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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer

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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

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ABBREVIATIONS

AE	Adverse event
AUC	Area Under the Curve
BNF	British National Formulary
BSA	Body surface area
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CTCAE	Common terminology criteria for adverse events
CTR	Clinical trial report
DIC	Deviance Information Criterion
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer core quality of life questionnaire
EORTC QLQ-LC13	A modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials
EPAR	European public assessment report
EQ-5D	EuroQol-5 dimension
ERG	Evidence Review Group
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
LY	Life year
MS	Manufacturer's submission
MTC	Mixed treatment comparison
NICE	National Institute for Health and Care Excellence (formerly known as the National Institute for Health and Clinical Excellence)
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease
PFS	Progression-free survival
PPS	Post-progression survival
PS	Performance status
PSA	Probability Sensitivity Analysis
PSS	Personal Social Services
QALY	Quality adjusted life year
SA	Sensitivity Analysis
SAE	Serious adverse event
SAP	Statistical analysis plan
STA	Single technology appraisal
StD	Standard deviation
TKI	Tyrosine kinase inhibitor
TTP	Time to progression

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence have been submitted to NICE from Boehringer Ingelheim in support of the use of afatinib (Giotrif) for the treatment of epidermal growth factor receptor mutation positive (EGFR-positive), locally advanced or metastatic non-small cell lung cancer (NSCLC). In Europe, afatinib is licensed for the treatment of EGFR tyrosine kinase inhibitor (TKI)-naïve adult patients with locally advanced or metastatic NSCLC with activating EGFR mutation(s), i.e. the EGFR-positive population.

1.2 Critique of the decision problem in the manufacturer's submission

The patient population and intervention addressed by the manufacturer's submission (MS) reflect its licence. However, the ERG notes that afatinib's licence is for patients who are TKI-naïve. The manufacturer presents clinical and cost-effectiveness evidence to support the use of afatinib for TKI-naïve patients in the first-line setting but does not present clinical or cost-effectiveness evidence to support the use of afatinib for TKI-naïve patients in a second- or third-line setting. The comparators (erlotinib and gefitinib) to which afatinib is compared are appropriate. Outcomes addressed in the decision problem include overall survival (OS), progression-free survival (PFS), response rates, adverse events (AEs) and health-related quality of life (HRQoL). These outcomes are standard in this disease area and are appropriate.

1.3 Summary of clinical effectiveness evidence submitted by the manufacturer

The manufacturer presents direct and indirect evidence to support use of afatinib. Direct evidence comes from two randomised controlled trials (RCTs) (LUX-Lung 3 and LUX-Lung 6) which compare afatinib (at a starting dose of 40mg/day) to chemotherapy (pemetrexed/cisplatin and gemcitabine/cisplatin, respectively) in patients who have both adenocarcinoma and activating EGFR mutations. In both trials afatinib results in statistically significantly improved PFS but not OS compared with chemotherapy; however, OS data are not yet fully mature. Additional evidence is presented from LUX-Lung 2, a single-arm phase II trial in patients treated in the first- and second-line setting (after chemotherapy) of EGFR TKI-naïve EGFR-positive patients. Initially all patients were started on 50mg/day but the trial protocol was amended and all new patients were then started on 40mg/day. The most

common AEs reported across the three trials are diarrhoea and rash/acne; these AEs are also commonly experienced by patients treated with erlotinib and gefitinib. There is currently no direct evidence comparing afatinib with erlotinib or gefitinib. Hence, the manufacturer undertook a mixed treatment comparison (MTC). The results of the MTC did not show any advantages or disadvantages for afatinib over either erlotinib or gefitinib.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG notes that patients in LUX-Lung 3 and LUX-Lung 6 are patients with adenocarcinoma with activating EGFR mutations in the first-line setting. In the final scope issued by NICE, the decision problem states that, in a first-line setting, erlotinib and gefitinib are the appropriate comparators to afatinib. However, the comparators in the two pivotal RCTs (LUX-Lung 3 and LUX-Lung 6) are chemotherapies (pemetrexed/cisplatin and gemcitabine/cisplatin, respectively). This means that the clinical effectiveness evidence derived from these two trials cannot be used directly to inform the decision problem.

Erlotinib and gefitinib are recommended by NICE for the treatment of EGFR-positive patients in a first-line setting. In 2010 gefitinib was the first targeted therapy (TKI) to be approved by NICE for patients with activating EGFR mutations. The Appraisal Committee decision was primarily driven by a statistically significant PFS gain for gefitinib patients compared with chemotherapy (paclitaxel/carboplatin) patients; at the time, the only OS data available were from an interim analysis of immature data (that is, only 37% of patients had died). The Appraisal Committee discussed whether PFS gain might correlate with OS gain for patients with lung cancer and they noted that there was uncertainty around this correlation. The ERG notes that guidance was based on evidence that did not include pemetrexed/cisplatin as a comparator for cost effectiveness. This was despite results of the updated MTC described in the manufacturer's clarification response showing that pemetrexed/cisplatin was superior to other doublet chemotherapy regimens and closer to gefitinib in terms of PFS and OS. In 2012, NICE approved erlotinib for patients with activating EGFR mutations. Again, the Appraisal Committee's decision was primarily driven by a statistically significant PFS gain for erlotinib patients compared with chemotherapy patients as, at the time, mature OS data were not available. The Appraisal Committee noted the advice provided by clinical experts, that erlotinib and gefitinib were similar treatments with similar efficacy and levels of adverse reactions, and concluded that an assumption of equal clinical benefit for erlotinib and gefitinib was appropriate. However, it is now known that final results of the pivotal gefitinib trial show no OS benefit for gefitinib patients compared with chemotherapy patients. The evidence from the LUX-Lung 3 and LUX-Lung 6 trials support these findings, i.e., that

despite a statistically significant improvement in PFS there does not appear to be a corresponding gain in OS for TKIs vs chemotherapy. High crossover rates in trials often mask real differences in OS, however, the ERG's analysis of LUX-Lung 3 data shows an OS advantage in non-Asian patients, despite treatment crossover, but continues to show no OS gain in the Asian subgroup. Therefore, crossover does not provide a simple explanation for the lack of OS gain in all trials. LUX-Lung 3 compares afatinib to pemetrexed/cisplatin and is the first trial to show a benefit (in terms of PFS but not OS) of a TKI over pemetrexed/cisplatin.

The ERG considered the results of the manufacturer's original MTC to be flawed, primarily due to inclusion of EGFR-positive and EGFR unknown/mixed patient populations in the networks. Via the clarification process, the ERG asked the manufacturer to limit the MTC to EGFR-positive patients only and to conduct a series of sensitivity analyses. By limiting the MTC to EGFR-positive patients only, there are seven studies in the networks and these comprise predominantly Asian patients. The results of all exploratory analyses show that in LUX-Lung 3, expected survival for both OS and PFS is longer in Asian patients than in non-Asian patients. Based on this evidence, the ERG considers that it is not appropriate to include the EURTAC trial, which included only European patients, in any MTC. However, excluding the EURTAC trial from the networks means that a) it is no longer possible to compare afatinib with erlotinib and b) the comparison of afatinib with gefitinib is based on clinical effectiveness data from a wholly Asian population, which means that the results may not be generalisable to patients in England and Wales. The ERG emphasises that the results of the Asian vs non-Asian survival analyses comprise new information that has not previously been available to the Appraisal Committee.

Furthermore, the ERG notes that results of the manufacturer's and the ERG's MTCs rely on the validity of the assumption of proportional hazards. The ERG considers that, for many of the studies included in the MTC, this assumption does not hold for PFS or OS hazard ratios. Careful examination of Kaplan-Meier curves by the ERG identified that several of the PFS and OS curves cross. The impact of this methodological weakness on size of the estimated hazard ratios is unknown.

In conclusion, due to data limitations, the ERG does not have full confidence in the results of any of the MTCs conducted by the manufacturer or the ERG. The ERG considers that none of the results from any of the MTCs should be used in the economic model to estimate incremental cost-effectiveness ratios (ICERs), as to do so would lead to results that were of uncertain reliability and/or not relevant to patients in England and Wales.

1.5 Summary of cost effectiveness evidence submitted by the manufacturer

The manufacturer developed a de novo partitioned survival model. It is constructed in Microsoft Excel and structured using three patient health states (PFS [stable disease], progressed disease and death). Variants of this model structure have been used in the modelling of metastatic oncology for a number of previous NICE STAs. Parametric survival models, based on hazard ratios produced from the MTC, have been used to project PFS and OS over the 10-year model period. Trial data have not been used directly in the model. The model perspective is that of the UK NHS. Resource use, costs and utilities were estimated based on information from LUX-Lung 3 and LUX-Lung 1 trials, as well as from published sources.

A Patient Access Scheme (PAS) has been accepted. For the comparison of afatinib vs erlotinib the manufacturer's ICER per quality adjusted life year (QALY) gained is £10,079 and the ICER per life year (LY) gained is [redacted]. For the comparison of afatinib vs gefitinib the ICER per QALY gained is £17,933 and the ICER per LY gained is £12,062. The manufacturer carried out a wide range of deterministic sensitivity analyses for these two comparisons. The results from the ten parameters that had the most influence on the ICER per QALY gained ranged from £9,104 to £36,718 per QALY gained for afatinib vs erlotinib and from £7,135 to £54,800 per QALY gained for afatinib vs gefitinib. The results of the manufacturer's probabilistic sensitivity analyses (PSA) suggest that there are 100% and 81% chances respectively that the ICERs for afatinib vs erlotinib and for afatinib vs gefitinib are less than £30,000 per QALY gained.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG is satisfied with the search strategy employed by the manufacturer to identify cost-effectiveness studies, and is reasonably confident that no other relevant published articles exist.

Overall, the ERG found that the manufacturer's model lacked credibility and could not be relied upon to generate robust ICERs for the comparison of afatinib vs erlotinib or afatinib vs gefitinib. This was demonstrated by the fact that the modelled PFS survival projection for afatinib did not reflect afatinib LUX-Lung 3 trial data from which it was derived. In addition, the ERG considered that, due to data limitations and methodological weaknesses, it was not appropriate to use the hazard ratios produced by the MTC in the submitted economic model. In particular, the ERG's analysis of the LUX-Lung 3 Kaplan-Meier curves shows that prognosis for Asian and non-Asian NSCLC patients with activating EGFR mutations cannot

be considered to be the same. This means that there is currently no reliable clinical evidence base to inform cost-effectiveness modelling for this population in a UK setting.

The ERG has also identified a number of other factors that limit confidence in the reliability of the manufacturer's model and/or results. These relate to inappropriate modelling of post-progression survival (PPS); over-estimation of utility values for patients receiving second-line and third-line therapy; and a mid-cycle correction error. Confidence in the manufacturer's model is further undermined by a number of costs used in (or omitted from) the submitted model, namely high docetaxel therapy and administration costs, reduced erlotinib administration costs, incorrect gefitinib PAS administration costs, out-of-date AE costs and omission of terminal care costs.

The ERG notes that ICERs reported in the MS are superseded by ICERs described in the manufacturer's approved PAS application. However, as these ICERs are generated by the submitted economic model and are based on results of the original MTC which includes both EGFR-positive and mixed/unknown EGFR patients, the ERG considers that they are not informative or reliable and cannot be used to inform the decision problem.

Given the limited clinical-effectiveness data available, the ERG compared the acquisition price and administration costs of afatinib, erlotinib and gefitinib. [redacted].

1.7 ERG commentary on the robustness of evidence submitted by the manufacturer

1.7.1 Strengths

The clinical data derived from LUX-Lung 3 (and LUX-Lung 6) are timely and informative. First, LUX-Lung 3 is the only trial to compare a TKI with chemotherapy in a mixed Asian and non-Asian patient population. Second, the results of subgroup analyses of LUX-Lung 3 data demonstrate support for the hypothesis that being of Asian ethnicity may be a treatment effect modifier in patients who have activating EGFR mutations. Third, LUX-Lung 3 presents much awaited clinical data on use of pemetrexed/cisplatin in an EGFR-positive population.

The manufacturer submitted a comprehensive MS and attempted to address the decision problem set by NICE from all perspectives. The ERG's requests for additional analyses and further information were completed on time and to a high standard by the manufacturer.

1.7.2 Weaknesses and areas of uncertainty

The ERG identified several clinical and economic weaknesses as well as a number of areas of uncertainty.

Clinical effectiveness

- Direct data from LUX-Lung 3 and LUX-Lung 6 can only be used to inform treatment decisions for patients who have adenocarcinoma and activating EGFR mutations in the first-line setting
- Main comparators in the presented afatinib trials are not specifically recommended by NICE for the first-line treatment of patients with activating EGFR mutations in England and Wales
- The ERG does not believe there are adequate clinical effectiveness data available to conduct a reliable MTC to produce findings that are generalisable to patients in England and Wales; this is largely due to the lack of NSCLC studies conducted in European populations
- Reliability of the results of the MTCs relies on the validity of the assumption of proportional hazards. Careful examination of the Kaplan-Meier curves of included studies suggests that this assumption is flawed
- The comparison of Asian vs non-Asian survival outcomes in LUX-Lung 3 demonstrate that ethnicity may be a treatment effect modifier in patients with activating EGFR mutations, this finding requires further research.

Cost effectiveness

- The modelled PFS survival projection for afatinib did not reflect the afatinib LUX-lung 3 trial data from which it was derived
- The ERG considers that the ICERs reported in the MS and in the PAS are not reliable as they were produced by the submitted economic model
- Given the complexity and depth of the problems associated with the submitted economic model, the ERG is unable to provide a set of revised ICERs for the Appraisal Committee. Therefore the ERG is of the opinion that there is no reliable cost-effectiveness evidence available to support the use of afatinib compared with erlotinib or compared with gefitinib.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

Given the clinical effectiveness and cost effectiveness weaknesses and areas of uncertainty described previously, the ERG is confident that the results generated by the manufacturer's

model cannot be considered to be reliable. For this reason, the ERG is unable to provide revised ICERs for the Appraisal Committee.

1.9 ERG conclusions

The ERG concludes that it is currently not possible to compare the clinical effectiveness or cost effectiveness of afatinib vs erlotinib or afatinib vs gefitinib. The two major areas of concern are (i) there are no results from head to head clinical trials comparing afatinib with erlotinib or gefitinib (ii) the manufacturer's modelled PFS survival projection for afatinib does not reflect the afatinib LUX-lung 3 trial data from which it was derived.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problems

Section 2.1 of the MS[1] provides a brief overview of NSCLC, section 2.2 provides data on the number of patients with NSCLC with activating EGFR mutations (EGFR-positive) and section 2.3 provides details about the life expectancy of people with lung cancer in England and Wales. These sections appropriately present the key issues in relation to the underlying health problems, as summarised in Box 1. The ERG agrees with the proportion of NSCLC patients who are EGFR-positive by the manufacturer, noting that the same proportion was identified in a recent study at the Royal Marsden Hospital.[2] It is further noted by the ERG that EGFR mutations predominate in adenocarcinomas that develop in non-smokers.[3]

Box 1 Lung cancer disease course and epidemiology

The disease course

- 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 major subtypes , called squamous cell carcinoma, adenocarcinoma and large cell carcinoma)
  - small cell lung cancer
- Lung cancer does not usually cause noticeable symptoms until it is locally advanced or has spread through much of the lungs or into other parts of the body (i.e. metastatic lung cancer)

Epidemiology

- Lung cancer is the second most common cancer in the UK with 42,026 people being diagnosed with the disease in 2010[4]
- 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[4]
- 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[5]
- Based on the projected population figures for England and Wales,[6] it is estimated that there will be a total of 1,692 advanced NSCLC patients with activating EGFR mutations in 2013, i.e. 11% of all patients with advanced NSCLC

2.2 Critique of manufacturer's overview of current service provision

As stated in section 2.1 of the MS,[1] the type of treatment planned for patients with lung cancer depends on several factors, including type of lung cancer (non-small cell or small cell), size and position of the cancer, how far advanced the cancer is (the stage) and overall health of the patient. Small tumours (stages 1 or 2) are often removed with surgery as are

some larger tumours (stage 3). Surgery for stage 3 tumours may be preceded by chemotherapy and/or radiotherapy. If a stage 3 tumour is too large or if the cancer has spread to other parts of the lung or body (stage 4), no surgery will be performed and traditionally chemotherapy or radiotherapy are used to attempt to reduce the tumour size or delay progression. The ERG notes that pemetrexed in combination with cisplatin is recommended by NICE as an option for first-line treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) only if histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma.[7] This recommendation is based on clinical evidence reporting OS to be statistically superior for pemetrexed/cisplatin compared with gemcitabine/cisplatin.[8]

However, in recent years, a new group of orally administered drugs, TKIs, have emerged as an alternative to chemotherapy and are known as 'targeted agents' because they block certain processes in cancer cells. The National Institute for Health and Care Excellence recommends both erlotinib and gefitinib as first-line treatments, providing specific conditions are met (see Table 1).[9,10] In particular, it is noted that both erlotinib and gefitinib must be provided at a discounted price as agreed under Patient Access Schemes (PAS). The manufacturer notes that, based on data from IMS Health,[11] an estimated 99% of eligible patients with EGFR mutations were treated with erlotinib or gefitinib in the first-line setting. The ERG notes local audits have suggested a small proportion do not receive first-line treatment with TKIs for various reasons but agrees that the vast majority (≥90%) of patients who are known to be EGFR-positive receive one of these TKIs as first-line treatment.

Table 1 NICE guidance on first-line treatment for patients with NSCLC with activating EGFR mutations

Drug	NICE Guidance (year)	Conditions for use
Erlotinib	TA258 (2012)[10]	1. Patients must test positive for an EGFR-TK mutation 2. The manufacturer must provide erlotinib at the discounted price agreed under the PAS (as revised in 2012)
Gefitinib	TA192 (2010)[9]	1. Patients must test positive for an EGFR-TK mutation 2. The manufacturer must provide gefitinib at the discounted price agreed under the PAS

EGFR-TK= Epidermal growth factor receptor tyrosine kinase; PAS=patient access scheme

It is noted by the ERG that NICE's recommendation for gefitinib in the treatment of NSCLC in 2010 was based on evidence showing statistically significant improved PFS and suggesting an OS benefit compared with paclitaxel/carboplatin from the IPASS[12] trial, despite evidence for OS not being mature as the pre-specified number of events (deaths) had not occurred. Subsequently published mature OS data[13] does not report an OS benefit

for gefitinib. Furthermore, the ERG notes that guidance was based on evidence that did not include pemetrexed/cisplatin as a comparator for cost effectiveness. This was despite results of the updated MTC described in the manufacturer of gefitinib's clarification response[14] showing that pemetrexed/cisplatin was superior to other doublet chemotherapy regimens and closer to gefitinib in terms of PFS and OS. In 2012, NICE recommended erlotinib for patients with activating EGFR mutations. Again, the Appraisal Committee decision was primarily driven by a statistically significant PFS gain for erlotinib patients compared with chemotherapy patients as, at the time, mature OS data were not available. The Appraisal Committee noted the advice provided by clinical experts, that erlotinib and gefitinib were similar treatments with similar efficacy and levels of AEs, and concluded that an assumption of equal clinical benefit for erlotinib and gefitinib was appropriate.

Regarding second-line treatment (treatment following one-line of treatment with chemotherapy or a TKI), the manufacturer highlights that clinical guidelines on the diagnosis and treatment of lung cancer (CG121)[15] do not include specific recommendations for EGFR-positive patients. These simply state: 'Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy' (page 22). The ERG also notes that erlotinib is recommended as an alternative to docetaxel as a second-line treatment option for patients with NSCLC progressing after previous chemotherapy.[16] However, this is only on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, AEs and monitoring costs) equal to that of docetaxel.

Afatinib is envisaged to be an alternative to erlotinib or gefitinib in the treatment pathway. Like erlotinib and gefitinib, afatinib is a TKI. In addition, it is noted that in vitro, afatinib has 'improved potency when compared to erlotinib and gefitinib. Afatinib may also prevent emergence of T790M resistance mutation which is commonly seen in patients relapsing after gefitinib or erlotinib' (page 44 of MS[1]).

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

Table 2 displays the decision problem presented in the MS[1] and that addressed by the manufacturer (Section 5, page 34).

Table 2 Decision problem specified by NICE and addressed in the MS

Parameter	Final scope issued by NICE	Decision problem addressed in the manufacturer's submission
Population	People with locally advanced or metastatic non-small cell lung cancer with positive epidermal growth factor receptor tyrosine kinase mutation	As per NICE scope
Intervention	Afatinib	As per NICE 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
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 NICE 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 NICE scope
Subgroups to be considered	None identified	As per NICE scope
Special considerations including equity or equality issues	None identified	As per NICE scope

3.1 Population

The patient population addressed by the MS[1] accurately reflects the patient population included in the European Medicines Agency (EMA)[17] marketing authorisation for afatinib, i.e. 'for the treatment of EGFR-TKI-naïve adult patients with locally advanced or metastatic

NSCLC with activating EGFR mutations.' This patient population is the population addressed in the MS.[1]

3.2 Intervention

The intervention (afatinib) specified in the NICE scope is the same as the intervention assessed in the LUX-Lung 3[18,19] and LUX-Lung 6[20,21] trials from which most evidence was derived. In these trials, the starting dose was 40mg/day which is adjusted according to tolerability. Specifically, the dose should be escalated to 50mg/day if limited AEs are observed in the first cycle of treatment and the dose should be reduced by 10mg/day in the event of common terminology criteria for adverse events (CTCAE) Grade 3 or prolonged Grade 2 AEs. The intervention accurately reflects that specified in the NICE final scope.

3.3 Comparators

The decision problem addressed by the manufacturer only includes first-line treatment and comparators, whereas the final NICE scope specifies a number of other possible comparators for second-line and third-/fourth-line treatment after first-line use of a TKI. The manufacturer's rationale for this apparent deviation is as follows: 'Afatinib will be licensed in patients untreated with a TKI, therefore TKIs are appropriate comparators' (page 34 of MS[1]). In the executive summary of the MS,[1] the manufacturer appears to expand upon this statement when it also states (page 11 of the MS): 'the opportunity to use an EGFR TKI as a second-line treatment in a TKI-naive patient population is unlikely.' The ERG notes that at the time the NICE scope was issued, afatinib was not licensed and so its marketing indication was unknown. In particular, it was not then known that patients would be required to be TKI-naïve. It also agrees that given most EGFR-positive patients currently receive a TKI as first-line treatment, there are few TKI-naïve patients in the second-line treatment setting.

The ERG notes that comparators in the trials from where most direct evidence in the MS is derived are pemetrexed/cisplatin (LUX-Lung 3[18,19]) and gemcitabine/cisplatin (LUX-Lung 6[20,21]). These comparators are not included in the scope and hence the manufacturer conducted a MTC to compare afatinib with erlotinib and gefitinib (discussed further in section4.3).

3.4 Outcomes

Direct evidence for afatinib vs chemotherapy is reported in the MS for all five outcomes specified in the scope: OS, PFS, response rate (reported as objective tumour response rate and disease control rate), AEs of treatment and HRQoL. Indirect evidence from the MTC

reports on OS, PFS and AEs. These are the most relevant outcomes for populating the economic model.

3.5 Economic analysis

As specified in the final NICE scope, the cost effectiveness of treatments was expressed in terms of the incremental cost per QALY gained. The time horizon was lifetime (maximum 10 years) which is sufficiently long to reflect any differences in costs or outcomes between the technologies. Costs were considered from an NHS perspective.

3.6 Subgroups

No relevant subgroups were identified in the final NICE scope or the MS. Relevant subgroups identified by the ERG were Asian and non-Asian populations.

3.7 Other relevant factors

No other relevant factors were identified in the final NICE scope, the MS[1] or by the ERG. No equity issues were identified in the MS and none have been identified by the ERG.

4 CLINICAL EFFECTIVENESS

This section provides a structured critique of the clinical evidence submitted by Boehringer Ingelheim in support of the use of afatinib in adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations.[1] Table 3 contains details of the location of key information within the MS.

Table 3 Location of key clinical information in the MS

Key information	Page number	Tables/figures
Decision problem	34 to 35	Table 3
Searches of the literature	37, 93 to 94, 243 to 252	Table 4
Study selection	38 to 43	Tables 5 to 7, Figure 4
Methodology of relevant RCTs of afatinib	44 to 50	Tables 8 to 9
Eligibility criteria in the RCTs of afatinib	51 to 54	Table 10
Trial characteristics of RCTs of afatinib	55 to 59	Tables 11 to 12
Statistical analyses in RCTs of afatinib	61 to 66	Table 13
Participant flow of RCTs of afatinib	66 to 67	Figures 5 to 6
Quality assessment of RCTs of afatinib	67 to 71	Table 14
Efficacy results of RCTs of afatinib	71 to 91	Tables 15 to 19, Figures 7 to 19
Eligibility criteria for inclusion into the MTC	94 to 96	Table 20
Studies included in MTC	96 to 109	Tables 21 to 26, Figures 20 to 22
Data included from studies in MTC	110 to 114	Tables 27 to 32
Methodology of MTC	114 to 115, 253 to 256	
Quality assessment of studies included in MTC	257	Table 143
Results of the MTC	115 to 124	Tables 33 to 44, Figures 23 to 24
Non-RCT evidence	124 to 139	Tables 45 to 55, Figures 25 to 30
Adverse events	113 to 114, 118 to 119, 140 to 150	Tables 30 to 32, 37 to 39, 56 to 61
Interpretation of clinical evidence	150 to 154	Figure 31

4.1 Critique of the methods of review(s)

The manufacturer conducted a systematic review to identify studies comparing afatinib with any other licensed drug. Anticipating that there are no trials that compare afatinib with erlotinib or gefitinib, the second aim of the search was also to identify trials that could be included in a MTC.

4.1.1 Searches

Sections 6.1 and 10.2 of the MS[1] describe the search strategies employed for the systematic review (direct evidence) and MTC (indirect evidence), respectively.

The following databases were searched on 6 March 2012 spanning the period from 2002 to 2012:

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)

While the manufacturer has searched key databases and documented search strategies adequately, the ERG notes that no search for conference abstracts from other sources (such as specific cancer conferences) was undertaken. Wider searching may have resulted in additional trials being identified although the ERG accepts that the usefulness of data from these trials may be limited.

For all databases, a combination of free text and index terms were used, the intention being to limit the search to RCTs of patients with NSCLC published in English after 2002. It is not clear from the MS[1] why searches were limited to publications from 2002 onwards. Searches included 'any of the interventions licensed for the treatment of locally advanced or metastatic NSCLC' (page 39 of MS[1]). Free text words for both generic and brand names of drugs were used. The ERG notes that search terms included a greater number of drugs than specified in the final scope issued by NICE. The ERG notes that the searches were conducted in March 2012 and have not been updated subsequently. The manufacturer's rationale for not updating the searches was that no major trials have been published since (other than those

relating to afatinib identified by the manufacturer's clinical experts). While accepting that clinical experts may be aware of major trials, the ERG believes that searches should have been updated in order to minimise risk of retrieval bias. The manufacturer conducted a supplementary search using the terms 'EGFR mutation NSCLC' and the same databases. This search aimed to identify systematic reviews of studies of EGFR-positive patients published after March 2012 and, according to the manufacturer's response to the ERG as part of the clarification process, was carried out on 6 August 2013. No further details were available for this search.

In summary, despite some limitations as outlined above, the ERG considers that the search strategies employed by the manufacturer were appropriate and sufficiently comprehensive to identify relevant studies.

4.1.2 Eligibility criteria

The inclusion and exclusion criteria used in the systematic reviews are presented in sections 6.2.1 and 6.7.1 of the MS[1] in Table 5 (page 38) and Table 20 (page 94) and summarised below in Table 4. The ERG notes that in addition to the eligibility criteria specified in the tables, studies were also limited to the first-line setting.

Based on the list of included studies in Table 21 of the MS (page 96), an additional eligibility criterion also appears to have been applied when considering studies for inclusion into the MTC, namely that the studies should include only populations of EGFR-positive patients. Given that it is now recognised that these patients are different (in terms of life expectancy[22]) to patients who are EGFR-negative, the ERG considers that this approach appears to be sensible and more likely to result in meaningful and robust findings than a MTC of patients with unknown/mixed EGFR status.

Table 4 Eligibility criteria used for systematic reviews (including MTC) in manufacturer's search strategy

Parameter	Included	Excluded
Population	Locally advanced or metastatic non-small cell lung cancer patients	Other populations; Non locally advanced or metastatic NSCLC patients
Interventions	Chemotherapy or targeted therapies[1]	Other interventions that are not licensed for NSCLC
Comparators	Chemotherapy, targeted therapies, placebo or BSC	Other comparators
Outcomes	OS 1 year survival PFS TTP ORR Toxicity	Other outcomes
Study design	RCT Systematic reviews Meta-analyses	Observational studies Prospective studies Cohort studies Case control studies Reviews Letters Commentaries
Language	English	Not English

BSC=best supportive care; ORR=overall response rate; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; RCT=randomised controlled trial; TTP=time to progression
[1] Although not explicitly stated, this would need to include studies of afatinib for the direct evidence

4.1.3 Quality assessment

The manufacturer conducted a quality assessment of three studies of afatinib, two RCTs (LUX-Lung 3,[18,19] LUX-Lung 6[20,21]) and a single-arm phase II study (LUX-Lung 2[23]) and all studies included in a MTC. This included elements of the tool for assessing risk of bias, as recommended by the Cochrane Collaboration.[24] The ERG agrees this is an appropriate tool for assessing quality of RCTs. No other trials were included in the systematic review.

4.1.4 Evidence synthesis

Two trials (LUX-Lung 3[18,19] and LUX-Lung 6[20,21]) were identified by the systematic review, both with different comparators (pemetrexed/cisplatin and gemcitabine/cisplatin). If it is assumed that these two comparators are of equal efficacy, then it may have been appropriate to have conducted a meta-analysis. However, as noted in section 2.2, there is evidence that pemetrexed/cisplatin is superior to gemcitabine/cisplatin in non-squamous NSCLC. Therefore the findings were appropriately presented narratively. Thus in order to compare afatinib to comparators of interest (erlotinib and gefitinib) it was necessary to conduct a MTC. The ERGs critique of the manufacturer's MTC is presented in section 4.3.

4.2 Critique of direct evidence of clinical effectiveness evidence

4.2.1 Identified studies in the systematic review

The systematic review identified two studies (both phase III trials; LUX-Lung 3[18,19] and LUX-Lung 6[20,21] comparing afatinib with chemotherapy. In addition to evidence from these two RCTs, data from a single-arm study, LUX-Lung 2[23] was also considered relevant to the decision problem. The ERG is not aware of any additional completed studies of afatinib relevant to this appraisal although it is noted that there is an ongoing phase IIb trial comparing afatinib with gefitinib (LUX-Lung 7).[25] This trial is enrolling 316 patients from Australia, Canada, Asia (China, Hong Kong, Singapore, South Korea, Taiwan) and Europe (France, Germany, Ireland, Norway, Spain, Sweden and the UK). The estimated study completion date for this trial is December 2014.

4.2.2 Characteristics of the trials included in the systematic review

The LUX-Lung 3[18,19] and LUX-Lung 6[20,21] trials were multicentre, phase III, randomised controlled studies. LUX-Lung 3[18,19] is described as being conducted globally (but around 70% of patients were recruited from Asia), while LUX-Lung 6[20,21] was conducted in Asia.

In both LUX-Lung 3,[18,19] and LUX-Lung 6[20,21] afatinib was compared to chemotherapy (pemetrexed/cisplatin and gemcitabine/cisplatin, respectively) in patients untreated with an EGFR-TKI with advanced adenocarcinoma of the lung harbouring EGFR mutations. Patients were randomised (2:1) to receive either afatinib at a starting dose of 40mg/day or chemotherapy by centralised allocation (i.e. interactive web response system/ interactive voice response system). Randomisation was stratified, in both trials, according to mutation category (L858R vs exon 19 deletion [del 19] vs other). In LUX-Lung 3,[18,19] randomisation was also stratified by ethnicity (Asian vs non-Asian). Randomisation schedules were generated using the Boehringer Ingelheim's standard validated random number generating system, verified by a trial-independent statistician. Allocation concealment was achieved by randomising patients centrally using an interactive voice response system. The ERG is satisfied that randomisation was carried out appropriately and allocations were adequately concealed in both trials.

LUX-Lung 2[23] was a non-RCT phase II proof-of-concept study and evidence from this trial was included in the Marketing Authorisation application submitted to the EMA Committee for Medicinal Products for Human Use (CHMP). It was partly as a result of findings from LUX-Lung 2[23] that the starting dose of afatinib in LUX-Lung 3[18,19] and LUX-Lung 6[20,21] was set at 40mg/day. Patients were recruited to LUX-Lung 2[23] from Taiwan and the USA. This study 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 in LUX-Lung 2[23] although a subsequent protocol amendment also allowed inclusion of treatment-naïve patients. In a second protocol amendment and as alluded to above, the initial starting dose of afatinib was reduced from 50mg/day to 40m/day to optimise the balance between efficacy and safety. Of 61 patients who received afatinib as a first-line treatment in this study, 23 (38%) were treated with 40mg/day, and 38 (62%) were treated with 50mg/day. Treatment cycles (4 weeks in length) continued until disease progression, intolerable AEs, or until patients withdrew.

Both LUX-Lung 3,[18,19] LUX-Lung 6[20,21] and LUX-Lung 2[23] measured outcomes specified in the NICE scope, namely OS, PFS, response rates (overall response rate [ORR]), HRQoL and AEs although, as expected in phase II trials, the primary outcome differed in LUX-Lung 2[23] (ORR) from the phase III trials (PFS as assessed by central independent assessment).

The ERG notes that LUX-Lung 3[18,19] is the first trial to compare a TKI with pemetrexed/cisplatin. It is also the first trial of a TKI conducted in both an Asian and non-Asian population and importantly, stratified for ethnicity, enabling comparisons to be made between potentially different patient populations.

The key trial characteristics are summarised in Table 5.

.

Table 5: Comparative summary of study characteristics of LUX-Lung 3, LUX-Lung 6 and LUX-Lung 2

Characteristic	LUX-Lung 3[18,19]	LUX-Lung 6[20,21]	LUX-Lung 2[23]
Location	International (133 centres in 25 countries)	Multi-centre trial in Asia (36 centres in 3 countries)	Taiwan (7 centres) and USA (30 centres)
Design	Randomised, open label, phase III trial	Randomised, open label, phase III trial	Single-arm, phase II study
Duration of study	August 2009 to February 2012	April 2010 to October 2012	August 2007 to April 2011
Intervention	Afatinib 40mg/day (n=230). Dose reductions to 30mg/day or 20mg/day permitted in the case of protocol defined AEs. Dose escalation was permitted if no AEs > Grade 1 in severity were experienced during course 1	Afatinib 40mg/day (n=242). Dose reductions to 30mg or 20mg permitted in the case of protocol defined AEs. Dose escalation was permitted if no AEs > Grade 1 in severity were experienced during course 1	Afatinib 50mg/day (n=99) or for newly enrolled patients after implementation of amendment 2, afatinib 40mg/day (n=30). For patients experiencing CTCAE Grade ≥3 or Grade ≥2 as specified in the protocol, a dose reduction was permitted. A maximum of two dose reductions were allowed after which afatinib was discontinued
Comparator	Pemetrexed 500mg/m^2 followed by cisplatin 75mg/m^2 (n=115). Up to 6 cycles (each 21 days) permitted	Gemcitabine 1000mg/m^2 and cisplatin 75mg/m^2 on day 1 followed by gemcitabine on day 8 of each 21 day cycle (n=122). Up to 6 cycles permitted	Not applicable
Primary outcome	PFS based on central independent assessment	PFS based on central independent assessment	ORR as determined by RECIST criteria
Timing of assessments for primary outcome	Tumour assessments were performed at screening, after 6 weeks, after 12 weeks and every 6 weeks thereafter. After week 48, assessments were performed every 12 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	An assessment of tumour response was performed at weeks 4, 8 and 12 and thereafter every 8 weeks
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	The maximum follow-up time for patients who received a starting dose of 40mg/day was around 10 months in contrast to patients who received a starting dose of 50mg/day whose maximum follow-up time almost reached 28 months. Initial follow-up visit at 28±7 days after the end of trial; an additional follow-up visit was to be performed in 12-week intervals from initial follow-up visit or earlier if appropriate

AE=adverse event; CTCAE=Common terminology criteria for adverse events; HRQoL=health-related quality of life; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

4.2.3 Participant characteristics in trials included in the systematic review

The key participant characteristics and differences between LUX-Lung 3,[20,21] LUX-Lung 6[18,19] and LUX-Lung 2[23] are summarised in Appendix 22.1.1. On the whole, patient populations in the three studies appear to be appropriate to that specified in the final scope by NICE. However, the ERG notes that all patients in LUX-Lung 6[20,21] and the majority of patients in LUX-Lung 3[18,19] are of Asian origin. In this respect, trial patients may not be representative of patients in the UK. To partly address this issue, as part of the clarification process, the ERG requested baseline data for Asian and non-Asian populations in LUX-Lung 3.[18,19] Apart from the obvious difference in terms of geographical region, the main differences between populations were [redacted]. The ERG notes that characteristics of disease stage and EGFR mutation category were not provided for Asian and non-Asian subgroups in the manufacturer's response.

4.2.4 Statistical approach of the trials included in the systematic review

The statistical approaches employed for the LUX-Lung 3,[20,21] LUX-Lung 6[18,19] and LUX-Lung 2[23] trials are summarised in Appendix 22.1.2. The ERG is satisfied that the specified primary endpoints, sample size calculations and methods of analysis used to analyse data from these trials were appropriate.

4.2.5 Quality assessment of the trials included in the systematic review

The manufacturer conducted a quality assessment of the included studies. This included elements of the tool for assessing risk of bias, as recommended by the Cochrane Collaboration.[24] LUX-Lung 3[20,21] and LUX-Lung 6[18,19] were deemed to be of good quality.

4.2.6 Results of the trials included in the systematic review

Progression-free survival data for LUX-Lung 3[18,19] and LUX-Lung 6,[20,21] are presented in the MS[1] (Table 15, page 73) and are reproduced in Table 6 below. The primary analysis in both trials was based on central independent assessments. Median PFS is reported to be similar for local and central independent assessment in LUX-Lung 3.[18,19] However, in LUX-Lung 6[20,21] local assessment estimated the difference in median PFS time between afatinib and chemotherapy arms to be 8.18 months, considerably higher than the 5.42 months estimated by central independent assessment. In LUX-Lung 3[18,19] central independent and investigator

assessment were reported to be in accordance in [redacted] in identifying a PFS event.

Table 6: PFS based on central independent and local investigator assessments

Endpoints	LUX-Lung 3[18]		LUX-Lung 6[20]	
	Afatinib (n=230)	Pemetrexed/ cisplatin (n=115)	Afatinib (n=242)	Gemcitabine/ cisplatin (n=122)
Central independent assessment				
Patients with event	152 (66.1%)	69 (60.0%)	157 (64.9%)	64 (52.5%)
Median PFS months	11.14	6.90	11.01	5.59
(95% CI)	(9.63 to 13.63)	(5.39 to 8.25)	(9.66 to13.73)	(5.06 to 6.70)
Hazard ratio vs chemotherapy (95% Confidence Interval)	0.577 (0.425 to 0.784)		0.279 (0.201 to 0.388)	
p-value (2-sided)	0.0004		<0.0001	
Local investigator assessment				
Patients with event	155 (67.4%)	83 (72.2%)	169 (69.8%)	78 (63.9%)
Median PFS months	11.07	6.70	13.73	5.55
(95% CI)	(9.66 to 13.60)	(5.42 to 8.11)	(11.50 to 13.86)	(5.13 to 6.80)
Hazard ratio vs chemotherapy (95% Confidence Interval)	0.488 (0.367 to 0.649)		0.262 (0.193 to 0.356)	
p-value (2-sided)	<0.0001		<0.0001	

PFS=Progression-free survival

For LUX-Lung 3[18,19] and LUX-Lung 6,[20,21] the MS[1] provides forest plots, pre-specified in the protocol, for key subgroup analyses of PFS based on central independent assessment. Subgroups include (but are not limited to) age, gender, ethnicity, types of EGFR mutations and smoking status and are summarised in Appendix 22.1.3. The findings of subgroup analysis are consistent with those of the PFS primary analysis

In response to the ERG's request as part of the clarification process for findings to be presented for Asian and non-Asian patients, the manufacturer presented a subgroup analysis of local investigator assessed PFS in LUX-Lung 3,[18,19] as summarised in Table 7. This exploratory analysis suggests that Asian patients may have improved PFS compared with non-Asian patients.

Table 7: PFS (assessed by local investigators) stratified by ethnicity in LUX-Lung 3

Endpoints	Asian patients		Non-Asian patients	
	Afatinib (n=166)	**Pemetrexed/ cisplatin (n=83)**	**Afatinib (n=64)**	**Pemetrexed/ cisplatin (n=32)**
Median PFS months (95% CI)	11.30 (10.02 to 13.70)	6.90 (5.49 to 8.21)	9.79 (6.77 to 13.70)	5.55 (4.01 to 9.46)
Hazard ratio vs chemotherapy (95% Confidence Interval) p-value (2-sided)	0.450 (0.327 to 0.619) p<0.0001		0.618 (0.359 to 1.064) p=0.0800	

PFS=Progression-free survival

Overall survival data presented in the MS[1] are not mature for either LUX-Lung 3[18,19] or LUX-Lung 6[20,21] as in neither trial, the planned number of events (deaths) to assess OS have not occurred. Most recent OS data for both trials are summarised in Table 8 below where it can be seen [redacted]. However, it is noted in the MS that this may be explained by crossover, with most patients in LUX-Lung 3[18,19] and a large minority in LUX-Lung 6[20,21] receiving chemotherapy following disease progression on afatinib (62.2% and 48.4% respectively); for patients starting on chemotherapy, the majority of patients in both trials received a TKI following progression on chemotherapy (64.9% and 54.6% respectively).

Table 8: OS reported in LUX-Lung 3 (updated) and LUX-Lung 6

Endpoints	LUX-Lung 3[18]		LUX-Lung 6[20]	
	Afatinib (n=230)	**Pemetrexed/ cisplatin (n=115)**	**Afatinib (n=242)**	**Gemcitabine/ cisplatin (n=122)**
Patients with event	116 (50.4%)	59 (51.3%)	104 (43.0%)	51 (41.8%)
Median OS months (95% CI)	[redacted]	[redacted]	[redacted]	22.24 (18.00 to NE)
Hazard ratio v chemotherapy (95% Confidence Interval)	[redacted]		0.949	
			[redacted]	
p-value (2-sided)			0.7593	

NE=not estimable; OS=overall survival

The manufacturer's subgroup analysis of OS in LUX-Lung 3[18,19] stratified by ethnicity is provided in Table 9. This exploratory analysis suggests that Asian patients may have improved OS compared with non-Asian patients.

Table 9: OS stratified by ethnicity in LUX-Lung 3

Endpoints	Asian patients		Non-Asian patients	
	Afatinib (n=166)	Pemetrexed/ cisplatin (n=83)	Afatinib (n=64)	Pemetrexed/ cisplatin (n=32)
Patients with event	82 (49.4%)	39 (47.0%)	34 (53.1%)	20 (62.5%)
Median OS months	30.13	29.14	26.58	20.73
(95% CI)	(24.74 to 37.45)	(22.90 to NE)	(21.06 to 31.51)	(16.79 to 33.51)
Hazard ratio* v chemotherapy (95% CI)	0.998 (0.681 to 1.462)		0.800 (0.458 to 1.396)	
p-value† (2-sided)	0.9925		0.4316	

* Hazard ratio from Cox proportional hazards model with treatment fitted as the only factor
† P−value from log−rank (two−sided)
NE=not estimable; OS=overall survival

The manufacturer also reports findings for ORR. These are presented in Appendix 22.1.3. Response rates in the afatinib arm were superior to those in the chemotherapy arms in both LUX-Lung 3[18,19] and LUX-Lung 6.[20,21]

The ERG notes that in LUX-Lung 2,[23] there were no significant differences in response rate by ethnicity. However in LUX-Lung 3[18,19] response rates were much lower in non-Asian than Asian patients. All efficacy findings (including OS and PFS) for LUX-Lung 2[23] are presented in Appendix 22.1.3.

4.2.7 ERG analysis of OS and PFS data from LUX-Lung-3 Clinical Trial

The ERG requested detailed information from the manufacturer of afatinib in the form of Kaplan-Meier survival analyses for OS, PFS and PPS distinguishing between two subgroups: those of Asian origin and those of non-Asian origin. The aim of this exercise was to determine whether there is evidence that the experience of patients in responding to treatment differed by ethnic origin, and whether alternative projective model formulations may represent more accurately the trial results than the Weibull functions employed by the manufacturer in the submitted model. The analysis was carried out for PFS and OS, but the number of patients and events in the PPS dataset proved to be inadequate for meaningful analysis.

The requested survival analyses involved use of the most recent data update, and a different censoring rule (censoring at time of data cut, not of last observation) to remove bias from informative censoring. It is important to note that origin (Asian vs non-Asian) is a stratification variable for this clinical trial, so that analyses using these subgroups should be free of biases inherent in post-hoc exploratory subgroup analyses.

[redacted]

Figure 1 Comparison of OS between Asian and non-Asian subgroups in the LUX-Lung-3 clinical trial (Confidential therefore not reported)

Figure 2 Comparison of cumulative mortality hazard between Asian and non-Asian subgroups in the LUX-Lung-3 clinical trial (Confidential therefore not reported)

Progression-free survival

[redacted]

Figure 3 Comparison of PFS between Asian and non-Asian subgroups in the LUX-Lung-3 clinical trial (confidential therefore not reported)

Figure 4 Comparison of cumulative progression hazard between Asian and non-Asian subgroups in the LUX-Lung-3 clinical trial (Confidential therefore not reported)

Estimated OS and PFS by subgroup

The fitted trendline models allow long-term expected OS and PFS to be estimated for both subgroups and for both treatments. The results are shown in Table 10, together with estimated PPS as the difference between OS and PFS.

Table 10 Estimated mean survival times (months) and incremental difference from treatment with afatinib vs pemetrexed/cisplatin

Endpoint	Subgroup	Afatinib	Pemetrexed/cisplatin	Difference
OS	Asian	[redacted]	[redacted]	[redacted]
	Non-Asian	[redacted]	[redacted]	[redacted]
PFS	Asian	[redacted]	[redacted]	[redacted]
	Non-Asian	[redacted]	[redacted]	[redacted]
PPS	Asian	[redacted]	[redacted]	[redacted]
	Non-Asian	[redacted]	[redacted]	[redacted]

OS=overall survival; PFS=progression-free survival; PPS=post-progression survival

Interpretation of subgroup analyses

In all cases, other than OS in the Asian subgroup, there is evidence of important differences in the temporal pattern of survival between treatments. The trial data are not consistent with general use of a simple conventional functional form for all patient groups and treatments. Therefore, the trial evidence indicates that employing a single parametric function to represent both treatment arms is generally inappropriate, since the proportional hazards assumption is clearly violated. As a consequence use of a single hazard ratio as a basis for informing a MTC is not appropriate or reliable as it cannot reflect the different PFS and OS trend patterns experienced for each treatment and each trial, where the hazard ratio can vary widely over different time periods within a trial and different follow-up periods between trials.

When the estimated mean OS for the LUX-Lung 3[18,19] trial is compared with other first-line trials of NSCLC patients, it is evident that the prognosis for patients with activating EGFR mutations is [redacted] than that generally of non-squamous NSCLC patients, who have a mean life expectancy of only 15 to 20 months.

[redacted]

ERG conclusions

1. Use of a simple hazard ratio to represent the relative effectiveness of afatinib vs pemetrexed/cisplatin in any indirect comparison across trials is unreliable. If differences in effectiveness seen in the LUX-Lung 3[18,19] trial are replicated in other trials of EGFR-TKIs then use of simple hazard ratios to form a network of trials as the basis for meta-analysis must also be considered unreliable and potentially misleading.

2. Use of a single parametric form as the basis for modelling survival curves for different treatments within a trial is also called into question. Such differences in trendline behaviour within a single trial are not unique to this appraisal but were previously noted by the ERG as reported in section 3.22 of the FAD for TA258[10] in which both erlotinib and gefitinib were compared to chemotherapy for the same indication as afatinib. These reflect the different modes of action of different active compounds on the disease process.

3. The use of combined Asian/non-Asian trial data form the LUX-Lung 3[18,19] trial for modelling cost-effectiveness is inappropriate as it is evident that the UK population is likely to be much closer in terms of characteristics and prognosis to the non-Asian subgroup than to the overall trial (of predominantly Asian origin). It should also be noted that estimated benefits experienced by the non-Asian subgroup are improved relative to the Asian subgroup; a similar PFS gain, but important additional OS gain for non-Asians compared with no OS gain for Asians.

4.3 [redacted] *Critique of indirect evidence of clinical effectiveness*

4.3.1 Methodological approach to MTC

The MTC used a Bayesian approach and was performed using the Markov chain Monte Carlo software package WinBUGs. This approach combines a prior probability distribution

with a likelihood distribution. The prior distribution reflects a prior belief of the possible values of the pooled relative effects of the pooled effect. The likelihood distribution is based on observed data in different studies to obtain a posterior distribution of the pooled relative treatment effect.

The manufacturer performed MTCs for three outcomes; PFS, OS and AEs. The metrics used in the MTC for OS and PFS were log hazard ratios and standard error. For the MTC of AEs, the incidence of AEs were used. All baseline and intervention effect parameters were given flat (uninformative) normal (0, 1000) priors so that data from the studies would have a greater influence than any prior belief about results from the analysis.

In all cases, analyses were run for at least 20,000 burn-in simulations to allow for convergence and then estimates were obtained from a further 50,000 iterations. Both fixed and random effects models were conducted.

The MS[1] explains that the deviation in credible intervals between fixed effects and random effects models was greater for PFS than for OS, suggesting that heterogeneity has a slightly larger impact on PFS than on OS. In the models for PFS, a smaller DIC (Deviance Information Criterion) statistic was observed for the random effects model than the fixed effects model. Total residual deviance was closer to the number of data points in the random effects model than in the fixed effects model. The MS[1] provides these reasons as justification for the choice of the random effects model for PFS.

As differences in credible intervals between fixed effects and random effects models were small for OS, the MS[1] claims heterogeneity has little effect on the results of the OS analyses. Furthermore, a smaller DIC statistic was observed for the fixed effects model, and total residual deviance was closer to the number of data points in the fixed effects than in the random effects model. Therefore the manufacturer concluded that a fixed effects model was deemed to be the most appropriate choice of model for OS.

4.3.2 Identified studies

The search conducted in March 2012 yielded 10,001 publications of which 66 were considered for inclusion in the MTC. The 66 publications included three papers[26-28] identified after the search was conducted. It is not stated how these three studies were identified in the MS.[1] However, via the clarification process, the manufacturer stated one study (LUX-Lung 1[27]) was known as it was sponsored by the manufacturer whereas the other two (First-SIGNAL[26] and EURTAC[28]) were high profile, phase III studies identified by the manufacturer's medical group as part of their regular horizon scanning procedures. Of the 66

publications, eight[12,13,26,28-32] reported findings in a population of EGFR-positive patients. Two of these eight publications[12,13] reported on the same study (IPASS). Two further studies were subsequently excluded; TALENT[29] because erlotinib was not used as a monotherapy and OPTIMAL[32] because of limitations with its study design (see Box 2 for details). OPTIMAL[32] was however included in a sensitivity analysis conducted by the manufacturer.

Box 2 Reasons for excluding the OPTIMAL study from the analysis

This investigator-initiated study assessed relative efficacy between erlotinib and carboplatin in combination with gemcitabine as first-line treatment for patients with advanced EGFR mutation-positive NSCLC in China. However, results reported in this study are notably different from a similar study (EURTAC[28]) therefore raising concerns over transferability of results. This difference between trials may be explained by an underperforming comparator arm in OPTIMAL[32] 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.[33] Also, the study has not been accepted by regulatory authorities including the Chinese Authorities and EMA.

The remaining studies were therefore included alongside LUX-Lung 3[18,19] and LUX-Lung 6.[20,21] resulting in seven studies of EGFR-positive patients. In two of these studies (IPASS[12,13] and First-SIGNAL[26]) the EGFR-positive patients constituted a subgroup of the total patient population. The studies included are listed in Table 11.

Table 11 Trials of patients with activating EGFR mutation status included in MTC

Trial	Primary reference	Additional references
LUX-Lung 3	Sequist et al 2013[18]	HRQoL data presented in Yang et al 2013[19] All results presented in CTR[34]
LUX-Lung 6	Wu et al 2013[20]	HRQoL data presented in Geater et al 2013[21] All results presented in CTR[35]
EURTAC	Rosell et al 2012[28]	
First-SIGNAL	Han et al 2012[26]	
IPASS	Mok et al 2009[12]	Updated OS results presented in Fukuoka et al 2011[13]
NEJGSG002	Maemondo et al 2010[30]	Updated PFS and OS results presented in Inoue et al 2012[36] *
WJTOG34053405	Mitsudomi et al 2010[31]	Updated OS results presented in Mitsudomi et al 2012[37] *

* Studies not included in the manufacturer's original MTC

The additional search for systematic reviews published after the manufacturer's original search identified 14 publications.[36,38-50] Nine of these were reviews[38-42,45,46,48,49] which did not include any additional trials considered eligible for inclusion. However, three[36,44,47] of the additional 14 publications were reported to be reports of RCTs. Jänne et al 2012[44] was excluded because the trial did not report necessary results as hazard ratios. While the ERG notes that the manufacturer could have attempted to contact the authors for these data, as not all patients were EGFR-positive, this may have been of limited value. Lee et al 2012[47]

compared erlotinib with placebo. It appears to have been excluded because placebo was not a relevant comparator for the MTC. It is unclear why Inoue et al 2012[36] was excluded as this presented an updated analysis for a trial (NEJGSG002[30]) that was included in the MTC. This trial was subsequently included at the request of the ERG via the clarification process (see section 7.1.2). The remaining two publications identified by the search for systematic reviews identified a protocol for a Cochrane Review[43] and a network meta-analysis that estimated PFS and OS of EGFR-positive patients in the Netherlands.[50]

Having identified seven studies[12,18,20,26,28,30,31] of EGFR-positive populations, the manufacturer then included an additional 12 studies[51-62] of patients of unknown/mixed EGFR status (all 12 studies had been included in a previous MTC[14]). The manufacturer stated that these additional studies were included in the MTC to provide consistency across submissions to NICE and to build a more extensive network which would produce more conservative findings.

Over and above the 12 additional studies,[51-62] the study by Scagliotti et al 2009[63] was also included in the manufacturer's MTC. The means by which this study was identified for inclusion are unclear. The ERG has recently conducted a systematic review of first-line chemotherapy for adult patients with locally advanced or metastatic NSCLC.[38] From this review, it is apparent that if the additional 13 studies[51-63] of patients of unknown/mixed EGFR status are considered eligible for inclusion in the MTC, an additional 13 studies[64-76] would also be eligible; the interventions assessed by these studies are summarised in Table 12.

Table 12 Additional studies potentially eligible for inclusion in a MTC of patients with unknown/mixed EGFR status

Study	Interventions	
Helbekkmo 2007[70]	Vinorelbine/carboplatin	Gemcitabine/carboplatin
Chen 2007[66]	Vinorelbine/cisplatin	Docetaxel/cisplatin
Douillard 2005[67]	Vinorelbine/cisplatin	Docetaxel/cisplatin
Tan 2009[75]	Vinorelbine/cisplatin	Docetaxel/cisplatin
Chang 2008[64] *	Vinorelbine/cisplatin	Gemcitabine/cisplatin
Gebbia 2003[68]	Vinorelbine/cisplatin	Gemcitabine/cisplatin
Martoni 2005[73]	Vinorelbine/cisplatin	Gemcitabine/cisplatin
Ohe 2007[74]	Vinorelbine/cisplatin	Gemcitabine/cisplatin and paclitaxel/carboplatin
Kelly 2001[71]	Vinorelbine/cisplatin	Paclitaxel/carboplatin
Chen 2004[65]	Vinorelbine/cisplatin	Paclitaxel/cisplatin
Treat 2010[76]	Paclitaxel/carboplatin	Gemcitabine/paclitaxel and gemcitabine/carboplatin
Langer 2007[72]	Paclitaxel/carboplatin	Gemcitabine/cisplatin

Grønberg 2009[69]	Pemetrexed/carboplatin	Gemcitabine/carboplatin

* It is possible that this is the same study as Chang et al 2001[51] which was included, however neither the manufacturer nor ERG have been able to obtain the source paper for Chang et al 2001[51]

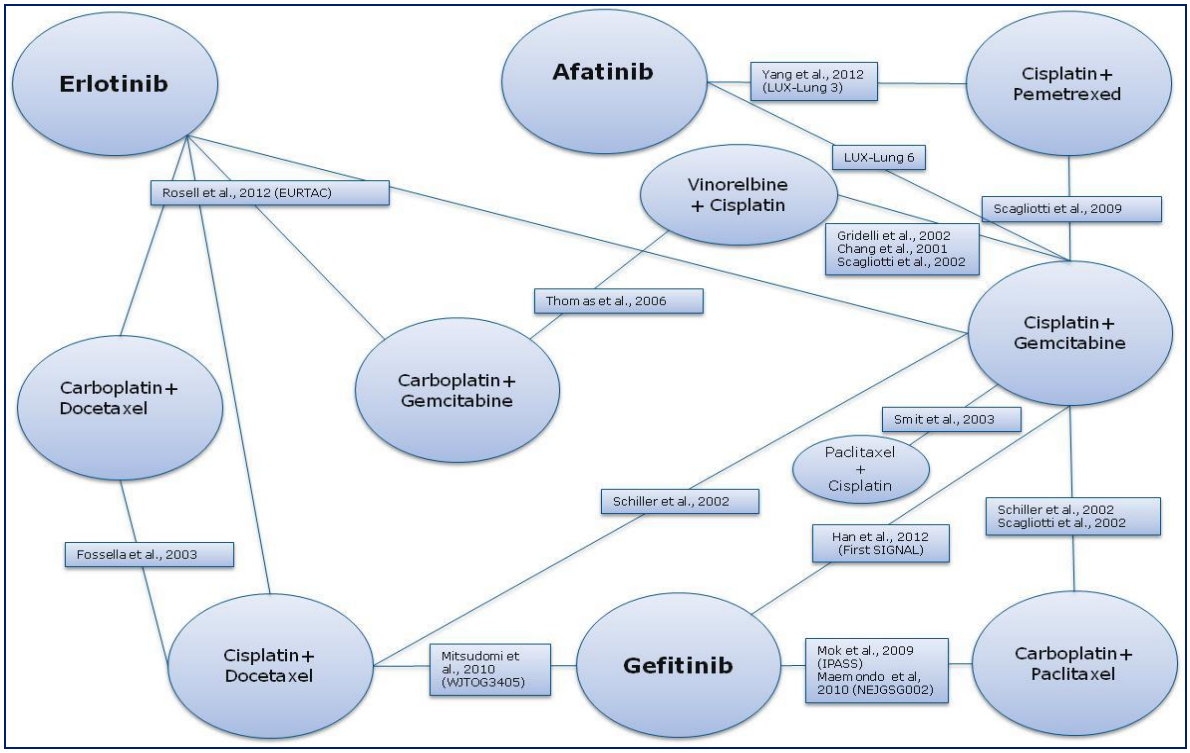

Figure 5: Evidence network used to inform the MTC for PFS

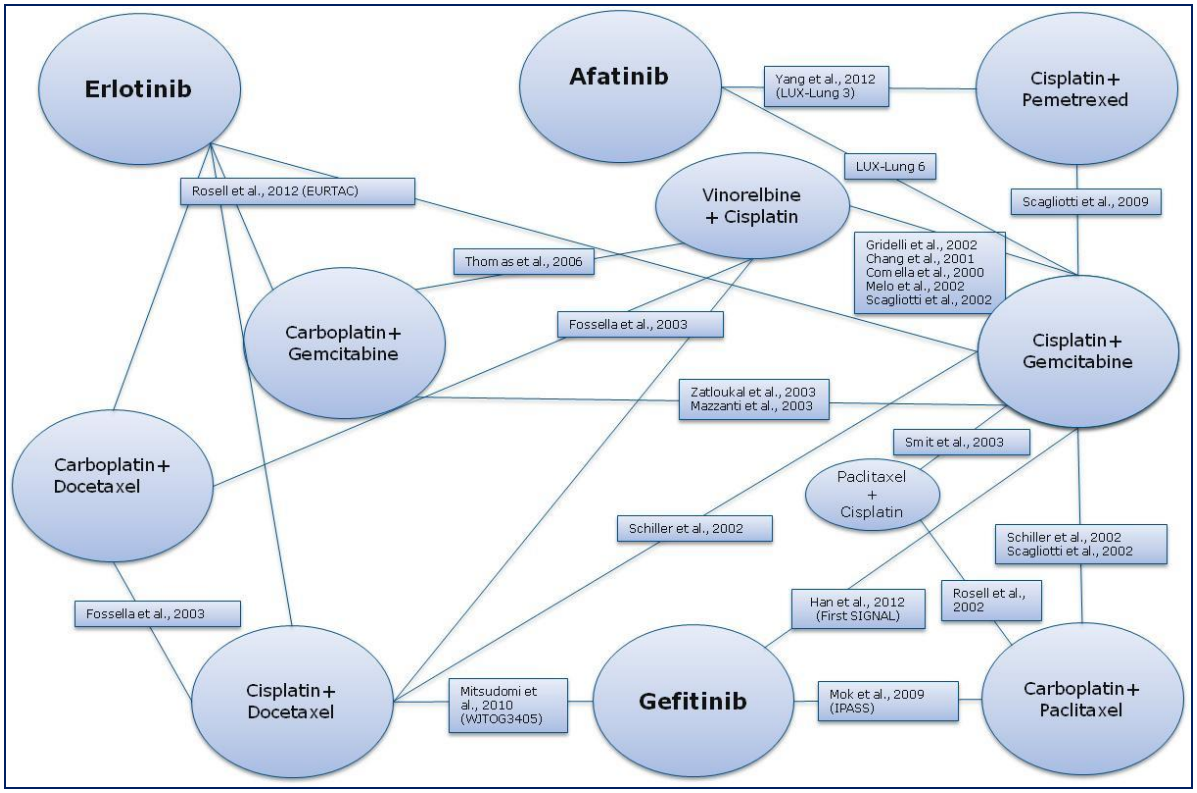

Figure 6: Evidence network used to inform the MTC for OS

The network of evidence used for PFS is shown in the MS (Figure 21, page 107)[1] and reproduced in Figure 5 and that used for OS is shown in the MS (Figure 22, page 108)[1] and reproduced in Figure 6. In both instances, treatments form a closed loop, indicating the inclusion of both direct and indirect evidence in the network.

Throughout the ERG report, studies which include only EGFR-positive patients (or a subgroup analysis of EGFR-positive patients) are referred to by their trial acronym (e.g. LUX-Lung 3[18]) whereas those which include a population of unknown/mixed EGFR status are referred to by the name of the first author (e.g. Scagliotti et al 2009[63]).

4.3.3 Characteristics of identified studies

Key details relating to the trials included in the network were presented in the MS[1] (Tables 21, 24 and 27). The ERG has compared key trial characteristics for patients with EGFR-positive status with characteristics of patients with unknown/mixed EGFR status (presented in detail in Appendix 37.1, summarised in Table 13. It is noted that there are differences in patient characteristics between studies of patients of EGFR-positive NSCLC and those of unknown/mixed EGFR status (particularly in relation to the proportions of males, never-smokers and patients with adenocarcinoma). Because of these differences the ERG considers that inclusion of trials involving patients of unknown/mixed EGFR status alongside patients of EGFR-positive status in a MTC may result in findings that are not robust. This view is reinforced by evidence that in terms of OS, patients who are EGFR-positive tend to have better prognoses than patients of unknown/mixed EGFR status.[22]

Table 13 Range of key trial characteristics of studies included in the MTC (for each trial arm)

EGFR status	Sample size (n)	Male (%)	Age (years)	Never smoked (%)	PS2+ (%)	Adeno-carcinoma (%)
EGFR-positive †	16 to 242	(10.7) to 36.8	57 to 64	57.9 to 100.0	0 to 14	89.7§ to 100.0
Unknown/mixed	29 to 863	59.7 to 93.0	56 to 65	11.5 to 14.8	0 to 21	26.4 to 56.9

† Only a sub-population of First-SIGNAL[26] and IPASS[12] were EGFR-positive and not all data were presented for this sub-population, data in parenthesis are data reported for the unknown/mixed population; data for EGFR-positive patients extracted by the ERG and not presented in the MS.
§ OPTIMAL[32] was included in a sensitivity analysis; in this trial 86.1% had adenocarcinoma in the gemcitabine/carboplatin arm
* Smoking status was only reported in two studies[62,63] of patients of unknown/mixed status
Note: in the MS it is stated that neither the proportion of never-smokers or adenocarcinoma were reported in First-SIGNAL[26] but all patients in this trial were never-smokers with adenocarcinoma.

Patient characteristics were largely similar across the trials of EGFR-positive patients. Some apparent differences are, however, noted by the ERG. Three trials (LUX-Lung 6,[20] First-SIGNAL,[26] and IPASS[12]) report a mean or median age of below 60 years old whereas in the other four[18,28,30,31] the mean/median age is 60 years or above. Although the majority of patients are non-smokers in all trials, this does vary from 57.9% in the paclitaxel/carboplatin

arm of NEJGSG002[30] to over 90% in IPASS[12] and 100% in First-SIGNAL.[26] EURTAC,[28] IPASS,[12] First-SIGNAL[26] and (to a lesser extent) NEJGSG002,[30] also included a number of patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2. However, it is difficult to compare characteristics of patients in IPASS[12] and First-SIGNAL[26] with the other five trials because the majority of data are presented for the whole trial population, i.e. patients unknown/mixed EGFR status rather than only EGFR-positive patients. Perhaps the most notable difference between the trials is that EURTAC[28] was conducted in a European patient population whereas in five others,[12,20,26,30,31] all patients were recruited from Asia. Patients were mostly from Asia in LUX-Lung 3[18] although as noted in section 4.2.2 and 4.2.7, this trial stratified for Asian and non-Asian patients.

4.3.4 Individual study findings

The hazard ratios for PFS (or Time to Progression [TTP] which is assumed to be the same as PFS by the manufacturer), OS and AEs were presented in tables in the MS (Table 28 to Table 32).

Mean or median PFS and OS in months for populations of patients who are EGFR-positive are presented here by the ERG in Table 14 and Table 15. The results suggest that use of TKIs result in prolonged PFS compared with chemotherapy for this patient group. However, no significant differences between treatment arms were reported for OS which may be explained by the fact all trials permitted treatment crossover. The ERG notes that these findings are, in general consistent with findings from recently published meta-analyses.[22,42,45,48]

Table 14 Progression-free survival from studies of patients with activating EGFR-mutations

Study	Treatments	Median PFS, hazard ratio (95% CI)	Median PFS (months)	Difference in mean PFS (months)
LUX-Lung 3[18]	Afatinib	0.49 (0.37 to 0.65)	11.1	4.4
	Pemetrexed/cisplatin		6.7	
LUX-Lung 6[20]	Afatinib	0.26 (0.19 to 0.36)	13.7	8.1
	Gemcitabine/cisplatin		5.6	
EURTAC[28]	Erlotinib	0.37 (0.25 to 0.54)	9.7	4.5
	Chemotherapy*		5.2	
OPTIMAL[32]§	Erlotinib	0.16 (0.10 to 0.26)	13.1	8.5
	Gemcitabine/carboplatin		4.6	
First-SIGNAL[26]	Gefitinib	0.54 (0.27 to 1.1)	8.0	1.7
	Gemcitabine/cisplatin		6.3	
IPASS[12,13]	Gefitinib	0.48 (0.34 to 0.67)	NR†	NR†
	Paclitaxel/carboplatin		NR†	
NEJGSG002[36]	Gefitinib	0.32 (0.24 to 0.44)§	10.8	5.4
	Paclitaxel/carboplatin		5.4	
WJTOG34053405[31,37]	Gefitinib	0.49 (0.34 to 0.71)	9.2	2.9
	Docetaxel/cisplatin		6.3	

Where both central independent and local assessment are available for PFS, all values are those as assessed by local investigators; CI=confidence interval; NR=not reported; PFS=progression-free survival
* Chemotherapy was gemcitabine or docetaxel in combination with cisplatin or carboplatin
§ OPTIMAL[32] was only included in a sensitivity analysis conducted for the MTC
† The median PFS in months is not reported for EGFR-positive patients but for all patients of mixed EGFR status is reported to be 9.5 months vs 6.3 months, a difference of 3.2 months
§ Updated PFS results are reported here whereas original PFS results were presented in the MS. In both cases the hazard ratio was similar (0.30; 95% CI: 0.22 to 0.41) and median PFS in both arms was reported to be the same as the updated PFS

Table 15 Overall survival from studies of patients with activating EGFR mutations

Study	Treatments	5 6 7 Median OS, Hazard Ratio (95% CI)	Median OS (months)	Difference in mean OS (months)
LUX-Lung 3[18]	Afatinib	[redacted]	[redacted]	[redacted]
	Pemetrexed/cisplatin		[redacted]	
LUX-Lung 6[20]	Afatinib	0.95	[redacted]	Not estimable
	Gemcitabine/cisplatin	[redacted]	Not estimable	
EURTAC[28]	Erlotinib	1.04	19.3	0.2
	Chemotherapy†	(0.65 to 1.68)	19.5	
OPTIMAL[32]§	Erlotinib	1.06	Not reported	Not reported
	Gemcitabine/carboplatin	(95% CI not reported)	Not reported	
First-SIGNAL[26]	Gefitinib	1.04	27.2	1.8
	Gemcitabine/cisplatin	(0.49 to 2.18)	25.6	
IPASS[12,13]	Gefitinib	1.00	21.6	0.3
	Paclitaxel/carboplatin	(0.76 to 1.33)	21.9	
NEJGSG002[30,36]*	Gefitinib	0.88	27.7	1.1
	Paclitaxel/carboplatin	(0.63 to 1.24)	26.6	
WJTOG34053405[31,37]	Gefitinib	1.64	30.9	Not estimable
	Docetaxel/cisplatin	(0.75 to 3.58)	Not estimable	

CI=confidence interval; OS=overall survival
† Chemotherapy was gemcitabine or docetaxel in combination with cisplatin or carboplatin
§ OPTIMAL[32] was only included in a sensitivity analysis conducted for the MTC; OS data were not mature at the time of the original publication but have been presented at the 2010 ASCO Annual Meeting[77]
* OS data were not reported in the MS or used in the MTC conducted; updated OS data presented here

7.1.1 Quality assessment of included studies

The manufacturer presented its quality assessment of the included studies in Appendix 10.5 of the MS[1] (Table 143) and summarised here in Appendix 37.2. All trials were rated by the manufacturer as being 'average' to 'good'. In studies of EGFR-positive patients, only LUX-Lung 3[18] and LUX-Lung 6[20] were assessed to be 'good'. The ERG notes that all studies of EGFR-positive patients carried out appropriate randomisation techniques, although three studies[26,30,31] did not report sufficient data to adequately assess concealment of treatment allocation. Due to inherent differences in mode of administration between treatment arms, all trials were conducted using an open label approach.

In most studies, baseline characteristics were well balanced between treatment groups. Differences between arms in proportions of never smokers were observed in three studies (LUX-Lung 6,[20] NEJGSG002[30] and EURTAC[28]). All studies used an intention-to-treat analysis, although only LUX-Lung 3[18] and LUX-Lung 6[20] reported the method used to deal with missing data. Both trials discussed censoring of missing data, and LUX-Lung 3[18] stated

that there were no missing primary endpoint values. There was little evidence of outcome reporting bias in any of the studies.

All of the trials permitted crossover after disease progression (potentially causing attenuation of OS). None of the trials mentioned any testing of the assumption of proportional hazards.

7.1.2 Results

The results of the MTC for PFS are presented in the MS[1] (Table 34, page 117). The findings for both PFS (random effects) and OS (fixed effects) for afatinib vs TKIs and afatinib vs chemotherapy are summarised in Table 16. Hazard ratios greater than 1 indicate that the comparator to afatinib is more effective. A trend in favour of afatinib over both erlotinib and gefitinib was observed for PFS and OS but the treatment differences were not statistically significant.

The manufacturer undertook an additional sensitivity analysis that included data from OPTIMAL.[32] The results for are reported in the MS[1] on page 120. The conclusions remain unaltered by the inclusion of this study (afatinib vs erlotinib, hazard ratio, 95% credible intervals: PFS 0.82, 0.42 to 1.57 and OS 0.89, 0.63 to 1.25; afatinib vs gefitinib, hazard ratio, 95% credible intervals: PFS 0.65, 0.33 to 1.21 and OS 0.85, 0.55 to 1.30).

Table 16: Findings from the manufacturer's MTC presented in the MS

Comparison	**PFS (random effects): hazard ratio (lower and upper credible intervals)**	**OS (fixed effects): hazard ratio (lower and upper credible intervals)**
Afatinib vs erlotinib	0.91 (0.53 to 1.50)	0.80 (0.56 to 1.14)
Afatinib vs gefitinib	0.78 (0.47 to 1.20)	0.84 (0.55 to 1.30)
Afatinib vs pemetrexed/cisplatin	0.46 (0.32 to 0.66)	0.99 (0.78 to 1.27)
Afatinib vs gemcitabine/cisplatin	0.36 (0.25 to 0.52)	0.86 (0.67 to 1.10)
Afatinib vs vinorelbine/cisplatin	0.35 (0.21 to 0.53)	0.74 (0.56 to 0.98)
Afatinib vs docetaxel/cisplatin	0.34 (0.21 to 0.53)	0.85 (0.64 to 1.12)
Afatinib vs docetaxel/carboplatin	0.34 (0.16 to 0.68)	0.78 (0.57 to 1.07)
Afatinib vs paclitaxel/carboplatin	0.32 (0.20 to 0.49)	0.78 (0.59 to 1.02)
Afatinib vs gemcitabine/carboplatin	0.31 (0.17 to 0.57)	0.83 (0.60 to 1.15)
Afatinib vs paclitaxel/cisplatin	0.30 (0.18 to 0.47)	0.86 (0.65 to 1.14)
Total residual deviance	19	19
Between-study standard deviation	0.14 (0.02 to 0.34)	Not applicable
Deviance information criterion	-2.859	-13.537
Data Points	20	26

The ERG has a number of concerns relating to the MTC described in the MS. In order of priority, these are:

1. The MTC utilises data from 20 RCTs[12,18,20,26,28,30,31,51-63] that include patients of unknown/mixed EGFR status as well as patients who have EGFR-positive disease. When treating patients with NSCLC it is important to identify disease type, i.e. whether or not a patient has squamous disease or non-squamous disease, and whether a patient is EGFR-positive or EGFR-negative, as response to treatment is affected by disease type. In the original MTC, seven studies[12,18,20,26,28,30,31] include EGFR-positive patients and 13 studies[51-63] include patients of unknown/mixed EGFR status. Including a mix of patients with different disease types of NSCLC in a single MTC increases heterogeneity. The ERG is of the opinion that patient populations in the included trials are not sufficiently similar and, therefore the results generated by the original MTC are not generalisable to a UK population.

2. The objective of the MTC is to estimate hazard ratios for afatinib vs erlotinib and afatinib vs gefitinib. The MTC described in the MS for PFS and OS are based on hazard ratios and rely on the assumption of proportional hazards. If the hazards of competing interventions cross then this assumption is implausible.[78] The ERG notes that in the seven studies[12,18,20,26,28,30,31] that include EGFR-positive patients, the OS hazard functions cross; this may in part be explained by patient crossover as all of these trials permitted patients to crossover following disease progression. It is also clear from the PFS curves of at least three of the main RCTs included in the MTC (LUX-Lung 3,[18] IPASS[12] and EURTAC[28]) and in First-SIGNAL[26] that the proportional hazards assumption does not hold for PFS. When conducting a MTC, it is important that transitivity (i.e. the consistency assumption) holds for the treatment effect measure of interest. Violations of the proportional hazards assumption compromise transitivity and can result in biased comparisons of survival outcomes.[78] The ERG has highlighted in two previous appraisals[9,10] that use of conventional proportional hazards methods to estimate hazard ratios in erlotinib and gefitinib trials vs any other drug is problematic. The ERG, therefore, considers that the OS and PFS hazard ratios generated by the MTC are not robust.

3. The ERG is concerned about the consequences of including data from the EURTAC trial[28] in the MTC. This study compared erlotinib with chemotherapy (docetaxel/cisplatin, docetaxel/carboplatin, gemcitabine/cisplatin or gemcitabine/carboplatin) and the choice of specific regimen was made at the

investigator's discretion. OS and PFS hazard ratios are only reported for erlotinib vs chemotherapy. In the manufacturer's original MTC, the same hazard ratio is repeated four times in order to compare erlotinib to each of the four distinct chemotherapy regimens administered. It is not clear whether, if calculated, the hazard ratios would be the same for each of the four chemotherapy regimens as currently there is no evidence to suggest that this is true in an EGFR-positive population; there is only evidence to suggest that this assumption may be appropriate in an unknown/mixed EGFR population.[79] Nor is it clear whether repeating the same hazard ratio for multiple comparators is a valid approach to use in an MTC. Finally, the ERG notes that the EURTAC trial[28] is different from all of the other studies of EGFR-positive patients as it includes only non-Asian patients.

4. The ERG also identified other problems with selection and use of data in the MTC. For example, inclusion criteria used to identify studies of unknown/mixed EGFR is unclear; the ERG has identified an additional 13 studies that could have been included in a MTC of unknown/mixed status; a mix of mature and immature OS data were used; a mix of PFS and TTP data were used; two source studies[51,56] could not be located to verify clinical data; data for PFS and OS extracted from one study[54] could not be wholly verified; the ERG prefers use of local assessment PFS data as these data provide a more accurate reflection of clinical decision-making than central independent assessments (which were preferred by the manufacturer); outcome data from two studies[55,59] did not include all randomised patients; the findings from one arm (vinorelbine/cisplatin) of a three-arm trial was excluded from another trial;[58] and use of subgroups from two trials (IPASS[12] and First-SIGNAL[26]) meant that evidence was from non-randomised data.

Because of these concerns, in its clarification letter to the manufacturer, the ERG requested that the following sensitivity analyses for the MTC be conducted:

i. Using local investigator assessments (where available) instead of independent assessment for PFS

ii. Using updated OS data (where available)

iii. Using only data from the population of patients with EGFR activating mutations for both PFS and OS. These should be analysed as in (i) and (ii)

iv. Excluding EURTAC from (i), (ii) and (iii), even if this precludes a comparison with erlotinib

Given the ERG's concern that the studies included in the MTC report hazard ratios for survival outcomes that are not valid (based on the violation of the proportional hazards assumption), the results of all of the MTCs described in this appraisal must be treated with caution. The results from the additional analyses requested by the ERG are described below.

Original MTC including studies with patients of unknown/mixed EGFR status

Using local investigator PFS produced results that appeared to be more favourable to afatinib when compared with erlotinib and gefitinib. While no significant differences were observed between afatinib and erlotinib using either fixed or random effects, the results for afatinib vs gefitinib were statistically significant in favour of afatinib [hazard ratio 0.73 (95% credible interval: 0.54 to 0.98)] for the fixed effects analysis. However, for reasons highlighted in section 4.3.1, the random effects model was considered the most appropriate model but this did not produce statistically significant findings [hazard ratio 0.70 (95% credible interval: 0.43 to 1.10)]. Using a fixed effects model and updated OS evidence, for the comparison of afatinib vs gefitinib, this resulted in an OS hazard ratio of 0.86 (95% credible interval: 0.6 to 1.23) and, for the comparison of afatinib vs erlotinib, an OS hazard ratio of 0.80 (95% credible interval: 0.5 to 1.14). Overall, the findings indicate that the conclusions of the original MTC remain unchanged.Excluding EURTAC from this MTC meant that it was not possible to compare afatinib with erlotinib. The comparison of afatinib with gefitinib, excluding EURTAC[57] and using a random effects model, yielded central independent assessed PFS hazard ratio of 0.78 (95% credible interval: 0.43 to 1.30) and locally assessed PFS HR 0.70 (95% credible interval: 0.40 to 1.14). The comparison of afatinib with gefitinib, excluding EURTAC and using a fixed effects model, yielded OS hazard ratio of 0.91 (95% credible interval: 0.86 to 0.60 [the ERG notes that this upper credible interval is incorrectly reported by the manufacturer]). Overall, the findings indicate that the conclusions of the original MTC with regard to afatinib vs gefitinib remain unchanged.

MTC: EGFR-positive patients only

The results from the MTC of only EGFR-positive patients, using random effects for PFS and fixed effects for OS are summarised in Table 17. The resultant hazard ratios suggest slightly more favourable results for afatinib compared with both TKIs in relation to PFS but not in relation to OS. However, no finding was statistically significant. The wider confidence

intervals around the hazard ratios for PFS (in particular) and OS show the uncertainty around the results. Overall, the findings indicate that the conclusions of the original MTC remain unchanged.

Table 17: Findings of MTC including only patients of EGFR-positive status*

Comparator and outcome measure	Hazard ratio	Lower credible interval	Upper credible interval
Afatinib vs erlotinib			
Central independent PFS	0.7541	0.1021	5.653
Local investigator PFS	0.6858	0.09341	4.816
OS (updated data)	0.9395	0.5478	1.608
Afatinib vs gefitinib			
Central independent PFS	0.5441	0.06891	4.111
Local investigator PFS	0.4976	0.06342	3.595
OS (updated data)	0.863	0.4596	1.62

* Using random effects for PFS and fixed effects for OS

The ERG notes that excluding studies of patients with unknown/mixed EGFR status results in a MTC that relies heavily on data derived from the First-SIGNAL[26] subgroup analysis to compare afatinib with gefitinib. This subgroup analysis is based on data from only 42 participants; the ERG considers reliance on this small subgroup of patients may lead to imprecision.

The ERG also notes that, in the clarification response, the manufacturer provided an exploratory analysis to allow a clearer understanding of the effect of using the same hazard ratio more than once in the MTC when comparing erlotinib vs chemotherapy in the EURTAC[57] trial. Results showed that hazard ratios were comparable to the hazard ratios generated by the original MTC in the original MS.[1]

Including EURTAC in EGFR-positive MTC

Having raised a number of issues with EURTAC,[28] the ERG also notes that there are a number of strengths to this study, most notably that unlike any of the other studies of EGFR-positive patients, it contains only patients from Europe. In this respect, it is likely to produce results that are generalisable to the UK population, alongside results from the small subgroup of non-Asian patients from LUX-Lung 3.[18]

Limiting the MTC to EGFR-positive populations results in the inclusion of five studies[12,20,26,30,31] conducted in wholly Asian populations, one study (LUX-Lung 3[18]) conducted in a predominantly (≥70%) Asian population and the EURTAC[28] study conducted

solely in a European population. The ERG notes that the results of the original MTC do not change when only studies which include EGFR-positive populations are included.

However, permitting use of EURTAC[28] data in the MTC raises the question of whether or not it is meaningful to include Asian and non-Asian patients in a single MTC. Whether patients respond to EGFR targeted therapy regardless of ethnicity is unclear, however both the manufacturer's and ERG's subgroup analysis of PFS and OS presented in sections 4.2.6 and 4.2.7 respectively suggest otherwise.

Excluding EURTAC from EGFR-positive MTC

As already discussed, there exist a number of reasons to support exclusion of EURTAC[28] data from the EGFR-positive MTC. Importantly, excluding EURTAC[28] from this MTC means that a comparison of afatinib with erlotinib cannot be carried out. In addition, excluding EURTAC[28] from the EGFR-positive MTC means that the MTC comparing afatinib with gefitinib only includes Asian patients. The findings of the EGFR-positive MTC when EURTAC[28] is excluded demonstrate that when afatinib is compared with gefitinib the results of the analysis do not change but the hazard ratio for PFS has a wider confidence interval. Using a random effects model, independent assessment of PFS yields HR 0.50 (95% credible interval: 0.02 to 10.72) and local investigator assessment of PFS yields HR 0.48 (95% credible interval: 0.03 to 9.57). Using a fixed effects model, conclusions also remain unchanged for OS, as a trend being shown in favour of afatinib over gefitinib (HR 0.91 [95% credible interval: 0.40 to 2.04]), although this trend was not found to be significant. It is not clear whether or not this analysis used updated OS data.

However, as noted above, the ERG does not believe the results of an MTC which only includes Asian patients can be used to inform treatment decisions for patients in the NHS.

ERG conclusions

The ERG is therefore not confident that the results of any MTC which includes a mix of Asian and non-Asian patients can produce valid survival outcomes appropriate for use in a cost-effectiveness analysis generalisable to patients in England and Wales. The ERG is aware that these conclusions are based on evidence from a single RCT; however, the topic has been discussed previously by the Appraisal Committee in at least two previous appraisals.[9,10] Indeed, the ERG agrees with the manufacturer of erlotinib who stated in their MS[80] that ethnicity may be a 'treatment effect modifier for erlotinib (with East Asian patients experiencing more impressive treatment effects than Caucasian patients).' (page 18)

In summary, the ERG considers that to inform the calibration of a cost-effectiveness model for appraising treatments for use in the UK, it is only appropriate to employ data which have been generated from a specifically non-Asian population of EGFR-positive patients, whether in terms of primary clinical trials or supporting evidence for use in a simple indirect comparison or MTC. Figure 7 shows that the only TKI data pertaining to EGFR-positive patients from non-Asian populations are derived from a subgroup of LUX-Lung 3[18] and EURTAC[28] and there is no way to link the results of these two studies. In terms of clinical effectiveness, there are no data to compare afatinib with erlotinib or afatinib with gefitinib.

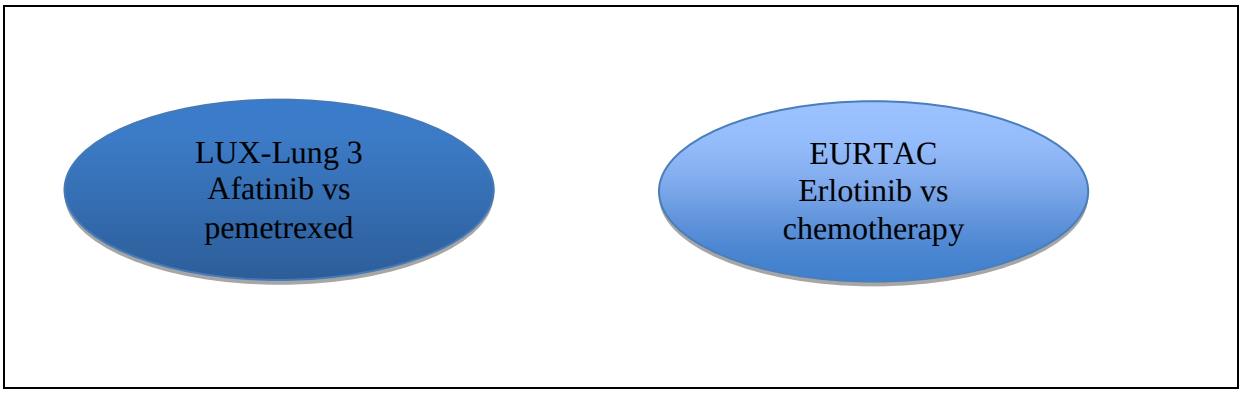

Figure 7 Evidence network used to inform MTC made up of non-Asian patients (OS or PFS)

7.2 Critique of the adverse event data

The manufacturer reported AEs of special interest from the phase III LUX-Lung 3[18] and LUX-Lung 6[20] RCTs and the single-arm phase II LUX-Lung 2[23] study. In addition, AEs of special interest are reported from the MTC. Additional information on AEs is presented in Appendix 32.1.1.

7.2.1 Adverse events of special interest reported from afatinib studies

Adverse events of special interest were identified to be diarrhoea and rash/acne. These were pre-specified as AEs of special interest due to the mechanistic action of TKIs. Leukopenia was a pre-specified AE of special interest due to the mechanistic action of chemotherapy. Hazard ratios were calculated for these three AEs and are reported in Table 18. As expected, the differences between treatment arms were significant for all of these AEs.

Table 18 Hazard ratios for adverse events of special interest, afatinib vs chemotherapy

Adverse event	LUX-Lung 3	LUX-Lung 6
Diarrhoea	11.49 (7.46 to 17.69) p<0.0001	12.44 (7.55 to 20.52) p<0.0001)
Rash/acne	17.97 (9.97 to 32.38) p<0.0001	11.50 (6.24 to 21.19) p<0.0001
Leukopenia*	0.05 (0.02 to 0.11) p<0.0001	[redacted]

*Not reported in MS but taken from CTR for LUX-Lung 6 (Table 12.2.2.3.4: 1)

Diarrhoea

The ERG notes that the proportion of patients with Grade 3 diarrhoea varied across studies from 5.9% (LUX-Lung 6[20]) to 20.2% (LUX-Lung 2[23]). The reasons for this difference are not clear. It may simply be a chance finding or may reflect differences in the populations of these studies, e.g. age, ethnicity, dose. No Grade 4 or 5 diarrhoea AEs were reported in any study. The first onset of diarrhoea tended to occur within the first 14 days after the start of treatment. Dose reductions and the need for therapy were common in all studies but discontinuation of treatment due to diarrhoea was rare.

Rash/acne

The ERG notes that the proportion of patients with Grade 3 rash/acne was similar in the two RCTs[18,20] but slightly higher in LUX-Lung 2.[23] The reasons for this difference are not clear but may be attributable to the higher dose of afatinib in LUX-Lung 2[23] . No Grade 4 or 5 rash/acne AEs were reported in any study. The onset of rash/acne was only reported for LUX-Lung 3[18] in the MS[1] and this was reported most frequently to occur within the first 2 weeks. Discontinuation of treatment due to rash/acne was rare in all studies. The ERG notes fewer patients were reported to require therapy for rash/acne in LUX-Lung 6[20] than in the other two studies.[20,23] The reasons for this are unclear.

7.2.2 Adverse events of special interest reported from indirect comparisons

In addition to the incidence of Grade 3/4 diarrhoea and rash/acne, the manufacturer also reports findings for Grade 3/4 fatigue from its MTC. It is not explicit why this particular AE was also chosen although the ERG notes it has been reported to be relatively common in patients treated with erlotinib.[28] The ERG also notes that with the exception of Scagliotti et al 2009,[63] all of the studies included only EGFR-positive populations.

The findings from the MTC suggest that diarrhoea is most likely in patients receiving afatinib (12.0%; 95% credible interval: 3.0% to 54.0%) followed by those receiving erlotinib (7.5%; 95% credible interval: 0.9% to 72.0%). Rash/acne is most probable in patients receiving

erlotinib (16.0%; 95% credible interval: 2.6% to 88.0%) followed by afatinib (14.0%; 95% credible interval: 3.5% to 56.0%). Fatigue is most probable for patients receiving gefitinib (5.2%; 95% credible interval: 0.11% to 74.0%) and pemetrexed/cisplatin (4.5%; 95% credible interval: 0.1% to 64.0%). However, as the manufacturer notes, the MTC models used to estimate the probability of AEs did not achieve convergence and therefore produced uncertain results (very wide credible intervals). This lack of convergence is caused by the low number of events in most treatment arms which in some instances, were reported to be zero.

Adverse event data for erlotinib and gefitinib were also derived from registration studies for these treatments (EURTAC[28] and IPASS[12] respectively). The ERG notes that a descriptive comparison of these data suggests that the incidence of diarrhoea was higher for those receiving afatinib compared with erlotinib or gefitinib; the incidence of rash/acne was reasonably similar for those receiving afatinib and erlotinib but lower for those receiving gefitinib. Erlotinib had higher rates of fatal serious AEs and gefitinib had the lowest proportion of patients requiring dose modification. Discontinuation rates were broadly similar across the trials. The manufacturer argues this indicates that AEs reported in afatinib trials are adequately managed with supportive care and appropriate dose reductions and that there is little impact on patient compliance.

7.3 Critique of the health related quality of life data

For the primary HRQoL outcomes, data were collected using the EORTC QLQ-C30[81] and EORTC QLQ-LC13[82] questionnaires which have been developed to assess the quality of life of cancer patients and lung cancer patients respectively. In addition, HRQoL data were collected using the EQ-5D,[83] a standardised instrument for measures of health outcome that is applicable to a wide range of health conditions.

Health-related quality of life data, as measured by the EORTC QLQ-C30 and presented in the MS[1] (Table 15, page 73) are summarised in Table 19 below. The results show a significant trend in favour of afatinib over pemetrexed/cisplatin in time to deterioration in coughing and time to deterioration in dyspnoea. No significant differences were observed for time to deterioration in pain. In comparison to gemcitabine/cisplatin, afatinib was found to significantly improve scores for time to deterioration in coughing, dyspnoea and pain.

Patients with missing HRQoL data were censored for time to event analyses. In case of more than one consecutive missed assessment, patients were censored at the date of the

last imaging assessment. No further information is provided regarding how missing data were dealt with.

The MS[1] reports compliance rates of 87% to 99% for HRQol questionnaire completion in LUX-Lung 3,[18,19] with compliance rates being similar between treatment groups. For LUX-Lung 6,[20] compliance rates were found to be higher than 90% for both treatment groups. The MS provides n values for the time to deterioration in coughing, dyspnoea, and pain related items of EORTC QLQ-C30 and EORTC QLQ-L13, and the ERG queried whether these values implied 100% response rates for these questions. The manufacturer clarified that the n values indicate the number at risk at the beginning of the study, rather than compliance. Therefore, the ERG found information regarding compliance to be insufficient.

In addition, results from a longitudinal model (adjusting for EGFR mutation category and ethnicity) of the effects of randomised treatment on EQ-5D are reported in brief. It is stated that these are reported in the Health Economic Report for LUX-Lung 3.[84] No significant differences between treatments were observed.

Table 19: HRQoL findings in LUX-Lung 3 and LUX-Lung 6

Endpoints	LUX-Lung 3[19]			LUX-Lung 6[21]		
	Afatinib (n=230)	Pemetrexed/ cisplatin (n=115)	Difference	Afatinib (n=242)	Gemcitabine/ cisplatin (n=122)	Difference
HRQOL (Status change in EORTC LC13/C30)						
LC13/C30)						
Dyspnoea	64.0%	50.0%	p=0.0103	70.9%	47.5%	p<0.0001
dyspnoea when climbing stairs	52.0%	37.0%	p=0.0109	62.8%	47.5%	p<0.0001
Shortness of breath	57.0%	36.0%	p=0.0004	58.2%	41.6%	p<0.0061
Pain	59.0%	48.0%	p=0.0513	64.3%	46.5%	p=0.0029
Have pain	56.0%	40.0%	p=0.0095			
Pain in chest	51.0%	37.0%	p=0.0184	50.0%	36.0%	p=0.0211
Pain in arm or shoulder	41.0%	26.0%	p=0.0103	47.6%	38.6%	p=0.1395
Cough	67.0%	60.0%	p=0.2444	75.9%	55.4%	p=0.0003
Global health status	50.0%	46.0%	p=0.4737	62.7%	32.7%	p<0.0001
Physical functioning	40.0%	34.0%	p=0.2321	54.2%	28.7%	p<0.0001
Role functioning	49.0%	45.0%	p=0.5119	49.6%	34.7%	p=0.0129
Social functioning	47.0%	49.0%	p=0.8070	55.3%	34.7%	p=0.0007
Fatigue	72.0%	57.0%	p=0.0087	77.2%	52.5%	p<0.0001
Time to deterioration (EORTC LC13/C30)						
Cough			0.60 (0.41 to 0.87)			0.45 (0.30 to 0.69)
Hazard Ratio (95% CI)			p=0.0072			p=0.0001
P value						
Dyspnoea			0.68 (0.50 to 0.93)			0.54 (0.40 to 0.73)
Hazard ratio (95% CI)			p=0.0145			p <0.0001
P value						
Pain			0.83 (0.62 to 1.10)			0.70 (0.51 to 0.96)
Hazard ratio (95% CI)			p=0.1913			p=0.0265
P value						

CI=confidence interval

7.4 Additional work on clinical effectiveness undertaken by ERG

In addition to the sensitivity analyses requested by the ERG in its clarification letter. the ERG undertook an MTC on the EGFR mutation positive population as a sensitivity analysis, assuming all chemotherapy doublets (except for pemetrexed/cisplatin) were the same (Figure 8).

Similar to the MTC reported in the MS, a burn-in of 20,000 simulations was discarded and the results presented are based on a further sample of 50,000 simulations. There are no loops in this network, so there is no scope to identify inconsistency.

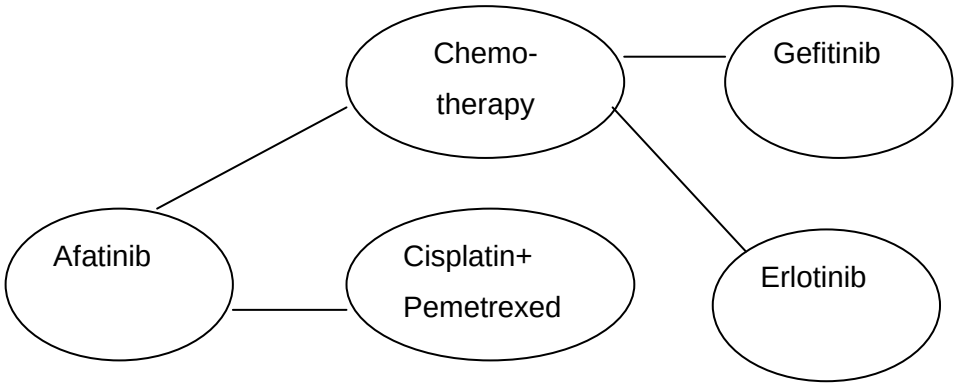

Figure 8: Evidence network used to inform the MTC

The fixed and random effects models were investigated for the MTC. As with the MTC reported in the MS, and for the same reasons (see section 4.3.1), the random effects model was used for PFS and the fixed effects model was used for OS. The results for PFS and OS are shown in Table 20 and indicate that there are no changes in the conclusions by treating the chemotherapy doublets as the same.

The ERG emphasises that this is an exploratory analysis and reiterates that it is not aware of any evidence suggesting that doublets are equally efficacious in populations of patients with EGFR-positive NSCLC. It also suffers from the same limitations as the manufacturer's MTCs, namely it assumes proportional hazards when there appears to be limited evidence for this assumption and the majority of patients included in the analyses are of Asian origin.

Table 20: Findings from the MTC of EGFR-positive population assuming chemotherapy doublets (except for pemetrexed/cisplatin) to be of equal efficacy

Comparator and outcome measure	Hazard ratio	lower credible interval	upper credible interval
Afatinib vs erlotinib			
Central independent PFS (Findings from manufacturer's MTC)*	0.7614 0.7541	0.1500 0.1021	3.8480 5.6530
Local investigator PFS (Findings from manufacturer's MTC)*	0.7072 0.6858	0.1377 0.0934	3.5780 4.8160
OS (updated data) (Findings from manufacturer's MTC)*	0.9137 0.9395	0.5108 0.5478	1.6260 1.6080
Afatinib vs gefitinib			
Central independent PFS (Findings from manufacturer's MTC)*	0.6597 0.5441	0.1770 0.0689	2.3220 4.1110
Local investigator PFS (Findings from manufacturer's MTC)*	0.6115 0.4976	0.1621 0.0634	2.1870 3.5950
OS (updated data) (Findings from manufacturer's MTC)*	0.9530 0.8630	0.6485 0.4596	1.4010 1.6200
Afatinib vs pemetrexed/cisplatin			
Central independent PFS (Findings from manufacturer's MTC)*	0.2808 Not reported	0.0887 Not reported	0.8783 Not reported
Local investigator PFS (Findings from manufacturer's MTC)*	0.2606 Not reported	0.08181 Not reported	0.8338 Not reported
OS (updated data) (Findings from manufacturer's MTC)*	0.9502 Not reported	0.6801 Not reported	1.3270 Not reported
Afatinib vs gemcitabine/cisplatin			
Central independent PFS (Findings from manufacturer's MTC)*	0.5777 Not reported	0.1847 Not reported	1.8130 Not reported
Local investigator PFS (Findings from manufacturer's MTC)*	0.4902 Not reported	0.1532 Not reported	1.5550 Not reported
OS (updated data) (Findings from manufacturer's MTC)*	0.9094 Not reported	0.6609 Not reported	1.2490 Not reported

PFS data are based on the random effects model and OS data are based on the fixed effects model

* The ERG analysis treats all chemotherapy doublets (other than pemetrexed/cisplatin) as the same and which therefore only includes the hazard ratio from EURTAC[28] in the analysis only once. The manufacturer's findings are from its MTC of EGFR-positive patients (reported in the response to the ERG's clarification letter) which treats all doublets separately

7.5 Conclusions of the clinical effectiveness section

Afatinib was directly compared with first-line chemotherapy in LUX-Lung 3[18,19] and LUX-Lung 6.[20,21] Both RCTs were of reasonable quality and the trial results suggest advantages in PFS for patients with adenocarcinoma and activating EGFR mutations who were treated with afatinib over patients treated with chemotherapy. There is no evidence of a similar OS advantage for these patients. The most common AEs in the afatinib arms of the trials were diarrhoea and rash/acne. Discontinuations due to AEs related to afatinib were uncommon. Self-reported HRQoL assessments appear to favour afatinib over chemotherapy.

The final scope issued by NICE states that the relevant comparators to afatinib are erlotinib and gefitinib. In LUX-Lung 3[18,19] and LUX-Lung 6[20,21] the comparators to afatinib are pemetrexed/cisplatin and gemcitabine/cisplatin respectively; these comparators are not specifically recommended by NICE for treatment of EGFR-positive patients in England and Wales. Nevertheless, LUX-Lung 3[18,19] is the first trial to compare a TKI directly with pemetrexed/cisplatin and therefore presents much awaited clinical data on use of pemetrexed/cisplatin in an EGFR-positive population.

Both gefitinib and erlotinib were recommended by NICE for the first-line treatment of patients with activating EGFR mutations based, primarily, on a PFS advantage for patients receiving TKIs compared with patients receiving chemotherapy. The ERG notes that, compared with chemotherapy, there is no evidence of OS gain for use of erlotinib or gefitinib in patients with activating EGFR mutations.

No direct evidence exists for the comparison of afatinib with erlotinib or the comparison of afatinib with gefitinib. The manufacturer considered the decision problem set by NICE by exploring whether indirect evidence comparisons could be carried out reliably using an MTC approach. The manufacturer presented the results of several MTCs which appeared to demonstrate that there was no clinical evidence to suggest that afatinib was any more or less efficacious than erlotinib or gefitinib.

The ERG considered the results of the MTCs and concluded that none of the results of the MTCs could be relied upon to inform the decision set by NICE. [redacted] Even if there were no evidence to suggest that Asian patients have improved survival outcomes compared to non-Asians, the

results of the MTCs would remain flawed as the required assumption of proportional hazards used in all of the MTCs appears to be violated in several, if not all, of the included studies.

High crossover rates in trials often mask real differences in OS. [redacted] crossover does not provide a simple explanation for the lack of OS gain in all trials.

The full range of results from all the different analyses are summarised in **Error! Reference source not found.Error! Reference source not found.** which enables the reader to compare the different values for the hazard ratios generated by the analyses. The ERG reiterates that hazard ratios are only valid if proportional hazards can be assumed, an assumption the ERG disputes based on the Kaplan-Meier curves of the included studies. The ERG also cautions that the findings are derived from populations in which the majority of patients are Asian and are therefore not generalisable to England and Wales.

Table 21: Comparison of all hazard ratios generated by different analyses explored

Approach	Comparison	PFS	OS
Descriptive comparisons (original trial results)[c]	Afatinib vs pemetrexed/cisplatin Afatinib vs gemcitabine/cisplatin Erlotinib vs chemotherapy Gefitinib vs gemcitabine/cisplatin	0.49 (0.37 to 0.65) 0.26 (0.19 to 0.36) 0.37 (0.25 to 0.54) 0.54 (0.27 to 1.10)	0.91 (0.66 to 1.25) 0.95 (0.68 to 1.33) 1.04 (0.65 to 1.68) 1.04 (0.49 to 2.18)
LUX-Lung 3 subgroup analysis requested by ERG	Afatinib vs pemetrexed/cisplatin: Asian subgroup Non-Asian subgroup	 0.45 (0.33 to 0.62) 0.62 (0.36 to 1.06)	 1.00 (0.68 to 1.46) 0.80 (0.46 to 1.40)
MTC in MS[a]	Afatinib vs erlotinib Afatinib vs gefitinib Afatinib vs pemetrexed/cisplatin Afatinib vs gem/cis	0.91 (0.53 to 1.50) 0.78 (0.47 to 1.20) 0.46 (0.32 to 0.66) 0.36 (0.25 to 0.52)	0.80 (0.56 to 1.14) 0.84 (0.55 to 1.30) 0.99 (0.78 to 1.27) 0.86 (0.67 to 1.10)
MTC minus EURTAC[b]	Afatinib vs erlotinib Afatinib vs gefitinib Afatinib vs pemetrexed/cisplatin Afatinib vs gemcitabine/cisplatin	Not estimable 0.70 (0.41 to 1.11) Not reported Not reported	Not estimable 0.91 (0.86 to 0.6)* Not reported Not reported
MTC with EGFR-positive population[b]	Afatinib vs erlotinib Afatinib vs gefitinib Afatinib vs pemetrexed/cisplatin Afatinib vs gemcitabine/cisplatin	0.69 (0.09 to 4.82) 0.50 (0.06 to 3.60) Not reported Not reported	0.94 (0.55 to 1.61) 0.86 (0.46 to 1.62) Not reported Not reported
8 M TC with EGFR-positive population minus EURTAC[b]	9 Afatinib vs erlotinib 10 Afatinib vs gefitinib Afatinib vs pemetrexed/cisplatin Afatinib vs gemcitabine/cisplatin	Not estimable 0.48 (0.03 to 9.57) Not reported Not reported	Not estimable 0.91 (0.40 to 2.04) Not reported Not reported

For all MTC analyses, the random effects results are presented for PFS and fixed effects for OS

a central independently assessed PFS where available b local investigator assessed PFS where available c LUX-Lung 3[18] , LUX-Lung 6,[20] EURTAC[28] and First-SIGNAL[26] respectively
* The upper confidence interval appears to be reported incorrectly in the manufacturer's clarification response

In summary, the ERG considers that, with the evidence currently available, it is impossible to demonstrate the relative clinical effectiveness of afatinib compared with erlotinib, or of afatinib compared with gefitinib, in a UK patient population. It is anticipated that the findings from the on-going LUX-Lung 7[25] trial, which is due to report in December 2014 on a direct comparison between afatinib and gefitinib, may shed some light on the issue. These results, which are not expected before the end of 2014, are eagerly awaited.

11 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by Boehringer Ingelheim in support of the use of afatinib in adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations. The two key components of the economic evidence presented in the MS are (i) a systematic review of the relevant literature and (ii) a report of the manufacturer's de novo economic evaluation. Table 22 contains details of the location of key information within the MS. The manufacturer also provided an electronic version of their economic model which was developed in Microsoft Excel.

Table 22 Location of key economic information in the MS

Key information	Page number	Tables/figures
Details of the systematic review of the economic literature	155 to 159	Tables 62 to 63, Figure 32
De novo analysis	159 to 163	Tables 64, Figure 33
Clinical parameters and variables	163 to 179	Tables 65 to 76, Figures 34
Measurement and valuation of health effects	179 to 192	Tables 77 to 86, Figures 35
Resource identification, measurement and valuation	193 to 208	Tables 87 to 116, Figures 36
Methods of sensitivity analysis	209 to 214	Tables 117 to 123
Results: base-case analysis	214 to 220	Tables 124 to 128, Figures 37 to 39
Results:sensitivity analysis	220 to 227	Tables 129 to 138, Figures 40 to 45
Validation	227	
Interpretation of economic evidence	229 to 230	
Assessment of factor relevant to the NHS and other parties	231 to 233	

11.1 ERG comment on manufacturer's review of cost-effectiveness evidence

11.1.1 Objective of the manufacturer's cost-effectiveness review

On page 155 of the MS[1] the manufacturer states that a systematic review was undertaken and explains that the scope of the review was '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'.

Details of the search strategies employed are included in the appendices of the MS[1] (pages 260-263). Embase, Medline & Medline In-process, and EconLit were searched via the OVID platform whilst the Cochrane Library was searched via the InterScience platform. The time horizon for the search was limited to studies published from 2002-2012 (inclusive).

The search of the literature yielded 3710 citations; however 149 were duplicates and so only 3561 records were screened. Following review, no studies that included afatinib as the intervention of interest were identified and, for this reason, all 3651 records were excluded.

The ERG is satisfied with the manufacturer's search strategy and is reasonably confident that the manufacturer did not miss any relevant published articles.

11.1.2 Inclusion/exclusion criteria used in the study selection

The inclusion/exclusion criteria used in the study selection are presented in Table 23. The ERG are satisfied that these are relevant to the decision problem.

Table 23 Economic evaluation search inclusion and exclusion criteria

Criterion	Choice of criterion	Rationale for choice of criterion
Disease	NSCLC	As decision problem
Gender	Male or female	As decision problem
Age groups	Adults (>18 years)	As decision problem
Ethnicity	Any	As decision problem
Aim of treatment	Improvement in PFS and HRQoL in patients with locally advanced or metastatic NSCLC with EGFR mutations	Only studies examining the effectiveness of therapies in terms of improvement in PFS and HRQoL in patients with NSCLC are relevant to the decision problem
Treatment lines	All lines of treatment for patients with locally advanced or metastatic NSCLC with EGFR mutations	As decision problem
Intervention	Afatinib	Only studies including afatinib are relevant to the decision problem
Study design	Economic evaluation (cost effectiveness, cost utility, cost-benefit or cost-minimisation)	As 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 language only	This is a simplifying criterion for the review; however, it is not expected that the restriction would limit results substantially

EGFR=epidermal growth factor receptor; HRQoL=health related quality of life; NSCLC=non-small cell lung cancer; PFS=progression-free survival

11.1.3 Included and excluded studies

No relevant studies were identified.

11.1.4 Conclusions of the cost-effectiveness review

The ERG notes that since afatinib monotherapy has only recently received marketing authorisation from the EMA CHMP for the treatment of EGFR-TKI-naïve adult patients with

locally advanced or metastatic NSCLC with activating EGFR mutations, the lack of economic evaluations of relevance to the decision problem is not unexpected.

The ERG is satisfied with the manufacturer's search strategy and eligibility criteria for inclusion and is reasonably confident that the manufacturer did not miss any relevant published articles.

11.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

The model compares afatinib monotherapy with other TKIs in a first-line setting. No comparison is made between afatinib and chemotherapy. No economic modelling been carried out to support the use of afatinib as a second-line treatment. However, the manufacturer reports that results from LUX-Lung 2[23] showed no significant difference in ORR in patients receiving afatinib as a first-line treatment (40/61 patients [66%]) and those receiving second-line treatment (39/68 [57%]; Odds ratio 0.71, 0.35 to 1.44). Although the manufacturer recognises that this trial was not powered to detect differences between the two groups they suggest that if afatinib is cost effective compared with gefitinib and erlotinib as a first-line treatment, and outcomes for first and second-line patients receiving afatinib are similar then, if afatinib were compared with gefitinib and erlotinib second-line ICERs would be similar. The manufacturer recognises that this would require the additional assumption that gefitinib and erlotinib were equally efficacious in second-line as in first-line.

11.2.1 NICE reference case checklist (TABLE ONLY)

Table 24 NICE reference case checklist

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by the Institute	Yes
Comparator(s)	Alternative therapies routinely used in the NHS	Yes, however, clinical advice suggests that non-squamous patients who have received a TKI first-line will go on to receive pemetrexed-cisplatin second-line
Perspective costs	NHS and Personal Social Services	Partial - only NHS costs were included in the model and, in addition, terminal care costs were not considered
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes
Synthesis of evidence on outcomes	Systematic review	A systematic review was undertaken.
Outcome measure	Quality adjusted life years	QALYs were used, which is appropriate
Health states for QALY	Described using a standardised and validated instrument	EQ-5D was used, with PFS values being derived from LUX-Lung 3 trial data[84]
Benefit valuation	Time-trade off or standard gamble	Time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	UK tariffs were used.[85]
Discount rate	An annual rate of 3.5% on both costs and health effects	Benefits and costs were discounted at a rate of 3.5%
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	All QALYs estimated by the economic model have the same weight
Sensitivity analysis	Probabilistic sensitivity analysis	Yes – deterministic, scenario and probabilistic analyses were undertaken by the manufacturer

TKI=tyrosine kinase inhibitor; QALY=Quality adjusted life year; QoL=quality of life

Table 25 Critical appraisal checklist for the economic analysis

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	No	The absence of any trial comparing the therapeutic regimens included in the scope has made the question very difficult to answer.
Was a comprehensive description of the competing alternatives given?	Yes	-
Was the effectiveness of the programme or services established?	No	The absence of trial data in the model, and the reliance on hazard ratios, leads to considerable uncertainty in relation to both PFS and OS outcomes for all therapies.
Were all the important and relevant costs and consequences for each alternative identified?	Mostly	The ERG notes that neither terminal care costs nor social care costs were considered in the model. Furthermore, health state costs were based on care received during various trials (mainly recruiting Asian patients) and it is unclear whether these costs reflect the care received by NHS patients in England and Wales
Were costs and consequences measured accurately in appropriate physical units?	Partial	BNF costs rather than eMit prices were used to estimate the purchase price of docetaxel, leading to a substantial overestimate in the cost of this therapy. Furthermore, the cost associated with Grade 3/4 fatigue lacks credibility
Were the cost and consequences valued credibly?		The ERG considers that the manufacturer's estimates of PFS and OS lack credibility
Were costs and consequences adjusted for differential timing?	Partial	The use of half-cycle correction was implemented incorrectly which led to underestimates in drug and health care costs for all comparators
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	ICERs calculated correctly
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic, scenario and probabilistic sensitivity analyses were undertaken
Did the presentation and discussion of study results include all issues of concern to users?	Yes	-

PFS=progression-free survival; OS=overall survival; eMit=Electronic Market Information Tool; ICER=incremental cost-effectiveness ratio; MTC=multiple treatment comparison; pem-cis=pemetrexed with cisplatin

11.2.2 Model structure

The manufacturer's cost-effectiveness model is a disease-state cohort model, a schematic of which is shown in Figure 9. The model comprises three health states, PFS, progressed disease (PD) and Death. All patients enter the model in the PFS health state. At the beginning of each time period patients can either remain in the same health state or progress to a 'worse' health state, i.e. from PFS to PD or Death; or from PD to Death. 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 PD state is estimated as the difference between OS and PFS. Estimates of OS and PFS are based on PFS and OS survival data from LUX-Lung 3[34] and LUX-Lung 6,[35] and the corresponding parametric survival models. Variants of this model structure have been used in the modelling of metastatic oncology for numerous NICE STAs, including NICE TA192[86] , NICE TA258[80] and NICE TA295[87] .

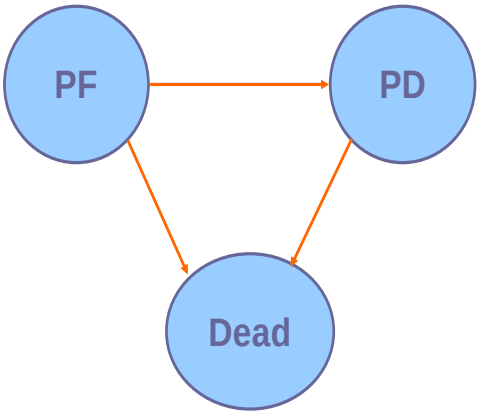

Figure 9 Schematic of manufacturer's model

The model has been developed in MS Excel and has a 1- month cycle length. It includes a half-cycle correction and the time horizon is set at 10 years. A discount rate of 3.5% has been used for both costs and outcomes and the perspective is stated to be that of the NHS and Personal Social Services (PSS).

11.2.3 Population

No population specific details are included in the economic model.

11.2.4 Interventions and comparators

The model allows two different first-line comparisons to be undertaken, namely afatinib vs gefitinib and afatinib vs erlotinib. Irrespective of first-line treatment, all patients are assumed to receive docetaxel as second-line therapy and this is followed by Best Supportive Care (BSC).

Patients receiving afatinib, gefitinib or erlotinib are assumed to receive one oral dose per day until disease progression. The MS states that docetaxel is administered every 3 weeks and patients may receive up to four cycles of treatment. Treatment doses are summarised in Table 26.

Table 26 Treatment doses

	Dose	Pack size	Comment
First-line			
Afatinib	Not specified	Not yet determined	
Gefitinib	1 x 250mg tablet/day	30 tablets	
Erlotinib	1 x 150mg tablet/day	30 tablets	
Second-line			
Docetaxel	75mg/m^2	20mg/ml, 4ml vial	4 cycles

11.2.5 Perspective, time horizon and discounting

The manufacturer states that the economic appraisal is undertaken from the perspective of the NHS and PSS. However, it should be noted that the model does not actually include any PSS costs and no justification is provided for their omission. Outcomes are expressed in terms of gains in life years and quality adjusted life years (QALYs). The time horizon is set at 10 years and, in line with the NICE Methods Guide to Technology Appraisal,[88] both costs and benefits are discounted at 3.5%.

11.2.6 Treatment effectiveness and extrapolation

The model considers the following lines of treatment:

- First-line: afatinib vs gefitinib or afatinib vs erlotinib
- Second-line: docetaxel
- Third-line: BSC

Modelling first-line PFS and OS

Hazard ratios for afatinib vs pemetrexed/cisplatin were calculated from LUX-Lung 3[34] data. Hazard ratios for erlotinib and gefitinib were calculated from MTCs (which did not include the OPTIMAL trial,[32] but did include LUX-Lung 6).[35] The MTC from which PFS hazard ratios were estimated used a random effects model whilst that used to estimate OS hazards used a fixed effects model.

Due to the use of hazard ratios it was necessary to choose a proportional hazards model (i.e. exponential, Weibull or Gompertz). The manufacturer reports that the Akaike Information Criterion Score (AIC) indicated that, for both PFS and OS, the Weibull model had the best goodness of fit to the Kaplan-Meier survival data from the LUX-Lung 3 trial.[34]

Survival for the afatinib arms was estimated by applying the calculated hazard ratios to the survival data from the pemetrexed/cisplatin arm of the LUX-Lung 3 trial.[34] Survival for the erlotinib and gefitinib arms was estimated by applying the calculated hazard ratios to the afatinib Weibull survival model. The hazard ratios used in the model base-case are displayed in Table 27.

Table 27 Hazard ratios used in the model base-case to generate Weibull survival models

	Value	CI	Location in MS	Source
PFS hazard ratios				
Afatinib vs pemetrexed/cisplatin	0.61	0.46 to 0.82	Table 65	LUX-Lung 3 trial[34]
Afatinib vs erlotinib	0.91	0.53 to 1.50	Values extracted from the model	MTC (RE model)
Afatinib vs gefitinib	0.78	0.47 to 1.20		MTC (RE model)
OS hazard ratios				
Afatinib vs pemetrexed/cisplatin	0.96	0.70 to 1.31	Table 66	LUX-Lung 3 trial[34]
Afatinib vs erlotinib	0.80	0.56 to 1.14	Values extracted from the model	MTC (FE model)
Afatinib vs gefitinib	0.84	0.55 to 1.30		MTC (FE model)

CI=confidence interval; FE=fixed effects; MS=manufacturer's submission; MTC=mixed treatment comparison; PFS=progression-free survival; OS=overall survival; RE=random effects; vs=versus

Survival in progressive disease (PD) was estimated by subtracting PFS from OS.

Modelling second-line treatment

The proportion of the PD period that patients are assumed to spend on active second-line treatment is based on a median PFS time for second-line treatment with docetaxel for EGFR-positive patients reported in the EMA's EPAR for gefitinib.[89] The time spent on treatment is assumed to remain constant across treatment arms irrespective of the relative period that the patients in the two arms spend in the PD state. A proportionally adjusted version (depending on overall length of time in PD) is considered as a sensitivity analysis (SA).

It is assumed that the second-line treatment, for all patients, is docetaxel monotherapy.

Modelling third-line treatment

It was assumed that during the remaining time in PD patients receive third-line therapy (i.e. BSC). The length of this period of time was calculated, for each arm, by subtracting the time spent on second-line therapy from the estimated total time spent in PD. The time spent on second-line therapy was based on published estimated median PFS times for second-line therapy.[89] The total time spent in PD was calculated based on the difference between OS and PFS derived from the parametric survival models. Details are displayed in Table 28.

Table 28 Time (in months) spent in each PD component by treatment arm

	First-line therapy		
	Afatinib	**Erlotinib**	**Gefitinib**
Estimated total period in PD (from parametric survival models)	19.45	15.95	18.14
Mean period in second-line (docetaxel monotherapy)*	4.10	4.10	4.10
Mean period in third-line (BSC)	15.35	11.85	14.04

* Note that this value is actually reported in the EMA report[89] as being the median - the manufacturer has assumed that the mean value equals the median value

11.2.7 Health related quality of life

Key model utility values for PFS and PD are displayed in Table 29 and Table 30 respectively.

Progression-free survival

Disutilities associated with key Grade 3/4 AEs were combined with the mean EQ-5D PFS utility score from the LUX-Lung 3 trial[34] for patients with no key AEs. The disutilities for diarrhoea and rash/acne were taken from the LUX-Lung 3 trial,[34] the disutility associated with fatigue was taken from the LUX-Lung 1 trial[90] and the disutilities associated with anaemia and neutropenia were taken (directly) from the Nafees et al study.[91]

The ERG notes that the PFS value used in the manufacturer's model (0.784) is noticeably higher than values reported in the Nafees et al study[91] (0.672 [responding] and 0.653 [stable disease]).

Progressive disease

Utility values in the PD state were extracted from the Chouaid et al poster.[92] Values for second-line and third-line therapy were weighted by the estimated time that patients stay in each of these states. The result is a utility value of 0.509 for the whole PD period.

Table 29 PFS utility values

State	Utility value	SE	Location in MS	Source
Estimated PFS utility				
Utility in progression-free state (no AEs)	0.784	0.009	Table 83	LUX-Lung 3[34]
Estimated PFS disutilities				
Diarrhoea (Grade 3/4)	-0.147	0.045	Table 86	LUX-Lung 3[34]
Rash/acne (Grade 3/4)	-0.202	0.028	Table 86	LUX-Lung 3[34]
Fatigue (Grade 3/4)	-0.179	0.053	Table 86	LUX-Lung 1[90]
Anaemia	-0.073	0.019	Table 86	MS for TA181:[93] Disutility for fatigue presented in Nafees et al[91] (2008) used for anaemia
Neutropenia	-0.090	0.015	Table 86	Nafees et al 2008[91]

AE=adverse event; SE=standard error: MS=manufacturer submission

Table 30 Progressive disease utility values

State	Utility value	Location in MS	Source
Utility in progressive disease state, afatinib	0.517	Table 85	Chouaid et al 2012[92]
Utility in progressive disease state, erlotinib	0.529	Table 85	Chouaid et al 2012[92]
Utility in progressive disease state, gefitinib	0.521	Table 85	Chouaid et al 2012[92]

MS=manufacturer's submission

11.2.8 Resources and costs

Drug acquisition and administration costs

Drug acquisition costs are displayed in Table 31 and administration costs are displayed in Table 32.

The list prices, rather than the PAS prices, for erlotinib and gefitinib have been used in the base-case comparison. The daily cost of afatinib has been set to equal the daily cost of gefitinib.

The docetaxel drug cost was calculated using the BNF price[94] under the assumption that there was no vial sharing. Patients were assumed to have received four cycles of chemotherapy.

Table 31 Drug acquisition costs

	Unit	BNF cost per pack	Dose	Cost per month*
Erlotinib	30 x 150mg	£1631.53	1 x 150mg daily	£1654.19
Gefitinib	30 x 250mg	£2167.71	1 x 250mg daily	£12,200 on receipt of third pack
Afatinib	28 x 40mg	£2167.71	1 x 40mg daily	£2197.82
Docetaxel	250mg/ml, 4ml vial	£534.75	4 cycles of 75mg/m^2 every 21 days	£1549.25

* 1 month=30.42 days

Table 32 Drug administration costs

	Afatinib, erlotinib and gefitinib	Docetaxel	Reference
Introductory cost	£163		DH 2013[95]
Monthly administration cost (SB14Z)		£302.41	DH 2013[95]
Gefitinib PAS			
PAS set up cost	£70		Roche, 2011[80]
PAS administration cost	£34		Roche, 2011[80]

PAS=patient access scheme

Health state costs

First-line costs were estimated from LUX-Lung 3[34] resource use data, second-line costs were taken from Lewis et al[96] and third line/progressive disease costs were estimated from LUX-Lung 1[96] resource use data. Summary details are provided in Table 33.

Table 33 Health state costs

	Included elements	Value/month	Source
First-line PFS	**Outpatient visits** (CT scan, MRI scan, surgical procedure, ultrasound, x-ray, radiotherapy, GP, specialist, nurse, occupational therapist, physiotherapist) **Unscheduled hospitalisations** (ICU visit, emergency room visit)	£220	LUX-Lung 3[34]
Second-line PFS	Not reported	£362	Lewis et al 2010[96]
Third-line/progressive disease	**Outpatient visits** (GP, specialist, nurse, occupational therapist, physiotherapist) **Outpatient interventions** (blood transfusion, CT scan, infusion, MRI scan, physical therapy respiratory therapy, surgical procedure, ultrasound, x-ray, radiotherapy) **Unscheduled hospital stay** (ICU visit, emergency room)	£418	LUX-Lung 1[90]

CT= computed tomography; GP=general practitioner; ICU=intensive care unit; MRI=magnetic resonance imaging

Adverse event costs were estimated from LUX-Lung 3[34] and LUX-Lung 1[90] trial data and also from a recent NICE NSCLC technology appraisal.[93] Details are summarised in Table 34.

Table 34 Adverse event costs

	Cost	Source
Diarrhoea	[redacted]	Resource use data extracted from LUX-Lung 3[34]
Rash/acne	[redacted]	Resource use data extracted from LUX-Lung 3[34]
Fatigue	[redacted]	Resource use data extracted from LUX-Lung 1[90]
Anaemia	[redacted]	Eli Lilly and Co 2008[93]
Neutropenia	[redacted]	Eli Lilly and Co 2008[93]

11.2.9 Cost effectiveness results

The base-case incremental results generated by the manufacturer's model are presented in Table 35. The results are taken from the manufacturer's approved PAS submission and are

different from the estimates provided in the MS. The ICERs for afatinib vs erlotinib are £10,079 per QALY gained and £5,286 per LY gained, whilst those for afatinib vs gefitinib are £17,933 per QALY gained and £12,062 per LY gained. Disaggregated costs for afatinib, erlotinib and gefitinib are presented in Table 36

Table 35 Base-case results

Technology	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALY	ICER versus baseline (QALYs)	ICER incremental (QALYs)
Gefitinib	[redacted]	2.291	1.421	-	-	-	-	-
Erlotinib	[redacted]	2.223	1.423	12 1,390	-0.068	0.002	13 695,000	14 D
Afatinib	[redacted]	2.549	1.594	15 1,723	0.326	0.171	16 17,933	17 10,076

ED=extended dominance: ICER=incremental cost-effectiveness ratio; LYG=life year gained; QALY=quality adjusted life year

Table 36 Disaggregated mean base-case costs*

	Afatinib	Erlotinib	Gefitinib
Drug acquisition	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
PFS health care	[redacted]	[redacted]	[redacted]
PD health care	[redacted]	[redacted]	[redacted]
PFS AEs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]

AE=Adverse event; PD=progressive disease; PFS=progression-free survival;
*The figures in this table have been extracted from the manufacturer's model

17.1.1 Sensitivity analyses and scenario analyses

One-way sensitivity analyses

The manufacturer undertook a large number of one-way sensitivity analyses. Tornado diagrams for afatinib vs gefitinib and afatinib vs erlotinib are included in the MS[1] (page 221).

The one-way SA results for the ten parameters that have the largest impact on cost effectiveness are displayed in Table 37 and Table 38. The lower and upper variations are set to the lower and upper bounds of confidence intervals.

Table 37 One-way sensitivity analysis results for afatinib compared with gefitinib

Variable	Low variation				High variation			
	Inc cost	Inc QALY	Inc LY	ICER/ QALY	Inc cost	Inc QALY	Inc LY	ICER/ QALY
MTC-based HR for PFS (afa vs gef)	£1,963	0.2447	0.2581	£8,023	£4,899	0.0894	0.2581	£54,800
MTC-based HR for OS (afa vs gef)	£8,532	0.4495	0.7876	£18,983	-£3,990	-0.1880	-0.4360	£21,221
Cost/month Progression-free, 1L	£2,858	0.1736	0.2581	£16,466	£5,854	0.1736	0.2581	£33,724
Cost/month in third-line progressive disease (BSC)	£2,953	0.1736	0.2581	£17,011	£4,568	0.1736	0.2581	£26,315
Weibull model HR for OS (afa vs pmc) for comparison with erl/gef	£3,316	0.1943	0.3037	£17,069	£2,914	0.1542	0.2156	£18,894
Discounting effect	£3,113	0.1900	0.2873	£16,386	£3,113	0.1635	0.2402	£19,045
Weibull model HR for PFS (afa vs pmc)	£5,675	0.1851	0.2581	£30,656	£1,171	0.1641	0.2581	£7,135
Cost per diarrhoea AE	£2,740	0.1736	0.2581	£15,786	£3,489	0.1736	0.2581	£20,098
Discounting cost	£3,515	0.1736	0.2581	£20,248	£2,859	0.1736	0.2581	£16,473
Freq of diarrhoea (Grade 3/4) in 1L afa patients	£2,857	0.1738	0.2581	£16,442	£3,369	0.1734	0.2581	£19,427

Afa=afatinib; AE=adverse event; BSC=best supportive care; erl=erlotinib; gef=gefitinib; Freq=frequency; HR=hazard ratio; MTC=mixed treatment comparison; OS=overall survival; PFS=Progression-free survival pmc=pemetrexed/cisplatin; 1L=first-line; LY=life year; QALY=quality adjusted life year; ICER=incremental cost-effectiveness ratio

Table 38 One-way sensitivity analysis results for afatinib compared with erlotinib

Variable	Low variation				High variation			
	Inc cost	Inc QALY	Inc LY	ICER/ QALY	Inc cost	Inc QALY	Inc LY	ICER/ QALY
Cost/month progressive disease, 3&4 line, both arms	£1,254	0.171	0.326	£7,339	£5,977	0.171	0.326	£34,970
MTC-based HR for PFS (afa vs erl)	£3,501	0.252	0.326	£13,893	-£648	0.063	0.326	-£10,302
MTC-based HR for OS (afa vs erl)	£6,560	0.405	0.768	£16,206	-£4,152	-0.113	-0.211	£36,718
Cost/month progression-free, 1L, both arms	£1,621	0.171	0.326	£9,482	£2,820	0.171	0.326	£16,500
Freq of diarrhoea (Grade 3/4) in 1L afa patients	£1,467	0.171	0.326	£8,572	£1,979	0.171	0.326	£11,589
Cost per diarrhoea AE	£1,484	0.171	0.326	£8,685	£1,963	0.171	0.326	£11,485
Discounting cost	£1,997	0.171	0.326	£11,681	£1,556	0.171	0.326	£9,104
Discounting effect	£1,723	0.189	0.362	£9,098	£1,723	0.160	0.304	£10,796
PD utility in third-line, progressive disease	£1,723	0.160	0.326	£10,767	£1,723	0.182	0.326	£9,473
No episodes diarrhoea per 1L patient suffering diarrhoea (Grade 3/4)	£1,625	0.171	0.326	£9,505	£1,820	0.171	0.326	£10,653

Afa=afatinib; AE=adverse event; BSC=best supportive care; erl=erlotinib; gef=gefitinib; Freq=frequency; HR=hazard ratio; MTC=mixed treatment comparison; OS=overall survival; PD=progressive disease; PFS=Progression-free survival pmc=pemetrexed/cisplatin; 1L=first-line; LY=life year; QALY=quality adjusted life year; ICER=incremental cost-effectiveness ratio

The sensitivity analyses carried out by the manufacturer suggest that the ICER per QALY gained values are particularly sensitive to variations in the PFS and OS hazard ratios.

Scenario analyses – structural and treatment variation

In the base-case, following treatment with any of the TKIs (afatinib, erlotinib or gefitinib), all patients are assumed to receive docetaxel as second-line treatment before proceeding to BSC. To test the impact of this assumption on the cost-effectiveness results, the manufacturer carried out a scenario analysis in which patients received pemetrexed instead of docetaxel second-line. The results for this scenario analysis are compared with the base-case analysis in Table 39.

Table 39 Alternate second-line treatment scenario analysis using PAS prices

	Docetaxel (base-case)	Pemetrexed
Afatinib vs gefitinib		
ICER per QALY gained	£17,933	£17,925
ICER per LY gained	£12,062	£12,076
Afatinib vs erlotinib		
ICER (QALY)	£10,079	£10,084
ICER (LY)	£5,286	£5,297

ICER=incremental cost-effectiveness ratio; LY=life-year; QALY=quality adjusted life year

Two further structural scenario analyses were conducted. In the first the time spent on second-line treatment was considered to be proportionate to the estimated length of time alive but not receiving first-line therapy. In the second this assumption was still employed and, in addition, it was assumed that patients received pemetrexed rather than docetaxel as second-line therapy. Results from these analyses may be found in Table 40.

Table 40 Alternate second- line treatment duration scenario analysis using PAS prices

	Second-line treatment duration		
	Constant (base-case)	Proportionate	
second-line treatment →	**Docetaxel**	**Docetaxel**	**Pemetrexed**
Afatinib vs gefitinib			
ICER (QALY)	£17,933	£19,904	£19,952
ICER (LY)	£12,062	£13,789	£13,727
Afatinib vs erlotinib			
ICER (QALY)	£10,079	£15,664	£15,718
ICER (LY)	£5,286	£8,871	£8,722

ICER=incremental cost-effectiveness ratio; LY=life-year; QALY=quality adjusted life year

The variation in structural assumptions has little impact on the ICERs as demonstrated by the results above.

Scenario analyses – utility variation

The ICER per QALY gained using the three sets of utility values identified by the manufacturer are displayed in Table 41.

Table 41 ICERs for sensitivity analysis with different utility values using PAS prices

	Afatinib vs gefitinib	Afatinib vs erlotinib
LUX-Lung 3 trial[34] data (basecase)	£17,933	£10,079
LUCEOR data (Chouaid et al 2012)[92]	£19,359	£10,390
Literature (Nafees et al 2008)[91]	£20,256	£10,588

Scenario analyses – variation in trials used in the MTC

The ICERs per QALY gained using only the afatinib data from LUX-Lung 3[34] in the MTC are shown in Table 42, whilst the ICERs per QALY gained using data from OPTIMAL[32] in the MTC are shown in Table 43.

Table 42 ICERs for sensitivity analysis using only afatinib data from LUX-Lung 3 in the MTC using PAS prices

	Afatinib vs gefitinib	**Afatinib vs erlotinib**
LUX-Lung 3[34] and LUX-Lung 6[35] data (base-case)	£17,933	£10,079
Only LUX-Lung 3[34] data	£24,339	Dominant

Table 43 ICERs for sensitivity analysis using only afatinib data from LUX-Lung 3 in the MTC using PAS prices

	Afatinib vs gefitinib	**Afatinib vs erlotinib**
Base-case with OPTIMAL[32] data excluded	£17,933	£10,079
Results with OPTIMAL[32] data included	£15,257	£13,013

Probabilistic sensitivity analyses (PSA)

Probabilistic sensitivity analyses (1000 simulations) was undertaken to derive the mean ICER of afatinib vs erlotinib and afatinib vs gefitinib in this setting. Scatter plots (see Figure 10 and Figure 11) and cost-effectiveness acceptability curves (CEACs) (see Figure 12 and Figure 13) that are included in the MS have been reproduced below. The ERG notes that these CEACs include only binary comparisons and that, in the case of multiple comparators, the production of binary CEACs is meaningless.

Figure 10 PSA scatter-plot afatinib vs gefitinib (red line = £30k/QALY) (Confidential therefore not reported)

Figure 11Cost effectiveness acceptability curve (afatinib vs gefitinib) (Confidential therefore not reported)

Figure 12 PSA scatter-plot afatinib vs erlotinib (red line = £30k/QALY) (Confidential therefore not reported)

Figure 13 Cost effectiveness acceptability curve (afatinib vs erlotinib) (Confidential therefore not reported)

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 44.

Table 44 Probability of cost effectiveness in the first-line setting (using PAS prices)

Intervention	Comparator	£20,000 per QALY gained	£30,000 per QALY gained
Afatinib	Erlotinib	100%	100%
	Gefitinib	72%	81%

QALY=quality adjusted life year

Deterministic and probabilistic results are compared in Table 45.

Table 45 A comparison of ICER per QALY gained results from the deterministic and probabilistic models (using PAS prices)

	Incremental cost	Incremental QALY	ICER per QALY gained
Afatinib vs gefitinib			
Deterministic values	£3,113	0.17	£17,933
Average value for PSA	£2,390	0.16	£15,027
Afatinib vs erlotinib			
Deterministic values	£1,723	0.17	£10,079
Average value for PSA	£1,058	0.16	£6,671

QALY=Quality adjusted life year; ICER=incremental cost-effectiveness ratio; PSA=probabilistic sensitivity analysis
Model validation and face validity check

Model validation

The manufacturer reports that a number of steps were taken to ensure that the analysis was validated, including:

- External review by a leading UK clinical expert to ensure that the model adhered to the clinical course of the disease and was reflective of current clinical practice
- Sensitivity analyses
- A senior modeller from the organisation that developed the afatinib model but who had had no involvement in model development undertook quality assurance checks
- Validation checks (varying parameter values and assumptions) were performed by the manufacturer
- Additional external validation by a health-economics consultancy previously unconnected to the submission.

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17.2 Critique of manufacturer's submitted economic evaluation by the ERG

17.2.1 Major model issues

Survival modelling

The model construction process carried out by the manufacturer comprised two steps. The first step involved determining hazard ratios. Hazard ratios (PFS and OS) for afatinib vs pemetrexed/cisplatin were estimated from LUX-Lung 3[34] trial data, and used to estimate PFS and OS by applying these hazard ratios to the pemetrexed/cisplatin survival data from that trial. Hazard ratios for afatanib vs erlotinib and afatanib vs gefitinib were calculated using MTCs.

The second step was to fit theoretical survival models to the LUX-Lung 3[34] trial data. Five parametric functions were compared (exponential, Weibull, Gompertz, LogLogisitic and LogNormal) and the Weibull model was selected as having the best goodness of fit to the Kaplan-Meier survival data for both PFS and OS projections, based on exhibiting the smallest AIC value.

The approach used by the manufacturer has several major flaws:

[redacted]

Figure 14 Comparison of manufacturer's Weibull models for PFS with LUX-Lung 3 updated trial results, and ERG two-phase exponential models (Confidential therefore not reported)

- Notwithstanding the lack of confidence in the Weibull model, the reliability of the projections for afatinib, erlotinib and gefitinib depend on the credibility of the hazard ratios used in the model. As fully explained in section 7.4, the results of the MTCs conducted by both the manufacturer and the ERG cannot be considered to be robust

and/or relevant to UK patients, and therefore are an inadequate basis for populating a cost effectiveness decision model

- In addition, the LUX-Lung 3[34] Kaplan-Meier analyses in section 4.2.7 show that the prognosis for Asian and non-Asian patients with EGFR-positive NSCLC cannot be considered to be the same. Therefore, in order to inform the calibration of a cost-effectiveness model for appraising treatments for use in the UK, it is only appropriate to employ data which have been generated from a specifically non-Asian EGFR-positive population of patients, both in terms of primary clinical trials or supporting evidence for use in a simple indirect comparison or MTC.

Together, these issues mean that results generated by the manufacturer's model cannot be considered to be reliable. The ERG has not been able to integrate alternative survival projections into the manufacturer's model because it is structured around the use of hazard ratios to generate outcomes for erlotinib and gefitinib, rather than by direct estimation. A full restructuring of the model would be required to accommodate alternative assumptions.

Minor model issues

In view of the serious nature of the major issues identified by the ERG, no attempt has been made to quantify the combined effect on the ICER per QALY gained of correcting the minor issues identified below. The ERG takes the view that to do so would give misleading credibility to the manufacturer's ICERs per QALY gained. Instead, the minor issues are described and the ERG's preferred input values have been presented to allow comparison with those used by the manufacturer.

Modelling post-progression survival

In the model, post-progression survival (PPS) was estimated by subtracting PFS from OS. It should be noted, however, that after discontinuing study treatment only [redacted] of patients in the afatinib arm received single agent docetaxel chemotherapy, whilst more than twice that proportion ([redacted]) received platinum-based chemotherapy. The manufacturer's model assumption that patients receive docetaxel monotherapy second-line does not, therefore, reflect the trial data upon which the manufacturer's afatinib survival model is based.

Estimation of utility values for patients receiving second-line and third-line therapy

For second- and third-lines of therapy a weighted average, weighted by time spent in different phases of therapy, was calculated using values published in a conference poster (Chouaid et al).[92] The reliability of the results presented by Chouaid et al[92] is unclear. The ERG notes that treatment received by patients included in the study is unknown.

Furthermore, the utility values are based on the views of small numbers of patients, particularly with regard to BSC where the authors point out that the number of patients was too small to warrant meaningful analysis.

The ERG notes that the Chouaid et al[92] utility values are noticeably higher than those published in a recent HTA report[38] which were generated using the Nafees et al[91] model. To allow comparison, the relevant utility values have been extracted from the MS[1] and the HTA report[38] and are displayed in Table 46.

Table 46 Estimated health-related utility values using the Nafees et al model

Treatment	Progression-free survival (PFS)	Post-progression survival	Terminal phase (2 weeks)
First-line			
MS[1] (figure calculated from LUX-Lung 3 trial results)	0.784		
Chouaid et al 2012[92]	0.710		
HTA report[38] - gefitinib (EGFR+ population)	0.6625	0.4896	-
Second-line			
Chouaid et al 2012[92]	0.73		
HTA report[38] - docetaxel	0.5927 on CTX 0.6559 post CTX	0.4275	0.0686
Third-line			
Chouaid et al 2012[92]	0.62		
Chouaid et al 2012[92] (BSC)		0.46	

BSC=best supportive care; CTX=chemotherapy; EGFR+=Epidermal growth factor receptor positive; HTA=health technology assessment

Continuity correction errors

It is conventional in state-based models, which update key variables at fixed cycle times, to estimate costs and outcomes which vary during the course of a cycle by averaging the value of the variable at the beginning and end of the cycle. In the manufacturer's model the time spent by patients in both the PFS and PD health states has been incorrectly calculated, and then applied to estimate treatment costs, health state costs, life-years and QALYs for afatinib and both erlotinib and gefitinib. The correct approach is to calculate time spent in PFS or PD as the average of patient numbers at the beginning and end of each cycle, and use this figure to calculate health state costs in each cycle, and also to estimate life-years and QALYs accumulating over the time horizon of the model. The costs of first line treatment with TKIs should be calculated differently: each cycle is 1-month long and afatinib, erlotinib and gefitinib are available in 30-tablet packs and are therefore dispensed approximately monthly. The correct population receiving treatment is therefore all those patients on treatment at the

beginning of each cycle to whom a new pack of tablets is issued. The effects of these errors are evident across all parts of the model:

- Cost of treatments (afatinib, and erlotinib) are underestimated by 50% of a monthly pack
- Health state costs are under-estimated (PF costs by 1-2% and PD costs by 7-8%)
- Life-years and QALYs are also under-estimated by a similar proportion

The net effect of these errors on estimated ICERs is not clear.

Method for estimating docetaxel therapy costs

Docetaxel monotherapy dose for second-line chemotherapy is calculated at 75mg/m^2 of body surface area (BSA). In the manufacturer's model it is assumed that patients receive 2 x 4ml vials (20mg/ml)at a price of £534.75 per vial. There are several problems with this approach:

- The drug cost calculation carried out by the manufacturer is not based on the BSA of a UK specific population[97]
- The calculation of doses takes no account of the wide variation of BSA within the population, so that some patients require several/larger vials and others fewer/smaller vials to achieve the required individual dose
- The most up to date BNF[98] docetaxel drug cost has not been used (£504.24). However, docetaxel is now a generic drug and the most recent eMIT[99] (electronic Medicines Information Tool) figures shows that the average price at which docetaxel was available to NHS organisations for the 6 months prior to June 2013 was £28.03, i.e. at about 5% of the cost used by the manufacturer.

Drug administration costs

In costing afatinib, erlotinib and gefitinib the model uses a one-off introductory administration cost of delivering oral chemotherapy (£163). The rationale behind this assumption is not clear as, in practice, it is likely that some cost will be incurred by the NHS each time a patient collects a new prescription. If, however, it is assumed that subsequent prescriptions are issued through a community pharmacy, then appropriate dispensing fees will be incurred monthly.

In the model, the drug administration cost for docetaxel is based on the NHS Reference Cost[100] for the delivery of complex chemotherapy, including prolonged infusion treatment at first attendance (SB14Z) at a cost of £302.41. However, ERG clinical advisors suggest that it is not appropriate to consider docetaxel monotherapy as a 'complex chemotherapy'.

The ERG's clinical advice is that it is appropriate to assume that oral medication packs are issued as part of a nurse-led out-patient visit and that docetaxel is delivered in a day-case setting. The ERG's preferred unit costs for drug administration, based on NHS Reference Costs 2011/12,[95] are displayed in Table 47.

Table 47 Unit costs of chemotherapy administration

Treatment setting	HRG code	Description	Mean	Standard error*
Out-patient visit	NCLFUSFF 370	Medical oncology	£106.00	£10.60*
Day-case unit	SB12Z	Simple parenteral chemotherapy at first attend	£203.16	£7.47
Day-case unit	SB15Z	Subsequent doses of chemotherapy	£283.89	£10.14

* 10% of mean assumed HRG=healthcare resource groups

Gefitinib PAS administration cost

The ERG notes that in the manufacturer's model the costs associated with administering the gefitinib PAS are a [redacted]. However, in a previous STA considering erlotinib for the first-line treatment of locally advanced or metastatic EGFR TK mutation-positive NSCLC[80] the prices used were [redacted].

Terminal care costs

Terminal care costs are not considered in the manufacturer's model. In a recent review of first-line chemotherapy for patients with NSCLC[38], a detailed estimate of terminal care costs was undertaken and the resultant estimate for inpatients was £2,655.55 per patient based on NHS Reference Cost 2009/10 prices. Inclusion of these costs is relevant when a model generates differential survival, due to the effects of discounting outcomes.

Adverse event costs

The manufacturer has estimated resource use associated with AEs based on data extracted from LUX-Lung 3,[34] LUX-Lung 1[90] and other published literature. The ERG has concerns about the validity of the values used, particularly with regard to the cost associated with fatigue. A Grade 3/4 AE is one, by definition, that requires hospitalisation[101] and therefore the manufacturer's figure of [redacted] per episode associated with this AE appears unrealistic.

In a recent HTA considering first-line chemotherapy for the treatment of NSCLC,[38] the cost associated with Grade 3/4 fatigue was estimated by assuming that a typical patient would have one hospital admission corresponding to HRG code WA17X (Other admissions related to neoplasms with intermediate complicating conditions) as a non-elective long-stay episode. The 2011/12 NHS Reference Cost[95] for this code is £2,233.40.

In addition, the ERG notes that the anaemia and neutropenia costs used by the manufacturer come directly from the MS for the NICE appraisal of pemetrexed for the first-line treatment of NSCLC.[93] This MS was produced in 2008 but the manufacturer has not inflated the presented costs before using them in this appraisal.

17.2.2 *Comparability of effect and cost*

If it is concluded that the three EGFR-TKI products are of equal effectiveness, the assessment of cost effectiveness reduces to a simple exercise of cost-minimisation, based primarily on the acquisition and administration cost of each drug.

Afatinib, erlotinib and gefitinib are all available as tablets and PAS prices are available for all three products. The PAS for afatinib and erlotinib [redacted]. The current list price for afatinib is £2023.28 (for 28 days' supply)[102] and that for erlotinib is £1631.53[98] (for 30 days' supply), i.e. daily costs of £72.26 and £54.38 respectively. If the relevant PAS discounts are applied to these prices the daily costs of treatment with afatinib and erlotinib become [redacted] respectively. This analysis shows that the [redacted].

The PAS for gefitinib is more complex, a cost of £12,200 being applied on receipt of the third monthly pack. For the monthly treatment cost of gefitinib therapy to be less than afatinib or erlotinib therapy, patients receiving gefitinib (rather than afatinib or erlotinib) would need to be progression free for at least [redacted] respectively. It should be noted that median trial PFS for afatinib, erlotinib and gefitinib (from LUX-Lung 3,[34] EURTAC[28] and IPASS[12] respectively) are 11.07, 9.7 and 9.5 months respectively. This means that treatment with gefitinib [redacted].

17.2.3 *Pemetrexed/cisplatin in the treatment pathway*

The scope for this appraisal included three EGFR-TKI products for first-line treatment of EGFR-positive NSCLC (afatinib vs erlotinib and afatinib vs gefitinib). In the first NICE appraisal for these drugs,[9] gefitinib was consider in comparison to pemetrexed/cisplatin which was then viewed as the most relevant existing treatment for adenocarcinoma NSCLC

patients. However, due to lack of direct trial evidence, and an insecure indirect evidence link, the intended comparison could not be assessed. Once gefitinib was approved, it became the natural comparator in the assessment of erlotinib (also in the absence of a direct trial comparison with pemetrexed/cisplatin). However, pemetrexed/cisplatin remains an important treatment option for this patient group. Clinical advice to the ERG indicates that the choice between an EGFR-TKI and pemetrexed/cisplatin is currently made by many oncologists on the assumption that they are probably equally effective, but that the oral medication is usually preferred for ease of use and patient acceptability. The LUX-Lung 3[34] trial has now provided head-to-head comparative evidence between an EGFR-TKI and pemetrexed/cisplatin, making it feasible to carry out the analysis for afatinib which was previously impossible for gefitinib or erlotinib compared to pemetrexed/cisplatin.

The ERG has carried out a simple 'accounting exercise' using results of the LUX-Lung 3[34] trial to obtain a rough estimate of the ICER which is likely to be obtained if a full economic model were to be undertaken, in order to provide a wider context to the problem of comparing the costs and benefits of all available treatments, and informing some of the uncertainty remaining from the early assessments made of gefitinib and erlotinib when trial data were immature. The ERG estimates are described in Appendix 37.3, and indicate that the combination of PAS pricing and use of data for the non-Asian subgroup of LUX-Lung 3,[34] is likely to indicate that afatinib is cost-effective when compared to pemetrexed/cisplatin in a mainly Caucasian population of EGFR-positive patients.

17.3 Conclusions of the cost effectiveness section

The ERG found that the manufacturer's model lacked credibility and could not be relied upon to generate robust ICERs for the comparison of afatinib vs erlotinib or afatinib vs gefitinib. This was demonstrated by the fact that the modelled PFS survival projection for afatinib did not reflect afatinib LUX-Lung 3[34] trial data from which it was derived. In addition, the ERG considered that, due to data limitations and methodological weaknesses, it was not appropriate to use the hazard ratios produced by the MTC in the submitted economic model. In particular, [redacted] This means that there is currently no reliable clinical evidence base to inform cost-effectiveness modelling for this population in a UK setting.

The ERG has also identified a number of other factors that limit confidence in the reliability of the manufacturer's model and/or results. These relate to inappropriate modelling of post-

progression survival (PPS); over-estimation of utility values for patients receiving second-line and third-line therapy; and a mid-cycle correction error. Confidence in the manufacturer's model is further undermined by a number of costs used in (or omitted from) the submitted model, namely high docetaxel therapy and administration costs, reduced erlotinib administration costs, incorrect gefitinib PAS administration costs, out-of-date AE costs and omission of terminal care costs.

18 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In view of the serious nature of the major issues identified by the ERG no attempt has been made to quantify the effect of correcting any of the identified issues on the size of the manufacturer's ICER per QALY gained The ERG takes the view that any corrections to the manufacturer's model could give misleading credibility to the ICERs per QALY gained generated by the manufacturer's submitted economic model.

19 END OF LIFE

No case has been presented by the manufacturer related to considering the use of afatinib under end of life criteria.

20 OVERALL CONCLUSIONS

There is no direct clinical evidence comparing afatinib with the comparators of interest specified in the final scope issued by NICE, namely erlotinib and gefitinib. To compare afatinib with erlotinib and gefitinib the manufacturer conducted an MTC. The ERG considers that the results of any MTC carried out using the currently available trial evidence are unreliable. It is therefore not possible to demonstrate the relative clinical effectiveness of afatinib compared to erlotinib or gefitinib in a population that is representative of UK patients.

Overall, the ERG found that the manufacturer's model lacked credibility and could not be relied upon to generate robust ICERs for the comparison of afatinib vs erlotinib or afatinib vs gefitinib. This was demonstrated by the fact that the modelled PFS survival projection for afatinib did not reflect afatinib LUX-Lung 3 trial data from which it was derived. In addition, the ERG considered that, due to data limitations and methodological weaknesses, it was not appropriate to use the hazard ratios produced by the MTC in the submitted economic model.

It is therefore not possible to demonstrate the relative cost effectiveness of afatinib compared to erlotinib or gefitinib in a population that is representative of UK patients.

20.1 Implications for research

This appraisal has highlighted the need for directly relevant evidence of clinical effectiveness for the first-line treatment of patients with NSCLC expressing an EGFR-positive mutation. Table 48 shows that a number of trials are currently on-going. However, none of these trials directly compare two (or more) TKIs. Ideally evidence for the comparative efficacy of TKIs should come from at least one RCT involving a substantial proportion of Caucasian patients, preferably with a significant UK element. The findings from LUX-Lung 7 which compares afatinib with gefitinib in both Asian and non-Asian patients are therefore eagerly awaited.

In addition, in view of the important uncertainties around the roles played by specific mutations (singly or in combination) in determining clinical benefit from TKIs and the current trend to carry out trials with an Asian population, it would be most valuable to have data from a long-term clinical registry of all UK patients treated with TKIs. Such a data source could provide a basis for research and audit to inform future assessments of TKIs in a UK specific population.

Table 48 Drugs in phase III development for the first-line treatment of patients with NSCLC expressing an EGFR-positive mutation

Drug	Possible indication	Clinical trials	Region	Manufacturer
Afatinib (Giotrif®) Oral	First-line monotherapy for patients with EGFR+ mutations	NCT01466660: LUX-Lung 7: A phase IIb trial of afatinib (BIBW2992) versus gefitinib for the treatment of first-line EGFR mutation positive adenocarcinoma of the lung. **Estimated completion December 2014**	Asia, Australia, Europe and North America (Canada)	Boehringer Ingelheim
Dacomitinib Oral	First-line monotherapy in EGFR mutation-positive disease	NCT01774721: ARCHER 1050: A PIII trial of dacomitinib versus gefitinib in patients with locally advanced or metastatic NSCLC, with EGFR activating mutation(s). **Estimated completion December 2016**	Asia and Europe	Pfizer
Erlotinib (Tarceva®) Oral	First-line monotherapy in EGFR mutation-positive disease	NCT01342965: ERL versus GEM/CIS in patients with mutations in the tyrosine kinase domain of the EGFR. **Estimated completion December 2014**	Asia	Genentech, Roche
Gefitinib (Iressa®) Oral	First-line monotherapy in EGFR mutation-positive disease	NCT00807066: RANGE PIII trial of gefitinib versus platinum chemotherapy in patients with locally advanced (IIIB with effusion) or metastatic NSCLC. **Estimated completion October 2010**	Europe (Italy)	AstraZeneca
Icotinib (Conmana®) Oral	First-line monotherapy in EGFR mutation-positive disease followed by maintenance therapy	NCT01665417: PIV trial of first-line icotinib versus first-line chemotherapy followed by maintenance icotinib. **Estimated completion April 2015** NCT01719536: CONVINCE PIII trial of icotinib versus induction and maintenance chemotherapy in first-line treatment of advanced NSCLC with EGFR mutation. First-line chemo: pemetrexed/cisplatin for 4 cycles. Maintenance: pemetrexed. **Estimated completion October 2014**	Asia (China)	Zhejiang Beta (China)
Necitumumab Intraveneous	First-line combination therapy in metastatic non-squamous NSCLC (previous EGFR inhibitor use excluded)	NCT00982111: INSPIRE PIII trial of necitumumab in combination with cisplatin and pemetrexed in the treatment of advanced NCSLC versus cisplatin/pemetrexed alone. **Estimated completion December 2013**	Australia, Europe, North America, South America and South Africa	ImClone Systems

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22 APPENDICES

22.1 Additional summary and critique of trials presenting direct evidence for afatinib

All data reported here is taken from the MS[1] except where stated.

22.1.1 Additional information on participant characteristics

The key characteristics of the LUX-Lung 3[18] and LUX-Lung 6[20] trials are presented in Table 11 of the MS (p.55)[1] and in Table 49 below. The MS[1] highlights (in green) characteristics which were commented on in the corresponding clinical trial reports for being different between treatment arms, namely a greater proportion of patients in the afatinib arms than the chemotherapy arms had stage IV disease or were never-smokers in LUX-Lung 3[18] and LUX-Lung 6[20] respectively. A smaller proportion of patients in the afatinib arm of LUX-Lung 6[20] were of ECOG PS 0 than in the chemotherapy arm. The MS[1] also comments on several characteristics reported to be different between trials which are highlighted in Table 49.

With the exception of between arm differences highlighted, baseline characteristics were largely similar across the RCTs, the most notable exception being median age in LUX-Lung 6[20] was slightly lower than LUX-Lung 3[18] (or indeed, LUX-Lung 2[23]), largely because of a greater proportion of patients aged 65 years or under in this trial. Regarding differences between LUX-Lung 2[23] and the RCTs, there were proportionately more males, patients of ECOG PS 0 and current smokers in LUX-Lung 2[23] than either of the RCTs. LUX-Lung 2[23] also reported a greater proportion of patients with 'other' EGFR mutations.

The ERG notes that 'other' mutations as reported in Table 49 include T790M which as highlighted in section 2.2, appears to be resistant to erlotinib and gefitinib but not afatinib. [redacted]

Table 49: Baseline characteristics in the LUX-Lung 3 and LUX-Lung 6 (differences commented on in the CTR are highlighted in green)

Patient characteristics		**LUX-Lung 3[18]**		**LUX-Lung 6[20]**	
		Afatinib (n=230)	**Pemetrexed/ cisplatin (n=115)**	**Afatinib (n= 242)**	**Gemcitabine/ cisplatin (n= 122)**
Age (mean, StD) years		[redacted]	[redacted]	[redacted]	[redacted]
Age (median, range) years		61.5 (28 to 86)[3]	60.5 (31 to 83)[3]	58.0 (29 to 79)	58.0 (27 to 76)
Age categories (N [%])	<65 years	140 [60.9][1]	71 [61.7][1]	176 (72.7)	102 (83.6)
	≥65 years	90 [39.1][1]	44 [38.3]	66 (27.3)	20 (16.4)
Gender (n [%])	Male	83 [36.1]	38 [33.0]	87 [36.0]	39 [32.0]
	Female	147 [63.9]	77 [67.0]	155 [64.0]	83 [68.0]
Ethnicity (n [%])	Caucasian	61 [26.5]	30 [26.1]	NR	NR
	Asian	165 [71.7]	83 [72.2]	[redacted]	[redacted]
	Other	4 [1.7]	2 [1.7]	NR	NR
Geographical region (n [%])	Europe	47 [20.4]	27 [23.5]	0	0
	Asia	160 [69.6]	83 [72.2]	242 [100.0]	122 [100.0]
	Other	23 [10.0]	5 [1.7]	0	0
Smoking status (n [%])	Never smoked	155 [67.4]	81 [70.4]	181 [74.8]	99 [81.1]
	Ex-smoker	70 [30.4]	32 [27.8]	44 [18.2]	13 [10.7]
	Current smoker	5 [2.2]	2 [1.7]	17 [7.0]	10 [8.2]
Stage (AJCC 6.0) (n [%])	IIIB (wet)	20 [8.7]	17 [14.8]	16 [6.6]	6 [4.9]
	IV	[redacted]	[redacted]	[redacted]	116 [95.1]
ECOG Performance Status (n [%])	0	92 [40.0]	41 [35.7]	[redacted]	[redacted]
	1	138 [60.0]	73 [63.5]	194 [80.2]	81 [66.4]
	2	0	1 [0.9]	0	0
EGFR mutation (n [%])	del19	113 [49.1]	57 [49.6]	124 [51.2]	62 [50.8]
	L858R[4]	91 [39.6]	47 [40.9]	92 [38.0]	46 [37.7]
	Other	26 [11.3]	11 [9.6]	26 [10.7]	14 [11.5]
Weight, mean (StD) kg		[redacted]	[redacted]	59.59 [8.99]	59.42 [9.54]
Body mass index, mean (StD) kg/m²		[redacted]	[redacted]	22.811 [2.722]	22.994 [3.156]

ECOG Eastern Cooperative Oncology Group; AJCC American Joint Committee on Cancer Staging 6th edition; StD Standard deviation EGFR Epidermal Growth Factor Receptor; 1 Taken from Table 11.2.1: 1 of the CTR 2 Taken from Table 15.1.4: 1 of the CTR; Taken from published paper[18] 4 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'

Table 50: Baseline characteristics in LUX-Lung 3 by ethnicity of patients (provided in clarification response)

Patient characteristics		Asian patients		Non-Asian patients	
		Afatinib (n=166)	Pemetrexed/ cisplatin (n=83)	Afatinib (n= 64)	Pemetrexed/ cisplatin (n= 32)
Age (median, range) years		[redacted]	[redacted]	[redacted]	[redacted]
Age categories (N [%])	<65 years	[redacted]	[redacted]	[redacted]	[redacted]
	≥65 years	[redacted]	[redacted]	[redacted]	[redacted]
Gender (n [%])	Male	[redacted]	[redacted]	[redacted]	[redacted]
	Female	[redacted]	[redacted]	[redacted]	[redacted]
Ethnicity (n [%])	Caucasian	[redacted]	[redacted]	[redacted]	[redacted]
	Asian	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]
Geographical region	Europe	[redacted]	[redacted]	[redacted]	[redacted]
	Asia	[redacted]	[redacted]	[redacted]	[redacted]
	Other	[redacted]	[redacted]	[redacted]	[redacted]
Smoking status (n [%])	Never smoked	[redacted]	[redacted]	[redacted]	[redacted]
	Ex-smoker	[redacted]	[redacted]	[redacted]	[redacted]
	Current smoker	[redacted]	[redacted]	[redacted]	[redacted]
ECOG Performance Status (n [%])	0	[redacted]	[redacted]	[redacted]	[redacted]
	1	[redacted]	[redacted]	[redacted]	[redacted]
	2	[redacted]	[redacted]	[redacted]	[redacted]
Weight, mean (StD) kg		[redacted]	[redacted]	[redacted]	[redacted]
Body mass index, mean (StD) kg/m²		[redacted]	[redacted]	[redacted]	[redacted]

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

Table 51 Baseline characteristics in LUX-Lung 2

Patient characteristics	First-line		Second-line		
	Afatinib 40mg (n=23)	Afatinib 50mg (n=38)	Afatinib 40mg (n=7)	Afatinib 50mg (n=61)	Total (n=129)
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)
Ethnicity					
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)

22.1.2 Additional information on statistical approach

Randomised studies

The pre-specified primary endpoint of both RCTs was PFS. The sample size calculation for both trials[18,20] was appropriately based on the primary outcome, PFS.

Progression-free survival was defined as the time from date of randomisation to date of disease progression (as assessed by central independent assessment by Response Evaluation Criteria in Solid Tumours (RECIST)) or death. While central independently assessed PFS is widely considered to be less biased than local investigator assessed PFS, the ERG believes that PFS based on local assessment is also informative as it is more closely related to standard clinical decision-making in the NHS. By contrast central independent assessment is conducted retrospectively and may result in many more patients being censored since patients are switched to a different treatment while the investigator's decision is questioned by the central independent assessment. Sensitivity analyses of PFS were performed to address the impact of differences between central independent assessment and investigator assessment.

LUX-Lung 3[18] and LUX-Lung 6[20] reported their statistical methods for the analysis of efficacy outcomes in their corresponding SAPs. The ERG is satisfied that these methods of analysis are appropriate.

A number of pre-specified subgroup analyses for PFS and OS were described in the SAP for both trials. In LUX-Lung 3[18] these included (but were not limited to) ethnicity (Far East Asian vs other) and in both trials included subgroup analyses based on mutation status (Common [L858R, Del 19, and L858R+Del 19] vs Other; L858R vs Del 19 vs Other; Del 19 vs L858R vs Exon 20 vs L861Q vsG719S/A/C vs T790M vs S768I vs Other; Del 19 vs L858R vs Exon 20 vs L861Q vsG719S/A/C vs T790M vs S768I vs Other; and in LUX-Lung 3[18] only: Reduced Del 19 [Del 6225 and Del 6223] vs Other Del 19). The ERG notes that there are a large number of subgroup analyses (15 and 9 respectively). This is not typically recommended as the likelihood of falsely identifying a non-significant result as a significant result increases with the number of characteristics tested.

Non-randomised study

For the single-arm LUX-Lung 2[23] study the analyses were descriptive and exploratory and no null or alternative hypotheses were tested. It is however noted that this study was divided into two stages to minimise the number of patients exposed to afatinib in case of lack of efficacy and initially a single cohort of second-line patients were enrolled. The starting dose for these patients was initially 50 mg/day but after the planned interim analysis at the end of stage 1, the protocol was amended twice and enrolment was expanded with three additional non-randomised cohorts being added. The four trial cohorts were defined by line of treatment (first or second-line) and afatinib starting dosage (40mg/day or 50mg/day), with patients assigned by order of trial entry, not randomised, to afatinib dosage. The primary

outcome for this study was ORR and sample size was appropriately determined on the basis of the precision with which the proportion of responders could be estimated.

22.1.3 Additional information on efficacy

Randomised studies

For LUX-Lung 3,[18] the MS[1] provides forest plots for key subgroup analyses pre-specified in the protocol for PFS based on central independent assessment (Figure 9, page 78), reproduced in Figure 15 below. The MS[1] states that a statistically significant interaction was found between treatment effect and 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). [redacted]. The CTR also notes that the same analyses were also presented for local investigator assessed PFS in appendices. The appendices were not made available to the ERG. However it is noted in the EPAR[17] that these findings were similar to central independent assessed PFS.

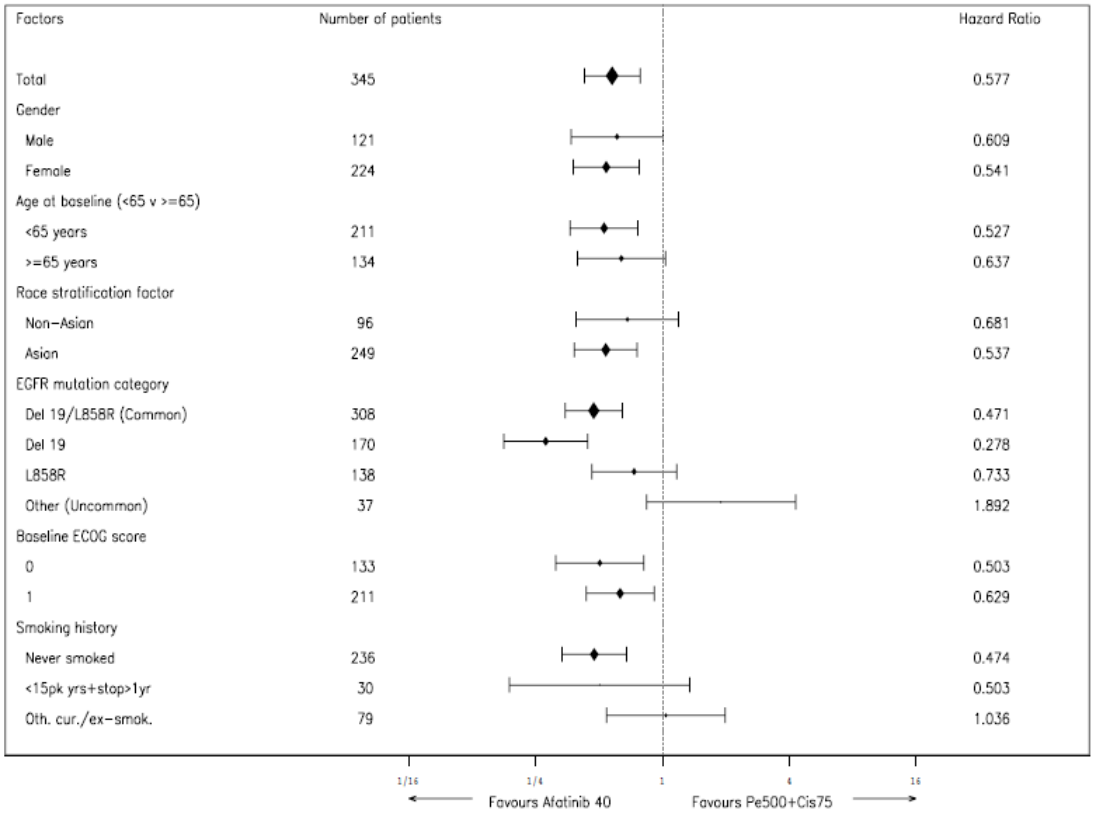

Figure 15: LUX-Lung 3 - Comparison of the treatment effect of afatinib vs pemetrexed/cisplatin on the primary endpoint PFS in the pre-defined subgroups, based on central independent assessment

For LUX-Lung 6,[20] the MS provides a forest plot of the subgroup analyses pre-specified in the protocol for PFS based on central independent assessment (Figure 17, page 87), reproduced in Figure 16. As most subgroups demonstrate a statistically significant treatment effect in favour of afatinib, the MS[1] states that the findings of the subgroup analysis are consistent with those of the PFS primary analysis. [redacted].

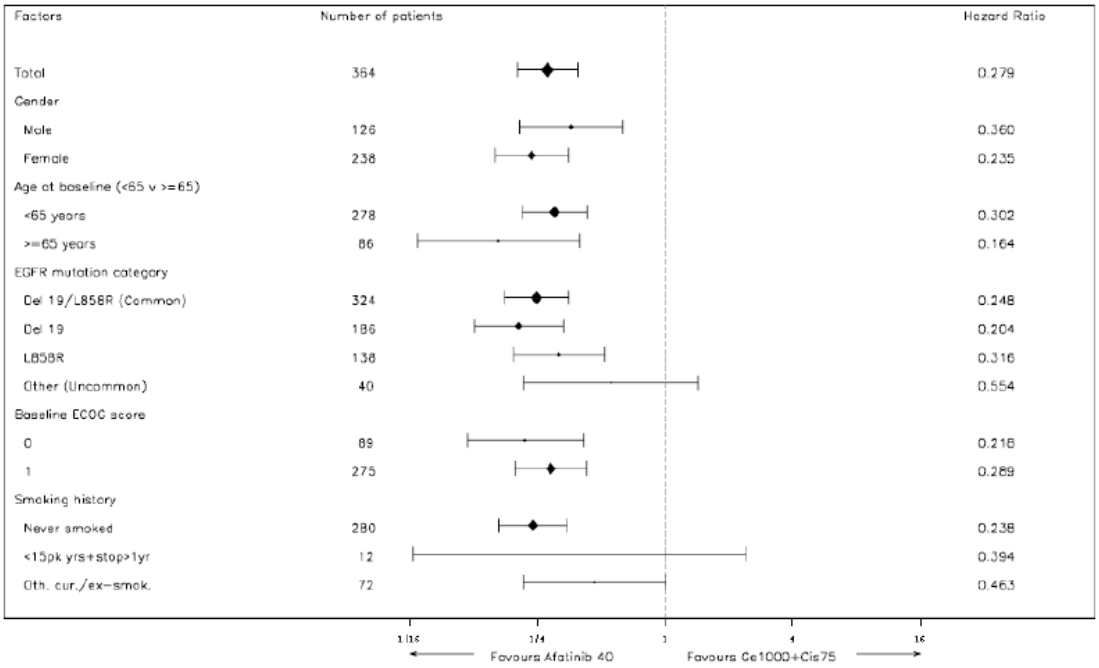

Figure 16: LUX-Lung 6 - Comparison of the treatment effect of afatinib vs gemcitabine/cisplatin on the primary endpoint PFS in pre-defined subgroups, based on central independent assessment

Additional findings on mutation status reported in the EPAR[17] are summarised in Table 52. They suggest that afatinib is most effective for patients with common mutations. The EPAR also presents the findings for uncommon mutations, pooled from LUX-Lung 2,[23] LUX-Lung 3[18] and LUX-Lung 6.[20] Findings for single or complex mutations which include T790M are summarised Table 53. These suggest that efficacy does differ depending on the particular type of EGFR mutation. However, extreme caution must be made when interpreting these findings given the small numbers of patients with uncommon mutations (in some cases, this is based on single cases for those harbouring the T970M mutation). Indeed, the ERG notes that the EMA[17] stated: 'Taking into account all available clinical and non-clinical data the CHMP did not find strong evidence to exclude patients harbouring uncommon mutations'

(page 92) and later added: 'Although a PFS benefit in patients with retrospectively defined secondary resistance to prior treatment with erlotinib/gefitinib has been shown, there are too many uncertainties related to the post-hoc nature of the analyses, the outcome in the complementary set pointing in the direction of imbalances in prognostic factors and also too sparse evidence as regards activity in relation to mutation T790M.'(page 127).

Table 52: PFS by EGFR mutation status (central independent assessment)

Endpoints	**LUX-Lung 3[18]**		**LUX-Lung 6[20]**	
Common mutations[1]	**Afatinib (n=204)**	**Pemetrexed/ cisplatin (n=104)**	**Afatinib (n=216)**	**Gemcitabine/ cisplatin (n=108)**
Patients with event	130 (63.7%)	61 (58.7%)	140 (64.8%)	57 (52.8%)
Median PFS months	13.60	6.90	11.04	5.55
Hazard ratio vs chemotherapy	0.471[2]		0.248[4]	
p-value (2-sided)	<0.0001[3]		<0.0001[5]	
Uncommon mutations[6]	**Afatinib (n=26)**	**Pemetrexed/ cisplatin (n=11)**	**Afatinib (n=26)**	**Gemcitabine/ cisplatin (n=14)**
Patients with event	22 (84.6%)	8 (72.7%)	17 (65.4%)	7 (50.0%)
Median PFS months	2.76	9.92	9.6	8.3
Hazard ratio vs chemotherapy	1.89		0.55	
p-value (2-sided)	0.1198		0.2149	

[1] Reported in Table 15 (page 73) of MS; [2] Hazard ratio derived from a Cox proportional hazard model stratified by EGFR mutation category and ethnicity; [3] Derived from a log-rank test stratified by EGFR mutation category and ethnicity; [4] Hazard ratio derived using a Cox proportional hazard model with treatment fitted as the only factor. [5] Derived using a 2-sided log-rank test; [6] Reported in Table 57 (page 90) of EPAR[17]
Confidence intervals were not reported for hazard ratios

Table 53: Pooled PFS for patients treated with afatinib harbouring the T790M mutation from LUX-Lung 2, LUX-Lung 3 and LUX-Lung 6

Exon	**Types of mutations**	**N**	**Median PFS (95% CI)**	
			Central independent	**Local investigator**
18	T790M alone	3	1.3 (1.3 to 2.8)	1.5 (1.3 to 2.8)
18+ 20	G719X+ T790M	1	5.5	5.5
20+ 19	T790M+ Del19	3	1.2 (0.3 to 3.0)	1.4 (1.2-3.0)
20+ 21	T790M+ L858R	6	7.5 (0.8 to 11.0)	8.9 (0.8 to 13.7*)
18+ 20+ 21	G719X + T790M+L858R	1	13.8	16.6*

*censored observation; NE=Not Estimable

Objective response and disease control rates are presented in the MS (Table 15, page 73)[1] and in Table 54 below. The ERG notes that objective response rates and disease control

rates are significantly higher in the afatinib group than the chemotherapy group in both LUX-Lung 3[18] and LUX-Lung 6.[20]

Table 54: Objective response and disease control rates based on central independent assessment

Trial	LUX-Lung 3[18]		LUX-Lung 6[20]	
Endpoints	**Afatinib (n=230)**	**Pemetrexed/cisplatin (n=115)**	**Afatinib (n=242)**	**Gemcitabine/cisplatin (n=122)**
Objective response [n (%)] (95% CI)	129 (56.1%) (49.4 to 62.6)	26 (22.6%) (15.3 to 31.3)	162 (66.9%) [redacted]	28 (23.0%) [redacted]
Odds ratio vs chemotherapy (95% CI) P value (2 sided)	[redacted] (2.774 to 7.828) <0.0001		7.282* [redacted] <0.0001	
Disease control [n (%)] (95% CI)	207 (90.0%) (85.4 to 93.6)	93 (80.9%) (72.5 to 87.6)	224 (92.6%) [redacted]	93 (76.2%) [redacted]
Odds ratio vs chemotherapy 95% CI P value (2 sided)	[redacted] (1.134 to 4.037) 0.0189		3.843* (2.039 to 7.240) <0.0001	

*Odds ratio, 95% confidence interval, and p-value derived from a logistic regression model stratified by EGFR mutation category

The manufacturer's subgroup analysis of objective response stratified by ethnicity is provided in Table 55. This exploratory analysis suggests that Asian patients treated with afatinib have vastly improved ORR compared with non-Asian patients who appear to have a better response to chemotherapy than do Asian patients. The difference between treatments arms is much greater in the Asian population than the non-Asian population.

Table 55: Objective response stratified by ethnicity in LUX-Lung 3

Trial	Asian patients		Non-Asian patients	
Endpoints	**Afatinib (n=166)**	**Pemetrexed/ cisplatin (n=83)**	**Afatinib (n=64)**	**Pemetrexed/ cisplatin (n=32)**
Objective response (%)	62.7%	20.5%	39.1%	28.1%
Odds ratio vs chemotherapy (95% CI) P value (2 sided)	6.512 (3.507 to 12.093) <0.0001		1.638 (0.653 to 4.109) 0.2930	

Two other outcomes not specified in the scope issued by NICE were also reported in the MS:[1] changes in mean body weight and changes in ECOG PS. Mean body weight of

patients remained fairly stable throughout both trials in afatinib and chemotherapy groups. In LUX-Lung 3,[18] treatment with afatinib improved ECOG PS in [redacted] of patients, and ECOG PS was maintained in [redacted] of patients. Treatment with chemotherapy improved ECOG PS in [redacted] of patients, and maintained ECOG PS in [redacted] of patients. [redacted]

Non-randomised study

The majority of patients achieved disease control and confirmed objective response according to RECIST 1.0 criteria in LUX-Lung 2.[23] The mean duration of confirmed response was 57.7 weeks per central independent assessment and 65.9 weeks per investigator assessment. No differences in ORR were reported by subgroup. Subgroups do not appear to have been defined a priori. The findings are summarised in Table 56 and Table 57 respectively.

Tumour response rates, PFS and OS were reported to be greater in first-line patients than second-line patients and in patients receiving 50mg/day of afatinib than 40mg/day. The findings are summarised in Table 58. The ERG notes that there were no significant differences by ethnicity.

As with the LUX-Lung 3[18] and LUX-Lung 6[20] RCTs, median PFS in LUX-Lung 2[23] was assessed to be longer by local investigator assessment than by central independent assessment (13.7 vs 10.1 months for all patients, 15.6 vs 12.0 months for first-line [40mg/day or 50mg/day] and 10.5 vs 8.0 months for second-line patients [40mg/day or 50mg/day]).

Table 56 Best overall response in LUX-Lung 2

Endpoint	Central independent assessment (n=129)	Local investigator assessment (n=129)
23 Disease control (CR, PR, SD) N (%) 24 95% CI	106 (82.2) 74.5 to 88.3	111 (86.0) 78.8 to 91.5
25 Objective response N (%) 26 95% CI 27 Complete response N (%) 28 Partial response N (%) 29 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)

Table 57 Best overall response in LUX-Lung 2 by subgroup

Subgroup	Objective response rates	Odds ratio, 95% CI
Line of treatment: First-line vs second-line	66% vs 57%	0.71, 0.35 to 1.44
Starting dose: 40mg/day vs 50mg/day	60% vs 62%	1.07, 0.46 to 2.47
EGFR mutation: del-19 vs L858R	69% vs 63%	0.76, 0.34 to 1.69*
Sex: male vs female	57% vs 64%	1.32, 0.64 to 2.70
Location: Taiwan vs USA	60% vs 68%	1.44, 0.57 to 3.64
Ethnicity: Asian vs non-Asian	60% vs 69%	1.48, 0.48 to 4.54
Brain metastasis: absence vs presence	60% vs 65%	1.20, 0.52 to 2.78

* Central independent assessment

Table 58 Summary of efficacy results by treatment cohorts in LUX-Lung 2 per central independent assessment

Endpoint	First-line		Second-line	
	Afatinib 40mg/day (n=23)	Afatinib 50mg/day (n=38)	Afatinib 40mg/day (n=7)	Afatinib 50mg/day (n=61)
31 Disease control n (%) 32 Objective response N (%)	18 (78.3) 14 (60.9)	35 (92.1) 26 (68.4)	5 (71.4) 4 (57.1)	48 (78.7) 35 (57.4)
PFS (months) 25th percentile Median 75th percentile	 3.4 11.9 NA	 6.5 13.8 NA	 2.1 4.5 18.4	 2.7 8.3 15.7
OS (months) 25th percentile median	 9.6 23.1	 18.3 NA	 10.0 14.6	 11.5 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 central independent assessment

PFS was based on central independent assessment using the primary censoring rules.
NA: Not available from the Kaplan-Meier curve

32.1.1 Additional information on adverse events

The overall summaries of AEs reported in the MS are summarised in Table 59. As noted above (Table 5), dose escalation of afatinib was permitted if no AEs > Grade 1 in severity were experienced during the first course of treatment. The ERG notes that the EPAR reports that: 'The proportion of EGFR-TKI-naïve patients who increased their daily afatinib dose from 40 mg to 50 mg was small' (page 97). This was 7.0% of patients in LUX-Lung 3 and 6% of patients from a pooled analysis of LUX-Lung 3,[18] LUX-Lung 6[20] and LUX-Lung 2.[23] Nearly all patients experienced an AE, regardless of treatment (afatinib or chemotherapy) or dose.

As the manufacturer highlights, it was noticeable that AEs that reached CTCAE Grade 3 were reported less frequently in the 40 mg starting dose group than in the 50 mg starting dose group in LUX-Lung 2.[23] The ERG also notes that greater proportion of patients who started on 50 mg than those who started on 40 mg received a dose reduction or discontinued afatinib altogether as a result of an AE. This is largely why the subsequent LUX-Lung 3[18] and LUX-Lung 6[20] trials and also the licence for afatinib stipulate a starting dose of 40mg/day, with dose escalation only occurring if no AE are experienced during the first cycle.

The median number of courses of afatinib treatment in LUX-Lung 3[18] was 16 (336 days) and in LUX-lung 6[20] it was 19 (398 days). Serious AEs (SAEs) including fatalities and SAEs requiring hospitalisation were more common in the afatinib arm of both trials than the chemotherapy arms although the difference between arms was always less than 5%. The causes of death in the afatinib arm of LUX-Lung 3[18] were dyspnoea, sepsis, acute respiratory distress syndrome and unknown. In LUX-Lung 6[20] the cause was recorded as sudden death. The ERG also notes that these SAEs appear to be more common in the afatinib arm of LUX-Lung 3[18] trial than the afatinib arm of LUX-Lung 6[20] trial. There also appeared to be a greater proportion of patients requiring a dose reduction or discontinuation of afatinib as a result of AEs in LUX-Lung 3[18] than LUX-Lung 6[20] (although the proportion of drug related AEs requiring discontinuation were similar across trials). These may be chance findings or may reflect differences in the patient populations (e.g. relating to the proportion of Asian patients).

In order to gain greater insight into whether AEs experienced by Asians may differ to non-Asian populations, during the clarification process the ERG requested the data for LUX-Lung 3[18] by Asian and non-Asian populations. These are summarised in Table 60. There did

appear to be the following differences between Asian and non-Asian populations: AEs leading to dose reduction (higher in Asian patients), AEs leading to a permanent discontinuation (higher in non-Asian patients) and fatal SAEs (higher in non-Asian patients).

Specific AEs experienced by patients are also reported in the MS and summarised in Table 61. The most common AEs reported by patients receiving afatinib were diarrhoea, rash/acne, stomatitis/mucositis and in LUX-Lung 3[18] only, paronychia. In those receiving chemotherapy, most common AEs were nausea, vomiting, decreased appetite, fatigue, neutropenia, leukopenia and in LUX-Lung 3[18] only, anaemia. Adverse events not reported in the two RCTs but reported to be common in LUX-LUNG 2[23] include rhinorrhoea and cough which were more prevalent with the 50mg dose (44.4% and 39.4% respectively) than 40mg (33.3% and 30.0% respectively).

The MS does not report the most common type of SAEs experienced by patients. These are however reported in the EPAR (page 71) where it is noted that in a pooled analysis of LUX-Lung 3,[18] LUX-Lung 6[20] and LUX-Lung 2,[23] the most common SAEs (and Grade 3 or higher SAEs) were: diarrhoea 3.2% (2.8%) vomiting 2.6% (1.8%), dyspnoea 1.6% (1.0%), metastases to central nervous system 1.4% (1.4%), fatigue 1.0% (0.6%) pneumonia 1.0% (0.8%) and respiratory failure 1.0% (1.0%).

During the clarification process, the ERG also requested additional AE data for LUX-Lung 3[18] by Asian and non-Asian populations. These are summarised in Table 62. Two specific AEs appeared to be much more prevalent in the Asian population than non-Asian populations: nail effect and stomatitis. Three other AEs also appeared to be more common in Asian populations: dry skin, ocular effect and vomiting. The two most prevalent AEs, diarrhoea and rash/acne did not appear to differ depending on population.

Table 59 Overall summary of adverse events in LUX-Lung 3, LUX-Lung 6 and LUX-Lung 2 during the on-treatment period

Adverse events	LUX-Lung 3[18]		LUX-Lung 6[20]		LUX-Lung 2[23]	
	Afatinib 40mg (n=229)	Pemetrexed/ cisplatin (n=111)	Afatinib 40mg (n=239)	Gemcitabine/ cisplatin (n=113)	Afatinib 40mg (n=30)	Afatinib 50mg (n=99)
Patients with any AE	100.0	98.2	100.0	99.1	100.0	99.0
Drug related[1]	99.6	95.5	98.7	99.1	100.0	99.0
AEs leading to dose reduction	57.2	16.2	32.2	26.5	36.7	67.7
AEs leading to a permanent discontinuation	14.0	15.3	9.6	39.8	26.7	17.2
Drug related AEs[2] leading to permanent discontinuation	7.9	11.7	5.9	39.8	NR	NR
SAEs[3]	28.8	22.5	15.1	10.6	26.7	42.4
Fatal	5.7	2.7	5.9	2.7	6.7	10.1
Immediately life-threatening	0.4	3.6	0.4	0.9	0	1.0
Disability/incapacity	0	0	0.4	0	NR	NR
Required hospitalisation	27.1	18.0	12.6	8.0	23.3	36.4
Prolonged hospitalisation	1.7	5.4	2.1	2.7	0	1.0
Other	0.9	0.9	NR	NR	6.7	6.1
By highest CTCAE Grade						
Grade 1	5.2	12.6	16.3	8.0	3.3	2.0
Grade 2	34.1	28.8	36.8	29.2	43.3	24.2
Grade 3	51.1	44.1	37.7	38.1	43.3	58.6
Grade 4	3.9	9.9	3.3	21.2	3.3	4.0
Grade 5	5.7	2.7	5.9	2.7	6.7	10.1
AEs of Grade ≥3	60.7	56.8	46.9	62.0	53.3	72.7

All data are presented as a proportion (%)
1 As defined by the investigator (LUX-Lung 2[23] only 2 As defined by the investigator; 3 These categories are not mutually exclusive
AE=adverse event; CTCAE=common terminology criteria for adverse events; NR=not reported; SAE=serious adverse event

Table 60 Overall summary of adverse events in LUX-Lung 3 during the on-treatment period according to Asian and non-Asian populations

Adverse events	Asian patients		Non-Asian patients	
	Afatinib 40mg (n=165)	Pemetrexed/ cisplatin (n=80)	Afatinib 40mg (n=64)	Pemetrexed/ cisplatin (n=31)
Patients with any AE	100	98.8	100.0	96.8
Drug related[1]	99.4	97.5	100.0	90.3
AEs leading to dose reduction	62.4	17.5	43.8	12.9
AEs leading to a permanent discontinuation	12.7	13.8	17.2	19.4
SAEs[2]	29.1	22.5	28.1	22.6
Fatal	4.2	2.5	9.4	3.2
Immediately life-threatening	0.6	2.5	0.0	6.5
Disability/incapacity	0.0	0.0	0.0	0.0
Required hospitalisation	27.3	17.5	26.6	19.4
Prolonged hospitalisation	1.8	6.3	1.6	3.2
Other	1.2	1.3	0	0
By highest CTCAE Grade				
Grade 1	5.5	12.5	4.7	12.9
33 Grade 2	33.3	32.5	35.9	19.4
34 Grade 3	52.1	42.5	48.4	48.4
35 Grade 4	4.8	8.8	1.6	12.9
36 Grade 5	4.2	2.5	9.4	3.2
37 AEs of Grade ≥3	61.1	53.8	60.2	64.5

[1] As defined by the investigator; [2] A patient may be counted in more than one seriousness criterion
AE=adverse event; CTCAE=common terminology criteria for adverse events; SAE=serious adverse event

Table 61 Frequency of drug related adverse events reported in LUX-lung 2, LUX-Lung 3 (incidence >10%) and LUX-Lung 6 (incidence >20%)

System organ/class/adverse events	LUX-Lung 3[18]				LUX-Lung 6[20]				LUX-Lung 2[23]	
	Afatinib (n=229)		Pemetrexed/cisplatin (n=111)		Afatinib (n=239)		Gemcitabine/cisplatin (n=113)		Afatinib 40mg (n=30)	Afatinib 50mg (n=99)
	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	All AEs
Diarrhoea	95.2	14.4	15.3	0	89.5	5.9	15.0	0	96.7	93.9
Rash/acne+	89.1	16.2	6.3	0	80.8	14.2	9.7	0	90.0	94.9
Stomatitis/mucositis†	72.1	8.3	15.3	0.9	52.3	5.4	5.3	0	50.0	90.9
Paronychia	61.1	11.8	0	0	NR	NR	NR	NR	NR	NR
Decreased appetite	20.5	3.1	53.2	2.7	15.5	2.5	42.5	1.8	33.3	39.4
Nail effect+	NR	NR	NR	NR	34.3	0	0	0	80.0	86.9
Fatigue+	17.5	1.3	46.8	12.6	17.2	2.1	38.9	0.9	33.3	29.3
Vomiting	17.0	3.1	42.3	2.7	13.4	1.3	80.5	20.4	26.7	17.2
Nausea	17.9	0.9	65.8	3.6	11.7	0.4	75.2	8.0	16.7	18.2
Dry skin	29.3	0.4	1.8	0	NR	NR	NR	NR	23.3	34.3
ALT increased	NR	NR	NR	NR	23.0	2.1	15.9	2.7	NR	NR
Pruritus	18.8	0.4	0.9	0	NR	NR	NR	NR	50.0	59.6
Ocular effect+	17.9	0.4	1.8	0	NR	NR	NR	NR	20.0	32.3
Lip effect+	14.4	0	1.8	0	NR	NR	NR	NR	6.7	14.1
Epistaxis	13.1	0	0.9	0.9	NR	NR	NR	NR	30.0	26.3
Hypokalaemia	NR	NR	NR	NR	11.3	4.6	23.0	11.5	6.7	12.1
Anaemia‡	3.1	0.4	27.9	6.3	7.9	0.4	28.3	8.8	NR	NR
Weight decreased	10.5	0	9.0	0	NR	NR	NR	NR	10.0	19.2
Alopecia	10.0	0	17.1	0	NR	NR	NR	NR	16.7	10.1
Leukopaenia‡	1.7	0.4	18.9	8.1	6.3	1.7	51.3	15.0	NR	NR
Constipation	2.6	0	18.9	0	4.2	0.4	27.4	0	10.0	19.2
Neutropenia	0.9	0.4	31.5	18.0	4.6	1.3	54.0	26.5	NR	NR
Haemoglobin reduced	1.3	0	10.8	2.7	NR	NR	NR	NR	NR	NR
White blood cell decreased	NR	NR	NR	NR	1.3	0	23.9	6.2	NR	NR
Neutrophil count decreased	NR	NR	NR	NR	0.8	0	25.7	9.7	NR	NR

All adverse events are reported as a proportion (%)
†Group term. ‡Numbers are based on the adverse events reported by the investigator and not derived from the laboratory data; NR=not reported

Table 62 Frequency of drug related adverse events (incidence >10%) in LUX-Lung 3, by treatment arm in Asian and non-Asian populations

Adverse event category	Asian patients				Non-Asian patients				All patients			
	Afatinib 40mg (n=165)		Pemetrexed/ cisplatin (n=80)		Afatinib 40mg (n=64)		Pemetrexed/ cisplatin (n=31)		Afatinib 40mg (n=229)		Pemetrexed/ cisplatin (n=111)	
	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3	All AEs	Grade ≥ 3
Diarrhoea	95.8	15.8	15.0	0	93.8	10.9	16.1	0	95.2	14.4	15.3	0
Rash/acne†	90.9	17.0	7.5	0	84.4	14.1	3.2	0	89.1	16.2	6.3	0
Nail effect†	69.7	14.5	0	0	39.1	4.7	0	0	61.1	11.8	0	0
Stomatitis†	84.8	9.1	18.8	1.3	39.1	7.8	6.5	0	72.1	8.7	15.3	0.9
Fatigue†	16.4	1.8	45.0	8.8	20.3	0	51.6	22.6	17.5	1.3	46.8	12.6
Nausea	17.0	0.6	66.3	3.8	20.3	1.6	64.5	3.2	17.9	0.9	65.8	3.6
Dry skin	33.3	0.6	1.3	0	18.8	0	3.2	0	29.3	0.4	1.8	0
Pruritus	20.6	0	1.3	0	14.1	1.6	0	0	18.8	0.4	0.9	0
Ocular effect†	20.0	0.6	2.5	0	12.5	0	0	0	17.9	0.4	1.8	0
Alopecia	9.7	0	15.0	0	10.9	0	22.6	0	10.0	0	17.1	0
Vomiting	19.4	3.6	47.5	3.8	10.9	1.6	29.0	0	17.0	3.1	42.3	2.7
Epistaxis	14.5	0	0	0	9.4	0	3.2	3.2	13.1	0	0.9	0.9
Decreased appetite	26.1	3.6	63.8	3.8	6.3	1.6	25.8	0	20.5	3.1	53.2	2.7
Constipation	2.4	0	21.3	0	3.1	0	12.9	0	2.6	0	18.9	0
Lip effect†	18.8	0	2.5	0	3.1	0	0	0	14.4	0	1.8	0
Haemoglobin decreased	1.2	0	12.5	3.8	1.6	0	6.5	0	1.3	0	10.8	2.7
Weight decreased	13.9	0	10	0	1.6	0	6.5	0	10.5	0	9.0	0
Anaemia	4.2	0.6	30	6.3	0	0	22.6	6.5	3.1	0.4	27.9	6.3
Leukopenia	2.4	0.6	23.8	11.3	0	0	6.5	0	1.7	0.4	18.9	8.1
Neutropenia	1.2	0.6	33.8	18.8	0	0	25.8	16.1	0.9	0.4	31.5	18.0

All adverse events are reported as a proportion (%)

37.1 Trial characteristics of studies included in MTC

Table 63 Key trial characteristics of studies of patients with activating EGFR mutation status

Trial	Region	Intervention	Sample size (n)	Male	Median age (years)	Never smoked	PS0	PS1	PS2+	Adeno-carcinoma
LUX-Lung 3[18,19]	Global (mainly Asia)	Afatinib	230	36.1	[redacted]	67.4	40.0	60.0	0.0	100.0
		Pemetrexed/cisplatin	115	33.0	60 (mean)	70.4	35.7	63.5	0.9	100.0
LUX-Lung 6[20]	Asia	Afatinib	242	36.0	[redacted]	74.8	19.8	80.2	0.0	100.0
		Gemcitabine/cisplatin	122	32.0	56 (mean)	81.1	33.6	66.4	0.0	100.0
EURTAC[28]	Europe	Erlotinib	86	32.6	65	66.3	31.4	54.6	14.0	95.4
		Chemotherapy*	87	21.8	65	72.4	34.5	51.7	13.8	89.7
OPTIMAL[32]§	China	Erlotinib	82	41.4	57	71.9	91.4	8.6	0.0	87.8
		Gemcitabine/carboplatin	72	40.3	59	69.4	95.8	4.2	0.0	86.1
First-SIGNAL[26] †	Korea	Gefitinib (unknown/mixed status)	26 (159)	(12.0)	(57)	(100.0)	(25.8)	(65.4)	(8.8)	100.0 (100.0)
		Gemcitabine/cisplatin (unknown/mixed status)	16 (150)	(10.7)	(57)	(100.0)	(20.7)	(70.0)	(9.3)	100.0 (100.0)
IPASS[12] †	Asia	Gefitinib (unknown/mixed status)	132 (609)	28.2 (20.5)	(57)	93.9 (93.8)	90.2 (25.8)	(64.2)	9.8 (10.0)	(95.4)
		Paclitaxel/carboplatin (unknown/mixed status)	129 (608)	21.2 (20.9)	(57)	94.6 (93.6)	94.6 (26.5)	(62.8)	5.4 (10.7)	(97.2)
NEJGSG002[30]	Japan	Gefitinib	114	36.8	64 (mean)	65.8	47.4	51.8	0.9	90.4
		Paclitaxel/carboplatin	114	36.0	63 (mean)	57.9	50.0	48.2	1.8	96.5
WJTOG34053405[31]	Japan	Gefitinib	86	31.4	64	70.9	65.1	34.9	0.0	96.5
		Docetaxel/cisplatin	86	30.2	64	66.3	60.5	39.5	0.0	97.7

All data presented as proportion (%) except where stated
PS=performance status
* Chemotherapy was gemcitabine or docetaxel in combination with cisplatin or carboplatin
§ This trial was excluded from the MTC but included in a sensitivity analysis; all data extracted by the ERG
† Only a sub-population of First-SIGNAL[26] and IPASS[12] were EGFR-positive and not all data were presented for this sub-population; data for EGFR-positive patients extracted by the ERG and not presented in the MS.
Note: in the MS it is stated that neither the proportion of never-smokers or adenocarcinoma were reported in First-SIGNAL[26] but all patients in this trial were never-smokers with adenocarcinoma.

Table 64 Key trial characteristics of studies of patients with unknown/mixed EGFR status

Trial	Region	Intervention	Sample size (n)	Male	Median age (years)	Never smoked	PS0	PS1	PS2+	Adeno-carcinoma
Scagliotti et al 2009[63]	Global*	Pemetrexed/cisplatin	862	70.2	61	14.8	35.5	64.5	0.0	50.6
		Gemcitabine/cisplatin	863	70.1	61	14.1	64.5	64.2	0.0	47.6
Schiller et al 2002[59]	USA*	Paclitaxel/cisplatin	303**	64	62	NR	29	65	6	NR
		Gemcitabine/cisplatin	301**	62	64	NR	33	62	5	NR
		Docetaxel/cisplatin	304**	63	63	NR	32	62	6	NR
		Paclitaxel/carboplatin	299**	62	63	NR	28	67	5	NR
Smit et al 2003[60]	Global (mainly Europe)*	Paclitaxel/cisplatin	159	59.7	57	NR	22.0	66.0	12.0	40.2
		Gemcitabine/cisplatin	160	70.6	57	NR	25.0	63.8	11.3	45.6
		Gemcitabine/paclitaxel	161	68.3	56	NR	23.6	64.6	11.8	39.8
Rosell et al 2002[57]	Europe	Paclitaxel/cisplatin	309	81.9	58	NR	16.2	66.4	17.5	45.0
		Paclitaxel/carboplatin	309	83.5	58	NR	16.8	66.0	17.2	47.0
Scagliotti et al 2002[58]	Italy	Gemcitabine/cisplatin	205	81.5	63	NR	94.6		5.4*	50.24
		Paclitaxel/carboplatin	201	75.6	62	NR	91.5		8.5*	47.76
		Vinorelbine/cisplatin*	201*	78.1*	63*	NR*	92.0*		8.0*	55.2*
Chang et al 2001[51] †	NR	Gemcitabine/cisplatin	29	NR	NR	NR	NR	NR	NR	NR
		Vinorelbine/cisplatin	34	NR	NR	NR	NR	NR	NR	NR
Comella et al 2000[52] ¥	Italy*	Gemcitabine/cisplatin	60	90	60	NR	30.0	70.0	0.0	NR
		Vinorelbine/cisplatin	60	93	61	NR	28.3	71.7	0.0	NR
Melo et al 2002[56] †	NR	Gemcitabine/cisplatin	62	NR	NR	NR	NR	NR	NR	NR
		Vinorelbine/cisplatin	62	NR	NR	NR	NR	NR	NR	NR
Zatloukal et al 2003[62]	Czech Republic*	Gemcitabine/cisplatin	87	77.0	63	11.5	NR	NR	NR	26.4
		Gemcitabine/carboplatin	89	76.4	62	12.4	NR	NR	NR	32.6
Mazzanti et al 2003[55]	Italy*	Gemcitabine/cisplatin	62	72.6*	60*	NR	21.0*	61.7*	21.0*	38.7*
		Gemcitabine/carboplatin	58	84.5*	65*	NR	20.7*	58.0*	13.8*	51.7*
Thomas et al 2006[61]	France*	Gemcitabine/carboplatin	51	82.4*	60*	NR	86.3*		13.7*	56.9*
		Vinorelbine/cisplatin	49	83.7*	56*	NR	87.8*		12.2*	34.7*

Trial	Region	Intervention	Sample size (n)	Male	Median age (years)	Never smoked	PS0	PS1	PS2+	Adeno-carcinoma
Fossella et al 2003[53]	Global (mainly Europe)*	Vinorelbine/cisplatin	404	74.8	61	NR	NR	NR	NR	40.6
		Docetaxel/carbplatin	406	71.9	59	NR	NR	NR	NR	41.6
		Docetaxel/cisplatin	408	72.1	61	NR	NR	NR	NR	44.4
Gridelli et al 2003[54] §	Global (mainly Europe)	Gemcitabine/vinorelbine	250	78	62	NR	32	55	14	43
		Gemcitabine/cisplatin or Vinorelbine/cisplatin	251	81	61	NR	32	55	13	42

All data presented as proportion (%) except where stated (note: Scagliotti et al 2009 is erroneously referred to as Scagliotti et al 2009 in the MS)
NR=not reported; PS=performance status
* Data not reported in the MS but extracted by the ERG; note: the data from the vinorelbine/cisplatin arm were not included in the MTC
** Only patients eligible were reported in MS, the total number of patients (eligible and ineligible) is reported here in order to be consistent with the reporting of Gridelli et al 2003[54]
† Data from extracted from characteristics reported for a previous MTC[14] original papers could not be located by either the manufacturer or ERG
¥ Trial also included a third arm consisting of triplet therapy (gemcitabine/vinorelbine/cisplatin)
§ The MS reports this trial as gemcitabine/cisplatin vs vinorelbine/cisplatin.

37.2 Quality of assessment of studies included in MTC

The manufacturer's assessment of the quality of RCTs included in the MTC is summarised in Table 65

Table 65 Criteria for the assessment of randomised 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
EGFR-positive status									
LUX-Lung 3[18]	Yes	No	No	Yes	No	Not Clear	Yes	Yes	Good
LUX-Lung 6[20]	Yes	No	No	Yes	Not Clear	Not Clear	Yes	Yes	Good
First-SIGNAL[26]	Not Clear	Not Clear	NA	Yes	No	No	Yes	Not Clear	Average
NEJGSG002[30]	Not Clear	No	N/A	Yes	No	No	Yes	Not Clear	Average
WJTOG34053405[31]	Yes	No	N/A	Yes	Not Clear	No	Yes	Not Clear	Average
IPASS[12]	Not Clear	No	N/A	Yes	Not Clear	No	Yes	Not Clear	Average
EURTAC[28]	Yes	No	No	Yes	Not Clear	Not Clear	Yes	Not Clear	Average
Unknown/mixed EGFR status									
Chang et al. 2001[51]	Source study could not be located								
Comella et al. 2000[52]	Yes	Not Clear	Not Clear	Yes	No	Not Clear	Yes	Yes	Good
Fossella et al. 2003[53]	Yes	No	N/A	Yes	Not Clear	No	Yes	Yes	Good
Gridelli et al. 2003[54]	Yes	No	Yes	Yes	No	No	Yes	Not Clear	Good
Mazzanti et al. 2003[55]	Yes	NR	NR	Yes	No	No	Yes	Yes	Good
Melo et al. 2002[56]	Source study could not be located								
Rosell et al. 2002[57]	Yes	Not Clear	Not Clear	Yes	No	Not Clear	Yes	Yes	Good
Scagliotti et al. 2002[58]	Yes	No	N/A	Yes	Not Clear	No	Yes	Not Clear	Average
Scagliotti et al. 2009[63]	Yes	Not Clear	Not Clear	Yes	Not Clear	Not Clear	Not Clear	Not Clear	Average
Schiller et al. 2002[59]	Yes	Not Clear	Not Clear	Yes	Not Clear	Not Clear	No	No	Average
Smit et al. 2003[60]	Yes	No	N/A	No	Not Clear	No	Yes	Yes	Average
Thomas et al. 2006[61]	Yes	Not Clear	No	Yes	No	Not Clear	Yes	Yes	Good
Zatloukal et al. 2003[62]	Not Clear	No	N/A	Yes	Not Clear	No	Yes	Not Clear	Average

37.3 Simple assessment of the cost effectiveness of afatinib vs pemetrexed/cisplatin using data from LUX-Lung-3 clinical trial

The approximate cost-effectiveness estimates for afatinib vs pemetrexed/cisplatin in an EGFR mutation positive population are shown below in Table 66 (full trial population) and Table 67 (non-Asian subgroup).

The estimates of health state costs and all outcomes are based on the ERG models described in sections 4.2.7 and 5.3.1. All other parameter values are consistent with those employed in the manufacturer's model to provide consistency and comparability with results quoted in the main body of the report.

[redacted]

Table 66 Approximate cost-effectiveness of afatinib vs pemetrexed/cisplatin based on LUX-Lung 3 trial results (full trial population)

	Afatinib	Pemetrexed/cisplatin	Increment
Costs			
Treatment (List price)	[redacted]	£8,300	[redacted]
Treatment (PAS price)	[redacted]	£8,300	[redacted]
PFS health state	[redacted]	£1,700	[redacted]
Adverse events	[redacted]	£200	[redacted]
PPS health state	[redacted]	£21,000	[redacted]
Outcomes			
PFS	[redacted]	7.7	[redacted]
PPS	[redacted]	27.7	[redacted]
OS	[redacted]	35.4	[redacted]
QALYs	[redacted]	1.68	[redacted]
ICER			
Using list price	[redacted] / QALY		
Using PAS price	£39,300 / QALY		

Table 67 Approximate cost-effectiveness of afatinib vs pemetrexed/cisplatin based on LUX-Lung 3 trial results (non-Asian trial population)

	Afatinib	Pemetrexed/cisplatin	Increment
Costs			
Treatment (List price)	[redacted]	£8,300	[redacted]
Treatment (PAS price)	[redacted]	£8,300	[redacted]
PFS health state	[redacted]	£1,500	[redacted]
Adverse events	[redacted]	£200	[redacted]
PPS health state	[redacted]	£12,700	[redacted]
Outcomes			
PFS	[redacted]	7.0	[redacted]
PPS	[redacted]	16.1	[redacted]
OS	[redacted]	23.2	[redacted]
QALYs	[redacted]	1.13	[redacted]
ICER			
Using list price	[redacted] / QALY		
Using PAS price	£23,700 / QALY		