NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Submission of evidence by Boehringer Ingelheim on the use of afatinib in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating Epidermal Growth Factor Receptor (EGFR) mutation(s)

November 2013

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Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 10.1 to 10.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

-of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with ‘see appendix X’. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, ‘Trial 123/Jones et al.[126]’ rather than ‘One trial[126]’).

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 11.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

- *The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.*

Afatinib, marketed as Giotrif, is an irreversible tyrosine kinase inhibitor (TKI), which differs to currently available reversible targeted therapies in that it irreversibly blocks the ErbB family of receptors. This means that afatinib blocks EGFR (ErbB1) as well as the other relevant members of the ErbB family, all of which can be involved in pathways that help tumour cells grow, migrate and metabolise. Investigation of the clinical relevance of afatinib's unique mode of action, which could potentially lead to a greater effect on the tumour, has provided the basis for initiation of the LUX-Lung trial programme.

Positive opinion for afatinib was granted from the EMA on 25th July. Marketing Authorisation is anticipated for the 30 September 2013. Pending regulatory authority approval, commercial stock is anticipated to be available in November 2013.

- *The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.*

Afatinib is available as film coated tablets in strengths of 50mg, 40mg, 30mg and 20mg. There will be 28 tablets per pack, with tablets taken orally once daily. Patients are expected to continue treatment continuously until disease progression or intolerable adverse events.

Anticipated NHS list price per pack of 28 tablets will be £2,023.28.

In the event of intolerable or prolonged adverse events, patients and clinicians may consider reducing the dose before considering permanent discontinuation.

- *The indication(s) and any restriction(s).*

CHMP positive opinion was received for afatinib (GIOTRIF) from EMA on 25/07/13 and states the following:

GIOTRIF as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naive adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s).

- *The main comparator(s).*

Recent data (IMS 2013) has shown that 99% of eligible patients receive either erlotinib or gefitinib as a first line treatment, both of which are recommended as first-line treatments by NICE.

Both erlotinib and gefitinib are EGFR TKIs, and given the high use of EGFR TKIs as a first line treatment, the opportunity to use an EGFR TKIs as a second line treatment in a TKI-naive patient population is unlikely. Any patients not receiving a TKI in 1st line might be expected to be treated with erlotinib is a likely 2nd line option.

- *Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.*

There are two phase III randomized controlled trials (RCTs) (LUX-Lung 3 and LUX-Lung 6) that support the use of afatinib in the anticipated indication. Supporting data also comes from the phase II single arm LUX-Lung 2 study. These trials are described in Section 6.

LUX-Lung 3 and LUX-Lung 6 evaluated the safety and efficacy of afatinib in the first-line setting. The efficacy of afatinib in first line patients was also explored in the LUX-Lung 2 non-randomised study, which allowed the enrolment of treatment naive patients following a protocol amendment. The LUX-Lung 2 non randomised study also evaluated the efficacy of afatinib in the second line setting in patients who were TKI-naive but had received chemotherapy in the first line.

No direct head-to-head data is available between afatinib and the other currently available reversible EGFR TKIs, erlotinib and gefitinib. Therefore a mixed-treatment comparison (MTC) incorporating a network meta-analysis was undertaken to establish the relative efficacy and safety of erlotinib, gefitinib and afatinib in Section 6.7.

- *The main results of the RCTs and any relevant non-RCT evidence.*

LUX-Lung 3 was a phase III open label trial in first line EGFR mutation-positive patients with stage IIIB/IV adenocarcinoma of the lung. 345 patients were randomised in a 2:1 ratio to receive continuous afatinib 40mg once daily (n=230), or a chemotherapy platinum doublet of cisplatin (75mg/m^2) and

pemetrexed (500mg/m^2) every 21 days, for up to 6 cycles (n=115). The primary end point was PFS, as determined by independent blinded review.

Afatinib treatment significantly increased median PFS compared to chemotherapy (11.1 months versus 6.9 months, respectively [HR=0.58, 95% CI 0.43-0.78; p<0.001]). Results in all patients showed an objective response rate (ORR) of 56.1% in the afatinib arm compared to 22.6% in the chemotherapy arm, by independent review (p<0.001).

In addition, a higher proportion of patients in the afatinib arm experienced an improvement of ≥10 points in HRQoL scores (a change that is accepted as the threshold for being clinically meaningful (Osoba et al. 2006)) using the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire for the three pre-specified NSCLC-related symptoms as compared to chemotherapy. Overall, 52% of patients receiving afatinib needed a dose reduction while 19% required two dose reductions. Discontinuation rates due to treatment-related AEs in the trial were 7.9% in the afatinib arm and 11.7% in the chemotherapy arm.

Additional evidence for the use of afatinib in TKI-naive EGFR mutation-positive patients is derived from the LUX-Lung 6 phase III multi-centre open label randomised controlled trial, conducted in Asia. The objective of this trial was to compare the efficacy and safety of 1st line afatinib treatment with cisplatin plus gemcitabine chemotherapy in patients with advanced adenocarcinoma of the lung (stage IIIB/IV) harbouring activating EGFR mutations. 364 patients were randomised in a 2:1 ratio to receive continuous afatinib 40mg once daily (n=242), or a chemotherapy platinum doublet of gemcitabine (1,000 mg/m^2) on day 1 and day 8 and cisplatin (75mg/m^2) on day 1 of each 21 day cycle, for up to 6 cycles (n=122). The primary endpoint was PFS by independent review.

PFS was significantly increased in the afatinib treatment group compared to chemotherapy (11.0 months versus 5.6 months, respectively [HR =0.28, 95% CI 0.20-0.39; p<0.0001] by independent review). ORR and DCR were also higher in the afatinib group compared to chemotherapy.

Furthermore, a higher proportion of afatinib-treated patients experienced ≥10 point improvements in HRQoL scores using the EORTC questionnaire, for the three pre-specified NSCLC-related symptoms, compared to chemotherapy. Improvements in global health status/QoL were observed in 63% of patients in the afatinib arm versus 33% in the chemotherapy arm (p<0.0001). Diarrhoea (88.3%, grade 3: 5.4%) and rash or acne (80.8%, grade 3: 14.2%) were the two most frequently observed AEs associated with afatinib treatment. 27% of patients receiving afatinib needed a dose reduction while 6% required two dose reductions. Discontinuation rates due to treatment-related AEs in the trial were 5.9% in the afatinib arm and 39.8% in the chemotherapy arm.

These data were used along with data from 18 other studies identified through a systematic review to construct the mixed-treatment comparison (MTC) incorporating a network meta-analysis.

The main results of the MTC are shown in Figure 1 and Figure 2, which show the hazard ratios for progressions free survival (PFS) and overall survival (OS) for afatinib compared to pemetrexed with cisplatin, gemcitabine with cisplatin, gefitinib, and erlotinib.

Figure 1 show that afatinib has statistically significantly better PFS outcomes relative to the combination of pemetrexed with cisplatin and gemcitabine with cisplatin. Relative to gefitinib and erlotinib, there is a non-significant trend in favour of afatinib. Figure 2, which is based on the current immature overall survival (OS) data for afatinib, shows a trend favouring afatinib compared with all four comparators. Further results from the MTC are presented in Section 6.7.

Figure 1 Estimated hazard ratios for PFS from the MTC

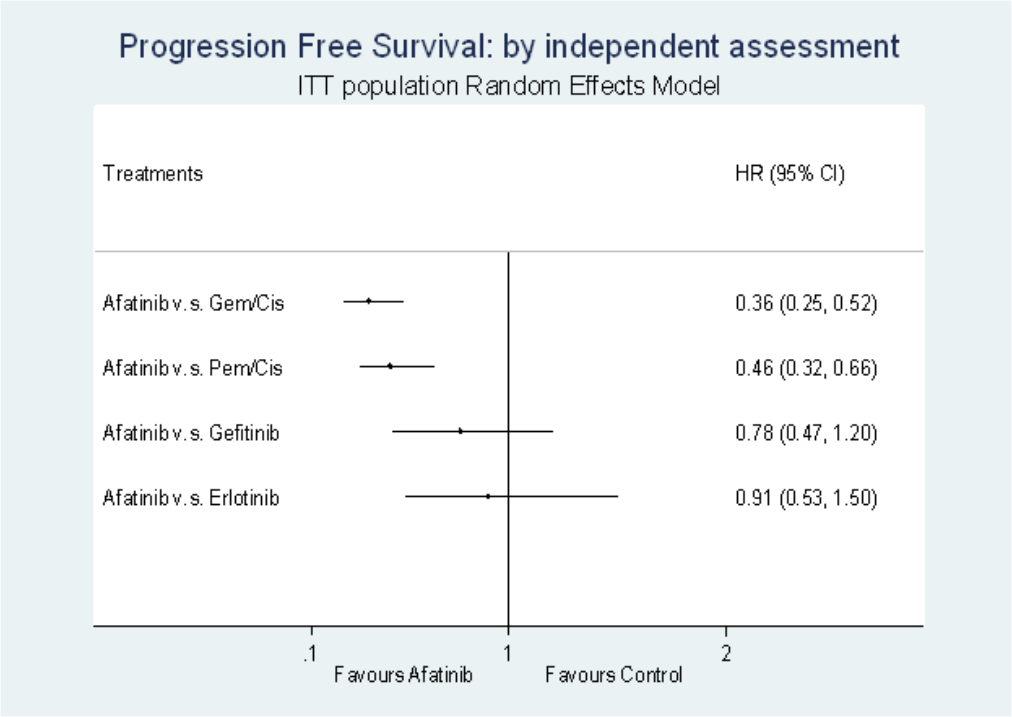
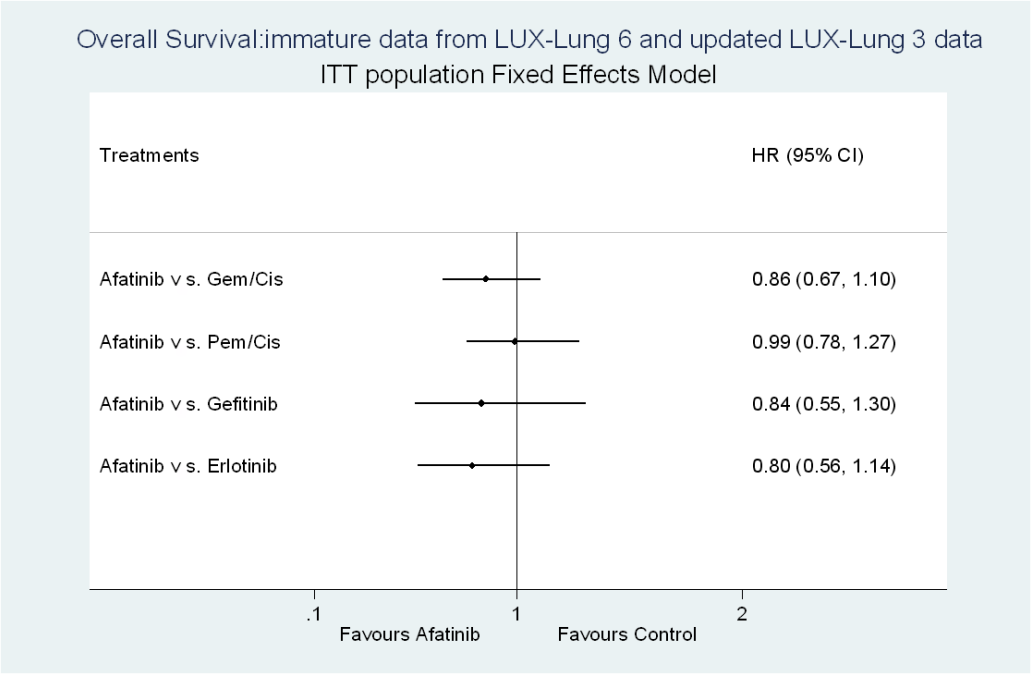


Figure 2 Estimated hazard rations for OS from the MTC



- *In relation to the economic evaluation, details of:*

  the type of economic evaluation and justification for the approach used

  the pivotal assumptions underlying the model/analysis

  the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.

A cost-utility analysis was undertaken to assess the cost-effectiveness of afatinib across its anticipated licensed indication. The main focus of the analysis is on 1st line use in patients who are EGFR TKI naive as this is the vast majority of patients that fail within the anticipated license.

The economic model is based predominantly on evidence from the LUX-Lung 3 and the MTC. The model is a disease-state cohort model which utilises the partitioned survival method to determine the proportion of patients in each of the three health states in each model cycle (Progression Free Disease, Progressed Disease, and Death). Both the model structure and health states are characteristic of modelling in metastatic oncology and have been used in previous NICE STAs and MTAs (NICE 2010c, NICE 2011, Hoyle et al. 2011). The model has been designed for the UK, and both the model structure and parameterisation aims to reflect UK clinical practice.

The sensitivity analysis in Section 7.7 shows that the key drivers behind the results are the assumptions around progression-free survival and overall survival. In particular, these are the values that compare afatinib to erlotinib and gefitinib derived from MTC. Due to their central important in the analysis, we have taken steps to ensure that the MTC is a robust analysis that uses standard and recognised techniques, validated software (WinBUGS), and

have ensured that the analysis is in line with previous submission to NICE in this indication (NICE 2010, NICE 2012) and NICE guidelines on the methods of technology appraisal (NICE 2013).

Results from the cost-effectiveness analysis are summarised in Table 1 and are based on the anticipated list price.

Table 1 Basecase cost-effectiveness results from Section 7

	Afatinib	Gefitinib	Erlotinib
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
LYG	2.55	2.29	2.22
LYG difference	N/A	0.26	0.33
QALYs	1.59	1.42	1.42
QALY difference	N/A	0.17	0.17
ICER	N/A	[redacted]	[redacted]

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand Name: Giotrif

Approved Name: Afatinib

Therapeutic Class: Antineoplastics; Protein Kinase Inhibitor

1.2 What is the principal mechanism of action of the technology?

Afatinib is a selective and irreversible inhibitor of all cancer-relevant homo- and heterodimers formed by the ErbB family members: epidermal growth factor receptor (EGFR; also termed ErbB1), human epidermal growth factor receptor 2 (HER2; also termed ErbB2), ErbB3 and ErbB4. EGFR and HER2 receptors are implicated in the development and progression of cancer. The role of ErbB4 in oncogenesis is less clear, but it may be involved in the inhibition of cell growth.

Irreversible binding of an agent is believed to help extend its efficacy and delay the development of resistance, whereas targeting more than one family member of the ErbB family may improve efficacy and overcome redundancy associated with receptor crosstalk.

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current

UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Afatinib does not currently have a UK Marketing Authorization. A Marketing Authorisation Application was submitted to the European Medicines Agency (EMA) on 19 September 2012 and Marketing Authorization is anticipated 30 September 2013.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

Not applicable.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

CHMP positive opinion was received for afatinib (Giotrif) from the EMA on 25/07/13 and states the following (EMA 2013):

Giotrif as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naive adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s)

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

There are two phase III randomized controlled trials (RCTs) (LUX-Lung 3, and LUX-Lung 6) that support the use of afatinib in this indication. Supporting data also comes from the phase II single arm LUX-Lung 2 study.

LUX-Lung 3 and LUX-Lung 6 evaluated the safety and efficacy of afatinib in the first-line setting for patients who were TKI-naive. The efficacy of afatinib in first and second line patients was also explored in the LUX-Lung 2 non-randomised study.

The LUX-Lung 2 and LUX-Lung 3 studies were submitted to the regulatory authorities as part of the Marketing Authorisation application. The results of the LUX-Lung 6 study were not yet available at the time of making the

Marketing Authorisation application. These have since been used to address questions by the regulatory authorities. Thus, this data will be used as supporting evidence in this submission.

LUX-Lung 2 (Yang et al. 2012, BI 2011)

The use of afatinib in TKI-naive patients was initially investigated in the proof-of-concept, single arm, phase II LUX-Lung 2 study. This trial explored afatinib use in 129 patients with advanced or metastatic adenocarcinoma of the lung whose tumours harboured activating EGFR mutations. Initially only patients who had progressed after one line of chemotherapy were included (n = 61); however a subsequent protocol amendment allowed the inclusion of treatment-naive patients (n = 68). In a second protocol amendment the initial starting dose of afatinib was reduced from 50mg to 40mg daily, to optimise the balance between efficacy and safety. Of the patients who received afatinib as a first line treatment in this study, 23 were treated with 40mg, and 38 were treated with 50mg afatinib daily. Treatment cycles (4 weeks in length) continued until disease progression, intolerable adverse events, or if patients withdrew.

The primary endpoint of this study was the proportion of patients with a confirmed objective response as determined by RECIST 1.0 confirmed by independent review. Secondary efficacy endpoints included disease control rates (DCR), progression free survival (PFS) and overall survival (OS).

Irrespective of line of treatment, 79 (61%) patients had an objective response by independent review and 78 (60%) by investigator assessment. The confirmed objective response rate (ORR) and DCR in the 61 patients who received afatinib as first line therapy were 66% and 87% respectively, by independent review. The median PFS in this group of patients was 12.0 months (95% CI, 8.21–15.64) by independent review, and the median OS had not yet been reached, although the lower 95% CI was 22 months.

The confirmed ORR and DCR in patients who received first line afatinib at the 40mg starting dose were 60.9% and 78.3% respectively, whereas the median PFS and OS were 11.9 months and 23.1 months, respectively.

In this study drug related adverse events (AEs) were experienced by 128 of 129 patients. Diarrhoea and skin-related events were the most frequently observed AEs in afatinib treated patients, regardless of line of therapy, or starting dose. However, the occurrence of both types of adverse events was substantially lower when patients received 40 mg of afatinib as an initial dose. Although the incidence of AEs was comparable in first line patients who received the 40mg and 50mg afatinib starting dose, CTCAE grade 3 adverse events were reported less frequently in patients receiving the 40mg afatinib starting dose (47.8%) than in those receiving the 50mg starting dose (73.7%).

Of the 61 patients receiving afatinib as first line therapy, 39.1% of patients on the 40mg starting dose and 71.1% of patients on the 50mg starting dose had

an AE that required a dose reduction, and 15.8% and 30.4% respectively had an AE that led to drug discontinuation.

In summary, this proof-of-concept phase II study suggested that afatinib is active in the first line treatment of patients with adenocarcinoma of the lung harbouring EGFR mutations. Although only a small proportion of patients were treated with afatinib 40 mg daily, the 40 mg starting dose was better tolerated then the 50mg dose, and there appeared to be no difference in efficacy according to starting dose. The findings of this study provided the rationale for further phase III studies of afatinib in first line patients with EGFR mutations, at a starting dose of 40 mg.

LUX-Lung 3 (Sequist et al. 2013, Yang et al. 2013, BI 2012)

The key RCT data supporting the use of afatinib in TKI-naive EGFR mutation-positive patients are derived from the LUX-Lung 3 study.

LUX-Lung 3 was a phase III open label trial in 1st line EGFR mutation-positive patients with stage IIIB/IV adenocarcinoma of the lung. 345 patients were randomised in a 2:1 ratio to receive continuous afatinib 40mg once daily (n=230), or a chemotherapy platinum doublet of cisplatin (75mg/m^2) and pemetrexed (500mg/m^2) every 21 days, for up to 6 cycles (n=115). The primary end point was PFS, as determined by independent blinded review.

Afatinib treatment significantly increased median PFS compared to chemotherapy (11.1 months versus 6.9 months, respectively [HR=0.58, 95% CI 0.43-0.78; p<0.001]).

Results in all patients showed an objective response rate (ORR) of 56.1% in the afatinib arm compared to 22.6% in the chemotherapy arm, by independent review (p<0.001). The median duration of these responses was 11.1 months for afatinib, compared to 5.5 months for chemotherapy.

In addition, a higher proportion of patients in the afatinib arm experienced an improvement of ≥10 points in HRQoL scores (a change that is accepted as the threshold for being clinically meaningful (Osoba et al. 1998)) using the EORTC questionnaire for the three pre-specified NSCLC-related symptoms as compared to placebo:

- 67% of patients in the afatinib arm experienced ≥10 point improvements in HRQoL scores relating to cough compared to 60% in the chemotherapy arm (p=0.2444)

- 64% of patients in the afatinib arm experienced ≥10 point improvements in HRQoL scores relating to dyspnoea compared to 50% in the chemotherapy arm (p=0.0103)

- 59% of patients in the afatinib arm experienced ≥10 point improvements in HRQoL scores relating to pain compared to 48% in the chemotherapy arm (p=0.0513)

Diarrhoea (all grades: 95.2%, ≥ grade 3: 14.4%) and rash or acne (all grades: 89.1%, ≥ grade 3: 16.2%) were the two most frequently observed AEs associated with afatinib treatment.

Overall, 52% of patients receiving afatinib needed a dose reduction to less than 40mg per day with 19% having two dose reductions. Discontinuation rates due to treatment-related AEs in the trial were 7.9% in the afatinib arm and 11.7% in the chemotherapy arm.

LUX-Lung 6 (Wu et al. 2013; Geater et al. 2013, BI 2013)

Additional evidence for the use of afatinib in TKI-naive EGFR mutation-positive patients is derived from the LUX-Lung 6 phase III multi-centre open label randomised controlled trial, conducted in Asia. The objective of this trial was to compare the efficacy and safety of 1st line afatinib treatment with cisplatin plus gemcitabine chemotherapy in patients with advanced adenocarcinoma of the lung (stage IIIB/IV) harbouring activating EGFR mutations. 364 patients were randomised in a 2:1 ratio to receive continuous afatinib 40mg once daily (n=242), or a chemotherapy platinum doublet of gemcitabine (1,000 mg/m^2) on day 1 and day 8 and cisplatin (75mg/m2) on day 1 of each 21 day cycle, for up to 6 cycles (n=122). The primary endpoint was PFS by independent review.

PFS was significantly increased in the afatinib treatment group compared to chemotherapy (11.0 months versus 5.6 months, respectively [HR =0.28, 95% CI 0.20-0.39; p<0.0001] by independent review). ORR and DCR were also higher in the afatinib group compared to chemotherapy:

- ORR of 66.9% in the afatinib arm versus 23.0% in the chemotherapy arm, by independent review (p<0.0001)

- DCR of 92.6% in the afatinib arm versus 76.2% in the chemotherapy arm, by independent review (p<0.0001).

Furthermore, a higher proportion of afatinib-treated patients experienced ≥10 point improvements in HRQoL scores using the EORTC questionnaire, for the three pre-specified NSCLC-related symptoms, compared to chemotherapy:

- 76% of patients in the afatinib arm experienced ≥10 point improvements in HRQoL scores relating to cough compared to 55% in the chemotherapy arm (p=0.0003)

- 71% of patients in the afatinib arm experienced ≥10 point improvements in HRQoL scores relating to dyspnoea compared to 48% in the chemotherapy arm (p<0.0001)

- 64% of patients in the afatinib arm experienced ≥10 point improvements in HRQoL scores relating to pain compared to 47% in the chemotherapy arm (p=0.003).

Overall, improvements in global health status/QoL were observed in 63% of patients in the afatinib arm versus 33% in the chemotherapy arm (p<0.0001). Diarrhoea (all grade: 88.3%, grade 3: 5.4%) and rash or acne (all grade 80.8%, grade 3: 14.2%) were the two most frequently observed AEs associated with afatinib treatment.

Overall, 27% of patients receiving afatinib needed one dose reduction while 6% required two dose reductions. Discontinuation rates due to treatment-related AEs in the trial were 5.9% in the afatinib arm and 39.8% in the chemotherapy arm.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

A Marketing Authorisation application for afatinib was submitted to the EMA on 19 September 2012, and Marketing Authorization is anticipated 30 September 2013. Pending regulatory authority approval, commercial stock is anticipated to be available from 30th October 2013.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Afatinib received FDA regulatory approval on 12th July 2013 under the trade name Gilotrif. In the USA, Gilotrif is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test.

Gilotrif was also granted approval for “First line EGFR mutation positive NSCLC” in Taiwan on 1st Aug 2013 and “treatment of locally advanced or metastatic NSCLC that express the EGFR gene mutation” in Mexico on 9th Sept 2013.

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

A submission to the Scottish Medicines Consortium (SMC) was made on 5 August 2013 and final guidance is expected to be published on the SMC website by 9 December 2013.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 2 Unit costs of technology being appraised

Pharmaceutical formulation	Film coated tablets in strengths of 50mg, 40mg, 30mg and 20mg.
Acquisition cost (excluding VAT)	NHS list price per pack of 28 tablets = £2,023.28
Method of administration	Oral
Doses	Initiation on 40mg tablet once daily with dose-adjustment based on tolerability, with treatment until disease progression or intolerable adverse events.
Dosing frequency	Once daily
Average length of a course of treatment	The average length of afatinib treatment is estimated to be 11.1 months based on PFS results from the LUX-Lung 3 trial; a PFS of 11.0 months for patients was demonstrated in the LUX-Lung 6 trial.
Average cost of a course of treatment	Anticipated NHS list price per course of treatment is expected to be around £22,000 per patient, based on a PFS of 11 months. This would be expected to be less in patients that have withdrawn from treatment due to intolerable adverse events.
Anticipated average interval between courses of treatments	Afatinib is administered continuously until disease progression or undue toxicity. Patients are therefore only expected to undergo one course of afatinib treatment.
Anticipated number of repeat courses of treatments	Afatinib is administered continuously until disease progression or undue toxicity. Patients are therefore only expected to undergo one continuous course of afatinib treatment with interruptions only for AE management according to the AE management dose reductions and interruptions schedule (see below – dose adjustments)
Dose adjustments	The starting afatinib dose is 40mg daily. In the event of prolonged or intolerable CTCAE grade 2 adverse events, or grade ≥3 adverse events, the recommendation is to interrupt afatinib treatment until the event has returned to baseline or grade ≤1. The recommendation is to then re-introduce afatinib at a dose reduced by 10mg. Two further dose reductions are permitted, after which permanent discontinuation should be considered. If after treatment interruption adverse events do not return to baseline within 14 days then the drug should be discontinued. Supportive care guidance will be provided for specific adverse events.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

EGFR mutation testing will be necessary to identify the NSCLC patients with EGFR activating mutations that are eligible for treatment with afatinib under its current indication of use. At present, EGFR testing is standard practice in

England and Wales when making decisions about the first-line treatment of locally advanced or metastatic NSCLC (NICE 2012).

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

No.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

None.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

The Disease Course (NHS Choices, 2013)

There are two main types of lung cancer. These are classified by the type of cells in which the cancer starts. They are:

- non-small cell lung cancer (of which there are three different types, called squamous cell carcinoma, adenocarcinoma and large cell carcinoma)
- small cell lung cancer.

Lung cancer does not usually cause noticeable symptoms until it has spread through much of the lungs or into other parts of the body. This is known as advanced or metastatic lung cancer. This means that the outlook for lung cancer is poor compared with other types of cancer (see Section 2.3 for estimated life expectancy).

The type of treatment for lung cancer depends on several factors, including:

- the type of lung cancer (non-small cell or small cell)
- the size and position of the cancer
- how far advanced the cancer is (the stage)
- overall health of the patient.

Depending on the type of cancer and how advanced it is, the patient may receive a combination of these treatments:

- surgery
- radiotherapy
- chemotherapy.

Small tumours (stages 1 or 2) can often be removed with surgery. The patient may have chemotherapy after surgery to reduce the chances of the cancer returning. In less healthy patients, radiotherapy may be used as an alternative.

Larger tumours (stage 3) may also be suitable for surgery, in which case chemotherapy and/or radiotherapy may be used before surgery. However, if

the tumour is too large to be removed, surgery won't be performed, and radiotherapy and/or chemotherapy will be used. If the cancer has spread to other parts of the lung or body (stage 4), chemotherapy or radiotherapy will be used to try and shrink the tumour.

A new group of drugs is emerging, which work in a different way to chemotherapy. They are given in tablet form, and are known as "targeted agents" because they block certain processes in the cancer cells. For patients with activating Epidermal Growth Factor Receptor (EGFR) mutation(s), EGFR-TKI treatments, such as afatinib, erlotinib, and gefitinib, may be used.

NSCLC within the Population

According to the National Lung Cancer Audit Report (2012), 83.3% of all lung cancers in the UK were of NSCLC histology (lung cancer cases excluding small cell and mesothelioma).

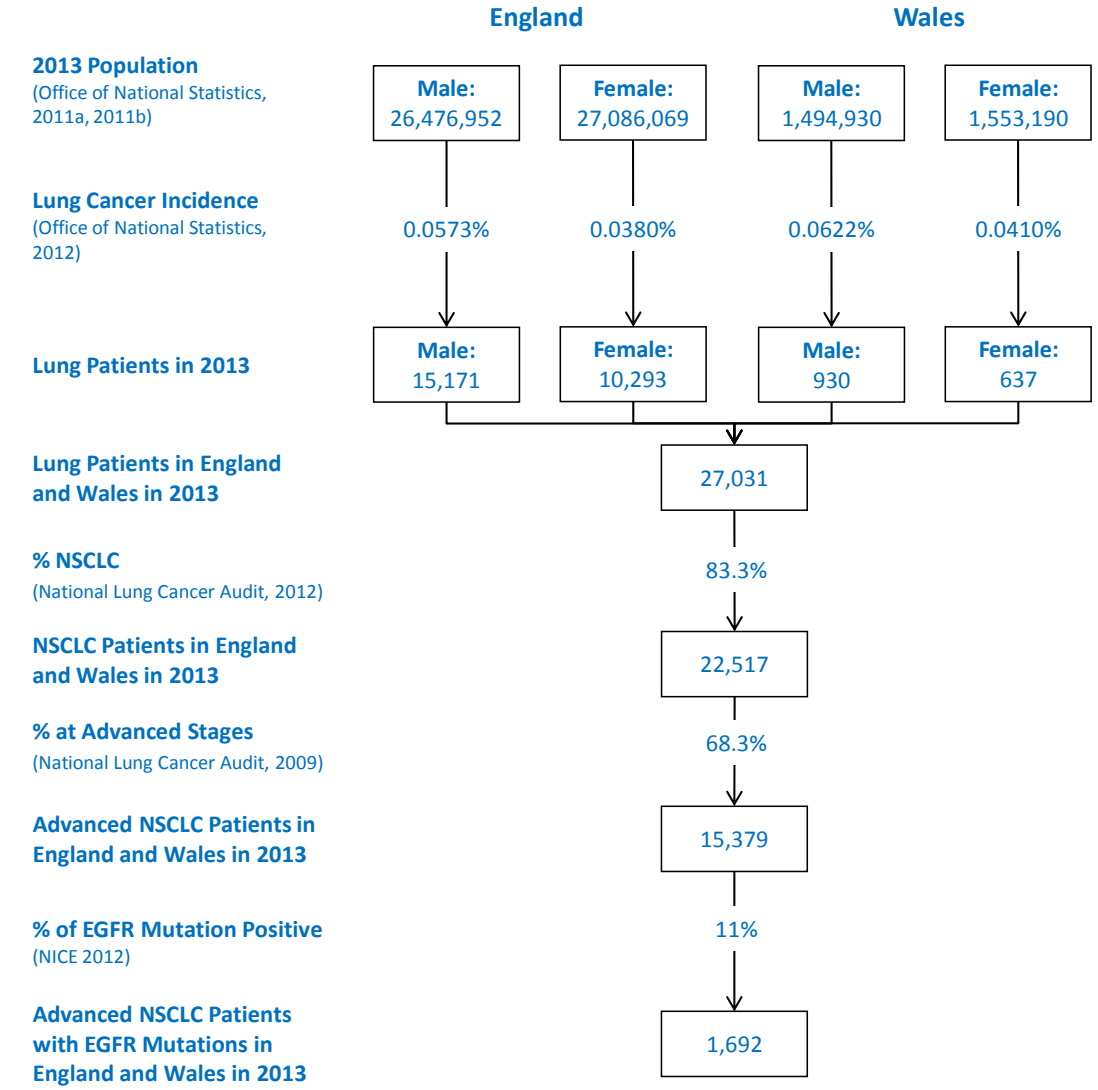
Lung cancer is the second most common cancer in the UK with 42,026 people being diagnosed with the disease in 2010 (Cancer Research UK 2010). Lung cancer is the most common cause of death from cancer in the UK, accounting for 34,859 or approximately 22% of all cancer deaths in 2010. Of these lung cancer deaths, 29,914 were reported in England and Wales (Cancer Research UK 2010a).

EGFR mutation rates vary considerably across different population ethnicities with reported rates amongst NSCLC patients with adenocarcinoma ranging from 10.4% in an Italian study (Marchetti et al. 2005) to 49% in a Japanese study (Kosaka et al. 2004). The estimated prevalence of activating EGFR mutations in NSCLC in England and Wales is 16.6% (Rosell et al. 2009).

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Based on the projected population figures for England and Wales (Office of National Statistics 2011), it is estimated that there will be a total of 1,692 advanced NSCLC patients with activating EGFR mutations in 2013. The basis of these estimates is detailed in Figure 3 below.

Figure 3 Algorithm for estimating total number of EGFR-mutation-positive advanced NSCLC patients



2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

In the most recent cancer survival publication by the Office of National Statistics, the one- and five-year survival rates of lung cancer patients in England, diagnosed between 2006 and 2010, were reported as 31.6% and 9.8% respectively (Office of National Statistics, 2012).

Similar survival rates were found in a separate study (Coleman et al. 2011) conducted by the International Cancer Benchmarking Partnership, in patients diagnosed between 1995 and 2007. In this study, the one- and five-year survival rates of lung cancer patients in England were reported to be 29.7% and 8.7% respectively between 2005 and 2007. This study also found the corresponding survival rates in Wales to be 28.5% and 9.0%.

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Currently, NICE technology appraisal guidance has been published for two technologies that are used in the first-line treatment of EGFR mutation positive NSCLC patients:

1. *Technology Appraisal No. 258, June 2012, 'Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer'. Review date April 2013.* (NICE 2012)

TA258 recommends erlotinib as an option for the first-line treatment of people with locally advanced or metastatic NSCLC provided that both of the following conditions are met:

- the patients test positive for the EGFR tyrosine kinase (EGFR-TK) mutation, and
- the manufacturer provides erlotinib at the discounted price agreed under the patient access scheme (as revised in 2012).

2. *Technology Appraisal No. 192, July 2010, 'Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer'. Review date April 2013.* (NICE 2010)

TA192 recommends gefitinib as an option for the first-line treatment of people with locally advanced or metastatic NSCLC provided that both of the following conditions are met:

- they test positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation, and
- the manufacturer provides gefitinib at the fixed price agreed under the patient access scheme.

<u>Other related technology appraisals:</u>

1. Technology Appraisal No. 227, June 2011, 'Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer'. Review date April 2013. (NICE 2011)

2. Technology Appraisal No. 190, June 2010, 'Pemetrexed for the maintenance treatment of non-small cell lung cancer.' Review date November 2012. (NICE 2010a)

3. Technology Appraisal No. 181, September 2009, 'Pemetrexed for the first-line treatment of non-small cell lung cancer'. (reviewed in January 2012). (NICE 2009)

4. Technology Appraisal No. 162, November 2008, 'Erlotinib for the treatment of non-small cell lung cancer'. Review date June 2010. (NICE 2008)

5. Technology Appraisal No. 124, November 2007, 'Pemetrexed for the treatment of non-small-cell lung cancer'. Review date January 2010. (NICE 2007)

6. Terminated Technology Appraisal No. 175, 'Gefitinib for the second-line treatment of locally advanced or metastatic non-small cell lung cancer.' (NICE 2009a)

7. Terminated Technology Appraisal No. 148, 'Bevacizumab for the treatment of non-small cell lung cancer.' (NICE 2008a)

8. Suspended Technology Appraisal, 'Afatinib for the treatment of locally advanced or metastatic non-small cell lung cancer after previous platinum containing chemotherapy and gefitinib or erlotinib.' (NICE 2010b)

9. Suspended Technology Appraisal, 'Cetuximab for the treatment of advanced non-small cell lung cancer.' (NICE 2007a).

Related Clinical Guidelines:

Clinical Guideline No.121. April 2011, 'The diagnosis and treatment of lung cancer' (update of Clinical Guideline 24). Review date April 2014. (NICE 2011a)

Related Quality Standards:

NICE Quality Standard 17. March 2012. Lung cancer for adults. (NICE 2012a)

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

NICE has published clinical guidelines on the diagnosis and treatment of lung cancer (NICE 2011a). The guidelines recommend the use of a platinum based doublet chemotherapy for advanced NSCLC patients of good performance status, however, the recommendations for EGFR TKIs are not covered within the clinical guidelines and are contained within the respective technology appraisals; gefitinib NICE technology appraisal guidance 192 and erlotinib NICE technology appraisal guidance 258 (NICE 2010; NICE 2012).

Current clinical pathway of care for advanced or metastatic EGFR mutation positive NSCLC:

1st line therapy

Gefitinib and erlotinib are recommended as options for the first-line treatment of patients with locally advanced or metastatic NSCLC provided that they test positive for the EGFR-TK mutation and the manufacturer provides the drugs at the price agreed under the respective patient access schemes (NICE 2010; NICE 2012).

An estimated 99% of eligible patients are treated with erlotinib or gefitinib in the 1st line setting (IMS 2013). However, if a TKI is not used, pemetrexed + cisplatin may be used.

2nd line therapy

There are no specific recommendations for locally advanced or metastatic NSCLC patients with EGFR activating mutations in the second line. The treatment options are described for the overall population of 2nd line treatment of locally advanced or metastatic NSCLC.

Docetaxel monotherapy can be considered for 2nd line treatment of locally advanced or metastatic NSCLC when the cancer has relapsed after previous chemotherapy (NICE 2011a). EGFR mutation positive patients who did not receive erlotinib or gefitinib in the first line but instead received a platinum doublet might be expected to receive erlotinib as an alternative to docetaxel for the 2nd line treatment of patients with NSCLC. However, this is only on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, adverse events and monitoring costs) equal to that of docetaxel (NICE 2008).

3rd and subsequent lines of therapy

Currently, there are no NICE-recommended technologies for 3rd and subsequent lines of treatment of patients with advanced or metastatic NSCLC.

Changes to the clinical pathway of care for advanced or metastatic NSCLC

Afatinib will provide an additional treatment option for patients with locally advanced or metastatic NSCLC with EGFR mutations who are previously untreated with either erlotinib or gefitinib.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Patients gain the most benefit when they receive the most efficacious treatment first; there is a risk that an individual patient may not receive additional lines of therapy due to rapid progression (Belani & Liao 2010). Currently gefitinib and erlotinib are approved by NICE for 1st line treatment of patients with NSCLC harbouring an activating mutation in the EGFR gene. Afatinib would provide an additional treatment option for these patients, and would provide access to an EGFR TKI with the longest median PFS reported in a 1st line registration study.

2.7 Please identify the main comparator(s) and justify their selection.

The main comparators to afatinib for use in 1st line treatment are erlotinib and gefitinib which are both recommended by NICE for treatment of locally advanced or metastatic NSCLC patients with EGFR mutations. Furthermore, data from IMS Oncology Analyser (IMS 2013) showed that 99% of the NSCLC patients with EGFR mutations receive 1st line treatment with erlotinib or gefitinib. Erlotinib could be considered an appropriate comparator in the second-line or later setting for TKI-naive patients.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Across the afatinib clinical trial programme diarrhoea and rash/acne (grouped term) were the most common adverse events. Adverse events can be managed with proactive supportive care and when required, afatinib treatment interruption and dose reductions.

In the afatinib clinical trials, diarrhoea was managed by use of loperamide at the onset of diarrhoea, along with ensuring adequate oral hydration and dietary restriction on foodstuffs likely to worsen the diarrhoea. Loperamide is recommended as the treatment for afatinib associated diarrhoea and TKI-associated diarrhoea (Yang et al. 2013).

Proactive and early management of rash is advised. Specific therapies that may be prescribed to treat afatinib associated rash/acneiform reaction include topical hydrocortisone (1% or 2.5%), clindamycin (1%), systemic antibiotics (such as doxycycline). and (short term) oral prednisolone. Pruritus may require the use of oral antihistamines (Lacouture et al. 2013, Hirsh 2011).

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

As an oral therapy, afatinib is associated with minimal resource use to the NHS. Erlotinib and gefitinib are currently standard treatments used in the NHS

and so afatinib, being an additional option to these two NICE-recommended EGFR-TKI's, will not result in an increase in the use of NHS resources.

Although EGFR mutation testing will be necessary to identify NSCLC patients who are eligible for afatinib treatment, such tests are currently standard practice in England and Wales when making decisions about the treatment of locally advanced or metastatic NSCLC and there will therefore not be an increase in testing-associated costs to the NHS.

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is required.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

We do not believe that afatinib treatment will be associated with any equality issues.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

As previously described in Section 1.2, afatinib is a selective and irreversible ErbB Family Blocker that inhibits EGFR, HER2 and ErbB4 receptor tyrosine kinases. Irreversible binding of an agent is believed to help extend its efficacy and delay the development of resistance, whereas targeting more than one family member of the ErbB family may improve efficacy and overcome redundancy associated with receptor crosstalk.

Gefitinib and erlotinib are licensed for the management of EGFR mutation positive NSCLC. Both of these compounds inhibit EGFR receptor tyrosine kinase but have limited activity against HER2 and ErbB4. They also exhibit reversible binding to the tyrosine binding domain of the EGFR receptor (Li et al. 2008).

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

The impact on carers has not been included in the QALY. Therefore the impact of prolonged progression-free survival may be expected to result in an improvement in carers' quality of life. This would not be captured in the QALY.

Other aspects of the patient experience, such as the psychological impact of maintaining basic physical functions are also expected to result in improved quality of life. Again, these are unlikely to be fully captured in the QALY.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

No evidence for the impact of quality of life for these patients was identified.

Details of the impact on quality of life associated with a number of day-to-day tasks are shown in Table 15.

5 Clinical evidence

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

Table 3 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	People with locally advanced or metastatic non-small cell lung cancer with positive epidermal growth factor receptor tyrosine kinase mutation TKI naive (first line) TKI pretreated (after at least one line of chemotherapy and an EGFR TKI)	As per scope.	
Intervention	Afatinib	As per scope.	
Comparator(s)	First line: gefitinib erlotinib Second line: gemcitabine, docetaxel, paclitaxel or vinorelbine in combination with carboplatin or cisplatin For people with non-small cell lung cancer other than predominantly squamous cell histology: pemetrexed in combination with cisplatin For people who are unable to tolerate a platinum combination: single-agent gemcitabine, docetaxel, paclitaxel or vinorelbine Third/ fourth line: docetaxel monotherapy best supportive care	First line: gefitinib erlotinib	Afatinib will be licensed in patients untreated with a TKI, therefore TKIs are appropriate comparators.
Outcomes	The outcome measures to be considered include: overall survival progression-free survival response rate adverse effects of treatment health-related quality of life	As per scope.	

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope.	
Subgroups to be considered	None identified.	As per scope.	
Special considerations, including issues related to equity or equality	None identified.	As per scope.	

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY(s), quality-adjusted life year(s)		

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

In line with the standard methodology for NICE submissions, multiple databases must be searched. For clinical evidence the three databases needed to be searched are in Table 4.

Table 4 Databases searched for clinical systematic reviews

1. Embase (via the OVID platform)
2. Medline & Medline In-Process (via the OVID platform)
3. Cochrane Library (via the InterScience platform) - includes:
   - Cochrane Database of Systematic Reviews (Cochrane Reviews)
   - Database of Abstracts of Reviews of Effects (Other Reviews)
   - Cochrane Central Register of Controlled Trials (Clinical Trials)
   - Cochrane Methodology Register (Methods Studies)
   - Health Technology Assessment Database (Technology Assessments)
   - NHS Economic Evaluation Database (Economic Evaluations)

The searches were conducted on 6th March 2012 and spanned 2002-2012. The systematic reviews have not been subsequently updated, as we are not aware of any major trials (other than those relating to afatinib identified by clinical experts at BI) being published since then.

The inclusion and exclusion criteria are provided in Table 5, and the flow diagram showing the inclusion and exclusion of studies is shown in Figure 4. Further details of the search strategy are shown in Section 10.2.

6.2 *Study selection*

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

The inclusion and exclusion criteria specified in Table 5 were selected to enable the identification of relevant studies investigating any of the interventions that are licensed for the treatment of locally advanced or metastatic NSCLC. The results of this search will be used to complete this section, where clinical evidence for afatinib will be presented.

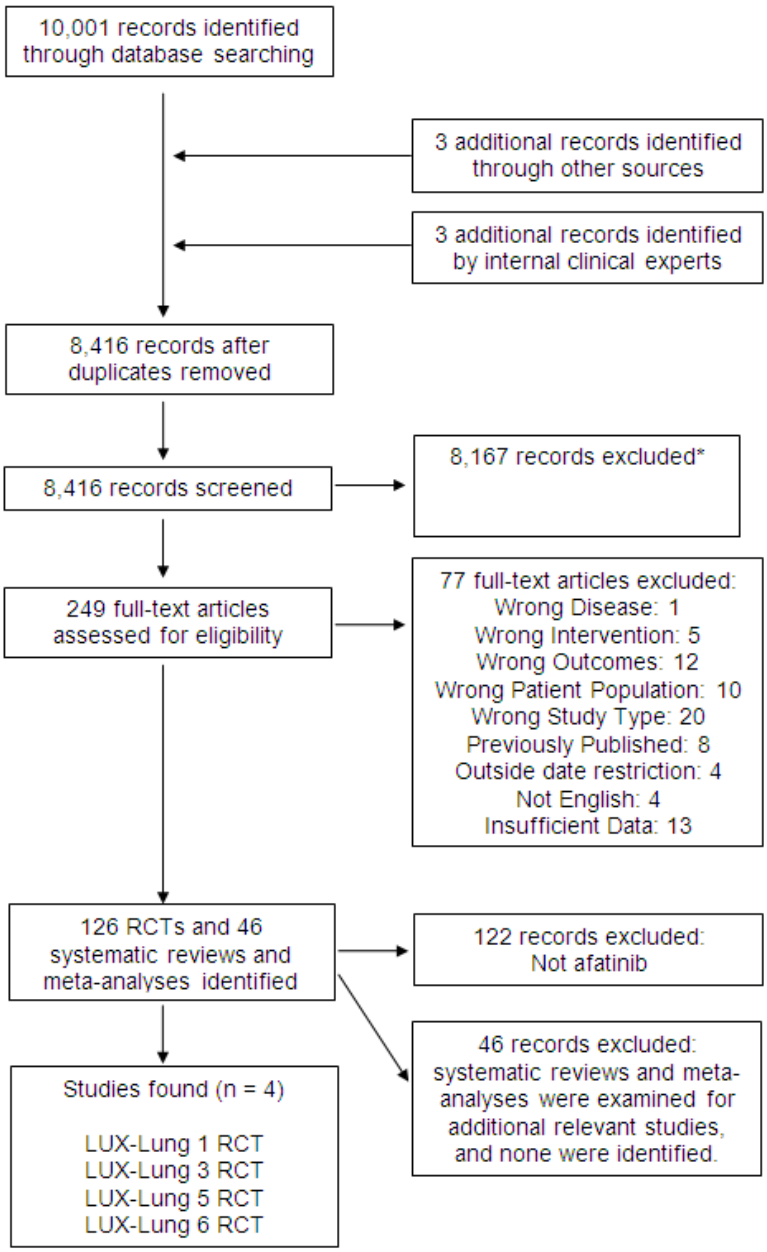
Table 5 Eligibility criteria used in search strategy

	Clinical effectiveness	Description
Inclusion criteria	Population	Locally advanced or metastatic non-small cell lung cancer patients
	Interventions	Chemotherapy or targeted therapies
	Comparator	Chemotherapy, targeted therapies, placebo or best supportive care (BSC)
	Outcomes	Overall Survival Progression Free Survival 1 year survival Time to progression Objective Response rate Toxicity
	Study design	Randomized Controlled Trials Systematic Reviews Meta-analyses
	Language restrictions	English
Exclusion criteria	Population	Other populations; Non locally advanced or metastatic NSCLC patients
	Interventions	Other interventions that are not licensed for NSCLC
	Comparator	Other comparators
	Outcomes	Other outcomes
	Study design	Observational studies Prospective studies Cohort studies Case control studies Reviews Letters Commentaries Other studies
	Language restrictions	Not English

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

The inclusion criteria of the search were made wide enough to enable the identification of relevant studies investigating any of the interventions licensed for the treatment of locally advanced or metastatic NSCLC. However, as this section presents afatinib clinical evidences only, all non-afatinib studies were subsequently excluded from the results of the search (see Figure 4).

Figure 4 Flow diagram for the inclusion and exclusion of clinical studies



*Not relevant according to criteria outlined in Table 5

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Four RCTs were identified. One based upon a publication (LUX-Lung 1), and three based on internally identified unpublished studies, which were not picked up by the search at the time it was conducted (LUX-Lung 3, LUX-Lung 5, and LUX-Lung 6). It should be noted that if the literature review was repeated now, these additional studies would be expected to be identified.

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Four RCTs were identified using the search strategy outlined in sections 6.2.1 and 6.2.2. Two were phase III RCTs (LUX-Lung 3 and LUX-Lung 6) comparing afatinib to a platinum doublet in patients untreated with an EGFR TKI with advanced adenocarcinoma of the lung harbouring EGFR mutations. Full details of these RCTs are provided below as they are directly relevant to the licensed indication and the basis for the model. Data from LUX-Lung 1 (Miller et al. 2012, Hirsh et al. 2013, BI 2011a) and LUX-Lung 5 (Schuler et al. 2012, BI 2012a) are excluded as they do not refer to the relevant patient group. A summary of the relevant RCTs is provided in Table 6.

Table 6 List of relevant RCT for EGFR TKI pretreated

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
LUX-Lung 3	Afatinib 40mg once daily until progression or undue toxicity Dose escalated to 50 mg if limited AEs observed in cycle 1. Dose reduced by 10 mg in the event of related CTCAE Grade 3 or prolonged Grade 2 AE.	Cisplatin 75 mg/m^2 + Pemetrexed 500 mg/m^2 i.v. q21 days, up to 6 cycles	- International trial - Pathologically confirmed stage IIIB (wet)/IV lung adenocarcinoma - EGFR mutation detected by central laboratory - Treatment-naive patients; no prior treatment with chemotherapy for relapsed and/or metastatic NSCLC, or EGFR targeting drugs -Performance status ECOG 0-1	Sequist et al 2013, Yang et al. 2013, BI 2012
LUX-Lung 6	Afatinib 40mg once daily until progression or undue toxicity Dose escalated to 50 mg if limited AEs observed in cycle 1. Dose reduced by 10 mg in the event of related CTCAE Grade 3 or prolonged Grade	Cisplatin 75 mg/m^2 d1 + Gemcitabine 1000 mg/m^2 i.v. d1+d8, q3w	- Trial conducted in China, Thailand and South Korea - Pathologically confirmed stage IIIB (wet)/IV lung adenocarcinoma - EGFR mutation in the tumour tissue - Treatment-naive patients; no prior treatment with chemotherapy for relapsed and/or	Wu et al. 2013, Geater et al. 2013, BI 2013

	2 AE.		metastatic NSCLC, or EGFR targeting drugs -Performance status ECOG 0-1	

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

Afatinib use in EGFR mutation positive patients was evaluated in the phase III randomised open-label LUX-Lung 3 study (Sequist et al 2013, Yang et al. 2013, BI 2012), which compared afatinib and cisplatin/pemetrexed in treatment-naive patients with advanced adenocarcinoma of the lung harbouring an activating EGFR mutation. This platinum doublet was, at the time of designing the trial, the standard of care for 1st line non-squamous NSCLC patients. Additional evidence for the use of afatinib in treatment-naive EGFR mutation positive patients was obtained from a second phase III study that was conducted in China, Thailand and South Korea (LUX-Lung 6) and compared afatinib to cisplatin/gemcitabine (Wu et al. 2013, Geater et al. 2013, BI 2013). The results of this study were not yet available at the time of making the application for Marketing Authorisation to the regulatory authorities; but have been used to address questions by the regulatory authorities and thus this unpublished data will be used as supporting evidence in this submission. Therefore none of the studies compares afatinib to the appropriate comparators referred to in the decision problem (i.e. erlotinib and gefitinib).

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Data from LUX-Lung 1 (Miller et al. 2012, Hirsh et al. 2013, BI 2011a) and LUX-Lung 5 (Schuler et al. 2012, BI 2012a) are excluded as they do not refer to the relevant patient group. They contain patients previously treated with an EGFR TKI and therefore fall outside of the licensed indication.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Further data supporting the use of afatinib in patients who are TKI-naive with advanced NSCLC patients with activating EGFR mutations has been derived from the phase II LUX-Lung 2 study. This was a single arm trial and was therefore not randomised. However, this study evaluated afatinib as a 1st or 2nd line treatment in patients with advanced adenocarcinoma of the lung harbouring EGFR mutations, and is therefore relevant to this submission. A summary of the study has been tabulated below. Further details have been provided in section 6.8.

Table 7 List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
LUX-Lung 2	Afatinib 50mg daily. Following a protocol amendment on 17 Dec 2008, the starting dose of afatinib was reduced to 40mg daily in newly enrolling patients. In case of related CTCAE Grade 3 or prolonged Grade 2 AE, afatinib treatment was interrupted until AE Grade 1 or lower. Then afatinib dose reduced by 10 mg. After third occurrence of AE, treatment was discontinued.	- Stage IIIB (with pleural effusion)/IV lung adenocarcinoma - Activating EGFR mutations within exons 18–21 of the EGFR receptor - Patients who have progressed or relapsed after one previous chemotherapy regimen. -Performance status ECOG 0-2 Following a protocol amendment on 01 Aug 2008, the study entry criteria were modified to include patients who had not received prior chemotherapy.	To explore the activity of afatinib in patients with activating EGFR mutations	Yang et al. 2012	This trial has been included in the submission as it provides evidence for the use of afatinib in the 1st and 2nd line setting, and is therefore relevant to this submission.

6.3 *Summary of methodology of relevant RCTs*

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to

submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.

Table 8 Summary of methodology of relevant RCTs

Trial no.	LUX-Lung 3	LUX-Lung 6
Scientific background rationale (2a)	In patients with advanced NSCLC (stage IIIb or IV) systemic chemotherapy is considered the first line treatment of choice (Azzoli et al. 2009). Novel targeted therapies based on molecular and biological characteristics of lung cancer have emerged as a new treatment paradigm (Heymach et al. 2006, Doroshow 2005, Sequist et al. 2007, Riely et al. 2006). The ErbB Family of receptors has been extensively studied in lung cancer (Engelman et al. 2006, Heymach et al. 2006, Sequist et al. 2007, Riely et al. 2006, Sharma et al. 2007). Activation of these receptors by ligands such as epidermal growth factor (EGF) triggers activation of multiple intracellular signal transduction pathways which are essential for malignant cell growth and metastasis (Engelman et al. 2006). EGFR (ErbB1) is a transmembrane receptor that is detectable in approximately 80 to 85% of patients with NSCLC. EGFR is one of four members of the ErbB family, other remaining members being Her2 (ErbB2), ErbB3 and ErbB4. The EGFR gene is located on the short arm of chromosome 7 and the most commonly found mutations are an in-frame deletion (E746 to A750) in exon 19 and the L858R point mutation in exon 21 which account for 45% and 40% of EGFR mutations respectively (Lynch et al. 2004, Paez et al. 2004, Pao et al. 2004, Shigematsu et al. 2005, Sharma et al. 2007, Yatabe et al. 2007). Both of these mutations result in activation of the EGFR tyrosine kinase domain resulting in aberrant oncogenic signalling and tumourigenesis. These mutations have also been found to be predictive of response to small molecule reversible EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib (Lynch et al. 2004, Paez et al. 2004, Pao et al. 2004). Approximately 90% of patients that respond to EGFR TKIs have these mutations, and patients with tumours harbouring these mutations show response rates of 70% to 80% and a median progression free survival of over 9 months. However, despite initially promising results, most responding patients with an activating EGFR mutation will eventually develop disease progression after 6 to 12 months of therapy. Molecular analysis of relapsed NSCLC after EGFR TKI treatment has shown the presence of the T790M mutation in about 50% of patients. As such, a strategy to overcome resistance is to develop targeted molecules with a higher binding affinity to the ErbB family. Afatinib irreversibly binds to and helps to inhibit oncogenic signalling from all cancer-relevant homo- and hetero-dimers of the ErbB family. *In-vitro* preclinical data demonstrates irreversible inhibition of the ErbB family by afatinib, and activity against activating EGFR mutations including the T790M mutation. Irreversible EGFR TKIs may overcome steric interference of T790M thought to hinder the access of erlotinib and gefitinib and may prevent the emergence of secondary resistance mutations, leading to improved efficacy in patients. Afatinib is an irreversible ErbB family TKI with improved potency when compared to erlotinib and gefitinib. Afatinib may also prevent the emergence of the T790M resistance mutation which is commonly seen in patients relapsing after gefitinib or erlotinib. Afatinib has been investigated as a first line therapy, and compared with standard platinum doublet chemotherapy in advanced adenocarcinoma of the lung harbouring an activating EGFR mutation.	
Objectives (2b)	LUX-Lung 3 was a phase III global open label RCT. The objectives of this trial were to compare the efficacy and safety of single	LUX-Lung 6 was a phase III multi centre open label RCT. The objective was to compare the efficacy and safety of first

	agent afatinib with cisplatin/pemetrexed chemotherapy as first line treatment in patients with advanced adenocarcinoma of the lung harbouring an EGFR activating mutation. The primary outcome was progression free survival (PFS) as assessed by central independent review by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. Secondary outcomes included objective response rate (ORR) (complete response [CR], partial response [PR]),) and disease control rate (DCR) (CR, PR, stable disease [SD]) as determined by RECIST 1.1 and overall survival (OS). Other secondary endpoints included: health-related quality of life(HRQoL), change of body weight and ECOG performance status, tumour shrinkage, pharmacokinetics and safety of afatinib as indicated by grade and incidence of adverse events according to CTCAE version 3.0 Hypotheses: H_0: The progression free survival time for patients treated with afatinib is equal to or worse than the progression free survival time for patients treated with chemotherapy H_1: The progression free survival time is longer for patients treated with afatinib than for those who receive chemotherapy.	line afatinib with cisplatin plus gemcitabine chemotherapy in patients with chemotherapy and TKI naive advanced adenocarcinoma of the lung (stage IIIb/IV) harbouring activating EGFR mutations. The primary outcome was progression free survival (PFS) as assessed by central independent review by RECIST 1.1. Secondary endpoints were ORR, DCR as determined by RECIST 1.1. Other secondary outcomes were overall survival (OS), change of body weight and ECOG performance status, tumour shrinkage, Health-related quality of life (HRQOL), pharmacokinetics and safety of afatinib as indicated by grade and incidence of adverse events according to CTCAE version 3.0 Hypotheses: H_0: The progression free survival time for patients treated with afatinib is less than or equal to the progression free survival time for those treated with cisplatin/ gemcitabine chemotherapy H_1: The progression free survival time for patients treated with afatinib is longer than for those treated with cisplatin/ gemcitabine chemotherapy

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table 9 Comparative summary of methodology of LUX-Lung 3 and LUX-Lung 6

Trial no. (acronym)	LUX-Lung 3	LUX-Lung 6
Location	Asia (Hong Kong, Japan, Korea, Malaysia, Philippines, Taiwan, Thailand), Europe (Austria, Belgium, France, Germany, Hungary, Ireland, Italy, Romania, Russia, Ukraine, UK), North America (USA, Canada), South America (Argentina, Brazil, Chile, Peru) and Australia	Multi-centre trial in Asia (China, Thailand and South Korea)
Design (3a)	Phase III multi centre open label RCT comparing the efficacy of first line afatinib with cisplatin plus pemetrexed chemotherapy in patients with chemotherapy/TKI naive advanced adenocarcinoma of the lung (stage IIIb/IV) harbouring activating EGFR mutations. Genotyping of EGFR mutations in this trial was conducted centrally using the TheraScreen®: EGFR29 Mutation Kit (QIAGEN Manchester Ltd, Manchester, UK)	Phase III multi centre open label RCT comparing the efficacy and safety of first line afatinib with cisplatin plus gemcitabine chemotherapy in patients with chemotherapy/TKI naive advanced adenocarcinoma of the lung (stage IIIb/IV) harbouring activating EGFR mutations. The TheraScreen®: EGFR29 Mutation Kit (QIAGEN Manchester Ltd, Manchester, UK) was used to categorise each patient's EGFR mutation status
Biomarker analytical determinants	The TheraScreen®: EGFR29 Mutation Kit is designed to detect 29 EGFR mutations against a background of wild-type genomic DNA, i.e. 19 deletions in exon 19, L858R, 3 insertions in exon 20, L861Q, G719S, G719A, G719C, T790M, and S768I. Samples testing positive for one of these mutations were reported as 'Positive' and the patient was eligible for the second screening visit. The EGFR mutation category for stratification (L858R vs. Del 19 vs. Other) was specified in the report to the investigator. If both L858R and a deletion in exon 19 were detected in the same sample, the patient was to be allocated to the stratification category 'L858R'. In other cases where more than 1 mutation was detected, the patient was to be allocated to the stratification category 'Other'. If no mutation was detected, the result was reported as 'Negative' and the patient was recorded as a screen failure. For inconclusive EGFR mutation tests, the investigator was allowed to send further tumour tissue samples.	The TheraScreen®: EGFR29 Mutation Kit is designed to detect 29 EGFR mutations against a background of wild-type genomic DNA, i.e., 19 deletions in exon 19, L858R, 3 insertions in exon 20, L861Q, G719S, G719A, G719C, T790M, and S768I. Samples testing positive for one of these mutations were reported as 'Positive' and the patient was eligible for the second screening visit. The EGFR mutation category for stratification (L858R vs. Del 19 vs. Other) was specified in the report to the investigator. If both L858R and a deletion in exon 19 were detected in the same sample, the patient was to be allocated to the stratification category 'L858R'. If no mutation was detected, the result was reported as 'Negative' and the patient was recorded as a screening failure. For inconclusive EGFR mutation tests, the investigator could send further tumour tissue samples.
Duration of study	August 2009 – February 2012	April 2010 – October 2012
Method of randomisation (8a, 8b, 9, 10)	Participants were randomised; this was carried out centrally using an Interactive Voice/Web Response System (IVRS/IWRS). The company that provides the IVRS/IWRS system received the randomisation list from Boehringer Ingelheim Clinical Trial Support Group or a CRO	Randomisation was carried out centrally using an Interactive Voice/Web Response System (IVRS/IWRS). Patients were randomised 2:1 to either afatinib (Arm A) or chemotherapy with Gemcitabine/Cisplatin (Arm B) stratified by EGFR mutation (L858R vs. del 19 vs. other)

	appointed by the sponsor. Patients were randomised in a 2:1 fashion to receive afatinib or cisplatin with pemetrexed. Randomisation was stratified by type of mutation present (L858R, exon 19 deletion, or other) and the ethnicity of the patient (Asian or non-Asian).	
Method of blinding (care provider, patient and outcome assessor) (11a, 11b)	Open label study All image data was sent to a central imaging unit to obtain an independent blinded confirmation of tumour response assessment. The review of the image data was performed by 2 independent radiologists, who were not affiliated with the study. In the case of disagreement on the radiological assessment at any timepoint between the two primary reviewers, a third adjudicating radiologist selected one of the primary reviewer's interpretations for all timepoints. The data was also reviewed by an oncologist who provided a final assessment for each patient.	Open Label study All image data was sent to a central imaging unit to obtain an independent blinded confirmation of tumour response assessment. In the case of disagreement on the radiological assessment at any time-point between the two primary reviewers, a third adjudicating radiologist selected one of the primary reviewer's interpretations for all timepoints. The data was reviewed by an oncologist who provided a final assessment for each patient.
Intervention(s) (n =) and comparator(s) (n =) (5)	Intervention (n=230) Afatinib at 40mg starting dose, taken once daily orally. Continuous daily dosing until disease progression or undue adverse events (40mg starting dose; dose reductions to 30mg or 20mg was allowed in cases of pre-specified, protocol defined adverse events). Dose escalation was permitted if no adverse events > grade 1 in severity were experienced during course 1. Comparator (n= 115) Pemetrexed 500mg/m^2 i.v. followed by cisplatin at 75mg/m^2 i.v. up to 6 three week (21 days) cycles. Patients received best supportive care (anti-emetics, hydration and vitamin supplements) during chemotherapy in accordance with the current SPC. In the event of adverse events treatment was delayed and/or the dose reduced as per SPC.	Intervention (n=242) Afatinib at 40mg starting dose, taken once daily orally. Continuous daily dosing until disease progression or undue adverse events (40mg starting dose; dose reduction to 30mg or 20mg was allowed in cases of pre-specified, protocol defined adverse events). Dose escalation was permitted if no adverse events > grade 1 in severity were experienced during course 1. Comparator (n= 122) Gemcitabine 1000mg/m^2 on day 1 and day 8 with cisplatin 75mg/m^2 on day 1 of each 21 day cycle for up to 6 cycles.
Primary outcomes (including scoring methods and timings of assessments) (6a,	The primary endpoint of this study is progression-free survival, defined as the time from the date of randomisation to the date of disease progression, or to the date of death if a patient died earlier. The analysis was based upon the evaluation of tumour imaging as	The primary endpoint is progression free survival defined as time from the date of randomization to the date of disease progression or to the date of death, whichever occurs first.

6b)	reviewed by an independent central unit, blinded to treatment assignments and determined according to RECIST criteria version 1.1. Tumour assessments were performed at screening, after six weeks, after twelve weeks and every six weeks thereafter. After week 48, assessments were performed every twelve weeks.	Tumour assessments were performed at screening visit 2, then 6 weekly until progression/start of further treatment. After 48 weeks the assessments were performed every 12 weeks. RECIST 1.1 was the standard for radiological assessment of tumours during the time period of the LUX-Lung 6 study. Tumour assessments were blinded for LUX-Lung 6.
Secondary outcomes (including scoring methods and timings of assessments) (6a, 6b)	The key secondary endpoints are: Objective response defined as complete response (CR) or partial response (PR) according to RECIST 1.1. (Time to objective response and duration of objective response as time from randomisation) Disease control defined as complete response (CR), partial response (PR) and stable disease (SD) according to RECIST 1.1. (duration of disease control) Overall survival (OS) defined as the number of days from the date of randomisation to the date of death. Health-related quality of life (HRQoL) assessments included EQ-5D health status self-assessment questionnaire EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) EORTC Lung cancer specific supplementary module (EORTC QLQ-LC13) Tumour shrinkage derived as the change in the size (i.e., the sum of diameters, SoD) of target lesions from baseline. Tumour shrinkage for each patient was measured (based on central independent review) as the minimum SoD of target lesions after randomisation. Change from baseline of body weight and ECOG performance status Safety of afatinib as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 3.0 Tumour assessments were performed at screening, after six weeks, after twelve weeks and every six weeks thereafter. After week 48, assessments were performed every twelve weeks.	Secondary endpoints are: Objective response (defined as complete response [CR], or partial response [PR]) according to RECIST version 1.1 Disease control (defined as a patient with objective response or stable disease [SD]) according to RECIST version 1.1 Overall survival (OS) defined as the number of days from the date of randomization to the date of death Health-related quality of life (HRQOL) assessments included EQ-5D health status self-assessment questionnaire, EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and EORTC Lung cancer specific supplementary module (EORTC QLQ-LC13) Change from baseline of body weight and ECOG performance status Tumour shrinkage Pharmacokinetics of afatinib and Safety of afatinib as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 3.0 and changes in safety laboratory parameters Tumour assessments were performed at screening visit 2 and every 6 weeks thereafter until progression/ start of further treatment. After week 48 assessments were performed every 12 weeks HRQoL assessments were performed at the start of treatment (day 1) and day 1 of every 3 week treatment cycle, at the end of the trial visit, and during the first follow-up visit after treatment discontinuation

	HRQoL assessments were performed at randomisation and 3 weekly until progression, at the end of the trial visit, and during the first follow-up visit after treatment discontinuation No changes were made to the trial endpoints	
Duration of follow-up	Primary analysis was performed with a database lock in February 2012; median follow-up of 16.4 months after 221 PFS events (152 patients (66.1%) in the afatinib arm and 69 patients (60.0%) in the chemotherapy arm).	The primary analysis of PFS was performed with a database lock in October 2012; median follow-up was 16.6 months after 221 PFS events (157 patients (64.9% in the afatinib arm and 64 patients (52.2%) in the chemotherapy arm.

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table 10 Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
LUX-Lung 3	- Pathologically confirmed diagnosis of Stage IIIB (with cytologically proven pleural effusion or pericardial effusion)/IV adenocarcinoma of the lung. Patients with mixed histology are eligible if adenocarcinoma is the predominant histology - EGFR mutation detected by central laboratory analysis of tumour biopsy material - Measurable disease according to RECIST 1.1 - Eastern Cooperative Oncology Group [ECOG] performance score of 0 or 1 - Age ≥18 years - Life expectancy of at least 3 months - Written informed consent that is consistent with ICH-GCP guidelines	- Prior chemotherapy for relapsed and/or metastatic NSCLC. Neoadjuvant/adjuvant chemotherapy is permitted if ≥12 months has elapsed between the end of chemotherapy and randomization - Prior treatment with EGFR targeting small molecules or antibodies - Radiotherapy or surgery (other than biopsy) within 4 weeks prior to randomization - Active brain metastases (defined as stable for <4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or leptomeningeal disease) - Any other current malignancy or malignancy diagnosed within the past 5 years (other than non-melanomatous skin cancer and in situ cervical cancer) - Known pre-existing interstitial lung disease - Significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom, e.g. Crohn's disease, malabsorption or CTCAE grade ≥2 diarrhoea of any aetiology - History or presence of clinically relevant cardiovascular abnormalities, such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia. Myocardial infarction within 6 months prior to randomization - Cardiac left ventricular function with resting ejection fraction of less than 50% - Any other concomitant serious illness or organ system dysfunction, which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the test drug - Absolute neutrophil count (ANC) <1500/mm^3 - Platelet count <100,000/mm^3 - Creatinine clearance <60 ml/min or serum creatinine >1.5 x upper limit of normal (ULN) - Bilirubin >1.5 x ULN - Aspartate aminotransferase or alanine aminotransferase >3 x ULN (if related to liver metastases >5 x ULN) - Women of childbearing potential, or men who are able to father a child, unwilling to use a medically acceptable method of contraception during the trial - Pregnancy or breastfeeding - Patients unable to comply with the protocol - Active hepatitis B infection, active hepatitis C infection or known HIV carrier - Known or suspected active drug or alcohol abuse - Requirement for treatment with any of the prohibited concomitant medications: • Patients should not receive any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment (with the exception of megestrol acetate) or radiotherapy

		(except palliative short-course radiotherapy to non-target lesions) between informed consent and the end of treatment visit. • In addition, patients randomised to treatment with Pemetrexed/ Cisplatin chemotherapy should not receive any maintenance therapy for NSCLC between informed consent and the end of treatment visit, or any of the prohibited medications as listed in the current summary of product characteristics (SPC) for the Pemetrexed/Cisplatin chemotherapy regimen. Following a protocol amendment on 6 May 2010, the following information was added to the above list of restrictions: [redacted] In any patient ongoing in the trial receiving afatinib and a concomitant potent P-gp inhibitor or inducer at the time of this amendment being implemented, the decision for continuation of either drug will be based on the individual circumstances of the patient upon discussion with the responsible BI clinical monitor. Following a protocol amendment on 01 Aug 2012, the information regarding restrictions on P-gp inhibitor and inducer use was amended as follows: • Afatinib is a substrate of the P-gp transporter. Caution should be exercised when combining afatinib with P-gp modulators. - Any contraindications for therapy with pemetrexed, cisplatin or dexamethasone - Known hypersensitivity to afatinib or the excipients of any of the trial drugs - Use of any investigational drug within 4 weeks of randomization (unless a longer time period is required by local regulations)
LUX-Lung 6	- Pathologically confirmed diagnosis of Stage II–B (with - cytologically proven pleural effusion or pericardial effusion) or	- Prior chemotherapy for relapsed and/or metastatic NSCLC. Neoadjuvant/adjuvant chemotherapy is permitted if at least 12 months has elapsed between the end of chemotherapy and randomization. - Prior treatment with EGFR targeting small molecules or antibodies. - Radiotherapy or surgery (other than biopsy) within 4 weeks prior to randomization.

	Stage IV adenocarcinoma of the lung. Patients with mixed histology are eligible if adenocarcinoma is the predominant histology. - EGFR mutation detected by central laboratory analysis of tumour biopsy material. - Measurable disease according to RECIST 1.1. - Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 - Age ≥ 18 years. - Life expectancy of at least three (3) months. - Written informed consent that is consistent with ICH-GCP guidelines.	- Active brain metastases (defined as stable for <4 weeks and/or symptomatic and/or requiring treatment with anticonvulsants or steroids and/or leptomeningeal disease). - Any other current malignancy or malignancy diagnosed within the past five (5) years (other than non-melanomatous skin cancer and in situ cervical cancer). - Known pre-existing interstitial lung disease. - Significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom e.g. Crohn's disease, malabsorption or CTC grade ≥2 diarrhoea of any aetiology - History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of 3, unstable angina or poorly controlled arrhythmia. Myocardial infarction within 6 months prior to randomization. - Cardiac left ventricular function with resting ejection fraction of less than 50%. - Any other concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the test drug. - Absolute neutrophil count (ANC) < 1500 / mm^3. - Platelet count < 100,000 / mm^3. - Creatinine clearance < 60 ml / min or serum creatinine > 1.5 times upper limit of normal. - Bilirubin > 1.5 times upper limit of normal. - Aspartate amino transferase (AST) or alanine amino transferase (ALT) > 3 times the upper limit of normal (ULN) (if related to liver metastases > 5 times ULN). - Women of childbearing potential, or men who are able to father a child, unwilling to use a medically acceptable method of contraception during the trial. - Pregnancy or breast-feeding. - Patients unable to comply with the protocol. - Active hepatitis B infection, active hepatitis C infection or known HIV carrier. - Known or suspected active drug or alcohol abuse. - Requirement for treatment with any of the prohibited concomitant medications: • Patients should not receive any additional experimental anti-cancer treatment, chemotherapy, immunotherapy, hormone treatment (with the exception of megestrol acetate) or radiotherapy (except palliative short-course radiotherapy to non-target lesions) between informed consent and the end of treatment visit. • In addition, patients randomized to treatment with Gemcitabine/Cisplatin chemotherapy should not receive maintenance therapy for NSCLC between informed consent and the end of treatment visit, nor any of the prohibited medications as listed in the current summary of product characteristics

		(SPC) for the Gemcitabine /Cisplatin chemotherapy regimen. Following a protocol amendment on 14 May 2010, the above restrictions were updated with the following information: [redacted] - Any contraindications for therapy with gemcitabine / cisplatin. - Known hypersensitivity to afatinib or the excipients of any of the trial drugs. - Use of any investigational drug within 4 weeks of randomization.
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee		

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table 11 Baseline characteristics in the LUX-Lung 3 and LUX-Lung 6 (differences commented on in the CTR are highlighted in green. No statistical analysis was performed to assess for differences between groups)

LUX-Lung 3 (n = 345)		Afatinib (n = 230)	Cisplatin/Pemetrexed (n = 115)
Age (years, range)		60.5 (28-86)	59.9 (31-83)
Gender (n [%])	Male Female	83 (36.1%) 147 (63.9%)	38 (33.0%) 77 (67.0%)
Ethnicity (n [%])	Caucasian Eastern Asian Other	61 (26.5%) 165 (71.7%) 4 (1.7%)	30 (26.1%) 83 (72.2%) 2 (1.7%)
Geographical region	Europe North America Asia Other	47 (20.4%) 2 (0.9%) 160 (69.6%) 21 (9.1%)	27 (23.5%) 0 83 (72.2%) 5 (1.7%)
Smoking status (n [%])	Never smoked Ex smoker Current smoker	155 (67.4%) 70 (30.4%) 5 (2.2%)	81 (70.4%) 32 (27.8%) 2 (1.7%)
Stage (AJCC 6.0) (n [%])	IIIB (wet) IV	20 (8.7%) 210 (91.3%)	17 (14.8%) 98 (85.2%)
ECOG Performance Status (n [%])	0 1 2	92 (40%) 138 (60%) 0	41 (35.7%) 73 (63.5%) 1 (0.9%)
EGFR mutation (n [%])	del19 L858R[1] Other	113 (49.1%) 91 (39.6%) 26 (11.3%)	57 (49.6%) 47 (40.9%) 11 (9.6%)
LUX-Lung 6 (n= 364)		Afatinib (n= 242)	Cisplatin/Gemcitabine (n= 122)
Age, median (min, max) [years]		58.0 (29, 79)	58.0 (27, 76)
Gender [N (%)]	Male Female	87 (36.0) 155 (64.0)	39 (32.0) 83 (68.0)
Age categories [N (%)]	<65 years ≥65 years	176 (72.7) 66 (27.3)	102 (83.6) 20 (16.4)
Smoking status [N (%)]	Never smoked Ex smoker Current smoker	181 (74.8) 44 (18.2) 17 (7.0)	99 (81.1) 13 (10.7) 10 (8.2)
Weight, mean (StD) [kg]		59.59 (8.99)	59.42 (9.54)
Body mass index, mean (StD) [kg/m²]		22.811 (2.722)	22.994 (3.156)
ECOG performance score at baseline [N (%)]	0 1	48 (19.8) 194 (80.2)	41 (33.6) 81 (66.4)
Stage (AJCC 6.0) (n [%])	IIIB (wet) IV	16 (6.6) 226 (93.4)	6 (4.9) 116 (95.1)
EGFR mutation (n [%])	del19	124 (51.2)	62 (50.8)

	L858R[1] Other	92 (38.0) 26 (10.7)	46 (37.7) 14 (11.5)

ECOG Eastern Cooperative Oncology Group; AJCC American Joint Committee on Cancer Staging 6th edition; StD Standard deviation EGFR Epidermal Growth Factor Receptor;

[1] If both L858R and a deletion in exon 19 were detected in the same sample, the patient was to be allocated to the stratification category 'L858R';

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT

Table 12 Primary and secondary outcomes from LUX-Lung 3 and LUX-Lung 6

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
LUX-Lung 3	The primary endpoint of this study is progression-free survival, defined as the time from the date of randomisation to the date of disease progression, or to the date of death if a patient died earlier. The analysis was based upon the evaluation of tumour imaging as reviewed by an independent central unit, blinded to treatment assignments and determined according to RECIST criteria version 1.1 Imaging examinations were performed at screening, after six weeks, after twelve weeks and every six weeks thereafter. After week 48, assessments were performed every twelve weeks. All image data was sent	Progression free survival is widely used as a primary endpoint and measures the efficacy of a drug. It is superior to time to tumour progression since PFS does not censor for patients who die from any cause. PFS is less influenced than OS by competing causes of death and is not influenced by post progression treatment administration (McCain 2010).	The key secondary endpoints are: Objective response defined as complete response (CR) or partial response (PR) according to RECIST 1.1. Time to objective response and duration of objective response as time from randomisation Disease control defined as complete response (CR), partial response (PR) and stable disease (SD) according to RECIST 1.1. Overall survival (OS) defined as the number of days from the date of randomisation to the date of death. Health-related quality of life (HRQoL) EQ-5D health status self-assessment questionnaire EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) EORTC Lung cancer specific supplementary module (EORTC QLQ-LC13) Safety of afatinib as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 3.0 Imaging examinations were performed at screening, after six weeks, after twelve weeks and every six weeks thereafter. After week 48, assessments were performed every twelve weeks. All image data was sent to a central imaging unit to obtain an independent blinded confirmation of tumour response	Objective response rate provides evidence of anti-tumour activity of the drug and is reachable earlier than OS or PFS, usually within 2 to 3 months (McCain JA, 2010). RECIST 1.1 was the standard for radiological assessment for tumours during the study period. HRQoL assessments are widely used in oncology trials to assess the impact of oncology agents of patients' quality of life. EQ-5D is a generic HRQoL assessment tool which has been shown to be valid and reliable in the general population and specific populations. The EORTC QLQ-C30 and LC13, the later being specific to lung cancer, are well validated and recognised HRQoL assessment tools. Overall survival is a recognised endpoint that reflects benefit from oncology treatments. It is arguably the most important endpoint and it is well validated due to its objectivity and benefit to patients. However, overall survival may be confounded by crossover after disease progression. It may also be confounded by

	to a central imaging unit to obtain an independent blinded confirmation of tumour response assessment. RECIST 1.1 was the standard for radiological assessment of tumours during the time period of the LUX-Lung 3 study		assessment. HRQoL assessments were performed at randomisation and 3 weekly until progression No changes were made to the trial endpoints Safety of afatinib as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 3.0 and pharmacokinetics of afatinib and deterioration of body weight and ECOG performance status	causes of mortality unrelated to cancer. CTCAE version 3.0 is a well validated tool for assessing adverse events in oncology trials
LUX-Lung 6	The primary endpoint is progression free survival defined as time from the date of randomization to the date of progression or to the date of death, whichever occurs first, as determined by RECIST 1.1 Tumour assessments were performed at screening visit 2, then 6 weekly until progression/start of further treatment. After 48 weeks the assessments were performed every 12 weeks.	Progression free survival is widely used as a primary endpoint and measures the efficacy of a drug. It is superior to time to tumour progression since PFS does not censor for patients who die from any cause. PFS is less influenced than OS by competing causes of death and is not influenced by post progression treatment administration.	Secondary endpoints are Complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) according to RECIST 1.1 Overall survival (OS) defined as the number of days from the date of randomization to the date of death Health-related quality of life (HRQOL) EQ-5D health status self-assessment questionnaire, EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and EORTC Lung cancer specific supplementary module (EORTC QLQ-LC13) Tumour assessments were performed at screening visit 2 and every 6 weeks thereafter until progression/ start of further treatment. After week 48, assessments were performed every 12 weeks. All image data was sent to a central imaging unit to obtain an independent blinded confirmation of tumour response assessment.	Objective response rate provides evidence of anti-tumour activity of the drug and is reachable earlier than OS or PFS, usually within 2 to 3 months. RECIST 1.1 was the standard for radiological assessment for tumours during the study period HRQoL assessments are widely used in oncology trials to assess the impact of oncology agents of patients' quality of life. EQ-5D is a generic HRQoL assessment tool which has been shown to be valid and reliable in the general population and specific populations. The EORTC QLQ-C30 and LC13, the later being specific to lung cancer, are well validated and recognised HRQoL assessment tools.

	All image data was sent to a central imaging unit to obtain an independent blinded confirmation of tumour response assessment. RECIST 1.1 was the standard for radiological assessment of tumours during the time period of the LUX-Lung 6 study.		HRQoL assessments were performed at the start of treatment (day 1) and day 1 of every 3 week treatment cycle. Deterioration of body weight and ECOG performance status Pharmacokinetics of afatinib and Safety of afatinib as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 3.0	Overall survival is a recognised endpoint that reflects benefit from oncology treatments. It is arguably the most important endpoint and it is well validated due to its objectivity and benefit to patients. However, overall survival may be confounded by crossover after disease progression. It may also be confounded by causes of mortality unrelated to cancer. CTCAE version 3.0 is a well validated tool for assessing adverse events in oncology trials

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table 13 Summary of statistical analyses in LUX-Lung 3 and LUX-Lung 6

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
LUX-Lung 3	The primary endpoint was progression free survival. Hypotheses: H_0: The progression free survival time for patients treated with afatinib is equal to or worse than the progression free survival time for patients treated with cisplatin/ pemetrexed chemotherapy H_1: The progression free survival time is longer for patients treated with afatinib than for those who receive cisplatin/ pemetrexed chemotherapy A stratified log-rank test was used to test the effect of afatinib; stratified by EGFR mutation (L858R vs.	The primary endpoint was progression-free survival (PFS) as assessed by central independent review according to the modified RECIST version 1.1 criteria. PFS was defined as the time from randomisation to progression (or death if the patient died before progression). The primary analysis of PFS included all data collected until the cut-off date (09 February 2012). A stratified log-rank test (2-sided, $\alpha = 0.05$) was used to test for the effect of afatinib on PFS compared with pemetrexed / cisplatin chemotherapy. The test included the 2 stratification factors used at randomisation, i.e., EGFR mutation category (L858R vs. Del 19 vs. Other) and race (Asian vs. Non-Asian). Information about the stratification factors was used as documented in the eCRF. A Cox proportional-hazards model, stratified by EGFR mutation category and race was used to estimate the hazard ratio and 95% confidence interval (CI) between the 2 treatment arms. Kaplan-Meier estimates and 95% CIs (using Greenwood's formula) were tabulated at 3-monthly time points and included a comparison of the treatment arms using a z-test (approximation of the normal distribution). Kaplan-Meier curves for the 2 treatment arms were also produced. The assumption of proportional hazards within each stratum and the homogeneity of the hazard ratio	It was calculated that 217 PFS failures would be required to provide 90% power for the log-rank test, presuming a hazard ratio of 0.64 for afatinib relative to chemotherapy. This equates to a PFS benefit of 11 months versus 7 months. The alpha level was 0.025 (one sided). The CTP described that the effect of afatinib on PFS compared with pemetrexed / cisplatin chemotherapy was to be tested at the 1-sided 0.025 significance level. This is identical to the effect of afatinib being tested at the more commonly used 2-sided 0.05 significance level if the treatment effect is in favour of afatinib. To aid in the	Patients without a PFS event prior to the cut-off date were censored at the date of the last evaluable tumour imaging. Patients who were randomised but never received any study medication were censored at the date of randomisation unless they died before the second scheduled assessment. The trial was conducted in compliance with the protocol, the principles laid down in the Declaration of Helsinki, local law and according to the principles of GCP and the company standard operating procedures (SOPs). Investigators were visited at regular intervals for on-site monitoring by a Boehringer Ingelheim employee or a clinical research associate (CRA) authorised by BI. Data quality review meetings were performed at regular intervals to evaluate the quality of the data collected. The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the CTMF. An imaging charter detailed all procedures, including quality control and the criteria needed to handle missing assessments. Patients were followed for both progression and death after discontinuation of study treatment. All clinical data were captured via the Oracle

	Del19 vs. Other) and ethnicity (Asian vs. Other)	across strata were checked descriptively Logistic regression was used to test for a difference between regimens for objective response and for disease control. The statistical model included the same stratification factors that were used for the analysis of PFS. Objective response rates were presented with exact 95% Clopper-pearson CIs. OS will be analyzed twice. The first analysis is the present analysis (at the time of the primary PFS analysis) and the second will be performed at a time when more complete information is available on OS. To preserve the overall 1-sided α-level of 0.025, a Haybittle-Peto stopping boundary was used (p-value <0.0001) for the first analysis. HRQoL time to deterioration in symptoms was analysed by the log-rank test. These time-to-event data were analysed and summarised using the same methodology as used for the primary efficacy endpoint. Additional analyses were conducted on the distribution of patients who were stable, improved or worsened for each of the QLQ LC13 and C30 subscales.	interpretation of this trial, 2-sided p-values were therefore used.	ClinicalTM RDC system. The trial site personnel entered and edited the data via a secure network with secure access features. A complete electronic audit trail was maintained. The investigator approved the data using an electronic signature, and this approval was used to confirm the accuracy of the data recorded. Electronic CRFs were used for all patients In general, in cases of more than one consecutive missed assessment, patients were censored at the date of the last imaging assessment at which non-PD was documented. An additional censoring rule for the determination of PFS was added to cover a scenario that had not been considered at the time of protocol writing. Patients with an assessment of 'Non-PD' by central independent review, more than 1 consecutive missed assessment, and an assessment of 'Non-PD' according to the imaging after the missed assessments were to be censored at the date of the last assessment of 'Non-PD
LUX-Lung 6	The primary endpoint was progression free survival H_0: The progression free survival time for patients treated with afatinib is less than or equal to the	The primary endpoint was PFS as assessed by central independent review according to modified RECIST version 1.1 criteria. A stratified log-rank test (2-sided, α = 0.05) was used to test for the effect of afatinib on PFS compared with gemcitabine / cisplatin chemotherapy. The test included the stratification factor used at randomisation, i.e. EGFR mutation category (L858R vs. Del 19 vs. Other). The	217 PFS failures would be expected to provide 90% power for the log-rank test (alpha level 0.025, one sided), presuming a hazard ratio of 0.64 for afatinib relative to chemotherapy. This	The trial was carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remained in the responsibility of the treating physician of the

	progression free survival time for those treated with cisplatin/ gemcitabine chemotherapy H_1: The progression free survival time for patients treated with afatinib is longer than for those treated with cisplatin/ gemcitabine chemotherapy The null hypothesis was tested at the one-sided 0.025 level	stratification factor was used as documented in the eCRF. A Cox proportional-hazards model, stratified by EGFR mutation category was used to estimate the hazard ratio and 95% confidence interval (CI) between the 2 treatment arms. Kaplan-Meier estimates and 95% CIs (using Greenwood's formula) were tabulated at 3-monthly time points and included a comparison of the treatment arms using a z-test (approximation of the normal distribution). Kaplan-Meier curves for the 2 treatment arms were also produced. The assumption of proportional hazards within each stratum and the homogeneity of the hazard ratio across strata were checked descriptively. For objective response based on central independent review (i.e. best overall response of CR or PR), a logistic regression model, stratified by EGFR mutation category was used to compare the objective response rate between the 2 treatment arms. Objective response rates were presented with exact 95% Clopper-pearson CIs. The statistical model included the same stratification factor used for the analysis of PFS. OS (months), defined as the time from randomisation to death, will be formally analysed twice. The first analysis is presented here and was conducted at the time of the primary PFS analysis. The second OS analysis is scheduled for when the data are considered mature enough for meaningful analysis, this is expected to be when approximately	equates to a median progression free survival of 11 months for afatinib versus 7 months for cisplatin/ gemcitabine chemotherapy. In a previous trial of gefitinib vs. chemotherapy the upper limit of the 95% confidence limit of the hazard ratio was observed to be 0.64 The CTP described that the effect of afatinib on PFS compared with gemcitabine / cisplatin chemotherapy was to be tested at the 1-sided 0.025 significance level. This is identical to the effect of afatinib being tested at the more commonly used 2-sided 0.05 significance level if the treatment effect is in favour of afatinib. To aid in the interpretation of this	patient. A Data and Safety Monitoring Committee (DMC) reviewed the safety data approximately every six months. However, the significance level for the primary analysis of PFS will not be adjusted for the interim looks by the DMC. This is because the trial will not be stopped for superiority of afatinib vs. chemotherapy in terms of PFS prior to the primary analysis, which is scheduled to occur after 217 PFS failures. The trial was performed by investigators specialising in the treatment of patients with lung cancer. Trial conduct at each site was supervised by the respective principal investigator. Electronic CRFs were provided by the sponsor, and all data were captured using the Oracle Clinical Remote Data Capture (RDC) web-based system. In general, in cases of more than one consecutive missed assessment, patients were censored at the date of the last imaging assessment at which non-PD was documented. Patients without a PFS event prior to the cut-off date were censored at the date of the last evaluable tumour imaging. Patients who were randomised but did not receive study medication were censored at the date of randomisation unless they died before the second scheduled assessment An additional censoring rule for the determination of PFS was added to cover a scenario that had not

		209 deaths have been observed. To preserve the overall 1-sided α-level of 0.025, a Haybittle-Peto stopping boundary was used (p-value <0.0001) for the first analysis. Time to deterioration in body weight and performance status was analysed by the stratified log-rank test HRQoL time to deterioration in symptoms was analysed by the log-rank test. These time to event data were analysed and summarised using the same methodology as used for the primary efficacy endpoint. Additional analysis was conducted on the distribution of patients who were stable, improved or worsened for each of the QLQ LC13 and C30 subscales	trial, 2-sided p-values were therefore used.	been considered at the time of protocol writing. Patients with an assessment of 'Non- PD' by central independent review, more than 1 consecutive missed assessment, and an assessment of 'Non-PD' according to the imaging after the missed assessments were to be censored at the date of the last assessment of 'Non-PD'.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

In LUX-Lung 3 the following pre-specified subgroup analyses were conducted on the primary endpoint of PFS by central independent assessment:

- ECOG performance score at baseline (0 vs. 1)
- Gender (male vs. female)
- Age at baseline (<65 vs. ≥65 years; <75 vs. ≥75 years)
- Sum of the diameters (SoD) for all target lesions at baseline using the quartiles of all randomised patients (SoD by central independent review); patients without target lesions at baseline were considered as having an SoD of zero
- Stratifications factors as recorded in the eCRF:
  - EGFR mutation category (L858R vs. Del 19 vs. Other)
  - Race (Asian vs. Non-Asian)
- Race (Caucasian vs. Eastern Asian vs. Other Asian vs. Other)
- Race (Far East Asian vs. Other). Far East Asian was defined as patients from sites in Hong Kong, Japan, Taiwan, and Korea.
- EGFR mutation category (Del 19 vs. L858R vs. Exon 20 vs. L861Q vs. G719S/A/C vs. T790M vs. S768I vs. Other). If a patient had multiple EGFR mutations the following rules applied: L858R + Del 19 = L858R; any other combination = Other.
- EGFR mutation category (Common vs. Other). Common was defined as L858R, Del 19, and L858R+Del 19
- Del 19 category (Reduced Del 19 [Del 6225 and Del 6223] vs. Other Del 19)
- Geographical region (Europe vs. North America vs. Asia vs. Other)
- Smoking history (Never smoked vs. <15 pack years and stopped >1 year prior to diagnosis vs. Other current or ex-smokers)
- Presence of brain metastases at baseline (Yes vs. No)

In LUX-Lung 6 the following pre-specified subgroup analyses were conducted on the primary endpoint of PFS by central independent and by investigator assessment:

- ECOG performance score at baseline (0 vs. 1)
- Gender (male vs. female)
- Age at baseline (<65 vs. ≥65 years)
- Sum of the diameters for all target lesions at baseline using the quartiles for all randomised patients (SoD by central independent review); patients without target lesions at baseline were considered as having an SoD of zero
- Stratification factor as recorded in the eCRF: EGFR mutation category (L858R vs. Del 19vs. Other)
- EGFR mutation category (Del 19 vs. L858R vs. Exon 20 vs. L861Q vs.G719S/A/C vs. T790M vs. S768I vs. Other) If a patient had multiple EGFR mutations the following rules applied: L858R + Del 19 = L858R; any other combination = Other.

- EGFR mutation category (Common vs. Other). Common was defined as L858R, Del 19, and L858R+Del 19.
- Smoking history (never smoked vs. <15 pack years and stopped >1 year prior to diagnosis vs. other current or ex-smokers)
- Presence of brain metastases at baseline (Yes vs. No)

No post hoc analyses were conducted in LUX-Lung 3 or LUX-Lung 6.

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 5 LUX-Lung 3 participant flow (Sequist et al. 2013)

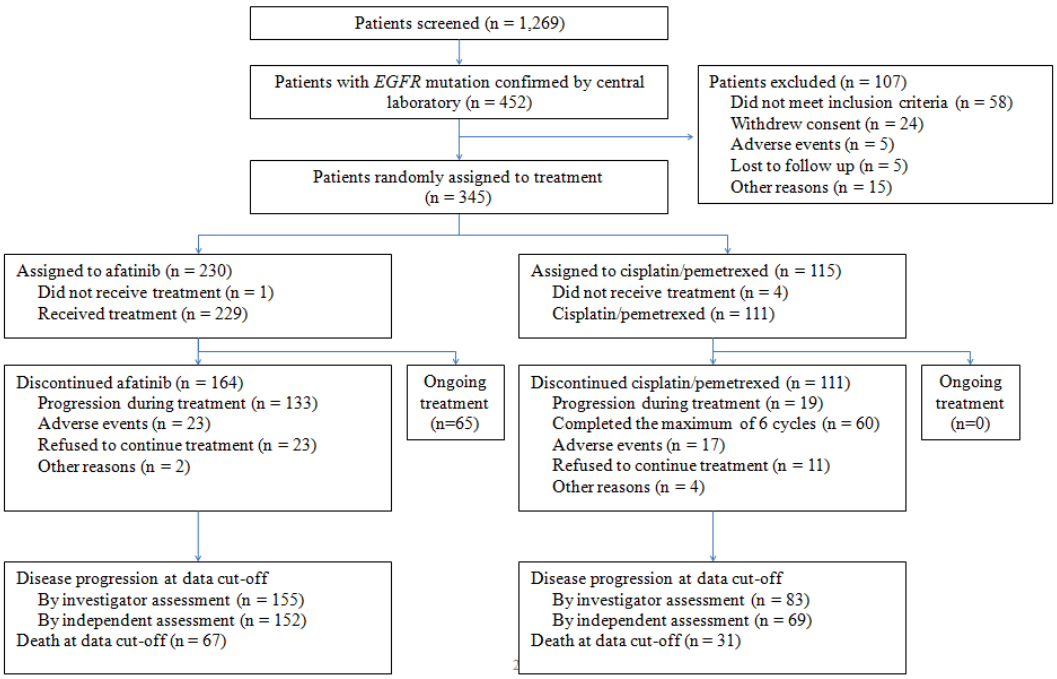
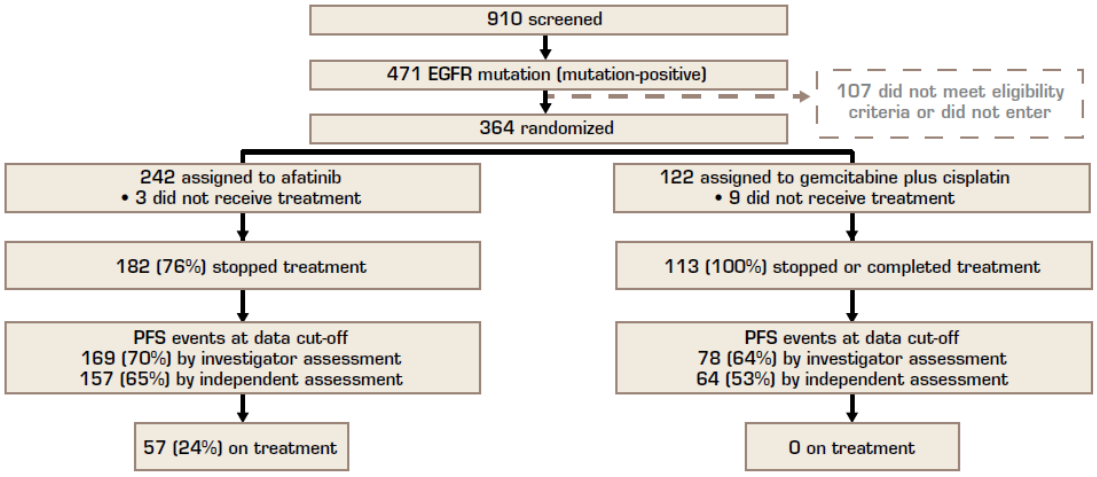


Figure 6 LUX-Lung 6 participant flow (Wu et al. 2013)



EGFR = epidermal growth factor receptor; PFS = progression-free survival.

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?

- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

As there are only three RCTs identified, the quality assessments are provided in Section 6.4.3 rather than the Section 10.3.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 14 Quality assessment results for LUX-Lung 3 and LUX-Lung 6

Trial no. (acronym)	LUX-Lung 3	LUX-Lung 6
Was randomisation carried out appropriately?	Patients were randomised in a 2:1 fashion to receive either afatinib or pemetrexed/cisplatin. Randomisation was stratified according to mutation category (L858R vs. del19 vs. other) and race (Asian vs. non-Asian). Randomisation was performed centrally using IVRS/IWRS. BI's standard validated random number generating system was used to generate the randomisation schedules, verified by a trial-independent statistician.	Patients were randomised in a 2:1 ratio to receive afatinib or gemcitabine/ cisplatin, stratified by EGFR mutation category (L858R vs. del 19 vs. other). Randomisation was performed centrally using IVRS/IWRS and BI's standard validated random number generating system was used to produce randomisation schedules which were verified by a trial-independent statistician.
Was the concealment of treatment allocation adequate?	Afatinib is an oral treatment and cisplatin/pemetrexed is administered intravenously. Therefore, due to the different modes of administration of the treatments in the two arms of the study, an open label design was selected. Blinding was not possible since the therapies used in the two arms have a different route of administration.	Afatinib is an oral treatment and cisplatin/gemcitabine is administered intravenously. Therefore, due to the different modes of administration of the treatments in the two arms of the study, an open label design was selected. Blinding was not possible since the therapies used in the two arms have a different route of administration.
Was a justification for the sample size provided?	The sample size was based on a statistical requirement to demonstrate a predetermined treatment effect. It was calculated that 217 PFS failures would be required to provide 90% power for	The sample size was based on a statistical requirement to demonstrate a predetermined treatment effect. 217 PFS failures would be expected to provide 90% power for the log-rank test (alpha

	the log-rank test, presuming a hazard ratio of 0.64 for afatinib relative to chemotherapy. This equates to a PFS benefit of 11 months versus 7 months. The alpha level was 0.025 (one sided)	level 0.025, one sided), presuming a hazard ratio of 0.64 for afatinib relative to chemotherapy. This equates to a median progression free survival of 11 months for afatinib versus 7 months for cisplatin/ gemcitabine chemotherapy
Were the groups similar at the outset of the study in terms of prognostic factors?	Age, gender, race, geographical region, smoking status, ECOG performance status at baseline and mutation category was well balanced between the two arms. More patients in the afatinib arm than the chemotherapy arm had stage IV disease at screening (91% v 85%). More patients in the afatinib arm had bone metastases compared to the chemotherapy arm (50% vs. 35%). Otherwise tumour burden was well balanced between the two arms. Non-oncological therapies (prior and concomitant) were well balanced between the two arms of the study.	Average age was slightly lower than seen in other trials in this disease area, such as the EURTAC trial (Rosell et al 2012) but was well balanced between the two treatment arms. Gender, weight and body mass index were balanced. The proportion of never smokers was higher in the chemotherapy arm compared with the afatinib arm (81% vs. 75%) and the proportion with performance status 0 was higher in the chemotherapy arm compared with the afatinib arm (34% vs. 20%). EGFR mutation category and clinical stage at screening were well balanced. Patients in the afatinib arm showed an indication of having a greater disease burden compared with the chemotherapy arm; 68% in the afatinib arm vs. 57% in the chemotherapy arm having 2 or more metastatic sites. More patients in the afatinib arm had bone metastases (48% vs. 36%) and pleural effusion (35% vs. 26%) compared with the chemotherapy arm. Afatinib treated patients had fewer prior non-oncological therapies (72% vs. 81%) but a greater number of concomitant non-oncological therapies 95% vs. 91%) compared with the chemotherapy arm.
Was follow-up adequate	Follow up was continued until a predetermined number of PFS events had occurred and was determined in the statistical plan. Primary analysis was performed with a database lock in February 2012 with a median follow-up of 16.4 months. This was after 221 PFS events.	Follow up was continued until a predetermined number of PFS events had occurred and was determined in the statistical plan. Primary analysis was performed with a database lock in October 2012 with a median follow-up of 16.6 months. This was after 221 PFS events.
Was the design parallel group or cross-over?	The design was parallel with no crossover permitted until disease progression, therefore the primary endpoint of PFS was unlikely to be affected. However, the secondary endpoint of overall survival may have been affected. Overall survival is considered to be influenced by second and later	The design was parallel with no crossover permitted until disease progression, therefore the primary endpoint of PFS was unlikely to be affected. However, the secondary endpoint of overall survival may have been affected. Overall survival is considered to be influenced by second-line and later line treatments

	line treatments (Maemondo et al. 2010).	(Maemondo et al. 2010).
Were the care providers, participants and outcome assessors blind to treatment allocation?	Care providers/participants were not blinded. Outcome assessors were blinded to treatment allocation. This was an open-label study due to the inherent differences in the mode of administration between treatment arms (afatinib is an oral therapy whereas cisplatin/ pemetrexed are administered intravenously). Central independent review to determine efficacy and disease progression was performed and all data remained blinded during this process. The trial was only un-blinded after it was considered final.	Care providers and participants were not blinded to the treatment arm. Outcome assessors were blinded to treatment allocation. This was an open label study due to the inherent differences in the mode of administration between treatment arms (afatinib is an oral therapy whereas cisplatin/ gemcitabine are administered intravenously). For efficacy assessment central imaging unit with independent blinded assessment of tumour response was used.
Were there any unexpected imbalances in drop-outs between groups?	There were no unexpected imbalances in drop-outs between the groups.	There were no unexpected imbalances in drop-outs between the groups.
Was the RCT conducted in the UK? Are the patients likely top be representative of a UK patient population?	The trial was an international study with UK sites contributing patients and approximately 20% of recruitment in both arms of the study being from Europe. The patient population is anticipated to be representative of the UK patient population with EGFR positive NSCLC.	The trial was conducted in China, South Korea and Thailand, however, it is anticipated that the patients are representative of UK patients with EGFR positive NSCLC. EGFR mutation positive patients are expected to respond to molecules that target EGFR, irrespective of their ethnicity (NICE 2010).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Pharmacokinetic data was collected and was a secondary outcome of the trial. Tumour shrinkage was a secondary outcome of the trial also. Both of these are available in the full clinical trial report but have not been included in submission since they are not relevant to the decision problem.	Pharmacokinetic data was collected as a secondary endpoint. Tumour shrinkage was also a secondary endpoint. Both of these are available in the full clinical trial report but have not been included in submission since they are not relevant to the decision problem
Were appropriate statistical analysis undertaken?	A statistical plan (TSAP) was determined and analysis followed this plan. Appropriate statistical analysis was performed. See section 6.3.6 for the outline of the statistical analysis	A statistical plan (TSAP) was determined and analysis followed this plan. Appropriate statistical analysis was performed. See section 6.3.6 for the outline of the statistical analysis
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to	Patients were allocated to treatment arms and with intention to treat analysis. In general missing data was not inputted. Patients with missing vital status, tumour assessment and HRQoL assessment were censored for time to event analyses. In case of	All efficacy analyses were performed on the randomised set following the intention to treat principle. In cases of more than one consecutive missed assessment, patients were censored at the date of the last imaging assessment at which non-PD was documented.

account for missing data?	more than one consecutive missed assessment patients were censored at the date of the last imaging assessment. There were no missing primary endpoint values.	Patients without a PFS event prior to the cut-off date were censored at the date of the last evaluable tumour imaging
Are there any confounding factors that may attenuate the results of the RCT?	Cross-over was permitted after disease progression; therefore the secondary endpoint of overall survival may be attenuated.	Cross-over was permitted after disease progression; therefore the secondary endpoint of overall survival may be attenuated.

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

See Section 6.5.3 for details.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

See Section 6.5.3 for details.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.

- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Table 15 Summary of results of the relevant RCTs

Trial	LUX-Lung 3		LUX-Lung 6	
Endpoints	Afatinib	Cisplatin/ pemetrexed	Afatinib	Cisplatin/ gemcitabine
Progression free survival (ITT population, independent review)				
Patients n (%)	230 (100%)	115 (100%)	242 (100)	122 (100)
Patients with PFS event n (%)	152 (66.1%)	69 (60.0%)	157 (64.9)	64 (52.5)
PFS time (months)				
25th percentile (95% C.I.)	5.32 (3.98, 6.87)	3.06 (2.56, 5.32)	6.87 (5.55, 8.08)	4.04 (3.06, 4.53)
Median (95% C.I.)	11.14 (9.63, 13.63)	6.90 (5.39, 8.25)	11.01 (9.66, 13.73)	5.59 (5.06, 6.70)
75th percentile (95% C.I.)	19.12 (16.49, 19.35)	10.84 (8.77, 16.39)	19.25 (16.56, 22.11)	8.08 (6.77, 9.17)
Hazard ratio v chemotherapy	0.577[1]		0.279[5]	
95% C.I.	(0.425, 0.784)		(0.201, 0.388)	
p-value (2-sided)	0.0004[2]		<0.0001[6]	
Progression free survival (Investigator review)				
Patients n (%)	230 (100%)	115 (100%)	242 (100)	122 (100)
Patients with PFS event n (%)	155 (67.4%)	83 (72.2%)	169 (69.8)	78 (63.9)
PFS time (months)				
Median (95% C.I.)	11.07 (9.66, 13.60)	6.70 (5.42, 8.11)	13.73 (11.50, 13.86)	5.55 (5.13, 6.80)
Hazard ratio v chemotherapy	0.488[1]		0.262[5]	
95% C.I.	(0.367, 0.649)		(0.193, 0.356)	
p-value (2-sided)	<0.0001[2]		<0.0001[6]	
Progression free survival (Common mutations, independent review (pre-specified analysis))				
Patients n (%)	204 (100%)	104 (100%)	216 (100)	108 (100)
Patients with PFS event n (%)	130 (63.7%)	61 (58.7%)	140 (64.8)	57 (52.8)
PFS time (months)				
Median (95% C.I.)	13.60 (10.84, 13.77)	6.90 (5.39, 8.25)	11.04 (9.66, 13.73)	5.55 (4.53, 6.21)
Hazard ratio v chemotherapy	0.471[1]		0.248[7]	
95% C.I.	(0.344, 0.646)		(0.175, 0.351)	
p-value (2-sided)	<0.0001[2]		<0.0001[8]	

Objective response and disease control based on central independent review				
Patients [n (%)]	230 (100%)	115 (100%)	242 (100)	122 (100)
Objective response [n (%)]	129 (56.1)	26 (22.6)	162 (66.9)	28 (23.0)
(95% C.I.)	(49.4, 62.6)[3]	(15.3, 31.3)	[redacted]	[redacted]
Odds ratio vs. chemotherapy	[redacted]		7.282[9]	
95% C.I.	(2.774, 7.828)		[redacted]	
P value (2 sided)	<0.0001		<0.0001	
Disease control [n (%)]	207 (90.0)	93 (80.9)	224 (92.6)	93 (76.2)
(95% C.I.)	(85.4, 93.6)[3]	(72.5, 87.6)	[redacted]	[redacted]
Odds ratio vs. chemotherapy	[redacted]		3.843[9]	
95% C.I.	(1.134, 4.037)		[redacted]	
P value (2 sided)	0.0189		<0.0001	
Overall Survival (interim analysis)				
Patients n (%)	230 (100)	115 (100)	242 (100)	122 (100)
Deaths n (%)	67 (29.1)	31 (27.0)	104 (43.0)	51 (41.8)
Survival time (months)				
25th percentile (95% C.I.)	[redacted]	14.82 (13.04, 21.62)	[redacted]	13.27 (9.43, 15.97)
Median (95% C.I.)		NE (21.62, NE)		22.24 (18.00, NE)
75th percentile (95% C.I.)		NE (NE, NE)		NE (25.56, NE)
Hazard ratio vs. chemotherapy	1.121[1]		0.949[5]	
95% C.I.	[redacted]		[redacted]	
P value	P=0.6046[2]		0.7593[6]	
Quality of life (Status change in EORTC LC13/C30)				
Dyspnoea P value	64.0% p = 0.0103	50.0%	70.9% p<0.0001	47.5%
dyspnoea when climbing stairs P value	52.0% p = 0.0109	37.0%	62.8% p<0.0001	47.5%
Shortness of breath P value	57.0% p = 0.0004	36.0%	58.2% p<0.0061	41.6%
Pain P value	59.0% p = 0.0513	48.0%	64.3% p = 0.0029	46.5%
Have pain P value	56.0% p = 0.0095	40.0%		
Pain in chest P value	51.0% p = 0.0184	37.0%	50.0% p = 0.0211	36.0%
Pain in arm or shoulder P value	41.0% p = 0.0103	26.0%	47.6% p = 0.1395	38.6%

Cough P value	67.0% p = 0.2444	60.0%,	75.9% p = 0.0003	55.4%
Global health status P value	50.0% p=0.4737	46.0%	62.7% p <0.0001	32.7%,
Physical functioning P value	40.0% 0.2321	34.0	54.2% p <0.0001	28.7%
Role functioning P value	49.0 0.5119	45.0	49.6% p = 0.0129	34.7%;
Social functioning P value	47.0 0.8070	49.0	55.3% p = 0.0007	34.7%;
Fatigue P value	72.0 0.0087	57.0	77.2% p <0.0001	52.5%;
Time to deterioration (EORTC LC13/C30)				
Cough	HR 0.595; 95% CI 0.406, 0.872		HR 0.453; 95% CI 0.299,	
P value	p = 0.0072		0.685; p = 0.0001	
Dyspnoea	HR 0.682; 95% CI 0.501, 0.928		HR 0.536; 95% CI 0.395,	
P value	p = 0.0145		0.727; p <0.0001	
Pain	HR 0.825; 95% CI 0.618, 1.101		HR 0.703; 95% CI 0.514,	
P value	p = 0.1913		0.961; p = 0.0265	

CI = confidence interval; NE= not estimable; [1] Hazard ratio derived from a Cox proportional hazard model stratified by EGFR mutation category and race. [2] Derived from a log-rank test stratified by EGFR mutation category and race. [3] Exact 95% confidence interval by Clopper and Pearson. [4] Odds ratio, 95% confidence interval, and p-value derived from a logistic regression model stratified by EGFR mutation category and race. [5] Hazard ratio derived from a Cox proportional hazard model stratified by EGFR mutation category. [6] Derived from a log-rank test stratified by EGFR mutation category. [7] Hazard ratio derived using a Cox proportional hazard model with treatment fitted as the only factor. [8] Derived using a 2-sided log-rank test. [9] Odds ratio, 95% confidence interval, and p-value derived from a logistic regression model stratified by EGFR mutation category.

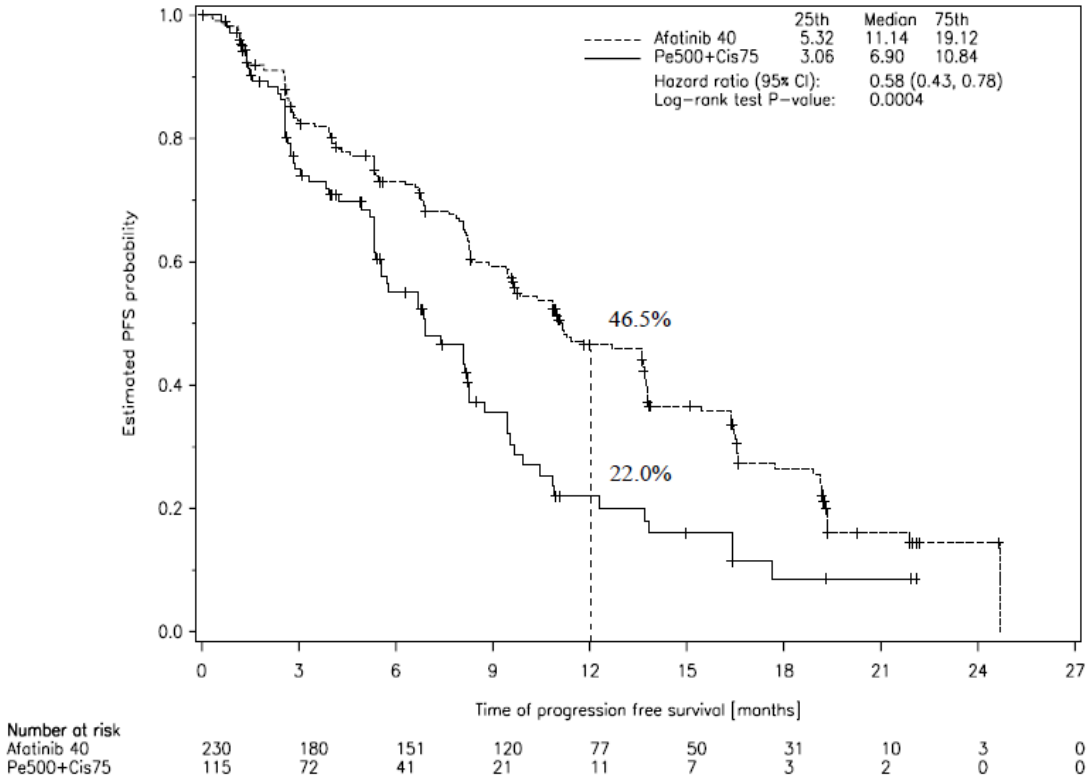
Results from LUX-Lung 3

Primary endpoint

Overall, 152 patients (66.1%) in the afatinib arm and 69 patients (60.0%) in the chemotherapy arm experienced an event contributing to the primary PFS analysis, i.e., disease progression as determined by central independent review or death, after incorporating the complete set of censoring rules. Treatment with afatinib led to a significantly prolonged PFS compared with chemotherapy; the median PFS was 11.14 months in the afatinib arm and 6.90 months in the chemotherapy arm (HR 0.577; p = 0.0004), i.e., the difference in median PFS time was 4.24 months (Table 15).

At 12 months, 46.5% of patients in the afatinib arm and 22.0% of patients in the chemotherapy arm were still alive and progression-free; at 18 months, 26.4% of patients in the afatinib arm and 8.6% of patients in the chemotherapy arm were still alive and progression-free. (Figure 7)

Figure 7 Probability of PFS based on central independent review

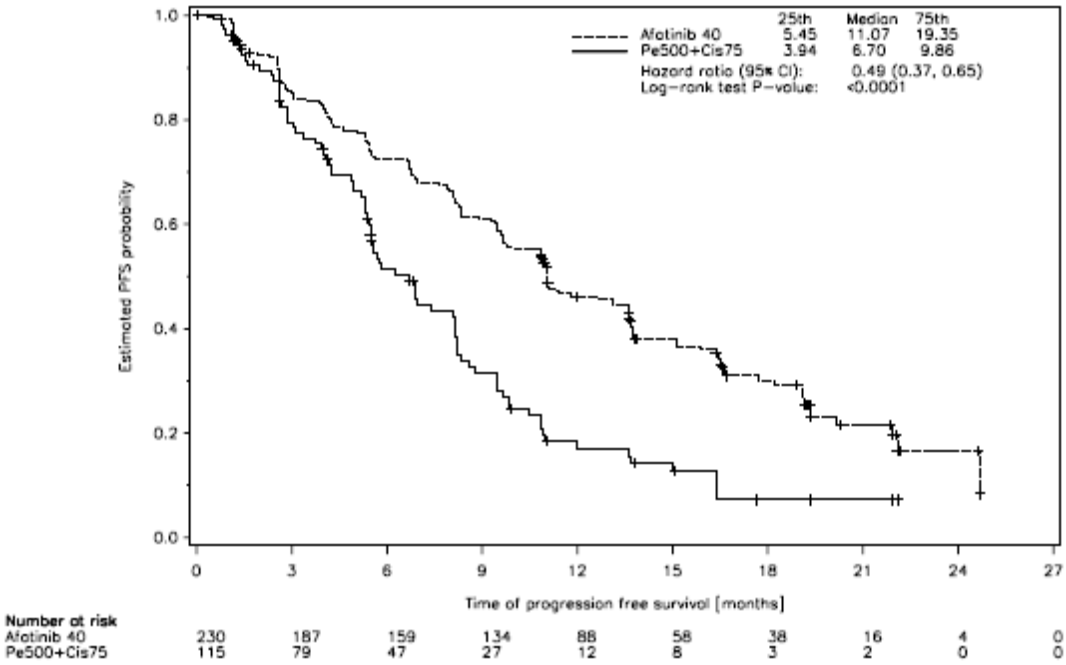


A total of 78 patients (33.9% of randomised patients) in the afatinib arm and 46 patients (40.0%) in the chemotherapy arm were censored for the primary PFS analysis. The main reasons for censoring differed between the 2 treatment arms: In the afatinib arm, 23.0% of patients were censored because they were alive and progression-free at the cut-off date. In contrast, 28.7% of chemotherapy patients were classified as having been censored due to the start of a new anti-cancer therapy.

Sensitivity Analysis

Progression-free survival was also analysed based on investigator assessment, using the same censoring rules as for the primary PFS analysis. The point estimates and 95% CIs for the median of PFS of this analysis were consistent with the results of the primary PFS analysis. The median PFS based on investigator assessment was 11.07 months in the afatinib arm and 6.70 months in the chemotherapy arm (HR 0.488; p <0.0001), i.e., the difference in median PFS time was 4.37 months (Table 15).

Figure 8 Probability of PFS based on investigator assessment



At 12 months, 46.1% of patients in the afatinib arm and 17.0% of patients in the chemotherapy arm were still alive and progression-free; at 18 months, 30.1% of patients in the afatinib arm and 7.2% of patients in the chemotherapy arm were still alive and progression-free. A total of 32.6% of randomised patients in the afatinib arm and 27.8% in the chemotherapy arm were censored for the analysis of PFS based on investigator assessment (Figure 8).

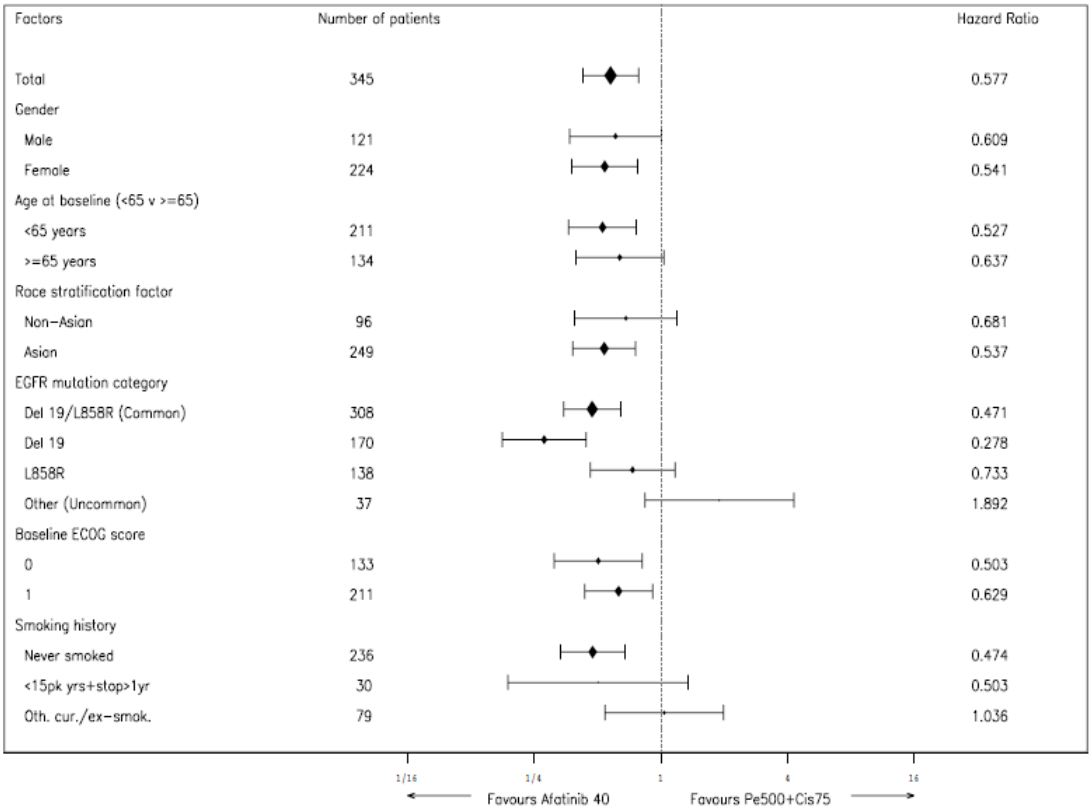
[redacted]

Subgroup Analyses

The consistency of the treatment effect of afatinib vs. cisplatin/pemetrexed was investigated for the following demographic and baseline characteristics: ECOG performance score at baseline, gender, age, size of target lesions at

baseline, race, EGFR mutation category, geographical region, smoking history, and presence of brain metastases at baseline. Comparison of the treatment effect of afatinib vs. Cisplatin/pemetrexed on the primary endpoint of PFS in the pre-defined subgroups, based on central independent review, is given in Figure 9. Based on central independent review a statistically significant interaction between treatment and subgroup was observed for the subgroups defined by EGFR mutation category (p=0.0012 for the EGFR mutation subgroup Common vs. other; p=0.0002 for the EGFR mutation subgroup L858R vs. del19 vs. Other.

Figure 9 Comparison of the treatment effect of afatinib vs. Pemetrexed/cisplatin on the primary endpoint PFS in the pre-defined subgroups, based on central independent review



PFS analysis in patient with Common EGFR mutations

The treatment effect of afatinib on PFS was stronger in the subgroup of patients with 'Common' EGFR mutations (deletions in exon 19 and the L858R substitution in exon 21) compared with chemotherapy. For patients with 'Common' EGFR mutations, the median PFS was 13.60 months in the afatinib arm and 6.90 months in the chemotherapy arm (HR 0.471; p <0.0001), i.e., the difference in median PFS time increased to 6.70 months in this patient subgroup (Table 15).

Secondary Endpoints

Tumour response

Objective response according to RECIST 1.1 and disease control according to RECIST 1.1 were key secondary endpoints. Both were assessed based on central independent review. The percentage of patients with an objective response was 56.1% in the afatinib arm and 22.6% in the chemotherapy arm; 1 patient in the afatinib arm had a complete response (Table 16). Consistent with the primary endpoint PFS, treatment with afatinib led to a statistically significant increase in the objective tumour response rate ([redacted]; p <0.0001) compared with chemotherapy. Hence the odds of having an objective response was approximately 4.7 times higher for patients treated with afatinib than those treated with chemotherapy (Table 15).

Table 16 Best overall tumour response based on central independent review

	Afatinib N (%)	Cisplatin/pemetrexed N (%)
Patients	230 (100%)	115 (100%)
Disease control Objective response [redacted]	207 (90.0%) 129 (56.1%) [redacted]	93 (80.9%) 26 (22.6%) [redacted]

Based on investigator assessment, the odds of having an objective response were approximately 3.0 times higher for patients treated with afatinib than those treated with chemotherapy). Treatment with afatinib led to a statistically significant increase in the objective tumour response rate ([redacted] p <0.0001) compared with chemotherapy. The response rates in both treatment arms were higher compared with central independent review; the percentage of patients with an objective response was 69.1% in the afatinib arm and 44.3% in the chemotherapy arm.

Duration of response

The tumour response of patients treated with afatinib occurred earlier and persisted longer than the tumour response of patients treated with chemotherapy. [redacted] The median duration of the objective tumour response was 11.10 months in the afatinib arm and 5.52 months in the chemotherapy arm.

Disease control

The majority of patients in this trial achieved disease control (best overall response of CR, PR or SD) based on central independent review, with a higher disease control rate in the afatinib arm than in the chemotherapy arm (afatinib 90.0% of randomised patients; chemotherapy 80.9%); the treatment difference was statistically significant ([redacted] p = 0.0189.

Overall survival (interim analysis)

The overall survival data were not mature by the cut-off date for the primary analysis. Only 67 patients (29.1%) in the afatinib arm and 31 patients (27.0%) in the chemotherapy arm had died by the cut-off date (Table 15). Hence, the median OS time was estimable at that time (Figure 9). The final analysis of OS will be performed when approximately 209 patients have died. However, an updated analysis has been submitted to the EMA and FDA and has been provided in Table 17 below.

Table 17 Overall survival from LUX-Lung 3

	OS analysis at primary PFS analysis		Update OS analysis	
	Afatinib N (%)	Cisplatin/pemetrexed N (%)	Afatinib N (%)	Cisplatin/pemetrexed N (%)
Patients n (%)	230 (100)	115 (100)	230 (100)	115 (100)
Deaths n (%)	67 (29.1)	31 (27.0)	116 (50.4)	59 (51.3)
Survival time (months) 25th percentile (95% C.I.) Median (95% C.I.) 75th percentile (95% C.I.)	[redacted]	[redacted]	[redacted]	[redacted]
Hazard ratio vs. chemotherapy [1] 95% C.I. P value [2]	[redacted]		[redacted]	

CI = confidence interval NE = not estimable; [1] Hazard ratio derived from a Cox proportional hazard model stratified by EGFR mutation category and race; [2] Derived from a log-rank test stratified by EGFR mutation category and race.

Figure 10 Probability of overall survival

[redacted]

Subsequent anti-cancer therapies

At the cut-off date, the majority of patients in this trial received at least 1 line of subsequent anti-cancer therapy after permanently stopping study medication (afatinib 72.0% of patients discontinuing study medication; chemotherapy 80.2%). The subsequent anti-cancer therapy resulted in some kind of cross-over in the treatment classes: patients in the afatinib arm most often received a chemotherapy treatment or a chemotherapy-based combination treatment after discontinuation of afatinib (62.2%); patients treated with pemetrexed / cisplatin were most frequently treated with an EGFR TKI (64.9%). Furthermore, substantial percentages of patients in the afatinib arm received another EGFR TKI ([redacted]) while a high proportion of patients in the chemotherapy arm ([redacted]) received a new, subsequent chemotherapy.

Changes in ECOG performance status and weight

[redacted]

[redacted]

Analyses of symptom control and quality of life

The analyses of symptom control and (Health related quality of life) HRQoL for this report focused on the pre-specified NSCLC-related symptoms of cough, dyspnoea, and pain measured by the EORTC QLQ-C30 and QLQ-LC13 questionnaires. High compliance rates for HRQoL questionnaire completion on treatment were observed (87% to 99%) and were found to be similar for both treatment arms.

Status change

Afatinib led to symptom improvement in a higher proportion of patients than chemotherapy (Table 15) for the symptom scale of dyspnoea (64.0% vs. 50.0%; p = 0.0103), for the individual item of ‘dyspnoea when climbing stairs’ (52.0% vs. 37.0%; p = 0.0109), and for shortness of breath (57.0% vs. 36.0%; p = 0.0004). While the higher proportion of patients with symptom improvement for pain in the afatinib arm did not reach statistical significance (59.0% vs. 48.0%; p = 0.0513), individual items of pain showed significance (‘Have pain’: 56.0% vs. 40.0%; p = 0.0095; ‘Pain in chest’: 51.0% vs. 37.0%; p

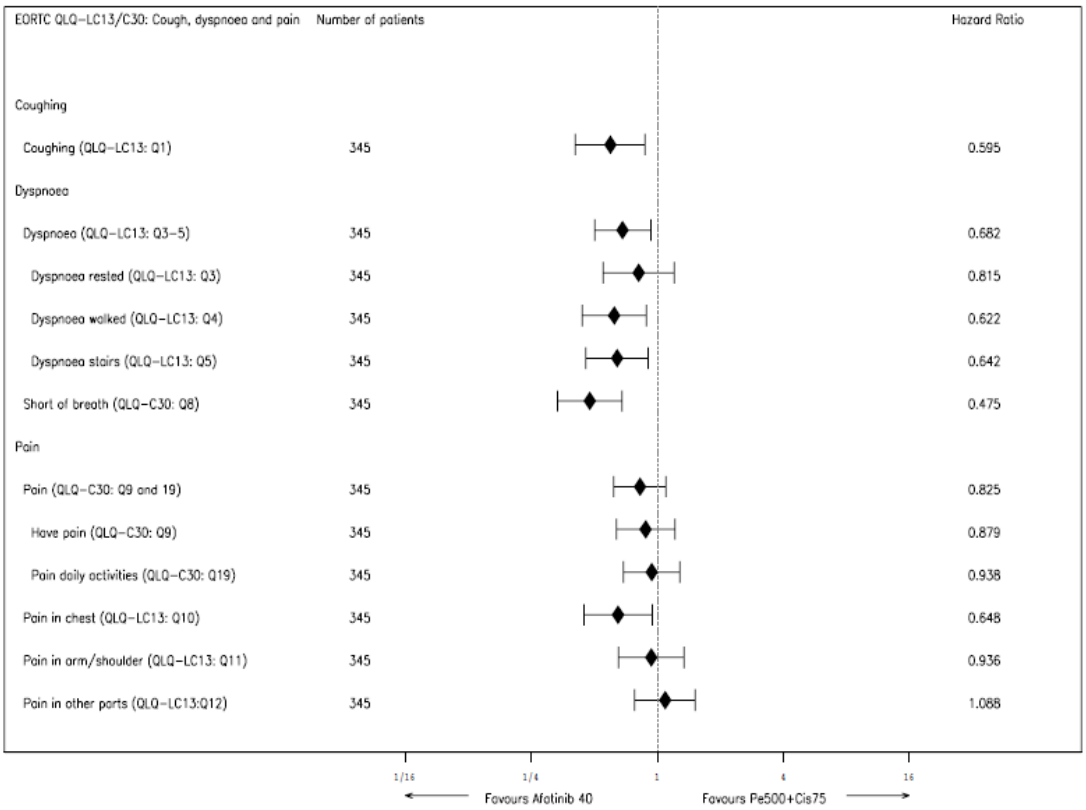
= 0.0184; 'Pain in arm or shoulder': 41.0% vs. 26.0%; p = 0.0103). No significant treatment difference was seen for cough (67.0% vs. 60.0%, p = 0.2444).

[redacted]

Time to deterioration

Compared with chemotherapy, afatinib statistically significantly delayed the time to deterioration for cough (HR 0.595; 95% CI 0.406, 0.872; p = 0.0072) and dyspnoea (HR 0.682; 95% CI 0.501, 0.928; p = 0.0145). A trend towards a delayed deterioration of pain did not reach statistical significance (HR 0.825; 95% CI 0.618, 1.101; p = 0.1913) (Table 15). Afatinib also delayed the time to deterioration of individual items of dyspnoea (i.e., dyspnoea when walking and when climbing stairs), shortness of breath, and pain in the chest. The forest plot of the hazard ratios for the time to deterioration in coughing, dyspnoea, and pain-related items of QLQ-C30 and QLQ-L13 is shown in Figure 11.

Figure 11 Comparison of the treatment effect of afatinib vs. pemetrexed / cisplatin on the time to deterioration in coughing, dyspnoea, and pain related items of QLQ-C30 and QLQ-L13



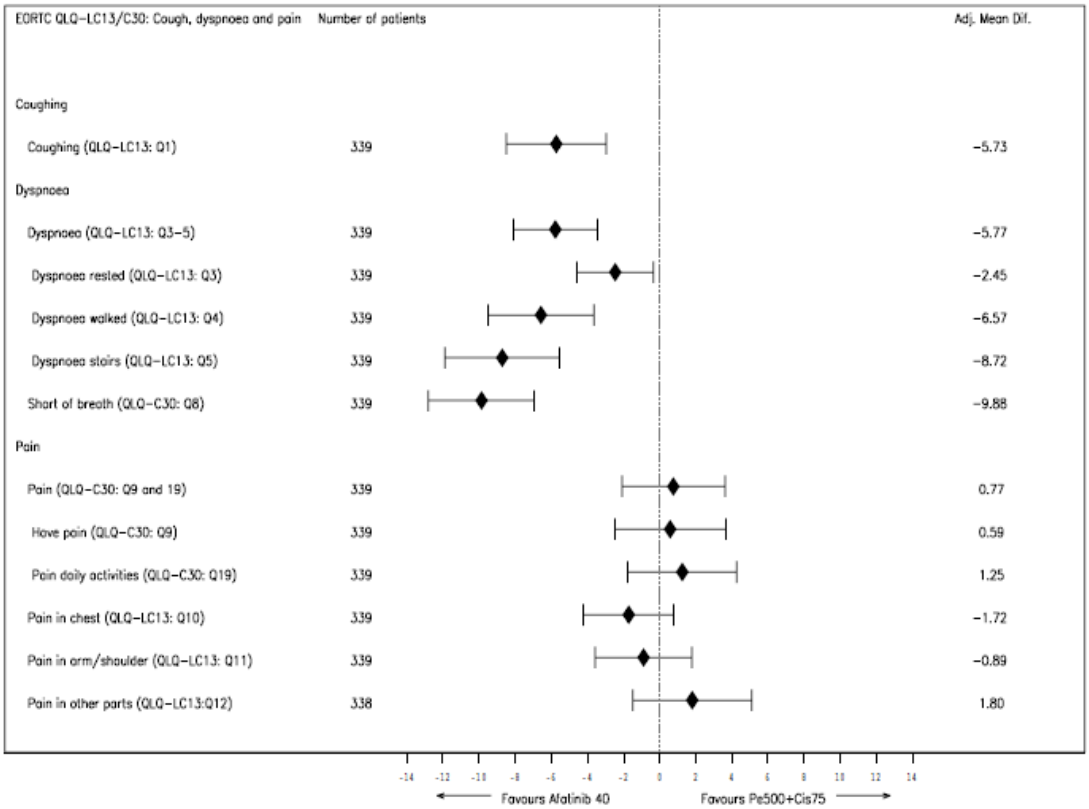
Cough: QLQ-LC13, Q1; dyspnoea: QLQ-LC13, Q3-Q5 (Q3: dyspnoea, rested; Q4: dyspnoea, walked; Q5: dyspnoea, climbed stairs); short of breath: QLQ-C30, Q8; pain: QLQ-C30, Q9 and Q19 (Q9: have pain; Q19: pain affecting daily activities); pain in the chest: QLQ-LC13, Q10; pain in arm or shoulder: QLQ-

LC13, Q11; pain in other parts of the body: QLQ-LC13, Q12. The size of the rhombus reflects the number of patients. Hazard ratios for afatinib vs. chemotherapy for each subgroup category are given on the right.

Changes in scores over time

Mean scores over time significantly favoured afatinib compared with chemotherapy for cough (p <0.0001) and dyspnoea (p <0.0001) as well as for the individual item of dyspnoea, but not for pain (See Figure 12).

Figure 12 Comparison of the treatment effect of afatinib vs. pemetrexed / cisplatin on the difference in mean scores (all data included) for changes in scores over time, in cough, dyspnoea, and pain-related items of QLQ-C30 and QLQ-LC13



Cough: QLQ-LC13, Q1; dyspnoea: QLQ-LC13, Q3-Q5 (Q3: dyspnoea, rested; Q4: dyspnoea, walked; Q5: dyspnoea, climbed stairs); short of breath: QLQ-C30, Q8; pain: QLQ-C30, Q9 and Q19 (Q9: have pain; Q19: pain affecting daily activities); pain in the chest: QLQ-LC13, Q10; pain in arm or shoulder: QLQ-LC13, Q11; pain in other parts of the body: QLQ-LC13, Q12. Adjusted mean differences for afatinib vs. chemotherapy are given on the right.

EQ-5D

[redacted]

[redacted]

Figure 13 Differences in mean scores over time for EQ-5D UK utility, EQ-5D Belgium utility*

[redacted]

Figure 14 Difference in mean scores over time for EQ-VAS*

[redacted]

Table 18 Mean scores to truncation time for EQ-5D UK utility, EQ-5D Belgium utility and EQ-VAS* Statistic UK utility Belgium utility VAS

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

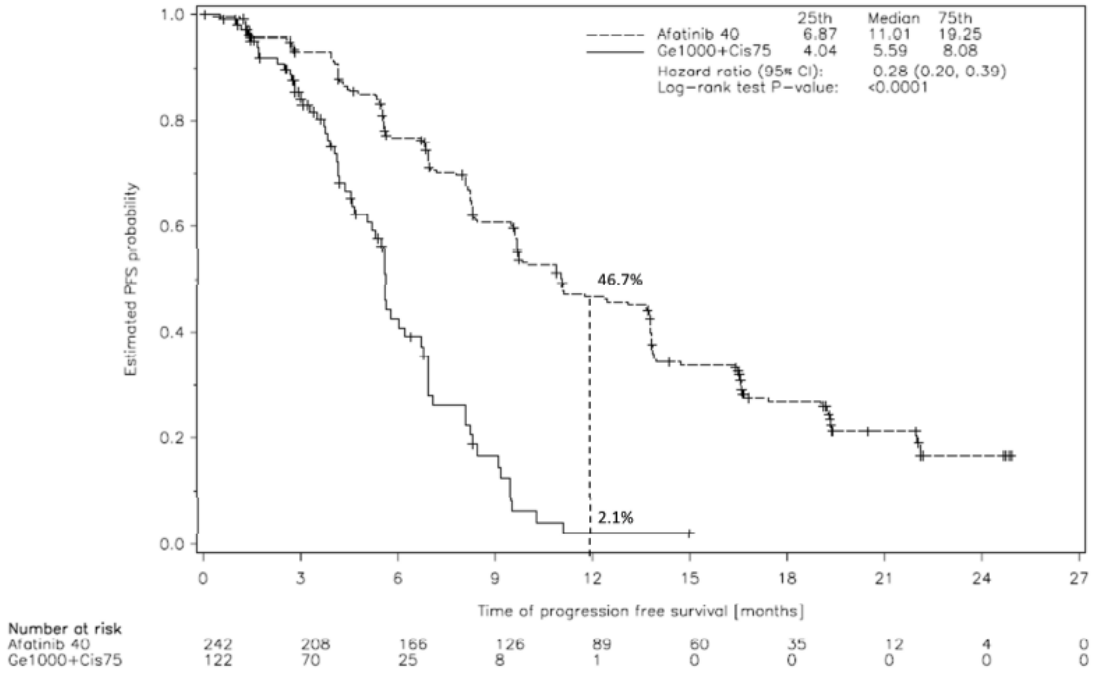
[redacted]

Results from LUX-Lung 6

Primary endpoint

Overall, 157 patients (64.9%) in the afatinib arm and 64 patients (52.5%) in the chemotherapy arm experienced an event contributing to the primary PFS analysis, i.e. disease progression as determined by central independent review or death, after incorporating the primary censoring rules (Table 15). Treatment with afatinib led to a significantly prolonged PFS compared with chemotherapy; the median PFS was 11.01 months in the afatinib arm and 5.59 months in the chemotherapy arm (HR 0.279; p <0.0001), i.e. the difference in median PFS time was 5.42 months.

Figure 15 Probability of PFS based on central independent review



At 12 months, 46.7% of patients in the afatinib arm and 2.1% of patients in the chemotherapy arm were still alive and progression-free; at 18 months (Figure 15), 26.8% of patients in the afatinib arm and 0.0% of patients in the chemotherapy arm were still alive and progression-free.

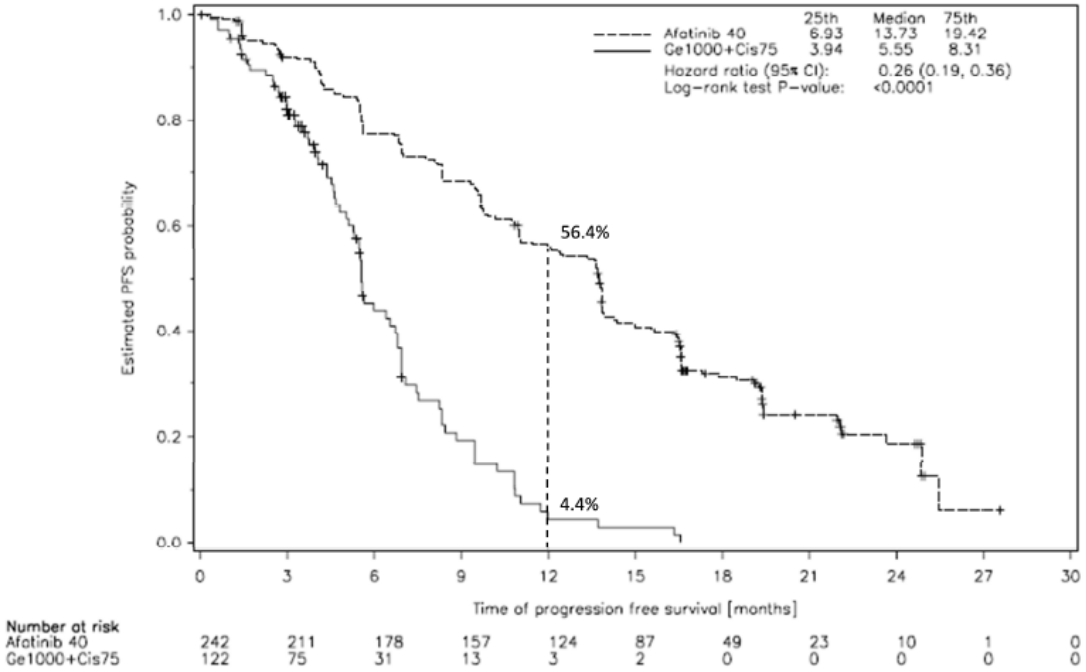
A total of 85 patients (35.1%) in the afatinib arm and 58 patients (47.5%) in the chemotherapy arm were censored for the primary PFS analysis. The main reasons for censoring differed between the 2 treatment arms: in the afatinib arm, 19.8% of patients were censored because they were alive and progression-free at the cut-off date; in contrast, 22.1% of chemotherapy patients were classified as having been censored due to the start of a new anti-cancer therapy.

Sensitivity analysis

Progression-free survival was also analysed based on investigator assessment, using the same censoring rules as for the primary PFS analysis.

The point estimate and 95% CI for median PFS based on investigator assessment was longer for patients in the afatinib arm (13.73 months vs. 5.55 months in the chemotherapy arm; HR 0.262; p <0.0001) than when assessed based on central independent review (Table 15). The difference in median PFS difference between treatment arms based on investigator review was 8.18 months, somewhat higher than the 5.42 months estimated by independent review.

Figure 16 Probability of PFS based on investigator assessment



At 12 months, 56.4% of patients in the afatinib arm and 4.4% of patients in the chemotherapy arm were still alive and progression-free (Figure 16); at 18 months, 31.2% of patients in the afatinib arm and 0.0% of patients in the chemotherapy arm were still alive and progression-free. A total of 30.2% of randomised patients in the afatinib arm and 36.1% in the chemotherapy arm were censored for analysis of PFS based on investigator assessment.

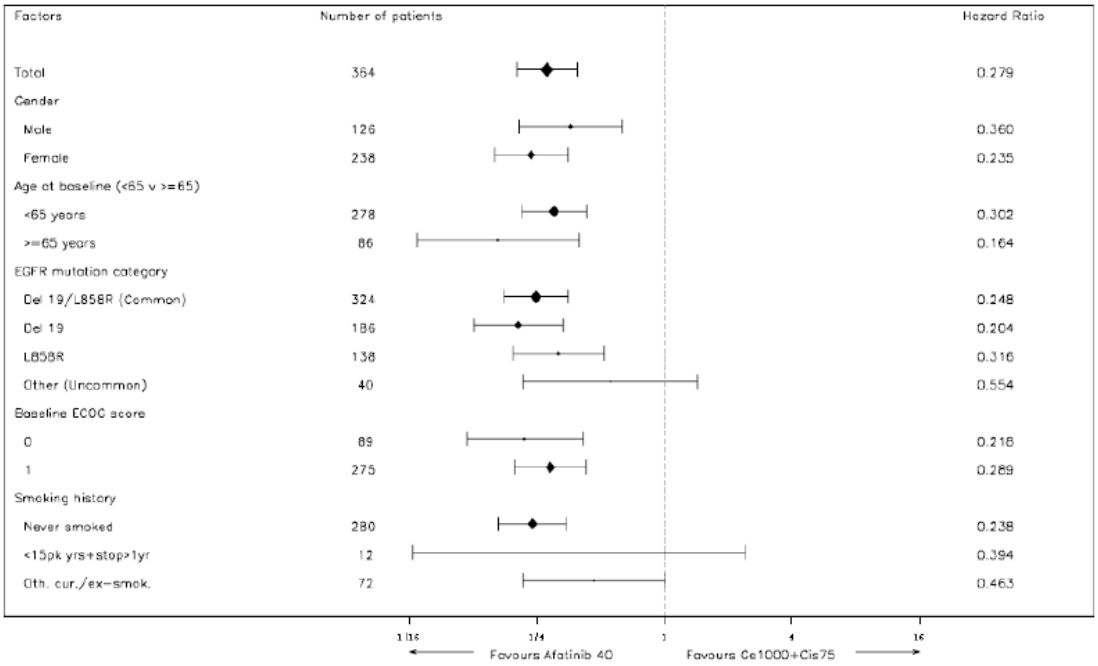
[redacted]

Subgroup Analysis

Subgroup analyses of progression free survival by independent review assessed the consistency of the treatment effect of afatinib vs. cisplatin/gemcitabine. The following demographic and baseline characteristics

were assessed; ECOG performance score at baseline, gender, age, sum of target lesion size at baseline, EGFR mutation category, smoking history, and the presence of brain metastases at baseline. The results were consistent with the PFS primary analysis showing statistically significant differences for most subgroups (Figure 17).

Figure 17 Comparison of the treatment effect of afatinib vs. gemcitabine/cisplatin on the primary endpoint PFS in pre-defined subgroups, based on central independent review



PFS in patients with common EGFR mutations

The treatment effect of afatinib on PFS in the subgroup with common EGFR mutations (pre-specified category comprising of L858R and Del 19) compared with chemotherapy was consistent with that seen for the PFS primary analysis (Table 15). For patients with common mutations the median PFS was 11.04 months in the afatinib arm vs. 5.55 months in the chemotherapy arm (HR 0.248 p<0.0001), equating to a difference in median PFS time of 5.49 months.

Secondary endpoints

Tumour Response

Objective response according to RECIST version 1.1 (i.e. best overall response of CR or PR) and disease control according to RECIST version 1.1 (i.e. best overall response of CR, PR, SD, or Non-CR / Non-PD) were key secondary endpoints in this trial and both were assessed based on central independent review. Overall 66.9% of patients in the afatinib arm and 23.0% in the chemotherapy arm experienced an objective response; 3 patients in the afatinib arm experienced a complete response (Table 19). Consistent with the primary endpoint, treatment with afatinib led to a statistically significant increase in the objective tumour response rate (OR 7.282; p <0.0001)

compared with chemotherapy. Hence the odds of having an objective response was approximately 7.3 times higher for patients treated with afatinib than for those receiving chemotherapy (Table 15).

Table 19 Best overall tumour response based on central independent review

	Afatinib N (%)	Cisplatin/pemetrexed N (%)
Patients	242 (100)	122 (100)
Disease control	224 (92.6)	93 (76.2)
Objective response	162 (66.9)	28 (23.0)
Complete response	3 (1.2)	0
Partial response	159 (65.7)	28 (23.0)
Stable disease	52 (21.5)	65 (53.3)
Progressive disease	9 (3.7)	6 (4.9)
Non evaluable	9 (3.7)	23 (18.9)

[redacted]

Time to and duration of tumour response

The tumour response of patients treated with afatinib occurred earlier and persisted longer than the tumour response of patients treated with chemotherapy. By Week 6, [redacted] of patients who responded to afatinib treatment and [redacted] of patients who responded to chemotherapy showed an objective tumour response. Though patients with an objective response in the afatinib arm generally experienced an early response, a few (4 patients) did not respond until somewhat later in treatment (ranging from 36 to 96 weeks). The median duration of objective tumour response was 9.72 months in the afatinib arm and 4.27 months in the chemotherapy arm.

Disease control

Most patients in this trial achieved disease control (best overall response of CR, PR or SD) based on central independent review, with a higher disease control rate in the afatinib arm than in the chemotherapy arm (afatinib 92.6% of patients; chemotherapy 76.2%), equating to a statistically significant treatment difference (OR 3.843; 95% CI 2.039, 7.240; p <0.0001; The median duration of disease control based on central independent review was 11.07 months for patients in the afatinib arm and 5.65 months for patients in the chemotherapy arm. [redacted]

Overall survival (interim analysis)

The overall survival data were not mature by the cut-off date for the primary analysis. Only 104 patients (43.0%) in the afatinib arm and 51 patients

(41.8%) in the chemotherapy arm had died by the cut-off date (Table 15). The primary OS analysis is scheduled for when the data are considered mature enough for meaningful analysis, this is expected to be when approximately 209 deaths have been observed.

Subsequent anti-cancer treatment

At the cut-off date, 58.4% of afatinib-treated patients who discontinued study medication and 60.7% of chemotherapy-treated patients who discontinued study medication had received at least 1 line of subsequent anti-cancer therapy. Subsequent anti-cancer therapy resulted in a degree of cross-over with respect to treatment class: patients discontinuing afatinib most often received chemotherapy or a chemotherapy-based combination (54.6%); patients discontinuing chemotherapy were most frequently treated with an EGFR TKI (48.4%).

[redacted]

[redacted]

[redacted]

Analysis of symptom control and quality of life

The analyses of symptom control and HRQoL for this report focused on the pre-specified NSCLC-related symptoms of cough, dyspnoea, and pain, as measured by the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Compliance rates for HRQoL questionnaire completion in excess of 90% for both treatment arms were observed during the on-treatment period.

Status change

Afatinib led to symptom improvement in a higher proportion of patients than chemotherapy for: cough (75.9% in the afatinib arm vs. 55.4% in the chemotherapy arm; $p = 0.0003$), dyspnoea (70.9% vs. 47.5%; $p < 0.0001$) including individual items, pain (64.3% vs. 46.5%; $p = 0.0029$) including individual items, and pain in the chest (50.0% vs. 36.0%; $p = 0.0211$) (Table 15).

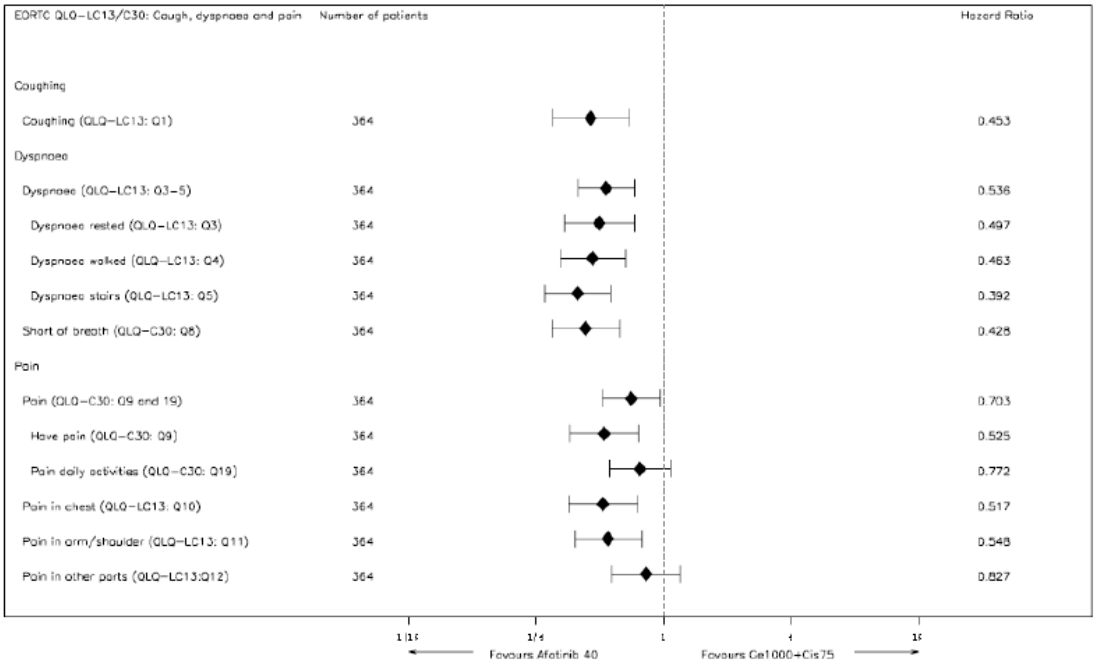
Greater improvement was also observed for afatinib compared with chemotherapy for: global health status (62.7% of patients in the afatinib arm vs. in the chemotherapy arm 32.7%, p <0.0001); physical (54.2% vs. 28.7%; p <0.0001), role (49.6% vs. 34.7%; p = 0.0129) and social (55.3% vs. 34.7%; p = 0.0007) functioning; and fatigue (77.2% vs. 52.5%; p <0.0001) (Table 15).

Time to deterioration

Compared with chemotherapy, afatinib statistically significantly delayed the time to deterioration for cough (HR 0.453; 95% CI 0.299, 0.685; p = 0.0001), dyspnoea (HR 0.536; 95% CI 0.395, 0.727; p <0.0001), and pain (HR 0.703; 95% CI 0.514, 0.961; p = 0.0265). Afatinib also delayed the time to deterioration of individual items for dyspnoea and pain (Table 15).

Afatinib also significantly delayed the time to deterioration in global health status (HR 0.560); all functional scales (physical HR 0.366, role HR 0.649, emotional HR 0.541, cognitive HR 0.698, and social HR 0.531); and all symptom scales ([redacted], and pain HR 0.703) (Figure 18).

Figure 18 Comparison of the treatment effect of afatinib vs. gemcitabine / cisplatin on the time to deterioration in coughing, dyspnoea, and pain-related items of QLQ-C30 and QLQ-LC13

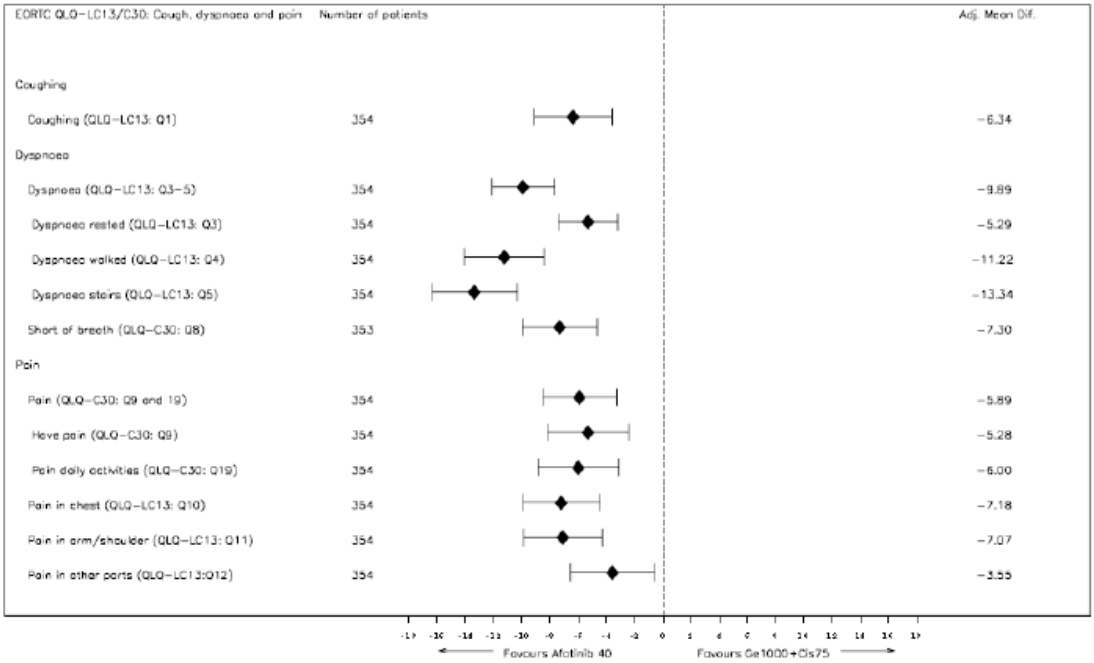


Cough: QLQ-LC13, Q1; dyspnoea: QLQ-LC13, Q3-Q5 (Q3: dyspnoea, rested; Q4: dyspnoea, walked; Q5: dyspnoea, climbed stairs); short of breath: QLQ-C30, Q8; pain: QLQ-C30, Q9 and Q19 (Q9: have pain; Q19: pain affecting daily activities); pain in the chest: QLQ-LC13, Q10; pain in arm or shoulder: QLQ-LC13, Q11; pain in other parts of the body: QLQ-LC13, Q12. The size of the rhombus reflects the number of patients. Hazard ratios for afatinib vs. chemotherapy for each subgroup category are given on the right.

Changes in scores over time

Mean scores over time significantly favoured afatinib compared with chemotherapy for cough (p <0.0001), dyspnoea (p <0.0001), and pain (p <0.0001) and for all individual items (Figure 19).

Figure 19 Comparison of the treatment effect of afatinib vs. gemcitabine / cisplatin on the difference in mean scores (all data included) for changes in scores over time, in cough, dyspnoea, and pain-related items of QLQ-C30 and QLQ-LC13



Cough: QLQ-LC13, Q1; dyspnoea: QLQ-LC13, Q3-Q5 (Q3: dyspnoea, rested; Q4: dyspnoea, walked; Q5: dyspnoea, climbed stairs); short of breath: QLQ-C30, Q8; pain: QLQ-C30, Q9 and Q19 (Q9: have pain; Q19: pain affecting daily activities); pain in the chest: QLQ-LC13, Q10; pain in arm or shoulder: QLQ-LC13, Q11; pain in other parts of the body: QLQ-LC13, Q12. Adjusted mean differences for afatinib vs. chemotherapy are given on the right.

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

No head-to-head randomised clinical trials were found that provided evidence of the efficacy and safety of afatinib versus gefitinib or erlotinib for patients with locally advanced or metastatic NSCLC harbouring an EGFR mutation. This information could only be obtained indirectly using statistical methods. On this basis, no direct meta-analysis was undertaken, and instead a mixed-treatment comparison (MTC) incorporating a network meta-analysis was formulated. Details of this analysis are provided in Section 6.7.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-

analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

Not applicable (See 6.6.2).

6.7 Indirect and mixed treatment comparisons

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

A systematic review of the literature was performed to identify randomized controlled trials, systematic reviews and meta-analyses published over the last ten years in NSCLC (2002-2012). The data extracted from included studies will inform a network meta-analysis and health economic modelling.

The systematic review was designed to capture randomized controlled trials, meta-analyses and systematic reviews comparing any licensed chemotherapy and targeted therapies for locally advanced or metastatic NSCLC for either 1st line or 3rd/4th line therapy. During the period when many of the studies were indentified, platinum doublets are the standard of care for 1st line treatment and these studies generally do not report EGFR status, which is relevant when comparing targeted therapies, such as erlotinib, gefitinib and afatinib. For these two reasons, the systematic review was not restricted to only studies that report EGFR status.

The objective was therefore to identify all available randomized controlled trials, meta-analyses or systematic reviews reporting the clinical efficacy of chemotherapy or targeted therapies for either 1st line or 3rd/4th line therapy locally advanced or metastatic NSCLC using a method acceptable to NICE. A

stringent systematic review methodology, adapted from the methodology published by the Centre of Reviews and Dissemination (CRD) has been used in this review which is recommended by NICE (Centre for Reviews and Dissemination 2009, NICE 2013). The format of this systematic review has been reported to be in line with NICE's STA requirements as outlined in Sections 6.1.1 – 6.2.2 of the NICE STA template.

Details of the review are provided in Section 10.4.

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

The search strategy developed consisted of three groups of search strings, designed to identify:

- the appropriate patient population (locally advanced or metastatic NSCLC)
- the appropriate study types (RCTs, systematic reviews, meta-analyses)
- the appropriate treatments (chemotherapy, targeted therapies, supportive care)

Separate versions of the search strings were created to conform to the different indexing terms and syntax requirements of the different databases searched. These have been provided in Section 10.4.4.

Articles identified by the searches of the different databases were combined and duplicates removed. A series of inclusion and exclusion criteria were subsequently applied to evaluate each article, based on their titles and abstracts. The inclusion/exclusion criteria were organised in the "PICOS" format (i.e. Population, intervention, comparator, outcomes, and study design) and is shown in Table 20.

Table 20 Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Population	Locally advanced or metastatic non small cell lung cancer patients	Other populations Non locally advanced or metastatic NSCLC patients
Intervention	Chemotherapy or targeted therapies	Other interventions that are not licensed for NSCLC
Comparator	Chemotherapy, targeted therapies, placebo or best supportive care (BSC)	Other comparators

	Inclusion	Exclusion
Outcomes	Overall survival Progression Free Survival 1 year survival Time to progression Objective response rate Toxicity	Other outcomes
Study design	Randomized controlled trials Systematic Reviews Meta-analyses	Observational studies Prospective studies Cohort studies Case control studies Reviews Letters Commentaries Other studies
Language	English	Not English

Bibliographies of systematic literature reviews and meta-analyses identified in the systematic search were checked to make sure no relevant publications had been missed. No studies were found that had not been captured in the systematic search.

Outcomes of interest in-line with the scoping that were collected were:

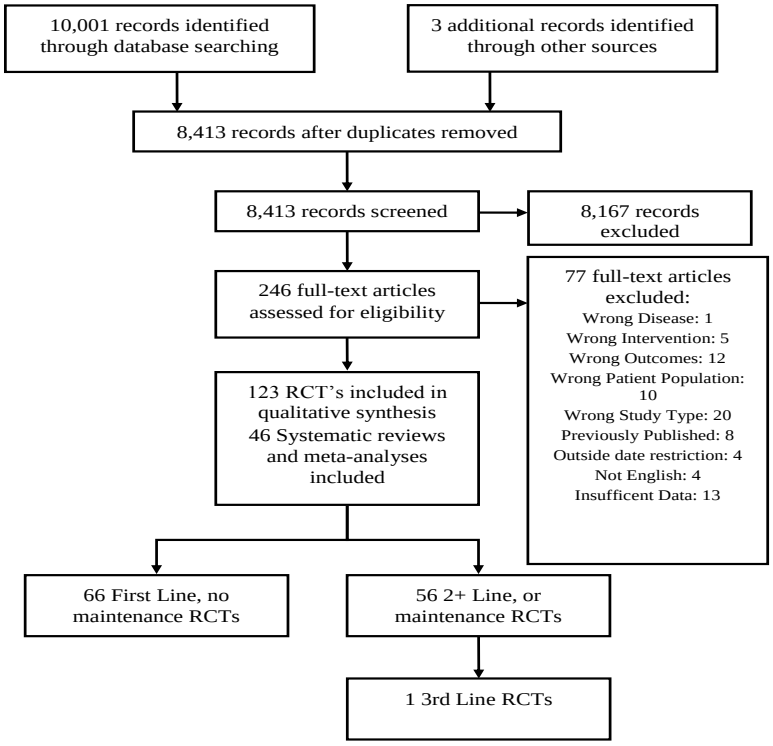
- Overall survival
- Progression-free survival
- 1 year survival
- Time to progression
- Objective response rate
- Toxicity

To prevent double-counting of studies, any systematic reviews or meta-analyses identified were reviewed to determine whether the studies they included were also captured by the literature search. Any studies they contained that had not been captured by the literature were incorporated into the literature search.

The search was completed on 6th March, 2012. This was not subsequently updated as there have been no major studies published or any new treatments licensed or approved in the UK for this indication (see section 10.2.8 for additional information). The results are presented as a PRIMSA flow diagram (Figure 20). The three additional records identified through other sources mentioned in the PRISMA diagram, were relevant articles that were published after the systematic search was completed Rosell et al. (2012), Han et al. (2012), and Miller et al. (2012). Since the SLR was intended to identify clinical data on 1st and 3rd line treatment regimens, no search terms related to line of therapy were included in the search strategy, and therefore the search results include studies for all lines of therapy. However, the MTC was concerned specifically with first line treatment options as this was the basis for the afatinib RCT data and the licensed indication. Therefore, after duplicate

articles were removed and inclusion and exclusion criteria were applied, the remaining studies were divided into groups, based on line of therapy, and a total of 66 first line studies were identified.

Figure 20: PRISMA Flow diagram of clinical studies identified for treatment for locally advanced or metastatic NSCLC



The only sources of data on the efficacy of afatinib for the first line treatment of NSCLC available for the MTC came from the LUX-Lung 3 and LUX-Lung 6 trials, which both used EGFR mutation positive patient populations. However, of the 66 first line studies identified in the systematic literature review, only 8 were conducted in an EGFR mutation positive population (4 studies), or reported outcomes for an EGFR mutation positive sub-group of the study population (4 studies). Table 21 lists the studies identified (including LUX-Lung 3 and LUX-Lung 6) that reported the outcomes of interest for EGFR mutation positive patients.

Table 21 First-line studies reporting data for EGFR mutation positive NSCLC

Author, year	Trial	Intervention	Comparator	EGFR mutation
Yang et al. 2012a, Sequist et al. 2013, BI 2012	LUX-Lung-3	Afatinib	Pemetrexed+Cisplatin	Entire population
Wu et al. 2013, Geater et al. 2013, BI 2013	LUX-Lung-6	Afatinib	Gemcitabine+Cisplatin	Entire EGFR mutation population
Rosell et al. 2012	EURTAC	Erlotinib	Cisplatin+Docetaxel or Cisplatin+Gemcitabine or Carboplatin+Docetaxel or Carboplatin+ Gemcitabine	Entire population
Zhou et al. 2011	OPTIMAL	Erlotinib	Carboplatin+ Gemcitabine	Entire population

Author, year	Trial	Intervention	Comparator	EGFR mutation
Gatzemeier et al. 2007	TALENT	Erlotinib+ Gemcitabine+ Cisplatin	Placebo+ Gemcitabine+ Cisplatin	Sub-group analysis
Maemondo et al. 2010	NEJSG002	Gefitinib	Carboplatin + Paclitaxel	Entire population
Mitsudomi et al. 2010	WJTOG3405	Gefitinib	Cisplatin + Docetaxel	Entire population
Mok et al. 2009	IPASS	Gefitinib	Carboplatin + Paclitaxel	Sub-group analysis
Fukuoka et al. 2011	IPASS	Gefitinib	Carboplatin + Paclitaxel	Sub-group analysis
Han et al. 2012	First Signal	Gefitinib	Cisplatin + Gemcitabine	Sub-group analysis

Some of the studies identified in the systematic review reporting 1st line data for EGFR mutation positive NSCLC were not included in the MTC network.

- The study by Gatzemeier et al (2007) was not included as it did not use erlotinib monotherapy.
- Zhou et al (2011) was excluded from the basecase analysis due to limitations in the clinical trial design. This investigator initiated study assessed the relative efficacy between erlotinib and carboplatin and gemcitabine in combination as first-line treatment for patients with advanced EGFR mutation-positive NSCLC in China. However, the results reported in this study are notably different from a similar study (EURTAC) therefore raising concerns of transferability of results. This difference between trials may be explained by an underperforming comparator arm in OPTIMAL or by better compliance and more aggressive adherence to the maximum possible dosage of erlotinib treatment in OPTIMAL, as stated by the ERG group in a recent Single Technology Appraisal (Greenhalgh et al. 2011). Also, the study has not been accepted by regulatory authorities including the Chinese Authorities and EMA.

Because of these limitations, a more extensive network was used in the MTC, including both the LUX-Lung 3 and LUX-Lung 6 studies, that was based on the base case MTC networks used for the 2009 Gefitinib FAD updated indirect comparison (NICE 2009b). To the 2009 Gefitinib FAD updated indirect comparison network, the following were added:

- Data from LUX-Lung 3 and LUX-Lung 6

- All the relevant 1st line papers from the systematic review that reported data for an EGFR mutation positive population. These incorporated erlotinib into the network and added additional gefitinib studies, published since the 2009 gefitinib FAD network

- The 1st line paper captured by the systematic review that included pem/cis (Scagliotti et al. 2009). This was because the pem/cis arm of LUX-Lung 3 could not be linked to the rest of the network based on the

gefitinib FAD network plus the EGFR mutation plus papers from the systematic review, since none of these studies had used pem/cis.

For additional clarification, the studies used to calculate the PFS network and the route by which they were identified is shown in Table 22 and for OS is shown in Table 23. The full list of studies is shown in Section 6.7.3.

Table 22 Data used to calculate PFS network and the route by which they were identified

Paper	Study	Arm 1	Arm 2	Population	Source
Chang et al. 2001*		Gem/Cis	Vin/Cis	NSCLC	NICE (2010)
Grideli et al. 2003		Gem/Cis	Vin/Cis	NSCLC	NICE (2010)
Scagliotti et al. 2002		Gem/Cis	Pac/Carb	NSCLC	NICE (2010)
Schiller et al. 2002		Gem/Cis	Doc/Cis Pac/Cis Pac/Carb	NSCLC	NICE (2010)
Smit et al. 2003		Gem/Cis	Pac/Cis	NSCLC	NICE (2010)
Thomas et al. 2006		Gem/Carb	Vin/Cis	NSCLC	NICE (2010)
Han et al. 2012	First SIGNAL	Gefitinib	Gem/Cis	EGFRm (SG)	SR
Maemondo et al. 2010	NEJGSG002	Gefitinib	Pac/Carb	EGFRm	SR
Mitsudomi et al. 2010	WJTOG3405	Gefitinib	Doc/Cis	EGFRm	SR
Mok et al. 2009; Fukuoka et al. 2011	IPASS	Gefitinib	Pac/Carb	EGFRm (SG)	SR
Rossell et al. 2012	EURTAC	Erlotinib	Doc/Cis Gem/Cis Doc/Carb Gem/Carb	EGFRm	SR
Scagliotti et al. 2009		Pem/Cis	Gem/Cis	NSCLC	SR
Yang et al. 2012a, Sequist et al. 2013, BI 2012	LUX-Lung 3	Afatinib	Pem/Cis	EGFRm	BI afatinib data
Wu et al. 2013, Geater et al. 2013, BI 2013	LUX-Lung 6	Afatinib	Gem/Cis	EGFRm	BI afatinib data

6 from gefitinib submission + 6 from IMS SLR + LL3 + LL6 = 14 trials in PFS network. SG = sub-group; SR = systematic review. *data from NICE (2009b) and NICE (2010)

Table 23 Data used to calculate OS network and the route by which they were identified

Paper	Study	Arm 1	Arm 2	Population	Source
Chang et al. 2001*		Gem/Cis	Vin/Cis	NSCLC	NICE (2010)
Comella et al. 2000		Gem/Cis	Vin/Cis	NSCLC	NICE (2010)
Fossella et al. 2003		Vin/Cis	Doc/Cis Doc/Carb	NSCLC	NICE (2010)
Gridelli et al. 2003		Gem/Cis	Vin/Cis	NSCLC	NICE (2010)
Mazzanti et al. 2003		Gem/Carb	Gem/Cis	NSCLC	NICE (2010)
Melo et al. 2002*		Gem/Cis	Vin/Cis	NSCLC	NICE (2010)
Rossell et al. 2002		Pac/Carb	Pac/Cis	NSCLC	NICE (2010)
Scagliotti et al. 2002		Gem/Cis	Pac/Carb	NSCLC	NICE (2010)
Schiller et al. 2002		Gem/Cis	Doc/Cis Pac/Cis Pac/Carb	NSCLC	NICE (2010)
Smit et al. 2003		Gem/Cis	Pac/Cis	NSCLC	NICE (2010)
Thomas et al. 2006		Gem/Carb	Vin/Cis	NSCLC	NICE (2010)
Zatloukal et al. 2003		Gem/Carb	Gem/Cis	NSCLC	NICE (2010)

Han et al. 2012	First SIGNAL	Gefitinib	Gem/Cis	EGFRm (SG)	SR
Mitsudomi et al. 2010	WJTOG3405	Gefitinib	Doc/Cis	EGFRm	SR
Mok et al. 2009; Fukuoka et al. 2011	IPASS	Gefitinib	Pac/Carb	EGFRm (SG)	SR
Rossell et al. 2012	EURTAC	Erlotinib	Doc/Cis Gem/Cis Doc/Carb Gem/Carb	EGFRm	SR
Scagliotti et al. 2009		Pem/Cis	Gem/Cis	NSCLC	SR
Yang et al. 2012a, Sequist et al. 2013, BI 2012	LUX-Lung 3	Afatinib	Pem/Cis	EGFRm	BI afatinib data
Wu et al. 2013, Geater et al. 2013, BI 2013	LUX-Lung 6	Afatinib	Gem/Cis	EGFRm	BI afatinib data

12 from gefitinib submission + 5 from IMS SLR + LL3 + LL6 = 19 trials in OS network.SG = sub-group; SR = systematic review. *data from NICE (2009b) and NICE (2010)

An assessment of the quality of the studies is found in Section 10.5.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Characteristics of the included studies

The underlying assumption in quantitative evidence synthesis is that the clinical studies are sufficiently homogeneous to be quantitatively combined, which requires that the patients included should be sufficiently similar in the sets of randomized-controlled studies. In addition to clinical similarity, methodological similarity (e.g., study protocol, definition of outcomes) is required for deriving valid estimates.

In these analyses the methodological similarity is warranted by the inclusion of good quality randomised controlled studies. However, it is observed that there may be some discrepancies regarding the homogeneity of patients in the included studies. The details of the studies included in the MTC can be found in Table 24.

Table 24 Characteristics of the studies included in the MTC

Study	Intervention	Comparators	Population	EGFR Mutation1, n (%)		
				EXON 19 deletion	L858R	Other
Chang et al. 2001*	Vinorelbine (20 mg/m^2) on day 1, 8, and 15 plus cisplatin (80 mg/m^2) on day 15	Gemcitabine (1000 mg/m2) on day 1, 8, and 15 plus cisplatin (80 mg/ m^2) on day 15	Chemo-naive Stage IIIb or IV, ECOG PS≤2	Not reported	Not reported	Not reported
Comella et al. 2000	Cisplatin 100 mg/m^2 on day 1 and Gemcitabine 1,000 mg/m^2 on day 1, 8, and 15 every 4 weeks	Cisplatin 120 mg/ m^2 on day 1 and 29 (and then every 6 weeks) and Vinorelbine 30 mg/ m^2 /week for 10 weeks	Chemo-naive Stage IIIb or IV, ECOG PS≤1	Not reported	Not reported	Not reported
Fossella et al. 2003	Docetaxel 75 mg/ m^2 plus cisplatin 75 mg/ m^2 (both as 1h iv infusions on day 1, repeated every 3 weeks)	Docetaxel 75 mg/ m^2 1h iv plus carboplatin iv AUC 6 mg/mL (both on day 1, repeated every 3 weeks) versus Vinorelbine 25 mg/m2 as a 6- to 10-min iv on days 1, 8, 15, and 22, plus cisplatin 100 mg/m2 iv on day 1, repeated every 4 weeks	Chemo-naive Stage IIIb or IV, Karnofsky PS≥70%	Not reported	Not reported	Not reported
Gridelli et al. 2003	Gemcitabine 1,000 mg/ m^2 plus vinorelbine 25 mg/ m^2 on days 1 and 8. Additional therapy was at the discretion of the investigators. Cycles were given every 3 weeks and a total of 6 planned.	Gemcitabine 1,200 mg/m2 on days 1 and 8 plus cisplatin 80 mg/ m^2 on day 1 versus Vinorelbine 30 mg/ m^2 on days 1 and 8 plus cisplatin 80 mg/ m^2 on day 1. Cycles were given every 3 weeks and a total of 6 planned	Chemo-naive Stage IIIb or IV, ECOG PS≤2	Not reported	Not reported	Not reported

[1] For a complete list of background characteristics of populations in the above studies refer to: *Table 22 Patients' baseline characteristics*

Study	Intervention	Comparators	Population	EGFR Mutation1, n (%)		
				EXON 19 deletion	L858R	Other
Han et al. 2012	Gefitinib: 250mg/day	Gemcitabine 1,250 mg/m2 on days 1 and 8; cisplatin 80 mg/ m^2 on day 1 every 3 weeks, for up to nine courses	Stage IIIB or IV lung adenocarcinoma, Eastern Cooperative Oncology Group performance status 0 to 2, and adequate organ function. EGFR-TK M+	Not reported	Not reported	Not reported
Maemondo et al. 2010	Gefitinib: 250mg/day (3 week cycles)	Carboplatin: AUC 5/6/mg/mL/min Paclitaxel: 200mg/ m^2 (3 week cycles)	Advanced non–small-cell lung cancer harbouring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M	Gef: 50.9% Pac/Carb: 51.8%	Gef: 43.0% Pac/Carb: 42.1%	Gef: 6.1% Pac/Carb: 6.1%
Mazzanti et al. 2003	Gemcitabine/Carboplatin over a 21 day cycle (Gemcitabine 1200 mg/ m^2 over 30 min on days 1 and 8); Carboplatin (AUC 5) given over 60 min on day 2)	Gemcitabine/Cisplatin over a 21 day cycle (Gemcitabine 1200 mg/m2 over 30 min on days 1 and 8); Cisplatin 80 mg/ m^2 over 45 min	Chemo-naive Stage IIIb or IV, ECOG PS≤2	Not reported	Not reported	Not reported
Melo et al. 2002*	Cisplatin 100 mg/ m^2 day 1, vinorelbine 30 mg/ m^2 day 1, 8, 15 q28d	Cisplatin 100 mg/ m^2 day 1, gemcitabine 1000 mg/ m^2 day 1, 8, 15 q28d Gemcitabine 1000 mg/ m^2 day 1, 8, 15, cisplatin 100 mg/m2 day 15 q28d	Locally advanced and metastatic NSCLC	Not reported	Not reported	Not reported
Mitsudomi et al. 2010	Gefitinib: 250mg/day	Cisplatin: 80mg/ m^2 (1x) Docetaxel: 60mg/ m^2 (1x) (every 3 weeks for 6 cycles)	Histologically or cytologically confirmed NSCLC, WHO performance status 0–1	Gef: 58.1% Doc/Cis: 43.0%	Gef: 41.9% Doc/Cis: 57%	
Mok et al. 2009	Gefitinib: 250mg/day	Carboplatin: AUC 5 or 6 (1x)	Chemo-naive stage IIIB or stage IV NSCLC, Eastern	Not reported	Not reported	Not reported

Study	Intervention	Comparators	Population	EGFR Mutation1, n (%)		
				EXON 19 deletion	L858R	Other
		Paclitaxel: 200mg/ m^2 (1x)(every 3 weeks for 6 cycles)	Cooperative Oncology Group performance status of 0 or 2			
Rosell et al. 2002	Paclitaxel 200 mg/ m^2 (3-h intravenous infusion) followed by carboplatin at an AUC of 6, all repeated every 3 weeks	Paclitaxel 200 mg/ m^2 (3-h intravenous infusion) followed by cisplatin at a dose of 80 mg/ m^2, all repeated every 3 weeks	Chemo-naive Stage IIIb or IV, ECOG PS≤2	Not reported	Not reported	Not reported
Rosell et al. 2012	Erlotinib: 150mg/day until disease progression	Cisplatin: 75 mg/ m^2 (1x) Docetaxel: 75 mg/ m^2 (1x) Or Cisplatin: 75 mg/ m^2 (1x) Gemcitabine: 1250 mg/ m^2 (2x) Or Carboplatin: AUC 6 (1x) Docetaxel: 75 mg/ m^2 (1x) Or Carboplatin: AUC 5 (1x) Gemcitabine: 1000 mg/ m^2 (2x) (for up to four 3-week cycles)	Chemo-naive stage IIIB (with pleural effusion) or stage IV NSCLC (based on the sixth TNM staging system), measurable or evaluable disease, presence of activating EGFR mutations (exon 19 deletion or L858R mutation in exon 21)	Erl: 66.3% Std. Tx: 33.7%	Erl: 33.7% Std. Tx: 33.3%	Erl: 0% Std. Tx: 0%

Study	Intervention	Comparators	Population	EGFR Mutation1, n (%)		
				EXON 19 deletion	L858R	Other
Scagliotti et al. 2002	Gemcitabine 1,250 mg/ m^2 days 1 and 8 plus cisplatin 75 mg/ m^2 day 2 every 21 days	Paclitaxel 225 mg/ m^2 (3-hour infusion) then carboplatin (AU the concentration-time curve of 6 mg/mL·min), both on day 1 every 21 days versus Vinorelbine 25 mg/ m^2 /wk for 12 weeks then every other week plus cisplatin 100 mg/ m^2 day 1 every 28 days	Chemo-naive Stage IV, ECOG PS≤2	Not reported	Not reported	Not reported
Scagliotti et al. 2009	Cisplatin: 75mg/m2 (1x) Pemetrexed: 500mg/ m^2 (1x) (repeated every 3 weeks)	Cisplatin: 75mg/ m^2 (1x) Gemcitabine: 1,250mg/ m^2 (2x) (repeated every 3 weeks)	Chemo-naive stage IIIB or stage IV NSCLC, Eastern Cooperative Oncology Group performance status of 0 or 1	Not reported	Not reported	Not reported
Schiller et al. 2002	Paclitaxel 135 mg/ m^2 administered over 24h on day 1, followed by Cisplatin 75 mgm2 on day 2 (3-week cycles)	Gemcitabine 1000 mg/ m^2 was administered on days 1, 8, and 15, and Cisplatin 100 mg/m^2 was administered on day 1 (4-week cycles) versus Docetaxel 75 mg/ m^2 and Cisplatin 75 mg/ m^2 on day 1 (3-week cycles) versus Paclitaxel 225 mg/ m^2 given over 3h on day 1, followed on the same day by Carboplatin (AUC 6.0), (3-week cycles)	Chemo-naive patients with NSCLC stage IIIB/IV or recurrent disease	Not reported	Not reported	Not reported

Study	Intervention	Comparators	Population	EGFR Mutation1, n (%)		
				EXON 19 deletion	L858R	Other
Smit et al. 2003	Paclitaxel 175 mg/ m^2 on day 1 followed by Cisplatin 80 mg/ m^2 on day 1 (3- week cycles)	Gemcitabine 1,250 mg/ m^2 on days 1 and 8 and Cisplatin 80 mg/ m^2 on day 1 after Gemcitabine (3- week cycles)	Chemo-naive Stage IIIb or IV, ECOG PS≤2	Not reported	Not reported	Not reported
Thomas et al. 2006	Gemcitabine 1250mg/ m^2 on days 1 and 8 plus Carboplatin (AUC 6) on day 1 (3-week cycles)	Vinorelbine 30mg/ m^2 weekly plus Cisplatin 80mg/ m^2 on day 1 (3-week cycles	Chemo-naive Stage IIIb or IV, WHO PS≤2	Not reported	Not reported	Not reported
Yang et al. 2012a, Sequist et al. 2013, BI 2012	Afatinib daily 40 mg	Pemetrexed 500 mg/ m^2 + Cisplatin 75 mg/ m^2 q21 days up to 6 cycles	Stage IIIB/IV, PS 0–1, chemo-naive	Afatinib: 49.1% Pem/Cis: 49.6%	Afatinib: 39.6% Pem/Cis: 40.9%	Afatinib: 11.3% Pem/Cis: 9.6%
Wu et al. 2013, Geater et al. 2013, BI 2013	Afatinib daily 40 mg	Gemcitabine 1000 mg/m^2 D1, 8 + Cisplatin 75 mg/m^2 q21 days up to 6 cycles	Stage IIIB/IV, PS 0–1, chemo-naive	Afatinib: 51.2% Gem/Cis: 50.8%	Afatinib: 38:0% Gem/Cis: 37.7%	Afatinib: 10.7% Pem/Cis: 11.5%
Zatloukal et al. 2003	Gemcitabine 1200 mg/ m^2 iv over 30 min on days 1 and 8 plus Cisplatin 80 mg/ m^2 iv. Platinum analogues were administered at least 4h after Gemcitabine injection on day 1. Two weeks of treatment followed by a week of rest (3-week cycles)	Gemcitabine 1200 mg/m2 iv over 30 min on days 1 and 8 plus carboplatin AUC=5 iv. Platinum analogues were administered at least 4h after gemcitabine injection on day 1. Two weeks of treatment followed by a week of rest (3-week cycles)	Chemo-naive Stage IIIb or IV, Karnofsky PS≥70%	Not reported	Not reported	Not reported

*data from NICE (2009b) and NICE (2010)

Besides the LUX-Lung 3 and LUX-Lung 6 trials, 4 of the included studies assessed the efficacy of treatments on EGFR mutation positive patients (Rosell et al. 2012; Han et al. 2012; Maemondo et al. 2010; Mitsudomi et al. 2010). The assumption of similarity of populations across these studies had to be made in order to allow the analyses. For instance, the study by Scagliotti et al. (2009) does not report survival data specifically for EGFR mutation positive patients. Instead, data for the adenocarcinoma sub-group of a broader NSCLC patient population are reported. A higher proportion of patients with adenocarcinoma have EGFR mutations than other histological sub-types of NSCLC (Boch et al. 2013), therefore this sub-group was used as a proxy for EGFR mutation positive NSCLC patients. This assumption seems reasonable as there is no mechanistic rationale to support differentiated activity in this NSCLC subgroup between different chemotherapies and, in addition, this has not been observed for those chemotherapy regimens that were compared to EGFR inhibitors in all relevant studies to date.

In the EURTAC trial (Rosell et al. 2012) erlotinib was compared against four chemotherapy regimens. These were assumed to be equally efficacious given the absence of specific outcomes reported for each of the four chemotherapy regimens. However, this assumption was criticised by the ERG in the erlotinib HTA (NICE 2011b), and as a consequence, this analysis is based on the outcomes from different chemotherapy regimens.

The characteristics of patients at baseline appear to vary between the included studies. For example, the proportion of patients who never smoked ranges approximately from 12% to 94%. This is important, since evidence from some studies suggests that improvements due to treatment with TKIs for former smokers are less pronounced than for never smokers despite EGFR mutation positivity (EURTAC (Rosell et al. 2012) IPASS (Fukuoka et al. 2011), LUX-Lung 3 (Yang et al. 2012a). Furthermore, differences were observed in the baseline ECOG performance status, particular types of EGFR mutation, ethnicity and histological diagnoses. This is a factor that should be taken into consideration when interpreting the results and conclusions of these analyses.

Investigator or independent assessed PFS

The relative treatment effects are measured by the hazard ratios of overall survival (OS) and progression-free survival (PFS) between the competing therapies. Overall survival is defined as the time from randomisation until death by any cause while progression free survival is defined as the time from randomisation until tumour progression or death by any cause.

Out of the 20 studies included in the NMA (see Table 5), in five studies PFS was assessed by a blinded independent review committee (LUX Lung 3, LUX-Lung 6, Scagliotti et al. 2002, Maemondo 2010, or single reviewer who was blinded to treatment assignment (Han et al 2012)). Among these, only the LUX-Lung 3 and LUX-Lung 6 studies provided PFS results using both central independent and investigator assessment.

Despite high concordance of central independent review and investigator assessment in identifying PFS events in both studies, the resulting hazard ratios for both assessment approaches differ:

For LUX-Lung 3, ITT population

- central independent review: HR 0.58 (95%CI: 0.43, 0.78).
- investigator assessment: HR 0.49 (95% CI 0.37, 0.65).

and for LUX-Lung 6, ITT population (Table 2, Table 26)

- central independent review: HR 0.28 (95%CI: 0.20, 0.39).
- investigator assessment: HR 0.26 (95% CI 0.19, 0.36).

Given that that LUX-Lung 3 and LUX-Lung 6 trials were open label, for the avoidance of doubt the more conservative 'central independent review' is used as the base case in the analysis.

New data for the MTC

In 2013, new evidence became available from the LUX-Lung 6 clinical trial where afatinib was compared against gemcitabine and cisplatin in combination. Also, upon request of regulatory authorities (FDA and EMA) an updated OS analyses was conducted for LUX-Lung 3. These details are in Table 25 and Table 26.

Table 25 Inputs from LUX-Lung 6

Parameter	Mean	95% CI	Significance
Efficacy			
HR for investigator assessed PFS for the ITT population	0.262	(0.193 - 0.356)	p < 0.0001
HR for investigator assessed PFS for the common mutation population	0.215	(0.154 - 0.299)	p <0.0001
HR for PFS by independent review for the ITT population	0.279	(0.201 - 0.388)	p <0.0001
HR for PFS by independent review for the common mutation population	0.248	(0.175 - 0.351)	p <0.0001
HR for OS (immature)	0.949	(0.676 - 1.330)	p <0.7593
AE, grade ¾	**Afatinib**	**GEM/CIS**	
Diarrhoea	5.9 %	0.0 %	
Rash/acne	14.2 %	0.0 %	
Fatigue	2.1 %	0.9 %	

95%CI is confidence interval. The numbers in this table were presented with higher precision, and these numbers in tables further in the report may be rounded.

Table 26 Inputs from LUX-Lung 3

Parameter	Mean	95% CI	Significance
Efficacy			
HR for OS (immature, updated)	0.907	(0.660 - 1.246)	p <0.5457

The network of evidence for PFS is illustrated in Figure 21 and for OS is illustrated in Figure 22.

Figure 21. Network of evidence – Progression Free Survival (PFS)

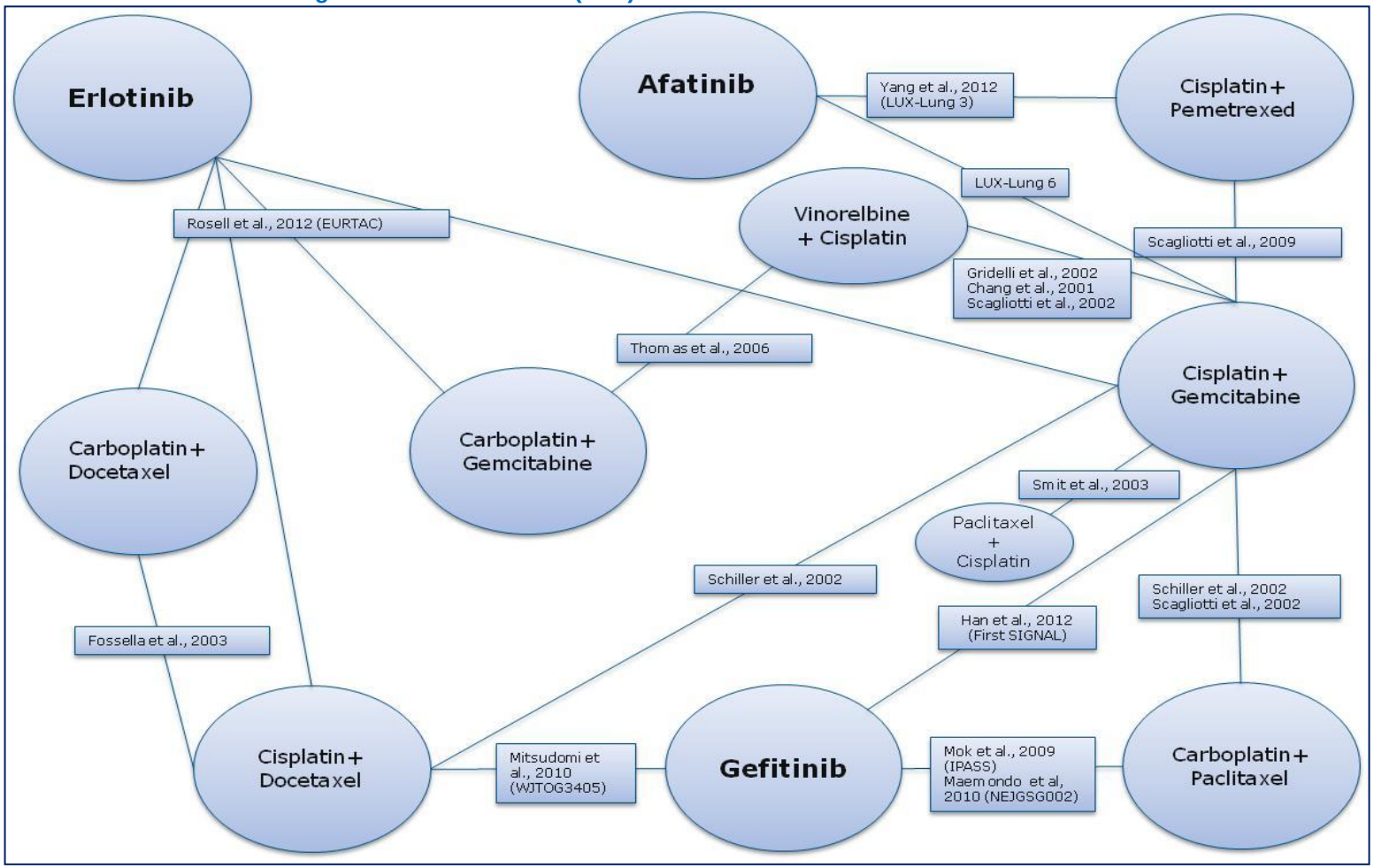
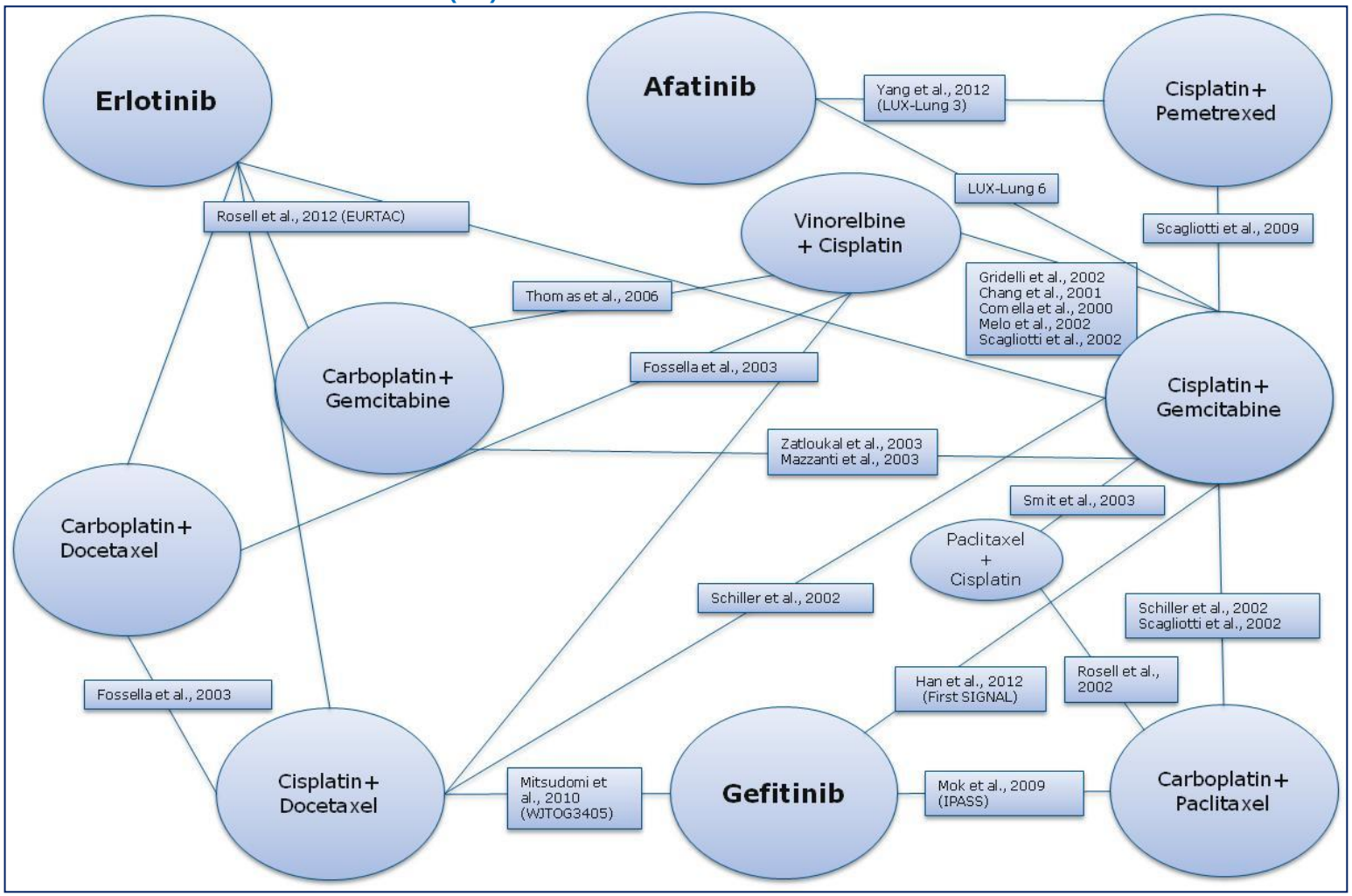


Figure 22 Network of evidence – Overall Survival (OS)



6.7.4 For the selected trials, provide a summary of the data used in the analysis.

A summary of the patient characteristics is shown in Table 27. Data used to calculate the PFS is in Table 28 and OS in Table 29. Data use for adverse events are also presented. These are for diarrhoea (grade 3/4) (Table 30), rash/acne (grade 3/4) (Table 31), and fatigue (grade 3/4) (Table 32).

Table 27 Patients' baseline characteristics from the studies that have been included in the MTC

Study	Tx.	N	Gender (% males)	age	Age Stat.	Ethnicity	Smoking status (%)		ECOG PS (%)				Histological diagnosis						Type of EGFR mutation		
							Never smoked	Previous or current smoker	0	1	2	3	Adenocarcinoma	Broncho-alveolar carcinoma	Large cell carcinoma	Squamous cell carcinoma	Other	Unknown	EXON 19 deletion	L858R	Other
Han et al. 2012	Gef	159	12	57	Median	Korean	NR	NR	25.8	65.4	8.8	0	NR	NR	NR	NR	NR				
	Gem/Cis	150	10.7	56.5	Median	Korean	NR	NR	20.7	70	9.3	0	NR	NR	NR	NR	NR				
Maemondo et al. 2010	Gef	114	36.8	63.9	Mean	Japan	65.8	34.2	47.4	51.8	0.9	0	90.35	0	0.88	4.39	4.39	0	50.9	43	6.1
	Pac/Carb	114	36	62.6	Mean	Japan	57.9	42.1	50	48.2	1.8	0	96.49	0	0	2.63	0.88	0	51.8	42.1	6.1
Mitsudomi et al. 2010	Gef	86	31.4	64	Median	Japan	70.9	29.1	65.12	34.88	0	0	96.51	0	0	1.16	2.33	0	58.1	41.9	0
	Doc/Cis	86	30.2	64	Median	Japan	66.3	33.7	60.47	39.53	0	0	97.67	0	0	1.16	1.16	0	43	57	0
Mok et al. 2009	Gef	609	20.5	57	Median	Asia	93.8	6.2	25.78	64.2	10.02	0	95.4	4.43	0	0	0	0.2			
	Pac/Carb	608	20.9	57	Median	Asia	93.6	6.4	26.48	62.83	10.69	0	97.2	2.47	0	0	0	0.3			
Rosell et al. 2002	Pac/Cis	309	81.9	58	Median	Europe	NR	NR	16.18	66.34	17.15	0.32	44.98	0	9.39	37.86	7.77	0			
	Pac/Carb	309	83.5	58	Median	Europe	NR	NR	16.83	66.02	17.15	0	46.93	0	10.03	37.22	5.83	0			
Rosell et al. 2012	Erl	86	32.6	65	Median	Europe	66.3	33.7	31.4	54.65	13.95	0	95.35	0	3.49	1.16	0	0	66.3	33.7	0
	Std.Tx.	87	21.8	65	Median	Europe	72.4	27.6	34.48	51.72	13.79	0	89.66	2.3	1.15	0	6.9	0	66.7	33.3	0
Yang et al. 2012a, Sequist et al. 2013, BI 2012	Afatinib	230	36.1	60.5	Mean	Global	67.4	32.6	40.0	60.0	0	0	100	0	0	0	0	0	49.1	39.6	11.3
	Pem/Cis	115	33.0	59.9	Mean	Global	70.4	29.5	35.7	63.5	0.9	0	100	0	0	0	0	0	49.6	40.9	9.6
Wu et al. 2013, Geater et al. 2013, BI 2013	Afatinib	242	36.0	56.7	Mean	Asian	74.8	25.2	19.8	80.2	0	0	100	0	0	0	0	0	51.2	38.0	10.7
	Gem/Cis	122	32.0	55.6	Mean	Asian	81.1	18.9	33.6	66.4	0	0	100	0	0	0	0	0	50.8	37.7	11.5
Scagliotti et al. 2002	Gem/Cis	205	81.5	63	Median	Italy	NR	NR	94.63		NR	NR	50.24	0	6.34	32.68	10.73	0			
	Pac/Carb	201	75.6	62	Median	Italy	NR	NR	91.54		NR	NR	47.76	0	9.95	32.34	9.95	0			
Scagliotti et al. 2009	Pem/Cis	862	70.2	61.1	Median		14.8	85.2		64.5			50.58	0	8.82	28.31	12.3	0			
	Gem/Cis	863	70.1	61	Median		14.1	85.9		64.19			47.62	0	8.92	26.54	16.92	0			
Schiller et al. 2002	Pac/Cis	288	64	62	Median		NR	NR	29	65	6	0	NR	NR	NR	NR	NR	NR			
	Gem/Cis	288	62	64	Median		NR	NR	33	62	5	0	NR	NR	NR	NR	NR	NR			
	Cos/Cis	289	63	63	Median		NR	NR	32	62	6	0	NR	NR	NR	NR	NR	NR			
	Pac/Carb	290	62	63	Median		NR	NR	28	67	5	0	NR	NR	NR	NR	NR	NR			
Smit et al. 2003	Pac/Cis	159	59.7	57	Median	NR			22.01	66.04	11.95	0	40.25	0	39.62	18.87	1.26	0			
	Gem/Cis	160	70.6	57	Median	NR			25	63.75	11.25	0	45.63	0	25	25.63	3.13	0.6			
	Pac/Gem	161	68.3	56	Median	NR			23.6	64.6	11.8	0	39.75	0	33.54	21.74	4.35	0.6			
Zatloukal et al. 2003	Gem/Cis	87	77	63	Median	NR	11.5	88.5	NR	NR	NR	NR	26.44	0	6.9	56.32	10.34	0			
	Gem/Carb	89	76.4	62	Median	NR	12.4	87.6	NR	NR	NR	NR	32.58	0	6.74	46.07	14.61	0			
Chang et al. 2001*	Gem/Cis	29	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			
	Vin/Cis	34	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			
Comella et al. 2000	Gem/Cis (PG)	60	90	60	Median	NR	NR	NR	30	70	0	0				52		48			
	Vin/Cis (PV)	60	93	61	Median	NR	NR	NR	28	72	0	0				47		53			
Fossella et al. 2003	Vin/Cis	404	75	61	Median	NR	NR	NR	NR	NR	NR	NR	41	2.7	12	35	10	0			
	Doc/Carb	406	72	59	Median	NR	NR	NR	NR	NR	NR	NR	42	2.7	12	34	10	0			
	Doc/Cis	408	72	61	Median	NR	NR	NR	NR	NR	NR	NR	44	3.7	10	32	10	0			

Study	Tx.	N	Gender (% males)	age	Age Stat.	Ethnicity	Smoking status (%)		ECOG PS (%)				Histological diagnosis						Type of EGFR mutation		
							Never smoked	Previous or current smoker	0	1	2	3	Adenocarcinoma	Broncho-alveolar carcinoma	Large cell carcinoma	Squamous cell carcinoma	Other	Unknown	EXON 19 deletion	L858R	Other
Gridelli et al. 2002	Gem/Cis	250	78	62	Median	Mainly Europe	NR	NR	32	55	14		43		8	35	2	15			
	Vin/Cis	251	81	61	Median	Mainly Europe	NR	NR	32	55	13		42		6	34	1	14			
Mazzanti et al. 2003	Gem/Carb	58	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			
	Gem/Cis	62	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			
Melo et al. 2002*	Gem/Cis	62	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			
	Vin/Cis	62	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			
Thomas et al. 2006	Gem/Carb	51	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			
	Vin/Cis	49	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR			

* data from NICE (2009b) and NICE (2010)

Table 28 Data for PFS used in the MTC

Data Progression Free Survival	Treatments		Mean	95% Confidence Interval	
Study			Hazard Ratio	Lower	Upper
Chang et al. 2001 *	Gem/Cis	Vin/Cis	0.94	0.5	1.78
Gridelli et al. 2002	Gem/Cis	Vin/Cis	0.91	0.7	1.18
Han et al. 2012	Gefitinib	Gem/Cis	0.544	0.27	1.1
Maemondo et al. 2010	Gefitinib	Pac/Carb	0.3	0.22	0.41
Mitsudomi et al. 2010	Gefitinib	Doc/Cis	0.49	0.34	0.71
Mok et al. 2009	Gefitinib	Pac/Carb	0.48 ‡	0.36	0.64
			0.44 ‡‡	0.33	0.59
Rosell et al. 2012	Erlotinib	Doc/Cis	0.37	0.25	0.54
		Gem/Cis	0.37	0.25	0.54
		Doc/Carb	0.37	0.25	0.54
		Gem/Carb	0.37	0.25	0.54
Scagliotti et al. 2002	Gem/Cis	Vin/Cis	0.95	0.77	1.17
		Pac/Carb	1.05	0.85	1.29
Scagliotti et al. 2009	Pem/Cis	Gem/Cis	0.9	0.78	1.03
Schiller et al. 2002	Gem/Cis	Doc/Cis	0.87	0.73	1.04
		Pac/Cis	0.79	0.66	0.94
		Pac/Carb	0.84	0.7	0.99
Smit et al. 2003	Gem/Cis	Pac/Cis	0.89	0.65	1.22
Thomas et al. 2006	Gem/Carb	Vin/Cis	1.21	0.72	2.03
Yang et al. 2012a, Sequist et al. 2013, BI 2012	Afatinib	Pem/Cis	0.58 †	0.43	0.78
			0.49 ††	0.37	0.65
			0.41 †††	0.31	0.55
			0.47††††	0.34	0.65
Wu et al. 2013, Geater et al. 2013, BI 2013	Afatinib	Gem/Cis	0.28†	0.20	0.39
			0.26 ††	0.19	0.36
			0.22 †††	0.15	0.30
			0.25 ††††	0.18	0.35

† ITT population, Independent assessment; †† ITT population, Investigator assessment; ††† Common mutation population, Investigator assessment; †††† Common mutation population, Independent assessment; ‡ ITT population; ‡‡ Common mutation. Derived by a meta-analysis conducted in the Del 19 and L858R subgroups of the IPASS trial. * data from NICE (2009b) and NICE (2010)

Table 29 Data for OS used in the MTC

Data Overall Survival	Treatments		Hazard Ratio	95% Confidence Interval	
Study				Lower	Upper
Chang et al. 2001*	Gem/Cis	Vin/Cis	0.93	0.4	2.16
Comella et al. 2000	Gem/Cis	Vin/Cis	0.71	0.45	1.13
Fossella et al. 2003	Vin/Cis	Doc/Cis	1.183	0.989	1.416
	Vin/Cis	Doc/Carb	1.048	0.877	1.253
Chang et al. 2001 NICE 2010	Gem/Cis	Vin/Cis	1.02	0.76	1.35
Han et al., 2012	Gefitinib	Gem/Cis	1.04	0.49	2.18
Mazzanti et al. 2003	Gem/Carb	Gem/Cis	1.09	0.75	1.59
Melo et al. 2002*	Gem/Cis	Vin/Cis	0.71	0.41	1.22
Mitsudomi et al., 2010	Gefitinib	Doc/Cis	1.64	0.75	3.58
Mok et al., 2009	Gefitinib	Pac/Carb	0.78	0.5	1.2
Rosell et al. 2002	Pac/Carb	Pac/Cis	1.22	1.03	1.43
Rosell et al. 2012	Erlotinib	Doc/Cis	1.04	0.65	1.68

Data Overall Survival	Treatments		Hazard Ratio	95% Confidence Interval	
Study				Lower	Upper
		Gem/Cis	1.04	0.65	1.68
		Doc/Carb	1.04	0.65	1.68
		Gem/Carb	1.04	0.65	1.68
Scagliotti et al. 2002	Gem/Cis	Vin/Cis	0.87	0.69	1.09
		Pac/Carb	1.04	0.83	1.31
Scagliotti et al. 2009	Pem/Cis	Gem/Cis	0.84	0.71	0.99
Schiller et al. 2002	Gem/Cis	Doc/Cis	0.94	0.79	1.14
		Pac/Cis	0.92	0.76	1.1
		Pac/Carb	0.96	0.8	1.15
Smit et al. 2003	Gem/Carb	Vin/Cis	0.89	0.53	1.49
Thomas et al. 2006	Gem/Cis	Pac/Cis	0.9	0.65	1.25
Yang et al. 2012a, Sequist et al. 2013, BI 2012	Afatinib	Pem/Cis	0.91	0.66	1.25
Wu et al. 2013, Geater et al. 2013, BI 2013	Afatinib	Gem/Cis	0.95	0.68	1.33
Zatloukal et al. 2003	Gem/Carb	Gem/Cis	0.98	0.69	1.39

* data from NICE (2009b) and NICE (2010)

Table 30. Adverse events - diarrhoea (grade 3/4)

Diarrhoea (grade 3/4)			Treatment		Comparator	
Study	Treatment	Comparator	N	events	N	events
Scagliotti et al 2009	Pem/Cis	Gem/Cis	839	8	830	17
Rosell et al., 2012	Erlotinib	Double CTX	84	4	82	0
Mok et al. 2009	Gefitinib	Pac/Carb	607	23	589	8
Mitsudomi et al. 2010	Gefitinib	Doc/Cis	87	1	88	0
Maemondo et al. 2010	Gefitinib	Pac/Carb	114	1	113	0
Yang et al. 2012a, Sequist et al. 2013, BI 2012	Afatinib	Pem/Cis	230	33	115	0

Table 31 Adverse events - Rash/acne (grade 3/4)

Rash/acne (grade 3/4)			Treatment		Comparator	
Study	Treatment	Comparator	N	events	N	events
Scagliotti et al 2009	Pem/Cis	Gem/Cis	839	0	830	8
Rosell et al. 2012	Erlotinib	Double CTX	84	11	82	0
Mok et al. 2009	Gefitinib	Pac/Carb	607	19	589	5
Mitsudomi et al. 2010	Gefitinib	Doc/Cis	87	2	88	0
Maemondo et al. 2010	Gefitinib	Pac/Carb	114	6	113	3
Yang et al. 2012a, Sequist et al. 2013, BI 2012	Afatinib	Pem/Cis	230	37	115	0

Table 32 Adverse events - Fatigue (grade 3/4)

Fatigue (grade 3/4)			Treatment		Comparator	
Study	Treatment	Comparator	N	events	N	events
Scagliotti et al. 2009	Pem/Cis	Gem/Cis	839	56	830	41
Rosell et al. 2012	Erlotinib	Double CTX	84	5	82	16
Mok et al. 2009	Gefitinib	Pac/Carb	607	NR	589	NR
Mitsudomi et al. 2010	Gefitinib	Doc/Cis	87	2	88	2
Maemondo et al. 2010	Gefitinib	Pac/Carb	114	3	113	1

Fatigue (grade 3/4)			Treatment		Comparator	
Study	Treatment	Comparator	N	events	N	events
Yang et al. 2012a, Sequist et al. 2013, BI 2012	Afatinib	Pem/Cis	230	3	115	14

6.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The analyses were conducted using WinBUGS version 1.4.3. WinBUGS is a Bayesian analysis (Lunn et al. 2000) software that, through the use of Monte Carlo Markov chains, calculates posterior distributions for the parameters of interest, given likelihood functions derived from data and prior probabilities. The Monte Carlo Markov chain simulation begins with an approximate distribution and, if the model is a good fit to the data, the distribution converges to the true distribution. The simulation framework using WinBUGS permits the computation of a wide range of other measures for inference and decision making. For example, the uncertainty can be summarized regarding which is the best intervention type with the probability that it is the most effective. (Welton et al. 2009)

These Bayesian analyses report the hazard ratios (HR) for survival outcomes and the probability of event for outcomes with a binary variable format – adverse events.

All baseline and intervention effect parameters were given flat (uninformative) Normal (0, 1000) priors and the between-study standard deviation flat Uniform distributions with an appropriately large range given the scale of measurement.

Both random and fixed effects models were conducted. The main difference between these two types of models is that the former takes into account the between study variance, producing therefore wider confidence intervals. Random effects models are preferred in the presence of heterogeneity. Nevertheless, a comparison is made by observing the Deviance Information Criterion (DIC) statistics and the total residual deviance, to ensure that the selected model's overall fit is adequate. The DIC provides a measure of model fit that penalises model complexity – lower values of the DIC suggest a more parsimonious model; however, differences of less than 3 are not considered to be important (Burnham et al. 2002). To check formally whether a model's fit is satisfactory we consider an absolute measure of fit: the overall residual deviance. We compare the value of overall residual deviance to the number of independent data points to check if the model fit can be improved. As the rule of the thumb each data point should contribute about 1 to the posterior mean deviance, hence these two values should be very close in the presence of a model that is a good predictor. Convergence was assessed by using the Brooks-Gelman-Rubin diagnostic in WinBUGS.

In all cases a burn-in of at least 20,000 simulations were discarded. All results are presented based on a further sample of 50,000 simulations.

Lastly, we observed the Monte Carlo error, which reflects both the number of simulations and the degree of autocorrelation. This should be no more than 5% of the posterior standard deviation of the parameters of interest (Welton et al. 2012).

The WingBugs code is in Appendix 10.4.6.

6.7.6 Please present the results of the analysis.

Results for Progression Free Survival

The results of the MTC show that afatinib has the highest expected probability of being the best treatment for the basecase analysis. These results are shown in Table 33.

Table 33 Probability of being the best treatment - Progression Free Survival: by independent assessment– ITT population

Treatments	Probability of being best
Afatinib	62.6%
Doc/Carb	0.0%
Doc/Cis	0.0%
Erlotinib	30.8%
Gefitinib	6.5%
Gem/Carb	0.0%
Gem/Cis	0.0%
Pac/Carb	0.0%
Pac/Cis	0.0%
Pem/Cis	0.0%
Vin/Cis	0.0%

The MTC shows that afatinib has statistically significant better PFS outcomes relative to the combination of pemetrexed with cisplatin and gemcitabine with cisplatin for the ITT population for both the fixed-effects model (Figure 23) and the random effects model (Figure 24). Relative to gefitinib and erlotinib, there is a non-significant trend in favour of afatinib.

Figure 23 PFS by independent assessment, ITT population (Fixed Effects Model)

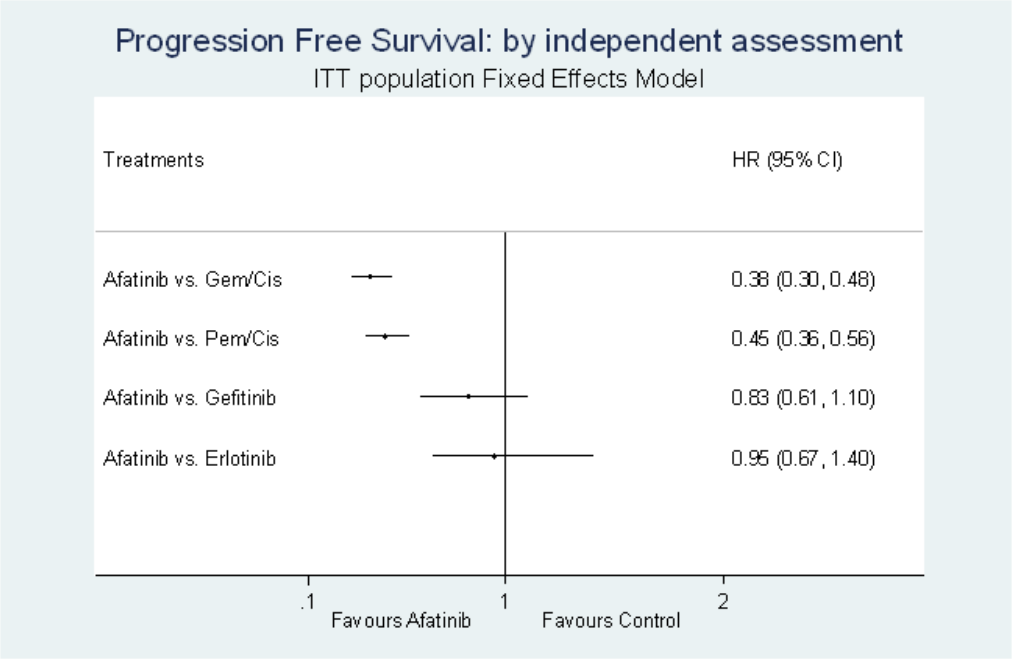
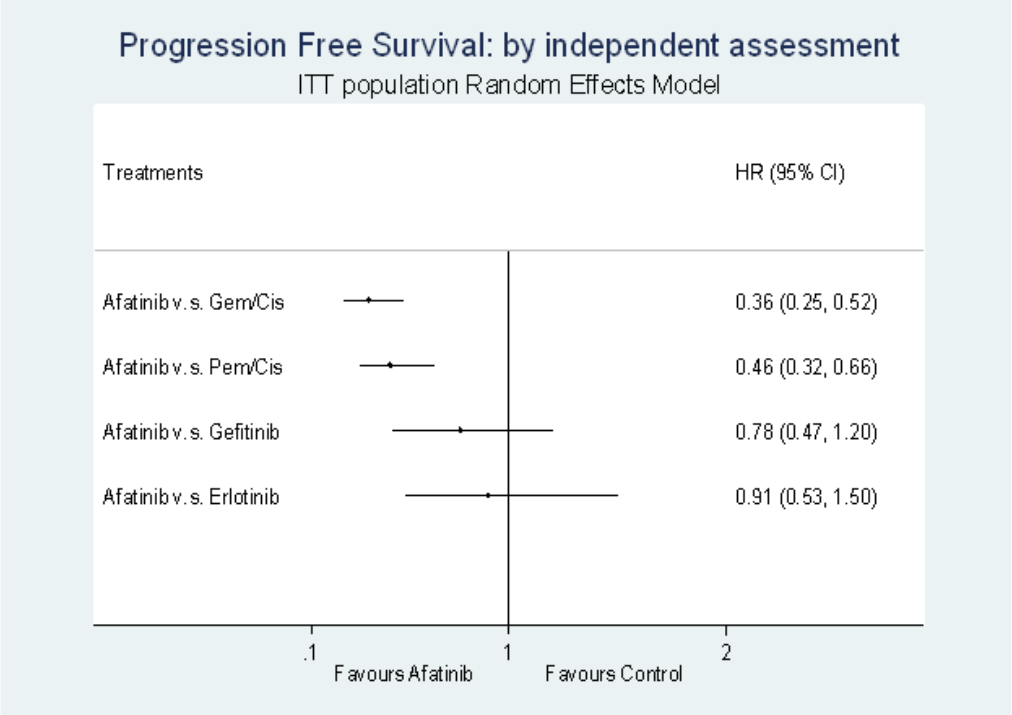


Figure 24 PFS by independent assessment, ITT population (Random Effects Model)



A pair-wise comparison for afatinib vs. all comparators for the fixed- and random-effects models, along with goodness of fit statistics are shown in Table 34.

Table 34 PFS by independent assessment - ITT population

Treatments	Fixed Effects			Random Effects		
	Hazard Ratio	lCr.Int	uCr.Int	Hazard Ratio	lCr.Int	uCr.Int
Afatinib vs. Gem/Cis	0.38	0.30	0.48	0.36	0.25	0.52
Afatinib vs. Vin/Cis	0.36	0.27	0.48	0.35	0.21	0.53
Afatinib vs. Pac/Carb	0.34	0.26	0.45	0.32	0.20	0.49
Afatinib vs. Pac/Cis	0.31	0.23	0.41	0.30	0.18	0.47
Afatinib vs. Gem/Carb	0.33	0.22	0.51	0.31	0.17	0.57
Afatinib vs. Doc/Cis	0.35	0.26	0.46	0.34	0.21	0.53
Afatinib vs. Pem/Cis	0.45	0.36	0.56	0.46	0.32	0.66
Afatinib vs. Gefitinib	0.83	0.61	1.10	0.78	0.47	1.20
Afatinib vs. Erlotinib	0.95	0.67	1.40	0.91	0.53	1.50
Afatinib vs. Doc/Carb	0.35	0.21	0.59	0.34	0.16	0.68
totresdev	26			19		
sd	n.a.			0.14	0.02	0.34
DIC	-0.967			-2.859		
Data Points	20					

lCr.Int – lower credible interval, uCr.Int – upper credible interval; DIC – deviance information criterion; totresdev – total residual deviance; sd – between-study standard deviation; n.a. – non applicable

Results for OS

The pair-wise comparisons for the random-effects and fixed-effects models for OS are shown in Table 35.

Table 35 OS: immature data from LUX-Lung 3 (updated) and LUX-Lung 6

Treatments	Fixed Effects			Random Effects		
	Hazard Ratio	lCr.Int	uCr.Int	Hazard Ratio	lCr.Int	uCr.Int
Afatinib vs. Gem/Cis	0.86	0.67	1.10	0.85	0.66	1.13
Afatinib vs. Vin/Cis	0.74	0.56	0.98	0.74	0.55	1.01
Afatinib vs. Pac/Carb	0.78	0.59	1.02	0.78	0.57	1.06
Afatinib vs. Pac/Cis	0.86	0.65	1.14	0.85	0.62	1.17
Afatinib vs. Gem/Carb	0.83	0.60	1.15	0.83	0.58	1.20
Afatinib vs. Doc/Cis	0.85	0.64	1.12	0.85	0.62	1.19
Afatinib vs. Doc/Carb	0.78	0.57	1.07	0.79	0.54	1.14
Afatinib vs. Pem/Cis	0.99	0.78	1.27	0.99	0.75	1.30
Afatinib vs. Gefitinib	0.84	0.55	1.30	0.83	0.54	1.34
Afatinib vs. Erlotinib	0.80	0.56	1.14	0.80	0.54	1.18
Totresdev	19.00			18.40		
Sd	n.a.			0.05	0.00	0.16
DIC	-13.537			-11.565		
Data Points	26					

lCr.Int – lower credible interval, uCr.Int – upper credible interval; DIC – deviance information criterion; totresdev – total residual deviance; sd – between-study standard deviation; n.a. – non applicable

As expected, the results from the fixed- and random-effects models are very similar (as discussed in Section 6.7.5). The fixed effects models are used to make inference as it presents a lower DIC and the total residual deviance closer to the number of data points than in the random effects model.

Taking into account immaturity of OS data for afatinib, the MTC results show a trend favouring afatinib versus chemotherapy and reversible TKIs (Figure 25) and afatinib has the highest expected probability of being the best treatment (43%, Table 36).

Figure 25 OS (immature data) from LUX-Lung 3 (updated) and LUX-Lung 6 (fixed-effects model)

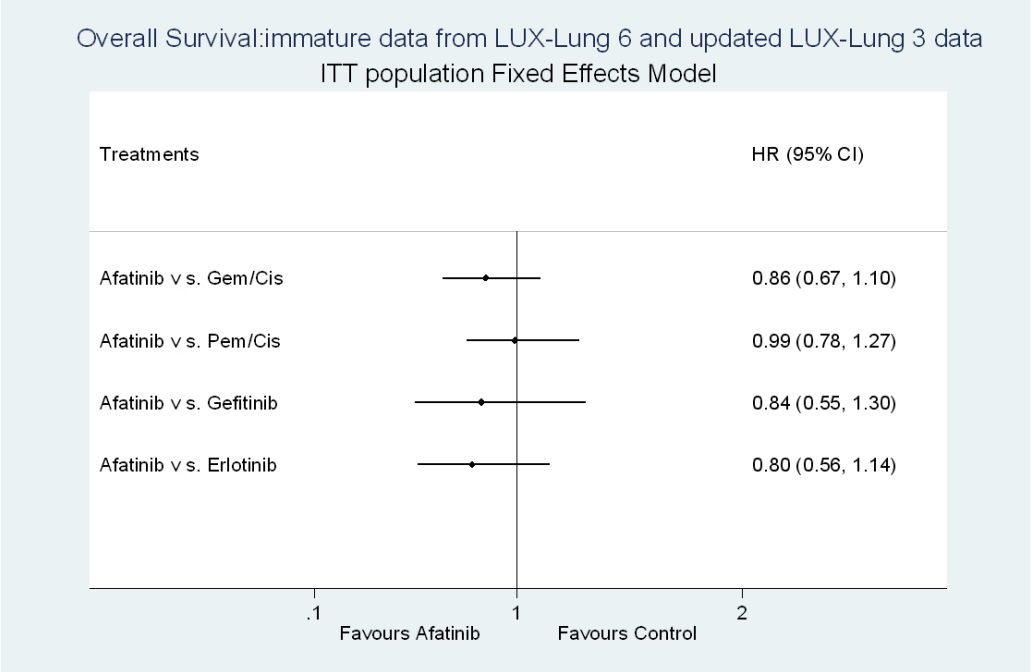


Table 36 Probability of being best - OS: immature data from LUX-Lung 3 (updated) and LUX-Lung 6

Treatments	Probability of being best
Afatinib	43%
Doc/Carb	1%
Doc/Cis	1%
Erlotinib	3%
Gefitinib	13%
Gem/Carb	3%
Gem/Cis	0%
Pac/Carb	0%
Pac/Cis	2%
Pem/Cis	34%
Vin/Cis	0%

Results for Adverse Events

The MTC models used to estimate the probability of adverse events did not achieve convergence, therefore producing uncertain results (very wide credible intervals, see Table 37 to Table 39). This lack of convergence is caused by the low number of events in most of the treatment arms (sometimes zero).

Table 37 Probability of event of diarrhoea (grade 3/4)

Treatment	Probability	lCr.Int	uCr.Int
Afatinib	12.00%	3.00%	54.00%
Cisplatin+Pemetrexed	0.64%	0.22%	1.80%
Double CTX	1.40%	0.75%	2.80%
Erlotinib	7.50%	0.85%	72.00%
Gefitinib	3.60%	1.40%	9.50%

Table 38 Probability of event of rash/acne (grade 3/4)

Treatment	Probability	lCr.Int	uCr.Int
Afatinib	14.00%	3.50%	56.00%
Cisplatin+Pemetrexed	0.20%	0.02%	0.97%
Double CTX	1.10%	0.57%	2.10%
Erlotinib	16.00%	2.60%	88.00%
Gefitinib	3.40%	1.20%	9.10%

Table 39 Probability of event of fatigue (grade 3/4)

Treatment	Probability	lCr.Int	uCr.Int
Afatinib	1.00%	0.03%	29.00%
Cisplatin+Pemetrexed	4.50%	0.13%	64.00%
Double CTX	2.90%	0.08%	53.00%
Erlotinib	0.73%	0.02%	24.00%
Gefitinib	5.20%	0.11%	74.00%

Sensitivity analysis

The following additional sensitivity analyses were undertaken to examine the impact of including different datasets from the LUX-Lung trials.

Table 40 Overall Survival: LUX-Lung 3 update only

Treatments	Fixed Effects			Random Effects		
	Hazard Ratio	lCr.Int	uCr.Int	Hazard Ratio	lCr.Int	uCr.Int
Afatinib vs. Gem/Cis	0.76	0.53	1.09	0.76	0.50	1.15
Afatinib vs. Vin/Cis	0.66	0.45	0.97	0.66	0.42	1.02
Afatinib vs. Pac/Carb	0.69	0.47	1.01	0.69	0.44	1.06
Afatinib vs. Pac/Cis	0.77	0.52	1.12	0.76	0.48	1.17
Afatinib vs. Gem/Carb	0.74	0.49	1.13	0.74	0.46	1.19
Afatinib vs. Doc/Cis	0.76	0.52	1.11	0.76	0.48	1.19
Afatinib vs. Doc/Carb	0.70	0.46	1.05	0.70	0.42	1.13
Afatinib vs. Pem/Cis	0.91	0.66	1.25	0.91	0.64	1.28
Afatinib vs. Gefitinib	0.75	0.46	1.24	0.75	0.43	1.31
Afatinib vs. Erlotinib	0.71	0.46	1.10	0.72	0.42	1.17
Totresdev	19.00			18.60		
Sd	n.a.			0.05	0.00	0.18
DIC	-11.867			-9.857		
Data Points	25					

Table 41 Progression Free Survival using LUX-Lung 3 data only

Treatments	Fixed Effects			Random Effects		
	Hazard Ratio	lCr.Int	uCr.Int	Hazard Ratio	lCr.Int	uCr.Int
Afatinib, Pem/Cis	0.58	0.43	0.78	0.58	0.39	0.86
Afatinib, Gefitinib	1.13	0.77	1.67	1.12	0.63	1.99
Afatinib, Erlotinib	1.30	0.86	1.98	1.30	0.72	2.37
Afatinib, Doc/Carb	0.48	0.27	0.85	0.48	0.23	1.03
Afatinib, Doc/Cis	0.47	0.33	0.68	0.47	0.28	0.85
Afatinib, Gem/Carb	0.46	0.28	0.74	0.45	0.23	0.88
Afatinib, Gem/Cis	0.52	0.38	0.73	0.52	0.31	0.86
Afatinib, Pac/Carb	0.47	0.33	0.67	0.46	0.27	0.80
Afatinib, Pac/Cis	0.42	0.30	0.61	0.42	0.24	0.75
totresdev	19.24			17.14		
sd	n.a.			0.09704	0.006989	0.2891

DIC	DIC = -6.211	DIC = -5.208
Data Points	19	

An additional sensitivity analysis was undertaken that included data from OPTIMAL (Zhou et al. 2011). These results for the OS and PFS are shown in Table 42.

Table 42 Estimated hazard ratios using from the MTC including data from OPTIMAL

	Fixed effects model			Random effects model		
	Hazard Ratio	lCr.Int	uCr.Int	Hazard Ratio	lCr.Int	uCr.Int
Afatinib vs. erlotinib						
PFS	0.8855	0.626	1.253	0.8218	0.4162	1.572
OS	0.8005	0.5719	1.127	0.8035	0.5639	1.172
Afatinib vs. gefitinib						
PFS	0.7309	0.5369	0.9976	0.6534	0.334	1.209
OS	0.8488	0.5553	1.303	0.8455	0.5488	1.351

6.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Both fixed and random effects models were investigated for the network meta-analyses. Whilst fixed effects models only account for variation within trials, random effects models incorporate variation between trials. Fixed effects analyses assume that the true treatment effect is the same across studies and the observed variability results from sampling error alone. Random effects analyses relax this assumption by allowing the true treatment effect to vary from study to study (the between-study heterogeneity). This heterogeneity can arise from several different factors such as different patient populations, and different timing associated with the intervention. Random effects analyses generally provide wider credible intervals due to the incorporation of heterogeneity.

The credible intervals from the fixed effects and random effects models for progression-free survival (presented in Table 34) are also similar. However, the deviation between the credible intervals in the random and fixed effects models is slightly larger than for the models for overall survival. This suggests that the variation that exists between studies has a small but slightly larger impact on progression-free survival than on overall survival. In the models for progression-free survival, a smaller DIC statistic is observed for the random effects model. Furthermore, the total residual deviance is closer to the number of data points in the random effects than in the fixed effects model. For these reasons, the random effects model is the most appropriate model choice for progression free survival.

Only small differences are observed in the credible intervals between the fixed and random effects models for overall survival (presented in Table 35), and the between-study heterogeneity, denoted sd, is small, which demonstrates that there is little heterogeneity between the trials included in the network of evidence. A smaller DIC value is observed in the fixed effects model and the

total residual deviance is slightly closer to the number of data points in the fixed effects than in the random effects model. Therefore use of the fixed effects model can be justified for overall survival.

The observation of some between-study heterogeneity may be due to assumptions made regarding the homogeneity of the patient populations in constructing the networks of evidence:

- Although the afatinib 1st line trials were conducted in an EGFR mutation positive population, evidence based on a broader population of NSCLC patients was also included in the network. This was necessary in order to incorporate the LUX-Lung 3 trial data comparing afatinib with pem/cis (Yang et al. 2012a) into the network of evidence. This required the assumption that the efficacy of chemotherapeutic regimes not targeting EGFR was not influenced by EGFR mutation status.
- In the EURTAC trial (Rosell et al. 2012) erlotinib was compared against four chemotherapy regimens. These were assumed to be equally efficacious given the absence of specific outcomes reported for each of the four chemotherapy regimens.
- Variations in baseline characteristics of patients across the studies used are observed, although homogeneity is assumed. For example, the proportion of patients who never smoked ranges approximately from 12% to 94%. Evidence from some studies suggests that there are some never-smoking patients in which EGFR mutation positive NSCLC may respond better to TKI therapy (Rossell et al. 2012, Mok et al. 2009, Yang et al. 2012a). Furthermore, differences were observed in the baseline ECOG performance status, particular types of EGFR mutation, ethnicity and histological diagnoses.

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

The networks of evidence used for overall survival (OS) and progression-free survival (PFS) have been presented in Section 6.7.3. All trials included in the MTC were considered relevant, and therefore there is no need for additional sensitivity analysis.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Overall survival

Table 43 presents the direct comparison overall survival hazard ratios (HRs) and associated confidence intervals used as inputs to the mixed-treatment

comparison (MTC) compared with the corresponding pairwise outputs produced by the MTC.

There is a reasonable degree of heterogeneity between the four direct comparisons for which there are multiple inputs, Gem/Carb vs. Gem/Cis (HRs of 0.98, 1.09), Gem/Cis vs. Pac/Cis (HRs of 0.90, 0.92), Gem/Cis vs. Pac/Carb (HRs of 0.96, 1.04), and Gem/Cis vs. Vin/Cis (HRs of 0.71, 0.71, 0.87, 0.93, 1.02).

The direct comparison HR input for gefitinib vs. Doc/Cis is considerably higher (1.64, Mitsudomi et al. 2010) than the direct comparison HRs for gefitinib vs. other chemotherapy regimens (1.04 vs. Gem/Cis and 0.78 vs. Pac/Carb). This may be due to differences between Doc/Cis and the other regimens (Gem/Cis and Pac/Carb), or due to the immaturity of the overall survival data (only 15.7% of patients had died at the data cut off) reported in Mitsudomi et al (2010), which is reflected in the wide boundaries of the confidence interval for this HR (0.75 to 3.58).

The differences observed between the direct comparison inputs to the MTC and the corresponding MTC outputs are mostly small. The differences between the direct evidence input and MTC output hazard ratios all ranged from 0.01 to 0.16, with the exception of the gefitinib vs. Doc/Cis comparison which had a difference of 0.63. The larger difference observed between the direct comparison input and MTC output for gefitinib vs. Doc/Cis is likely due to the issue raised above regarding the immaturity of the direct comparison data for overall survival from the Mitsudomi et al. (2010) study and the consequently wide confidence intervals. All of the hazard ratios calculated in the MTC were within the 95% confidence intervals for the corresponding direct comparison inputs.

Table 43 Overall survival - direct comparison inputs & corresponding MTC outputs

Study	Treatment A	Treatment B	Input values			MTC outputs (fixed effects)		
			Hazard Ratio	95% confidence interval		Hazard Ratio	95% credible interval	
				Low	High		Low	High
Fossella et al. 2003*	Vin/Cis	Doc/Cis	1.18	0.99	1.42	1.15	0.67	1.44
	Vin/Cis	Doc/Carb	1.05	0.88	1.25	1.06	0.89	1.25
Rosell et al. 2002*	Pac/Carb	Pac/Cis	1.22	1.03	1.43	1.11	0.97	1.26
Zatloukal et al. 2003*	Gem/Carb	Gem/Cis	0.98	0.69	1.39	1.03	0.83	1.28
Mazzanti et al. 2003*	Gem/Carb	Gem/Cis	1.09	0.75	1.59	1.03	0.83	1.28
Schiller et al. 2002*	Gem/Cis	Doc/Cis	0.94	0.79	1.14	0.99	0.86	1.14
	Gem/Cis	Pac/Cis	0.92	0.76	1.10	1.00	0.88	1.14
	Gem/Cis	Pac/Carb	0.96	0.80	1.15	0.91	0.80	1.02
Chang et al. 2001**	Gem/Cis	Vin/Cis	0.93	0.40	2.16	0.86	0.76	0.98

Study	Treatment A	Treatment B	Input values			MTC outputs (fixed effects)		
			Hazard Ratio	95% confidence interval		Hazard Ratio	95% credible interval	
				Low	High		Low	High
Comella et al. 2000*	Gem/Cis	Vin/Cis	0.71	0.45	1.13	0.86	0.76	0.98
Gridelli et al. 2002*	Gem/Cis	Vin/Cis	1.02	0.76	1.35	0.86	0.76	0.98
Melo et al. 2002**	Gem/Cis	Vin/Cis	0.71	0.41	1.22	0.86	0.76	0.98
Scagliotti et al. 2002*	Gem/Cis	Vin/Cis	0.87	0.69	1.09	0.86	0.76	0.98
	Gem/Cis	Pac/Carb	1.04	0.83	1.31	0.91	0.80	1.02
Thomas et al. 2002*	Gem/Carb	Vin/Cis	0.89	0.53	1.49	0.89	0.71	1.12
Smit et al. 2003*	Gem/Cis	Pac/Cis	0.90	0.65	1.25	1.00	0.88	1.14
Scagliotti et al. 2009	Pem/Cis	Gem/Cis	0.84	0.71	0.99	0.86	0.74	1.01
Han et al. 2012	Gefitinib	Gem/Cis	1.04	0.49	2.18	1.01	0.72	1.43
Yang et al. 2012a, Sequist et al. 2013, BI 2012	Afatinib	Pem/Cis	0.91	0.66	1.25	0.99	0.78	1.27
Mok et al. 2009	Gefitinib	Pac/Carb	0.78	0.5	1.2	0.92	0.65	1.29
Mitsudomi et al. 2010	Gefitinib	Doc/Cis	1.64	0.75	3.58	1.01	0.70	1.45
Rosell et al. 2012	Erlotinib	Doc/Cis	1.04	0.65	1.68	1.07	0.82	1.39
	Erlotinib	Gem/Cis	1.04	0.65	1.68	1.07	0.83	1.38
	Erlotinib	Doc/Carb	1.04	0.65	1.68	0.98	0.74	1.30
	Erlotinib	Gem/Carb	1.04	0.65	1.68	1.04	0.78	1.39
Wu et al. 2013, Geater et al. 2013, BI 2013	Afatinib	Gem/Cis	0.95	0.68	1.33	0.86	0.67	1.10

* These are the original papers describing the studies from which these data are derived. However the specific analyses of the data from these trials used as inputs in the MTC are taken from two papers, Ardizzani et al (2007), and Le Chavalier et al (2005), as per the Astra Zeneca NICE submission (TA 192) for gefitinib. ** data from NICE (2009b) and NICE (2010)

Progression-free survival

Table 44 compares the direct comparison progression-free survival HRs (and associated confidence intervals) used as inputs to the MTC to the corresponding pairwise outputs produced by the MTC.

There is a reasonable degree of heterogeneity between the four direct comparisons for which there are multiple inputs, Gem/Cis vs. Pac/Cis (HRs of 0.79, 0.89), Gem/Cis vs. Pac/Carb (HRs of 0.84, 1.05), Gem/Cis vs. Vin/Cis (HRs of 0.94, 0.91, 0.95) and gefitinib vs. Pac/Carb (HRs of 0.48, 0.30).

The differences observed between the direct comparison inputs to the MTC and the corresponding MTC output hazard ratios are small, ranging from 0.01 to 0.16. All of the hazard ratios calculated in the MTC were within the 95% confidence intervals for the corresponding direct comparison inputs.

Table 44 Progression-free survival - direct comparison inputs & corresponding MTC outputs

Study	Treatment A	Treatment B	Input values			MTC outputs (random effects)		
			Hazard Ratio	95% confidence interval		Hazard Ratio	95% credible interval	
				Low	High		Low	High
Schiller et al. 2002*	Gem/Cis	Doc/Cis	0.87	0.73	1.04	0.93	0.69	1.25
	Gem/Cis	Pac/Cis	0.79	0.66	0.94	0.82	0.62	1.12
	Gem/Cis	Pac/Carb	0.84	0.70	0.997	0.89	0.68	1.13
Chang et al. 2001**	Gem/Cis	Vin/Cis	0.94	0.50	1.78	0.95	0.73	1.23

Study	Treatment A	Treatment B	Input values			MTC outputs (random effects)		
			Hazard Ratio	95% confidence interval		Hazard Ratio	95% credible interval	
				Low	High		Low	High
Gridelli et al. 2002*	Gem/Cis	Vin/Cis	0.91	0.70	1.18	0.95	0.73	1.23
Scagliotti et al. 2002*	Gem/Cis	Vin/Cis	0.95	0.77	1.17	0.95	0.73	1.23
	Gem/Cis	Pac/Carb	1.05	0.85	1.29	0.89	0.68	1.13
Thomas et al. 2002*	Gem/Carb	Vin/Cis	1.21	0.72	2.03	1.09	0.69	1.73
Smit et al. 2003*	Gem/Cis	Pac/Cis	0.89	0.65	1.22	0.82	0.62	1.12
Scagliotti et al. 2009	Pem/Cis	Gem/Cis	0.90	0.78	1.03	0.80	0.55	1.07
Mok et al. 2009	Gefitinib	Pac/Carb	0.48	0.36	0.64	0.41	0.31	0.54
Mitsudomi et al. 2010	Gefitinib	Doc/Cis	0.49	0.34	0.71	0.43	0.31	0.62
Maemondo et al. 2010	Gefitinib	Pac/Carb	0.30	0.22	0.41	0.41	0.31	0.54
Han et al. 2012	Gefitinib	Gem/Cis	0.54	0.27	1.1	0.46	0.34	0.64
Yang et al. 2012a, Sequist et al. 2013, BI 2012	Afatinib	Pem/Cis	0.58	0.43	0.78	0.45	0.32	0.66
Rosell et al. 2012	Erlotinib	Doc/Cis	0.37	0.25	0.54	0.37	0.25	0.54
	Erlotinib	Gem/Cis	0.37	0.25	0.54	0.40	0.28	0.57
	Erlotinib	Doc/Carb	0.37	0.25	0.54	0.37	0.22	0.62
	Erlotinib	Gem/Carb	0.37	0.25	0.54	0.35	0.22	0.53
Wu et al. 2013, Geater et al. 2013, BI 2013	Afatinib	Gem/Cis	0.28	0.20	0.39	0.36	0.25	0.52

* These are the original papers describing the studies from which these data are derived. However the specific analyses of the data from these trials used as inputs in the MTC are taken from two papers, Ardizzani et al, 2007, and Le Chavalier et al, 2005, as per the Astra Zeneca NICE submission (TA 192) for gefitinib. ** data from NICE (2009b) and NICE (2010)

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

A systematic review was not conducted as non-RCT evidence was not considered appropriate for the appraisal due to the extensive comparative RCT data that was available.

However, as noted in Section A, and in Section 6.2.7, data from a single arm study, LUX-Lung 2, was included in the Marketing Authorisation application submitted to the regulatory authorities, and was considered relevant to the decision problem. LUX-Lung 2 was a non-RCT phase II proof-of-concept study which enrolled 129 patients who were TKI naive who had received less than or equal to one prior line of chemotherapy. The study was identified by the manufacturer as supportive evidence for the use of the technology.

Of particular importance, this data forms the basis for the licence for the use of afatinib in patients who are TKI-naive but treated with chemotherapy.

Table 45 Overview of LUX-Lung 2

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
LUX-Lung 2	Afatinib 50mg daily. Following a protocol amendment on 17 Dec 2008, the starting afatinib dose was reduced to 40mg daily in newly enrolling patients.	- Stage IIIB (with pleural effusion)/IV lung adeno-carcinoma - Activating EGFR mutations within exons 18–21 of the EGFR receptor - Patients who have progressed or relapsed after one previous chemotherapy regimen. Following a protocol amendment on 01 Aug 2008, the study entry criteria were modified to include patients who had not received prior chemotherapy.	To explore the activity of afatinib in patients with activating EGFR mutations	Yang et al. 2012	This trial has been included in the submission as it provides supporting evidence for the use of afatinib in the 1st line setting, and is therefore relevant to this submission.

Table 46 Methods for LUX-Lung 2

Trial no. (acronym)	LUX-Lung 2
Scientific Rationale	Oral small-molecule first-generation EGFR TKIs are considered the first line treatment of choice in advanced adenocarcinoma harbouring an activating EGFR mutation. Prospective and retrospective studies have shown that patients with pulmonary adenocarcinoma who have a base-pair deletion at exon 19 (Del746-A750) or a point mutation at exon 21 (L858R) are highly responsive to EGFR TKIs. In addition to these two most common EGFR mutations, "Other" mutations in exons 18-21 have also been reported, although quite rarely. Patients with these atypical mutations have variable responses to EGFR TKIs. However, two or more concomitant sites of EGFR mutations have also been detected in approximately 6% of patients. The T790M mutation in exon 20, typically observed after EGFR TKI treatment in patients with Del19 or L858R, confers high resistance to EGFR TKI treatment. Two phase II studies of patients harbouring exon 20 insertions EGFR mutations demonstrated no response to reversible EGFR TKIs. One strategy to prevent the emergence of acquired resistance to EGFR TKI therapy is the development of small molecule inhibitors with higher binding affinity, i.e., "irreversible" EGFR kinase inhibitors. Afatinib is an irreversible ErbB family TKI inhibitor with *in vitro* activity against EGFR kinases with known activating mutations, including the T790M resistance mutation. The aim of this study was to explore the efficacy of afatinib in patients with advanced Stage IIIB (pleural effusion) or IV adenocarcinoma of the lung whose tumours harbour activating mutations within exon 18 to exon 21 of the EGFR receptor. The results of this trial could allow prospective identification of a susceptible population of second-line NSCLC patients likely to respond to targeted EGFR therapy in order to avoid the unnecessary exposure to an inefficient treatment. In addition, the use of an irreversible EGFR inhibitor in NSCLC patients harbouring activating EGFR mutations could forestall the emergence of a drug resistance mutation, resulting in more durable clinical responses to second-line treatment. Therefore, LUX-Lung 2 investigated the clinical efficacy of continuous oral treatment of afatinib in NSCLC patients harbouring an activating EGFR mutation in exon 18 to exon 21 who progressed after an initial regimen of cytotoxic chemotherapy (stage 1 and 2) or had not received first-line cytotoxic chemotherapy (only in Stage 2).
Objectives	To evaluate the efficacy, safety and pharmacokinetics of afatinib in patients with advanced adenocarcinoma of the lung whose tumours harbour an activating EGFR mutation (exon 18 to 21) who had failed one line of chemotherapy (stage 1 of trial) or who had failed one line of chemotherapy (stage 2 of trial). This was a non randomised proof of concept trial at an initial starting dose of 50 mg daily that followed a two-stage design. In the first stage only patients progressing or relapsing after one prior cytotoxic chemotherapy regimen (including neoadjuvant or adjuvant chemotherapy) were allowed to enter into the trial (second-line patients). After the end of Stage 1 Interim Analysis (03 March 2009) and amendments to the trial protocol, the trial was opened to first-line patients and subsequently the starting dose was lowered to 40mg, resulting in four trial cohorts defined by line of treatment and afatinib starting dosage (40 mg and 50 mg).
Location	Multi centre Trial in USA and Taiwan
Design	LUX-Lung 2 was a single arm phase II proof of concept trial designed to explore the efficacy and safety of afatinib as defined by the objective response rate (complete response, partial response) as determined by Response Criteria in Solid Tumours (RECIST 1.0) in patients with advanced NSCLC Stage IIIB or IV whose tumours harbour activating mutations within exon 18 to exon 21 of EGFR. Local sequencing data had to confirm the presence of at least one of the listed exon 18-21 EGFR mutations. Secondary objectives were to explore the safety and pharmacokinetics of afatinib. Patients progressing or relapsing after one prior cytotoxic chemotherapy regimen were allowed to enter into the trial throughout the study. In addition, chemotherapy-naive patients were allowed to enter the second stage of this two-stage study with the implementation of Amendment 1.
Duration of study	August 2007 to April 2011
Method of	Eligible patients were screened and entered. In this uncontrolled, non-randomized trial, patients were assigned by order of trial entry, not randomized, to afatinib dosage.

randomisation	
Method of blinding (care provider, patient and outcome assessor)	Neither patients nor investigators were blinded since this was a single arm open label study with no comparator.
Intervention(s) (n =) and comparator(s) (n =)	Starting dose of 50 mg (consisting of two 20 mg tablets and two 5 mg tablets) or for newly enrolled patients after implementation of Amendment 2 starting dose of 40 mg (consisting of two 20 mg). Continuous daily dosing (one course consisted of 28 days). Patients were eligible for repeated treatment courses in the absence of clinical disease progression and undue adverse events. For patients experiencing CTCAE grade ≥3 or grade ≥2 as specified in the protocol, a dose reduction as permitted in the protocol was permitted. A maximum of two dose reductions were permitted after which afatinib was discontinued. No deviations from the schedule were permitted. Treatment was continued until disease progression or undue adverse event(s).
Primary outcomes (including scoring methods and timings of assessments)	The primary endpoint was objective tumour response rate (CR, PR) as determined by Response Criteria in Solid Tumours (RECIST 1.0). An assessment of tumour response was performed at weeks 4, 8 and 12 and thereafter every 8 weeks.
Secondary outcomes (including scoring methods and timings of assessments)	Clinical benefit (CR, PR, SD) determined by RECIST 1.0, Time to objective response, Duration of objective response, Progression-free survival (PFS) time, Overall survival (OS) time, Safety of afatinib as indicated by intensity and incidence of adverse events graded according to NCI CTCAE Version 3.0, Evaluation of pharmacokinetic (PK) parameters
Duration of follow-up	The maximum follow-up time for patients who received a starting dose of 40 mg was around 10 months in contrast to patients who received a starting dose of 50 mg whose maximum follow-up time almost reached 28 months. This was a result of the trial design; patients at a starting dose of 40 mg daily were enrolled later than patients at a starting dose of 50 mg daily based on a protocol amendment. Initial follow-up (FU) visit at 28±7 Days after End-of-Trial; an additional FUV was to be performed in 12-week intervals from initial FU visit or earlier if appropriate

Table 47 Participant in LUX-Lung 2

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
LUX-Lung 2	• Patients with pathologically confirmed diagnosis of NSCLC Stage IIIB (with pleural effusion) adenocarcinoma or Stage IV adenocarcinoma (Amendment 1) • Presence of activating mutation(s) in exon 18 to exon 21 of the EGFR-receptor confirmed by direct DNA sequencing of NSCLC tumour tissue • Progressive disease following a first-line cytotoxic chemotherapy regimen or recurrent disease after prior neoadjuvant or adjuvant chemotherapy. Patients who had not received first-line cytotoxic chemotherapy could be enrolled in Stage 2 of the trial, after the criteria for entering Stage 2 were met (Amendment 1) • Patients with at least one tumour lesion that could accurately be measured by computed tomography (CT) or magnetic resonance imaging (MRI) in at least one dimension with longest diameter to be recorded as ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan. • Male or female patient aged ≥18 years. • Life expectancy of at least three (3) months. • Written informed consent that was consistent with ICH-GCP guidelines. • Eastern Cooperative Oncology Group (ECOG), performance score 0, 1 or 2.	• More than one (1) prior cytotoxic chemotherapy treatment regimen with relapsed or metastatic NSCLC. • Chemo-, hormone- (other than Megace®) or immunotherapy within the past 4 weeks or within less than four half-lives of the previous drug prior to treatment with the trial drug and/or persistence of toxicities of prior anticancer therapies which were deemed to be clinically relevant. • Previous treatment with erlotinib (Tarceva®), gefitinib (Iressa®) or any other EGFR inhibiting small molecule or antibody • Brain metastases, which were symptomatic; patients with treated, asymptomatic brain metastases were eligible with stable brain disease for at least four (4) weeks without the requirement for steroids or anti-epileptic therapy. • Significant or recent acute gastrointestinal disorders with diarrhoea as a major symptom e.g., Crohn's disease, malabsorption, or CTCAE Grade >2 diarrhoea of any aetiology at baseline. • Patients with any other life-threatening illness or organ system dysfunction, whose participation in the opinion of the investigator would have either compromised their safety or interfered with the evaluation of the safety of the test drug. • Other malignancies diagnosed within the past five (5) years (other than non-melanomatous skin cancer and *in situ* cervical cancer). • Radiotherapy within the past 2 weeks prior to treatment with the trial drug. • Patients with any serious active infection (i.e., requiring an i.v. antibiotic, antifungal, or antiviral agent). • Patients with known HIV, active hepatitis B or active hepatitis C infection. • Known or suspected active drug or alcohol abuse. • Women of child-bearing potential or men who are able to father a child unwilling to use a medically acceptable method of contraception during the trial. • Pregnancy or breast feeding. • Patient unable to comply with the protocol. • History of clinically significant or uncontrolled cardiac disease, including congestive heart failure, angina, myocardial infarction, arrhythmia, including New York Heart Association (NYHA) functional classification of 3. • Cardiac left ventricular function with resting ejection fraction of less than 50% measured by multigated blood pool imaging of the heart (MUGA scan) or echocardiogram. • QTc interval >0.47 second. • Prior treatment with anthracyclines with a cumulative dose of doxorubicin (or equivalent) >400 mg/m^2. • Absolute neutrophil count less than 1,500/mm^3. • Platelet count less than 100,000 /mm^3. • Bilirubin greater than 1.5 mg / dL (>26 µmol / L, SI unit equivalent) • Aspartate amino transferase (AST) or alanine amino transferase (ALT) greater than three times the upper limit of normal (if related to liver metastases, greater than five times the upper limit of normal). • Serum creatinine greater than 1.5 times the upper normal limit or calculated/measured creatinine clearance ≤45 mL / min. • Patients with known pre-existing interstitial lung disease • Requirement of treatment with any of the prohibited concomitant medications listed in the protocol Restrictions regarding concomitant treatment

Table 48 Patient characteristics in LUX-Lung 2

LUX-Lung 2 Trial Baseline characteristic	First Line		Second line		
	Afatinib 40mg	Afatinib 50mg	Afatinib 40mg	Afatinib 50mg	Total
Total treated	23 (100.0)	38 (100.0)	7 (100.0)	61 (100.0)	129 (100.0)
Gender					
Male	10 (43.5)	11 (28.9)	4 (57.1)	29 (47.5)	54 (41.9)
Female	13 (56.5)	27 (71.1)	3 (42.9)	32 (52.5)	75 (58.1)
Age					
Mean (Std)	64 (11.0)	62 (9.6)	57 (14.5)	61 (11.5)	62 (11.1)
Age <65 years	11 (47.8)	22 (57.9)	5 (71.4)	35 (57.4)	73 (56.6)
Age ≥ 65 years	12 (52.2)	16 (42.1)	2 (28.6)	26 (42.6)	56 (43.4)
Race					
Asian	18 (78.3)	30 (78.9)	6 (85.7)	58 (95.1)	112 (86.8)
Black	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Caucasian	4 (17.4)	8 (21.1)	1 (14.3)	3 (4.9)	16 (12.4)
Baseline ECOG PS					
0	16 (69.6)	28 (73.7)	3 (42.9)	36 (59.0)	83 (64.3)
1	6 (26.1)	10 (26.3)	4 (57.1)	22 (36.1)	42 (32.6)
2	1 (4.3)	0 (0.0)	0 (0.0)	3 (4.9)	4 (3.1)
Smoking history					
Never smoked	15 (65.2)	26 (68.4)	3 (42.9)	38 (62.3)	82 (63.6)
Ex-smoker <15 pack years	2 (8.7)	2 (5.3)	2 (28.6)	6 (9.8)	12 (9.3)
Current/ other ex smoker	6 (26.1)	10 (26.3)	2 (28.6)	17 (27.9)	35 (27.1)
Clinical stage at screening					
IIIb	2 (8.7)	3 (7.9)	0 (0.0)	3 (4.9)	8 (6.2)
IV	21 (91.3)	35 (92.1)	7 (100.0)	58 (95.1)	121 (93.8)
EGFR mutation					
Del 19	12 (52.2)	17 (44.7)	0 (0.0)	23 (37.7)	52 (40.3)
L858R	7 (30.4)	15 (39.5)	7 (100.0)	25 (41.0)	54 (41.9)
Other	4 (17.4)	6 (15.8)	0 (0.0)	13 (21.3)	23 (17.8)

Table 49 Outcomes from LUX-Lung 2

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
LUX-Lung 2	Objective response rate (ORR) based on Response Criteria in Solid Tumours (RECIST 1.0) Tumour assessments were performed at screening then at 4, 8 and 12 weeks. Thereafter every 8 weeks. All imaging data were sent to a central imaging unit by the study sites to obtain an independent image interpretation. Centralised imaging core laboratory services and image data management services were conducted by BioClinica, Inc in order to obtain an independent, blinded assessment of tumour response	Objective response rate provides evidence of anti-tumour activity of the drug and is reachable earlier than OS or PFS, usually within 2 to 3 months.	Clinical benefit (complete response, partial response, stable disease) determined by RECIST 1.0. Tumour assessments were performed at screening then at 4, 8 and 12 weeks. Thereafter every 8 weeks. All imaging data were sent to a central imaging unit by the study sites to obtain an independent image interpretation. Centralised imaging core laboratory services and image data management services were conducted by BioClinica, Inc in order to obtain an independent, blinded assessment of tumour response. Time to objective response, duration of objective response. Progression free survival determined by RECIST 1.0 defined as the duration of time from the start of treatment until the day of objective tumour progression was confirmed by tumour imaging or death. Tumour assessment, performed at screening then at 4, 8 and 12 weeks. Thereafter every 8 weeks Overall survival determined as the time from enrolment to death. Incidence of adverse events graded according to NCI common terminology criteria for adverse events (CTCAE Version 3.0) (day 1 and 15 of every cycle) Cardiac left ventricular function performed at Screening Visit, repeated within 7 days prior to Day 1 of Course 3 and every 12 weeks thereafter and end of treatment. ECG performed at Screening and on Day 1 of Courses 3, 5, 7, all odd numbered courses thereafter and end of treatment Laboratory evaluation, patient performance and vital signs (screening and day 1 and 15 of every cycle)	Progression free survival is widely used as a primary and secondary endpoint and measures the efficacy of a drug. It is superior to time to tumour progression since PFS does not censor for patients who die from any cause. PFS is less influenced than OS by competing causes of death and is not influenced by post progression treatment administration. Overall survival is a recognised endpoint that reflects benefit from oncology treatments. It is arguably the most important endpoint and it is well validated due to its objectivity and benefit to patients. However, overall survival may be confounded by crossover after disease progression. It may also be confounded by causes of mortality unrelated to cancer.

Table 50 Statistical analysis and definition of study groups in LUX-Lung 2

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
LUX-Lung 2	The analyses in this trial were descriptive and exploratory. There were no null or alternative hypotheses being tested in this trial. The primary efficacy objective of the study was to estimate the proportion of patients who achieved response according to RECIST 1.0 separately for each cohort Protocol amendment 1 (effective 1st August 2008) modified entry criteria to allow chemotherapy naive patients to enter stage 2. Planned number of patients for entry increased from 80 to 120 to reflect modified inclusion criteria. Specified that first and second line patients were to be analysed separately as well as combined in overall summary. Amendment 2 (effective 17 Dec 2008) reduced the starting dose for newly enrolled first and second line patients from 50mg to 40mg once daily	This was a non randomized, exploratory trial of afatinib in non-small cell lung cancer patients whose tumours harboured activating EGFR mutations. Initially patients were entered into a single cohort of second-line patients started on afatinib at 50 mg/day. After an interim analysis (end of Stage 1) the protocol was amended twice and enrolment was expanded with three additional non-randomized cohorts being added. The four trial cohorts were defined by line of treatment and afatinib starting dosage, with patients assigned by order of trial entry, not randomized, to afatinib dosage.	This study was divided into two stages to minimise the number of patients exposed to afatinib in case of lack of efficacy. In Stage 1, up to 40 second-line patients who had undergone tumour imaging at least once during treatment was evaluated. Once the decision was made to enter Stage 2, up to an additional 80 patients (120 total) were to be treated. Although no specific quota was imposed, the goal was for these 80 additional patients to be evenly divided between first and second-line patients (Amendment 1). The sample size was determined on the basis of the precision with which the proportion of responders could be estimated. With 80 second-line patients and a response rate of 55%, the width of the exact 95% confidence interval would have been 0.226 and the standard error 0.056	The trial was conducted in compliance with the protocol, the principles contained in the Declaration of Helsinki, local law and according to GCP/ICH guidelines and the company SOPs and in accordance with applicable regulatory requirements. The trial team met at regular intervals during the course of the study for data quality review meetings. Investigators were visited at regular intervals for on-site monitoring by a Boehringer Ingelheim Pharmaceuticals, Inc. employee or a CRA authorized by Boehringer Ingelheim Pharmaceuticals, Inc. If not stated otherwise, missing data were not imputed and remained missing

Subgroup analysis

Exploration of factors that may have been relevant to efficacy included:

- EGFR mutation type (deletion 19 in exon 19 vs. L858R in exon 21 vs. "Other" mutations)
- starting afatinib dose (50 mg vs. 40 mg)
- line of treatment (first-line vs. second-line)
- gender (Male vs. Female)
- age (<65 years-old vs. ≥ 65 years-old)
- race (Asian vs. Caucasian)
- baseline ECOG performance score (0 vs. 1)
- country of patient enrolment (Taiwan vs. US)
- smoking history (non-smoker and ex-smoker with < 15 pack years vs. current and other ex-smokers)
- presence of brain metastases at baseline

Figure 26 Participant flow in LUX-Lung 2 (Yang et al. 2012)

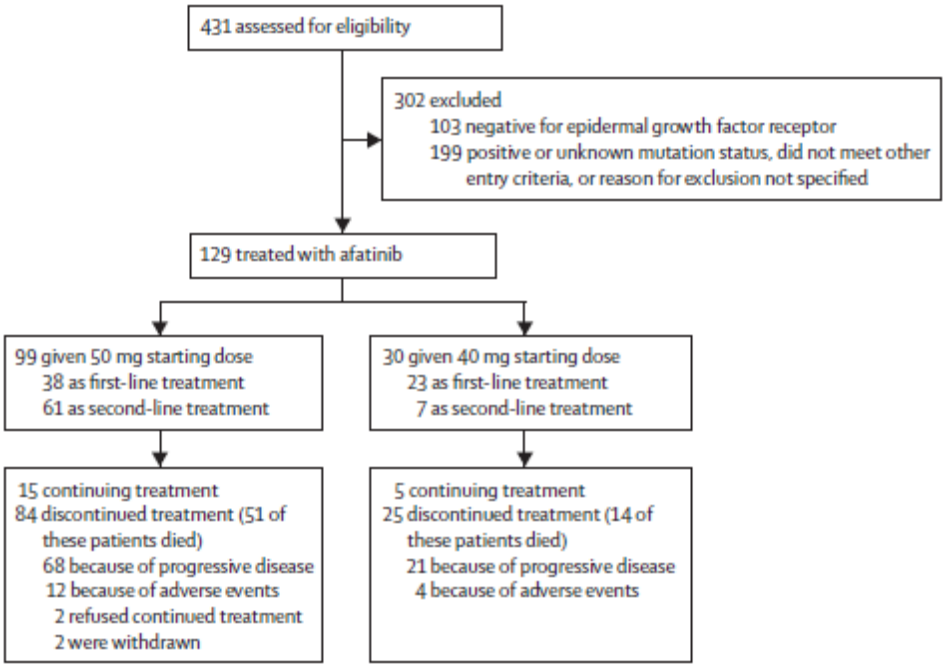


Table 51 Quality assessment for LUX-Lung 2

Trial no. (acronym)	LUX-Lung 2
Was randomisation carried out appropriately?	Not applicable. This was a single-arm study and, as such, there was no randomisation. Patients were assigned to afatinib dosage by order of trial entry, and not by randomisation.
Was the concealment of treatment allocation adequate?	Not applicable. This was a single arm study and there was no blinding of treatment assignments. Neither patients nor investigators were blinded.
Were the groups similar at the outset of the study in terms of prognostic factors?	Not applicable, as this was a single arm study, and a single group of participants.
Were the care providers, participants and outcome assessors blind to treatment allocation?	This was a single arm study and treatment assignment was therefore not blinded. However, imaging scans were sent for central review, where two radiologists independently established response to treatment, and any discrepancies were adjudicated by a third radiologist. Final review was by an oncologist and the adjudicator, with integration of radiological assessments with clinical information.
Were there any unexpected imbalances in drop-outs between groups?	Not applicable, as this was a single-arm study, and a single group of participants.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The primary endpoint of this study was the proportion of patients with a confirmed objective response, as determined by RECIST 1.0. Secondary efficacy endpoints included the proportion of patients with disease control, time to objective response, duration of objective response, tumour shrinkage, and progression-free and overall survival. All of these efficacy endpoints, except for time to objective response, have been reported in the LUX-Lung 2 publication, published in the Lancet Oncology in 2012. Information on time to objective response can be found in the clinical trial report. Safety and pharmacokinetic parameters were additional secondary endpoints in this trial. Safety outcomes were reported in the *Lancet Oncology* publication, and are detailed more fully in the clinical trial report. Pharmacokinetic parameters included an evaluation of afatinib plasma concentrations. The results of this evaluation have not yet been reported, either in the published paper, or the clinical trial report, and have not been included in this submission as they were not considered relevant to the decision problem.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	As this was a single-arm study, there was no randomisation, and no intention to treat population. The populations analysed for both efficacy and safety consisted of patients who received at least one dose of trial medication (treated set).

Primary endpoint: confirmed objective response

Independent review concluded that 61.2% (79/129) of patients achieved confirmed objective response according to RECIST 1.0. An additional 20.2% of patients exhibited stable disease for at least six weeks, yielding a disease control rate of 82.2% (106/129). The confirmed response and disease control

rates by investigator assessment (60.5% and 86.0%, respectively) were similar to the independent review rates. In general, there was a good degree of agreement between the confirmed best overall response determined by the investigator assessment and the independent review (Table 52).

Table 52 Best overall response (BOR) confirmed – treated set

	Independent review	Investigator review
Total treated	129 (100)	129 (100)
Disease control (CR, PR, SD) N (%) 95% C.I.	 106 (82.2) 74.5, 88.3	 111 (86.0) 78.8, 91.5
Objective response N (%) 95% C.I. Complete response N(%) Partial response N (%) Stable disease N (%)	 79 (61.2) 52.3, 69.7 2 (1.6) 77 (59.7) 26 (20.2)	 78 (60.5) 51.5, 69.0 0 78 (60.5) 33 (25.6)
Progressive disease N (%) Not evaluable N (%)	18 (14.0) 5 (3.9)	9 (7.0) 9 (7.0)

In general, there was a good degree of agreement between the confirmed best overall response determined by the investigator assessment and the independent review.

Sub-group analyses of primary endpoint

No significant difference was detected in objective response rates in patients receiving afatinib as a first-line treatment (40/61 patients [66%]) and those receiving it as a second-line treatment (39/68 [57%]; OR 0.71, 0.35–1.44). Similarly, no difference was detected in objective response rates in patients whose first afatinib dose was 40 mg (18/30 [60%]) compared to 50 mg (61/99 [62%]; 1.07, 0.46–2.47). In addition, no significant difference in objective response rates was recorded between the following subgroups: deletion-19 mutations (36/52 patients [69%]) versus L858R mutations (34/54 [63%]; odds ratio [OR] 0.76, 95% CI 0.34–1.69; independent review), men (31/54 [57%]) versus women (48/75 [64%]; 1.32, 0.64–2.70), Taiwan (62/104 [60%]) versus USA (17/25 [68%]; 1.44, 0.57–3.64), Asian people (67/112 [60%]) versus white people (11/16 [69%]; 1.48, 0.48–4.54), and absence (59/98 [60%]) versus presence of brain metastasis (20/31 [65%]; 1.20, 0.52–2.78).

Time to response and duration of response

The mean duration of confirmed response was 57.7 weeks per independent review and 65.9 weeks per investigator assessment.

Secondary endpoints

Progression free survival

Median PFS with afatinib treatment was long (>10 months) by either independent review or by investigator assessment. With the primary censoring

rules, 91 (70.5%) of the 129 patients were considered as having a PFS event per independent review. The median PFS time was estimated from the Kaplan-Meier curve to be 10.1 months (95% CI: 8.1, 13.8) and the probability of being alive without disease progression was around 45% at 12 months after start of treatment (Table 53).

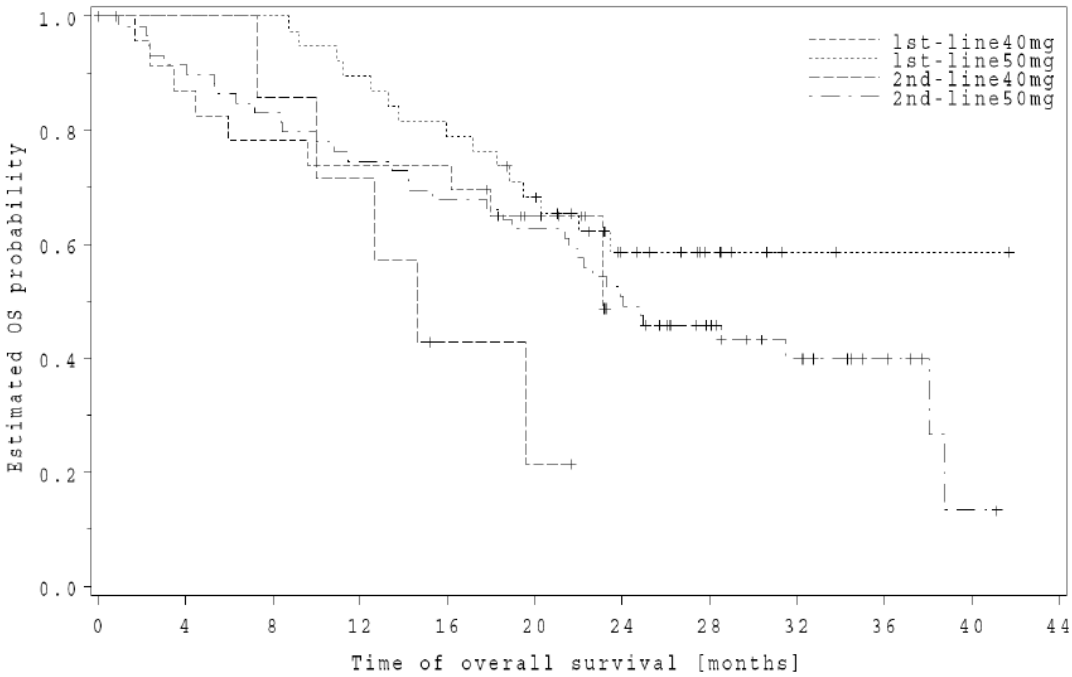
Table 53 Summary of PFS with primary censoring rules – treated set

	Independent review	Investigator
Total treated	129 (100)	129 (100)
Patients who had disease progression or who died	91 (70.5)	96 (74.4)
PFS time (months) 25th percentile (95% C.I.) Median (95% C.I.) 75th percentile (95% C.I.)	 4.5 (2.7, 6.3) 10.1 (8.1, 13.8) 20.1 (15.6, NA)	 6.3 (3.3, 8.1) 13.7 (10.9, 16.1) 25.9 (20.7, 28.6)

Overall survival

Among the 129 treated patients, 65 (50.4%) had died. Median survival time was estimated to be 24.8 months (95% CI: 22.0 – 38.7). The Kaplan-Meier curves of overall survival by patient cohort are shown in Figure 27.

Figure 27 Kaplan-Meier curves of overall survival by patient cohort– treated set



Subgroup analysis

Assigned treatment cohort

The four treatment cohorts (first-line 40 mg, first-line 50 mg, second-line 40 mg, and second line 50 mg,) were defined by line of treatment and afatinib starting dose, with patients assigned to afatinib dose by order of trial entry not randomization. The confirmed objective response and disease control rate are high and similar across cohorts with first-line confirmed response rates of

60.9% and 68.4% for the 40 mg and 50 mg starting dose groups, respectively. In each cohort, a large percentage of patients showed decrease in target lesion size: 64% to 74% showed >30% reduction and 39% to 57% showed >50% reduction (Table 54).

Table 54 Summary of efficacy results by treatment cohorts per independent review

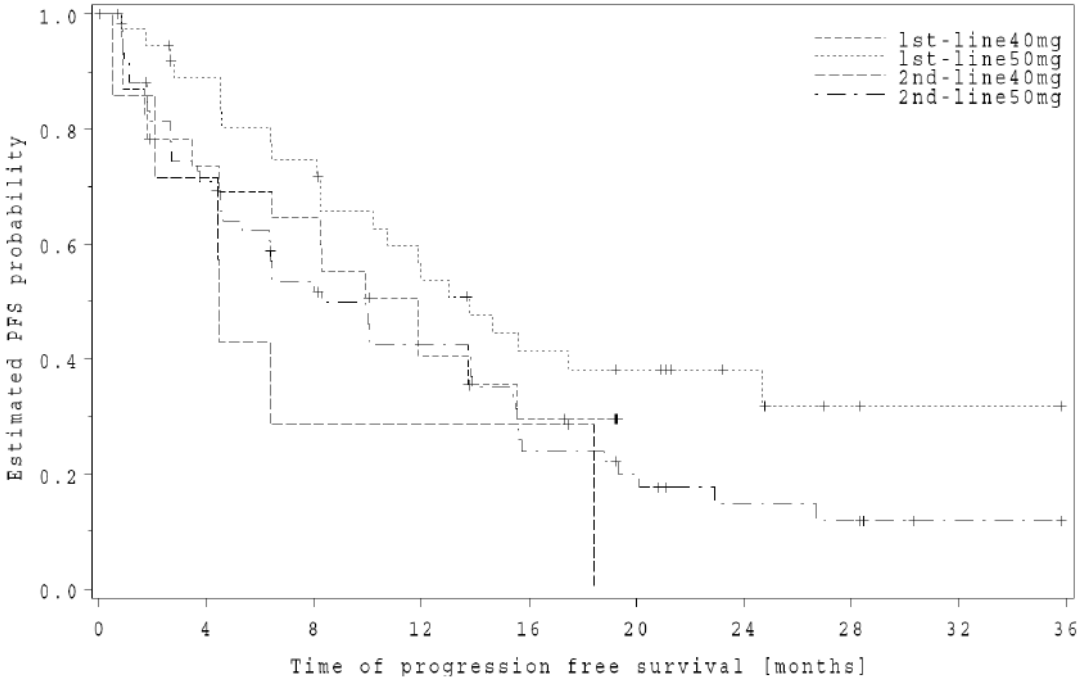
	First line		Second line	
	Afatinib 40mg	Afatinib 50mg	Afatinib 40mg	Afatinib 50mg
Total treated n (%)	23 (100)	38 (100)	7 (100)	61 (100)
Disease control n (%)	18 (78.3)	35 (92.1)	5 (71.4)	48 (78.7)
Objective response N (%)	14 (60.9)	26 (68.4)	4 (57.1)	35 (57.4)
PFS (months)				
25th percentile	3.4	6.5	2.1	2.7
Median	11.9	13.8	4.5	8.3
75th percentile	NA	NA	18.4	15.7
Overall survival (months)				
25th percentile	9.6	18.3	10.0	11.5
median	23.1	NA	14.6	24.0

Note: The sample size of the second-line 40 mg starting dose cohort was very small, with only 7 patients.
Disease control and objective response were determined by confirmed response per independent review
PFS was based on independent review using the primary censoring rules.
NA: Not available from the Kaplan-Meier curve

PFS by treatment line

In terms of PFS, independent review and investigator assessment of PFS gave similar results for the four treatment cohorts (Figure 28).

Figure 28 Kaplan-Meier curves of PFS by starting dose and line of treatment primary censoring rules: independent review



Analysis by line of treatment

Median PFS by independent review was 12.0 months in the first-line setting versus 8.0 months in the second-line setting. Median PFS values by investigator assessment were 15.6 months for first-line patients and 10.5 months for second-line patients (Figure 29 and Figure 30).

Figure 29 Kaplan-Meier curves of PFS by line of treatment per independent review using primary censoring rules

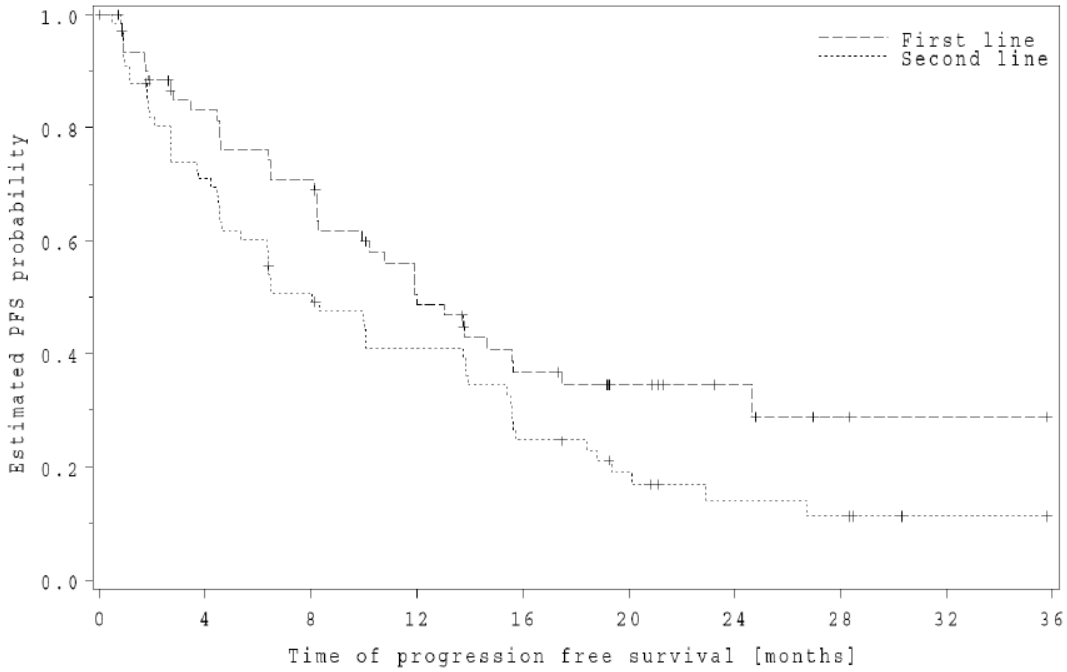
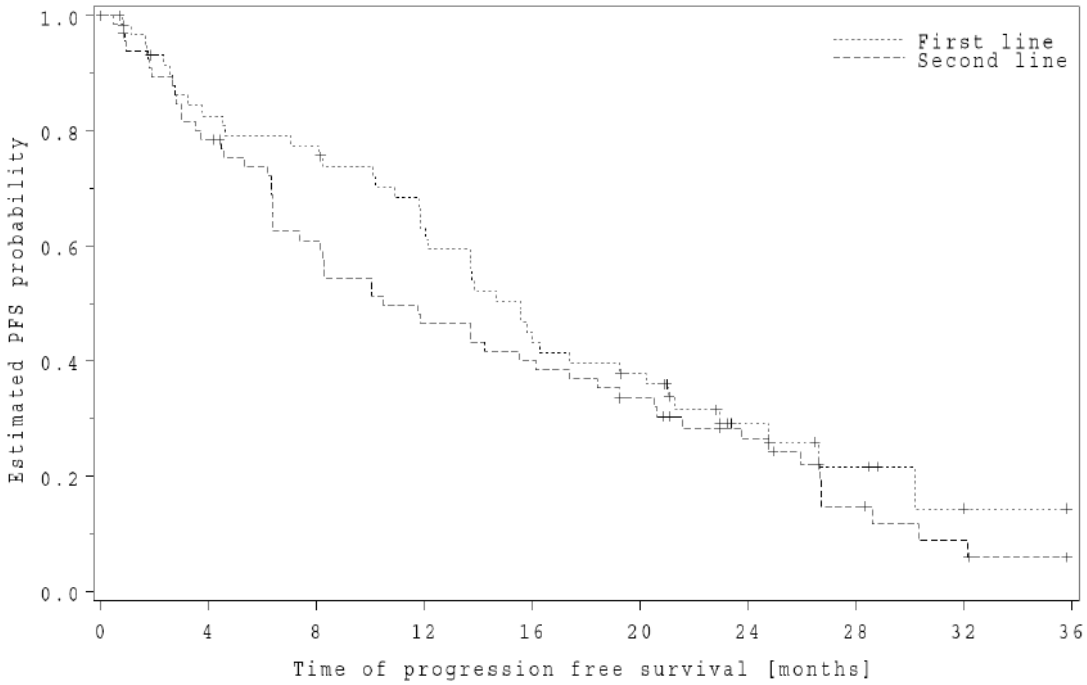


Figure 30 Kaplan-Meier curves of PFS by line of treatment per investigator assessment using primary censoring rules



Secondary endpoints: time to objective response and median response duration

Most responses were observed within the first 8 weeks from start of treatment (69/79 according to independent review [87.3%], and 61/78 according to investigator assessment [78.2%]). For all patients, the median response duration was 12.9 months (95% CI 10.0–14.9) by independent review, and 14.0 months (95% CI 10.9–18.5) by investigator assessment. Table 55 outlines the time to response, and duration of response, based on confirmed responses.

Table 55 Time to response and duration of response based on confirmed response – treated set

	Independent review	Investigator assessment
Total treated, N (%)	129 (100.0)	129 (100.0)
Patients with objective response, N (%)	79 (61.2)	78 (60.5)
Time to first response, N (%)		
Week 4 (Day 22-35)	53 (41.1)	43 (33.3)
Week 8 (Day 50-63)	16 (12.4)	18 (14.0)
Week 12 (Day 78-91)	2 (1.6)	5 (3.9)
Week 20 (Day 134-147)	5 (3.9)	7 (5.4)
Week 28 (Day 190-203)	1 (0.8)	2 (1.6)
Week 36 (Day 246-259)	2 (1.6)	2 (1.6)
Week 44 (Day 281−336)	0 (0.0)	1 (0.8)
Duration of response (Weeks)		
Mean (Std)	57.7 (35.8)	65.9 (37.1)
Median (min-max)	54.4 (4.1-164.9)	60.6 (8.1-152.1)

Source data: Tables 15.2.1.1: 2 and 15.2.1.1: 4

6.9 *Adverse events*

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

This is not applicable since adverse event data was a secondary endpoint in first line studies (LUX-Lung 3 and LUX-Lung 6). Safety data in LUX-Lung 2 was a secondary endpoint and adverse event data has been included by afatinib dose.

In LUX-Lung 3 safety analysis and pharmacokinetic data were represented by descriptive statistics. Adverse event data was reproduced for special populations of female sex and elderly age groups. In LUX-Lung 6 safety analysis was exploratory with adverse event table produced for special populations. Since adverse event data was descriptive no statistical analysis was performed to assess for differences between the two treatment arms.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

LUX-Lung 3 Adverse Events

A summary of the adverse events for patients on treatment during LUX-Lung 3 are shown in Table 56. The results are descriptive therefore the incidence is presented.

Table 56 Overall summary of AEs during the on-treatment period

	Afatinib N (%)	Chemotherapy N (%)
Patients	229 (100)	111 (100)
Patients with any AE	229 (100)	109 (98.2)
Drug related	228 (99.6)	106 (95.5)
AEs leading to dose reduction	131 (57.2)	18 (16.2)
AEs leading to a permanent discontinuation	32 (14.0)	17 (15.3)
Drug related AEs[1] leading to permanent discontinuation	18 (7.9)	13 (11.7)
SAEs[2]	66 (28.8)	25 (22.5)
Fatal	13 (5.7)	3 (2.7)
Immediately life-threatening	1 (0.4)	4 (3.6)
Disability/incapacity	0	0
Required hospitalisation	62 (27.1)	20 (18.0)
Prolonged hospitalisation	4 (1.7)	6 (5.4)
Other	2 (0.9)	1 (0.9)
By highest CTCAE grade		
Grade 1	12 (5.2)	14 (12.6)
Grade 2	78 (34.1)	32 (28.8)
Grade 3	117 (51.1)	49 (44.1)
Grade 4	9 (3.9)	11 (9.9)
Grade 5	13 (5.7)	3 (2.7)
AEs of grade ≥3	139 (60.7)	63 (56.8)

[1]As defined by the investigator; [2] These categories are not mutually exclusive; CTCAE Common terminology criteria for adverse events, AE = adverse event, SAE = serious adverse event

In the afatinib arm, 57.2% of patients experienced AEs that led to dose reduction; 14.0% of patients experienced AEs that led to permanent discontinuation of trial treatment. In 7.9% of patients, the AEs leading to treatment discontinuation were considered drug-related by the investigator. Serious adverse events were reported for 28.8% of patients in the afatinib arm, most of them were considered serious because they required hospitalisation (27.1% of patients); 5.7% of patients had SAEs with fatal outcome. The maximum CTCAE Grade of AEs was 3 for 51.1% of patients; 9.6% of patients experienced AEs of CTCAE Grade 4 or 5.

In the chemotherapy arm, 16.2% of patients experienced AEs leading to dose reduction and 15.3% of patients experienced AEs leading to permanent treatment discontinuation; AEs leading to treatment discontinuation were considered drug-related in 11.7% of patients. A total of 22.5% of the patients had SAEs, in the majority of cases, SAEs were considered serious because they required hospitalisation (18.0% of patients); SAEs with fatal outcome were reported for 2.7% of patients. The most common maximum CTCAE Grade was Grade 3 (44.1% of patients); 12.6% of patients experienced AEs of CTCAE Grade 4 or 5. The frequency of drug related AEs with an incidence >10% in either treatment arm by treatment arm are shown in Table 57.

Table 57 Frequency drug related AEs with an incidence >10% in either treatment arm by treatment arm

System organ/ class/adverse events	Afatinib (n = 229)		Cisplatin/pemetrexed (n = 111)		Hazard Ratio[1] (95% C.I.)
	All Grades	Grade ≥3	All Grades	Grade ≥3	P value
Diarrhoea	218 (95.2)	33 (14.4)	17 (15.3)	0	11.492 (7.46, 17.69) <0.0001
Rash/acne†	204 (89.1)	37 (16.2)	7 (6.3)	0	17.966 (9.97, 32.38) <0.0001
Stomatitis/mucositis†	165 (72.1)	19 (8.3)	17 (15.3)	1 (0.9)	
Paronychia	140 (61.1)	27 (11.8)	0	0	
Dry skin	67 (29.3)	1 (0.4)	2 (1.8)	0	
Decreased appetite	47 (20.5)	7 (3.1)	59 (53.2)	3 (2.7)	
Pruritus	43 (18.8)	1 (0.4)	1 (0.9)	0	
Nausea	41 (17.9)	2 (0.9)	73 (65.8)	4 (3.6)	
Ocular effect†	14 (17.9)	1 (0.4)	2 (1.8)	0	
Fatigue†	40 (17.5)	3 (1.3)	52 (46.8)	14 (12.6)	
Vomiting	39 (17.0)	7 (3.1)	47 (42.3)	3 (2.7)	
Lip effect†	33 (14.4)	0	2 (1.8)	0	
Epistaxis	30 (13.1)	0	1 (0.9)	1 (0.9)	
Weight decreased	24 (10.5)	0	10 (9.0)	0	
Alopecia	23 (10.0)	0	19 (17.1)	0	
Anaemia‡	7 (3.1)	1 (0.4)	31 (27.9)	7 (6.3)	
Constipation	6 (2.6)	0	21 (18.9)	0	
Leukopaenia‡	4 (1.7)	1 (0.4)	21 (18.9)	9 (8.1)	0.05 (0.023,0.109) <0.0001
Haemoglobin reduced	3 (1.3)	0	12 (10.8)	3 (2.7)	
Neutropaenia‡	2 (0.9)	1 (0.4)	35 (31.5)	20 (18.0)	

†Group term. ‡Numbers are based on the adverse events reported by the investigator and not derived from the laboratory data; Adverse events graded using NCI CTCAE version 3.0

[1] Hazard ratio of first diarrhoea from Cox proportional hazards model with treatment fitted as only factor; p-value derived from log-rank test.

Hazard ratios were calculated for the following adverse events of diarrhoea, rash and leucopaenia (Table 57). These were pre-specified as adverse events of special interest (AESIs) due to the mechanistic action of ErbB Family blockade (diarrhoea and rash) and chemotherapy (leucopaenia).

Median treatment duration for afatinib was 16 cycles (336 days) and for cisplatin/pemetrexed 6 cycles (105 days).

- Drug related adverse events occurred in 99.6% of patients taking afatinib compared with 95.5% of patients taking cisplatin/pemetrexed.

- Grade 3 or above adverse events occurred in 60.7% of patients taking afatinib compared with 56.8% of patients taking cisplatin/pemetrexed. Grade 3 and above adverse events considered by the investigator to be drug related occurred in 48.9% of patients taking afatinib and 47.7% taking cisplatin/pemetrexed.
- Drug related discontinuation rates were low, and occurred in 7.9% of patients taking afatinib and 11.7% of patients taking cisplatin/pemetrexed.

Serious adverse events occurred in 28.8% of patients taking afatinib compared with 22.5% of patients taking cisplatin/pemetrexed. Drug related serious adverse events occurred in 14.4% of patients in both arms of the study, but there were 4 deaths considered by the investigator to be drug related in the afatinib arm (1.7%) compared to none in the cisplatin/pemetrexed arm. The causes of death in the afatinib arm were dyspnoea, sepsis, acute respiratory distress syndrome and unknown.

Diarrhoea

Diarrhoea occurred at all grades in 95.2% of patients and grade 3 or above in 14.4% of patients. Diarrhoea was reported as an SAE in 6.6% of patients. In the majority of patients in the afatinib arm (83.4%), the first onset of diarrhoea occurred within 14 days after start of treatment. Diarrhoea led to dose reduction of afatinib in 19.7% of patients, however, there were only 3 patients that discontinued afatinib due to diarrhoea (1.3%). In the chemotherapy arm, 22.5% of patients experienced diarrhoea; it was considered drug related by the investigator in 15.3% of patients. Most of the events were of CTCAE Grade 1.

Rash/acne

Rash and acneiform reaction was a group term. Rash occurred at all grades in 89.1% of patients and grade 3 or above in 16.2% of patients treated with afatinib. There were no discontinuations of afatinib due to rash. 64.3% of patients experienced rash between days 1 and 14 and 79.7% of patients experienced rash by day 15 to 28.

In the chemotherapy arm, the proportion of patients with rash/acne was 10.8% and all events were of CTCAE Grade 1 or 2.

Stomatitis

Stomatitis and mucositis was a group term and occurred in all grades in 72.1% of patients and at grade 3 or above in 8.7% of patients receiving afatinib.

Reduced appetite across all grades occurred in 53.2% of patients taking cisplatin/pemetrexed and 20.5% of patients taking afatinib. All grade incidence of nausea occurred in 65.8% of patients taking cisplatin/pemetrexed compared to 17.9% of patients taking afatinib. Fatigue occurred in 46.8% of

patients taking cisplatin/pemetrexed at all grades compared with 17.5% of patients taking afatinib. Vomiting across all grades occurred in 42.3% of patients taking cisplatin/pemetrexed compared to 17.0% of patients taking afatinib.

Haematological adverse effects were more common in those patients taking cisplatin/pemetrexed. Anaemia at all grades occurred in 27.9%, leucopaenia in 18.9% and neutropaenia in 31.5% of patients taking cisplatin/pemetrexed compared to 3.1%, 1.7% and 0.9% respectively for the afatinib treatment arm.

LUX-Lung 6 Adverse Events

The median duration of afatinib treatment was 398.0 days. Overall 45.6% of patients received more than 20 afatinib treatment courses, with the maximum duration of treatment observed by the cut-off date being 871 days.

In the chemotherapy arm, the median treatment duration was 89.0 days. Overall, 72.6% of patients received 4 or more chemotherapy courses, with the maximum number of treatment courses administered to 35.4% of patients.

In the course of the study, 239 patients received afatinib 40 mg, whilst 38 patients received the 50mg dose. Overall 66.5% of patients did not require afatinib dose reduction; 27.2% of patients had 1 dose reduction and 6.3% had 2 dose reductions.

A summary of the adverse events for patients on treatment during LUX-Lung 6 are shown in Table 58.

Table 58 Overall summary of AEs during the on-treatment period

	Afatinib N (%)	Chemotherapy N (%)
Patients	239 (100)	113 (100)
Patients with any AE	239 (100)	112 (99.1)
Drug related	236 (98.7)	112 (99.1)
AEs leading to dose reduction	77 (32.2)	30 (26.5)
AEs leading to a permanent discontinuation	23 (9.6)	45 (39.8)
Drug related AEs[1] leading to permanent discontinuation	14 (5.9)	45 (39.8)
SAEs[2]	36 (15.1)	12 (10.6)
Fatal	14 (5.9)	3 (2.7)
Immediately life-threatening	1 (0.4)	1 (0.9)
Disability/incapacity	1 (0.4)	0
Required hospitalisation	30 (12.6)	9 (8.0)
Prolonged hospitalisation	5 (2.1)	3 (2.7)
By highest CTCAE grade		
Grade 1	39 (16.3)	9 (8.0)
Grade 2	88 (36.8)	33 (29.2)
Grade 3	90 (37.7)	43 (38.1)
Grade 4	8 (3.3)	24 (21.2)
Grade 5	14 (5.9)	3 (2.7)

[1] As defined by the investigator; [2] These categories are not mutually exclusive
AE = adverse event, SAE = serious adverse event

Almost all patients in the afatinib arm (98.7%) were reported as having drug-related AEs by the investigators. The profile of drug-related AEs was very similar to the overall AE profile in the afatinib arm, with the most frequent events being diarrhoea (88.3% of patients), rash/acne (grouped term) (80.8%), stomatitis (grouped term) (51.9%), and nail effects (grouped term) (33.9%); in addition 20.1% of patients in the afatinib treatment arm experienced drug-related ALT increase and 15.1% experienced AST increase but most cases were of CTCAE Grade 1 or 2. The most frequent drug-related CTCAE Grade 3 events were rash/acne (group term) 14.2%, diarrhoea 5.4%, and stomatitis 5.4%. One case each of Grade 3 neutropaenia, leukopaenia and thrombocytopenia was considered drug related. In addition, 3 patients each experienced Grade 3 drug-related hyponatraemia or hypokalaemia. Three patients (1.3%) in the afatinib arm experienced drug related AEs of Grade 4, comprising rash/acne, ILD, and dysphagia.

AEs with an incidence >20% by treatment, highest CTCAE grade, grouped terms and MedDRA preferred term are shown in Table 59.

Table 59 AEs with an incidence >20% by treatment, highest CTCAE grade, grouped terms and MedDRA preferred term

System organ/ class/adverse events	Afatinib (n = 239)			Cisplatin/gemcitabine (n = 113)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Patients with AEs	239 (100.0)	90 (37.7)	8 (3.3)	112 (99.1)	43 (38.1)	24 (21.2)
Diarrhoea	214 (89.5)	14 (5.9)	0 (0.0)	17 (15.0)	0 (0.0)	0 (0.0)
Rash/acne+	193 (80.8)	34 (14.2)	1 (0.4)	11 (9.7)	0 (0.0)	0 (0.0)
Stomatitis+	125 (52.3)	13 (5.4)	0 (0.0)	6 (5.3)	0 (0.0)	0 (0.0)
Nail effects+	82 (34.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT increased	55 (23.0)	5 (2.1)	0 (0.0)	18 (15.9)	2 (1.8)	1 (0.9)
Fatigue+	41 (17.2)	5 (2.1)	0 (0.0)	44 (38.9)	1 (0.9)	0 (0.0)
Decreased appetite	37 (15.5)	6 (2.5)	0 (0.0)	48 (42.5)	2 (1.8)	0 (0.0)
Vomiting	32 (13.4)	3 (1.3)	0 (0.0)	91 (80.5)	19 (16.8)	4 (3.5)
Nausea	28 (11.7)	1 (0.4)	0 (0.0)	85 (75.2)	8 (7.1)	1 (0.9)
Hypokalaemia	27 (11.3)	10 (4.2)	1 (0.4)	26 (23.0)	12 (10.6)	1 (0.9)
Anaemia	19 (7.9)	1 (0.4)	0 (0.0)	32 (28.3)	8 (7.1)	2 (1.8)
Leukopenia	15 (6.3)	4 (1.7)	0 (0.0)	58 (51.3)	15 (13.3)	2 (1.8)
Neutropenia	11 (4.6)	3 (1.3)	0 (0.0)	61 (54.0)	20 (17.7)	10 (8.8)
Constipation	10 (4.2)	1 (0.4)	0 (0.0)	31 (27.4)	0 (0.0)	0 (0.0)
White blood cell decreased	3 (1.3)	0 (0.0)	0 (0.0)	27 (23.9)	7 (6.2)	0 (0.0)
Neutrophil count decreased	2 (0.8)	0 (0.0)	0 (0.0)	29 (25.7)	8 (7.1)	3 (2.7)

+ grouped term

CTCAE = Common Terminology Criteria for Adverse Events; AE = adverse event

Adverse events of special interest

In total, 89.5% of patients treated with afatinib experienced diarrhoea during the course of the study. The diarrhoea was considered drug-related by the investigator for 88.3% of patients treated with afatinib and was reported as an SAE in 0.8% of patients. For 71.5% of patients in the afatinib arm the first onset of diarrhoea occurred within the first 14 days after the start of treatment. Overall, 5.9% of patients treated with afatinib experienced CTCAE Grade 3 diarrhoea with all other events of CTCAE Grade 1 or 2. In the chemotherapy

arm 15.0% of patients experienced diarrhoea, which was considered drug-related by the investigator in 10.6% of patients. Most events were of CTCAE Grade 1. The Hazard ratio for diarrhoea in the afatinib vs. Chemotherapy arm was 12.443 (C.I. 7.547, 20.515; p<0.0001)

Overall, 80.8% of patients in the afatinib treatment arm experienced rash/acne (grouped term) and in most cases (73.2% of patients) the preferred term reported was rash. All patients with rash/acne had an event that was considered drug-related by the investigator. Rash/acne required therapy in 42.7% of patients in the afatinib arm and led to permanent treatment discontinuation for 5 patients (2.1%). In the chemotherapy arm 9.7% of patients experienced rash/acne, with all events being of CTCAE Grade 1 or 2. The Hazard ratio for rash/acne in the afatinib vs. chemotherapy arm was 11.502 (C.I.6.244, 21.188; p<0.0001).

There was one patient in the afatinib arm that had an ILD like event, with none in the chemotherapy arm.

There was one death in the afatinib arm deemed drug related by the investigator; cause was recorded as sudden death. There was also one death in the cisplatin/gemcitabine arm deemed drug related with the cause of death as cardiac failure.

LUX-Lung 2 adverse event data

The mean total treatment time was slightly longer for first-line patients compared with second-line patients receiving a given starting dose. The mean total treatment time was 11.9 months for first-line and 9.3 months for second-line among patients who received the 40 mg starting dose and 17.0 months for first-line and 13.4 months for second-line among patients who received the 50 mg starting dose

Dose reductions by treatment group

Across treatment groups AEs that led to dose reduction were reported for 59.7% of patients (77/129), In the 40mg treatment group dose reductions occurred in 36.7% of patients (11 of 30) and in the 50mg treatment group dose reductions occurred in 66.7% of patients (66 of 99 patients) (Table 60).

Table 60 Adverse events by dose

Adverse event	Afatinib 40mg	Afatinib 50mg
Number of patients	30 (100.0)	99 (100.0)
Total with adverse events	30 (100.0)	98 (99.0)
Diarrhoea	29 (96.7)	93 (93.9)
Rash/acne+	27 (90.0)	94 (94.9)
Nail effect+	24 (80.0)	86 (86.9)
Stomatitis+	15 (50.0)	90 (90.9)
Pruritus	15 (50.0)	59 (59.6)
Rhinorrhoea	10 (33.3)	44 (44.4)
Decreased appetite	10 (33.3)	39 (39.4)
Cough	9 (30.0)	39 (39.4)

Dry skin	7 (23.3)	34 (34.3)
Fatigue+	10 (33.3)	29 (29.3)
Ocular effect+	6 (20.0)	32 (32.3)
Epistaxis	9 (30.0)	26 (26.3)
Dizziness	8 (26.7)	21 (21.2)
Insomnia	3 (10.0)	24 (24.2)
Vomiting	8 (26.7)	17 (17.2)
Dyspnoea	3 (10.0)	20 (20.2)
Nausea	5 (16.7)	18 (18.2)
Oropharyngeal pain	2 (6.7)	21 (21.2)
Constipation	3 (10.0)	19 (19.2)
Upper respiratory tract infection	6 (20.0)	16 (16.2)
Urinary tract infection	4 (13.3)	18 (18.2)
Weight decreased	3 (10.0)	19 (19.2)
Headache	6 (20.0)	15 (15.2)
Back pain	3 (10.0)	17 (17.2)
Abdominal pain	2 (6.7)	15 (15.2)
Oedema peripheral	7 (23.3)	10 (10.1)
Lip effect+	2 (6.7)	14 (14.1)
Alopecia	5 (16.7)	10 (10.1)
Muscle spasms	1 (3.3)	14 (14.1)
Hypokalaemia	2 (6.7)	12 (12.1)
Pyrexia	3 (10.0)	10 (10.1)

Overall summary of adverse events on treatment by starting dose is given in (Table 61).

Table 61 Overall summary of adverse events on treatment by starting dose – number (%) of patients – treated set

	Afatinib 40mg	Afatinib 50mg
Total treated	30 (100)	99 (100)
Investigator defined drug related AE	30 (100)	98 (99.0)
Any AE leading to dose reduction	11 (36.7)	66 (67.7)
AE leading to discontinuation of trial drug	8 (26.7)	17 (17.2)
SAEs	8 (26.7)	42 (42.4)
Fatal	2 (6.7)	10 (10.1)
Required hospitalisation	7 (23.3)	36 (36.4)
Prolonged hospitalisation	0	1 (1.0)
Other	2 (6.7)	6 (6.1)
Immediately life-threatening	0	1 (1.0)
CTCAE grade 3 or higher	16 (53.3)	72 (72.7)
Maximum CTCAE grade		
Grade 1	1 (3.3)	2 (2.0)
Grade 2	13 (43.3)	24 (24.2)
Grade 3	13 (43.3)	58 (58.6)
Grade 4	1 (3.3)	4 (4.0)
Grade 5	2 (6.7)	10 (10.1)

CTCAE = Common terminology criteria for adverse events, AE = adverse event, SAE = serious adverse event.

AEs that reached CTCAE Grade 3 were reported less frequently in the 40 mg starting dose group (43.3%) than in the 50 mg starting dose group (58.6%).

Adverse events of special interest

Diarrhoea

For most patients (74.4%), the highest reported CTCAE grade of diarrhoea was Grade 1 or 2. Overall, for 20.2% of patients, diarrhoea was reported as Grade 3 at the highest during the course of the event, with most of these patients (24/26) in the 50 mg starting dose group. No Grade 4 or 5 diarrhoea was reported. Diarrhoea was reported as an SAE for 1.6% of patients (2/129); both of whom received a starting dose of 50 mg. Importantly, although 24.8% of patients (32/129) had their dose reduced due to diarrhoea, no patients discontinued from the study due to diarrhoea.

Rash/Acne

Rash/acne was reported by 93.8% of patients (121/129) overall, including 90.0% (27/30) in the 40 mg starting dose group and 94.9% (94/99) in the 50 mg starting dose group. Overall, 23.3% of patients (30/129) developed Grade 3 rash/acne, with most (28/30) of these patients in the 50 mg starting dose group. No Grade 4 or 5 rash/acne was reported. Rash/acne was reported as an SAE for 3.9% of patients (5/129), all of whom received a starting dose of 50 mg. Two patients (both taking afatinib at 50mg) discontinued drug due to rash/acne.

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

In LUX-Lung 3 treatment with afatinib has been compared with cisplatin plus pemetrexed chemotherapy and the incidence of diarrhoea, rash/acne, stomatitis/mucositis and paronychia was higher, with rates of 95% v. 15%, 89% v 16%, 72% v 15% and 57% v 0% respectively, compared with cisplatin/pemetrexed chemotherapy across all grades. However, compared with afatinib, cisplatin/pemetrexed use was associated with a higher incidence of reduced appetite (53% v 21%), nausea (66% v 18%), fatigue (47% v 18%), vomiting (42% v 17%) and haematological abnormalities (anaemia 28% v 3%, leukopaenia 19% v 2% and neutropaenia 32% v 1%) across all grades. Treatment related discontinuation rates were lower than cisplatin/pemetrexed (7.9% v 11.7%) indicating that adverse events were generally well tolerated and dose reductions and supportive care adequately managed adverse events. Dose reductions occurred in 57% of patients taking afatinib, 38% had one dose reduction and 19% had two dose reductions. There were 3 cases of interstitial lung disease like events. The adverse event data in LUX-Lung 6 shows a lower incidence of grade 3 diarrhoea with only 5.9% of patients reporting this. Dose reductions occurred in 32.2% of patients and discontinuation due to drug related adverse events in only 5.9% of patients.

In the absence of head to head comparisons, adverse event data from erlotinib and gefitinib is derived from the registration studies for these treatments (EURTAC and IPASS respectively). In IPASS (Mok et al. 2009)

gefitinib treated patients experienced all grade diarrhoea at 47% and grade 3 or above occurred in 4% of patients. Rash or acne occurred in 66% of patient and at grade 3 or above in 3% of patients. Stomatitis occurred in 17% of patients and at grade 3 or above in <1% of patients. Treatment discontinuation occurred in 6.9% of patients compared with 13.6% receiving carboplatin and paclitaxel. 16.1% of patients taking gefitinib had a dose modification compared with 35.2% of patients taking chemotherapy. Serious adverse events occurred in 16.3% of patients taking gefitinib compared with 15.6% of patients taking chemotherapy. There were 16 cases (2.6% of patients) of interstitial lung disease events in the gefitinib treatment arm compared with 8 (1.4%) in the chemotherapy treatment arm. Therefore, whilst the incidence of diarrhoea, rash/acne, stomatitis/mucositis is slightly higher with afatinib compared with gefitinib, discontinuation rates are broadly similar indicating that these adverse effects are adequately managed with supportive care and dose reductions and that there is little impact of patient compliance.

In EURTAC, (Rosell et al. 2012) the rates of diarrhoea were 57% for all grade and 5% for grade 3. Rash occurred at all grades in 80% of patients and 13% of patients at grade 3. Rates of stomatitis and mucositis were not reported in the publication. However, the rate of fatigue at all grades in EURTAC was 57% and grade 3 in 6% of patients. In LUX-Lung 3 fatigue was reported in 18% of patients and just 1% of patients reported grade 3 fatigue. Reduced appetite was reported in EURTAC at 31% for all grades, and in LUX-Lung 3 21% of patients reported reduced appetite. Treatment related serious adverse events occurred in 6% of patients receiving erlotinib compared with 20% in the chemotherapy arm. The rates of drug related discontinuation was 6% in EURTAC compared with 20% in the chemotherapy arm of the study. Dose reductions due to drug related adverse events occurred in 21% of patients treated with erlotinib compared with 26% of chemotherapy treated patients. Interstitial lung disease-like events were seen in 1% of patients in both arms of EURTAC study. Aminotransferase increase was observed in 6% of patients taking erlotinib and 6% of patients taking chemotherapy at all grades.

In conclusion whilst the overall incidence of diarrhoea, rash/acne, stomatitis and paronychia was higher with afatinib the discontinuation rate was comparable with other technologies (erlotinib and gefitinib) and adverse events were adequately managed through supportive care and dose reduction schemes.

Adverse event data in LUX-Lung 2 shows a higher rate of dose reductions (66.7% of patients) at the 50mg dosing compared to 36.7% at the 40mg dosing. The incidence of grade 3 adverse events in the 50mg arm was 58.6% of patients, compared to 43.3% of patients in the 40mg dosing arm. All grade diarrhoea and rash/acne was similar in the two arms of LUX-Lung 2, however, stomatitis at all grades was observed at a higher incidence, 90.9% of patients, in the 50mg arm compared to the 40 mg arm (50.0% of patients).

Erlotinib and gefitinib have been studied in the second line setting after prior chemotherapy (one or two lines) in an EGFR wild type population. The

adverse events in these trials may not be directly comparable but will provide the closest estimate of the toxicity profile of competitor therapies in the second line. Erlotinib has been assessed in the 2nd/3rd line after one to two rounds of chemotherapy in an EGFR wild type population that included mixed histologies (Shepherd et al. 2005). The rate of diarrhoea was 55% of patients at all grades and 6% of patients at grade 3 or above. 5% of patients discontinued erlotinib due to drug related adverse events. Rash occurred at all grades in 76% of patients and at grade 3 or above in 9% of patients. Dose reductions occurred in 19% of patients. Gefitinib was studied vs. placebo in the ISEL study (Thatcher et al. 2005) which enrolled NSCLC patients who had received either one or two prior lines of chemotherapy. The commonest adverse events from this study were rash (all grades 37% and grade 3-4, 2% of patients) and diarrhoea (all grades 27% and grade 3-4 3% of patients). Interruptions (dose reduction was not permitted) occurred in 11% of patients in the gefitinib arm and 5% of patients in the gefitinib group withdrew due to adverse events,

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Afatinib has been studied first line in LUX-Lung 3 and LUX-Lung 6. The primary endpoint of LUX-Lung 3 was progression free survival and this endpoint was met, with treatment on afatinib associated with a median progression free survival of 11.1 months versus 6.9 month for cisplatin/pemetrexed chemotherapy. The hazard ratio for treatment with afatinib compared with cisplatin/pemetrexed chemotherapy was 0.58 ($p<0.001$). The secondary endpoint of objective response (complete and partial response) was met resulting in response rate of 56% vs. 23% on cisplatin/pemetrexed chemotherapy ($p<0.001$). Self reported quality of life assessments by EORTC questionnaires, revealed that afatinib was associated with a significant improvement in the status change of dyspnoea (64.0% vs. 50.0%; $p = 0.0103$) and individual items of pain ('Have pain': 56.0% vs. 40.0%; $p = 0.0095$; 'Pain in chest': 51.0% vs. 37.0%; $p = 0.0184$; 'Pain in arm or shoulder': 41.0% vs. 26.0%; $p = 0.0103$). Time to deterioration of cough and dyspnoea was significantly prolonged with afatinib treatment compared with chemotherapy (HR 0.595; $p = 0.0072$ and HR 0.682; $p = 0.0145$ respectively). In LUX-Lung 3 the adverse events associated with afatinib use included diarrhoea (occurring in 95% of patients), rash/acne (occurring in 89% of patients), stomatitis (occurring in 72% of patients) and nail effect (occurring in 61% of patients). Discontinuations due to drug related adverse events occurred in 1.3% of patients due to diarrhoea and no patients due to rash. The proportion of patients taking afatinib that discontinued due to treatment related adverse events was 7.9% of patients. There were 4 drug related fatal adverse events in the afatinib treated group compared to none in the chemotherapy arm.

The results of LUX-Lung 6 show very similar efficacy with a median progression free survival on afatinib treatment of 11.0 months vs. 5.6 months with cisplatin/gemcitabine (HR 0.279; p<0.0001). The objective response was 67% in the afatinib treated arm compared with 23% in the chemotherapy arm. There were similar improvements in quality of life measures with a higher proportion of patients taking afatinib having improvements in cough (76% vs. 55%) and dyspnoea (71% vs. 48%). Time to deterioration was significantly prolonged for cough (HR 0.45 p=0.0001), dyspnoea (HR 0.54 p<0.0001) and pain (HR0.70 p=0.0265).

Adverse events in LUX-Lung 6 were similar with diarrhoea occurring in 89% of patients and rash/acne in 81% of patients. The proportion of patients discontinuing afatinib due to treatment related adverse events was 5.9% of patients. One patient taking afatinib suffered a drug related fatality and one patient in the chemotherapy arm suffered a drug related fatality.

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

The first line study of LUX-Lung 3 is the largest international registration study assessing afatinib use versus chemotherapy in EGFR mutation positive adenocarcinoma of the lung patients. LUX-Lung 6 is the largest study of afatinib in patients with EGFR mutation positive adenocarcinoma of the lung. Both are open label randomised controlled trials, with central independent review and met their primary endpoints showing a significant improvement in progression free survival compared to chemotherapy. Due to the nature of the treatments in the different arms of the two trials, both investigator and patients were unblinded to the treatment arm that they had been assigned to. However, imaging was performed at a central centre for independent review by two board certified radiologists and a further final review by an oncologist, who would have the final decision in the case of disagreement between the radiologists' assessments. Despite a non significant difference in immature overall survival at interim analysis, other secondary endpoints of objective response rate are significantly better with afatinib compared to chemotherapy in both studies. It should also be noted that an overall survival benefit has not been observed in registration trials of other EGFR TKIs that are licensed in the first line setting in similar populations (Fukuoka at al. 2012). Despite a high rate of adverse events, namely diarrhoea and rash/acne being the most common, these were generally well managed as evidenced by the low discontinuation rates and significant improvement in quality of life displayed in both studies.

These studies favour the use of afatinib compared to chemotherapy in EGFR mutation positive NSCLC patients. It must be noted that no direct head to head comparison studies against reversible EGFR TKIs (that are currently the standard of case for patients with advanced NSCLC EGFR mutation positive tumours in the first line setting), exist at present. However, the use of cisplatin/pemetrexed in the UK is the standard of care for those NSCLC

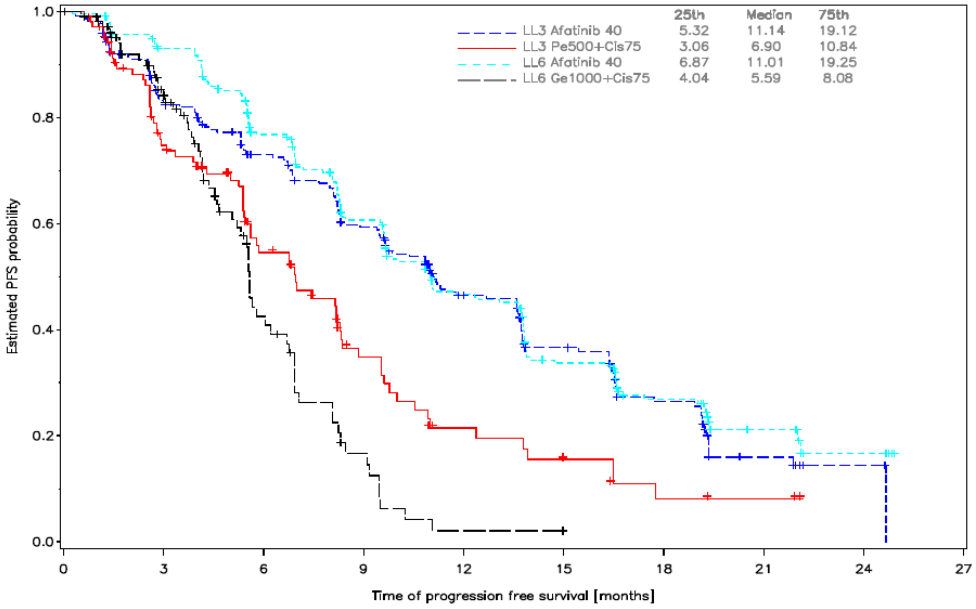
patients without an EGFR mutation and in China cisplatin/ gemcitabine is considered the standard of care for this patient population.

LUX-Lung 3 was an international study with sites across Europe and the UK and is therefore likely to be representative of the UK patient population. LUX-Lung 6 was conducted in China, South Korea and Thailand and therefore, despite enrolling EGFR positive NSCLC patients, may be less representative of a UK population. The LUX-Lung 6 trial, investigating afatinib vs. gemcitabine/cisplatin as first line treatment of Asian patients with EGFR mutation positive NSCLC, supplements the results of the global LUX-Lung 3 trial. The LUX-Lung 6 trial is the largest trial in EGFR mutation positive NSCLC with a similar design to LUX-Lung 3. The presentation of these results provides additional insights into the activity of afatinib and helps address the question about potential impact of ethnic differences. Both afatinib trials have been prospectively designed with registration intent in EGFR mutation positive NSCLC.

One of the areas of scientific interest remains whether EGFR mutant tumours display similar biological characteristics in both Asian and Caucasian patients. Currently there is no convincing data to highlight major differences between these groups either at molecular level or in terms of clinical outcomes on EGFR TKIs. Molecularly, EGFR mutations identified in Asian and non-Asian patients similarly affect the tyrosine kinase domain (exons 18-20) and share similar patterns of acquired resistance. Clinically, EGFR mutations are associated with similar demographic (female, non-smoker) and disease characteristics (adenocarcinoma) in Asian and non-Asian patients. Sensitivity to EGFR TKIs, manifesting in substantial clinical and radiologic responses in Asian and non-Asian populations appear in the similar range, comparing LUX-Lung 3 (mixed ethnicity), EURTAC (non-Asian), IPASS (Asian) and LUX-Lung 6 (Asian).

Progression free survival (PFS) data were consistent for patients treated with afatinib during both LUX-Lung 3 and LUX-Lung 6. Median PFS for patients treated with afatinib during LUX-Lung 3 was 11.1 months, which was similar for the afatinib arm of LUX-Lung 6 (11.0 months). In addition, the probability of being progression-free after 12 months following treatment with afatinib in LUX-Lung 3 was 47% and was matched by the 12-month PFS probability of 47% for patients given afatinib during LUX-Lung 6 (Figure 31).

Figure 31 Progression free survival curves for patients treated with afatinib in LUX-Lung 3 and LUX-Lung 6



Number at risk										
LL3 Afatinib 40	230	180	151	120	77	50	31	10	3	0
LL3 Pe500+Cis75	115	72	41	21	11	7	3	2	0	0
LL6 Afatinib 40	242	208	166	126	89	60	35	12	4	0
LL6 Ge1000+Cis75	122	70	25	8	1	0	0	0	0	0

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The decision problem in Section A highlights the unmet need in this patient population that experiences rapid progression and high mortality rates. Both prevalence and incidence are high necessitating the need for additional treatment option for health care professional.

A key objective of treatment is to sustain existing levels of quality of life by preventing disease progression. Treatment provided aims to do this whilst minimising adverse events.

The evidence base is structured to illustrate these key outcomes. The key outcomes relate to disease progression and overall survival, whilst also measures the impact of adverse events.

The clinical trials were designed before the current 1st line comparators (erlotinib and gefitinib) became routine clinical practice in the UK, and therefore no direct head-to-head data is available. However, since erlotinib and gefitinib have been licensed, testing for EGFR mutations has become standard practice, and the evidence of the effective of the TKI class of drug in these patients has grown. This has enabled us to undertake the mixed-

treatment comparison network meta-analysis (MTC) in Section 6.7 to enable us to compare the relative efficacy profiles of erlotinib and gefitinib to afatinib.

These results enable us to illustrate the comparative benefits of afatinib in the context of current clinical practice. We are able to see that there are non-significant treads in favour of afatinib compared to erlotinib and gefitinib with regards to Progression-Free Survival and Overall Survival. The clinical evidence further supports the use of afatinib as a relatively safe and tolerable medicine.

Both of these are in-line with patients' expectations and requirements when receiving first line treatment for NSCLC. This will enable them to experience tangible benefits of treatments and improved quality of life, albeit for a short period of time.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The main factors are discussed in Section 6.10.2. In addition to these:

- In both clinical trials, patients were started on afatinib at 40mg with the possibility of dose escalating if the therapy was tolerated well, and dose reducing in the event of adverse events. This is expected to be in line with the anticipated SPC.

- Patients would be selected for EGFR TKIs on the basis of testing positive for EGFR mutation(s), a test which is widely available in the UK, and has established testing at local levels. NICE have issued guidance on EGFR mutation testing (NICE diagnostics guidance 9, August 2013).Testing and testing strategies for EGFR TK mutations in adults with previously untreated locally advanced or metastatic NSCLC is recommended in accredited laboratories.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

The objective of this search was to identify any previously published cost-effectiveness studies that could address the decision problem. This was done using a systematic review. The format of this systematic review has been reported to be in line with NICE's STA requirements as outlined in the NICE STA template. To date, NICE's requirements are the most stringent with respect to systematic review requirements.

The scope of this systematic review is to review all available published data on economic evaluations of first-line therapies for locally advanced or metastatic NSCLC that could inform a HTA submission, based on BI's first line comparative trials of afatinib.

The time horizon of this search has been limited to the last ten years. This is within the NICE guidance of a systematic review timeline, and also is long enough to capture the most relevant and recent of studies on NSCLC. A time period longer than 10 years will capture studies that have been conducted in a method that is not current clinical practice, and thus could supplement bias to the review.

The population of interest is locally advanced or metastatic NSCLC patients, in particular EGFR positive patients. All possible chemotherapy and targeted therapies are analyzed within this systematic review. This literature review is intended to support afatinib across a potentially broad indication (i.e. all EGFR positive patients), and therefore splits studies into those reporting outcomes by line of treatment.

In line with the standard methodology for NICE submissions, multiple databases must be searched. The databases searched for cost-effectiveness studies are provided in Table 62.

Table 62 Databases searched for cost-effectiveness evidence

- Embase (via the OVID platform)
- Medline & Medline In-Process (via the OVID platform)
- Cochrane Library (via the InterScience platform) - includes:
  - Cochrane Database of Systematic Reviews (Cochrane Reviews)
  - Database of Abstracts of Reviews of Effects (Other Reviews)
  - Cochrane Central Register of Controlled Trials (Clinical Trials)
  - Cochrane Methodology Register (Methods Studies)
  - Health Technology Assessment Database (Technology Assessments)
  - NHS Economic Evaluation Database (Economic Evaluations)
- EconLit (via the OVID platform)

The data extraction was conducted (on the 6th March, 2012) using a Microsoft Access and Microsoft Excel-based extraction template. The search terms for the databases are in Section 10.10.4.

The time horizon of the search was limited to studies published from 2002-2012 (inclusive). The rationale for this was that a ten year time period was considered sufficient to capture the results of studies expected to be of greatest relevance to current clinical practice in the treatment of NSCLC. Thus, inclusion of studies published prior to 2002 does not reflect current clinical practice in the treatment of this disease and therefore may bias the outcome of the review.

Publications identified through the systematic review are evaluated in a three-step procedure in order to assess whether or not they should be included for data extraction and model population. The identified abstracts through the database search (1st step) were reviewed in using an inclusion/exclusion criteria (listed in Table 63), and if the abstract contained sufficient information to state that the publication did not meet this criteria, the publication was excluded. If the publication was not excluded, the full paper was retrieved, and again reviewed and subjected to the same inclusion/exclusion criteria. If the publication did meet the inclusion criteria after full paper review, the publication was included in the systematic review.

First review of citations

Duplicates of citations (due to overlap in the coverage of the databases) were excluded. The remaining citations were first screened using the abstract available with the citation. Those abstracts not meeting the eligibility criteria for inclusion in the systematic review were excluded. Full-text publications of remaining citations were retrieved and assessed for inclusion.

Second review of citations

The same inclusion/exclusion criteria were to be applied to the full-text publications remaining after the first review. If a full-text publication met the inclusion criteria, it was included as part of the systematic review.

Table 63 Inclusion and exclusion criteria for systematic review of economic studies

Criterion	Rationale
Patient population and intervention	
Disease: NSCLC	As per the decision problem
Gender: male or female	As per the decision problem
Age Group: Adults (> 18 years)	As per the decision problem
Race: any	As per the decision problem
Aim of treatment: Improvement in Progression-Free Survival and Health-Related Quality of Life in patients with locally advanced or metastatic NSCLC with EGFR mutation(s).	Only studies examining the effectiveness of therapies in terms of improvement in Progression-Free Survival and Health-Related Quality of Life in patients with NSCLC are relevant to the decision problem.
Treatment Lines: All lines of treatment of patients with locally advanced or metastatic NSCLC with EGFR mutation(s).	As per the decision problem
Intervention: afatinib	Only studies including afatinib are relevant to the decision problem.
Study Design	
Economic evaluation (cost-effectiveness, cost-utility, cost-benefit and cost-minimisation analyses)	As per the decision problem
Publication timeframe	
2002-2012 for literature searches	Given the rapidly changing treatment landscape of NSCLC, it is reasonable to assume that studies published from 2002-2012 are likely to be more reflective of current clinical practice than those published earlier than this.
Language Restrictions	
English only	This is a simplifying criterion for the review; however, it is not expected that the restriction would limit results substantially.

Extraction Strategy

Following a second review, information extracted from the identified articles included:

- Type of economic evaluation
- Study Objective Interventions
- Analytical Approach
- Effectiveness Data
- Monetary benefit and utility valuations
- Measure of benefit
- Cost data
- Analysis of uncertainty results
- Authors' conclusions
- Country(ies) where study was performed
- Summary of model
- Patient population (average age in years)
- QALYs (intervention, comparator)
- Costs (currency) (intervention, comparator)
- ICER (per QALY gained)

Quality assessment

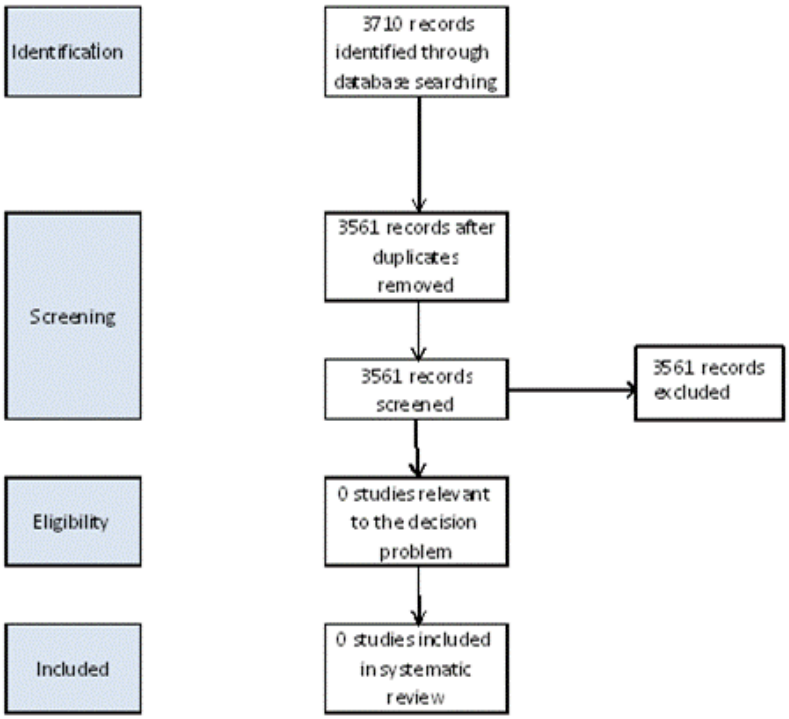
To ensure the methodological quality of each study eligible for inclusion in the systematic review, each study was quality assessed in accordance to the criteria outlined in the report of the Centre for Reviews and Dissemination (Centre for Reviews and Dissemination, 2009). A checklist was used to

assess the quality of each study included in the review with respect to methodological criteria for economic evaluations.

Results

The search of the literature yielded 3710 citations. De-duplication resulted in the removal of 149 overlapping citations. The titles and abstract of the remaining 3561 records were screened. Following first review, no studies that included afatinib as the intervention of interest were identified. For this reason (i.e. wrong intervention), all 3651 records were excluded. The flow of studies in the systematic review is presented in Figure 32.

Figure 32 PRISMA Flow Diagram of economic evaluation studies identified for locally advanced or metastatic NSCLC



As no studies relevant to the decision problem were identified, a de novo economic evaluation was required. Additional literature searches conducted since the cut-off date of the systematic review failed to identify any relevant economic studies.

Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Not applicable (see Section 7.1.1).

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Not applicable (see Section 7.1.1).

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

CHMP positive opinion was received for afatinib (GIOTRIF) from EMA on 25/07/13 and states the following:

GIOTRIF as monotherapy is indicated for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naive adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s) (EMA 2013)

The model is based on a first-line positioning comparing afatinib with other first-line TKIs. The model does not compare afatinib to TKIs in chemotherapy experienced patients, who fall within the licensed indication. Whilst 2nd line data after chemotherapy is available from LUX-Lung 2, this is a single arm study, albeit with disaggregated result from 1st and 2nd line patients. Whilst this

[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

data was sufficient to enable afatinib to be licensed in this population, afatinib cannot be compared to other second line patients and so cannot be used in a comparative cost-effectiveness analysis.

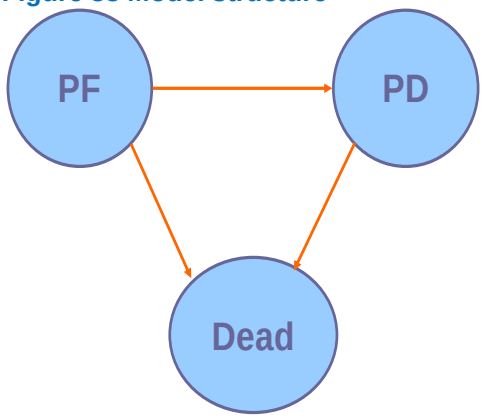
An estimated 1% of patients may be treated with a TKI after chemotherapy, as it does not necessarily represent good clinical practice (IMS 2013). We therefore believe this is a valid approximation to current clinical practice as erlotinib and gefitinib are both recommended as first line treatments and sufficient to form the basis of an assessment across the full license.

Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

The cost-effectiveness (CE) model is a disease-state cohort model consisting of three health states (Figure 33). These are progression-free (PF), progressive disease (PD), and death.

Figure 33 Model structure



7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model structure is in line with the clinical pathway of care in NSCLC treatment. Both the model structure and health states are characteristic of modelling in metastatic oncology and have been used in previous NICE STAs and MTAs (NICE 2010c, NICE 2011, Hoyle et al. 2011).

The model uses the partitioned survival (also known as area under the curve or AUC) method to determine the proportion of patients in each of the three health states during each model cycle. The proportion of patients in the progressive disease state is estimated as the difference between OS and PFS. Estimates of OS and PFS in the model are based on the progression-free and overall survival data from LUX-Lung 3 and LUX-Lung 6 and the corresponding parametric survival models.

Each health state (PF and PD) is associated with a cost and a health-related utility to estimate QALY over the time horizon of the analysis. The cycle length in the model is one month, which allows an adequate granularity when assessing progression and survival. QALYs in the treatment arms are estimated as the sum of area under the curves for the PF state and PD states, weighted by the respective health related utilities. Costs relating to health state management (excluding treatment costs or costs relating to adverse events) are also introduced into the model by weighting the respective areas under the curve by the health state management costs for the PF and PD health states.

Cost and utility reduction due to adverse events (AEs) are applied in the model based on the estimated proportions of patients suffering from adverse events in each treatment arm. The impact of adverse events on health outcomes (QALY) is calculated using information on the duration of adverse events and their impact on health-related utility.

7.2.4 Please define what the health states in the model are meant to capture.

The PFS state represents the period patients' cancer does not worsen whilst receiving active treatment. Patients in the PFS health state experience a relatively high quality of life prior to disease progression. The PD state involves the spreading of the disease during which time patients suffer a relatively poor quality of life. These health states are characteristic of those used in the modelling of metastatic oncology.

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

NSCLC is characterised by rapid progression and high mortality rates. The proposed three-state model reflects this type of disease progression, and is typically used to model progression of metastatic cancer (NICE 2011, McNamara et al. 2010).

The model fits with the course of the disease outlined in Section 2.1, where patients experience disease progression that can be affected through therapeutic interventions. By the time patients have locally advanced or metastatic non-small cell lung cancer, their treatment options are limited to EGFR-TKIs and chemotherapy. This is reflected in the model, whereby patients remain in a progression-free state whilst on treatment or progress when their treatment fails. Further treatment options are available for patients

before going onto best supportive care (BSC). Patients in both the progression free and the progressed disease states may die, and this is reflected in the model.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Key features are shown in Table 64.

Table 64 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	10 years	Set to cover the lifetime of the patients, in order to fully incorporate the costs and health outcomes of NSCLC.	NICE 2013
Cycle length	1 month	Allows an adequate granularity when assessing progression and survival.	NICE 2013
Half-cycle correction	Yes	Mitigate bias due to cycle length	NICE 2013
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE Reference Case	NICE 2013
Discount of 3.5% for utilities and costs	Yes	NICE Reference Case	NICE 2013
Perspective (NHS/PSS)	Yes	NICE Reference Case	NICE 2013
Additional Model Parameters are shown below:			
Number of patients per cohort	1	To estimate cost and outcomes per patient	NA
Days per monthly cycle	30.42	= 365 / 12	NA
Days per year	365	NA	NA

NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

As discussed in Section 7.2.1, the indication outlined as expected in the marketing authorisation in Section 1.3 to 1.5 is modelled as to be consistent with the available data.

In clinical practice, the doses may be adjusted by the clinicians, in the same way that they were during the clinical trials. As the model is based on the clinical trial data, the outcomes from the model would be expected to mirror both the clinical trial data (See section 7.7.1) and hence clinical practice.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The model assumes that patients are treated continuously with afatinib, erlotinib, or gefitinib until disease progression or treatment discontinuation for any reason. Disease progression is typically assessed by a CT scan every 3 months and this cost is incorporated in the model.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

The model presents the survival models and Kaplan Meier curves for progression-free and overall survival for the LUX-Lung 3 trial, which compares afatinib and pemetrexed/cisplatin as treatments for first line, EGFR mutation positive NSCLC. Using the default survival model settings, survival for afatinib patients is calculated by applying treatment effects (LUX-Lung 3-derived afatinib vs. pemetrexed/cisplatin hazard ratios) to the survival for pemetrexed/cisplatin patients. Survival of erlotinib and gefitinib patients is calculated by applying NMA-based hazard ratios to the survival calculated for afatinib patients (on the 'Survival IDC' worksheet). The reason for including pemetrexed/cisplatin in the calculations, rather than applying the NMA-based hazard ratios for erlotinib and gefitinib vs. afatinib directly to the independent survival models for the afatinib arm of the LUX-Lung 3 trial is for consistency with an earlier model which included pemetrexed/cisplatin as a comparator. Pemetrexed/cisplatin has been removed as a comparator from this model for the sake of simplification, since it is not required for this submission.

OS and PFS efficacy data from LUX-Lung 3

PFS and OS data used for the direct comparison are incorporated into the cost-effectiveness model either by using full parametric approximation or by using the Kaplan Meier data from the clinical trials extrapolated using parametric survival models. The former method is used in the model base case and details of the latter method are discussed below. Five parametric survival models have been included as options in the model. Three types of parametric survival models explored are proportional hazard (PH) models: exponential, Weibull and the Gompertz. The Log-Logistic and Log-Normal survival models have additionally been included as options in the cost-effectiveness model for sensitivity analysis.

The full parameterisations of the OS and PFS models are based on statistical analyses conducted on data from the LUX-Lung 3 trial. These parameterisations, along with calculation of confidence intervals (95%), variance-covariance matrices for the use in uncertainty analysis, and goodness of fit statistics were generated by the statistical services consultancy contracted by BI (the details are presented in health economics statistical analysis plans (BI 2013a). The parameterisations were conducted for single and separate survival models.

The option to use a single or separate parametric survival models for the two treatment arms has been included into the cost effectiveness model. Using a single model means that the treatment effect can be expressed via a single parameter (a hazard ratio, HR). The intercept parameter can vary across treatment arms; however the shape parameter remains constant across treatment arms. Using separate models means that both the intercept and shape parameters of the survival distribution can vary across treatment arms.

Hence, the hazard ratios presented in Table 65 and Table 66 are generated from RCT survival data calculated from single parametric models.

Because the indirect comparison is implemented via a hazard ratio approach it is necessary to use one of the three proportional hazard models, parameterised as a single model as the base case method of approximating OS and PFS within the cost-effectiveness model. The model base case uses the single proportional hazard parametric model which provides the best fit to approximate OS and PFS (the Weibull model in each case).

Table 65 RCT-based efficacy data from LUX-Lung 3 used in the model

Parametric model	Hazard ratio*	Lower 95% CI	Upper 95% CI
Progression free survival (PFS)			
Exponential	0.69	0.52	0.92
Weibull	0.61	0.46	0.82
Gompertz	0.62	0.46	0.83

* HR is determined for afatinib vs. pemetrexed/cisplatin; CI = Confidence interval

Table 66 RCT-based efficacy data from LUX-Lung 3 used in the model

Parametric model	Hazard ratio*	Lower 95% CI	Upper 95% CI
Overall survival (OS)**			
Exponential	0.96	0.70	1.31
Weibull	0.96	0.70	1.31
Gompertz	0.95	0.70	1.30

* HR is determined for afatinib vs. pemetrexed/cisplatin; CI = Confidence interval; ** Assumption of equivalent OS has been made

Choice of model

The Akaike Information Criterion score (AIC) is used to assess goodness of fit of the parametric survival models. The AIC can only be compared across models using the same number of observations, for two models using the same number of observations the model with the minimum AIC score has the best model fit. Table 67 and Table 68 present the AIC for the parametric OS and PFS models respectively using data from LUX-Lung 3. These tables demonstrate that for the single parametric survival models the Weibull model has the best goodness of fit to the Kaplan-Meier survival data for OS and for PFS. The Weibull model is therefore used as the base case model for OS and PFS in the cost-effectiveness model.

Table 67 Goodness of fit measure (AIC) for overall survival parametric models from LUX-Lung 3

Model type	Treatment	Exponential	Gompertz	Weibull	LogLogistic	LogNormal
Separate	**Afatinib**	367.96	360.49	360.44	361.73	365.27
	Pem/cis	177.76	176.22	173.57	172.73	172.89
Single	**Combined**	546.06	536.04	533.29	533.64	537.18

Table 68 Goodness of fit measure (AIC) for overall survival parametric models from LUX-Lung 3

Model type	Treatment	Exponential	Gompertz	Weibull	LogLogistic	LogNormal
Separate	**Afatinib**	501.68	482.08	482.23	485.27	493.78
	Pem/cis	246.47	237.43	233.45	234.56	236.65

Single	**Combined**	752.97	725.22	721.25	724.10	734.99

OS and PFS efficacy data - Efficacy data for the indirect comparison

In the base case analysis, the progression free survival (PFS) is from the random-effects model. The basecase for OS is the fixed effects model in Table 69. The other combinations in both Table 76 and Table 70 presented are explored further in the sensitivity analysis.

Table 69 Efficacy data from the MTC based on LUX-Lung 3 data and including LUX-Lung 6 data

Comparator	Hazard ratio*	Lower 95% CI**	Upper 95% CI**
Overall survival (OS)			
Erlotinib (FE)	0.80	0.56	1.14
Erlotinib (RE)	0.80	0.54	1.18
Gefitinib (FE)	0.84	0.55	1.30
Gefitinib (RE)	0.83	0.54	1.34
Overall survival (OS) including OPTIMAL trial			
Erlotinib (FE)	0.80	0.57	1.13
Erlotinib (RE)	0.80	0.56	1.17
Gefitinib (FE)	0.85	0.56	1.30
Gefitinib (RE)	0.85	0.55	1.35

FE: fixed effects model, RE: random effects model; * HR is determined for afatinib vs. comparator; All HRs presented have been constructed using random effects models; ** Credible interval.

Table 70 Efficacy data from the MTC based on LUX-Lung 3 data and excluding LUX-Lung 6 data used in the TKI-naive model

Comparator	Hazard ratio*	Lower 95% CI**	Upper 95% CI**
Overall survival (OS)			
Erlotinib (FE)	0.75	0.46	1.24
Erlotinib (RE)	0.75	0.43	1.31
Gefitinib (FE)	0.91	0.66	1.25
Gefitinib (RE)	0.91	0.64	1.28
Overall survival (OS) including OPTIMAL trial			
Erlotinib (FE)	0.71	0.47	1.10
Erlotinib (RE)	0.72	0.44	1.14
Gefitinib (FE)	0.75	0.43	1.30
Gefitinib (RE)	0.76	0.46	1.25

FE: fixed effects model, RE: random effects model; * HR is determined for afatinib vs. comparator; All HRs presented have been constructed using random effects models; ** Credible interval.

The MTC-based hazard ratios are applied to afatinib survival to generate survival estimates for gefitinib and erlotinib. The cost-effectiveness model includes an option which determines whether the MTC-based hazard ratios will be applied to RCT-based survival for afatinib or survival for afatinib which is set equal to that of pemetrexed/cisplatin. The cost-effectiveness model allows the user to assume equivalence in OS efficacy between afatinib and each of the MTC-based comparators.

Incidence and duration of adverse events

Adverse event rates from the LUX-Lung 1 (Miller et al. 2012, Hirsh et al. 2013, BI 2011a) and LUX-Lung 3 trials, or from the MTC, are used to estimate the

burden of drug toxicity for the different treatments included in the model. Costs and health outcomes (i.e. loss of QALY) associated with treatment-related adverse events are added to the sum of the overall costs and QALYs in the model cohort. The costs and health outcomes associated with adverse events are therefore applied within the first year, making the assumption that adverse events happen shortly after patients start receiving treatment, and that there is no need to discount the costs and health outcomes associated with them.

NICE have previously accepted economic models with similar mechanisms for incorporating adverse events without separate adverse event health states. For example, the evidence review group report for NICE (2008b), states, (in the last two bullet points on page 90), “Using the total incidence figures for the number of adverse events in each arm of the trial, the mean number of events per patient of each of the 4 AE types was calculated. Each of these mean numbers of events per patient was then multiplied by the mean cost of the event depending upon which one of the 4 cost categories described above it fell into, to give the total cost of adverse event management.”

In the model patients can experience five possible adverse events (diarrhoea, rash/acne, fatigue, anaemia, and neutropenia). Consistent with previous findings for other TKI’s (Maemondo et al. 2010, Zhou et al. 2011), the LUX-Lung 3 trial data shows that for patients on afatinib the incidence of anaemia and neutropenia events is very small (0.4% frequency for anaemia and neutropenia events). Therefore, these events are not treated as key adverse events when gefitinib or erlotinib are the comparator of interest.

Table 71 displays data on the frequency, number of episodes and average duration of adverse events used in the model. Adverse events are assumed to only occur while patients are progression-free (and therefore on treatment).

Data on the frequency of diarrhoea, rash/acne and fatigue adverse events in progression-free patients are derived from the LUX-Lung 3 trial for the afatinib treatment arm. However, data on the number of episodes per patient experiencing an adverse event and on the duration of each adverse event are only available for diarrhoea and rash/acne from LUX-Lung 3. Data on the number of episodes of adverse events and on the duration of adverse events are taken from LUX-Lung 1 for fatigue.

Table 71 Incidence and duration of adverse events by therapy during 1st line treatment

AE	Frequency of AE	Episodes per patient experiencing AE	Duration of AE
Afatinib arm			
Diarrhoea	14.4% (LL3)	1.36 (LL3)	6.6 (LL3)
Rash/acne	16.2% (LL3)	1.08 (LL3)	12.3 (LL3)
Fatigue	1.3% (LL3)	2.00 (LL1)	32.0 (LL1)
Anaemia	0.4% (LL3)	2.00 [1]	32.0 [1]
Neutropenia	0.4% (LL3)	2.00 [1]	32.0 [1]
Erlotinib arm			
Diarrhoea	7.5% (MTC)	1.36 [2]	6.6 [2]
Rash/acne	16.0% (MTC)	1.08 [2]	12.3 [2]
Fatigue	0.7% (MTC)	2.00 [2]	32.0 [2]
Anaemia	0.4% (MTC)	2.00 [2]	32.0 [2]
Neutropenia	0.4% (MTC)	2.00 [2]	32.0 [2]
Gefitinib arm			
Diarrhoea	3.6% (MTC)	1.36 [2]	6.6 [2]
Rash/acne	3.4% (MTC)	1.08 [2]	12.3 [2]
Fatigue	5.2% (MTC)	2.00 [2]	32.0 [2]
Anaemia	0.4% (MTC)	2.00 [2]	32.0 [2]
Neutropenia	0.4% (MTC)	2.00 [2]	32.0 [2]

LL3 = LUX-Lung 3; MTC = mixed treatment comparison; LL1 = LUX-Lung 1; [1] Assumed the same as fatigue; [2] Assumed the same as for afatinib;

The frequencies of the diarrhoea, rash/acne and fatigue adverse events for the erlotinib and gefitinib arms have been derived from the MTC. The number of episodes per patient with an adverse event, and the duration of adverse events are not available for erlotinib- or gefitinib-associated adverse events. Therefore, the model assumes that these values are the same for erlotinib and gefitinib treated patients as they are for pemetrexed/cisplatin and afatinib treated patients.

The durations of AEs for patients in the progressed state disease were calculated from LUX-Lung 1. Here the estimated duration of diarrhea AE (grade 3/4) until improvement was 10.8 days, for rash/acne was 22.3 days, and fatigue was 32 days.

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

The model includes three health states, progression-free (PF), progressive disease (PD), and death. The proportion of patients in each of the three health states during each model cycle is determined by the “area under the curve” (AUC), or partitioned survival approach, based on parametric survival models for progression-free and overall survival. Therefore the model does not use transition probabilities and includes no transition matrix.

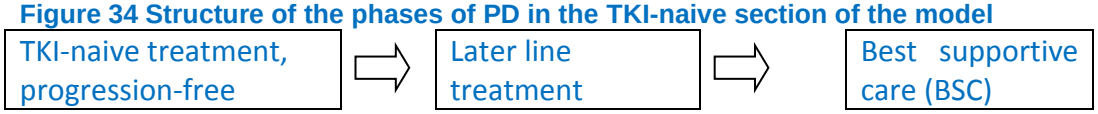
The proportion of the model cohort in each health state each model cycle is calculated by partitioning the area under the overall survival curve into the proportion of patients in PF and the proportion of patients in PD. For each

cycle, the proportion of patients in the PD health state is defined as the difference between the overall survival and progression-free survival for that cycle (OS – PD). The total time spent in the PF and PD health states for the time horizon considered by the model is the sum of the time spent in each health state over the time horizon of the analysis.

Time spent in PD

Progressive disease is represented in the model by a single health state. However, in order to reflect the progression and treatment of patients after progression in the 1st line section of the model, assumptions are made with regard to the likely patient treatment pathway after progression. Here TKI-naive is represented by the fist-line model. This allows estimates to be made of resource use and health related quality of life during the time between progression and death. No explicit modelling of post-progression treatment lines was conducted. This section describes the methods applied to the progressive disease health state in this model.

Figure 34 Structure of the phases of PD in the TKI-naive section of the model



During the PD period in the 1st line part of the model, patients are assumed to initially receive 2nd line treatment before progressing and moving on to BSC (Figure 34). The 2nd line treatment patients receive will depend on their 1st line therapy, as shown in Table 72. Total time spent in the entire PD period is calculated based on the difference between the OS and PFS derived from the parametric survival models. The portion of the PD period that patients are assumed to spend on active 2nd line treatment is based on published median PFS times for 2nd line. The rest of the time in PD is assumed to be spent in 3rd line BSC and this is calculated by subtracting the time spent on second line treatment from the total time spent in PD for each treatment arm.

Table 72 Therapy received 2nd line and source of 2nd line PFS data by treatment arm

First line therapy	Second line therapy	Source of 2nd line PFS data
Afatinib	Docetaxel	INTEREST trial*
Erlotinib	Docetaxel	INTEREST trial*
Gefitinib	Docetaxel	INTEREST trial*

*as reported in Gefitinib EMA SPC (EMA 2009).

Based on discussions with clinical experts (See Section 7.3.5) it is not clear whether the PFS for a particular 2nd line drug would be influenced by changes in the period a patient spends in the PD health state, following 1st line treatment in the model. Because of this, the model can be set to use either one of two different assumptions:

2nd line treatment period constant

- For a particular 2nd line treatment regimen, the time spent on 2nd line treatment is assumed to be remain constant across treatment arms,

irrespective of the relative period the two arms spend in the PD state (as shown in Table 73).

2nd line treatment period proportionally adjusted according to overall time in PD state

- With this setting, patients spending longer in the PD state are assumed to spend correspondingly longer periods on 2nd line treatment. To model this, a proportionate adjustment to the period on 2nd line treatment is made, relative to the pemetrexed/cisplatin treatment arm (as shown in Table 74).

In the model base case, the 2nd line treatment period remains constant across treatment arms. The relative time that patients spend on 2nd line treatment vs. BSC is used to determine weighted utility and cost per month values for each treatment group during the PD health state.

Table 73 Time spent in each PD component by treatment arm, with 2nd line treatment period constant

Time per PD component in use by 1L therapy (months)			
	Afatinib	Erlotinib	Gefitinib
Mean total period in PD (months)	19.45	15.95	18.14
Mean period in 2L (months)	4.10	4.10	4.10
Mean period in 3L BSC (months)	15.35	11.85	14.04

Table 74 Time spent in each PD component by treatment arm, with 2nd line treatment period proportionally adjusted according to overall time in PD state

Time per PD component in use by 1L therapy (months)			
	Afatinib	Erlotinib	Gefitinib
Mean total period in PD (months)	19.45	15.95	18.14
Mean period in 2L (months)	3.56	2.92	3.32
Mean period in 3L BSC (months)	15.89	13.03	14.82

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

As discussed in Section 7.3.2, the model does not use transition probabilities because it assumes the area under the curve approach. However, the time-dependent aspects of NSCLC are captured in the model through the incorporation of trial-based parametric survival models describing progression-free survival and overall survival.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what

sources of evidence were used, and what other evidence is there to support it?

No surrogate markers were used in this model.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Boehringer Ingelheim selected clinical experts to review assumptions within the submission on the basis that they were widely published, were involved in clinical trials, and also guidelines and guidance development.

Boehringer Ingelheim approached two clinical experts to review the assumptions. We received one response from the two and went ahead to seek clinical validation from this clinical expert. The clinician was [redacted]

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

A one hour telephone interview with [redacted] was conducted, and no background information was provided prior to this. During this interview the clinical assumptions of the model were checked, and full questions and answers from this interview are provided in xxxxxx75.

It should be noted that this interview was conducted prior to us knowing that the indication for afatinib would be structured by TKI-naive patients, and therefore it reflect our prior expectations that afatinib would be indicated by line of treatment.

[redacted]

- **Interviewee**

[redacted]

- **Model structure**

[redacted] agreed that the structure of the model is acceptable to reflect the pathway of patients with non-small cell lung cancer (NSCLC).

It was noted that there are further phases within PF and PD. However [redacted] agreed that it would be very difficult to capture these analytically.

- **Treatment**

[redacted] stressed that there is a large degree of variation in the uptake of NSCLC treatments, and that clinicians typically assess a wide range of factors when making treatment decisions.

- **Comparators**

First Line:

All comparators were deemed as relevant and appropriate by [redacted].

For EGFR mutation positive patients, erlotinib and gefitinib are the most common treatments.

[redacted] verified that patients receiving pemetrexed would receive between 4-6 cycles in England and Wales and 4 cycles in Scotland.

Second Line:

[redacted] stated that many NSCLC patients are unlikely to receive a second line of treatment as they will often proceed directly to best supportive care (BSC) following first line treatment because of toxicities from the first line therapy.

For those patients that do go on to receive an active second line treatment, docetaxel or pemetrexed could be used for those who received an EGFR TKI as first line treatment. This is likely to be administered for 2-4 cycles depending on the patient's response.

For those who received pemetrexed/cisplatin as first line treatment, Erlotinib or Gefitinib are likely to be used as second line treatment.

Third/Fourth Line:

[redacted] agreed that BSC was the relevant comparator for third/fourth line treatment.

• **Adverse events** [redacted] agreed that Diarrhea, rash/acne and fatigue are the main adverse events to be considered, whereas nail effect is not a significant concern.
• **Resource use and costs** [redacted] agreed that all resource use items considered are relevant. It was suggested that it may be useful to factor in the cost of palliative care nurse visits. [redacted] provided information on the pre-medications used for a dose of pemetrexed/cisplatin treatment: - 1mg of vitamin B12 one week before treatment and one further dose after three cycles. - 400mg folic acid per day for one week before treatment and throughout treatment. - 3mg Dexamethasone at each dose of pemetrexed/cisplatin - 3 days of oral antiemetics with each dose of pemetrexed/cisplatin [redacted] stated that there are regional differences in the uptake of EGFR mutation testing for NSCLC patients – all NSCLC patients in England and Wales are tested, whereas testing is focussed on non-squamous NSCLC patients in the North and West of Scotland. [redacted] also mentioned that EGFR mutation tests in Scotland routinely looked for the most common exon 19 and 21 mutations; however he was not sure if this was also the case in the rest of the UK.
• **Time spent in the progressive disease state** [redacted] advised that current thinking is in line with the idea of keeping patients progression-free for as long as possible, at a cost of reducing survival time in the progressive disease state.

All of the recommendations from [redacted] were addressed in the analysis.

In addition, a Canadian expert was consulted on developing this model for the Canadian market. The notes from this meeting are not provided as they were not used to adapt the model to the UK.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 76 Summary of Clinical Variables

Category	Variable	Value	Variance	Reference	Source
General Settings	Discounting cost	3.5%	0%-6%	Table 64	NICE 2013
	Discounting effect	3.5%	0%-6%	Table 64	NICE 2013
	Years per cycle	8%	None	Table 64	NICE 2013
	Weeks per model cycle (pem/cis)	4.33	NA	=52 weeks/12 months	NA
	Weeks per chemo cycle	3	None	2nd line treatment duration	BNF 2011
	Time horizon (years)	10	None	Table 64	NICE 2013
	Number of patients per cohort	1	None	Table 64	NA
	Days per monthly cycle	30.42	None	Table 64	NA
	Days per year	365	None	Table 64	NA
	Max time on afatinib (months)	200	NA	Modelling assumption	NA
	Max time on Erlotinib (months)	200	NA	Modelling assumption	NA
	Max time on Gefitinib (months)	200	NA	Modelling assumption	NA
	Max number cycles on 2L treatment (Docetaxel)	6.0	3.0-8.0	Table 105	BNF 2011
Efficacy (PFS hazard ratios)	Cox PH model HR for PFS (afatinib vs. pmc)	0.58	0.43-0.78(CI)	Table 15	LUX-LUNG 3
	Expo model HR for PFS (afa vs. pmc)	0.69	0.52-0.92 (CI)	Table 65	LUX-LUNG 3
	Weibull model HR for PFS (afa vs. pmc)	0.61	0.46-0.82 (CI)	Table 65	LUX-LUNG 3
	Gompertz model HR for PFS (afa vs. pmc)	0.62	0.46-0.83 (CI)	Table 65	LUX-LUNG 3
	MTC-based HR for PFS (afa vs. erl)	0.91	0.53-1.50 (Cr.I)	Table 34	MTC
	MTC-based HR for PFS (afa vs. gef)	0.78	0.47-1.20 (Cr.I)	Table 34	MTC
Efficacy (OS hazard ratios)	Cox PH model HR for OS (afatinib vs. pmc)	1.12	0.73-1.73	Table 15	LUX-LUNG 3
	Expo model HR for OS (afa vs. pmc)	0.96	0.70-1.31 (CI)	Table 66	LUX-LUNG 3
	Weibull model HR for OS (afa vs. pmc)	0.96	0.70-1.31 (CI)	Table 66	LUX-LUNG 3
	Gompertz model HR for OS (afa vs. pmc)	0.95	0.70-1.30 (CI)	Table 66	LUX-LUNG 3
	Expo model HR for OS (afa vs. pmc) for comparison with erl/gef	0.96	0.70-1.31 (CI)	Table 66	LUX-LUNG 3
	Weibull model HR for OS (afa vs. pmc) for comparison with erl/gef	0.96	0.70- 1.31 (CI)	Table 66	LUX-LUNG 3
	Gompertz model HR for OS (afa vs. pmc) for comparison with erl/gef	0.95	0.70-1.30 (CI)	Table 66	LUX-LUNG 3
	MTC-based HR for OS (afa vs. erl)	0.80	0.56-1.14 (CI)	Table 35	MTC
	MTC-based HR for OS (afa vs. gef)	0.84	0.55-1.30 (CI)	Table 35	MTC
Utility	Utility in progression-free afatinib arm	0.784	SE = 0.009	Table 83	LUX-LUNG 3
	Utility in progressive disease state, Afatinib	0.517	[5]	Table 85	Chouaid et al. 2012
	Utility in progressive disease state, Erlotinib	0.529	[6]	Table 85	Chouaid et al. 2012
	Utility in progressive disease state, Gefitinib	0.521	[7]	Table 85	Chouaid et al. 2012
	PD Utility in 2nd Line, progression-free	0.73	SE = 0.015	Table 84	Chouaid et al. 2012
	PD Utility in 3rd Line, progression-free	0.62	SE = 0.46	Table 84	Chouaid et al. 2012

[5] Utility based on LUCEOR values, weighted by relative period in PD spent on 2nd line therapy vs. best supportive care
[6] Utility based on LUCEOR values, weighted by relative period in PD spent on 2nd line therapy vs. best supportive care
[7] Utility based on LUCEOR values, weighted by relative period in PD spent on 2nd line therapy vs. best supportive care

	PD Utility in 3rd Line, progressive disease	0.46	SE = 0.021	Table 84	Chouaid et al. 2012
	Disutility for diarrhea (grade 3/4)	-0.147	SE = 0.045	Table 86	LUX-Lung 3
	Disutility for rash/acne (grade 3/4)	-0.202	SE = 0.028	Table 86	LUX-Lung 3
	Disutility for fatigue (grade 3/4)	-0.179	SE = 0.053	Table 86	LUX-Lung 1
	Disutility for anaemia (grade 3/4)	-0.074	SE = 0.019	Table 86	Nafees et al 2008
	Disutility for neutropenia (grade 3/4)	-0.090	SE = 0.015	Table 86	Nafees et al 2008
Frequency of patients with AE	Freq of diarrhea (grade 3/4) in 1L gef patients	3.6%	1.4%-9.5%	Table 37	MTC
	Freq of rash/acne (grade 3/4) in 1L gef patients	3.4%	1.2%-9.1%	Table 38	MTC
	Freq of fatigue (grade 3/4) in 1L gef patients	5.2%	0.1%-74%	Table 39	MTC
	Freq of anaemia (grade 3/4) in 1L gef patients	0.4%	0.3%-0.5%	Table 71	LUX-Lung 3
	Freq of neutropenia (grade 3/4) in 1L gef patients	0.4%	0.3%-0.5%	Table 71	LUX-Lung 3
	Freq of diarrhea (grade 3/4) in 1L erl patients	7.5%	0.9%-72%	Table 37	MTC
	Freq of rash/acne (grade 3/4) in 1L erl patients	16.0%	2.6%-88%	Table 38	MTC
	Freq of fatigue (grade 3/4) in 1L erl patients	0.7%	0%-24%	Table 39	MTC
	Freq of anaemia (grade 3/4) in 1L erl patients	0.4%	0.3%-0.5%	Table 71	LUX-LUNG 3
	Freq of neutropenia (grade 3/4) in 1L erl patients	0.4%	0.3%-0.5%	Table 71	LUX-LUNG 3
	Freq of diarrhea (grade 3/4) in 1L afa patients	14%	10%-19%	Table 71	LUX-LUNG 3
	Freq of rash/acne (grade 3/4) in 1L afa patients	16%	11%-21%	Table 71	LUX-LUNG 3
	Freq of fatigue (grade 3/4) in 1L afa patients	1%	0%-3%	Table 71	LUX-LUNG 3
	Freq of anaemia (grade 3/4) in 1L afa patients	0.40%	0.3%-0.5%	Table 71	LUX-LUNG 3
	Freq of neutropenia (grade 3/4) in 1L afa patients	0.40%	0.3%-0.5%	Table 71	LUX-LUNG 3
Duration of AEs (progression –free disease)	Duration (days) of diarrhea AE (grade 3/4) until improvement	6.6	5.95-7.25	Table 71	LUX-LUNG 3
	Duration (days) of rash/acne AE (grade 3/4) until improvement	12.3	11.51-13.09	Table 71	LUX-LUNG 3
	Duration (days) of fatigue AE (grade 3/4) until improvement	32.0	27.76-36.24	Table 71	LUX-LUNG 1
	Duration (days) of anaemia AE (grade 3/4) until improvement	32.0	27.76-36.24	Table 71	Assumption same as fatigue
	Duration (days) of neutropenia AE (grade 3/4) until improvement	32.0	27.76-36.24	Table 71	Assumption same as fatigue
Duration of AEs (progressed disease)	Duration (days) of diarrhea AE until improvement	10.8	9.96-11.64 (SE)	See Section 7.3.1	LUX-LUNG 1
	Duration (days) of rash/acne AE until improvement	22.3	20.13-24.47 (SE)	See Section 7.3.1	LUX-LUNG 1
	Duration (days) of fatigue AE until improvement	32	27.76-36.24 (SE)	See Section 7.3.1	LUX-LUNG 1
Rate of AEs	No episodes diarrhea per 1L pt suffering diarrhea	1.36	1.02-1.70	Table 71	LUX-LUNG 3
	No episodes rash/acne per 1L pt suffering rash/acne	1.08	0.81-1.35	Table 71	LUX-LUNG 3
	No episodes fatigue per 1L pt suffering fatigue	2.0	1.50-2.50	Table 71	LUX-LUNG 1
	No episodes anaemia per 1L pt suffering fatigue	2.0	1.50-2.50	Table 71	Assumption same as fatigue
	No episodes neutropenia per 1L pt suffering fatigue	2.0	1.50-2.50	Table 71	Assumption same as fatigue

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Data for overall survival in LUX-Lung 3 and 6 were extrapolated beyond the trial period due to the immaturity of the survival data. PFS was primary endpoint and at time of primary analysis of the data, the OS data was immature.

The overall survival data for LUX-Lung 3 and for LUX-Lung 6 were not mature by the cut-off date for the primary analysis of each trial. In LUX-Lung 3, only 67 patients (29.1%) in the afatinib arm and 31 patients (27.0%) in the chemotherapy arm had died by the cut-off date (98 out of 345, 28.4% maturity) (Table 15). Hence, the median OS time was not estimable. The final analysis of OS will be performed when approximately 209 patients have died.

In LUX-Lung 6 only 104 patients (43.0%) in the afatinib arm and 51 patients (41.8%) in the chemotherapy arm had died by the cut-off date (Table 15). The primary OS analysis is scheduled for when the data are considered mature enough for meaningful analysis, this is expected to be when approximately 209 deaths have been observed.

Please see response to 7.3.1 for details of the extrapolation methods.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

1st line treatment assumptions

- All 1st line patients are assumed to receive oral daily TKI treatment until progression, based on the labels for each of the three agents (afatinib, erlotinib and gefitinib).
- The analysis is based on 1st-line treatment, with the assumption that the results are applicable to patients who may have received previous chemotherapy. The effectiveness of afatinib in these patients was considered as part of the LUX-Lung 2 study, though this cannot be modelled as there was no comparator arm in the trial. However, it should be noted that gefitinib and erlotinib are established treatments for EGFR positive patients, and therefore the population size for patient who are TKI-naive who have received previous chemotherapy is small. Market research data showed that 99% of the NSCLC patients with

EGFR mutations receive first line treatment with erlotinib or gefitinib (IMS 2013).

Cost assumptions

- Disease management costs (monthly costs that do not include cancer drug treatment nor adverse events costs) were assumed to be the same across all treatment arms.
- The 1st line progression-free and 3rd line progressed disease management costs are derived from the average disease management resource use across both arms of the LUX-Lung 3 trial (for progression-free patients) and LUX-Lung 1 trial (for 3rd line progressed patients), respectively. Detailed data on resource use were not available from either the erlotinib or the gefitinib trials, therefore the LUX-Lung 3 and LUX-Lung 1 data were used for all treatment arms.

Progressive disease health state assumptions

- Progressive disease (PD), following 1st line TKI treatment, is represented in the model by a single health state. This makes the use of the AUC modelling method possible, allowing the model structure to be based on the standard oncology outcomes of PFS and OS, and thereby increasing its face validity.
- Because data were not available from LUX-Lung 3 on treatments following 1st line progression, assumptions were made about the likely patient treatment pathway. These assumptions allowed the estimation of resource use and health-related utility during the time between progression and death. The model assumes all patients receiving TKIs (afatinib, erlotinib, gefitinib) as 1st line treatment receive docetaxel as 2nd line therapy. The model assumes that patients receive docetaxel for an average of 4.1 months (based on the median PFS reported for 2nd line docetaxel in EGFR mutation positive NSCLC patients in the INTEREST trial) and that patients remain on 2nd line therapy for the same time, regardless of the 1st line therapy they received. The assumption that UK EGFR mutation positive patients progressing on a 1st line TKI would subsequently receive docetaxel is based on feedback from a UK clinical expert (see Section 7.3.5) that this patient group would receive either docetaxel or pemetrexed. Section 7.6.1 reports a scenario analysis in which pemetrexed is assumed as the 2nd line treatment, instead of docetaxel. The model assumes that following progression from 2nd line therapy, all patients will go on to receive best supportive care for the remainder of their time in the PD health state. This assumption is also based on feedback from the same UK clinical expert.

Adverse events assumptions

- Adverse events during therapy in TKI-naive patients are assumed to occur only while patients are in the progression-free health state, because this is when they are receiving treatment. Furthermore,

adverse events are assumed to occur within the first year in the model. Consequently, the costs and disutilities associated with adverse events are not discounted. Given that the mean progression-free time for these patients is approximately one year, the assumption that these adverse events will occur within the first year is reasonable.

- Adverse events (AEs) are not taken into account during 2nd line treatment, as the 2nd line part of the model is based on assumptions that include the 2nd line treatment regimen and its duration. The impact of AEs in 2nd line is not expected to be a key driver of the cost-effectiveness, based on the impact of AEs in 1st line.

Utility assumptions

- Health-related utilities are assumed to be specific to the line of treatment a patient is on, but common across all treatment arms. Thus in the base case analysis, patients on afatinib, erlotinib, and gefitinib will all have the same health-related utility of 0.784 while they are on 1st line treatment, but they will have a health-related utility of 0.73 while they are on 2nd line treatment. This is because there is good evidence that health-related utility differs depending on line of treatment, but there is no strong evidence that utilities should differ between the different treatment arms in the study.
- Utilities for the PD health state as a whole can differ between arms, based on the proportion of time patients in each treatment arm spend on 2nd line treatment and in 3rd line (on best supportive care).

2nd line treatment assumptions

- The license for afatinib is expected to cover patients who are EGFR positive who have been treated with chemotherapy but are TKI naive. The data for these patients is limited, though sufficiently robust to demonstrate clinical effectiveness upon which the licence was granted.
- This data is from LUX-Lung 2 which was a single arm study and therefore could not be used in the cost-effectiveness analysis. However, it contained data from patients who were 1st line and 2nd line, where the outcomes in these patient groups were sufficiently similar to infer that afatinib would be clinically effective in both these two groups. No significant difference was detected in objective response rates in patients receiving afatinib as a first-line treatment (40/61 patients [66%]) and those receiving it as a second-line treatment (39/68 [57%]; OR 0.71, 0.35–1.44). However, the trail was not powered to detect differences between the two groups.
- A consequence of this inference is that if afatinib is cost-effective compared to gefitinib and erlotinib as a first line treatment, and outcomes for 1st line patients on afatinib are similar to 2nd line patients on afatinib, than if afatinib were compared to gefitinib or erlotinib 2nd line, it would have similar ICERs. This would require an additional assumption that gefitinib and erlotinib were equally efficacious in 2nd line as first line, and we note that both are licensed for second line use in these patient populations.

- Whilst this is not supported by economic modelling due to limitation of the evidence base, we note that this is a small patient population and that, on balance, these patients would be expected to be as cost-effective as the first line patients.

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

Advanced EGFR positive NSCLC is a progressive disease with most patients sadly dying as a result of the disease. Quality of life may be reduced by direct tumour spread and the associated symptoms of breathlessness, cough or pain in the chest. Systemic spread throughout the body may then be associated with deterioration in global health status and activities of daily living and associated HRQL outcomes such as role function, emotional, cognitive, social and physical functions. There may also be associated deterioration in symptoms such as fatigue, nausea and vomiting and reduced appetite.

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

Quality of life may be reduced by direct tumour spread and the associated symptoms of breathlessness, cough or pain in the chest. Systemic spread throughout the body may then be associated with deterioration in global health status and activities of daily living and associated HRQoL outcomes such as role function, emotional, cognitive, social and physical functions. There may also be associated deterioration in symptoms such as fatigue, nausea and vomiting and reduced appetite.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

Estimation of HRQL data over time and by randomised treatment arm using statistical models were estimated using:

- Estimation of mean utility scores (European QOL – 5 dimensions [EQ-5D]) calculated using Belgium and UK tariffs by randomised treatment arm over time using statistical models, and estimated disutilities associated with progression and adverse events (AEs)

- Estimation of mean EQ-5D and EQ-VAS (visual analogue scale) scores by randomised treatment over time using statistical models, and estimation of changes associated with progression and AE.

A summary of this data is provided in Section 6.5.3. The EQ-5D is a health status self-assessment questionnaire applicable to a wide range of health conditions and treatments. It is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each of which can take one of three responses. The responses record three levels of severity (‘no problems’, ‘some or moderate problems’, ‘extreme problems’) within a particular EQ-5D dimension. The EQ-VAS is a standard vertical 20 cm visual analogue scale for recording an individual’s rating for their current health-related quality of life state.

Profiles for UK utility scores and EQ-VAS score over time for progression-free patients with no key AEs are shown in Table 77. Insufficient data were available to show other disease states.

Table 77 Estimated EQ-5D UK utility profile for 'progression-free and no key AEs'*

Weeks	Estimate	SE
0	0.758	0.012
3	0.795	0.012
6	0.787	0.012
12	0.784	0.012
18	0.783	0.010
24	0.784	0.010
36	0.786	0.012
48	0.789	0.016
57	0.790	0.019
Mean#	0.784	0.009

*Results from the longitudinal model adjusting for EGFR mutation type and race
#Estimated from the AUC to the truncation time (39 weeks)

The frequency of EQ-5D assessments with key AEs present is shown in Table 78. Estimated effects of key AEs in terms of EQ-5D disutilities are shown in Table 79.

Table 78 Frequency of EQ-5D assessments with key AE present

Key AE	No. of EQ5D assessments	Frequency of EQ5D assessments with key AE	Percentage (%) of EQ5D assessments with key AE
Diarrhoea	3624	13	0.36
Rash/Acne	3624	28	0.77
Leucopaenia	3624	30	0.83
Neuropathy	3624	0	0.00

Table 79 Estimated EQ-5D UK disutilities for key AEs

Effect of:	Estimate	SE	p-value
Diarrhoea (Grade 3/4)	-0.147	0.045	0.0010
Rash/acne (Grade 3/4)	-0.202	0.028	<0.0001

Diarrhoea and rash/acne were each associated with statistically significantly ($p<0.05$) reduced utility and EQ-VAS scores.

The 1st line model uses utility values derived from the LUX-Lung trials in the base case. Utility values from literature are also tested within the model.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

As EQ-5D was directly measured, no mapping was required.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

The utility search was developed to identify studies reporting the utility in the three stages of the Markov model: progression free disease, progressive disease and death. The disutility due to adverse events was also captured. Studies that reported QoL (as a measure of change between pre-treatment and treatment completion), while included at an abstract review stage, were excluded at a full paper review stage, as this data would not support a HTA submission.

In line with the standard methodology for NICE submissions, multiple databases must be searched. These are shown in Table 62.

The search strings were used to identify relevant clinical studies for the systematic review are shown in Section 10.12.4.

Review Process

Publications identified through the systematic review are evaluated in a three-step procedure in order to assess whether or not they should be included for data extraction and model population. The identified abstracts through the database search (1st step) were reviewed in using an inclusion/exclusion criteria (listed in Table 80), and if the abstract contained sufficient information to state that the publication did not meet this criteria, the publication was excluded. If the publication was not excluded, the full paper was retrieved, and again reviewed and subjected to the same inclusion/exclusion criteria. If the publication did meet the inclusion criteria after full paper review, the publication was included in the systematic review. The inclusion / exclusion criteria used against the publications were in the PICOS format (i.e., population, intervention, comparators, outcomes, study type) (Table 80).

Table 80: Inclusion and Exclusion Criteria

	Inclusion	Exclusion
Population	Locally advanced or metastatic non small cell lung cancer patients	Other populations Non locally advanced or metastatic NSCLC patients
Intervention	Chemotherapy or targeted therapies	Other interventions that are not licensed for NSCLC
Comparator	Chemotherapy, targeted therapies, placebo or best standard care (BSC)	Other comparators

	Inclusion	Exclusion
Outcomes	ICER/ICUR Cost of illness Resource Use Utilities	Other outcomes
Study design	Randomized controlled trials Systematic Reviews Meta-analyses Observational studies Prospective studies Cohort studies Case control studies Economic Evaluations	Reviews Letters Commentaries
Language	English	Not English

Randomised controlled trials, observation studies etc. were included in the search to capture any data collected on utilities.

The search was conducted on the 6th March 2012 using a Microsoft Access and Microsoft-Excel based extraction template, processed through Reference Manager 11. The time span of the search was 2002 to 2012 inclusive. The following information regarding the studies was captured:

- Sample Size
- Health States
- Method of Elicitation
- Method of Valuation
- Results

Quality assessment strategy

The methodological quality of the studies included in the systematic review was assessed using the criteria for methodological quality indicated in the Centre for Reviews and Dissemination (CRD) report 4 (Centre for Reviews and Dissemination 2009) which is also the quality assessment criteria listed in NICE's guidance (NICE 2013).

The aim of the critical assessment is to evaluate the validity of studies chosen for inclusion in the review. The framework assesses the potential for studies to be impacted by biases affecting validity, including:

- Selection bias, arising from systematic differences between comparison groups in terms of performance and prognosis;
- Measurement bias, arising from systematic differences in how outcomes are ascertained and measured;
- Attrition bias arising from systematic differences between comparison groups in how participants are withdrawn or excluded from the study groups.

Search Results

This section summarizes the findings of the systematic review using the PRISMA Flow diagram (Moher et al. 2009) (formerly the QUORUM statement). 5076 studies were identified through the systematic search, and after duplicates were removed, 149 studies were screened for relevance. Of these papers, 3 papers were deemed to have significance to the systematic review using the PICO criteria outlined in Table 80.

146 studies were excluded in the full paper review. These papers were excluded because while they reported a change in HRQoL in RCTs, these studies did not report utility for each disease stage, as required for the cost-effectiveness model. A list of these excluded studies is shown in Table 144 in Section 10.12.7. Studies that reported QoL outcomes not suitable for an economic model (the change in a patient reported outcome measure from baseline to post-therapy) were excluded as “Wrong Outcomes”. Studies reporting outcomes in a NSCLC population, without subgroup analysis of locally advanced or metastatic were excluded as “Wrong Patient Population”. Studies reporting outcomes in a patient population that was not NSCLC (e.g. small cell lung cancer) were excluded as “Wrong Disease”. Studies reporting 2nd line or maintenance treatments that did not specify 3rd or 4th line therapy were exclude as “Wrong Intervention”.

Three (n=3) studies were identified in the systematic search. These studies were all conducted within the UK and a general public population was used to elicit utility values. A list of these identified studies is shown in Table 81. The PRISMA flow diagram for the systematic review is in Figure 35.

Figure 35: PRISMA Flow Diagram of HRQoL studies identified for locally advanced or metastatic NSCLC

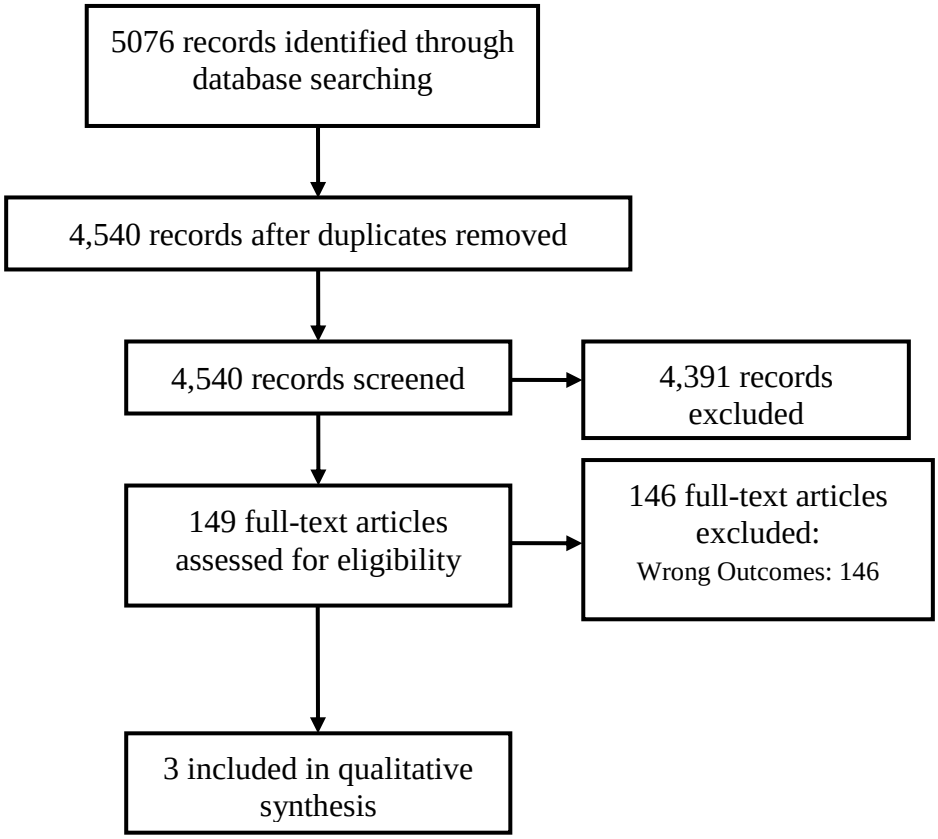


Table 81: List of relevant utility studies

	Author, year	Country	Population
1	Doyle et al. 2008	UK	General Public
2	Lewis et al. 2010	UK	General Public
3	Nafees et al. 2008	UK	General Public

7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.

- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

All the selected studies captured societal utility scores for non-small cell lung cancer health states and toxicities commonly associated with chemotherapy treatments. EuroQol-5D (EQ-5D), visual analogue scale (VAS) and standard gamble (SG) were valuation methods used and the elicitation techniques included interviews conducted by trained interviewers in a quiet private room. Models were based on responding, stable and progressive health states or progression-free, progression and death health states. Among those, the health state associated with the highest utility score was treatment responding (0.712) in advanced NSCLC (Doyle et al. 2008).

Adverse events captured across the studies were caught, pain, dyspnoea, diarrhoea, rash, fatigue, nausea/vomiting, hair loss, stomatitis and neuropathy. Rash (0.64) and diarrhoea (0.626) in responding NSCLC patients were given the greatest scores, whereas febrile neutropenia (0.19) and neuropathy (0.31) in advanced NSCLC yielded the lowest utility scores (Lewis et al. 2010).

Data from these studies is presented in Table 82.

Table 82 Utility studies reporting health states for NSCLC

Study	Population	Recruitment	Sample size and response	Description of health states, & appropriateness	Adverse events	Methods of elicitation, valuation and mapping	Results with CIs	Appropriateness for cost-effectiveness analysis	Appropriateness to this submission
Doyle et al. 2008	Random sample representative of the UK general adult population	Participants were recruited from the Greater London area through a volunteer database, advertisements and a study recruitment website.	101	Treatment response Stable disease (no additional symptoms) Stable disease (with cough) Stable disease (with dyspnoea) Stable disease (with pain) Stable disease (with cough, dyspnoea, and pain)	NA	Standard Gamble and Visual Analogue Scale	Treatment response: 0.712 Stable disease (no additional symptoms): 0.626 Stable disease (with cough): 0.580 Stable disease (with dyspnoea): 0.576 Stable disease (with pain): 0.557 Stable disease (with cough, dyspnoea, and pain): 0.461	Highly appropriate.	Highly appropriate.
Lewis et al. 2010	Random sample representative of the UK general adult population	NR	154	Progression Free (oral therapy) Progression Free (intravenous therapy) Disease progression	Rash Diarrhoea Grade 4 Neutropenia Febrile neurtopenia Nausea Stomatitis Neutropathy	EQ-5D	Progression Free (oral therapy): 0.451 Progression Free (intravenous therapy): 0.426 Disease progression: 0.217 Rash: 0.4 Diarrhoea: 0.32 Grade 4 neutropenia: 0.32 Febrile neurtopenia: 0.19 Nausea: 0.32 Stomatitis: 0.32 Neutropathy: 0.31	Highly appropriate.	Highly appropriate.
Nafees et al. 2008	Random sample representative of the UK general adult population	Participants were recruited from the Greater London area through a volunteer database, advertisements and a study recruitment website.	100	Progressive disease Treatment response Treatment response (with diarrhoea) Treatment response (with fatigue)	Diarrhoea Fatigue Febrile neutropenia Hair loss Nausea/vomiting	Standard Gamble and Visual Analogue Scale	Progressive disease: 0.473 Treatment response: 0.673 Treatment response (with diarrhoea): 0.626	Highly appropriate.	Highly appropriate.

Study	Population	Recruitment	Sample size and response	Description of health states, & appropriateness	Adverse events	Methods of elicitation, valuation and mapping	Results with CIs	Appropriateness for cost-effectiveness analysis	Appropriateness to this submission
				Treatment response (with febrile neutropenia) Treatment response (with hair loss) Treatment response (with nausea/vomiting) Treatment response (with neutropenia) Treatment response (with rash) Stable disease Stable disease (with diarrhoea) Stable disease (with fatigue) Stable disease (with febrile neutropenia) Stable disease (with hair loss) Stable disease (with nausea/vomiting) Stable disease (with neutropenia) Stable disease (with rash)	Neutropenia Rash		Treatment response (with fatigue): 0.599 Treatment response (with febrile neutropenia): 0.582 Treatment response (with hair loss): 0.628 Treatment response (with nausea/vomiting): 0.624 Treatment response (with neutropenia): 0.583 Treatment response (with rash): 0.640 Stable disease: 0.653 Stable disease (with diarrhoea): 0.606 Stable disease (with fatigue): 0.580 Stable disease (with febrile neutropenia): 0.563 Stable disease (with hair loss): 0.608 Stable disease (with nausea/vomiting): 0.605 Stable disease (with neutropenia):0.563 Stable disease (with rash): 0.621		

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The model uses utility values derived from the LUX-Lung trials in the base case. Utility values from literature are also tested within the model.

Table 83 Utility values used in the model in the progression free health state

	Mean	Standard error
LUX-Lung trial results		
Progression free	0.784	0.009
Chouaid et al. 2012		
1L, progression-free	0.710	0.014
Nafees et al. 2008		
Progression-free	0.672	0.029
Progression-free (stable)	0.653	0.022
Progression-free (weighted)	0.663	0.026

Table 83 illustrates the utility values used for the progression free health state in the 1st line model, the base case uses the value obtained from the LUX-Lung 3 trial data and the model includes options to use the values reported in the literature. The progression free utility values reported by Nafees et al. (2008) are given by whether the patient was stable or responding. The weighted value shown in Table 83 is based on an assumption that 50% of patients in the progression free group will be stable and 50% responding. The model allows the functionality to change the assumed proportions.

The utility values shown in Table 84 are those used to value the various components of the progressive disease health state in the TKI-naive model (Figure 34). These utility values are weighted by the proportion of total progressive disease time spent in each component in order to generate an overall utility value to assign to the progressive disease health state in the model (Table 85).

Table 84 Utility values used in the model in the progressive disease health state

	Mean	Standard error	Source
Utility in 2L	0.73	0.015	Chouaid et al. 2012 (2L, PF)
Utility in 3L BSC	0.46	0.021	Chouaid et al. 2012 (3L, PD)
Utility in 3rd line, progression-free	0.62	0.46	Chouaid et al. 2012

Table 85 Weighted utility assigned to the progressive disease state in the 1st line model by treatment arm

2nd Line treatment period option	Pem/cis	Afatinib	Erlotinib	Gefitinib
Constant (base case)	0.487	0.517	0.529	0.521
Proportionally adjusted	0.487	0.509	0.509	0.509

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Table 86 displays the disutilities (relative to progression free) used to value the adverse events occurring in the 1st line model. For diarrhea, rash/acne and fatigue events the model base case uses the values from the LUX-Lung trials but it is also possible to explore the impact of the two disutilities derived from the Nafees et al. (2008). For the anaemia and neutropenia events the model base case uses the disutilities extracted from the Nafees et al. (2008).

Table 86 Disutilities used in the model for valuing adverse events

	Mean	Standard error	Source / comment
LUX-Lung trial results			
Estimated disutilities (relative to being progression free)			
Diarrhoea (grade 3/4)	-0.147	0.045	LUX-Lung 3
Rash/acne (grade 3/4)	-0.202	0.028	LUX-Lung 3
Fatigue (grade 3/4)	-0.179	0.053	LUX-Lung 1
Nafees et al. (2008)			
Estimated disutilities (relative to being progression free)			
Anaemia	-0.073	0.019	ERG report for pem/cis: Disutility for fatigue presented in Nafees et al. (2008) can be used for anaemia
Neutropenia	-0.090	0.015	Nafees et al. 2008

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Please see Table 76 for summary of variables.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[8]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission

[8] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Please see details in Section 7.3.5.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

Unless an event occurs, the HRQL level of patients remains constant within each health state and from cycle to cycle. Changes in HRQL occur for the following reasons:

- When a patient's diseases progresses
- Experience of adverse events: diarrhoea; rash/acne; fatigue; anaemia; neutropenia
- Death

The variation in HRQL whilst being in the progression-free disease state can be seen in Table 77. This shows that over the 57 weeks, the mean utility value does not vary by much.

However, what we haven't been able to capture is how the patient's quality of life varies as a result of suffering with cancer for a prolonged period of time, particularly in the final stages post-progression, when the patient's expected life expectancy becomes increasingly short. During this period, quality of life might be expected to decrease, especially so if the progression-free period is relatively short.

Also not captured may be some of the additional burdens caused by loss of functionality outlined in Table 15.

In addition, the decreases in quality of life of carers have not been captured.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Some of the additional burdens caused by loss of functionality outlined in Table 15 may not have been adequately captured by the QALY. The scale of this is not known therefore the impact could not be accurately assessed.

This is also discussed in Section 4.12 and Section 4.1.3.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

The baseline quality of life was the same as the quality of life of patients in progression free disease state. This is appropriate as this is the starting point for the analysis and the cohort.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Please see the response to 7.4.11.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

The values in Sections 7.4.3 to 7.4.8 have not been amended.

7.5 *Resource identification, measurement and valuation*

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The management of NSCLC in the NHS involves many treatment options. The treatments currently used are: cisplatin/pemetrexed, gefitinib, erlotinib and docetaxel. A breakdown on the costs to the NHS is given in section 7.5.5. They fall under the currency codes in Table 87, which are incorporated in this model.

Table 87 National Schedule of Reference Costs Year: 2010-11 - NHS Trusts and PCTs combined Non-Elective Inpatient (Long Stay) HRG Data (Department of Health, 2013)

Currency Code	Currency Description
DZ17A	Respiratory Neoplasms with Major CC
DZ17B	Respiratory Neoplasms with CC
DZ17C	Respiratory Neoplasms without CC

They are chosen as they represent the disease of interest and the NHS and PCT combined elective inpatient stay HRG data. The HRG codes in Table 88 are used in order to represent all relevant resource use associated with the delivery of chemotherapy in England and Wales.

Table 88 National Schedule of Reference Costs Year: 2010-11 - NHS Trusts and PCTs combined Chemotherapy Delivery: Outpatient (Department of Health, 2013)

Currency Code	Currency Description
SB11Z	Deliver exclusively Oral Chemotherapy
SB12Z	Deliver simple Parenteral Chemotherapy at first attendance
SB13Z	Deliver more complex Parenteral Chemotherapy at first attendance
SB14Z	Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance
SB15Z	Deliver subsequent elements of a Chemotherapy cycle
SB17Z	Deliver chemotherapy for regimens not on the national list

These are chosen as they are representative costs of chemotherapy delivery in outpatients and are more comprehensive than previous HTA submissions for gefitinib and erlotinib.

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

For the reasons discussed above (Section 7.5.1) the appropriate reference costs were used for this model.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

The resource use and cost of illness sections were extracted from the studies identified through the economic evaluation search. While more weight is placed on UK studies, all reported resource use and costs were extracted. In line with the standard methodology for NICE submissions, multiple databases must be searched. These are shown in Table 62.

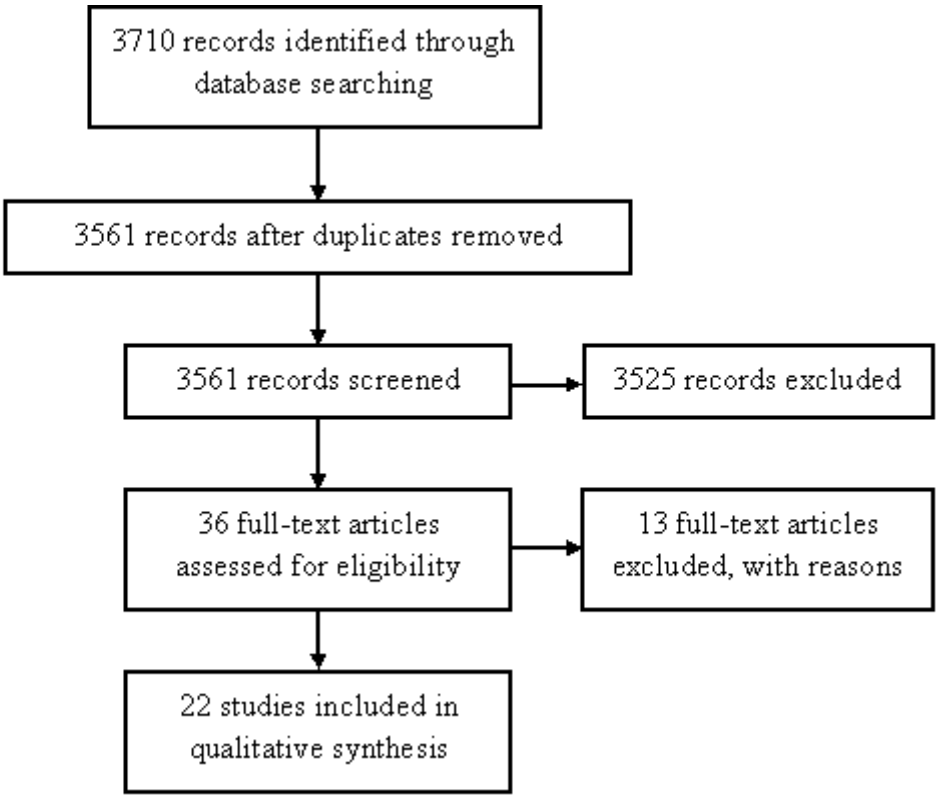
The data extraction was conducted (on the 6th March, 2012) using a Microsoft Access and Microsoft Excel-based extraction template. The search strings were used to identify relevant clinical studies for the systematic review are shown in Section 10.13.4.

Publications identified through the systematic review are evaluated in a three-step procedure in order to assess whether or not they should be included for data extraction and model population. The identified abstracts through the database search (1st step) were reviewed in using an inclusion/exclusion criteria (listed in Table 80), and if the abstract contained sufficient information

to state that the publication did not meet this criteria, the publication was excluded. If the publication was not excluded, the full paper was retrieved, and again reviewed and subjected to the same inclusion/exclusion criteria. If the publication did meet the inclusion criteria after full paper review, the publication was included in the systematic review. The inclusion / exclusion criteria to use against the publications were in the PICOS format (i.e. population, intervention, comparators, outcomes, study type) (Table 80).

Data extraction and quality assessment strategy are provided in Section 10.13. The PRISMA flow diagram outlining the selection of studies is shown in Figure 36.

Figure 36 PRISMA Flow Diagram of economic evaluation studies identified for locally advanced or metastatic NSCLC



Data was extracted from the 22 economic evaluations to analyse the resource use for therapies for locally advanced or metastatic NSCLC. Of these 22 studies, 1 reported resource use for the UK and 4 included costs for the UK. Resources are shown in Table 89 and costs in Table 90 to Table 98.

Table 89: Studies reporting resource use data for the use of cisplatin. Ifosfamide, mitomycin and palliative care for locally advanced or metastatic NSCLC – per patient (Billingham et al. 2002)

Resource	No.
Hospital in-patient days	17.8 (14.6)
Chemotherapy related	6.2 (7.2)
Non-chemotherapy related	11.6 (13.1)
Out-patient visits	5.6 (4.6)

Resource	No.
MIC chemotherapy courses	2.7 (1.5)
Radiotherapy fractions	5.6 (6.5)
GP surgery visits	12.3 (13.3)
GP/consultant home visits	1.6 (3.1)
District nurse/hospice care nurse/	2.2 (4.9)
Hospice care team visits	
Hospice in-patient days	2.5 (7.5)
Hospice out-patient visits	0.8 (2.2)
Palliative care	
Hospital in-patient days	6.9 (10.7)
Chemotherapy related	0
Non-chemotherapy related	6.9 (10.7)
Out-patient visits	5.5 (4.1)
MIC chemotherapy courses	0
Radiotherapy fractions	6.8 (5.4)
GP surgery visits	11.9 (11.2)
GP/consultant home visits	0.8 (2.2)
District nurse/hospice care nurse/	2.6 (7.6)
Hospice care team visits	
Hospice in-patient days	3.8 (7.6)
Hospice out-patient visits	0.3 (1.3)

Table 90: Economic evaluation studies reporting costs involved with carboplatin and paclitaxel treatment for locally advanced or metastatic NSCLC

Resource	No.	Reference
Chemotherapy drugs	£6,981	Lees et al. 2002 – UK (2000 Costs, £)
	£6981(€11106)	Schiller et al. 2004 – UK (2000 Costs, €)
Chemotherapy administration	£379	Lees et al. 2002 – UK (2000 Costs, £)
	£379(€603)	Schiller et al. 2004 – UK (2000 Costs, €)
Hospitalisations	£321	Lees et al. 2002 – UK (2000 Costs, £)
	£515(€819)	Schiller et al. 2004 – UK (2000 Costs, €)
Radiotherapy	£3	Lees et al. 2002 – UK (2000 Costs, £)
Transfusions	£414	Lees et al. 2002 – UK (2000 Costs, £)
Visits to health professionals	£223	Lees et al. 2002 – UK (2000 Costs, £)
Concomitant medications	£123	Lees et al. 2002 – UK (2000 Costs, £)
Other medical resources	£613(€975)	Schiller et al. 2004 – UK (2000 Costs, €)
Total treatment costs	£8,444	Lees et al. 2002 – UK (2000 Costs, £)
Total	£8488(€13504)	Schiller et al. 2004 – UK (2000 Costs, €)

Table 91: Economic evaluation studies reporting costs involved with cisplatin and docetaxel for locally advanced or metastatic NSCLC

Resource	No.	Reference
Chemotherapy drugs	£4129(€6569)	Schiller et al. 2004 – UK (2000 Costs, €)
	£4,129	Lees et al. 2002 – UK (2000 Costs, £)
Chemotherapy administration	£372(€592)	Schiller et al. 2004 – UK (2000 Costs, €)
	£372	Lees et al. 2002 – UK (2000 Costs, £)
Hospitalisations	£561(€892)	Schiller et al. 2004 – UK (2000 Costs, €)
	£548	Lees et al. 2002 – UK (2000 Costs, £)
Other medical resources	£1257(€2000)	Schiller et al. 2004 – UK (2000 Costs, €)
Chemotherapy administration	£372	Lees et al. 2002 – UK (2000 Costs, £)
Radiotherapy	£3	Lees et al. 2002 – UK (2000 Costs, £)
Transfusions	£414	Lees et al. 2002 – UK (2000 Costs, £)
Visits to health professionals	£190	Lees et al. 2002 – UK (2000 Costs, £)
Concomitant medications	£123	Lees et al. 2002 – UK (2000 Costs, £)

Resource	No.	Reference
Total treatment costs	£6319(€10053)	Schiller et al. 2004 – UK (2000 Costs, €)
	£5,779	Lees et al. 2002 – UK (2000 Costs, £)

Table 92: Economic evaluation studies reporting costs involved with cisplatin and gemcitabine for locally advanced or metastatic NSCLC

Resource	No.	Reference
Chemotherapy drugs	£3,338	Lees et al. 2002 – UK (2000 Costs, £)
	£3338(€5310)	Schiller et al. 2004 – UK (2000 Costs, €)
Chemotherapy administration	£1,088	Lees et al. 2002 – UK (2000 Costs, £)
	£1088(€1731)	Schiller et al. 2004 – UK (2000 Costs, €)
Hospitalisations	£372	Lees et al. 2002 – UK (2000 Costs, £)
	£580(€923)	Schiller et al. 2004 – UK (2000 Costs, €)
Radiotherapy	£3	Lees et al. 2002 – UK (2000 Costs, £)
Transfusions	£414	Lees et al. 2002 – UK (2000 Costs, £)
Visits to health professionals	£199	Lees et al. 2002 – UK (2000 Costs, £)
Concomitant medications	£123	Lees et al. 2002 – UK (2000 Costs, £)
Other medical resources	£1055(€1678)	Schiller et al. 2004 – UK (2000 Costs, €)
Total treatment costs	£6061(€9642)	Schiller et al. 2004 – UK (2000 Costs, €)
	£5,537	Lees et al. 2002 – UK (2000 Costs, £)

Table 93: Economic evaluation studies reporting costs involved with cisplatin, ifosfamide, mitomycin and palliative care for locally advanced or metastatic NSCLC

Resource	No.	Reference
Hospital in-patient days	£222 (first day of emergency stays costed at 359)	Billingham et al 2002 - UK(1999 Costs, £)
Out-patient visits	£63	Billingham et al 2002 - UK(1999 Costs, £)
MIC chemotherapy	£310.52 per cycle	Billingham et al 2002 - UK(1999 Costs, £)
Radiotherapy	£115 per fraction	Billingham et al 2002 - UK(1999 Costs, £)
GP surgery visits	£18	Billingham et al 2002 - UK(1999 Costs, £)
GP/consultant home visits	£54	Billingham et al 2002 - UK(1999 Costs, £)
District nurse/hospice care nurse/hospice care team visits	£64	Billingham et al 2002 - UK(1999 Costs, £)
Hospice in-patient days	£250	Billingham et al 2002 - UK(1999 Costs, £)
Hospice out-patient visits	£394.80	Billingham et al 2002 - UK(1999 Costs, £)

Table 94: Economic evaluation studies reporting costs involved with cisplatin and paclitaxel for locally advanced or metastatic NSCLC

Resource	No.	Reference
Chemotherapy drugs	£4,317	Lees et al. 2002 – UK (2000 Costs, £)
	£4317(€6868)	Schiller et al. 2004 – UK (2000 Costs, €)
Chemotherapy acquisition	£802(€1274)	Schiller et al. 2004 – UK (2000 Costs, €)
Chemotherapy administration	£3,353	Lees et al. 2002 – UK (2000 Costs, £)
	£682(€1085)	Schiller et al. 2004 – UK (2000 Costs, €)
Hospitalisations	£627	Lees et al. 2002 – UK (2000 Costs, £)
	£1277(€2032)	Schiller et al. 2004 – UK (2000 Costs, €)
Radiotherapy	£3	Lees et al. 2002 – UK (2000 Costs, £)
Transfusions	£414	Lees et al. 2002 – UK (2000 Costs, £)
Visits to health professionals	£206	Lees et al. 2002 – UK (2000 Costs, £)
Concomitant medications	£123	Lees et al. 2002 – UK (2000 Costs, £)
Other medical resources	£7077(€11259)	Schiller et al. 2004 – UK (2000 Costs, €)
Total treatment costs	£9,043	Lees et al. 2002 – UK (2000 Costs, £)
	£4317(€6868)	Schiller et al. 2004 – UK (2000 Costs, €)

Table 95: Economic evaluation studies reporting costs involved with docetaxel for locally advanced or metastatic NSCLC

Resource	No.	Reference
IV Docetaxel - 100 mg/m2		
Inpatient Day	£1,763	Le Lay et al. 2007 – UK (2003 Costs, £)
Outpatient Visit	£1,529	Le Lay et al. 2007 – UK (2003 Costs, £)
Home Care	-	Le Lay et al. 2007 – UK (2003 Costs, £)

Table 96: Economic evaluation studies reporting costs involved with gemcitabine for locally advanced or metastatic NSCLC

Resource	No.	Reference
IV Gemcitabine - 1000 mg/m2		
Inpatient Day	£731	Le Lay et al. 2007 – UK (2003 Costs, £)
Outpatient Visit	£497	Le Lay et al. 2007 – UK (2003 Costs, £)
Home Care	-	Le Lay et al. 2007 – UK (2003 Costs, £)
IV Gemcitabine - 1250 mg/m2		
Inpatient Day	£769	Le Lay et al. 2007 – UK (2003 Costs, £)
Outpatient Visit	£562	Le Lay et al. 2007 – UK (2003 Costs, £)
Home Care	-	Le Lay et al. 2007 – UK (2003 Costs, £)

Table 97: Economic evaluation studies reporting costs involved with paclitaxel for locally advanced or metastatic NSCLC

Resource	No.	Reference
IV Paclitaxel - 175 mg/m2		
Inpatient Day	£1,560	Le Lay et al. 2007 – UK (2003 Costs, £)
Outpatient Visit	£1,326	Le Lay et al. 2007 – UK (2003 Costs, £)
Home Care	-	Le Lay et al. 2007 – UK (2003 Costs, £)
IV Paclitaxel - 200 mg/m2		
Inpatient Day	£1,810	Le Lay et al. 2007 – UK (2003 Costs, £)
Outpatient Visit	£1,575	Le Lay et al. 2007 – UK (2003 Costs, £)
Home Care	-	Le Lay et al. 2007 – UK (2003 Costs, £)

Table 98: Economic evaluation studies reporting costs involved with vinorelbine for locally advanced or metastatic NSCLC

Resource	No.	Reference
Oral Vinorelbine – 60 mg/m2		
Inpatient Day	-	Le Lay et al. 2007 – UK (2003 Costs, £)
Outpatient Visit	£424	Le Lay et al. 2007 – UK (2003 Costs, £)
Home Care	£285	Le Lay et al. 2007 – UK (2003 Costs, £)
Oral Vinorelbine – 80 mg/m2		
Inpatient Day	-	Le Lay et al. 2007 – UK (2003 Costs, £)
Outpatient Visit	£512	Le Lay et al. 2007 – UK (2003 Costs, £)
Home Care	£373	Le Lay et al. 2007 – UK (2003 Costs, £)
IV Vinorelbine - 25 mg/m2		
Inpatient Day	£585	Le Lay et al. 2007 – UK (2003 Costs, £)
Outpatient Visit	£351	Le Lay et al. 2007 – UK (2003 Costs, £)
Home Care	-	Le Lay et al. 2007 – UK (2003 Costs, £)
IV Vinorelbine - 30 mg/m2		
Inpatient Day	£616	Le Lay et al. 2007 – UK (2003 Costs, £)
Outpatient Visit	£382	Le Lay et al. 2007 – UK (2003 Costs, £)
Home Care	-	Le Lay et al. 2007 – UK (2003 Costs, £)

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[9]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

See Section 7.3.5.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

All unit costs have all been inflated to 2012 UK pounds. This was carried out using the Hospital & Community Health Services (HCHS) index

Inpatient intervention resource use has been provided in the H-SAP section of the model, however unit costs for these interventions have been excluded from the analysis of total costs of model health states in order to avoid double-counting of in-hospital costs. The unit cost included for an unscheduled hospitalisation stay is the average total cost of an acute inpatient case for

[9] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

patients with Malignant Neoplasm of the Respiratory System and will therefore include the costs of interventions needed by these patients whilst in hospital. All costs reported throughout the rest of the report are in UK pounds. Table 99 shows the unit costs associated with the technologies needed in order to treat NSCLC patients.

Table 99 Unit costs associated with the technology in the economic model

Resource	Unit cost	Source	Comment
Outpatient visits			
GP	£37	PSSRU (2011)	
Specialist	£126	Department of Health (2013)	
Nurse	£14	PSSRU (2011)	
Occupational therapist (OT)	£77	PSSRU (2011)	
Physiotherapist	£49	PSSRU (2011)	
Outpatient interventions			
Blood transfusion	£923	Varney & Guest 2003	
CT scan	£118	Department of Health (2013)	
Infusion	£76	Department of Health (2013)	
MRI scan	£182	Department of Health (2013)	
Physical therapy	£183	Department of Health (2013)	Unit cost of chest physiotherapy
Respiratory therapy	£224	Department of Health (2013)	Unit cost of Lung Function Exercise Testing
Surgical procedure	£105	Department of Health (2013)	Unit cost of a lung transplant
Ultrasound	£58	Department of Health (2013)	
Chest X-ray	£19	NICE (2006)	
Radiotherapy	£113	Department of Health (2013)	
Unscheduled hospitalisations			
Unscheduled hospital admission	£1,997	Department of Health (2013)	
ICU admission	£1,256	Department of Health (2013)	
Emergency room visit	£122	Department of Health (2013)	
EGFR test costs			
EGFR mutation test	£140	SMC (2012)	

Drug acquisition and administration costs

The model uses the list price for gefitinib in the default settings (Table 100). However, gefitinib is available on the NHS through a patient access scheme (PAS). The scheme means that the NHS is charged with a fixed cost of £12,200 once the patient receives their third monthly pack of the drug (Table 101). The cost of gefitinib is independent of the amount of the drug received, and patients who are on the treatment for less than three months receive gefitinib free of charge. The model includes the functionality to choose between using the list price or the PAS cost for gefitinib. Gefitinib incurs a one-off introductory administration cost of delivering the oral chemotherapy which is applied at the beginning of treatment (Table 102). If the PAS cost for gefitinib is used two additional administration costs are applied; a set-up cost and a monthly administration cost (Table 102).

Table 100 List price for gefitinib

Therapy	Unit	Cost	Dose	Cost per dose	Cost per 30 days	Ref.
Gefitinib	30 x 250mg tablets	£2,167.71	1 250mg tablet per day	£72.26	£2,167.71	BNF 2011

Table 101 PAS cost for gefitinib

Therapy	Dose	One off fixed cost	Fixed cost applies at	Ref.
Gefitinib	250mg tablet	£12,200	3rd model cycle	NICE (2010)

Table 102 Drug administration costs for gefitinib

Item of administration cost	Cost	Cost applies at	Cost ref.
Introductory administration cost	£163	1st model cycle	Department of Health (2013)
PAS set up cost	£34	1st model cycle	NICE (2011b)
PAS monthly administration cost	£70	Every model cycle	NICE (2011b)

The list price unit cost of erlotinib is presented in Table 103. The list price for erlotinib is used in the model base case. Erlotinib also incurs the one-off introductory administration cost of delivering the oral chemotherapy (Table 104).

Table 103 List price for erlotinib

Therapy	Unit	Cost	Dose	Cost per dose	Cost per month	Ref.
Erlotinib	150mg	£54.38	1 150mg tablet per day	£54.38	£1,631.40	BNF 2011

Table 104 Drug administration cost for erlotinib

Item of administration cost	Cost	Cost applies at	Cost ref.
Introductory administration cost	£163	1st model cycle	Department of Health (2013)

The unit drug acquisition cost used for afatinib is set equal to the daily cost of gefitinib (Table 100) at £72.26. The model includes the functionality to enter a different list price for afatinib. Additionally, the user can assume a discount is applied to the list price and can enter their choice of discount. Patients receiving gefitinib, erlotinib or afatinib are assumed to receive one oral dose per day until progression.

The drug acquisition (Table 105) and administration (Table 106) costs of docetaxel are presented as patients who receive a TKI as 1st line treatment are assumed to be treated with docetaxel as second line therapy. The administration cost used for docetaxel is the delivery of complex chemotherapy, including prolonged infusion treatment at 1st attendance.

Table 105 Drug acquisition cost for docetaxel

Therapy	Unit	Cost	Dose per treat. cycle	Units per treat. cycle inc. wastage	Cost per treat. cycle	Cycles per treat. course	Total cost treat. course	Ref.
Docetaxel	20mg/ml, 4ml vial	£534.75	75mg/m2	2	£1,069.50	4	£1,069.50	BNF 2011

Table 106 Drug administration cost for docetaxel

Item of administration cost	Cost	Cost applies at	Cost ref.
Monthly administration cost	£302.41	Every model cycle	Department of Health (2013)

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Structure of costing health states

Disease management or health state specific costs are assigned to each model health state and to each adverse event episode. 1st line drug costs are additionally incurred in the PF health state. Second line drug costs are also incurred in the PD health state in the 1st line model, unlike with the PF health state these drug costs are directly incorporated into the health state specific costs (method of PD costing is described below).

In the 1st line model progression from the PF health state moves patients straight to second line treatment and on progression from this treatment patients move into a best supportive care phase (Figure 34).

In the 1st line model, time spent in 1st line progression free is modelled using PFS as generated by parametric survival models or the Kaplan Meier data. Overall time spent in the post progression health states is dictated by OS. Within the entire PD period, the time spent in second line treatment is obtained from literature.

First line progression-free health state specific costs from RCT data

Table 107 illustrates the disease management resource use, weighted costs and total cost associated with the 1st line treatment progression free health state. The H-SAP from LUX-Lung 3 (BI 2013a) provided resource use tables based on resource use over 3 week periods for patients in the progression free health state. The total monthly cost of disease management is assumed

to be equivalent across the separate treatment arms within the cost-effectiveness model.

Table 107 Disease management resource use and cost associated with TKI-naive progression free health state

Resource	Resource use per 3 weeks	Unit cost	Weighted cost
Outpatient visits			
GP	0.0326	£37	£1.21
Specialist	0.1003	£126	£12.62
Nurse	0.0870	£14	£1.19
Occupational therapist	0.0000	£77	£0.00
Physiotherapist	0.0016	£49	£0.08
Outpatient interventions			
CT scan	0.0226	£118	£2.68
MRI scan	0.0071	£182	£1.29
Surgical procedure	0.0054	£105	£0.57
Ultrasound	0.0056	£58	£0.33
X-ray	0.0280	£19	£0.53
Radiotherapy	0.0021	£113	£0.24
Unscheduled hospitalisations			
Unscheduled hospitalisation stay	0.0495	£1,997	£98.83
ICU visit	0.0238	£1,256	£29.89
Emergency room visit	0.0383	£122	£2.89
Total cost per 3 weeks			£152
Total cost per month			£220

Second line progression free health state specific cost from literature

The disease management costs assigned to the second line treatment progression free health state have been extracted from a literature review (Table 108). The cost is derived from a UK based study of patients receiving 2nd line treatment for NSCLC (Lewis et al. 2010).

Table 108 Disease management cost associated with second line progression free health state

Paper	2nd Line PF cost
Lewis et al. 2010	£362

Third line progressive disease health state specific cost from RCT data

Table 109 illustrates the disease management resource use, weighted costs and total cost associated with the third line treatment progressive disease health state. The disease management cost for third line progressive disease is assigned to the 3rd line BSC period in the progressive disease health state in the cost-effectiveness model. The H-SAP from LUX-Lung 1 (BI 2011b) provided resource use tables based on resource use over one month periods for patients in the progressive disease health state. The total monthly disease management cost is assumed to be equivalent across the separate treatment arms within the cost-effectiveness model.

Table 109 Disease management resource use and cost associated with third line progressive disease health state

Resource	Resource use per month	Unit cost	Weighted cost
	Progressive disease		
Outpatient visits			
GP	0.0414	£37	£1.54
Specialist	0.1380	£126	£17.36
Nurse	0.0039	£14	£0.05
Occupational therapist	0.0000	£77	£0.00
Physiotherapist	0.0000	£49	£0.00
Outpatient interventions			
Blood transfusion	0.0019	£923	£1.75
CT	0.0044	£118	£0.52
Infusion	0.0034	£76	£0.26
MRI	0.0013	£182	£0.24
Physical therapy	0.0014	£183	£0.26
Respiratory therapy	0.0000	£224	£0.00
Surgical procedure	0.0072	£105	£0.76
Ultrasound	0.0020	£58	£0.12
X-ray	0.0086	£19	£0.16
Radiotherapy	0.5057	£113	£57.04
Unscheduled hospitalisations			
Unscheduled hospitalisation stay	0.169	£1,997	£336.42
ICU visit	0.009	£1,256	£0.00
Emergency room visit	0.0921	£122	£1.05
Total cost per month			**£418**

Total post first line progression costs by treatment arm

In the TKI-naive model, costing post progression from 1st line treatment relies on calculating the relative time spent in the two post-progression states (shown in Figure 34). A time-weighted total cost for the entire post-progression period can be assigned to each treatment arm. Time spent in PD is dependent on PFS and OS, because PFS differs across treatment arms in the model base case time spent in PD will also differ. However, assumptions need to be made concerning whether the difference in time spent in PD will occur in second line therapy or in BSC, or in both of these components of PD.

The costs in Table 110 are based on the assumption of a proportionate adjustment in the duration of both components of PD, for each treatment arm relative to pemetrexed/cisplatin. The time spent in each PD component used to generate the following calculations is that shown in Table 74 (using the assumption that the second line treatment period length is constant across the arms receiving the same second line treatments).

Table 110 Total disease management costs per PD component

Component of PD	Monthly cost	Total costs by treatment arm			Ref
		Afatinib	Erlotinib	Gefitinib	
Disease management cost in 2L	£362	£1,484	£1,484	£1,484	Table 108
Disease management cost in 3L BSC	£418	£6,410	£4,949	£5,862	Table 109

The disease management cost used for the 2nd line progression free period has been derived from literature (Table 108) and the cost used for BSC is the disease management cost derived from the patients who experienced progressive disease in the LUX-Lung 1 trial. The total costs by treatment arm take into account the amount of time spent in each PD period by each treatment arm (Table 73).

Table 111 Total drug costs per PD component by treatment arm

Total drug costs in PD by treatment arm- drug costs only incurred in 2nd line				
Treatment arm	**2nd line therapy**	**Cost of treatment per month**	**Total cost of 2nd line therapy**	**Cost reference**
Afatinib	Docetaxel	£2,344	£9,609	*Table 105-adjusted for model cycle length and including admin costs*
Erlotinib	Docetaxel	£2,344	£9,609	*Table 105-adjusted for model cycle length and including admin costs*
Gefitinib	Docetaxel	£2,344	£9,609	*Table 105-adjusted for model cycle length and including admin costs*

In the post progression period further medication costs are only incurred in the second line therapy period. The figures presented in Table 111 assume that patients receive second line treatments until progression. The total drug costs per month include the drug acquisition and the drug administration costs. The second line therapy received by patients was decided by clinical expert interview (See Section 7.3.5). Patients who received a TKI in 1st line receive docetaxel as second line treatment. The model also includes the option for pemetrexed as second line treatment for patients receiving a TKI in 1st line. The total cost of second line therapy presented in Table 111 takes into account the amount of time spent in second line treatment by each treatment arm (Table 73).

Table 112 Total monthly cost of PD state by treatment arm

Total costs PD (disease management and drug costs) by treatment arm			
	Afatinib	**Erlotinib**	**Gefitinib**
Total monthly cost in 2L	£2,344	£2,344	£2,344
Total monthly cost for 3L (BSC)	£418	£418	£418

Table 113 Overall total cost of the entire PD state by treatment arm

Total costs PD (disease management and drug costs) by treatment arm			
	Afatinib	**Erlotinib**	**Gefitinib**
Total cost in 2L	£9,609	£9,609	£9,609
Total cost for 3L (BSC)	£6,410	£4,949	£5,862
TOTAL COST FOR PD	£16,019	£14,558	£15,471

The figures in Table 112 have been constructed using the total disease management costs PD (Table 110) and the total drug costs PD (Table 112). The total cost in second line comprises of disease management and drug costs, in the BSC period this is simply the disease management costs.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

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Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

Not applicable.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

There is uncertainty around the patient treatment pathway following progression from 1st line treatment, during the PD health state in the model. This uncertainty concerns which 2nd line treatment patients receive before they move onto best supportive care (3rd line treatment) and for how long they receive it. This is explored as part of the structural sensitivity analysis.

The mean times spent on 2nd line treatment with docetaxel and pemetrexed are based on the reported median PFS times of 4.1 months (INTEREST trial) and 2.9 months (Hanna et al. 2004), respectively. Because PD is modelled as one health state, including both 2nd line treatment and 3rd line treatment (best supportive care), the costs and health-related utilities accrued during PD are

weighted, based on the proportion of time PD patients from each treatment arm spend on 2nd line and 3rd line treatment.

Currently, there is no clinical consensus on whether PFS time for 2nd line treatment of NSCLC is constant regardless of 1st line therapy, or whether gains in overall survival achieved through 1st line therapy extend the period on 2nd line therapy. The base case analysis assumes that for a particular 2nd line treatment regimen, the time spent on 2nd line treatment is constant across treatment arms, irrespective of the total time spent in progressive disease. To test the impact of this assumption on the cost-effectiveness of afatinib for 1st line EGFR mutation positive NSCLC, a scenario analysis was conducted in which patients spending longer in the PD state were assumed to spend a correspondingly longer time on active 2nd line treatment. To model this, a proportionate adjustment to the mean time on 2nd line treatment was made, relative to the control 1st line (pemetrexed/cisplatin) treatment arm in the model. Patients in the control (pemetrexed/cisplatin) treatment arm received erlotinib as 2nd line treatment for 2.2 months, based on the median PFS reported in Shepherd et al. (2005).

The mean duration on 2nd line therapy using the proportionate adjustment is shown, together with the base case durations for 2nd line therapy, in Table 117.

Table 117 Time on 2nd line treatments for 2nd line duration scenario analysis

	First line treatment			
	Control (Pem/Cis)	Afatinib	Erlotinib	Gefitinib
2nd line duration constant (base case)	2.20	4.1	4.1	4.1
2nd line duration proportionate	2.20	3.56	2.92	3.32

Note: time is expressed in months

These different scenarios, including a scenario in which both the 2nd line treatment regimen and the 2nd line treatment duration are changed from the base case, are explored as part of the sensitivity analysis in Section 7.7.9.

Additional structural sensitivity analysis regarding different sources for the utility data were undertaken as described in Section 7.4.7, the results from the MTC using only LUX-Lung 3 data, and the results from the MTC when the OPTIMAL data is included, described in Section 6.7.6.

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Deterministic one-way sensitivity analyses (OWSA) were carried out to assess the robustness of the conclusions when the values of uncertain variables are altered, and to identify parameters with the highest impact on the incremental

cost-effectiveness. Table 118 shows the variables used in the 1st line model tested in the OWSA and the upper and lower values tested for each variable. Where possible, upper and lower bounds of the variables are based on the 95% confidence intervals (95% CI) around the mean values of the variables.

Table 118 Upper and lower bounds of variables tested in the OWSA (Taken from Sheet 'OWSA' in the Excel model)

	Base value	Alternative low	Alternative high
Discounting cost	0.04	0.00	0.06
Discounting effect	0.04	0.00	0.06
Body surface area	1.85	1.75	1.95
Cox PH model HR for PFS (afatinib vs. pmc)	0.58	0.43	0.78
Expo model HR for PFS (afa vs. pmc)	0.69	0.52	0.92
Weibull model HR for PFS (afa vs. pmc)	0.61	0.46	0.82
Gompertz model HR for PFS (afa vs. pmc)	0.62	0.46	0.83
Cox PH model HR for OS (afatinib vs. pmc)	1.12	0.73	1.73
Expo model HR for OS (afa vs. pmc)	0.96	0.70	1.31
Weibull model HR for OS (afa vs. pmc)	0.96	0.70	1.31
Gompertz model HR for OS (afa vs. pmc)	0.95	0.70	1.30
Expo model HR for OS (afa vs. pmc) for comparison with erl/gef	0.96	0.70	1.31
Weibull model HR for OS (afa vs. pmc) for comparison with erl/gef	0.96	0.70	1.31
Gompertz model HR for OS (afa vs. pmc) for comparison with erl/gef	0.95	0.70	1.30
Utility in progression-free afatinib arm	0.78	0.77	0.80
Disutility for diarrhea (grade 3/4)	-0.15	-0.24	-0.06
Disutility for rash/acne (grade 3/4)	-0.20	-0.26	-0.15
Disutility for fatigue (grade 3/4)	-0.18	-0.28	-0.08
Freq of diarrhea (grade 3/4) in 1L afa patients	0.14	0.10	0.19
Freq of rash/acne (grade 3/4) in 1L afa patients	0.16	0.11	0.21
Freq of fatigue (grade 3/4) in 1L afa patients	0.01	0.00	0.03
Duration (days) of diarrhea AE (grade 3/4) until improvement	6.60	5.95	7.25
Duration (days) of rash/acne AE (grade 3/4) until improvement	12.30	11.51	13.09
Duration (days) of fatigue AE (grade 3/4) until improvement	32.00	27.76	36.24
No episodes diarrhea per patient suffering diarrhea (grade 3/4)	1.36	1.02	1.70
No episodes rash/acne per patient suffering rash/acne (grade 3/4)	1.08	0.81	1.35
No episodes fatigue per patient suffering fatigue (grade 3/4)	2.00	1.50	2.50
Cost/month Progression-free, both arms	£220	£97	£1,542
Cost/month best supportive care, both arms	£418	£268	£1,779
[redacted]	[redacted]	[redacted]	[redacted]
NMA-based HR for PFS (afa vs. erl)	0.91	0.53	1.50
NMA-based HR for PFS (afa vs. gef)	0.78	0.47	1.20
NMA-based HR for OS (afa vs. erl)	0.80	0.56	1.14
NMA-based HR for OS (afa vs. gef)	0.84	0.55	1.30
PD Utility in 2nd Line, progression-free	0.73	0.71	0.75
PD Utility in 3rd Line, progression-free	0.62	0.57	0.67
PD Utility in 3rd Line, progressive disease	0.46	0.42	0.50
Disutility for anaemia (grade 3/4)	-0.07	-0.11	-0.04
Disutility for neutropenia (grade 3/4)	-0.09	-0.12	-0.06

Freq of anaemia (grade 3/4) in 1L gef patients	0.00	0.00	0.01
Freq of neutropenia (grade 3/4) in 1L gef patients	0.00	0.00	0.01
Freq of anaemia (grade 3/4) in 1L erl patients	0.00	0.00	0.01
Freq of neutropenia (grade 3/4) in 1L erl patients	0.00	0.00	0.01
Freq of anaemia (grade 3/4) in 1L afa patients	0.00	0.00	0.01
Freq of neutropenia (grade 3/4) in 1L afa patients	0.00	0.00	0.01
Duration (days) of anaemia AE (grade 3/4) until improvement	32.00	27.76	36.24
Duration (days) of neutropenia AE (grade 3/4) until improvement	32.00	27.76	36.24
No episodes anaemia per patient suffering anaemia (grade 3/4)	2.00	1.50	2.50
No episodes neutropenia per patient suffering neutropenia (grade 3/4)	2.00	1.50	2.50
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis (PSA) was conducted to estimate the simultaneous impact of uncertainties of all the model parameters on the probability of a treatment being cost-effective. In the PSA, model input variables are regarded as stochastic and their values are sampled from relevant distributions. Random sampling technique is used to generate a sample of model outputs that are used to generate PSA scatter plots and cost-effectiveness acceptability curves (CEAC).

Uncertainty is sampled around efficacy, utility, cost, frequency of AE events, and duration of AE events. Not all parameters were varied in the PSA due to some being fixed tariffs that may not be required in the PSA, and for some parameters the reported standard errors were small.

The information displayed in Table 119 to Table 122 shows the efficacy, utility, frequency of AE and duration of AE inputs to PSA in the 1st line model.

Uncertainty around the OS and PFS RCT-based hazard ratios for afatinib versus pemetrexed/cisplatin has been generated as an output of the uncertainty around the OS and PFS parametric survival models. Using covariance matrices from the statistical analyses of the LUX-Lung 3 survival data, the Cholesky decomposition is used to simultaneously model the uncertainty around the related parameters for each single survival model (as opposed to modelling each related parameter independently). For the MTC-based hazard ratios for afatinib versus erlotinib and gefitinib, lognormal distributions are fitted around the OS and PFS hazard ratios using information on the standard error and the log normal values of the mean and upper and lower credible intervals.

Table 119 Efficacy inputs for PSA - sampled using lognormal distribution

Variable	Expected mean	LN mean	SE	LN Lower CI	LN Upper CI
MTC based HR for PFS (afa v gef)	0.78	-0.25	0.24	-0.76	0.18
MTC based HR for PFS (afa v erl)	0.91	-0.09	0.27	-0.63	0.41
MTC based HR for OS (afa v gef)	0.84	-0.17	0.22	-0.60	0.26
MTC based HR for OS (afa v erl)	0.80	-0.22	0.18	-0.58	0.13

Table 120 Utility inputs for PSA- sampled using beta distribution

Variable	Expected mean	SE	Alpha	Beta
Utility in PF- afa	0.784	0.009	1639.08	451.58
Utility in PF- pmc	0.784	0.009	1639.08	451.58
Utility in 2L PF	0.730	0.011	1255.49	464.36
Utility in BSC	0.460	0.021	249.26	292.61
Disutility of diarrhea	-0.147	0.045	9.10	52.82
Disutility of rash/acne	-0.202	0.028	41.53	164.07
Disutility of fatigue	-0.179	0.053	9.36	42.95
Disutility of anaemia	-0.073	0.018	14.62	184.46
Disutility of neutropenia	-0.090	0.015	30.76	312.20
Disutility of febrile neutropenia	-0.090	0.016	27.65	279.53

Table 121 Frequency of AE inputs for PSA sampled using beta distribution

Variable	Expected mean	SE	Alpha	Beta
Frequency of diarrhoea- afatinib	14%	0.02	33.0	196.0
Frequency of rash/acne- afatinib	16%	0.02	37.0	192.0
Frequency of fatigue- afatinib	1%	0.01	3.0	226.0
Frequency of fatigue- pem/cis	13%	0.03	14.0	97.0
Frequency of anaemia- pem/cis	5%	0.01	58.41	1116.86
Frequency of neutropenia- pem/cis	15%	0.02	52.31	298.75
Frequency of febrile neutropenia- pem/cis	1%	0.00	60.67	4605.99
Frequency of diarrhoea- gefitinib	4%	0.02	2.89	73.49
Frequency of rash/acne- gefitinib	3%	0.02	2.21	67.48
Frequency of fatigue- gefitinib	13%	NA	NA	NA
Frequency of neutropenia- gefitinib	1%	0.001	60.85	6024.24
Frequency of diarrhoea- erlotinib	8%	0.18	0.17	2.00
Frequency of rash/acne- erlotinib	16%	0.22	0.47	2.41
Frequency of fatigue- erlotinib	2%	NA	NA	NA

Table 122 Duration of AE inputs for PSA sampled using lognormal distribution

Variable	Expected mean	LN mean	SE	LN Lower CI	LN Upper CI
Duration of diarrhea	6.60	1.89	0.33	1.78	1.98
Duration of rash/acne	12.30	2.51	0.40	2.44	2.57
Duration of fatigue	32.00	3.47	2.16	3.32	3.59

[redacted]

Table 123 Cost of AE inputs from literature for PSA sampled using a normal distribution

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7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any

differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 124 presents the 25th percentile, median, and 75th percentile for the PFS and OS values for afatinib in the LUX-Lung 3 and LUX-Lung 6 trials, along with the 95% confidence intervals. Also shown is the 25th percentile, median, and 75th percentile from the predicted PFS and OS from the model.

Table 124 Summary of the model results compared with clinical data for the 1st line model

Outcome	Endpoints	LUX-Lung 3 (months)	LUX-Lung 6 (months)	Model result (months)
Progression free survival (months)*	25th percentile (95% C.I.)	5.32 (3.98, 6.87)	6.87 (5.55, 8.08)	5-6
	Median (95% C.I.)	11.14 (9.63, 13.63)	11.01 (9.66, 13.73)	10-11
	75th percentile (95% C.I.)	19.12 (16.49, 19.35)	19.25 (16.56,22.11)	17-18
Overall survival (months)*	25th percentile (95% C.I.)	16.39 (13.93, 18.60)	14.23 (11.60,16.30)	15-16
	Median (95% C.I.)	28.06 (24.64, 32.95)	22.11 (20.01, NE)	28-29
	75th percentile (95% C.I.)	37.45 (NE, NE)	NE (NE, NE)	44-45

* Endpoints taken from Table 15 and Table 17. NE = not estimable; C.I. = Confidence Interval.

The results from the model fall within the confidence intervals from the LUX-Lung trials, providing confidence that the model is able to reproduce the course of the disease to an acceptable degree of certainty.

7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The Markov model contains three states – Progressive Disease (PD), Progression Free (PF) and Death. The Markov trace for these three states is shown for afatinib in Figure 37, for gefitinib in Figure 38 and erlotinib in Figure 39. These are for the first-line indication using the base-case assumptions.

Figure 37 Markov trace for afatinib first-line using base-case assumptions

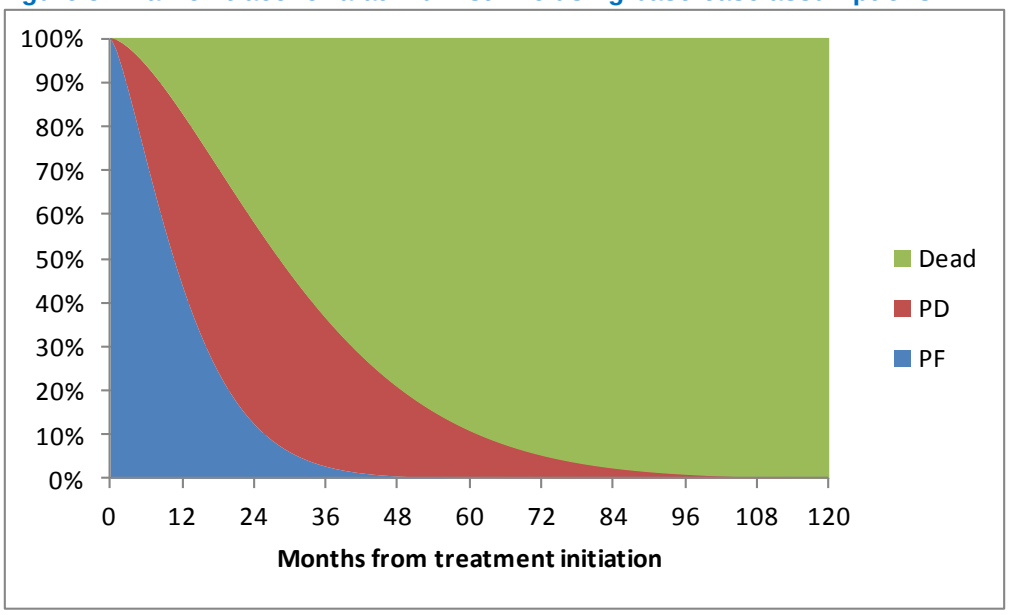


Figure 38 Markov trace for gefitinib first-line using base-case assumptions

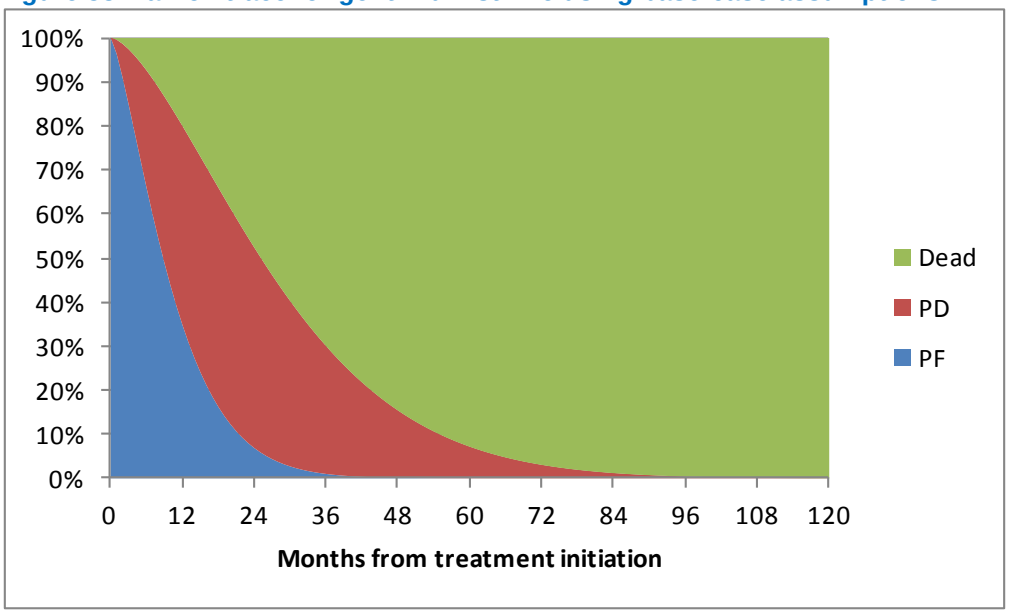
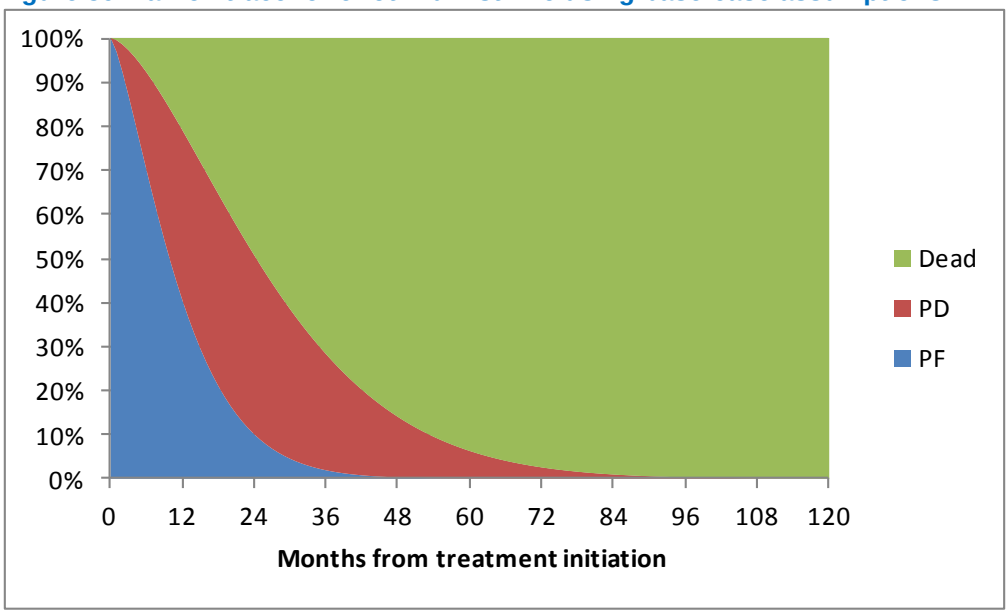


Figure 39 Markov trace for erlotinib first-line using base-case assumptions



It should be noted that the majority of the cohort has died before the 10 year time horizon for the model, indicating that the maximum time horizon used is adequate.

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The markov model has three health states - Progressive Disease (PD), Progression Free (PF) and Death. Each live health state (PF, PD) is associated with a health-related utility to estimate the QALY over time horizon of the analysis. The cycle length in the model is one month, and patients transition between states at each cycle. This component of the QALY is calculated monthly based on the distribution of the cohort across the health states and the utility associated with being in the health state.

Utility reduction (disutility) due to adverse events (AEs) are applied in the model based on the estimated proportions of patients suffering from adverse events in each treatment arm and are considered to occur during the progression-free health state. The impact of adverse events on health outcomes (QALY) is calculated using information on the duration of adverse events and their impact on health-related utility on a monthly basis.

The model's default time horizon is 10 years. This has been set to cover the lifetime of the patients and fully incorporate the health outcomes of NSCLC. No discounting is required during the first year of the model; after year 1, discounting is applied at 3.5% per annum to QALYs.

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a

combination of other states, please present disaggregated results. For example:

Table 125 contains a breakdown of the costs, QALY and life years of the different 1st line treatments.

Table 125 Model outputs by clinical outcomes, 1st line treatment

Health State	Afatinib	Gefitinib	Erlotinib
Progression-free survival			
LY	1.0448	0.8720	0.9756
QALY	0.8191	0.6837	0.7649
Cost (£) [1]	£30,616	£25,605	£22,245
Post-progression survival			
LY	1.5042	1.4188	1.2474
QALY	0.7775	0.7393	0.6604
Cost (£)	£14,864	£14,521	£13,660
AE 1 Diarrhea			
QALY	-0.001	0.000	0.000
[redacted]	[redacted]	[redacted]	[redacted]
AE 2 Rash/Acne			
QALY	-0.001	0.000	-0.001
[redacted]	[redacted]	[redacted]	[redacted]
AE 3 Fatigue			
QALY	0.000	-0.002	0.000
[redacted]	[redacted]	[redacted]	[redacted]
AE 4 Anaemia			
QALY	0.000	0.000	0.000
[redacted]	[redacted]	[redacted]	[redacted]
AE 5 Neutropenia			
QALY	0.000	0.000	0.000
[redacted]	[redacted]	[redacted]	[redacted]
AE 6 Febrile Neutropenia			
QALY	0.000	0.000	0.000
[redacted]	[redacted]	[redacted]	[redacted]
Total AEs			
QALY	-0.002	-0.002	-0.002
[redacted]	[redacted]	[redacted]	[redacted]
LY	2.5490	2.2909	2.2230
QALY	1.5944	1.4208	1.4235
[redacted]	[redacted]	[redacted]	[redacted]

[1] Inclusive of cost of administration (if TKI) and cost of EGFR mutation test, which are assumed to occur during the first cycle only. This cost is used in subsequent tables in this section.

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Disaggregated incremental QALYs by health state are shown in Table 126, and disaggregated incremental costs in Table 127.

Table 126 Summary of QALY gain by health state

Health state	QALY Afatinib	QALY Gefitinib	Increment	Absolute increment	% absolute increment	QALY Erlotinib	Increment	Absolute increment	% absolute increment
Progression-free survival	0.819	0.684	0.135	0.135	76%	0.765	0.054	0.054	31%
Post-progression survival	0.778	0.739	0.038	0.038	22%	0.660	0.118	0.118	68%
AE 1 Diarrhea	-0.001	0.000	-0.001	0.001	1%	0.000	-0.001	0.001	1%
AE 2 Rash/Acne	-0.001	0.000	-0.001	0.001	1%	-0.001	0.000	0.000	0%
AE 3 Fatigue	0.000	-0.002	0.002	0.002	1%	0.000	0.000	0.000	0%
AE 4 Anaemia	0.000	0.000	0.000	0.000	0%	0.000	0.000	0.000	0%
AE 5 Neutropenia	0.000	0.000	0.000	0.000	0%	0.000	0.000	0.000	0%
AE 6 Febrile Neutropenia	0.000	0.000	0.000	0.000	0%	0.000	0.000	0.000	0%
Total AEs	-0.002	-0.002	0.000	0.000	2%	-0.001	-0.001	0.001	1%
Total	1.595	1.421	0.174	0.178	100%	1.424	0.171	0.173	100%

Table 127 Summary of costs by health state

Health state	Cost Afatinib	Cost Gefitinib	Increment	Absolute increment	% absolute increment	Cost Erlotinib	Increment	Absolute increment	% absolute increment
Progression-free survival	£30,616	£25,605	£5,011	£5,011	83%	£22,245	£8,371	£8371	84%
Post-progression survival	£14,864	£14,521	£343	£343	6%	£13,660	£1,204	£1,204	12.1%
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 128 Base-case results using list prices:

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Erlotinib	[redacted]	2.223	1.423	-	-	-		
Gefitinib	[redacted]	2.291	1.421	[redacted]	0.068	-0.002	[redacted]	[redacted]
Afatinib	[redacted]	2.549	1.594	[redacted]	0.258	0.173	[redacted]	[redacted]

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Results for the base case are shown in Table 128.

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The ten variables which have the largest impact on the base case incremental cost-effectiveness ratio are shown in Table 129 and Table 130. Figure 40 and Figure 41 show the results of the OWSA in tornado diagram format.

The hazard ratios for OS and PFS have a large impact on the base case incremental cost-effectiveness ratio for all comparisons. The disease management cost associated with the 3rd line BSC component of the progressive disease health state additionally has a large impact on the cost-effectiveness of afatinib in the first line treatment of NSCLC.

Table 129 OWSA results for afatinib compared to gefitinib

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

Table 130 OWSA results for afatinib compared to erlotinib

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

[redacted]

Figure 40 Tornado diagram for afatinib compared with gefitinib, first line setting using list prices (NMA = MTC)

[redacted]

Figure 41 Tornado diagram for afatinib compared with erlotinib, first line setting using list prices (NMA = MTC)

[redacted]

Given the levels of variation seen in the one-way sensitivity analysis, this appears insufficient to affect the reliability of the base-case analysis.

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The probability of cost effectiveness, at different willingness to pay thresholds for the pair wise comparisons in the first line setting is shown in Table 131.

Table 131 Probability of cost-effectiveness in the 1st line setting

Intervention	Comparator	£20,000 per QALY	£30,000 per QALY
Afatinib	[redacted]	[redacted]	[redacted]

The comparison between the determinist and probabilistic results for afatinib vs. gefitinib is shown in Table 132.

Table 132 comparing the ICER values obtained from both deterministic and probabilistic sensitivity analysis for afatinib vs. gefitinib

	Incremental cost	Incremental QALY	ICER
Deterministic Values	[redacted]	[redacted]	[redacted]
Average value for PSA	[redacted]	[redacted]	[redacted]

The cost-effectiveness planes and acceptability curves for afatinib vs. gefitinib are displayed Figure 42 and Figure 43.

Figure 42 Incremental cost-effectiveness scatter plot for afatinib as compared to gefitinib, first line setting using list prices

[redacted]

Figure 43 CEAC for afatinib as compared to gefitinib, first line setting using list prices

[redacted]

The comparison between the determinist and probabilistic results for afatinib vs. erlotinib is shown in Table 133.

Table 133 comparing the ICER values obtained from both deterministic and probabilistic sensitivity analysis for afatinib vs. erlotinib

	Incremental cost	Incremental QALY	ICER
Deterministic Values	[redacted]	[redacted]	[redacted]
Average value for PSA	[redacted]	[redacted]	[redacted]

The cost-effectiveness planes and acceptability curves for afatinib vs. erlotinib are displayed Figure 44 and Figure 45.

Figure 44 Incremental cost-effectiveness scatter plot for afatinib as compared to erlotinib, first line setting using list prices

[redacted]

Figure 45 CEAC for afatinib as compared to erlotinib, first line setting using list prices

[redacted]

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

In the base case, following 1st line treatment with any of the TKIs (afatinib, erlotinib or gefitinib), all patients are assumed to receive docetaxel as 2nd line treatment, before proceeding to best supportive care. To test the impact of this assumption on the cost-effectiveness of afatinib for 1st line EGFR

mutation positive NSCLC, a scenario analysis was conducted in which patients received another possible 2nd line treatment, pemetrexed, instead of docetaxel. The results for this scenario analysis are compared with the base case analysis in Table 134.

Table 134 Alternate 2nd line treatment scenario analysis

	Docetaxel (base case)	Pemetrexed
[redacted]		
ICER (QALY)	[redacted]	[redacted]
ICER (LY)	[redacted]	[redacted]
ICER (PFLY)	[redacted]	[redacted]
[redacted]		
ICER (QALY)	[redacted]	[redacted]
ICER (LY)	[redacted]	[redacted]
ICER (PFLY)	[redacted]	[redacted]

The results for the scenario analysis outlined in the second part of Section 7.6.1 are shown in Table 135, including a scenario in which both the 2nd line treatment regimen and the 2nd line treatment duration are changed from the base case.

Table 135 Alternate 2nd line treatment duration scenario analysis

	2nd line treatment duration		
	Constant (base case)	Proportionate	Proportionate
2nd line treatment →	Docetaxel	Docetaxel	Pemetrexed
[redacted]			
ICER (QALY)	[redacted]	[redacted]	[redacted]
ICER (LY)	[redacted]	[redacted]	[redacted]
ICER (PFLY)	[redacted]	[redacted]	[redacted]
[redacted]			
ICER (QALY)	[redacted]	[redacted]	[redacted]
ICER (LY)	[redacted]	[redacted]	[redacted]
ICER (PFLY)	[redacted]	[redacted]	[redacted]

The variation in structural assumptions has little impact on the ICERs as demonstrated the results in Table 134 and Table 135.

The ICERs using the three sets of utility values are shown in Table 136.

Table 136 ICERs for sensitivity analysis with different utility values

	Afatinib vs. gefitinib	Afatinib vs. erlotinib
LUX-Lung trial data (basecase)	[redacted]	[redacted]
LUCEOR data (Chouaid et al. 2012)	[redacted]	[redacted]
Literature (Nafees et al. 2008)	[redacted]	[redacted]

The ICERs using only the afatinib data from LUX-Lung 3 in the MTC are shown in Table 139.

Table 137 ICERs for sensitivity analysis using only afatinib data from LUX-Lung 3 in the MTC

	Afatinib vs. gefitinib	Afatinib vs. erlotinib
LUX-Lung 3 and LUX-Lung 6 data (basecase)	[redacted]	[redacted]
Only LUX-Lung 3 data	[redacted]	[redacted]

The ICERs using data from OPTIMAL in the MTC are shown in Table 139.

Table 138 ICERs for sensitivity analysis using only afatinib data from LUX-Lung 3 in the MTC

	Afatinib vs. gefitinib	Afatinib vs. erlotinib
Basecase with OPTIMAL data excluded	[redacted]	[redacted]
Results with OPTIMAL data included	[redacted]	[redacted]

7.7.10 What were the main findings of each of the sensitivity analyses?

PSA was carried out using 2,000 iterations of the cost-effectiveness model. The incremental cost-effectiveness scatter plots are presented in (section 7.7.8). On all graphs the red dashed line represents a willingness to pay threshold of £30,000 per QALY. [redacted]

First line treatment with afatinib extends progression free survival and overall survival time versus both comparators considered in the model. Afatinib has the largest PFS and OS benefits when compared to erlotinib.

The base case ICER's in the first line setting are highly sensitive to changes in the PFS and OS hazard ratios and to the costs and utilities associated with the third line BSC component of the PD health state in the first line setting. Therefore the assumptions on the patient treatment pathway and health outcomes between progression and death have a great impact on cost-effectiveness. While the data on resource use, costs and health-related utility during the time before progression are available from the clinical trials, costs and health-related utility for the time after progression require assumptions. Given the uncertainty of the costs and health-related utility during the post-progression period and their significance for the CE of afatinib, these assumptions are key elements in defending the cost-effectiveness of afatinib as a treatment for first line NSCLC.

7.7.11 What are the key drivers of the cost-effectiveness results?

When looking at the absolute incremental values in Table 126, the key drivers of the cost-effectiveness results can be seen. When comparing afatinib with all comparators, both the Progression-Free Survival and the Post-Progression Survival constitute to the main cause of QALY difference. However, Progression-Free Survival for Gefitinib is the main driver and Post-Progression Survival is the main driver for the differences in erlotinib.

The key cost drivers from Table 127 can be seen as those associated with the progression-free survival state. These are driving by the treatment costs.

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

A number of steps were taken to ensure that the analysis was validated. These include:

- External review by leading UK clinical expert (see section 7.3.5)
  - The model structure was developed in conjunction with leading clinicians. This clinical validation serves to ensure that the model adheres to the clinical course of the disease and is reflective of current clinical practice.
- Sensitivity analysis outlined in Section 7.6.
- Validation by model developers
  - Apart from the interviews with the UK and Canadian clinical experts (discussed in Section 7.3.5), a senior modeller within the model developers organization (with no involvement in the afatinib model's development) perform a detailed QA check on the model.
- Validation by manufacturer
  - This involved increasing and decreasing various parameters or changing assumptions in the model and then monitoring the impact on outputs. If the outputs were unexpected, further checks were made to determine whether this was the result of an error in the model.
- Additional external validation was undertaken by a health-economics consultancy previously unconnected to the submission (Double Helix).

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No subgroup analysis was undertaken.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

No.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

This is the first economic evaluation of afatinib in this indication. Therefore there are no published studies with which to draw comparison.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes. The economic evaluation covers the relevant patient group.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strength of the economic evaluation is high-quality data that underpins it from the LUX-LUNG 3 and LUX-LUNG 6 trials. These pivotal trials provide a wealth of robust clinical data for the various modelled outcomes for the principle comparison of interest. This strength provides confidence in the results of the analysis.

The model structure was developed in conjunction with leading clinicians. This clinical validation serves to ensure that the model adheres to the clinical course of the disease and is reflective of current clinical practice.

Most of the model inputs have previously been used in the NICE submission process as discussed in section 7.2.3. This ensures that they conform to the standard required by NICE.

Extensive systematic reviews were undertaken to parameterise the model, leading to the best available evidence being included in the analysis via transparent and reproducible methods.

The base case is conservative and is likely to be biased against afatinib: the given patient populations of common mutations and investigator assessment

endpoints in gefitinib and erlotinib. Data from the network meta-analysis shows that afatinib also perform well in this patient subgroup.

Extensive sensitivity analysis and validation of the model was undertaken to ensure that analysis was robust. The comparators used are those currently adopted in clinical practice.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The incorporation of the final overall survival results from LUX-Lung 3 and LUX- Lung 6 would add to the robustness of the evaluation.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The estimated number of patients eligible for afatinib in England and Wales is shown in Table 139.

Table 139 Estimated numbers of patients eligible for treatment with afatinib

	England		Wales	
	Male	Female	Male	Female
2013 population (Office of National statistics, 2011a, 2011b)	26,476,952	27,086,069	1,494,930	1,553,190
Lung cancer incidence (Office of national statistics, 2012)	0.0573%	0.0380%	0.0622%	0.0410%
Number of new lung cancer patients in 2013	15,171	10,293	930	637
Total number of new lung cancer patients in England and Wales in 2013	27,031			
Percentage of NSCLC (National lung cancer audit, 2012)	83.3%			
New NSCLC patients in England and Wales in 2013	22,517			
Percentage at advanced stages (National lung cancer audit, 2009)	68.3%			
New advanced NSCLC patients in England and Wales in 2013	15,379			
Percentage of EGFR mutation (NICE 2012)	11%			
New advanced NSCLC patients with EGFR mutations in England and Wales in 2013	1,692			

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

It is assumed that for all diagnosed patients there is an equal treatment split between the two NICE approved technologies for this indication, gefitinib and erlotinib.

8.3 What assumption(s) were made about market share (when relevant)?

It is assumed that the market share for afatinib is split equally from gefitinib and erlotinib, as presented in Table 140. It is also assumed a population growth of 0.5% per year.

Table 140 Estimate number of patient on afatinib from 2013-2017

	2013	2014	2015	2016	2017
Eligible patients	1,692	1,700	1,709	1,717	1,726
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

No additional costs are expected.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Unit costs are calculated as per the economic model.

8.6 Were there any estimates of resource savings? If so, what were they?

Resource use in patients receiving treatment with afatinib, erlotinib or gefitinib is related to initiation of therapy, ongoing monitoring, and to adverse events associated with the treatment. Since all these treatments are oral TKIs that can be initiated in the same setting and require similar follow-up, it is anticipated that NHS resource use would be similar for afatinib, erlotinib and

gefitinib in this respect. Furthermore, the MTC presented in Section 6.7 supports the claim that there are no clinically meaningful differences between afatinib, erlotinib and gefitinib when administered to comparable patients under comparable conditions. It can reasonably be assumed therefore that resource use would be similar for afatinib, erlotinib and gefitinib due to their comparable clinical and administration profiles, and no resource savings available with the introduction of afatinib.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated cost per patient is in Table 141. This is based on the assumption that there is equal PFS for each of the treatments in line with the findings from the mixed treatment comparison (Figure 23). The average treatment duration is estimated at 10.1 months, based on the estimated PFS for erlotinib of 9.7 months, gefitinib if 9.5 months, and afatinib of 11.1 months (Rosell et al. 2012, Mok et al. 2009, Yang et al 2012a). The cost for erlotinib is from Table 141 and gefitinib is a fixed cost of £12,200 to be paid after the dispensing of a patient's third pack of gefitinib (day 60 of their treatment). If a patient experiences disease progression prior to this third pack the NHS is not charged for the gefitinib received.

Table 141 Cost of treatment with afatinib

	Erlotinib 150mg 30-tablet pack	Gefitinib 250mg 30-tablet pack	Afatinib 28 tablet pack
Cost per pack	£1,631.40		£2,023.28
Cost per day	£54.38		£72.26
Duration of treatment (months)	10.1	10.1	10.1
Duration of treatment (days)	307	307	307
Cost of treatment	£16,706	£12,200	£22,196

Based on the costs in Table 141, the estimated budget impact is in Table 142. The costs for erlotinib and gefitinib represent the costs without switching patients to afatinib, and the cost of afatinib represents the cost of switching erlotinib and gefitinib patients to afatinib.

Table 142 Estimated budget impact

	2013	2014	2015	2016	2017
Cost of erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None have been identified.

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

This is provided in the references (SPC 2013)

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

See Table 4 in Section 6.1.1.

10.2.2 The date on which the search was conducted.

The search was completed on the 6th March, 2012

10.2.3 The date span of the search.

2002 to 6 March 2012

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Searches in EMBASE

#	Original Search	hits
1	exp lung tumo?r/	171312
2	lung neoplasms.mp.	3345
3	exp lung non small cell cancer/	43774

4	(lung: adj3 canc:).mp.	164473
5	(lung: adj3 carcinoma:).mp.	37722
6	(lung: adj3 tumo?r:).mp.	93160
7	(lung: adj3 neoplasm:).mp.	14647
8	1 or 2 or 3 or 4 or 5 or 6 or 7	222722
9	Clinical trial/	811422
10	Randomi?ed controlled trial/	328589
11	Randomi?ation/	69255
12	Single blind procedure/	15744
13	Double blind procedure/	99629
14	Crossover procedure/	33616
15	Placebo/	163615
16	Randomi?ed controlled trial$.tw.	73073
17	Rct.tw.	8944
18	Random allocation.tw.	1023
19	Randomly allocated.tw.	15621
20	Allocated randomly.tw.	1667
21	(allocated adj2 random).tw.	495
22	Single blind$.tw.	10826
23	Double blind$.tw.	107293
24	((treble or triple) adj blind$).tw.	231
25	Placebo$.tw.	155000
26	Prospective study/	194906
27	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26	1159304
28	Case study/	13188
29	Case report.tw.	185954
30	Abstract report/ or letter/	658445
31	28 or 29 or 30	853316
32	27 not 31	1127345
33	Methotrexate.mp,ti,ab,kw,tw,tn.	93453
34	59-05-2.rn.	86639
35	Abitrexatemp.mp,ti,ab,kw,tw,tn.	0
36	Folex.mp,ti,ab,kw,tw,tn.	60
37	Mexate.mp,ti,ab,kw,tw,tn.	40
38	amethopterin.mp,ti,ab,kw,tw,tn.	64
39	Pemetrexed.mp,ti,ab,kw,tw.	4449
40	137281-23-2.rn.	0
41	Alimta.mp,ti,ab,kw,tw,tn.	770
42	Bevacizumab.mp,ti,ab,kw,tw.	21993
43	216974-75-3.rn.	19037
44	Avastin.mp,ti,ab,kw,tw,tn.	6114
45	Gemcitabine.mp,ti,ab,kw,tw.	26043
46	95058-81-4.rn.	0
47	Gemzar.mp,ti,ab,kw,tw,tn.	1647
48	Gefitinib.mp,ti,ab,kw,tw.	12710
49	184475-35-2.rn.	11692
50	Iressa.mp,ti,ab,kw,tw,tn.	4263
51	Paclitaxel.mp,ti,ab,kw,tw.	55345
52	33069-62-4.rn.	50063
53	Paxene.mp,ti,ab,kw,tw,tn.	38
54	Taxol.mp,ti,ab,kw,tw,tn.	10489
55	Carboplatin.mp,ti,ab,kw,tw.	37431
56	41575-95-4.rn.	0

57	Paraplat.mp,ti,ab,kw,tw,tn.	0
58	Paraplatin.mp,ti,ab,kw,tw,tn.	587
59	Cisplatin.mp,ti,ab,kw,tw.	101552
60	15663-27-1.rn.	92845
61	Platinol.mp,ti,ab,kw,tw,tn.	964
62	Erlotinib.mp,ti,ab,kw,tw.	11577
63	113321-74-6.rn.	0
64	Tarceva.mp,ti,ab,kw,tw,tn.	3037
65	Crizotinib.mp,ti,ab,kw,tw.	436
66	877399-52-5.rn.	327
67	Xalkori.mp,ti,ab,kw,tw,tn.	40
68	Docefrez.mp,ti,ab,kw,tw,tn.	2
69	Docetaxel.mp,ti,ab,kw,tw,tn.	26823
70	Taxotere.mp,ti,ab,kw,tw,tn.	3366
71	Vinorelbine.mp,ti,ab,kw,tw.	3797
72	71486-22-1.rn.	10658
73	Navelbine.mp,ti,ab,kw,tw,tn.	11182
74	(best adj3 support$).mp,ti,ab,kw,tw,tn.	3022
75	(optim$ adj3 support$).mp,ti,ab,kw,tw,tn.	2140
76	(support$ adj3 care$).mp,ti,ab,kw,tw,tn.	23108
77	(support$ adj3 caring).mp,ti,ab,kw,tw,tn.	355
78	(supportive adj3 treatment$).mp,ti,ab,kw,tw,tn.	3697
79	Or/33-78	294623
80	afatinib.mp,ti,ab,kw,tw.	179
81	439081-18-2.rn.	157
82	BIBW 2992.mp,ti,ab,kw,tw.	290
83	Tomtovok.mp,ti,ab,kw,tw,tn.	1
84	Tovok.mp,ti,ab,kw,tw,tn.	26
85	Or/80-84	358
86	79 or 85	294646
87	8 and 32 and 86	16945
88	87 and 2002:2012.(sa_year).	13572
89	limit 88 to (human and english language)	12249
90	89 and "Journal: Article" [Publication Type]	4800

Searches in MEDLINE

#	Original Search	hits
1	exp Lung Neoplasms/	156065
2	exp Carcinoma, Non-Small-Cell Lung/	25882
3	(lung$ adj3 canc$).mp.	81709
4	(lung$ adj3 carcinoma$).mp.	22603
5	(lung$ adj3 tumo?r$).mp.	16064
6	(lung$ adj3 neoplasm$).mp.	145314
7	1 or 2 or 3 or 4 or 5 or 6	183252
8	"randomi*ed controlled trial".pt.	326636
9	controlled clinical trial.pt.	84050
10	"randomi*ed".ab.	289881
11	placebo.ab.	135669
12	drug therapy.fs.	1527422
13	randomly.ab.	177683
14	trial.ab.	250722
15	groups.ab.	1160805
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	2931231

#	Original Search	hits
17	Methotrexate.mp,ti,ab,kw,tw.	39323
18	59-05-2.rn.	29765
19	Abitrexate.mp,ti,ab,kw,tw.	0
20	Folex.mp,ti,ab,kw,tw.	3
21	Mexate.mp,ti,ab,kw,tw.	1
22	amethopterin.mp,ti,ab,kw,tw.	368
23	Pemetrexed.mp,ti,ab,kw,tw.	1295
24	137281-23-2.rn.	0
25	Alimta.mp,ti,ab,kw,tw.	144
26	Bevacizumab.mp,ti,ab,kw,tw.	6332
27	216974-75-3.rn.	0
28	Avastin.mp,ti,ab,kw,tw.	851
29	Gemcitabine.mp,ti,ab,kw,tw.	8347
30	95058-81-4.rn.	0
31	Gemzar.mp,ti,ab,kw,tw.	210
32	Gefitinib.mp,ti,ab,kw,tw.	3518
33	184475-35-2.rn.	2556
34	Iressa.mp,ti,ab,kw,tw.	680
35	Paclitaxel.mp,ti,ab,kw,tw.	21138
36	33069-62-4.rn.	16775
37	Paxene.mp,ti,ab,kw,tw.	3
38	Taxol.mp,ti,ab,kw,tw.	5742
39	Carboplatin.mp,ti,ab,kw,tw.	11128
40	41575-95-4.rn.	0
41	Paraplat.mp,ti,ab,kw,tw.	0
42	Paraplatin.mp,ti,ab,kw,tw.	82
43	Cisplatin.mp,ti,ab,kw,tw.	48077
44	15663-27-1.rn.	36408
45	Platinol.mp,ti,ab,kw,tw.	128
46	Erlotinib.mp,ti,ab,kw,tw.	2611
47	113321-74-6.rn.	0
48	Tarceva.mp,ti,ab,kw,tw.	235
49	Crizotinib.mp,ti,ab,kw,tw.	110
50	877399-52-5.rn.	0
51	Xalkori.mp,ti,ab,kw,tw.	2
52	Docetaxel.mp,ti,ab,kw,tw.	7889
53	114977-28-5.rn.	5615
54	Docefrez.mp,ti,ab.	0
55	Taxotere.mp,ti,ab,kw,tw.	922
56	Vinorelbine.mp,ti,ab,kw,tw.	2932
57	71486-22-1.rn.	2055
58	Navelbine.mp,ti,ab,kw,tw.	356
59	((best adj3 support$).mp,ti,ab,kw,tw.	2186
60	(optim$ adj3 support$).mp,ti,ab,kw,tw.	1744
61	(support$ adj3 care$).mp,ti,ab,kw,tw.	23975
62	(support$ adj3 caring).mp,ti,ab,kw,tw.	324
63	(supportive adj3 treatment$).mp,ti,ab,kw,tw.	2962
64	Or/17-63	154622
65	afatinib.mp,ti,ab,kw,tw.	21
66	BIBW 2992.mp,ti,ab,kw,tw.	46
67	439081-18-2.rn.	0

#	Original Search	hits
68	Tomtovok.mp,ti,ab,kw,tw.	0
69	Tovok.mp,ti,ab,kw,tw.	1
70	Or/65-69	54
71	64 or 70	154628
72	7 and 16 and 71	14166
73	72 and 2002:2012.(sa_year).	6850
74	limit 73 to (human and english language and yr="2002 -Current")	6648
75	74 and "Journal: Article" [Publication Type]	6140

Searches in Cochrane

#	Original Search	hits
1	exp Lung Cancer/ or exp Carcinoma, Non-Small-Cell Lung/	3833
2	non small cell lung cancer.mp.	3214
3	non small cell lung carcinoma.mp.	125
4	non small cell lung tumor.mp.	0
5	non small cell lung tumour.mp.	0
6	nsclc.mp.	2241
7	nonsmall cell lung cancer.mp.	77
8	nonsmall cell lung carcinoma.mp.	33
9	carcinoma/	836
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	6464
11	clinical trial/	2
12	clinical trial.mp.	63510
13	randomized controlled trial/	34
14	(randomized controlled trial or randomised controlled trial).mp.	54016
15	randomization/	20377
16	(randomization or randomisation).mp.	24283
17	single blind procedure/ or double blind procedure/	0
18	(single blind or double blind or triple blind or treble blind or placebo).mp.	199993
19	crossover procedure/	0
20	crossover procedure.mp.	3682
21	placebo/	0
22	placebo.mp.	130076
23	(rct or random allocation or randomly allocated or allocated randomly).mp.	46168
24	Prospective Study/	58598
25	prospective Study.mp.	13562
26	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	323401
27	(Pemetrexed or Alimta).mp.	178
28	(Bevacizumab or avastin).mp.	582
29	(Gemcitabine or Gemzar).mp.	1221
30	(Gefitinib or Iressa).mp.	176
31	(Paclitaxel or Paxene or Taxol).mp.	2541
32	(Carboplatin or Paraplat or Paraplatin).mp.	2132
33	(Cisplatin or Platinol).mp.	6155
34	(Erlotinib or Tarceva).mp.	148
35	(Crizotinib or Xalkori).mp.	0
36	(docetaxel or Docefrez or Docetaxel or Taxotere).mp.	1448
37	(Vinorelbine or Navelbine).mp.	720
38	(Methotrexate or Abitrexate or Folex or Mexate or amethopterin).mp.	4747

#	Original Search	hits
39	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	14973
40	(afatinib or tomtovok or tovok).mp.	3
41	39 or 40	14975
42	10 and 26 and 41	1023
43	42 and 2002:2012.(sa_year).	511
44	limit 43 to humans [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]	507

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

Additional searches were conducted internal to BI by clinical experts.

10.2.6 The inclusion and exclusion criteria.

The inclusion and exclusion strategy are in Table 5.

10.2.7 The data abstraction strategy.

Data was abstracted manually from clinical trial reports and publications.

10.2.8 Supplementary literature review

As the systematic literature review was undertaken in March 2012, a literature search was done using the same databases as before. The terms searched for were "EGFR mutation NSCLC," the reference sections for each paper identified were checked to ensure that no articles were missed. The search aimed to identify systematic reviews that had taken place on EGFR mutation positive patients after March 2012. Each article was assessed and the results compared to existing data, to ensure the values originally used were correct.

- Cardarella 2013 undertook a meta-analysis of EGFR kinase inhibitors. It did not include any studies that had already been identified in the original information search. It also includes results that are not relevant to the patient population of interest. These included patients with wild type EGFR. The article has further information on second and third line treatments.

- Chen 2013, was identified but not considered as it undertook a meta-analysis of maintenance therapy of both gefitinib and erlotinib.

- Chi 2013 looked at the current treatments in advanced stage NSCLC. The trials that were relevant to 1st line treatment were already identified in the original search.

- The results from Inoue 2012 were an update from Maemondo 2010. Updated results showed PFS values were HR = 0.322, 95% CI =0.236 to 0.438, which were within the original confidence interval. The OS values

originally obtained were HR = 0.798, 95% CI = 0.517 to 1.232. Updated values were HR = 0.887, 95% CI =0.634 to 1.241.

- Green 2013 produced a protocol for a Cochrane review, thus no results were reported. Kao 2013 discusses trial results already considered, in addition it identifies trials that are do not involve 1st line treatment.

- Khoon 2013 undertook a meta-analysis on the impact of EGFR inhibitors in NSCLC on PFS and OS. Some information on maintenance therapy and EGFR negative mutations were not relevant to search.

- Petrelli 2012 undertook a meta-analysis of TKI in EGFR mutation positive NSCLC patients, which was not applicable to the search as it measure response rates.

- Gao 2012 undertook a meta-analysis on of TKI in EGFR mutated NSCLC patients. However the six trials considered, have already been included in the NMA.

- Lee 2012 randomly assigned 350 patients to receive erlotinib and 320 to receive placebo. The median overall survival did not differ between groups (erlotinib, 3·7 months, 95% CI 3·2–4·2, vs placebo, 3·6 months, 3·2–3·9.) The unadjusted hazard ratio was HR = 0·94, 95% CI = 0·81–1·10, p=0·46.

- Jänne 2012 undertook a phase II RCT consisiting of erlotinib monotherapy or with carboplatin and paclitaxel in people who have never smoked or were light smokers. The trial did not report the necessary results as HR and not all patients had EGFR mutation positive advanced NSCLC.

- Kao(2013) analysis of EGFR inhibitors as 1st line treatment in NSCLC analysed articles that had been identified in the above article or in the original search.

- The Liverpool Reviews and Implementation Group undertook a summary of first-line chemotherapy for locally advanced or metastatic NSCLC (HTA 2013). This reference was not used as the search took place during the period of January 1990 to August 2010.

- Ren 2012 undertook a meta-analysis in patients with NSCLC who were either smokers or non-smokers, which was not applicable to the search strategy.

- Verduyn 2012 estimated the PFS amongst EGFR positive mutation NSCLC patients in the Netherlands .This NMA was based on a systematic literature search performed in May 2009 thus not included.

References

Brown 2013 Brown T, Pilkington G, Bagust A, Boland A, Oyee J, Tudur-Smith C, Blundell M, Lai M, Martin Saborido C, Greenhalgh J, Dundar Y, Dickson R. Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. Health Technol Assess 2013;17(31).

Cardarella 2013 Cardarella S, Johnson BE. Meta-Analysis of EGFR Kinase Inhibitors: Not Always Greater Than the Sum of Its Parts. J Natl Cancer Inst. 2013.

Chen 2013 Chen XF, Liu YQ, Røe OD, Qian YY, Guo RH, Zhu LJ, Yin YM, Shu YQ. Gefitinib or Erlotinib as Maintenance Therapy in Patients with Advanced Stage Non-Small Cell Lung Cancer: A Systematic Review. PLoS ONE 2013; 8(3):e59314

Chi 2013 Chi A, Remick S, Tse W. EGFR inhibition in non-small cell lung cancer: current evidence and future directions. Biomarker Research 2013, 1:2

Gao 2012 Gao G, Ren S, Li A, et al. Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomized controlled trials. Int J Cancer. 2012:131(5):E822–829.

Green 2013 Green JA, Bates V, Greenhalgh J, Boland A, Jain P, Dickson RC, Dwan K, Vecchio. First-line treatment of advanced epidermal growth factor receptor (EGFR) mutation positive non-squamous non-small cell lung cancer (Protocol) Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd

Inoue 2012 Inoue A, Kobayashi K, Maemondo M, et al: Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatinpaclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol 2012.

Jänne 2012 Jänne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol. 2012;30(17):2063–2069.

Kao 2013 Kao HF, Lin CC, Y JCH. EGFR inhibitors as the first-line systemic treatment for advanced non-small-cell lung cancer. Future Medicine Ltd Future Oncol. (2013) 9(7), 991–1003.

Lee 2012 Lee SM, Khan I, Upadhyay S, et al. First-line erlotinib in patients with advanced non-small-cell lung cancer unsuitable for chemotherapy (TOPICAL): a double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2012;13(11):1161–1170.

Lee 2013 Lee CK, Brown C, Gralla RJ, et al. Impact of epidermal growth factor receptor inhibitor in non–small cell lung cancer on progression-free and overall survival: a meta-analysis. J Natl Cancer Inst. 2013.

Petrelli 2012 Petrelli F, Borgonovo K, Cabiddu M, Barni S. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non–small-cell lung cancer: a meta-analysis of 13 randomized trials. Clin Lung Cancer. 2012;13(2):107–114.

Ren 2012 Ren JH, He WS, Yan GL, Jin M, Yang KY, Wu G. EGFR Mutations in Non-Small-Cell Lung Cancer among Smokers and Non-Smokers: A Meta-Analysis. Environmental and Molecular Mutagenesis 53:78-82 (2012)

Verduyn 2012 Verduyn SC, Biesma B, Schramel FMNH, van der Scheer FW, Langenfeld MK, de Peuter MA, Dingemans AMC. Estimating quality adjusted progression free survival of first-line treatments for EGFR mutation positive non small cell lung cancer patients in The Netherlands. Health and Quality of Life Outcomes 2012, 10:108

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Quality assessments are provided in Section 6.4.3.

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

In line with the standard methodology for NICE submissions, multiple databases were searched. A list of the databases searched is in Table 4.

10.4.2 The date on which the search was conducted.

6 March 2012. Note that this has not been updated as there have been no major studies published or new treatments licensed in the intervening period.

10.4.3 The date span of the search.

2002 to 6 March 2012.

10.4.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategies for the systematic reviews to identify relevant clinical studies and studies for the indirect comparison were the same. Therefore the search terms for EMBASE, MEDLINE and Cochrane are the same as those listed in Section 10.2.4.

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

The three additional records identified through other sources mentioned in the PRISMA diagram, were relevant articles that were published after the systematic search was completed Rosell et al. 2012, Han et al. 2012, and Miller et al. 2012. In addition data from LUX-Lung 6 was included when this was made available.

An additional literature review, detailed in 10.2.8, was also conducted to identify any studies that may have been missed.

10.4.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria are in Table 20. Additional inclusion/exclusion criteria are listed in Section 6.7.2.

10.4.7 The data abstraction strategy.

The data extraction was conducted using a Microsoft Access and Microsoft Excel-based extraction template and include information on the following:

- Study Characteristics (type of study, name of trial/study if applicable, selection criteria, methods of randomization, country, duration, sample size, etc)
- Patient demographics (age, gender, etc)
- Intervention / comparators assessed
- Outcomes of interest (point estimate and measure of variability)
- Statistical analysis conducted

WinBUGS codes

Meta-Analyses of baseline arms for absolute effects – Binary Data

```
# Binomial likelihood, logit link
# Baseline random effects model

model{                                          # *** PROGRAM STARTS
for (i in 1:ns){                                # LOOP THROUGH STUDIES
r[i] ~ dbin(p[i],n[i])                  # Likelihood
logit(p[i]) <- mu[i]                    # Log-odds of response
mu[i] ~ dnorm(m,tau.m)                  # Random effects model
  }
mu.new ~ dnorm(m,tau.m)                         # predictive dist. (log-odds)
m ~ dnorm(0,.0001)                              # vague prior for mean
var.m <- 1/tau.m                                # between-trial variance
tau.m <- pow(sd.m,-2)                   # between-trial precision = (1/between-trial
variance)
sd.m ~ dunif(0,5)                               # vague prior for between-trial SD
logit(R) <- m                                   # posterior probability of response
logit(R.new) <- mu.new                          # predictive probability of response
}
```

Fixed Effects Model for Binary Data

```
# Binomial likelihood, logit link, MTC
# Fixed effects model

model{                                                  # *** PROGRAM STARTS
for(i in 1:ns){                                         # LOOP THROUGH STUDIES
mu[i] ~ dnorm(0,.0001)                                  # vague priors for all trial
baselines
for (k in 1:na[i]) {                                    # LOOP THROUGH ARMS
r[i,k] ~ dbin(p[i,k],n[i,k])            # binomial likelihood
logit(p[i,k]) <- mu[i] + d[t[i,k]]-d[t[i,1]]            # model for linear predictor
rhat[i,k] <- p[i,k] * n[i,k]            # expected value of the numerators
dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))        #Deviance contribution
+ (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
  }
resdev[i] <- sum(dev[i,1:na[i]])                        # summed residual deviance
contribution for this trial
}
totresdev <- sum(resdev[])                              #Total Residual Deviance
d[1]<- 0                                # treatment effect is zero for reference
treatment
for (k in 2:nt)  { d[k] ~ dnorm(0,.0001) }              # vague priors for treatment
effects

# pairwise ORs and LORs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
or[c,k] <- exp(d[k] - d[c])
lor[c,k] <- (d[k]-d[c])
      }
}

# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A, with precision (1/variance)
precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }
```

Fixed Effects model for time-to-event data

```
# Normal likelihood, Relative Effect Data
# Fixed Effects model.

model{                                  # *** PROGRAM STARTS

for(i in 1:ns){                                 # LOOP THROUGH STUDIES
delta[i,1] <- 0                                 # treatment effect is zero for control
arm
for (k in 2:na[i]) {                            # LOOP THROUGH ARMS
prec[i,k]<- 1/(se[i,k]*se[i,k])
LHR[i,k] ~ dnorm(delta[i,k],prec[i,k])                  # binomial likelihood
dev[i,k]<- (LHR[i,k] - delta[i,k])*(LHR[i,k] - delta[i,k])*prec[i,k]
  }
resdev[i] <- sum(dev[i,2:na[i]])                        # summed residual deviance
                                        #contribution for this trial

for (k in 2:na[i]) {                            # LOOP THROUGH ARMS
                                        # trial-specific LOR distributions
delta[i,k] <- d[t[i,k]] - d[t[i,1]]                           # mean of LOR
distributions
   }
}
totresdev <- sum(resdev[])                      #Total Residual Deviance
d[1]<- 0                                        # treatment effect is zero
                                        #for reference treatment
for (k in 2:nt)  { d[k] ~ dnorm(0,.0001)}               # vague priors for treatment
effects


# pairwise HRs and LHRs for all possible pair-wise comparisons
for (c in 1:(nt-1)) {  for (k in (c+1):nt) {
HR[c,k] <- exp(d[k] - d[c])
HR[k,c] <- exp(d[c] - d[k])

      }
# ranking
for (k in 1:nt) {
   rk[k] <- rank(d[],k)
   best[k] <- equals(rk[k],1)                           #calculate probability that
                                        #treat k is best
}
```

Random Effects model for time-to-event data

```
# Normal likelihood, Relative Effect Data
# Random Effects model.

model{                        # *** PROGRAM STARTS

for(i in 1:ns){                       # LOOP THROUGH STUDIES

delta[i,1] <- 0                       # treatment effect is zero for control arm

for (k in 2:na[i]) {                  # LOOP THROUGH ARMS

prec[i,k]<- 1/(se[i,k]*se[i,k])

LHR[i,k] ~ dnorm(delta[i,k],prec[i,k])       # binomial likelihood

dev[i,k]<- (LHR[i,k] - delta[i,k])*(LHR[i,k] - delta[i,k])*prec[i,k]
  }

 resdev[i] <- sum(dev[i,2:na[i]])             # summed residual deviance
contribution for this trial

for (k in 2:na[i]) {                  # LOOP THROUGH ARMS
delta[i,k] ~ dnorm(md[i,k],tau)              # trial-specific LOR distributions

md[i,k] <- d[t[i,k]] - d[t[i,1]]             # mean of LOR distributions

   }

}

totresdev <- sum(resdev[])            #Total Residual Deviance

d[1]<- 0                              # treatment effect is zero for reference
treatment

for (k in 2:nt)  { d[k] ~ dnorm(0,.0001)}    # vague priors for treatment effects

sd ~ dunif(0,2)

tau <- pow(sd,-2)

# pairwise HRs and LHRs for all possible pair-wise comparisons

for (c in 1:(nt-1)) {  for (k in (c+1):nt) {

HR[c,k] <- exp(d[k] - d[c])

HR[k,c] <- exp(d[c] - d[k])

      }

# ranking
for (k in 1:nt) {
   rk[k] <- rank(d[],k)
   best[k] <- equals(rk[k],1)         #calculate probability that treat k is best
}
```

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

A grading system was devised to rank these RCT's according to their quality. A score of 3 was given for any question that was answered "Yes". A score of 1 was given to any question that was answered as "Not Clear" and a score of 0 was given to "No" or "N/A". For questions 5 and 6, an answer of "No" receives 3 points and "Yes" 0 points.

The maximum possible score would be 24 (eight questions of three points). Using this scoring, the following grades were given to each study:

A score of 19-24: Excellent
A score of 13-18: Good
A score of 7-12: Average
A score of 0-6: Poor

Table 143: Criteria for the assessment of randomized trials included in the MTC

	Was randomis-ation carried out appro-priately?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Was the conceal-ment of treatment allocation ade-quate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis?	If so, was this appropriate and were appropriate methods used to account for missing data?	Overall Grade
Chang et al. 2001	Information taken from TA192 NICE submission, which was included in the MTC (NICE 2009a, 2010)								
Comella et al. 2000	Yes	Not Clear	Not Clear	Yes	No	Not Clear	Yes	Yes	Good
Fossella et al. 2003	Yes	No	N/A	Yes	Not Clear	No	Yes	Yes	Good
Gridelli et al. 2003	Yes	No	Yes	Yes	No	No	Yes	Not Clear	Good
Han et al. 2012	Not Clear	Not Clear	NA	Yes	No	No	Yes	Not Clear	Average
LUX-Lung 6	Yes	No	No	Yes	Not Clear	Not Clear	Yes	Yes	Good
Maemondo et al. 2010	Not Clear	No	N/A	Yes	No	No	Yes	Not Clear	Average
Mazzanti et al. 2003	Yes	NR	NR	Yes	No	No	Yes	Yes	Good
Melo et al. 2002									
Mitsudomi et al. 2010	Yes	No	N/A	Yes	Not Clear	No	Yes	Not Clear	Average
Mok et al. 2009	Not Clear	No	N/A	Yes	Not Clear	No	Yes	Not Clear	Average
Rosell et al. 2002	Yes	Not Clear	Not Clear	Yes	No	Not Clear	Yes	Yes	Good
Rossell et al. 2012	Yes	No	No	Yes	Not Clear	Not Clear	Yes	Not Clear	Average
Scagliotti et al. 2002	Yes	No	N/A	Yes	Not Clear	No	Yes	Not Clear	Average
Scagliotti et al. 2009	Yes	Not Clear	Not Clear	Yes	Not Clear	Not Clear	Not Clear	Not Clear	Average
Schiller et al. 2002	Yes	Not Clear	Not Clear	Yes	Not Clear	Not Clear	No	No	Average
Smit et al. 2003	Yes	No	N/A	No	Not Clear	No	Yes	Yes	Average
Thomas et al. 2006	Yes	Not Clear	No	Yes	No	Not Clear	Yes	Yes	Good
LUX-Lung 3	Yes	No	No	Yes	No	Not Clear	Yes	Yes	Good
Zatloukal et al. 2003	Not Clear	No	N/A	Yes	Not Clear	No	Yes	Not Clear	Average

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable as no non-RCT studies were considered appropriate for this analysis.

10.6.2 The date on which the search was conducted.

Not applicable as no non-RCT studies were considered appropriate for this analysis.

10.6.3 The date span of the search.

Not applicable as no non-RCT studies were considered appropriate for this analysis.

10.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable as no non-RCT studies were considered appropriate for this analysis.

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable as no non-RCT studies were considered appropriate for this analysis.

10.6.6 The inclusion and exclusion criteria.

Not applicable as no non-RCT studies were considered appropriate for this analysis.

10.6.7 The data abstraction strategy.

Not applicable as no non-RCT studies were considered appropriate for this analysis.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable as no non-RCT studies were considered appropriate for this analysis.

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable as the main trials were not designed primarily to assess safety outcomes.

10.8.2 The date on which the search was conducted.

Not applicable as the main trials were not designed primarily to assess safety outcomes.

10.8.3 The date span of the search.

Not applicable as the main trials were not designed primarily to assess safety outcomes.

10.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable as the main trials were not designed primarily to assess safety outcomes.

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable as the main trials were not designed primarily to assess safety outcomes.

10.8.6 The inclusion and exclusion criteria.

Not applicable as the main trials were not designed primarily to assess safety outcomes.

10.8.7 The data abstraction strategy.

Not applicable as the main trials were not designed primarily to assess safety outcomes.

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable as the main trials were not designed primarily to assess safety outcomes.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline

- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Databases that were searched are given in Table 62.

10.10.2 The date on which the search was conducted.

The data extraction was conducted (on the 6th March, 2012) using a Microsoft Access and Microsoft Excel-based extraction template.

10.10.3 The date span of the search.

2002 to 6 March 2012.

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Searches in Embase

	Search String	Hits
1	exp pharmacoeconomics/	134953
2	pharmacoeconomics.mp.	6612
3	pharmacoeconomic$.mp.	8631
4	exp health economics/	473892
5	health economics.mp.	19663
6	exp economic aspect/	820881
7	economic aspect.mp.	55090
8	economic aspect.mp.	55090
9	economic evaluation.mp.	10843
10	exp "cost utility analysis"/	4097
11	cost utility.mp.	5346
12	(cost$ and (effect$ or utili$ or benefit$)).mp.	293737
13	(cost$ and minim$).mp.	29286
14	(cost$ or (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$))).mp.	502084
15	(economic$ and (evaluat$ or analy$)).mp.	125033
16	(economic$ and model$).mp.	40022
17	exp "cost minimization analysis"/	2055
18	cost minimisation analysis.mp.	177
19	exp "cost effectiveness analysis"/	78695
20	cost effectiveness.mp.	91793
21	cost effectiveness analysis.mp.	80239
22	cost effectiveness ratio.mp.	3711
23	cost efficiency analysis.mp.	38
24	exp "cost benefit analysis"/	55601
25	cost benefit.mp.	58848
26	cost benefit analysis.mp.	56650

	Search String	Hits
27	(cost$ or costly or costing$ or costed).tw.	340565
28	or/1-27	1018560
29	exp lung tumo?r/	172111
30	lung neoplasms.mp.	3354
31	exp lung non small cell cancer/	44057
32	(lung adj3 canc:).mp.	123699
33	(lung adj3 carcinoma:).mp.	35428
34	(lung adj3 tumo?r:).mp.	53961
35	(lung adj3 neoplasm:).mp.	7326
36	29 or 30 or 31 or 32 or 33 or 34 or 35	196665
37	28 and 36	8751
38	limit 37 to (human and english language)	6898
39	38 not (editorial or letter or comment).pt.	6312
40	limit 39 to yr="2002 - 2012"	5091
41	40 and "Journal: Article" [Publication Type]	2405

Searches in Medline

	Search String	Hits
1	Economics, Hospital/	9532
2	Economics, Nursing/ or Economics/ or Economics, Medical/ or Economics, Pharmaceutical/	40725
3	pharmacoeconomic$.tw.	2821
4	health economic$.tw.	3087
5	economic evaluation.tw.	4240
6	economic aspect.tw.	119
7	cost utility.tw.	2009
8	cost utility analysis.tw.	992
9	cost minimisation.tw.	179
10	cost minimization.tw.	563
11	exp Cost-Benefit Analysis/	53855
12	cost benefit analysis.tw.	2365
13	cost benefit.tw.	6406
14	cost effectiveness analysis.tw.	4617
15	cost effectiveness.tw.	29059
16	cost effectiveness ratio.tw.	2682
17	cost efficiency analysis.tw.	30
18	exp "Costs and Cost Analysis"/	164383
19	cost analysis.tw.	3384
20	(cost$ and (effect$ or utili$ or benefit$)).tw.	162457
21	(cost$ and (minim$ or stud$ or effic$)).tw.	160478
22	(cost$ or costly or costing$ or costed).tw.	301872
23	(cost$ or (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$))).tw.	301872
24	(economic$ and (evaluat$ or analy$)).tw.	53240
25	models, economic/	5032
26	(economic$ and model$).mp.	30320
27	(economic$ and model$).tw.	19237
28	or/1-27	460957
29	exp Lung Neoplasms/	156417
30	exp Carcinoma, Non-Small-Cell Lung/	25982
31	(lung$ adj3 canc$).mp.	82034
32	(lung$ adj3 carcinoma$).mp.	22653
33	(lung$ adj3 tumo?r$).mp.	16106
34	(lung$ adj3 neoplasm$).mp.	145654
35	or/30-34	173979
36	28 and 35	2849

	Search String	Hits
37	36 not (editorial or letter or comment).pt.	2734
38	limit 37 to (english language and humans)	2150
39	limit 38 to yr="2002 - 2012"	1244

Searches in EconLit

	Search String	Hits
1	nonsmall or (non small) or (large cell) {No Related Terms}	1840
2	pulmonary or lung {No Related Terms}	31
3	1 and 2	1
4	nsclc or nscpc {No Related Terms}	0
5	3 or 4	1

Searches in NHS EED

	Search String	Hits
1	nonsmall or (non small) or (large cell) {No Related Terms}	109
2	pulmonary or lung {No Related Terms}	251
3	1 and 2	59
4	nsclc or nscpc {No Related Terms}	2
5	3 or 4	60

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable as no additional searches were carried out.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

Not applicable as no eligible studies were identified.

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Databases that were searched are given in Table 62.

10.12.2 The date on which the search was conducted.

The data extraction was conducted (on the 6th March, 2012) using a Microsoft Access and Microsoft Excel-based extraction template.

10.12.3 The date span of the search.

2002 to 6 March 2012.

10.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Searches in Embase

	Search String	Hits
1	non small cell lung cancer$.mp.	30964
2	non small cell lung carcinoma$.mp.	3392
3	non small cell pulmonary carcinoma$.mp.	14
4	non small cell lung tumo?r$.mp.	130
5	non small cell pulmonary tumo?r$.mp.	1
6	non small cell lung neoplasm$.mp.	11
7	non small cell pulmonary neoplasm$.mp.	0
8	nsclc.mp.	22101
9	nscpc.mp.	2
10	nonsmall cell lung cancer$.mp.	1583
11	nonsmall cell pulmonary cancer$.mp.	1
12	nonsmall cell lung carcinoma$.mp.	426
13	nonsmall cell pulmonary carcinoma$.mp.	0
14	nonsmall cell lung tumo?r$.mp.	6
15	nonsmall cell pulmonary tumo?r$.mp.	0
16	nonsmall cell lung neoplasm$.mp.	0
17	nonsmall cell pulmonary neoplasm$.mp.	0
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	37546
19	((European Organisation for Research and Treatment of Cancer) or EORTC-QLQ-C30 or EORTC QLQ-C30 or EORTC QLQ C30).mp.	2329
20	(EORTC-QLQ-LC13 or EORTC QLQ-LC13 or EORTC QLQ LC13).mp.	24
21	(FACT-G or FACT G or FACTG or FACT-L or FACT L or FACTL).mp.	580
22	LCSS.mp.	95
23	(hui or health utilities index).mp.	1524
24	(TTO or time trade off).mp.	1105
25	(visual analog or visual analogue).mp.	40306
26	(euroqol 5d or eq5d or eq-5d or euroqol).mp.	4367
27	(SF-36 or Short form 36).mp.	19053
28	(SF-6D or Short form 6d).mp.	437
29	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	65146
30	18 and 29	269

Searches in Medline

	Search String	Hits

	Search String	Hits
1	exp Lung Neoplasms/	156417
2	exp Carcinoma, Non-Small-Cell Lung/	25982
3	(lung$ adj3 canc$).mp.	82034
4	(lung$ adj3 carcinoma$).mp.	22653
5	(lung$ adj3 tumo?r$).mp.	16106
6	(lung$ adj3 neoplasm$).mp.	145654
7	or/1-6	183745
8	quality adjusted life.mp.	7859
9	(qaly$ or qald$ or qale$ or qtime$).tw.	4056
10	qol.mp.	14933
11	qaly.mp.	3249
12	quality adjusted.mp.	8099
13	adjusted life.mp.	8578
14	quality of life.mp.	158255
15	exp "quality of life"/	98827
16	exp Quality-Adjusted Life Years/	5623
17	Quality adjusted life year$.mp.	7719
18	disability adjusted life.tw.	940
19	daly$.tw.	948
20	Health$ year$ equivalent$.tw.	37
21	exp "Value of Life"/	5212
22	Health-related quality of life.mp.	17007
23	Health quality.mp.	635
24	Health related quality.mp.	17034
25	hrqol.mp.	5427
26	hrql.mp.	1944
27	Quality of well being.mp.	299
28	qwb.mp.	151
29	Wellbeing.mp.	4079
30	health utilities index.mp.	453
31	HUI.mp.	578
32	health utilit$.mp.	862
33	(hui or hui1 or hui2 or hui3).tw.	753
34	disutil$.tw.	177
35	utility.mp.	95777
36	utility analysis.mp.	1081
37	assessment of quality of life.mp.	1010
38	time trade off.mp.	637
39	TTO.mp.	492
40	person trade off.mp.	36
41	pto.mp.	498
42	standard gamble.mp.	595
43	SG.mp.	4803
44	visual analog$ scale.mp.	19683
45	VAS.mp.	23988
46	rating scale.mp. or rating scale/	25588
47	euroqol.mp.	1635
48	(euroqol 5d or eq5d or eq-5d or euroqol).mp.	2854
49	short form 36.mp. or exp Short Form 36/	5076
50	(shortform36 or sf36 or sf-36).mp.	10955
51	(short form 6d or shortform 6d or sf6d or sf-6d or sf 6d).mp.	297
52	(willingness adj3 pay).mp.	1779
53	wtp.mp.	693
54	exp Health Surveys/	355074
55	survey.mp.	271172
56	exp Questionnaires/	257567

	Search String	Hits
57	health assessment questionnaire.mp.	2242
58	general health questionnaire.mp.	2932
59	exp Health Status/	89037
60	exp Health Status Indicators/	167107
61	Health status.mp.	89943
62	patient satisfaction.mp. or exp patient satisfaction/	59768
63	wtp.mp.	693
64	or/8-63	1109863
65	7 and 64	10414
66	limit 65 to (english language and humans)	8132
67	66 and "Journal Article" [Publication Type]	7731
68	limit 67 to yr="2002 -Current"	4773

Searches in EconLit

	Search String	Hits
1	non small cell lung cancer$.mp.	8
2	non small cell lung carcinoma$.mp.	0
3	non small cell pulmonary carcinoma$.mp.	0
4	non small cell lung tumo?r$.mp.	0
5	non small cell pulmonary tumo?r$.mp.	0
6	non small cell lung neoplasm$.mp.	0
7	non small cell pulmonary neoplasm$.mp.	0
8	nsclc.mp.	1
9	nscpc.mp.	0
10	nonsmall cell lung cancer$.mp.	0
11	nonsmall cell pulmonary cancer$.mp.	0
12	nonsmall cell lung carcinoma$.mp.	0
13	nonsmall cell pulmonary carcinoma$.mp.	0
14	nonsmall cell lung tumo?r$.mp.	0
15	nonsmall cell pulmonary tumo?r$.mp.	0
16	nonsmall cell lung neoplasm$.mp.	0
17	nonsmall cell pulmonary neoplasm$.mp.	0
18	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	8
19	((European Organisation for Research and Treatment of Cancer) or EORTC-QLQ-C30 or EORTC QLQ-C30 or EORTC QLQ C30).mp.	2
20	(EORTC-QLQ-LC13 or EORTC QLQ-LC13 or EORTC QLQ LC13).mp.	0
21	(FACT-G or FACT G or FACTG or FACT-L or FACT L or FACTL).mp.	0
22	LCSS.mp.	2
23	(hui or health utilities index).mp.	67
24	(TTO or time trade off).mp.	101
25	(visual analog or visual analogue).mp.	39
26	(euroqol 5d or eq5d or eq-5d or euroqol).mp.	78
27	(SF-36 or Short form 36).mp.	26
28	(SF-6D or Short form 6d).mp.	25
29	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28	261
30	18 and 29	0

Searches in NHS EED

	Search String	Hits
1	exp Neoplasms/	1775
2	non small cell lung cancer$.mp. [mp=title, text, subject heading word] {No Related Terms}	50
3	non small cell lung carcinoma$.mp. [mp=title, text, subject heading word] {No Related Terms}	50

	Search String	Hits
4	non small cell pulmonary carcinoma$.mp. [mp=title, text, subject heading word] {No Related Terms}	1
5	non small cell lung tumo?r$.mp. [mp=title, text, subject heading word] {No Related Terms}	50
6	non small cell pulmonary tumo?r$.mp. [mp=title, text, subject heading word] {No Related Terms}	1
7	non small cell lung neoplasm$.mp. [mp=title, text, subject heading word] {No Related Terms}	50
8	non small cell pulmonary neoplasm$.mp. [mp=title, text, subject heading word] {No Related Terms}	1
9	nsclc.mp. [mp=title, text, subject heading word] {No Related Terms}	0
10	nscpc.mp. [mp=title, text, subject heading word] {No Related Terms}	0
11	nonsmall cell lung cancer$.mp. [mp=title, text, subject heading word] {No Related Terms}	0
12	nonsmall cell pulmonary cancer$.mp. [mp=title, text, subject heading word] {No Related Terms}	0
13	nonsmall cell lung carcinoma$.mp. [mp=title, text, subject heading word] {No Related Terms}	0
14	nonsmall cell pulmonary carcinoma$.mp. [mp=title, text, subject heading word] {No Related Terms}	0
15	nonsmall cell lung tumo?r$.mp. [mp=title, text, subject heading word] {No Related Terms}	0
16	nonsmall cell pulmonary tumo?r$.mp. [mp=title, text, subject heading word] {No Related Terms}	0
17	nonsmall cell lung neoplasm$.mp. [mp=title, text, subject heading word] {No Related Terms}	0
18	nonsmall cell pulmonary neoplasm$.mp. [mp=title, text, subject heading word] {No Related Terms}	0
19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	1775
20	((European Organisation for Research and Treatment of Cancer) or EORTC-QLQ-C30 or EORTC QLQ-C30 or EORTC QLQ C30).mp. [mp=title, text, subject heading word] {No Related Terms}	21
21	(EORTC-QLQ-LC13 or EORTC QLQ-LC13 or EORTC QLQ LC13).mp. [mp=title, text, subject heading word] {No Related Terms}	0
22	(FACT-G or FACT G or FACTG or FACT-L or FACT L or FACTL).mp. [mp=title, text, subject heading word] {No Related Terms}	0
23	LCSS.mp. [mp=title, text, subject heading word] {No Related Terms}	0
24	(hui or health utilities index).mp. [mp=heading words, abstract, title, country as subject] {No Related Terms}	3
25	(TTO or time trade off).mp. [mp=heading words, abstract, title, country as subject] {No Related Terms}	41
26	(visual analog or visual analogue).mp. [mp=heading words, abstract, title, country as subject] {No Related Terms}	3
27	(euroqol 5d or eq5d or eq-5d or euroqol).mp. [mp=heading words, abstract, title, country as subject] {No Related Terms}	6
28	(SF-36 or Short form 36).mp. [mp=heading words, abstract, title, country as subject] {No Related Terms}	138
29	(SF-6D or Short form 6d).mp. [mp=heading words, abstract, title, country as subject] {No Related Terms}	64
30	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	216
31	19 and 30	34

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable as not additional databases were searched.

10.12.6 The inclusion and exclusion criteria.

These are shown in Table 80.

10.12.7 The data abstraction strategy.

The search was conducted using a Microsoft Access and Microsoft-Excel based extraction template, processed through Reference Manager 11. The following information regarding the studies was captured:

- Sample Size
- Health States
- Method of Elicitation
- Method of Valuation
- Results

The methodological quality of the studies included in the systematic review was assessed using the criteria for methodological quality indicated in the Centre for Reviews and Dissemination (2009) which is also the quality assessment criteria listed in NICE's guidance (2013).

The aim of the critical assessment is to evaluate the validity of studies chosen for inclusion in the review. The framework assesses the potential for studies to be impacted by biases affecting validity, including:

- Selection bias, arising from systematic differences between comparison groups in terms of performance and prognosis
- Measurement bias, arising from systematic differences in how outcomes are ascertained and measured
- Attrition bias arising from systematic differences between comparison groups in how participants are withdrawn or excluded from the study groups.

The types of study and reason for rejection are provided in Table 144.

Table 144: Summary of Excluded Studies from the HRQL Systematic Review

	Disease	Intervention	Patient Population	Outcomes	Study Type
Cross-Sectional	1	1	3	5	0
Meta-analysis	0	0	0	2	0
Retrospective	1	0	2	0	0
Prospective	7	8	3	32	0
Randomized Cohort	0	0	0	1	0
RCT	1	8	3	43	0
Systematic Review	1	3	3	3	0
Economic	0	3	0	7	1
Review	1	0	1	2	0

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Databases that were searched are given in Table 62.

10.13.2 The date on which the search was conducted.

The data extraction was conducted (on the 6th March, 2012) using a Microsoft Access and Microsoft Excel-based extraction template.

10.13.3 The date span of the search.

2002 to 6 March 2012.

10.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategies for the systematic review to identify relevant cost-effectiveness studies were the same as those used for the cost and resource-

use systematic reviews. Therefore the search terms for EMBASE, MEDLINE, NHS EED and EconLit are the same as those listed in Section 10.2.4.

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No other searches were undertaken.

10.13.6 The inclusion and exclusion criteria.

Publications identified through the systematic review are evaluated in a three-step procedure in order to assess whether or not they should be included for data extraction and model population. The identified abstracts through the database search (1st step) were reviewed in using an inclusion/exclusion criteria (listed in Table 80), and if the abstract contained sufficient information to state that the publication did not meet this criteria, the publication was excluded. If the publication was not excluded, the full paper was retrieved, and again reviewed and subjected to the same inclusion/exclusion criteria. If the publication did meet the inclusion criteria after full paper review, the publication was included in the systematic review. The inclusion / exclusion criteria to use against the publications were in the PICOS format (i.e. population, intervention, comparators, outcomes, study type) (Table 80).

10.13.7 The data abstraction strategy.

The data extraction was conducted using a Microsoft Access and Microsoft Excel-based extraction template, processed through Reference Manager 11 and included information on the following for the economic evaluation section:

- Type of economic evaluation
- Study Objective Interventions
- Location/Setting Methods
- Analytical approach
- Effectiveness data
- Monetary benefit and utility valuations
- Measure of benefit
- Cost data
- Analysis of uncertainty Results
- Authors' conclusions
- Country(ies) where study was performed
- Summary of model
- Patient population (average age in years)
- QALYs (intervention, comparator)
- Costs (currency) (intervention, comparator)
- ICER (per QALY gained)

Unit costs, resource use and costs of illnesses were tabulated by item and utilization or cost. The methodological quality of the studies included in the systematic review was assessed using the criteria for methodological quality indicated in the Centre for Reviews and Dissemination (2009)which is also the quality assessment criteria listed in NICE's guidance (NICE 2013). The aim of the critical assessment is to evaluate the validity of studies chosen for inclusion in the review. The framework assesses the potential for studies to be impacted by biases affecting validity, including:

- Selection bias, arising from systematic differences between comparison groups in terms of performance and prognosis;
- Measurement bias, arising from systematic differences in how outcomes are ascertained and measured;

Attrition bias arising from systematic differences between comparison groups in how participants are withdrawn or excluded from the study groups.

11 Related procedures for evidence submission

11.1 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission.

There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential

information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been

put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.