (31 months)	N/A	Public
Cromwell[72]	CEA	Cost per QALY gained	Retrospective review of medical records (costs and outcomes) of patients who had	2012	British Colombia Health Care System	Controls: April 2002 and March 2004(2 years) Intervention: April 2004 and	N/A	Public

Study	Method of economic evaluation	Measure of cost effectiveness	Study design/model	Year published	Perspective	Time horizon	Discounting	Funding body
			received treatment vs historical controls			November 2006 (32 months)		
Lewis[73]	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[74]	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[75]	CUA	Cost per QALY gained	Decision-analytic model	2008	US payer perspective	2 years	Costs and benefits were discounted at 3%	Pharma
Vergnenegre[65]	CUA	Cost per LY gained Cost per QALY gained	Economic analysis alongside an RCT	2011	French payer perspective	34 months	3% discount rate used for costs	Pharma

CUA=cost utility analysis; CMA=cost minimisation analysis; QALY=quality adjusted life year gained; LYG=life year

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[66]	ERL vs BSC ERL vs DOC ERL vs PEM	Advanced or metastatic NSCLC, stage IIIA, IIIB or IV (hypothetical cohort)	Failed at least one prior treatment	Median OS, mean OS, PFS	TAX317 (DOC vs BSC) JMEI (PEM vs DOC) BR.21 (ERL vs PLA)	**QALYs**: ERL=0.250, BSC=0.186, DOC=0.225, PEM= 0.241 **LYG**: ERL=0.77, BSC=0.62, DOC=0.77, PEM=0.77
Asuki[67]	PEM vs DOC	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 sub-group analysis of the JMEI trial (PEM vs DOC)	**QALYs:** PEM=0.52, DOC=0.42, DIFF=0.1 **LYG:** PEM=1.03, DOC= 0.89, DIFF=0.14
Bradbury[68]	ERL vs PLACEBO	Advanced NSCLC	Previously treated	Median OS, mean OS	BR.21 (ERL vs PLA)	**Median OS**: ERL=6.7 months, PLA=4.7 months, HR=0.70, P<0.001, DIFF=2.0 months (0.16 years) **Mean OS**: ERL=9.0 months, PLA=7.4 months, HR=not reported, DIFF=1.6 months (0.13 years)
Holmes[69]	DOC vs BSC	Second-line treatment of NSCLC	Prior treatment with a platinum containing chemotherapy regime (no taxanes)	Mean OS calculated using an area under the curve analysis	TAX317 (DOC vs BSC)	**LYG:** DOC=8.89 months, BSC=5.16 months, DIFF=3.82 months (0.32 years)
Thongprasert[70]	GEF vs DOC ERL vs DOC PEM vs DOC	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 ERL and GEF had the same mean OS/PFS	INTEREST (GEF vs DOC) – data used for GEF/ERL and DOC JMEI (PEM vs DOC) – data used for PEM	**OS (years):** DOC=0.97, GEF=0.96, ERL=0.96, Pem=0.97 DIFF GEF vs DOC=0.013, DIFF ERL vs DOC=0.013, DIFF PEM vs DOC=0 **QALYs:** DOC=0.160, GEF=0.174, ERL=0.174, Pem=0.171 DIFF GEF vs DOC=0.014, DIFF ERL vs DOC=0.014, DIFF PEM vs DOC=0.011
Cromwell[71]	ERL vs DOC	Stage IIIb/IV advanced NSCLC	Previously treated patients	Mean and median OS and PFS and 1 year OS	BC Cancer Agency medical records	**Mean OS (95% CI):** ERL=311 days (264 to 344), DOC=310 (248 to

Study	Comparison (intervention vs comparator)	Characteristics of population	Details of prior treatments	Clinical outcomes	Clinical data source	Total benefits
				AUC analysis		333), DIFF=1 day **Mean PFS (95% CI):** ERL=64 days (61 to 66), DOC=75 (43 to 77), DIFF=-11 day **1 year OS:** ERL=36%, DOC=32.4%
Cromwell[72]	ERL vs BSC	Stage IIIb/IV advanced NSCLC	Patients who had progressed after 2nd-line treatment	Mean and median OS and PTD and 1 year OS AUC analysis	BC Cancer Agency medical records	**Mean OS (95% CI):** ERL=291 days (233 to 349), BSC=181 days (141 to 222), DIFF=110 days **Mean PTD days (95% CI):** ERL=195 days (148 to 242), BSC=105 days (82 to 129), DIFF=90 days **1 year OS:** ERL=36%, DOC=32.4%
Lewis[73]	ERL vs DOC	Stage III/IV patients with advanced NSCLC	One or more prior chemotherapy treatments	Mean OS and mean PFS Utility scores	TAX317 (DOC vs BSC) BR.21 (ERL vs PLS) EQ-5D scores (general population – visual analogue method)	**QALY progression free health state:** ERL=0.150, DOC=0.104 **QALY progression health state:** ERL=0.088, DOC=0.102 **Total QALY** ERL=0.238, DOC=0.206, DIFF=0.032
Leighl[74]	DOC 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	TAX317 (DOC vs BSC)	**Mean OS months (95% CI):** DOC=9.1 (7.51 to 10.69), BSC=5.60 to 8.62, p=0.07
Carlson[75]	ERL vs DOC ERL vs PEM PEM vs DOC	60 year +patients with advanced stage III to IV NSCLC	Failed at least one platinum-based chemotherapy	Mean PFS and mean OS. Assumed PFS and OS were the same for all three drugs AE rates and utility scores	BR.21 (ERL vs PLA) TAX317 (DOC vs BSC) TAX 320 (DOC vs BSC) JMEI (PEM vs DOC) Published literature and Nafees EQ-5D	**Mean OS:** ERL, DOC, PEM=0.75 years **Mean PFS**: ERL, DOC, PEM=0.34 years **QALY:** ERL, DOC, PEM=0.42, 0.41, 0.41

Study	Comparison (intervention vs comparator)	Characteristics of population	Details of prior treatments	Clinical outcomes	Clinical data source	Total benefits
					study	
Vergnenegre[65]	DOC vs BSC PEM vs BSC DOC vs PEM	Patients with stage IIIB or IV NSCLC	Failed after 1st-line cisplatin based chemotherapy	Median PFS, median OS and objective response rate. Utility scores	GFPC 05-06 study Nafees EQ-5D study	**Objective response rates:** DOC=10.7%, PEM=12% **Median PFS:** DOC= 2.8months, PEM= 2.5months **Median OS:** DOC =8months, PEM= 6.4months **QALY:** DOC=0.42, PEM= 0.41

BSC=best supportive care; PEM=pemetrexed; GEF=gefininib; DOC=docetaxel; ERL=erlotinib; PTD=progression-to-death; QALY=quality adjusted life year gained; LYG=life year gained

Table 28 Cost inputs, data sources total costs

Study	Types of costs	Cost data sources	Cost year/ Currency	Costs
Araujo[66]	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 ERL was supplied by Roche and the cost of PEM was estimated through the price supplied by two hospital pharmacies. Cost of DOC 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%	**Total cost per patient:** ERL = €26,478, BSC=€16,112, DOC= €29,262, PEM=€32,762
Asuki[67]	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 SOIKOS databases. Other costs were obtained from two IMS reports.	€/2007	**Total cost per patient:** PEM= €34,677, DOC=€32,343
Bradbury[68]	Chemotherapy treatment, diagnostic tests, outpatient visits, concomitant medications, management of treatment-related toxicity, hospitalisations, radiation therapy, 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.	Canadian $/2007	**Mean cost per patient (Can$):** ERL=$16,487, PLA=$4184
Holmes[69]	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	British National Formulary and Unit Costs of Health and Social Care	UK £/2000-2001	**Mean net cost per patient:** DOC= £4432, BSC=£0.00
Thongprasert[70]	Direct medical costs: drug acquisition costs, drug administration and monitoring, and adverse event management	Drug and Medical Supply Information Center, standard cost list for health technology assessment (HITAP), Prices of Services of Health Facilities under the Ministry of Public Health	Thai Baht/2010 - converted to US dollars using exchange rate of 30.28 Baht = 1USD (Bank of Thailand website)	**Total cost per patient (USD):** DOC= $6483, GEF= $6237, ERL=$8229, PEM= $9092
Cromwell[71]	CTX drugs, radiation therapy, physician appointments, diagnostic tests and hospital admission	Drug costs from PPS Pharma Publication, hospital costs per diem from the Ontario Case Costing Acute Inpatient Database, transfusion costs from Canadian Blood Services, other costs from medical opinion and	Canadian dollars/2009	**Mean overall cost/patient (Can$) (range):** ERL=$35,708 (32,241 to 39,174) DOC=$32,817 (27,940 to 37,693)

Study	Types of costs	Cost data sources	Cost year/ Currency	Costs
		trial database		DIFF=$2891
Cromwell[72]	CTX drugs, radiation therapy, physician appointments, diagnostic tests and hospital admission	Provincial Medical Services Plan, provincial PharmaCare plan, home and community care (HCC) and hospital specific mean case costs	Canadian dollars/2009	**Mean overall cost/patient (Can$) (range):** ERL= $34,326 (6569 to 99,370) BSC=$23,224 (1095 to 78,775)
Lewis[73]	Monthly medical resource utilisation, treatment related AEs and drug administration costs for 3 health states were agreed upon by a panel of lung cancer clinicians	Unit costs from BNF(2006) and PSSRU (2008)	UK £/2009	**Lifetime per patient costs:** ERL=£13,730 DOC=£13,956
Leighl[74]	Outpatients assessments, chemotherapy administration, hospitalisation, radiation therapy, community-based nursing and supportive care, and miscellaneous items	Costs derived from trial data, hospital medical records as well as other facilities at which care was received. All physician services were based on the 1999 Ontario Health Insurance Plan fee schedule	Canadian dollars/1999	**Average cost per patient arm (Can$) in TAX317:** DOC (75mg/m^2)=$17,738.96 BSC=$6935.04
Carlson[75]	Drug utilisation, drug administration, hospital inpatient admission, outpatient appointments AE treatments	Wholesale drug acquisition costs from First Data Bank I online database, medical services from CMS physicians fee schedule and inpatient prospective payment system, disease progression from a Kaiser Permanente study	US dollars/2007	**Total cost (US$):** ERL=$36,977 DOC=$39,104 PEM=$43,795
Vergnenegre[65]	Chemotherapy drugs, drug administration, supportive treatment, hospitalisation for any reason, outpatient follow-up attendance, medical transport and grade 3/4 AE management costs	2009 Euros, 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	**Total cost:** DOC=€13,714 +/- €7387 PEM=€16,802 +/-€7852 Authors compared DOC with BSC and PEM with BSC and assumed costs and benefits of BSC were equal to zero.

BSC=best supportive care; PEM=pemetrexed; GEF=gefininib; DOC=docetaxel; ERL=erlotinib

Table 29 Cost-effectiveness results, sensitivity analysis and conclusions

Study	Cost-effectiveness results	Sensitivity analysis	Conclusions
Araujo[66]	**Cost/QALY gained**: ERL vs BSC= €161,742, ERL vs DOC=ERL dominates, ERL vs PEM=ERL dominates **Cost/LY gained:** ERL vs BSC: €70,424, ERL vs DOC= ERL reduces costs, ERL vs PEM=ERL reduces costs	Sensitivity analyses undertaken generate results similar to the base-case	Use of ERL instead of DOC or PEM could contribute to annual savings for the Portuguese NHS and a gain in QALYs
Asuki[67]	**Cost/QALY gained:** PEM vs DOC= €23,967 **Cost/LYG gained:** PEM vs DOC=€17,225	Model is most sensitive to variation in OS. The PSA results show that PEM has a 62% likelihood of having a QALY below €30,000 and a 77% likelihood of having a cost per LYG below €30,000	In the Spanish setting, PEM for the 2nd-line treatment of patients with NSCLC other than predominately squamous cell histology is indicated as a cost-effective chemotherapy option compared to the standard DOC, based on its superior OS benefit and toxicity profile
Bradbury[68]	**Cost/LY gained (Can$):** ERL vs PLA=$94,638 **Subgroup analyses**: Cost/LYG (never-smokers)=$39,487 Cost/LYG (high EGFR gene copy number)= $33,353	Magnitude of the survival benefit was the main influence on the size of the ICER. Subgroup analyses revealed that ERL may be more cost-effective in never-smokers or patients with high EGFR gene copy number	Authors conclude that ERL for patients with previously treated advanced NSCLC is marginally cost-effective and that the use of molecular predictors of benefit for targeted agents may help identify more or less cost-effective subgroups for treatment
Holmes[69]	**Cost/LY gained:** DOC vs BSC=£13,863	Sensitivity analysis showed that the number of treatment cycles per patient had most influence on the cost/LY gained	Authors conclude that DOC 75mg/m^2 in 3-weekly cycles is a cost-effective 2nd-line treatment from the perspective of the UK NHS for pre-treated NSCLC in terms of survival gains made for a reasonable increase in costs
Thongprasert[70]	**Cost/QALY gained (US$):** GEF vs DOC=GEF dominates, ERL vs DOC=$124,703, PEM vs DOC= $237,150	Sensitivity analyses showed that varying DOC cost and the duration of DOC treatment had the greatest effect on cost-effectiveness	Authors conclude that GEF is a dominant cost saving strategy compared with DOC for the 2nd-line treatment of advanced NSCLC from the Thai payer perspective

Study	Cost-effectiveness results	Sensitivity analysis	Conclusions
Cromwell[71]	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	ERL=DOC in terms of costs and benefits. Choice of treatment should depend on patient preferences
Cromwell[72]	**Cost per LY gained (Can$)** ERL vs BSC=$36,838 Incremental mean OS = 110 days Incremental mean cost = $11,102	Univariate SA (from varying total treatment costs) yielded ICERs ranging from $21,300/LYG to $51,700/LYG. Other parameters varied included mean drug cost/patient and hospital cost/patient	Analyses suggest that ERL may be an effective and cost-effective third-line treatment for advanced NSCLC compared to BSC
Lewis[73]	**Cost per QALY gained** ERL vs DOC = £-£7106, net monetary benefit = £1181 Incremental benefit=0.032, incremental cost=-£226.	Sensitivity analyses showed the robustness of the baseline analysis i.e., that ERL was cost effective compared with DOC	From a health economics perspective, for the treatment of patients with relapsed stage III-IV in the UK, ERL has advantages over DOC
Leighl[74]	**Cost per LY gained (Can$)** DOC (75mg/m^2) vs BSC=$31,776	In univariate SA, cost-effectiveness ratios were most sensitive to changes in survival ranging from $18,374 to $117,434 with 20% variation in survival at recommended (75mg/m2) dose	Authors concluded that the estimated cost per life year gained is within an acceptable range of health care expenditures
Carlson[75]	**Cost per QALY gained (US$)** ERL vs DOC=ERL dominates ERL vs PEM=ERL dominates PEM vs DOC=$1,743,359	Estimates of treatment duration were among the most influential parameters in the AS, others were time in PFS, drug costs and values of some health state utilities. In the PSA, ERL was cost-saving in 65% and 87% of the simulations compared to DOC and PEM respectively	Results of the study suggest that ERL in the treatment of refractory NSCLC in the US is less costly compared with alternative treatments and may lead to a slight improvement in QALYs
Vergnenegre[65]	**Cost per QALY gained** DOC vs BSC=€32,652 PEM vs BSC=€40,980 **Cost per LY gained** DOC vs BSC=€15,545 PEM vs BSC=€22,798	SA showed that the price of PEM 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 DOC than with PEM. Both strategies have acceptable cost-effectiveness ratios compared with commonly used and reimbursed regimes for advanced NSCLC

BSC=best supportive care; PEM=pemetrexed; GEF=gefininib; DOC=docetaxel; ERL=erlotinib

6.1.5 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 economic evaluations (Table 29). These differ from evaluation to evaluation. Each economic evaluation 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.[54] The AG therefore considers that the 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[65]) and pemetrexed vs erlotinib (n=2[66,75]]. 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[66,68,71] focussed on the comparison of erlotinib vs 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 only useful when making treatment decisions for patients whose EGFR status is unknown as the EGFR mutation status of this patient group an 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.

The AG concludes that the results of the systematic review are of limited value to decision-makers in the UK NHS. This is due to relatively recent changes in (i) price of docetaxel and (ii) increased significance of EGFR mutation testing for patients with NSCLC. The AG does not summarise or draw conclusions from any other MS 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 economic evaluations in this complex clinical area will make use of the most up-to-date clinical effectiveness and cost data available.

6.2 Critique of economic analyses submitted by manufacturers

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

The manufacturer of erlotinib (Roche) states (MS, pg 41) 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." The manufacturer's base-case analysis therefore compares erlotinib vs 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 vs BSC for patients with EGFR M- tumours. The AG provides a summary and critique of the economic evaluation presented in the MS submitted by Roche.

The AG notes that the manufacturer of erlotinib (Roche) 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 retreated with a EGFR-TKI as part of second-line treatment. The manufacturer therefore has not carried out an economic evaluation 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 economic evaluation comparing erlotinib with gefitinib for this patient population.

6.2.1 Review of Roche economic model: erlotinib vs BSC

Table 30 NICE reference case checklist

NICE reference case requirements	Reference case	Does the *de novo* economic evaluation match the reference case?
Defining the decision problem	The scope developed by the Institute	Partial. DOC was not considered. The manufacturer stated that they do not believe it would be possible to demonstrate that ERL is cost effective compared with DOC following the availability of generic DOC. No comparison with GEF.
Comparators	Therapies routinely used in the NHS, including technologies currently regarded as best practice	
Perspective on costs	NHS and PSS	Yes
Perspective on outcomes	All health effects on individuals	Yes
Type of economic evaluation	Cost-effectiveness analysis	Yes
Synthesis of evidence on outcomes	Based on a systematic review	N/A - only evidence from BR.21 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

QALY=quality adjusted life years, NICE= National Institute for Health and Care Excellence, HRQoL= health related quality of life, PSS= personal social services

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 vs BSC using ITT data from the BR.21[31] trial. In a separate subgroup analysis, the manufacturer compares erlotinib vs 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,[29] TA227[79] and TA295[80]). 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 MS Excel and has a 1-week cycle length.

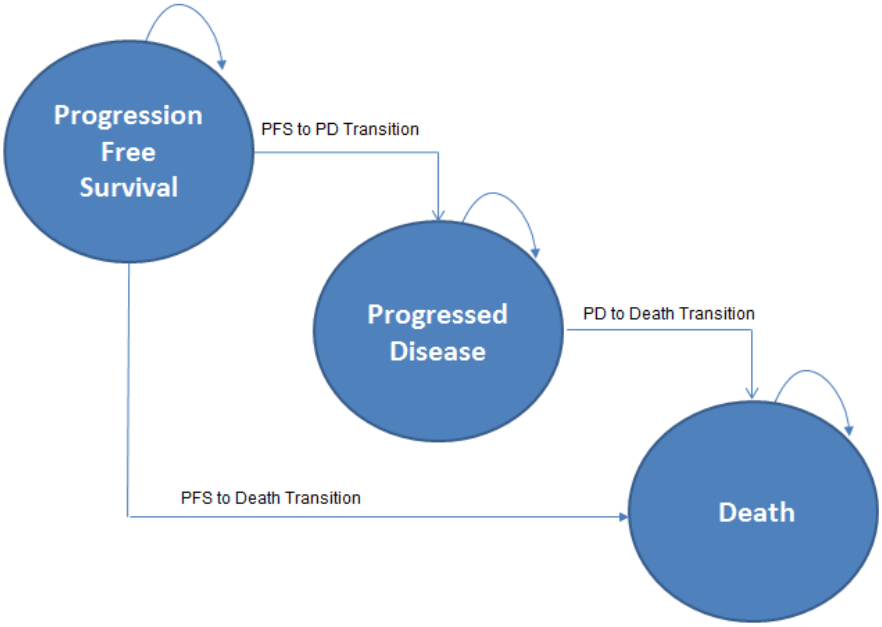

Figure 2 Schema of manufacturer's model

6.2.2 Population

The population was assumed to be the same as that recruited to the BR.21[31] trial i.e. patients 18 years of age or older with an ECOG PS 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).

6.2.3 Interventions and comparators

The manufacturer believes that, following the availability of generic docetaxel at less than 10% of the list price, it is not possible to demonstrate that erlotinib is cost effective when compared with docetaxel. They have, therefore, only presented an analysis comparing erlotinib (maximum of one 150mg 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.

6.2.4 Perspective, time horizon and discounting

The economic evaluation is undertaken from the perspective of the NHS and Personal Social Services. Outcomes are expressed in terms of LYs gained and QALYs gained. The time horizon is set at 6 years and, in line with the NICE Methods Guide to Technology Appraisal,[81] both costs and benefits are discounted at 3.5%.

6.2.5 Treatment effectiveness and extrapolation

Data from BR.21[31] 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 for erlotinib only two patients 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.

6.2.6 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 (TA296[82]). 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[83] (described in TA296[82]) is anaplastic lymphoma kinase ALK positive and that the utility values from this population are

relatively high for patients with NSCLC. Furthermore, the patient group in PROFILE 1007[83] was younger and less fit than those patients enrolled in the BR.21[31] trial.

Utility values used in the model are presented in Table 31.

Table 31 Key model parameters: utility

State	Utility value	Standard error	Source
Progression-free survival	0.747	0.049	TA296[82]
Progressed disease	0.610	0.038	TA296[82]

6.2.7 Resources and costs

Erlotinib acquisition costs

The model assumes that erlotinib is dispensed in packs of 30 tablets (150mg) 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[29] and TA258[19] (see Table 32).

Table 32 Erlotinib costs

Cost	Value	95% confidence interval	Source
Pharmacy costs per pack of erlotinib dispensed	£18.20 (12 mins of pharmacy time @£91/hr)	£9.28 to £27.12[†]	Millar 2008,[84] PSSRU 2011[85] MS Section 4.5
Erlotinib drug costs	30 tab x 150 mg = £1631.53 30 tab x 100 mg: £1324.14 30 tab x 25mg - 50mg: £378.33 [redacted]	N/A	BNF Sept 2013[54] list price MS Table 12, Section 4.5

[†]Gamma distribution applied under assumption standard error was a quarter of base-case value

Supportive care costs

The supportive care resources described in the MS are in line with those used in TA162[29] which were elicited from an expert panel and updated using NHS reference costs (2011/12[86]), PSSRU (2011[85]), BNF (2012[49]) and the electronic market information tool (eMIT[87]). 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 due to the fact that 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.

Table 33 Supportive care costs

	Included elements (per month)		Value
	Visits and hospitalisation	**Tests, procedures and medications**	**Weekly**
PFS BSC cost (including monitoring)	• Hospital stay episode (2.5% pts) • Cancer nurse (20% pts x 1 visit) • Palliative care nurse (30% pts x 1 visit) • Palliative care physician (7.5% pts x 1 visit) • OP attendance (0.75 visits) • GP visit (10% pts x 1 visit)	• Blood count (all pts x 0.75) • Palliative radiotherapy (12.5% pts x 1) • CT scan (30% pts x 0.75) • X-ray (all pts x 0.75) • Biochemistry (all pts x 0.75)	£84.67
PD BSC cost	• Hospital stay episode (30% pts) • Cancer nurse (10% pts x 1 visit) • Palliative care nurse (20% pts x 1 visit) • Palliative care physician (80% pts x 2 visits) • OP attendance (1 visits) GP visit (28% pts x 1 visit)	• Blood count (all pts x 1) • Palliative radiotherapy (20% pts x 1) • CT scan (5% pts x 0.75) • X-ray (30% pts x 0.75) • Biochemistry (all pts x 0.75) • Home oxygen (20%pts x 1) • Steroids (dexamethasone) (50% pts 0,5mg x 160) • NSAIDS (aspirin) (30% pts 200mg x 60 • Morphine (75% of patients 60mg x 7) • Bisphosphonate (ibandronic acid) 7.5% pts 5mg x 28)	£220.34

Adverse events

Adverse event rates were taken from BR.21[31] and only those AEs where 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 TA162.[29] Costs were taken from NHS Reference Costs (2011/12[86]), PSSRU (2012[88]), BNF (2012[49]) and eMIT[87] and are displayed in Table 34.

Table 34 Adverse event costs

	Included elements	Value
Rash	Outpatient attendance, oral tetracycline	£275.36
Anorexia	Dietician, 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	£1,813.65
Fatigue	GP visit, Macmillan nurse	£4.29

6.2.8 Cost-effectiveness results

The base-case incremental results generated by the manufacturer's model are presented in Table 35. The incremental ICER for the comparison of erlotinib vs 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 life year gained. Disaggregated costs for the target population are presented in Table 36.

Table 35 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER per QALY gained (£)
BSC	5,993	0.656	0.432				
Erlotinib	13,522	0.867	0.579	7,529	0.212	0.148	51,036

Inc=incremental, ICER=incremental cost-effectiveness ratio, LYG=life years gained, QALYs=quality adjusted life years

Table 36 Disaggregated mean costs for the base-case analysis

Element	Cost (£)		Increment (£)	Absolute increment (£)	Absolute increment (%)
	Erlotinib	BSC			
Drug	[redacted]	0	[redacted]	[redacted]	[redacted]
Pharmacy	[redacted]	0	[redacted]	[redacted]	[redacted]
AEs	[redacted]	113	[redacted]	[redacted]	[redacted]
PFS BSC	[redacted]	1,020	[redacted]	[redacted]	[redacted]
PD BSC	[redacted]	4,860	[redacted]	[redacted]	[redacted]
Total	**13,522**	**5,993**	**7,529**	**7,529**	**100**

AEs=adverse events, PFS=progression-free survival, PD=progressed disease

6.2.9 Sensitivity analyses

The manufacturer carried out a large number of one-way sensitivity analyses. A tornado diagram is included in the MS (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.

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 utility values for PFS and PD		£61,317
Variation (± 20%) from the base case of PFS utility	£44,900 (-£6,136)	£59,116 (£8,080)
ERL dose reduction in 19% of patients and PFS cost reduction by 50%	£44,121 (-£6,915)	
Reduction of PFS costs (-50%) for the ERL arm	£45,565 (-£5,471)	
Variation (± 20%) from the base case of PD utility	£47,997 (-£3,039)	£54,487 (£3,451)

PFS=progression-free survival, PD=progressed disease, ICER=incremental cost-effectiveness ratio

Probabilistic sensitivity analysis (PSA) was undertaken (5,000 iterations of the model) by the manufacturer. A scatter plot (incremental cost versus QALY) and a cost-effectiveness acceptability curve are included in the MS (pg 70) and reproduced in Figure 3 and Figure 4.

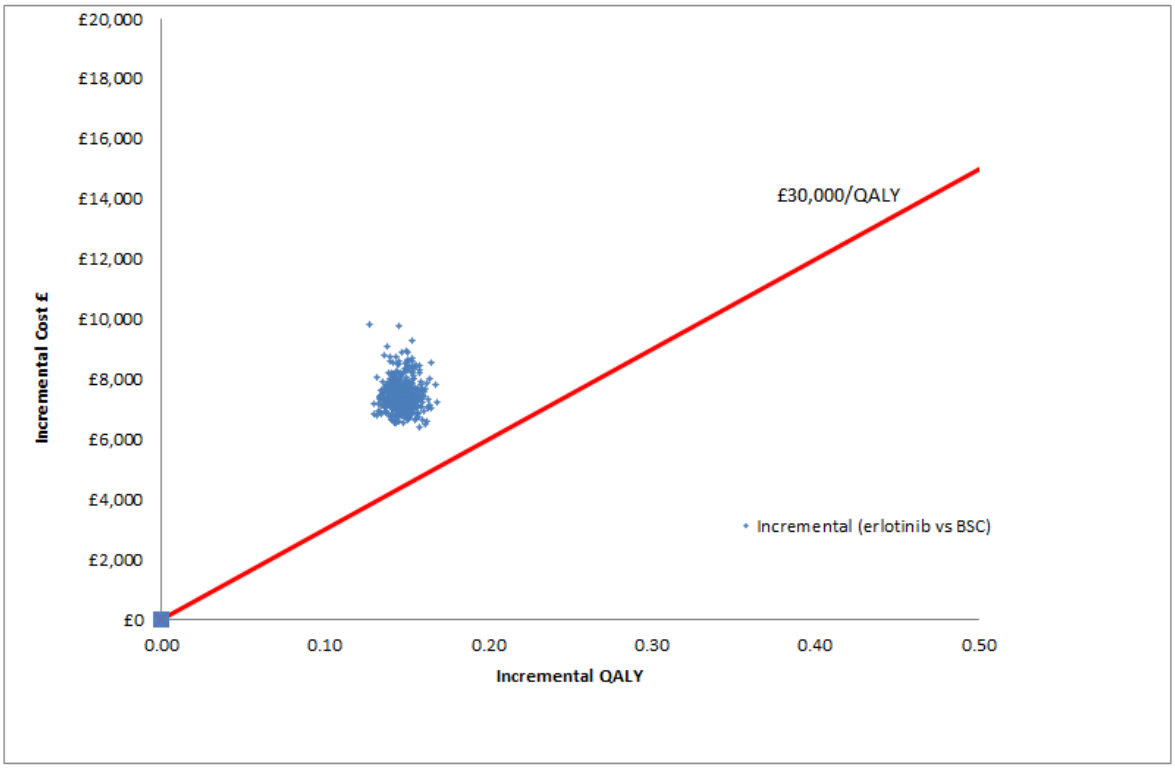

Figure 3 PSA Scatter-plot erlotinib vs BSC (diagonal line = £30,000 per QALY gained)

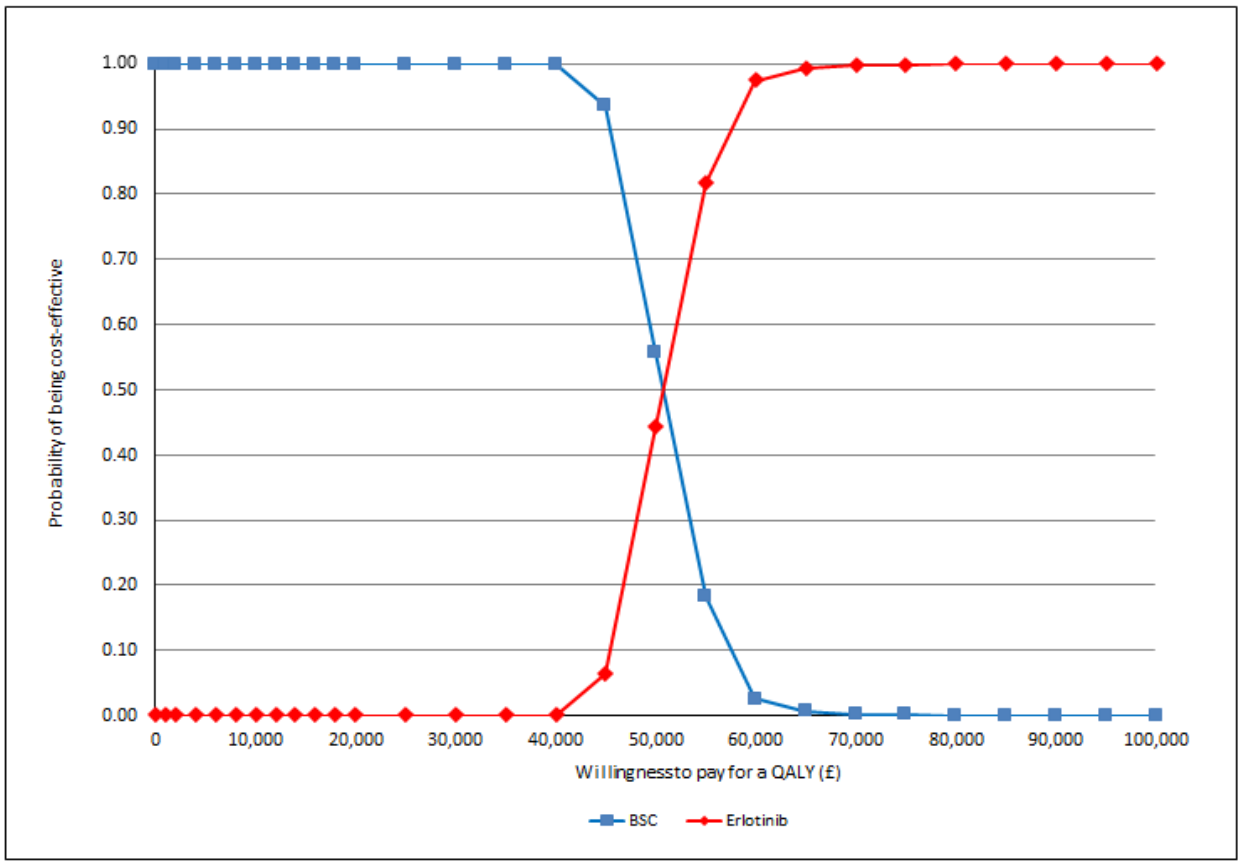

Figure 4 Cost-effectiveness acceptability curve

Results from 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.

Table 38 Probabilistic sensitivity analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER/QALY gained (£)	Difference from base-case ICER (£)
BSC	5,775	0.431				
Erlotinib	13,265	0.578	7,490	0.147	50,825	-211

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

6.2.10 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[43] by Zhu et al. 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 due to the limitations of the available data.

Table 39 EGFR M- results

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER per QALY gained (£)
BSC	6,362	0.682	0.447				
Erlotinib	13,853	0.850	0.574	7,490	0.168	0.128	58,579

Inc=incremental, ICER=incremental cost-effectiveness ratio, LYG=life years gained, QALYs=quality adjusted life years

6.2.11 Critique of 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 MS. 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 an EGFR-unknown population of patients with NSCLC, 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[77] replaced values from PROFILE 1007[83] in the manufacturer's base-case analysis.

The AG has several concerns about the use of PROFILE 1007[83] 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 points 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 EQ-5D scores is unknown. As the predominant data source in the PROFILE 1007[83] trial is the US, 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[83] utility scores the PFS average (US) 0.747 changes to 0.667. The Nafees et al[77] model gives 0.653 for stable disease PFS and 0.673 for responder PFS. Similarly, the PD average utility of 0.61 (US) converts to 0.475 (UK), which compares closely with the Nafees et al[77] PD utility of 0.473.

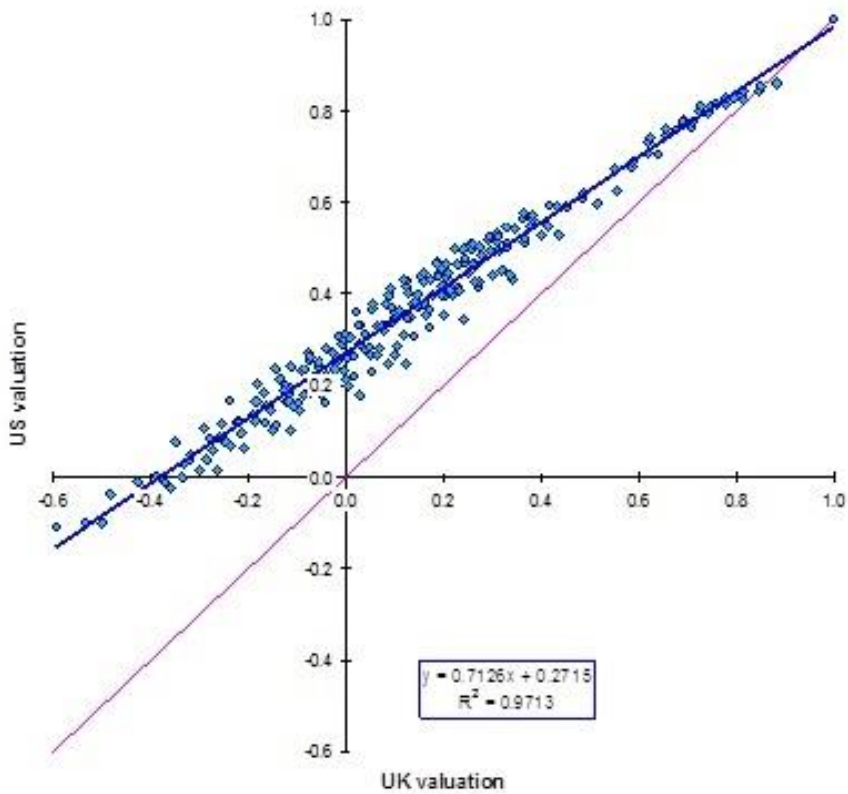

Figure 5 Relationship between health state scores using UK and US tariffs

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[85]) has been used in the model but the most up to date value is £67 (PSSRU 2012[88]).

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.

6.3 Assessment Group de novo economic model

To allow all therapy options for the post-progression treatment of patients with NSCLC to be compared using a consistent framework, the AG has developed a de novo cost-effectiveness model.

6.3.1 Methods

Assessment perspective

Costs and outcomes are 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 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 <u>not</u> 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 only be used for patients with disease that exhibits EGFR activating mutations.
- Pemetrexed may only be used 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 is not within the scope of the current re-appraisal.

Additionally, it is generally considered that a patient is unlikely to be retreated 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 (where 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, were 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.[81] 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-week 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 to either 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.

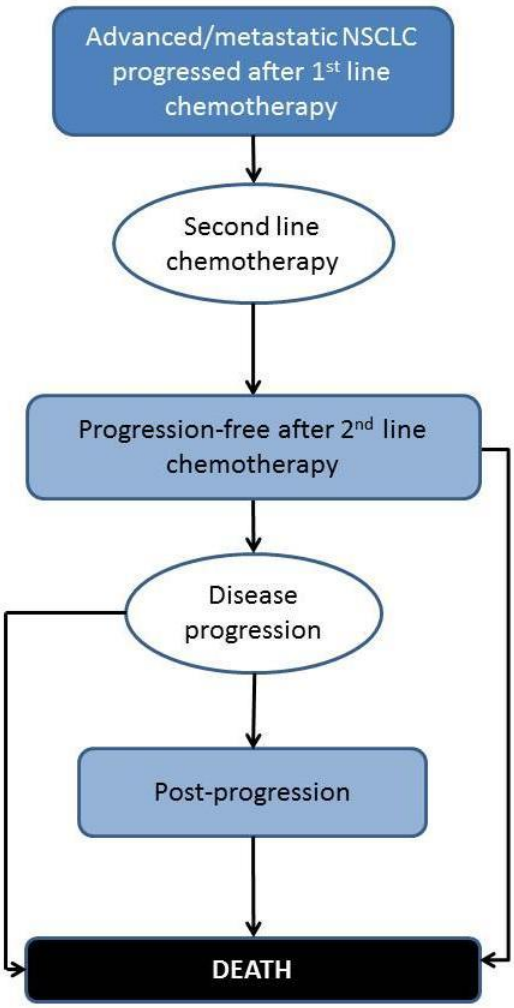

Figure 6 Conceptual model of second/third-line decision model, indicating health states (rectangles), events/procedures (ovals) and transitions (arrows)

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.

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 likely 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: PFS and OS

EGFR M+ population

No clinical trials have been identified which compare second-line treatments in a population of only patients with EGFR activating mutations. The manufacturer of gefitinib has presented evidence of an exploratory post-hoc analysis of patients from the IPASS[46] trial, patients were included in the analysis if they were randomised to the chemotherapy arm of the IPASS[46] trial (i.e. not randomised to gefitinib). Subsequently, some patients received EGFR-TKI therapy and some did not. Comparison of subsequent survival in these two subgroups appears to show strong evidence of substantial gain in OS attributable to later use of gefitinib. Examination of baseline patient characteristics and PFS does not show any evidence of potential selection bias with the exception of racial origin where Chinese and Japanese patients were more likely to receive EGFR-TKI treatment than other patients.

The AG has carried out an exploratory analysis of the OS results presented by the manufacturer of gefitinib and has concluded that these data suggest much longer mean OS than normally reported in trials of either EGFR-TKI treatment or chemotherapy, with an apparent gain of more than [redacted] associated with second-line EGFR-TKI use (i.e. post-chemotherapy). If this finding were to be validated by full independent RCT evidence this would represent a very important therapeutic advance.

EGFR M- population

Clinical effectiveness data for this patient group are restricted to the TAILOR[34] trial which compares erlotinib with docetaxel. Published Kaplan-Meier survival curves were digitized 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 the TAILOR[34] trial 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 3-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.

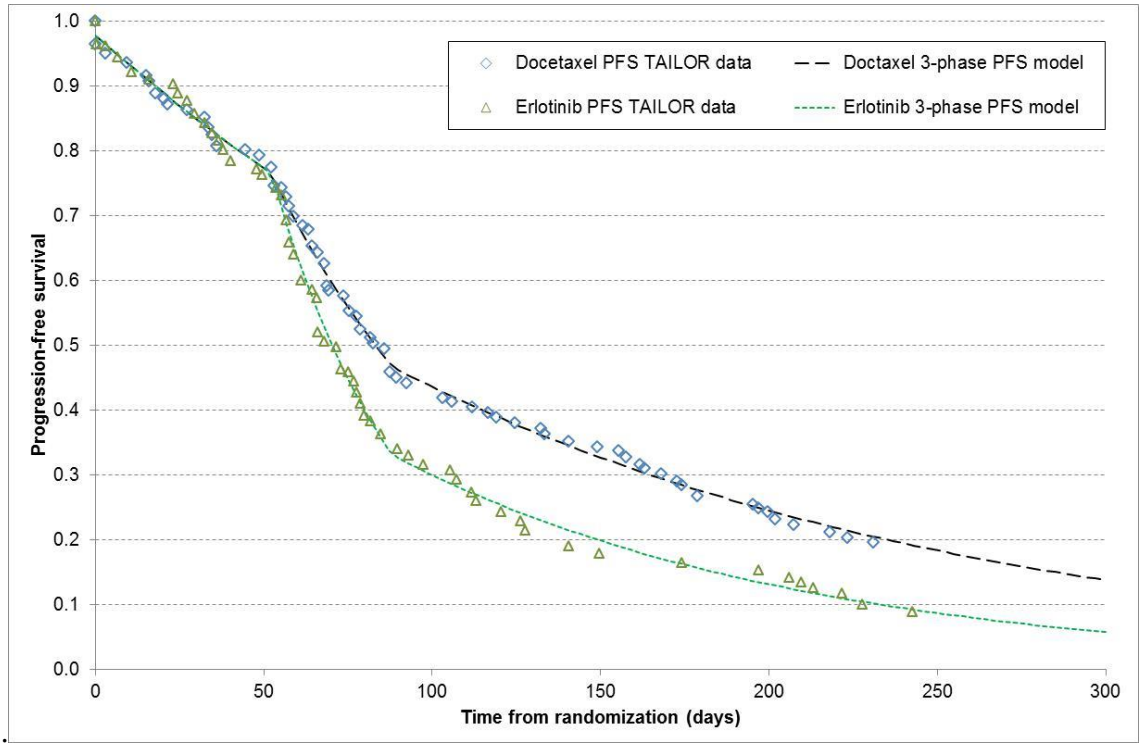

Figure 7 3-phase projective spline models fitted to PFS data from the TAILOR clinical trial

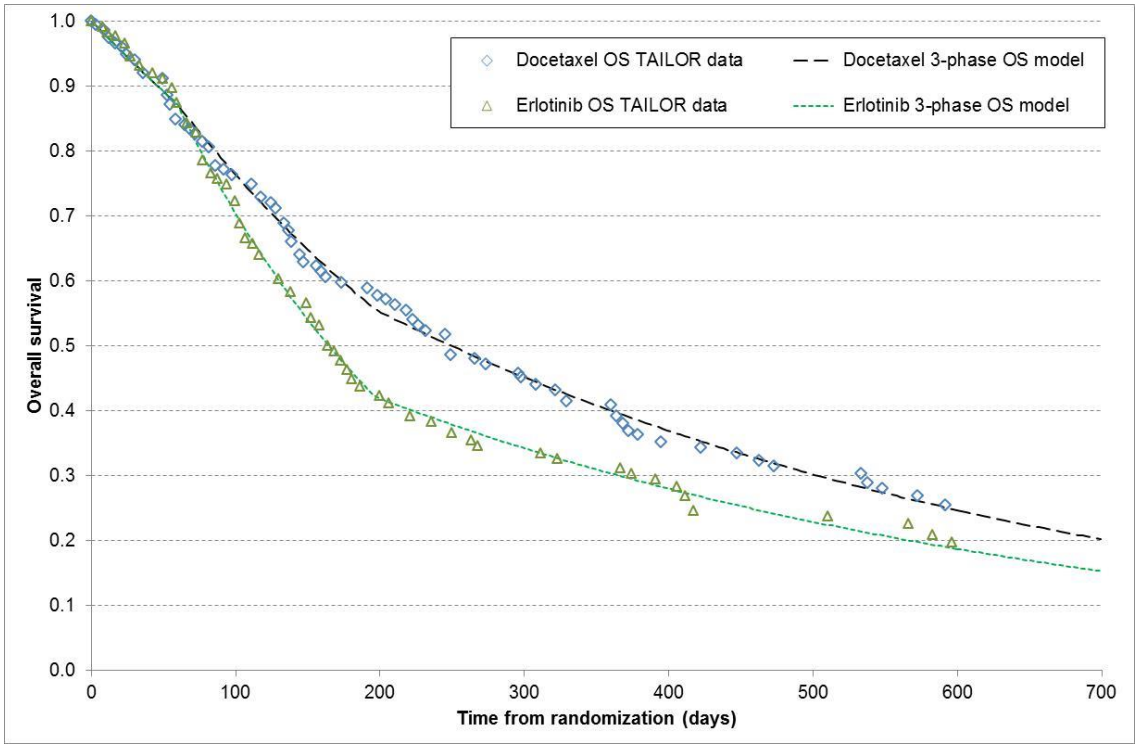

Figure 8 3-phase projective spline models fitted to OS data from the TAILOR clinical trial

Figure 7 and Figure 8 demonstrate the correspondence between the TAILOR[34] trial 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 patient experience subject to different degrees of modelling error. For PFS, projection began 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.

EGFR-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 the TAILOR[34] trial. Therefore, a similar 3-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 focussed 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, limiting 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).

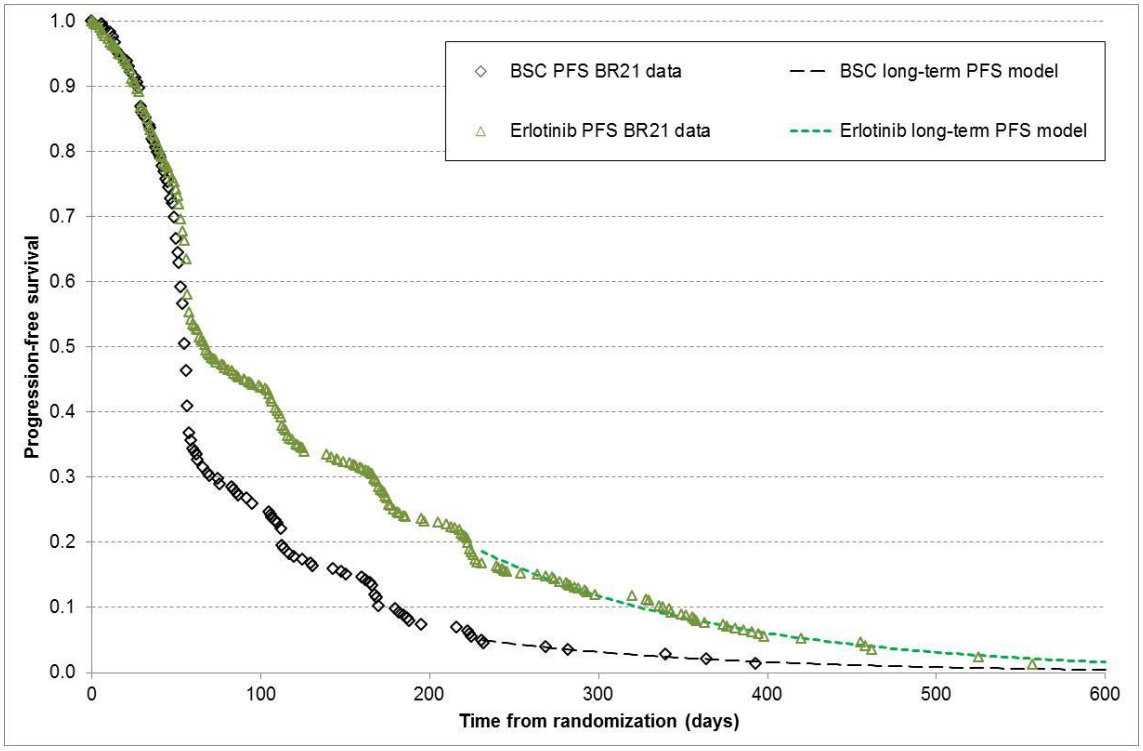

Figure 9 Long-term projective models fitted to PFS data from the BR.21 clinical trial

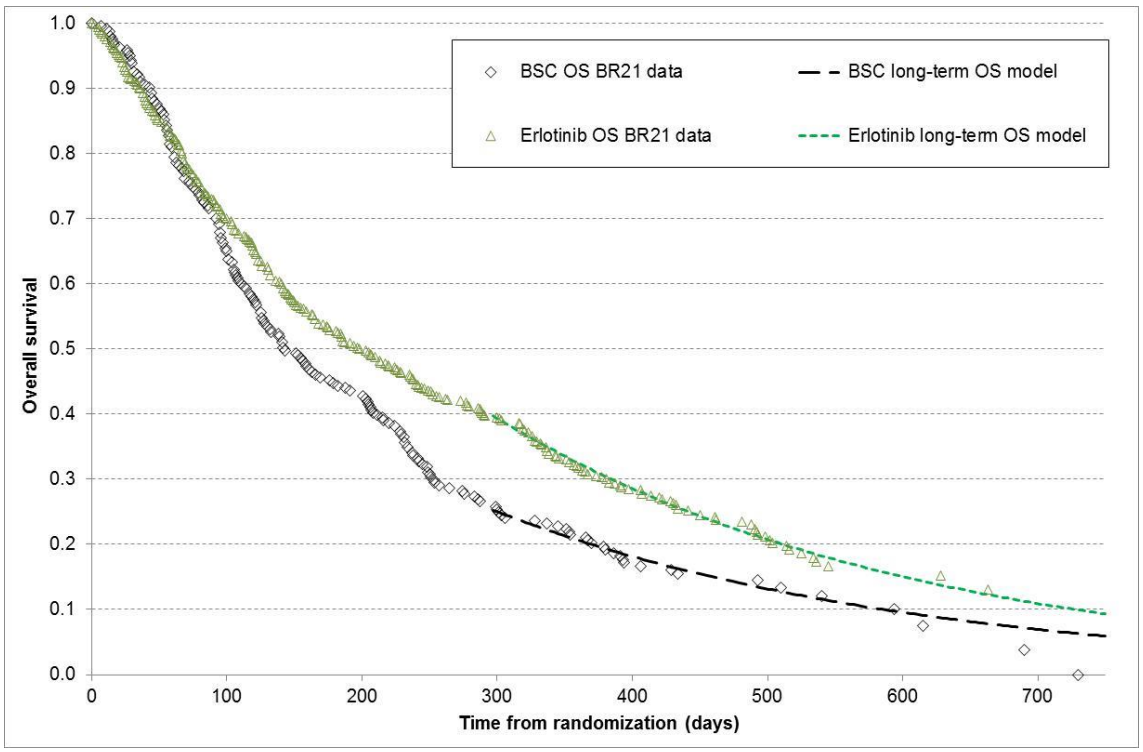

Figure 10 Long-term projective models fitted to OS data from the BR.21 clinical trial

Figure 9 and Figure 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 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.

Synthesis of outcome data: response rates to second-line chemotherapy

The Nafees et al[77] multi-variate 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[31,35,38-41,51,65,76,89-94] involving patients undifferentiated by mutation status and only one trial each for the EGFR M+ population (Kim 2012[42]) and the EGFR M- population (the TAILOR[34] trial). The KIM trial[42] 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 response rates (%) for second-line chemotherapy

	Responders (%)		**Stable disease (%)**	
	Mean	**95% CI**	**Mean**	**95% CI**
EGFR M+ population				
ERL	39.6	26.4 to 53.6	27.1	15.6 to 40.4
GEF	47.9	34.1 to 61.9	30.2	27.8 to 32.6
EGFR M- population				
DOC	15.5	9.0 to 23.3	28.9	20.3 to 38.2
ERL	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
DOC	8.5	7.2 to 9.9	36.2	33.1 to 39.3
ERL	8.7	6.8 to 10.7	29.8	26.6 to 33.0

CI=confidence interval

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 multi-variate model by Nafees et al[77] described in detail below): diarrhoea, fatigue, neutropenia, febrile neutropenia, hair loss, nausea/vomiting and skin rash.

Reported incidence of grade 3/4 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 in consistency. Table 41 details the incidence rates obtained for each second-line chemotherapy agent.

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

	Diarrhoea	Fatigue	Febrile neutropenia	Hair loss	Nausea/ vomiting	Neutro-penia	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
DOC							
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
GEF							
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
ERL							
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

CI = confidence interval

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 the TAILOR[34] trial have been used directly as shown in Table 42.

Table 42 Grade 3/4 AE incidence rates (%) for second-line chemotherapy in an EGFR M- population (TAILOR trial)

	Diarrhoea	Fatigue	Febrile neutropenia	Hair loss	Nausea/ vomiting	Neutro-penia	Skin rash
DOC							
Mean (%)	1.9	9.6	3.9	14.4	2.9	20.2	0.0
95% CI	0.2 to 5.3	4.8 to 15.9	1.1 to 8.3	8.4 to 21.8	0.6 to 6.8	13.1 to 28.4	0.0 to 2.4
ERL							
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

CI = confidence interval

Active treatment cost estimation

Second-line active treatment doses for docetaxel were calculated individually on the basis of the patient's body surface area (BSA). Calculations are carried out separately for males and females, and a weighted average cost is obtained using the relative proportions of recorded deaths[95] 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 BNF66[54] (July 2013), and the prices reported in eMIT[87] 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

Product	Vial content (mg)	BNF 66 price[54]	eMIT price[87]
		Mean	Mean
DOC*	20	£138.33	£7.93
	80	£454.53	£32.40
	140	£900.00	£39.13
GEF§	per patient	£12,200	£12,200
ERL	30 x 150mg	£1,631.53	£1,631.53
	NHS discount	[redacted]	[redacted]
Dexamethasone*	50 x 2mg	£6.96	£1.80

* best generic price used
§ Patient Access Scheme price per patient applies only to patients receiving treatment beyond 60 days

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[87] prices for docetaxel and co-medication, with BNF[54] 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.

Table 44 Estimated acquisition cost per cycle of chemotherapy

	Estimated cost - BNF 66 prices[54]		Estimated cost - eMIT prices[87]	
Second-line treatment	**Per cycle**	**Per patient**	**Per cycle**	**Per patient**
Docetaxel	£922.81*	N/A	£44.88*	N/A
Erlotinib	[redacted]#	N/A	[redacted]#	N/A
Gefitinib	N/A	£12,200	N/A	£12,200

N/A not applicable * 3-week cycle for docetaxel # 4-week cycle for erlotinib

The unit costs employed for chemotherapy administration, based on NHS Reference Costs 2011/12,[86] 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 out-patient visit.

Table 45 Unit costs of chemotherapy administration

Treatment setting	HRG code	Description	Mean	Standard error*
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
Out-patient visit	NCLFUSFF 370	Medical oncology	£106.00	£10.60*

* 10% of mean assumed HRG=healthcare resource groups

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 out-patient consultations, and periodic diagnostic tests (chest X-ray, CT scan and ECG). During PPS patients are assumed to have been discharged to community-based supportive care where care is provided by the patient's GP (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 46 details the mean volumes of each resource assumed and Table 47 summarises the unit costs employed together with the relevant sources, more detailed information describing cost assumptions is presented in the publication by Brown et al.[2]

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[96]
Chest X-ray	6.79 pa	-	-	Big Lung Trial[96]
CT scan (chest)	0.62 pa	-	-	Big Lung Trial[96]
CT scan (other)	0.36 pa	-	-	Big Lung Trial[96]
ECG	1.04 pa	-	-	Big Lung Trial[96]
Hospital/hospice episode	-	-	8.93 days	Average stay for non-elective long-stay IP episode plus average IP excess days for HRG DZ17A - NHS Reference Costs 2011/12[86]
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[97] Marie Curie report[98]
Clinical nurse specialist	12 hours contact time pa	52 hours contact time pa	-	Appendix 1 of NICE Guideline CG81[97]
GP surgery	12 consultations pa	-	-	Appendix 1 of NICE Guideline CG81[97]
GP home visit	-	26 visits pa	7 visits (alternate days)	Marie Curie report[98]
Therapist visit	-	26 hours pa	-	Appendix 1 of NICE Guideline CG81[97]
Macmillan nurse	-		50 hours	Marie Curie report[98]
Drugs/equipment	-	-	As required	Marie Curie report[98]
Location of terminal care	-	-	Hospital 55.8% Hospice 16.9% Home 27.3%	Office of National Statistics death Tables 5.2 and 12[95]

PFS=progression-free survival, PPS=post-progression survival

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[86]
Chest X-ray	£30.26	NHS Reference Costs 2011/12, code DAPF - direct access plain film[86]
CT scan (chest)	£124.99	NHS Reference Costs 2011-12, HRG code RA12Z (2 areas with contrast)[86]
CT scan (other)	£134.57	NHS Reference Costs 2011-12, HRG code RA13Z (3 areas with contrast)[86]
ECG	£60.73	NHS Reference Costs 2011/12, code EA47Z - direct access ECG[86]
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)[88]
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)[88]
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)[88]
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)[88]
Therapist	£44.00	PSSRU Unit costs of health and social care 2012, page 194 cost per hour (including training)[88]
Terminal care in-patient care	£2,716.53 + 0.84 excess days @ £232.90 per day	NHS Reference Costs 2011/12, code DZ17A (Respiratory Neoplasms with Major CC) Non-elective Inpatient (long stay - episode / excess days)[86]
Terminal care in hospice	25% increase on hospital IP care	Assumption
Macmillan nurse	66.7% of community nurse cost	Assumption
Drugs and equipment	£500	Marie Curie report figure of £240 increased for inflation[98]

pa=per annum

Adverse event cost estimation

The costs of treating Grade 3/4 AEs of second-line therapy are spread over 12 weeks (four cycles) and estimated using NHS Reference Costs for 2011/12,[86] as follows:

Diarrhoea

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.

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 5to7 days costing £2233.40.

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.

Skin rash

It is assumed that a typical patient will have one additional out-patient 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.

Neutropenia (non-febrile)

It is assumed that 10% of patients will require hospital treatment, each requiring two episodes 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 HIV/AIDS with complicating condition) and PA48A (Blood cell disorders with complicating condition) across non-elective long and short-stay episodes and day-case admissions.

Febrile neutropenia

The NICE Decision Support Unit report on the cost of febrile neutropenia[99] has been updated for current NHS Reference Costs.[86] This assumes 1.4 episodes per patient during the second-line treatment. The estimated cost per patient is £7,066.63.

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 response rates 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[100] between 1999 and 2002 attempted to obtain such data (using the EuroQol 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 toward higher values.

One clinical trial with relevant data compared two radiotherapy regimens for poor prognosis patients with NSCLC in 13 Dutch radiotherapy centres.[101] Patients completed EuroQol 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[102] 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.[77] 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 3/4 AEs - neutropenia, febrile neutropenia, fatigue, diarrhoea, nausea and vomiting, hair loss (alopecia) and rash. The range of AEs in the Nafees et al[77] model is sufficient to cover all the major problems experienced with current treatments.

Applying the treatment-specific AE incidence rates (Table 41 and Table 42) and treatment response rates (Table 40) to the Nafees et al[77] 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 of van den Hout et al 2006 study[101] of palliative radiotherapy in patients with NSCLC).

Table 48 Estimated health-related utility values using Nafees model

2nd-line therapy	PFS	PPS (>2 weeks prior to death)	Terminal period (2 weeks)
EGFR M- population (TAILOR trial)			
DOC	0.6225	0.4734	0.2488
ERL	0.6450	0.4734	0.2488
EGFR M- population (WT subgroup of BR.21 trial) and EGFR-unknown population (BR.21 trial)			
ERL	0.6351	0.4734	0.2488
BSC	0.6353	0.4734	0.2488

PFS=progression-free survival, PPS=post-progression survival

Modelling assumptions

Following disease progression it is assumed that subsequent experience of health care (and associated health and social costs) and QoL are 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 vs oral therapy vs 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 confidence intervals 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 probabilisitic sensitivity analysis was carried out and through a probabilistic ICER, a scatterplot of replication incremental costs and QALYs and cost-effectiveness acceptability curves (CEACs).

Beta distributions are employed in both univariate sensitivity analyses and PSA for parameters involving proportions (response rates, AE rates, gender 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.

6.3.2 Results

EGFR M+ 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 concludes that the information made available to the AG in the MS does not allow any formal decision modelling to be undertaken. This is because, at the very least, compatible PFS data and treatment response rates would be required in addition to OS estimates to allow a decision model to be populated.

EGFR M- population

<u>Docetaxel vs erlotinib</u>

Deterministic results from the main EGFR M- model based on data from the TAILOR[34] trial are summarised in Table 49. The estimated survival advantage of using docetaxel rather than erlotinib is 2.5 months - of which 1.5 months occurs prior to disease progression. The corresponding gain in mean discounted QALYs is 0.108 per patient. Despite the substantial reduction in incremental drug acquisition costs, the overall incremental cost per patient is higher for docetaxel use (+£1,652 discounted), due to drug administration costs and treatment of AEs. The estimated ICER of £15,359 per QALY gained is well within the range normally considered to be cost effective. The results of univariate sensitivity analyses are summarised in Figure 11, indicating that these results are unaffected by uncertainty in almost all model parameters. The only exceptions are the price used for docetaxel (the base-case analysis applies the eMIT[87] average NHS price, which is much lower than the BNF66[54] list price), and the incidence of febrile neutropenia when docetaxel is used. It is

noticeable that the reported incidence of grade 3/4 neutropenia and febrile neutropenia in the TAILOR[34] trial are half the values obtained from the pooling of other trials. This could be attributable to improved clinical practice compared to historic trials, or to the availability of a weekly dosing option within the TAILOR[34] trial.

Probabilistic sensitivity analysis incorporating uncertainty in all model parameters indicates a slightly lower estimated ICER of £12,719 per QALY gained. Examination of the PSA scatterplot (Figure 12 using 1000 random simulations), and the cost-effectiveness acceptability curves (Figure 13) indicate strong general confidence that docetaxel is more cost effective than erlotinib in this population (75% of simulations favour docetaxel at a willingness to pay threshold of £20,000 per QALY gained, and 91% at £30,000 per QALY gained).

Table 49 Base-case deterministic cost-effectiveness results for docetaxel vs erlotinib 2nd-line treatment in the EGFR M- population using evidence from the TAILOR trial

		Docetaxel		Erlotinib		Incremental	
		Years	Months	Years	Months	Years	Months
Survival (mean)	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

		Docetaxel		Erlotinib		Incremental	
		Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
QALYs	PFS	0.2546	*0.2535*	0.1853	*0.1850*	0.0693	*0.0685*
	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	0.6100	*0.5939*	0.4984	*0.4863*	0.1116	*0.1076*

		Docetaxel		Erlotinib		Incremental	
		Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
Costs	2L Tx acquisition	£341.77	*£340.44*				
	2L Administration	£2,313.94	*£2,305.09*				
	2L Tx Adverse events	£2,783.27	*£2,783.27*				
	PFS BSC	£1,530.85	*£1,524.30*				
	PPS BSC	£5,147.58	*£4,928.27*				
	Terminal care	£3,917.36	*£3,820.28*				
	Total costs	£16,034.78	*£15,701.64*	£14,302.08	*£14,049.00*	£1,732.69	*£1,652.63*

ICER Cost per QALY gained **£15,359.37**
for docetaxel vs erlotinib

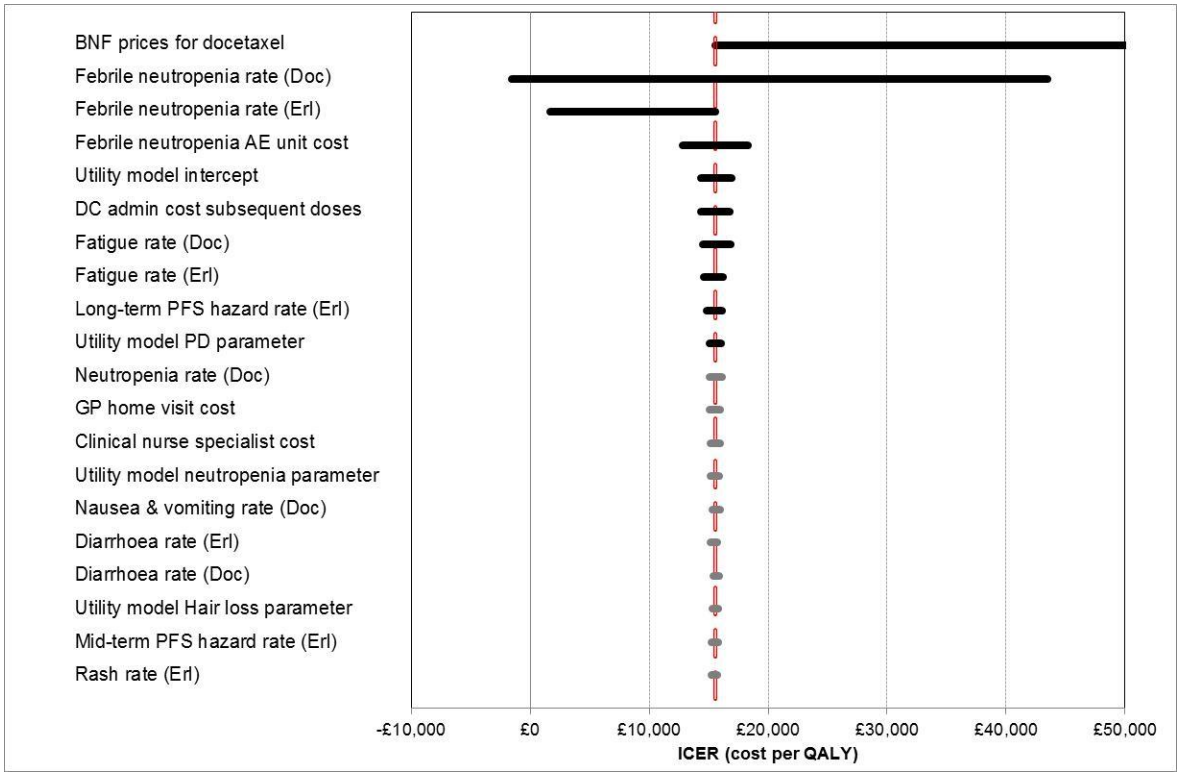

Figure 11 Univariate sensitivity analysis: docetaxel vs erlotinib 2nd-line treatment in the EGFR M- population from the TAILOR trial – 20 most influential parameters

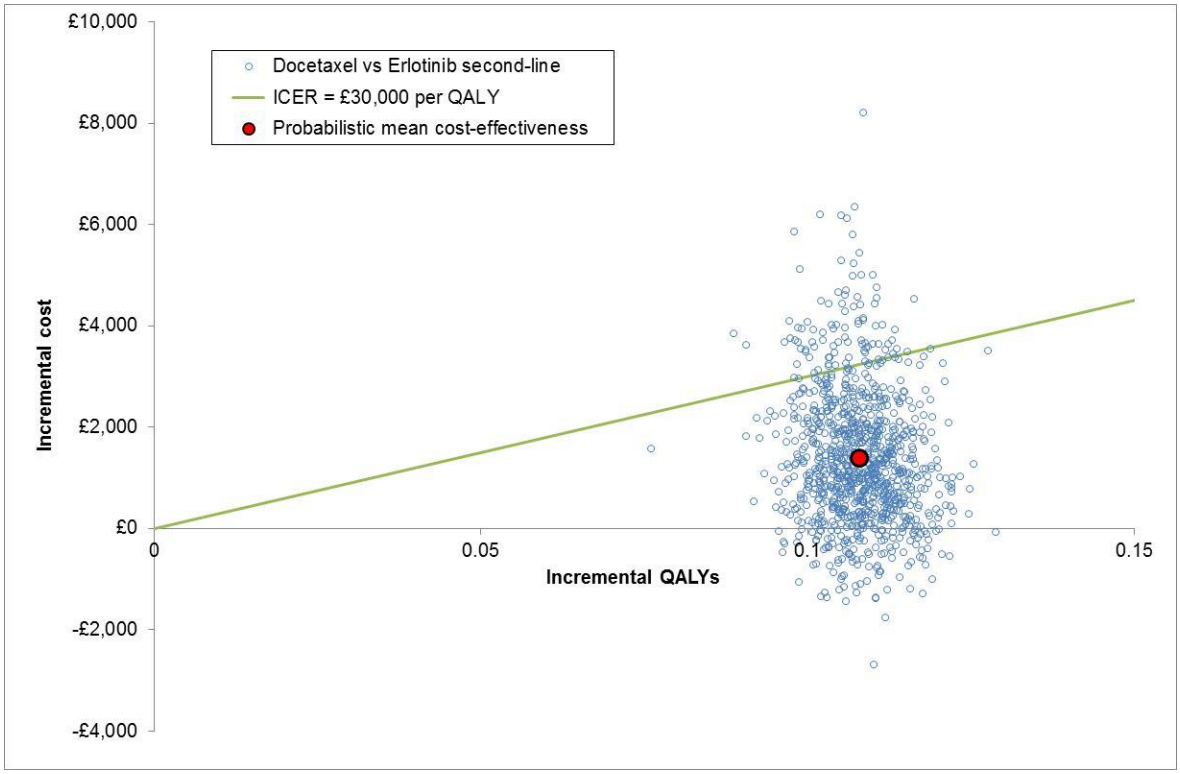

Figure 12 Probabilistic sensitivity analysis: scatterplot of the base-case analysis for docetaxel vs erlotinib 2nd-line treatment in the EGFR M- population using evidence from the TAILOR trial

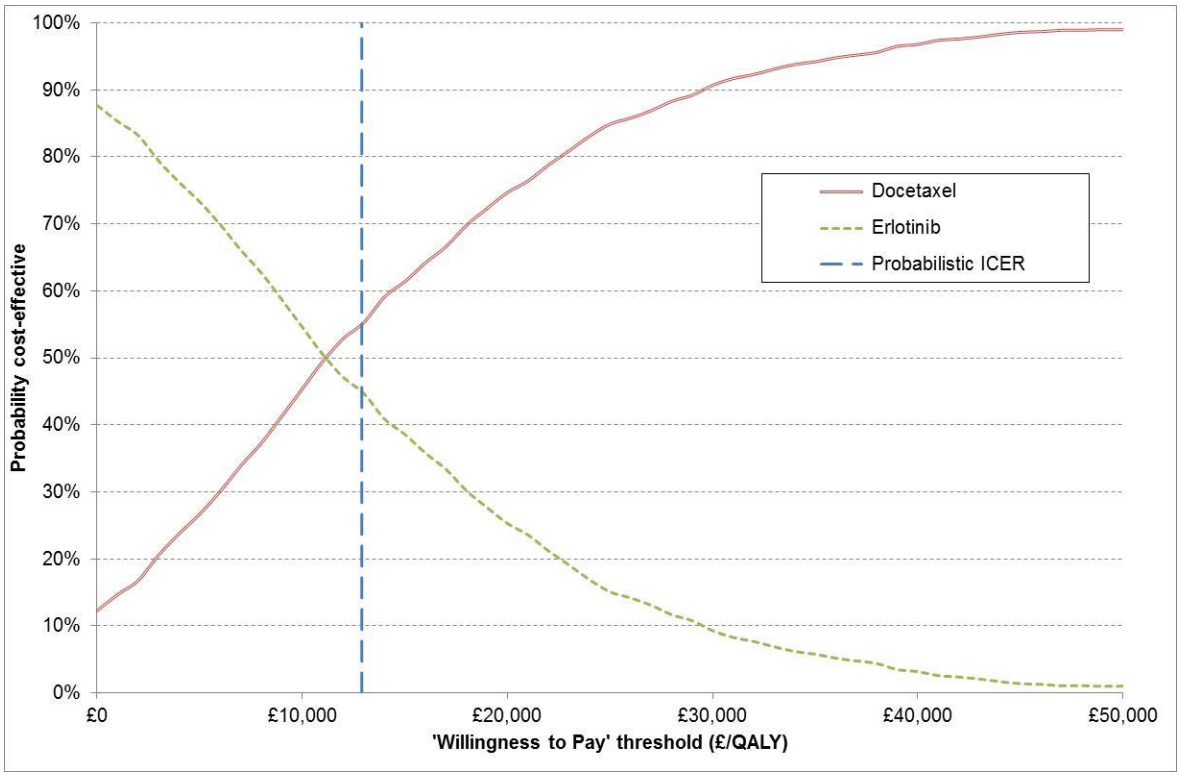

Figure 13 Cost-effectiveness acceptability curves for the comparison of docetaxel vs erlotinib 2nd-line treatment in the EGFR M- population using evidence from the TAILOR trial

Erlotinib vs BSC

The manufacturer of erlotinib submitted a sensitivity analysis of their main economic analysis of the EGFR-unknown population (see below), using survival data from a post-hoc reanalysis[43] 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, i.e. only EGFR M- [or EGFR wild-type (WT)] disease. Inevitably the source data[43] are less reliable than the main ITT analysis of BR.21[31] results due to 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 described above. Figure 14 and Figure 15 show the trajectories fitted to the trial data to populate the decision model.

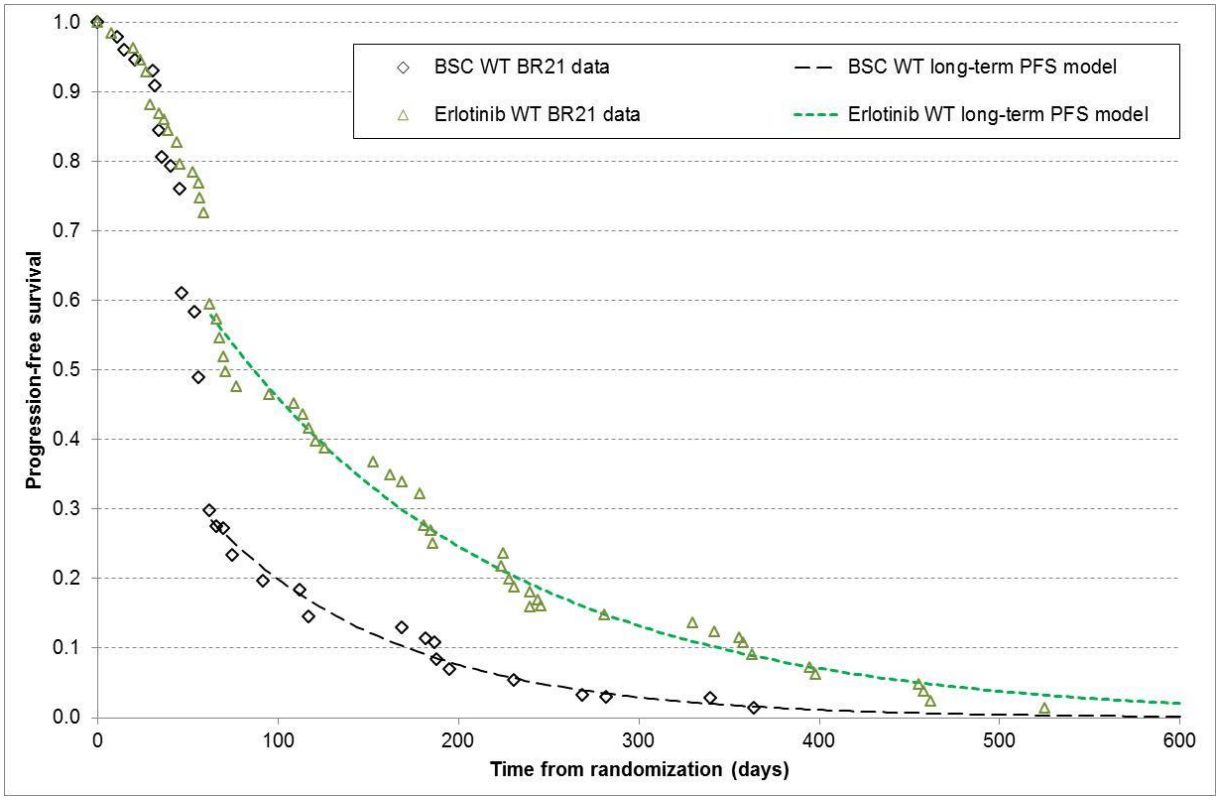

Figure 14 Projective models fitted to PFS data from the EGFR M- subgroup of the BR.21 clinical trial

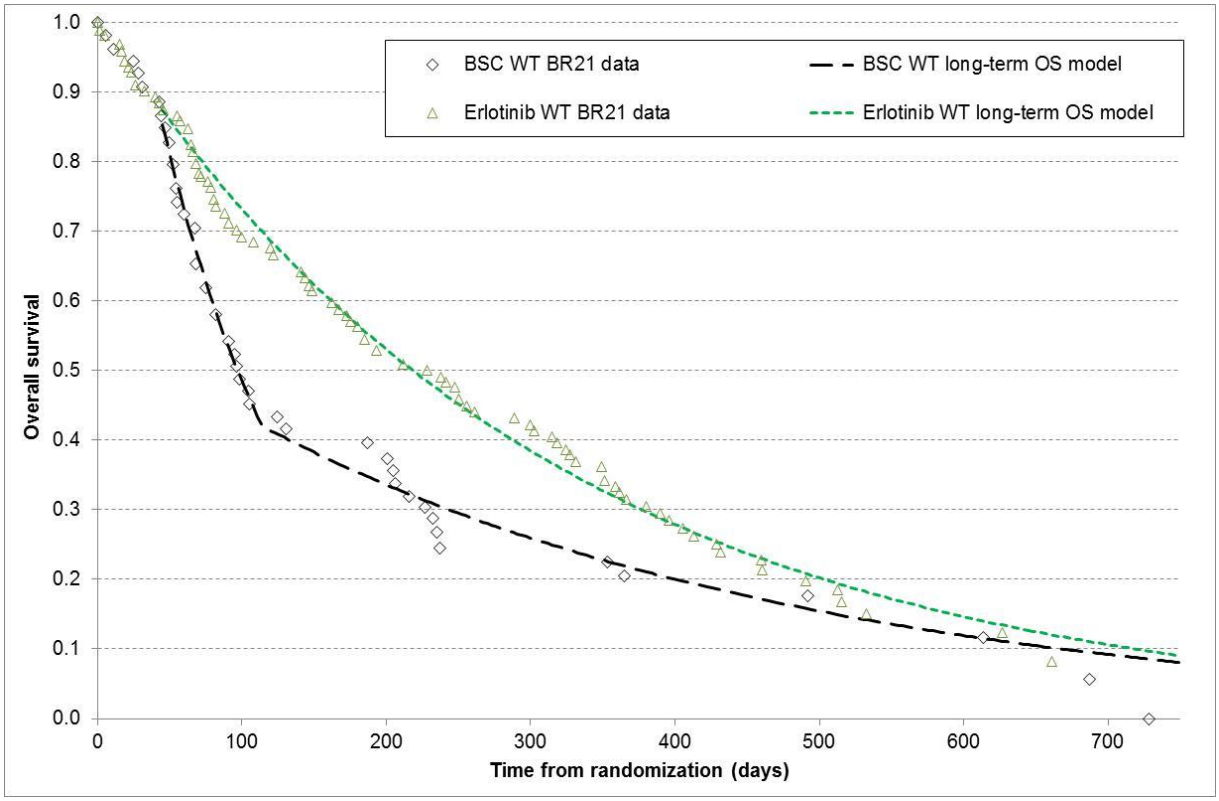

Figure 15 Projective models fitted to OS data from the EGFR M- subgroup of the BR.21 clinical trial

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 2nd-line treatment in the EGFR M- population (EGFR M- subgroup from the BR.21 trial)

		BSC		Erlotinib		Incremental (ERL vs BSC)	
		Years	Months	Years	Months	Years	Months
Survival (mean)	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**

		BSC		Erlotinib		Incremental (ERL vs BSC)	
		Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
QALYs	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*
	Overall	**0.3475**	***0.3416***	**0.4641**	***0.4579***	**0.1167**	***0.1163***

		BSC		Erlotinib		Incremental (ERL vs BSC)	
		Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
Costs	2L Tx acquisition	£0.00	*£0.00*				
	2L Administration	£0.00	*£0.00*				
	2L Tx Adverse events	£533.70	*£533.31*				
	PFS BSC	£827.93	*£827.33*				
	PPS BSC	£2,961.94	*£2,878.02*				
	Terminal care	£3,882.90	*£3,836.73*				
	Total costs	**£8,206.46**	***£8,075.39***	**£14,596.93**	***£14,436.92***	**£6,390.47**	***£6,361.53***

ICER	Cost per QALY gained	**£54,686.73** for erlotinib vs BSC

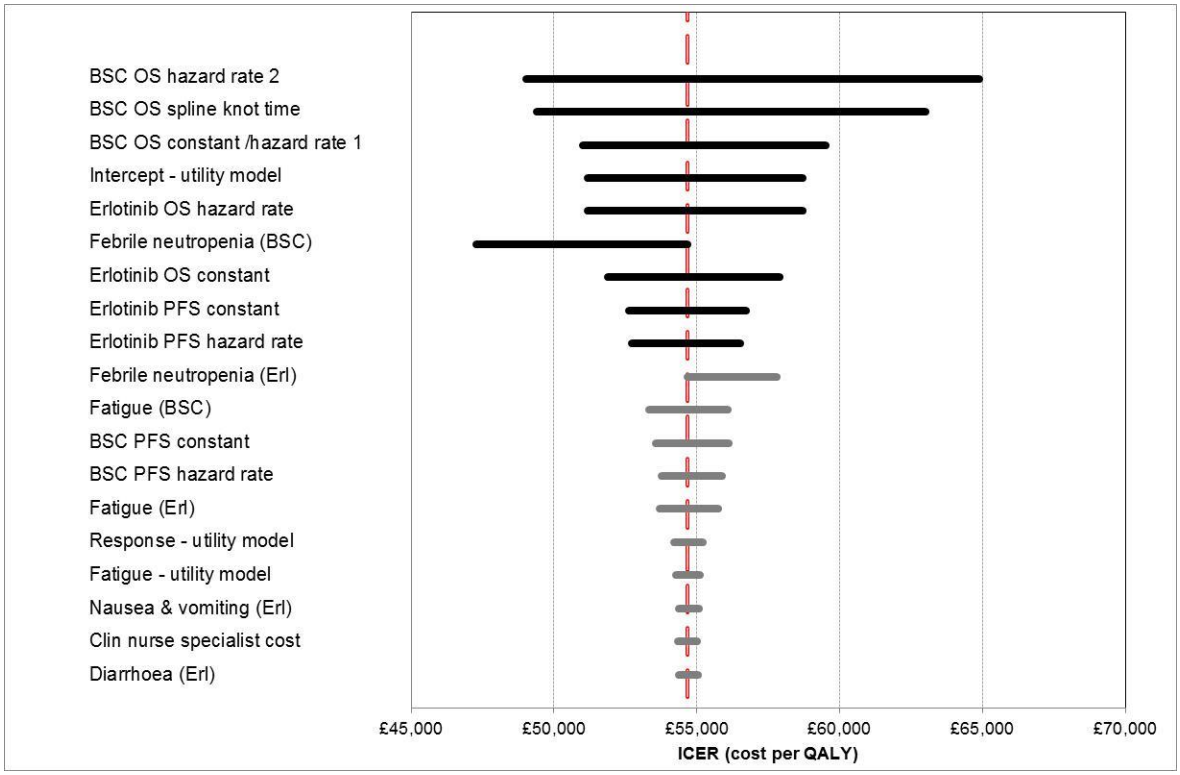

Figure 16 Univariate sensitivity analysis: erlotinib vs BSC 2nd-line treatment in the EGFR M- population subgroup of the BR.21 trial – 20 most influential parameters

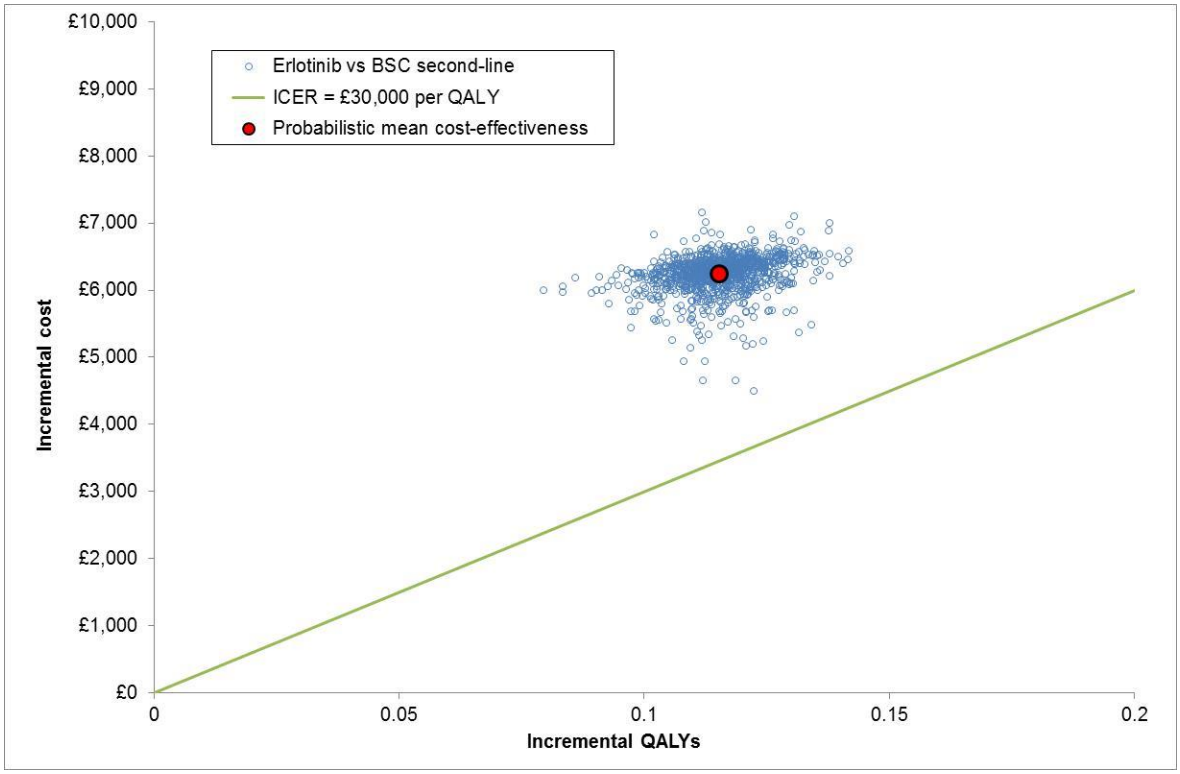

Figure 17 Probabilistic sensitivity analysis: scatterplot of the base-case cost-effectiveness analysis for erlotinib vs BSC 2nd-line treatment in the EGFR M- subgroup of the BR.21 trial

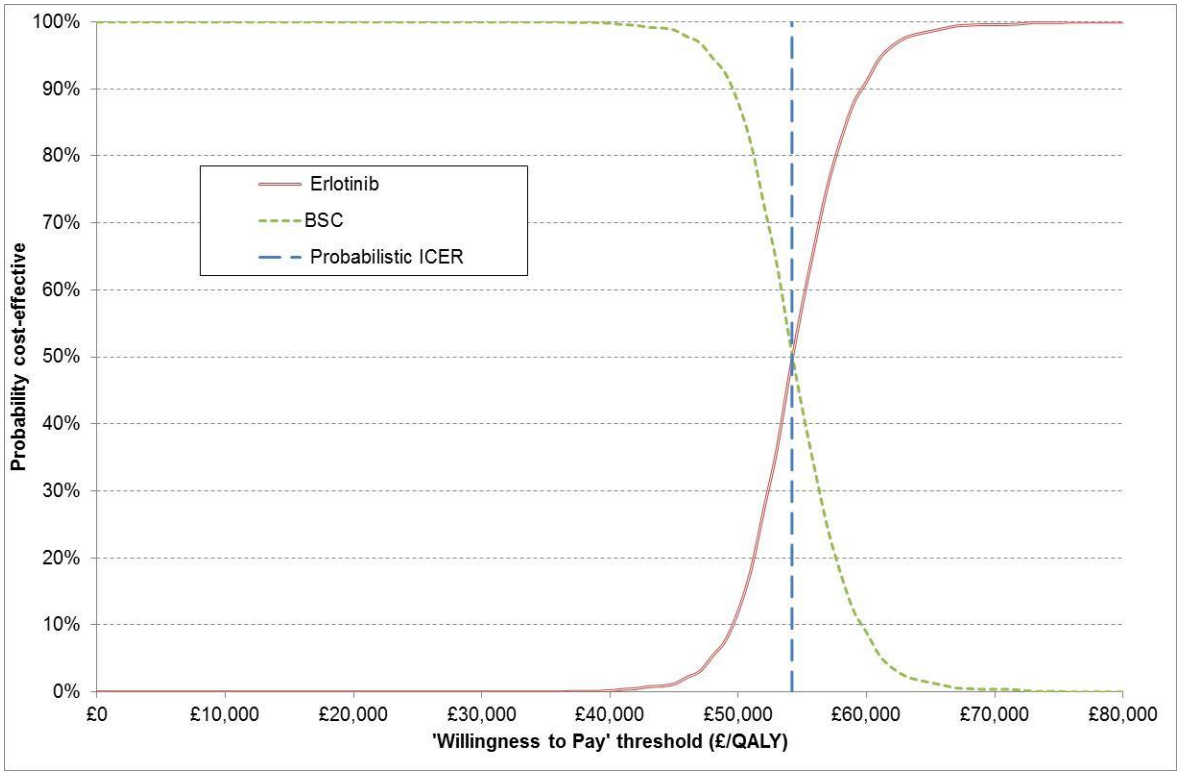

Figure 18 Cost-effectiveness acceptability curves for the comparison of erlotinib vs BSC 2nd-line treatment in the EGFR M- subgroup from the BR.21 trial

EGFR-unknown population

Deterministic results from the EGFR-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 occur 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 (+£6,314 discounted), due primarily to the acquisition cost of erlotinib (+£5,677 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[77] utility model (i.e. the baseline NSCLC population utility value in patients with stable disease), and the incidence of febrile neutropenia when docetaxel is used.

Table 51 Base-case deterministic cost-effectiveness results for erlotinib vs BSC 2nd-line treatment in the EGFR-unknown population using evidence from BR.21 trial

		BSC		Erlotinib		Incremental (ERL vs BSC)	
		Years	Months	Years	Months	Years	Months
Survival (mean)	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**

		BSC		Erlotinib		Incremental (ERL vs BSC)	
		Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
QALYs	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*
	Overall	**0.3491**	***0.3452***	**0.4548**	***0.4484***	**0.1057**	***0.1033***

		BSC		Erlotinib		Incremental (ERL vs BSC)	
		Undiscounted	Discounted	Undiscounted	Discounted	Undiscounted	Discounted
Costs	2L Tx acquisition	£0.00	*£0.00*	[redacted]			
	2L Administration	£0.00	*£0.00*				
	2L Tx Adverse events	£562.53	*£561.77*				
	PFS BSC	£873.25	*£872.06*				
	PPS BSC	£2,853.14	*£2,798.84*				
	Terminal care	£3,938.22	*£3,900.12*				
	Total costs	**£8,227.15**	***£8,132.79***	**£14,610.64**	***£14,446.38***	**£6,383.49**	***£6,313.59***

ICER	Cost per QALY gained	**£61,131.81** for erlotinib vs BSC

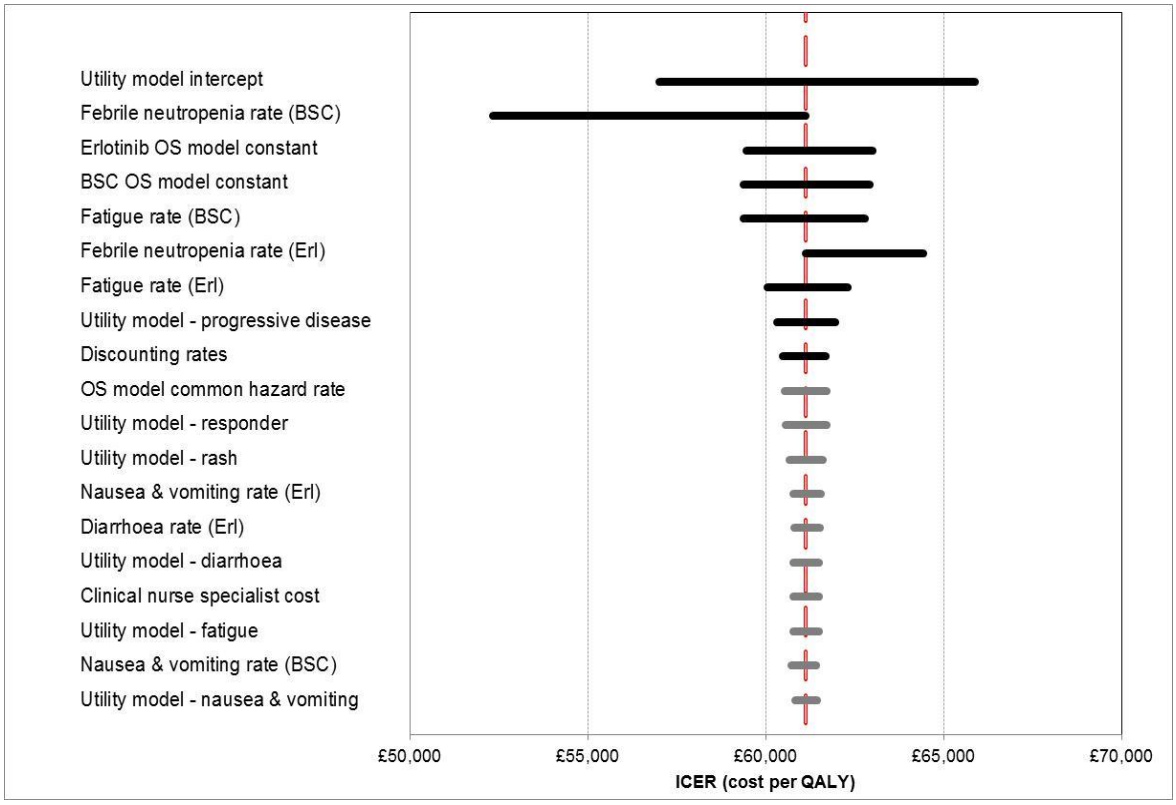

Figure 19 Univariate sensitivity analysis: erlotinib vs BSC 2nd-line treatment in the EGFR-unknown subgroup of the BR.21 trial – 20 most influential parameters

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).

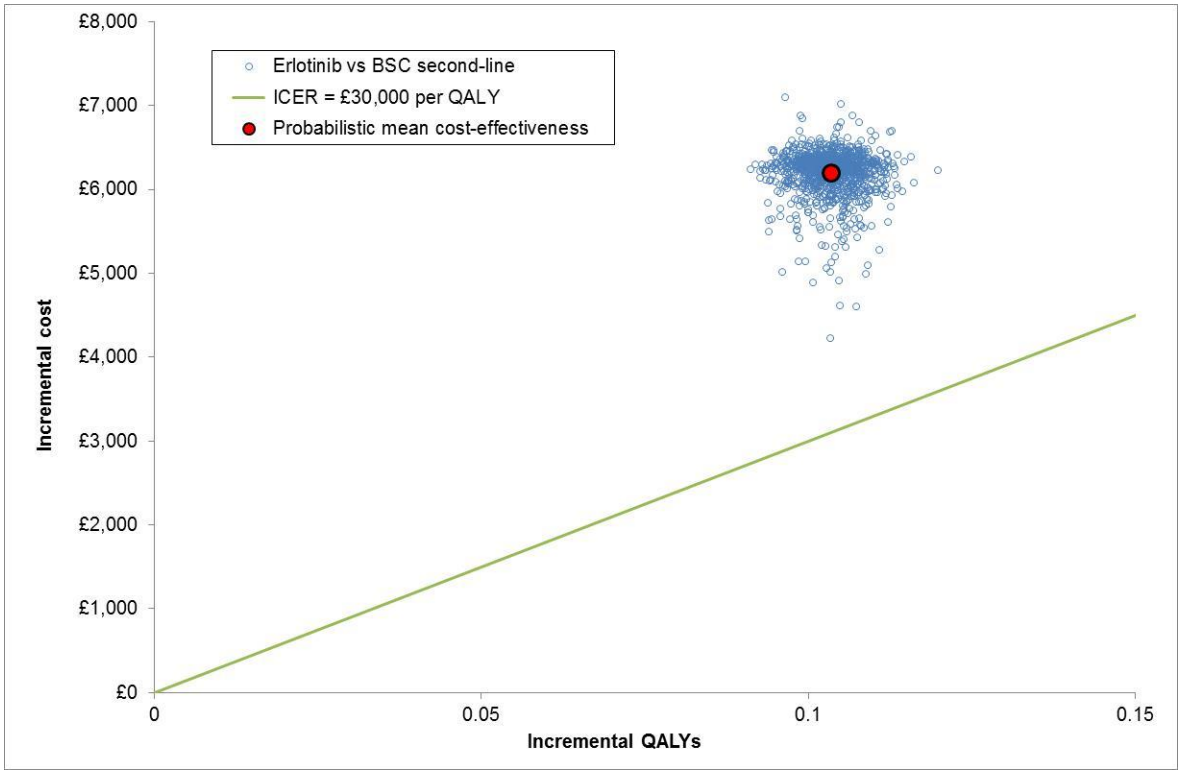

Figure 20 Probabilistic sensitivity analysis: scatterplot of the base-case cost-effectiveness analysis for erlotinib vs BSC 2nd-line treatment in the EGFR-unknown population from the BR.21 trial

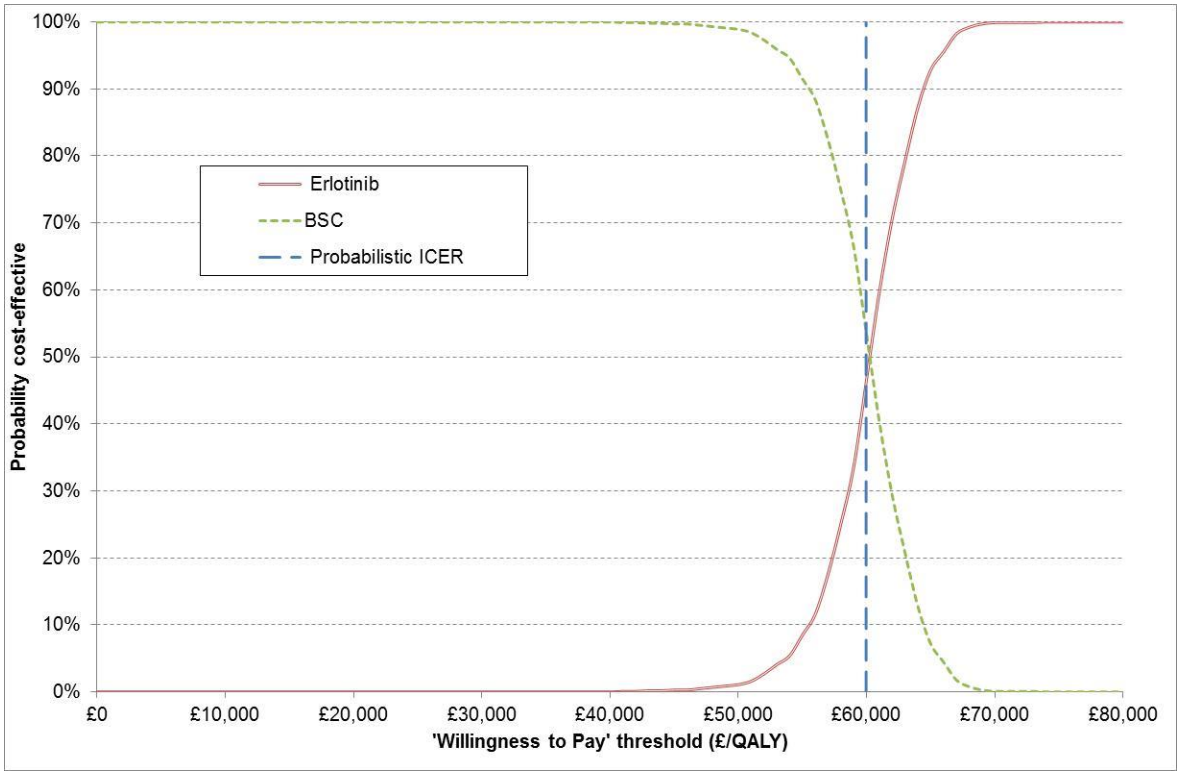

Figure 21 Cost-effectiveness acceptability curves for the base for erlotinib vs BSC 2nd-line treatment of NSCLC in the EGFR-unknown population using results from the BR.21 trial

6.3.3 Summary and discussion of AG 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 only licensed for use 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.

The TAILOR[34] trial comparing the effectiveness of docetaxel monotherapy and erlotinib is the only RCT data currently available in a population with confirmed disease lacking EGFR activating mutations. Cost-effectiveness analysis using data from this trial indicates that a significant survival benefit for docetaxel may be translated into good cost effectiveness over erlotinib (£15,359 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 (ICER rises to over £77,000 per QALY gained). When additional studies are published for the EGFR M- population, it will become clearer whether this result is confirmed or brought into question.

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 only affects 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 'bonus' 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 'bonus' increment at the level which corresponds to returning a patient to the average QoL experienced in the general population at the equivalent mean age (about 0.8). This requires raising the EQ-5D score by 0.155, and increases the estimated ICER of docetaxel vs erlotinib in the EGFR M- population from £15,359 to £26,176 per QALY gained. This result is within the range normally considered cost effective in the NICE Methods Guide[81] - £20,000 to £30,000 per QALY gained. 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.

7 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

This review has highlighted that a key development since TA162[29] 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,[29] 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 docetaxel with erlotinib 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 due to unavailability of testing facilities and inconclusive results.

In patient populations where 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 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.

8 DISCUSSION

8.1 Statement of principle findings

8.1.1 Clinical-effectiveness results

EGFR M+ 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 (INTEREST,[35] ISEL,[40] KIM,[42] TITAN,[41] BR.21,[31] V-15-32[39]). 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.

The manufacturer of gefitinib has presented evidence of an exploratory post-hoc analysis of patients from a first-line trial of gefitinib compared with paclitaxel and carboplatin (IPASS[46,47]). The analysis considered the EGFR M+ subgroup from the chemotherapy arm of the trial and compared OS for those who did or did not receive post-progression TKI treatment. The AG has carried out an exploratory analysis of the OS results presented by the manufacturer and concludes that these data suggest a much longer mean OS than previously reported in trials of either EGFR-TKI treatment or chemotherapy, with an apparent gain of more than [redacted] associated with second-line gefitinib following prior chemotherapy. Whilst this finding is based on a post-hoc analysis of a single trial arm, this treatment regime would represent an important advance on current treatment if findings were replicated in a RCT.

EGFR M- population

The clinical effectiveness data available for the EGFR M- population were derived from an RCT that only randomised EGFR M- patients (TAILOR[34]) and an RCT that was designed to assess clinical outcomes in an EGFR M- population (DELTA[33]). In addition, EGFR mutation status data were retrospectively derived from BR.21,[31] KIM,[42] TITAN,[41] INTEREST[35] and ISEL,[40] 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[35] and ISEL[40] 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 the TAILOR[34] trial and the DELTA[33] trial. The response rate in the TAILOR[34] trial was statistically significantly greater for the docetaxel arm of the trial compared with erlotinib.

EGFR-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[34] only reported 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 to docetaxel, only one of the four trials (ISTANA[36]) reported a statistically significant benefit for gefitinib (using 90% confidence limits). When compared to BSC, gefitinib was reported to have a statistically significant benefit in the ISEL[40] 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 vs gefitinib (KIM[42]) 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.

8.1.2 Cost-effectiveness results

The AG developed a de novo economic model for the specific purpose of this MTA 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 the TAILOR[34] trial. In this comparison docetaxel yielded a survival advantage over erlotinib of 2.5 months, with an incremental QALY gain of 0.108. The overall treatment cost of docetaxel was £1,652 higher than the cost of erlotinib. The AG estimated the size of the docetaxel vs erlotinib ICER to be £15,359 per QALY gained. This ICER is within the range normally accepted to be cost effective. However, if published list prices are used instead of eMIT prices, the ICER increases to over £77,000 per QALY gained. Probabilistic sensitivity analysis incorporating uncertainty in all model parameters indicates a slightly lower ICER of £12,719 per QALY gained.

For the EGFR M- population, the AG also compared erlotinib vs BSC in a sensitivity analysis using data from the post-hoc reanalysis of BR.21[43] described in the MS submitted by Roche. 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 £6,362 higher than the cost of BSC.

The AG estimated the size of the erlotinib vs BSC ICER to be £54,687 per QALY gained. This ICER is above the range normally accepted to be cost effective. Probabilistic sensitivity analysis 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 vs 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 £6,312 higher than the cost of BSC. The AG estimated the size of the erlotinib vs BSC ICER to be £61,132 per QALY gained. This ICER is outside the range normally accepted to be cost effective. Probabilistic sensitivity analysis incorporating uncertainty in all model parameters indicates a slightly lower ICER of £59,973 per QALY gained.

8.2 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 and cost effectiveness of gefitinib and erlotinib in patients who have progressed 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 economic evaluations carried out by the AG where 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 'bonus' 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. The ICER estimated by the AG in this extreme sensitivity analysis (£26,176 per QALY gained) remains within the range normally considered cost effective in the NICE Methods Guide[81] - £20,000 to £30,000 per QALY gained.

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 and cost-effectiveness of relevant treatments. Specifically, the AG was unable to carry out an economic evaluation 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).

8.3 Uncertainties

The results of the recent TAILOR[34] 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 the TAILOR[34] trial and it is as yet uncertain whether the reported PFS benefit seen in an Italian population would be achieved by patients in clinical practice in England and Wales.

The results of the manufacturer's post-hoc analysis of clinical data from the control arm of the IPASS trial, which compared gefitinib with chemotherapy in a first-line setting, appear to suggest a substantial OS benefit of second-line treatment with a TKI following chemotherapy. The AG considers the analysis presented by the manufacturer in the MS to be of interest to the decision problem, however, these findings require careful and detailed validation in a robustly designed RCT before they can be used to inform decision-making in this complex clinical area.

8.4 Other relevant factors

There is a clear and well expressed argument in the MS submitted by Roche that some clinicians are not in favour of a move from oral erlotinib to i.v. docetaxel for patients with NSCLC. In the MS (pg 11) Roche 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)". It is not within the AG's remit to address these concerns. The AG has instead focussed on providing a systematic review of the clinical and cost-effectiveness evidence available and has carried out robust, relevant cost-effectiveness analyses based on its own de novo economic model.

9 CONCLUSIONS

9.1 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 docetaxel vs erlotinib in patients who have progressed 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.

9.2 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 for patients with activating EGFR mutations is weak and not sufficiently robust to inform decision-making.

Even where there is a wealth of evidence available (e.g. EGFR M 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 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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104. Kris M, Mok T, Kim E, Douillard JY, Fukuoka M, Thatcher N. 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. European Journal of Cancer, Supplement. 2009; 7 (2-3):505-6.
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11 APPENDICES

Appendix 1: Literature search strategies

OVID MEDLINE 1946 to April Week 3 2013

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**

OVID EMBASE 1974 to April 26 2013

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 April 28 2013

#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 April 28 2013

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

Filters: Clinical Trial, Publication date from 2010/01/01 to 2013, Humans, English

Search details:

(("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

Trial	Randomisation			Baseline Comparability		Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawals		ITT	Other outcomes
	Truly random	Allocation concealment	Number stated	Presented	Achieved*			Assessors	Administration	Participants	Procedure assessed	>80% in final analysis	Reasons stated		
Bhatnagar 2012[a]	NS	NS	✔	✕	NS	✔ ✕	NS	NS	NS	NS	NS	NS	NS	NS	Unclear
BR.21 2005	✔	✔	✔	✔	✔	✔	NS	✔ [c]	✔ [c]	✔	NS	✔	✔	✔	✕
DELTA 2013[a]	✔	NS	✔	✕	NS	✔	NS	NS	NS	✕	NA	NS	NS	NS	Unclear
INTEREST 2008	✔	✔	✔	✔	✔	✔	✔	NS	✕	✕	NA	✔	✔	✔	✕
ISEL 2005	✔	✔	✔	✔	✔	✔	NS	NS	✔	✔	NS	✔	✔	✔	✕
ISTANA 2010	NS	NS	✔	✔	✔	✔	NS	NS	✕	✕	NA	✔	✔	✔	✕
Kim 2012[b]	NS	NS	✔	Unclear	Unclear	✔	NS	NS	✕	✕	NA	✔	NA	Unclear	✕
LI 2010	NS	NS	✔	✔	✔	✔	✔	NS	NS	NS	NS	✔	NS	NS	✕
SIGN 2006	Unclear	✔	✔	✔	✔	✔	✔	✕	✕	✕	NA	✔	✔	✔	✕
TAILOR 2013	✔	✔	✔	✔	✔ ✕[f]	✔	NS	✔ ✕[d]	✕	✕	NA	✔	✔	✔	✕
TITAN 2012	✔	✔	✔	✔	✔ ✕	✔	NS	✕	✕	✕	NA	✔	✔	✔	✕
V-15-32 2008	NS	NS	✔	✔	✔	✔	NS	✔ ✕[e]	✕	✕	NA	✔	✔	✔	✕

NA=not applicable, NS=not stated, ✔ = yes, ✔ ✕= partially,
[a] abstract only, [b] no details presented for historical control group, [c] assumed from 'double-blind', [d] two independent radiologists, masked to treatment assignment, did post-hoc reviews of all the scans of responding patients, [e] primary ORR results that were based on investigator judgment were generally consistent with those obtained from independent response evaluation committee assessment
f differences between groups for smokers and non-smokers and adenocarcinoma

Appendix 3: Table of included studies and associated publications

Trial	Associated publications
Bhatnagar	Bhatnagar AR, Singh DP, Sharma R, Kumbhaj P. Docetaxel versus geftinib in patients with locally advanced or metastatic NSCLC pretreated with platinum-based chemotherapy. Journal of Thorac Oncol 2012, 3):S159.
BR.21	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. Annual Meeting Proceedings of the American Society of Clinical Oncology 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	Okano Y AM, Asami K, Fukuda M, Nakagawa H, Ibata H, Kozuki T, 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) ASCO 2013, Chicago. Journal of Clinical Oncology.
INTEREST	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(9652) 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	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. Journal of Thorac Oncol 2006,1(8):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	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(15S part I):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.

KIM	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 2010,1
LI	Li H, Wang X, Hua F. Second-line treatment with gefitinib or docetaxel for advanced non-small cell lung cancer. [Chinese]. Chinese Journal of Clinical Oncology. 2010, 37:16-8.
SIGN	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]. Annual Meeting Proceedings of the American Society of Clinical Oncology.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 (4) 401-9
TAILOR	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. Clinical 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). 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 Oncology. 2013, 14:981-8.*
TITAN	Ciuleanu T, Stelmakh L, Cicens S, Gonzlez EE. Efficacy and safety of erlotinib verus 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. The Lancet Oncology. 2012, 13:300-8.
V-15-32	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. Annals of Oncology : 2009, 20:1483-8.

*paper published after searches were completed

Appendix 4: Table of excluded publications with rationale

Full reference	Reason for exclusion
2012 Chicago Multidisciplinary Symposium in Thoracic Oncology. Journal of Thorac Onc 2012,4).	Not 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(36):5247-56.	Sub-group 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). European Journal of 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(10):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(5-6):423-9.	Not 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 (Structured abstract). Health Technology Assessment Database 2005 (1).	Not RCT
Augustovski F, Pichon Riviere A, Alcaraz A, Bardach A, Ferrante D, Garcia Marti S, *et al*. Gefitinib for advanced lung cancer treatment (Structured abstract). Health Technology Assessment Database 2005 (1).	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(13):2946-54.	No relevant comparator
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) [abstract]. Proceedings of the American Society of Clinical Oncology 2002,21 (Pt 1):299a, Abstract 1195.	No relevant comparator
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 (Project record). Health Technology Assessment Database 2009 (1).	Not RCT
Erlotinib for the treatment of non-small cell lung cancer (Structured abstract). Health Technology Assessment Database 2008 (1).	Not RCT
Erlotinib improves symptoms as well as survival in NSCLC. Oncology Report 2005(FALL):99-100.	Not RCT
Erlotinib: new drug. Non small-cell lung cancer: like gefitinib, no established advantage. Prescrire international 2006,15(83):86-9.	Review
Erratum: 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. Clinical Lung Cancer 2011,12(4):258.	No relevant comparator
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(18s):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. Journal of Thorac Onc 2006,1(4):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) [abstract]. Proceedings of the American Society of Clinical Oncology 2002,21 (Pt 1):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(12):2237-46.	No relevant comparator
Fukuoka. Erratum: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol (June 15, 2003) 21 (2237-2246)). J Clin Oncol 2004,22(23):4811.	Erratum
Gefitinib for advanced or metastatic non-small cell lung cancer (Structured abstract). Health Technology Assessment Database 2004 (1):4.	Review
Gefitinib for inoperable or recurrent non-small cell lung cancer (Structured abstract). Health Technology Assessment Database 2004 (1).	Review
Gefitinib for the second-line treatment of locally advanced or metastatic non-small-cell lung cancer (terminated appraisal) (Structured abstract). Health Technology Assessment Database 2009 (1).	Not RCT
Gefitinib: a second look. Non-small cell lung cancer: still very disappointing. Prescrire international 2009,18(102):145-7.	Review
Gefitinib: Disappointing. Prescrire International 2006,15(83):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(1):70-3.	No relevant comparator
Health technology assessment of erlotnib (Tarceva) for palliative treatment of non-small cell lung cancer - accelerated assessment (Structured abstract). Health Technology Assessment Database 2005 (1).	Review
Highlights from: The 2009 annual meeting of the american society of clinical oncology. Clinical Lung Cancer 2009,10(4):217-22.	Review
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 2008,112(5):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(3):294-300.	Not RCT
Iressa for non-small cell lung cancer - Early Warningon New Health Technology 2002 1(2) (Structured abstract). Health Technology Assessment Database 2002 (1).	Non-English abstract
Iressa for NSCLC - horizon scanning review (Structured abstract). Health Technology Assessment Database 2002 (1):4.	Review
Johnson DH, Arteaga CL. Gefitinib in recurrent non-small-cell lung cancer: an IDEAL trial? J Clin Oncol. 2003,21(12):2227-9.	Editorial
Kris MG, Natale RB, Herbst RS, Lynch Jr TJ, 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(16):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]. Proceedings of the American Society of Clinical Oncology 2002,21 (Pt 1):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]. Annals of Oncology 2009,19(Supplement 8):109-10.	No relevant outcome

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. Annals of Oncology 2008,19 (S8):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. Journal of Thorac Onc. 2012,7(2):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 2010,1).	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. Pharmacoepidemiology and 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). Journal of Cancer Research & Clinical Oncology 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(3):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 Resistance Updates 2011,14(3):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]. Proceedings of the American Society of Clinical Oncology 2002,21 (Pt 1):292a, Abstract 1167.	No relevant comparator
Niho S. V15-32 and INTEREST. [Japanese]. Japanese Journal of Lung Cancer 2009,49(6):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. Cancer & chemotherapy 2004,31(4):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. Current Medical Research and Opinion 2006,22(3):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(3):556-60.	Not RCT
Reinmuth N, Thomas M. An approach to personalized medicine: The BATTLE trial. Clinical Investigation 2011,1(5):699-705.	No relevant comparator
Robinson DM, Keating GM, Perry CM. Erlotinib. American Journal of Cancer 2005,4(4):247-52.	Review
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 2012,1).	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. Annals of Oncology 2008,19 (S8):viii93.	Not 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(4):231-5.	Not RCT
Sequist LV, Muzikansky A, Engelman JA. A new BATTLE in the evolving war on cancer. Cancer Discovery 2011,1(1):14-6.	Review
Sim EHA, Yang IA, Fong K, Wood-Baker R, Bowman R. Gefitinib for advanced non-small cell lung cancer. Cochrane Database of Systematic Reviews	Protocol

2007,(4)(CD006847).	
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. [German] Tyrosinkinase-Hemmer Erlotinib (Tarceva) verlangert das Uberleben von mehrfach vorbehandelten Patienten. Krankenpflege Journal 2004,42(5-6):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(14):2350-7.	Sub-group analysis
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(7):1042-7.	No relevant outcome
Zielinski SL, Travis K. Randomized trial of gefitinib for advanced lung cancer closed early. Journal of the National Cancer Institute 2005,97(10):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 (Bianic[103] and Kris[104]) and a third (Guo[105]) was a Chinese language publication with an English abstract and data extraction tables in English. These latter three reviews did not lend themselves well to the quality assessment exercise. In the three full publications, the reporting quality was high, these reviews however pooled data from the included trials. The AG considers this pooling to be inappropriate.

Quality criterion	Bianic *et al*. (2011)*	Guo *et al*. (2011)**	Hawkins *et al*. (2008)	Jiang *et al*. (2011)	Kris *et al*. (2009)*	Petrelli *et al*. 2012
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	✔	✔	✔	✔	✔	✔
Was the search strategy adequate and appropriate?	NS	✔	✔	✔ ✕b	NS	✔
Were preventative steps taken to minimize 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? Where preventative steps taken to minimize bias and errors in the QA process?	NS	✔	✔	✔	NS	✕
Were preventative steps taken to minimize 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	✕a	✕a	unclear	✕a
Do the authors' conclusions accurately reflect the evidence that was reviewed?	Unclear from abstract	Unclear from abstract	✔ ✕a	✕a	Unclear from abstract	✕a

*abstract data only, **Chinese language with English abstract, a AG does not agree that studies should be pooled. Conclusions of review concur with procedures but AG is of opinion that MA is flawed, b only PubMed and CENTRAL databases were searched

Table of identified systematic reviews: summary

Review	Title	Patient population	Stated purpose and studies included	Main conclusions
Bianic (2011)*[103]	Network meta-analysis of second and third-line treatments on overall response and overall survival in patients with metastatic non-small cell lung cancer. European Journal of Cancer 47: S616-S617.	Metastatic NSCLC who have progressed after 1st-line treatment	To perform a network meta-analysis of recommended 2nd/3rd-line treatments for overall response and survival in metastatic NSCLC. Included seven RCTs: JMEI, TAX317, V-15-32, INTEREST, ISTANA, ISEL, BR.21	Evidence for 2nd/3rd 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)	Gefitinib for non-small cell lung cancer: a meta-analysis. Chinese Journal of Lung Cancer 14, 351-7	1st- and 2nd- 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 [106](2008)	Time to broaden our horizons, the case for network meta-analysis within relapsed non-small cell lung cancer (NSCLC). Annals of Oncology 19 (S8): viii115.	Locally advanced/metastatic NSCLC who have progressed after 1st-line treatment	Network meta-analysis of six RCTs including SIGN, JMEI, TAX317, BR.21, INTEREST, 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)[107]	Gefitinib versus docetaxel in previously treated advanced non-small-cell lung cancer: A meta-analysis of randomized controlled trials. Acta Oncologica 50(4): 582-588.	Previously treated NSCLC	to compare the efficacy, quality of life (QOL),symptom improvement and toxicities of gefitinib with docetaxel in previously treated advanced NSCLC. Analysis of four RCTs: ISTANA, V-15-32, INTEREST, SIGN	Although similar for OS and PFS, gefitinib showed an advantage over docetaxel in terms of objective response rate, QOL and tolerability. Therefore, gefitinib is an important and valid treatment option for previously treated advanced NSCLC patients.
Kris (2009)*[104]	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." European Journal of Cancer, Supplement 7 (2-3): 505-	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)[108]	Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated nonsmall-cell lung cancer: A meta-analysis of 13 randomized trials. Clinical Lung Cancer. 2012, 13:107-14.	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, V-15-32	Selecting patients with NSCLC for EGFR mutations and offering them an EGFR-TKI results in a better response rate 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.

*conference abstract

Appendix 6: Data abstraction tables

Key inclusion and exclusion criteria of included trials

Trial	Key inclusion criteria	Key exclusion criteria
Bhatnagar 2012[a]	Locally advanced/metastatic NSCLC previously treated with cisplatin -based chemotherapy Progressive/recurrent disease ECOG 0-2	NS
BR.21 2005	≥18 years ECOG 0 TO 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 hematologic and biochemical values	prior breast cancer, melanoma, or hypernephroma other malignant diseases (except basal-cell skin cancers) within five years Symptomatic brain metastases
DELTA 2013 [a]	stage IIIB or IV (AJCC version 6) previously treated with one or two chemotherapy regimens including at least one platinum agent evaluable or measurable disease ECOG 0-2.	NS
INTEREST 2008	≥18 years locally advanced or metastatic NSCLC at least one previous platinum-based chemotherapy regimen (1 to 2 regimens allowed) WHO 0–2 measurable or non-measurable disease by RECIST no previous EGFR TKI adequate hepatic function	NS
ISEL 2005	>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 0–2 (PS 3 if PS not due to 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	>18 years stage IIIB or IV NSCLC one previous platinum-doublet chemotherapy WHO 0 to 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
Kim 2012[b]	stage IIIB or IV NSCLC failure of first-line chemotherapy adequate organ function ≥ one measurable lesion ≥18 years WHO PS 0 to 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 5 4 weeks
Li 2010	Advanced NSCLC failed first-line CTX	NR
SIGN 2006c	stage IIIB or IV progression after first-line chemotherapy ≥18 years WHO PS 0 to 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)

Trial	Key inclusion criteria	Key exclusion criteria
		unresolved toxicity from previous therapy laboratory values outside requested limits psychiatric disorder that may affect completion of the FACT-L questionnaire
TAILOR 2013	WT EGFR NSCLC previously treated with a first line platinum-based regimen no previous taxanes no previous EGFR drugs >ECOG 2 adequate vital functions	NR
TITAN 2012	Patients with disease progression during first-line treatment in SATURN trial Recurrent or metastatic NSCLC. ECOG PS 0 to 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	≥20 years stage IIIB to IV prior treatment with one or two chemotherapy (1 platinum-based) ≥3 months life expectancy WHO PS 0 to 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

*based on conference abstract CNS=central nervous system, RECIST= Response evaluation criteria in solid tumours

Appendix 7: Details of probabilistic sensitivity analysis – survival model parameters

All survival parameters are assumed to be drawn from normal distributions.

TAILOR trial: OS model

Parameters (monthly)	Estimate	Standard error	Lower 95% confidence level	Upper 95% confidence level
1st spline knot (S1)	1.95859	0.09800	1.76442	2.15277
2nd spline knot (S2)	6.46245	0.14348	6.17816	6.74675
Hazard rate –phase 1 (R1)	0.06972	0.00226	0.06525	0.07420
Hazard rate –phase 2 (erlotinib) (R2E)	0.16142	0.00342	0.15465	0.16820
Hazard rate –phase 2 (docetaxel) (R2D)	0.10000	0.00177	0.09651	0.10350
Hazard rate –phase 3 (R3)	0.06118	0.00136	0.05849	0.06388

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

TAILOR trial: PFS model

Parameters (monthly)	Estimate	Standard error	Lower 95% confidence level	Upper 95% confidence level
Zero time hazard (S0)	0.02216	0.00424	0.01384	0.03048
1st spline knot (S1)	1.71743	0.01793	1.68229	1.75257
2nd spline knot (S2)	2.88616	0.03963	2.80848	2.96385
Hazard rate –phase 1 (R1)	0.14308	0.00466	0.13395	0.15222
Hazard rate –phase 2 (erlotinib) R2E)	0.71455	0.01608	0.68303	0.74607
Hazard rate –phase 2 (docetaxel) (R2D)	0.42007	0.00939	0.40167	0.43848
Hazard rate –phase 3 (erlotinib) (R3E)	0.25035	0.01025	0.23025	0.27044
Hazard rate –phase 3 (docetaxel) (R3D)	0.17527	0.00497	0.16554	0.18501

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

BR.21 trial: Time to Off Treatment

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

Correlation	Intercept	Hazard rate
Intercept	1	-0.878
Hazard rate		1

BR.21 trial (ITT): OS model

Parameters (daily)	Estimate	Standard error	Lower 95% confidence level	Upper 95% confidence level
BSC intercept (B)	0.42445	0.02050	0.38371	0.46519
Erlotinib intercept (E)	-0.02941	0.02048	-0.07011	0.01128
Common hazard rate (R)	0.00320	0.00005	0.00311	0.00330

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

BR.21 trial (ITT): PFS model

Parameters (daily)	Estimate	Standard error	Lower 95% confidence level	Upper 95% confidence level
BSC intercept (B)	1.46083	0.05163	1.35702	1.56464
Erlotinib intercept (E)	0.14557	0.05047	0.04409	0.24705
Common hazard rate (R)	0.00664	0.00015	0.00634	0.00694

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

BR.21 trial (WT): Erlotinib OS model

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

Correlation	Intercept	Hazard rate
Intercept	1	-0.856
Hazard rate		1

BR.21 trial (WT): BSC OS model

Parameters (monthly)	Estimate	Standard error	Lower 95% confidence level	Upper 95% confidence level
BSC phase 1 intercept (A)	-0.30146	0.05571	-0.41539	-0.18752
BSC phase 1 hazard rate (R1)	0.31157	0.02270	0.26515	0.35799
Spline knot time (S)	3.75313	0.19346	3.35747	4.14880
BSC phase 2 hazard rate (R2)	0.07890	0.00414	0.07043	0.08737

Correlation	A	R1	S	R2
A	1	-0.957	0.574	0.000
R1		1	-0.708	0.000
S			1	-0.466
R2				1

BR.21 trial (WT): Erlotinib PFS model

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

Correlation	Intercept	Hazard rate
Intercept	1	-0.882
Hazard rate		1

BR.21 trial (WT): BSC PFS model

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

Correlation	Intercept	Hazard rate
Intercept	1	-0.885
Hazard rate		1