NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- The manufacturer's submission only includes first- line treatment of epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer Is it appropriate to consider afatinib as a second-line treatment?
- LUX Lung 3 and 6 were conducted in a population which included patients with a predominantly Asian ethnicity. In light of the evidence presented by the manufacturer indicating a better prognosis in terms of progression free survival and overall survival for Asians compared with non-Asians, are the results of these trials to be generalisable to clinical practice in the UK?
- The LUX Lung trials demonstrated a statistically significant benefit in PFS compared with chemotherapy (pemetrexed + cisplatin/gemcitabine + cisplatin) but no difference in overall survival based on immature overall survival data. What is the Committee view on the overall survival benefit for afatinib compared with chemotherapy and what impact may treatment crossover have on overall survival?

- The manufacturer's MTC reported no significant difference in PFS or OS with afatinib compared with erlotinib or gefitinib. The ERG noted several limitations of the manufacturer's MTC (including the heterogeneity of the trials, populations of people with a mixed EGFR status, outcomes based on central independent assessments). Is the methodology underpinning the manufacturer's MTC to be robust?
- Do the methodological issues with the manufacturers MTC prevent the indirect comparison of afatinib with either erlotinib or gefitinib?
- The ERG requested that the manufacturer conduct an exploratory analysis on the impact of local outcome assessment, updated overall survival, EGFR positive patients alone and exclusion of the EURTAC trial (which prevents the comparison of afatinib and erlotinib). Does the Committee consider the results of these updated MTC to be more robust than the manufacturer's original MTC?

Cost effectiveness

- The ERG considered the way in which PFS had been projected in the manufacturer's model to lack credibility as it did not reflect the LUX Lung data from which it was derived. Are the hazard ratios generated by this method considered to be appropriate to inform the economic model?
- The hazard ratios generated by the MTC include a population of mixed EGFR status and include Asian and non-Asian patients which is known to be a treatment effect modifier. Is the population used in the economic model considered to be representative of the UK population? Are the cost-effectiveness estimates from the manufacturers' economic model considered therefore generalisable to the UK?
- Are the results of the ERGs simple cost minimisation analysis to estimate the cost effectiveness of afatinib compared with erlotinib and gefitinib considered to be sufficient for decision making?
- Although the manufacturer's economic model focuses on first line treatment they note that there is no difference in the clinical efficacy of afatinib used first and second line. Should the cost effectiveness of afatinib as a second line treatment for EGFR mutation positive locally advanced or metastatic non-small cell lung cancer be considered?

1 Background: clinical need and practice

1.1 Lung cancer is classified by the cells in which the cancer starts. There are 2 types: small-cell lung cancer, and non-small-cell lung cancer (NSCLC). NSCLC is further classified by 3 different histological types called squamous cell carcinoma, adenocarcinoma and large cell carcinoma. In general lung cancer does not cause noticeable symptoms until it has spread through the lungs or into other parts of the body and is therefore advanced or metastatic. The prognosis is therefore poor compared to other cancers.

1.2 Lung cancer is the second most common cancer in the UK. There are 42,026 people diagnosed, and 34,859 deaths from lung cancer annually in the UK (based on 2010 data). About 83.3% of lung cancers are NSCLC. The estimated prevalence of EGFR mutations in NSCLC in England and Wales is 16.6%. However, the rate of EGFR mutations varies considerably across different ethnicities, with a higher prevalence in Asian populations. The population of people with advanced EGFR positive NSCLC is estimated to be 1,692 in England and Wales.

1.3 The prognosis for people with advanced EGFR positive NSCLC is poor. In a cancer survival publication by the Office of National Statistics, the one- and 5--year survival rates of people with lung cancer in England, diagnosed between 2006 and 2010, were reported as 31.6% and 9.8% respectively. Similarly survival rates in Wales have been reported to be 28.5% and 9.0%.

1.4 The aim of treatment for NSCLC is to extend progression free survival and overall survival without adverse events, and with the best quality of life possible for the remaining months of life. Treatment for NSCLC includes a combination of surgery, radiotherapy or chemotherapy. The type of treatment depends on the size and position of the cancer, how advanced the cancer is, and the overall health of the patient. Smaller tumours can be removed with surgery. However, if the tumour is too

large for surgery, and/or if it has spread through the lungs and/or to other parts of the body then radiotherapy or chemotherapy will be used to shrink the tumour. A new group of drugs is emerging, which work in a different way to chemotherapy and are known as "targeted agents" because they block certain processes in the cancer cells. For patients with activating Epidermal Growth Factor Receptor (EGFR) mutation(s), EGFR-tyrosine kinase inhibitor treatments, such as afatinib, erlotinib, and gefitinib, may be used. NICE Technology Appraisal Guidance No. 258 and No. 192 recommend erlotinib and gefitinib (respectively) as an option for the first-line treatment of people with locally advanced or metastatic NSCLC if :

- They test positive for the epidermal growth factor tyrosine kinase (EGFR-TK) mutation and
- The manufacturer provides erlotinib or gefitinib at the price agreed under the patient access scheme.

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

2 The technology

2.1 Afatinib (giotrif, Boehinger Ingelheim) is an irreversible tyrosine kinase inhibitor (TKI) that blocks EGFR (ErbB1) as well as other members of the ErbB family. The ErbB family are involved in growth, migration and metabolism of tumour cells. The irreversible binding of afatinib is what makes it different to the current TKIs (gefitinib and erlotinib). It has a marketing authorisation as a monotherapy, for the treatment of Epidermal Growth Factor Receptor (EGFR) TKI-naïve adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutation(s)

2.2 The summary of product characteristics lists the following adverse reactions for afatinib: diarrhoea, rash/acne, bullous, blistering and exfoliative skin conditions, stomatitis (inflammation in the mouth) and paronychia (nail infection). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The aanticipated NHS list price, provided by the manufacturer, is £2,023.28 per pack of 28 tablets. The anticipated NHS list price per course of treatment is expected to be around £22,000 per patient, based on a progression free survival of 11 months The manufacturer of afatinib has agreed a patient access scheme with the Department of Health. The Department of Health have approved a proposal for a simple discount scheme which represents a [redacted] discount on the list price of afatinib, with the discount applied at the point of purchase or invoice [redacted] The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost-effectiveness of afatinib within its licensed indication for the treatment of epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with locally advanced or metastatic non-small cell lung cancer with positive epidermal growth factor receptor tyrosine kinase mutation	
Intervention	Afatinib	
Comparators	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 Rationale for difference to NICE scope Afatinib will be licensed in patients untreated with a TKI, therefore TKIs are appropriate comparators Recent data (IMS 2013) has shown that 99% of eligible patients receive either erlotinib or gefitinib as a first line treatment, both of which are recommended as first-line treatments by NICE. Both erlotinib and gefitinib are EGFR TKIs, and given the high use of EGFR TKIs as a first line treatment, the opportunity to use an EGFR TKIs as a second line treatment in a TKI-naive patient population is unlikely. Any patients not receiving a TKI in firstt line might be expected to be treated with erlotinib is a likely second line option (Source: Manufacturer's submission page 11)
Outcomes	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	
Economic evaluation	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. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account.	

3.2 The manufacturer's decision problem focuses on the first line use of afatinib compared with gefitinib and erlotinib because they received a positive CHMP opinion for use as 'monotherapy for the treatment of EGFR positive TKI naive adult patients with locally advanced or metastatic non-small cell lung cancer with activating EGFR mutations'. . The manufacturer stated that afatinib is licensed for patients who have not had previous treatment with a TKI (gefitinib and erlotinib).

3.3 The ERG judged that the comparison of afatinib with gefitinib and erlotinib to be appropriate as they are recommended by NICE as a first line treatment for EGFR-positive NSCLC. The ERG also noted that although no relevant subgroups were identified in the final NICE scope or the manufacturers submission differences in the prognosis and treatment effect with Asian compared with non-Asian populations suggest that they are a relevant subgroup.

3.4 The manufacturer's submission focuses on afatinib use in TKI naïve patients who have EGFR positive locally advanced NSCLC. This could be first line, or after chemotherapy. It is being considered as an alternative to gefitinib and erlotinib.

4 Clinical-effectiveness evidence

4.1 The clinical effectiveness data presented by the manufacturer was predominantly from 2 phase 3 open label randomised controlled clinical trials, LUX Lung 3 and LUX Lung 6, and a mixed treatment comparison. LUX Lung 3 was an international trial (ethnicity: 26% Caucasian, 72% Eastern Asian, 2.0% other) that compared afatinib (40 mg daily, n=230) with cisplatin and pemetrexed (n=115) which was considered to be standard care in the UK for people with EGFR positive NSCLC at the time. LUX Lung 6 was conducted in China, Thailand and South Korea and compared afatinib (40 mg daily, n=242) with cisplatin and gemcitabine (n=122) which was considered at the time to be standard care in China for the EGFR positive population. Both trials included

people with advanced EGFR positive NSCLC (adenocarcinoma was the predominant histology) who had received no prior treatment with chemotherapy or EGFR targeting drugs. The primary outcome of both trials was progression free survival, as assessed by central independent review by Response Evaluation Criteria in Solid Tumours (RECIST version 1.1). Secondary outcomes included objective response rate and overall survival. In LUX-Lung 3 the overall survival data were not mature by the cut-off date for the primary analysis as 67 patients (29.1%) in the afatinib arm and 31 patients (27.0%) in the chemotherapy arm had died. The overall survival estimate was therefore estimated at this time The manufacturer presented the results of the updated analysis (using data up to March 2009 and the results of an updated analysis submitted to the EMA using data up to January 2013, see table 17 page 80 of the manufacturer's submission). The manufacturer stated that final analysis of overall survival will be performed when approximately 209 patients have died .The manufacturer also presented data from the phase II LUX-Lung 2 trial which included people who had received prior treatment with chemotherapy (section 4.5). Data from this trial was used to support the marketing authorisation. The overall survival data were not mature by the cut-off date for the primary analysis for both LUX-Lung 3 and 6. The manufacturer presented the results of the updated analysis.

4.2 LUX-Lung 3 and LUX-Lung 6 showed that treatment with afatinib, compared with chemotherapy, resulted in a statistically significant increase in median progression free survival (both independent review and investigator review), proportion achieving objective response and proportion with disease control (Table 1). No statistically significant difference in overall survival was seen on Lux-Lung 3 or Lux Lung-6 between afatinib and chemotherapy (Table 1). However, the overall survival data are still immature. Treatment crossover occurred on both LUX-Lung 3 and LUX-Lung 6, with the majority of patients receiving at least 1 line of subsequent anti-cancer therapy after stopping study medication (Table 1). This was not accounted for when estimating

overall survival. The manufacturer conducted a subgroup analysis for pre-specified baseline characteristics such as gender, age, race and common EGFR mutations which were consistent with the analysis in the ITT population.

Table 1 Progression free survival, objective response, disease control and overall survival from LUX-Lung 3 and LUX-Lung 6.

Outcome	**LUX-Lung 3 (95% CI)**		**LUX-Lung 6 (95% CI)**	
	afatinib	**Cisplatin/ pemetrexed**	**afatinib**	**Cisplatin/ gemcitabine**
Median progression free survival (ITT population, independent review)	11.14 months (9.63-13.63)	6.90 months (5.39-8.25)	11.01 months (9.66-13.73)	5.59 months (5.06-6.70)
	HR: 0.577 (0.425-0.784) P = 0.0004		HR: 0.279 (0.201-0.388) P < 0.0001	
Median progression free survival (ITT, investigator review)	11.07 months (9.66-13.60)	6.70 months (5.42-8.11)	13.73 months (11.50-13.86)	5.55 months (5.13-6.80)
	HR: 0.488 (0.367-0.649) P < 0.0001		HR: 0.262 (0.193-0.356) P < 0.0001	
Objective response based on central independent review	56.1% (49.4-62.6)	22.6% (15.3-31.3)	66.9% [redacted]	23.0% [redacted]
	OR: [redacted] (2.774-7.828) P < 0.0001		OR: 7.282 [redacted] P < 0.0001	
Disease control based on central independent review	90.0% (85.4-93.6)	80.9% (72.5-87.6)	92.6% [redacted]	76.2% [redacted]
	OR: [redacted] (1.134-4.037) P = 0.0189		OR: 3.843 [redacted] P < 0.0001	
Overall survival (interim analysis – at primary PFS analysis)	Deaths: 29.1%	Deaths: 27.0%	Deaths: 43.0%	Deaths:41.8%
	HR:1.121 [redacted] P = 0.6046		HR: 0.949 [redacted] P = 0.7593	
Overall survival (interim analysis – update for EMA and FDA)	Deaths: 50.4%	Deaths: 51.3%	Not applicable	
	HR: [redacted]			
Treatment crossover (patients could receive more than one further line of treatment)	72.0% crossed over 62.2% received chemotherapy [redacted] received another EGFR TKI	80.2% crossed over 64.9% crossed over to an EGFR TKI	58.4% crossed over 54.6% received chemotherapy	60.7% crossed over 48.4% crossed over to an EGFR TKI

Source: Tables 15 and 17 of the manufacturer's submission.

4.3 Health related quality of life data from LUX-Lung 3 and LUX-Lung 6 was reported for the pre-specified NSCLC-related symptoms of cough, dyspnoea and pain, measured by the EORTC QLQ-C30 and QLQ-LC13 questionnaires (Table 2). More than 87% of patients completed the questionnaires.

- Afatinib led to symptom improvement in more people than chemotherapy (cisplatin in combination with either pemetrexed or gemcitabine) for all the symptoms investigated
- There was a statistically significant increase in the proportion of people who achieved symptom improvement for dyspnoea, and specific items of dyspnoea when climbing stairs and shortness of breath with afatinib compared with chemotherapy in both LUX-Lung 3 and LUX-Lung 6.
- There was no statistically significant difference between afatinib and chemotherapy in the general pain category in LUX-Lung 3. Although statistically significantly more people achieved symptom improvement in the specific items of the pain score for pain in chest and pain in arm or shoulder with afatinib than chemotherapy.
- LUX-Lung 6 showed that statistically significantly more people achieved symptom improvement in non-specific pain and pain in chest with afatinib compared with chemotherapy, although there was no statistically significant difference between afatinib and chemotherapy for pain in arm or shoulder in LUX-Lung 6.
- There was no statistically significant difference between afatinib and chemotherapy for improvement in cough on LUX-Lung 3 and LUX-Lung 6.
- LUX-Lung 3 showed that there were no statistically significant difference between afatinib and chemotherapy in the proportion of people for whom [redacted], physical functioning, role functioning, or social functioning improved whereas afatinib was associated with a statistically significant improvement in the same domains in LUX-Lung 6.
- There was a statistically significant greater increase in the proportion of people for whom [redacted] improved with afatinib compared with chemotherapy in both LUX-Lung 3 and LUX-Lung 6.
- Time to deterioration for cough, dyspnoea and pain was reduced with afatinib compared with chemotherapy. This was statistically significant

for cough and dyspnoea on both LUX-Lung 3 and LUX-Lung 6, and pain on LUX-Lung 6.

Table 2 Proportion of people who achieved symptom improvement on LUX-Lung 3 and LUX-Lung 6

	LUX-Lung 3			**LUX-Lung 6**		
	Afatinib	**Cisplatin/pemetrexed**	**P value**	**afatinib**	**Cisplatin/gemcitabine**	**P value**
Quality of life (Status change in EORTC 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	0.2321	54.2%	28.7%	p <0.0001
Role functioning	49.0	45.0	0.5119	49.6%	34.7%	p = 0.0129
Social functioning	47.0	49.0	0.8070	55.3%	34.7%	p = 0.0007
Fatigue	72.0	57.0	0.0087	77.2%	52.5%	p <0.0001
Time to deterioration (EORTC LC13/C30)						
Cough	HR 0.595 95% CI 0.406, 0.872		p = 0.0072	HR 0.453 95% CI 0.299, 0.685		p = 0.0001
Dyspnoea	HR 0.682 95% CI 0.501, 0.928		p = 0.0145	HR 0.536 95% CI 0.395, 0.727		p <0.0001
Pain	HR 0.825 95% CI 0.618, 1.101		p = 0.1913	HR 0.703 95% CI 0.514, 0.961		p = 0.0265

Source: Manufacturer's submission Table 15, page 75.

4.4 The manufacturer also presented EQ-5D (UK and Belgium) and EQ-VAS data that was collected on the LUX-Lung 3 clinical trial (Table 3).

[redacted]

[redacted]

Table 3 Mean scores for EQ-5D and EQ-VAS from LUX-Lung 3

Statistic	UK utility	Belgium Utility	VAS
Mean score for afatinib	[redacted]	[redacted]	[redacted]
Mean score for chemotherapy	[redacted]	[redacted]	[redacted]
Difference in mean scores	[redacted]	[redacted]	[redacted]
Lower 95% confidence interval	[redacted]	[redacted]	[redacted]
Upper 95% confidence interval	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]

Source: Manufacturers submission, Table 18, page 84.

4.5 A mixed treatment comparison was presented to compare relative effectiveness of afatinib with gefitinib and erlotinib for progression free survival (Figure 1) and overall survival (Figure 2). The studies used were identified through systematic review. Fixed and random effects models were used. The MTC was based on an a previous MTC conducted for a previous appraisal (NICE technology appraisal guidance 192 'Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer) which was adapted to include data on the effectiveness of afatinib based on the LUX-Lung 3 and 6 studies, The results of the random effects model are presented for progression free survival. The results of the fixed effects model are presented for overall survival. The mixed treatment comparison showed that although there was no statistically significant difference in progression free survival or overall survival between afatinib and gefitinib or erlotinib (Figure 3 and Figure 4) the hazard ratios however favoured afatinib (Figure 3 and Figure).

Figure 1 Network of evidence for progression free survival

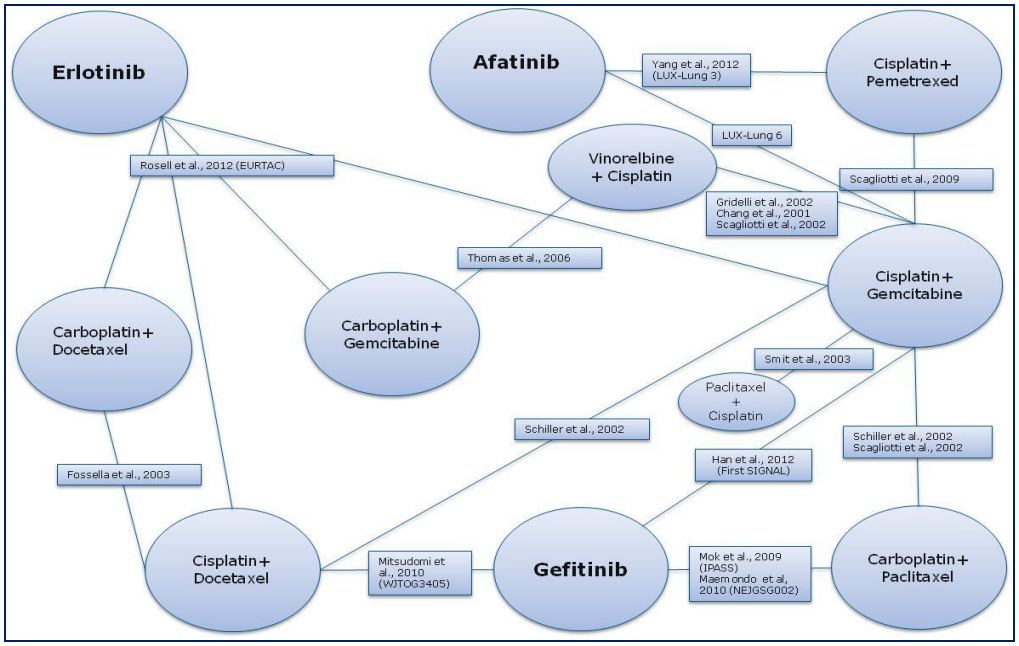


Figure 2 Network of evidence for overall survival

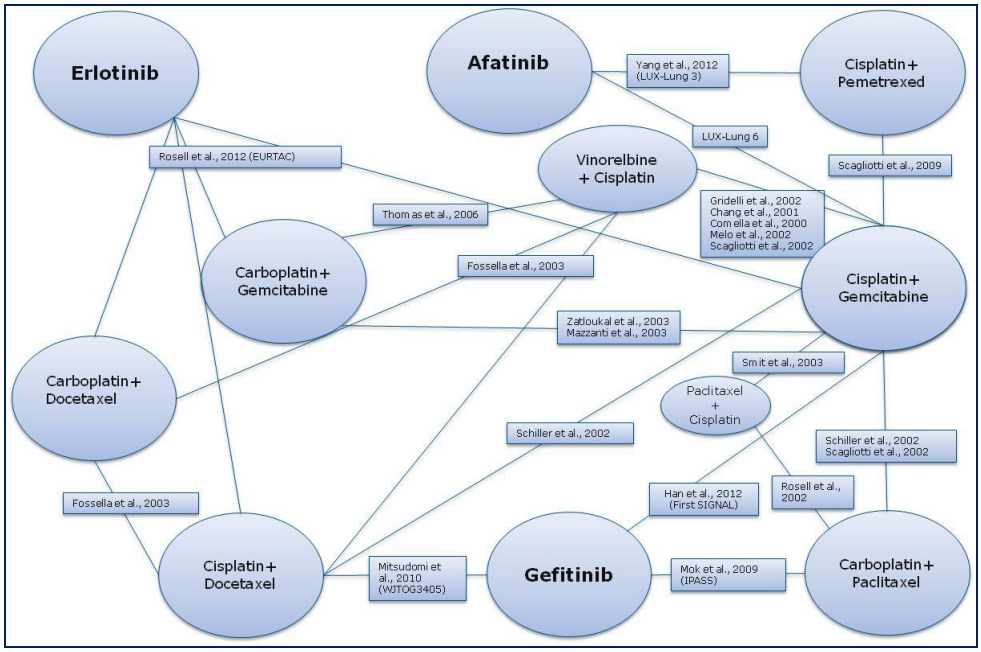


Figure 3 Mixed treatment comparison results: progression free survival

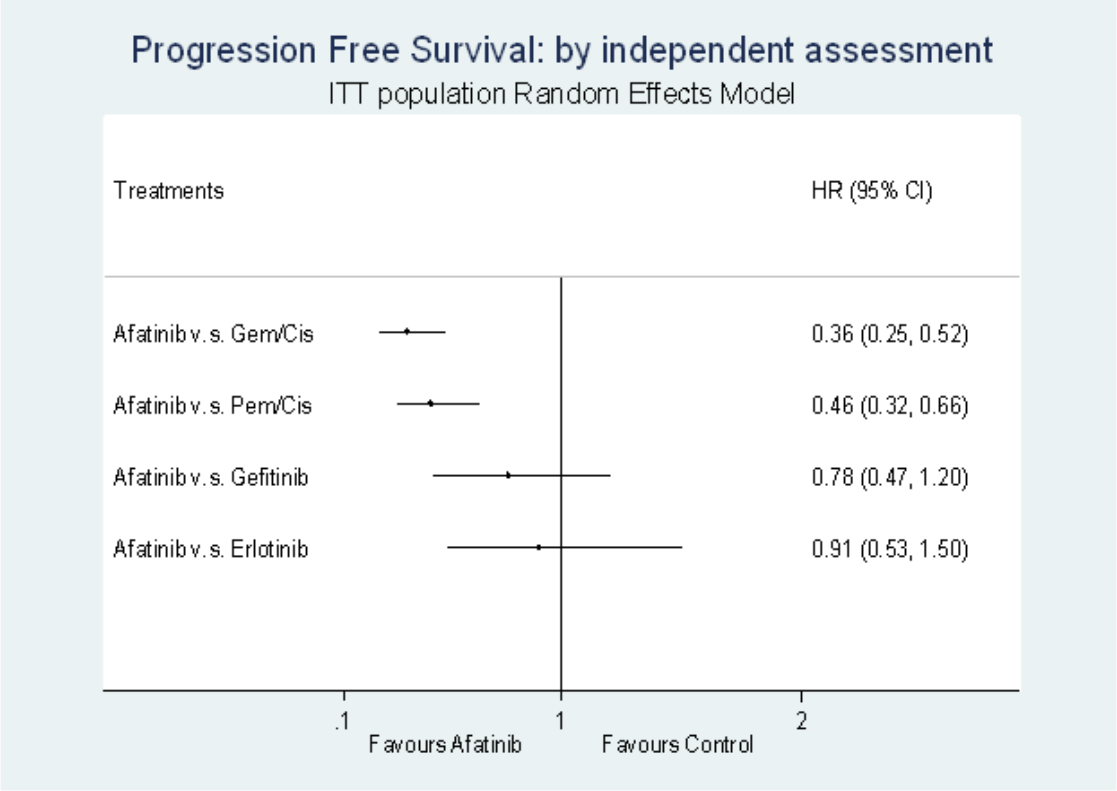


Figure 4 Mixed Treatment comparison results: overall survival

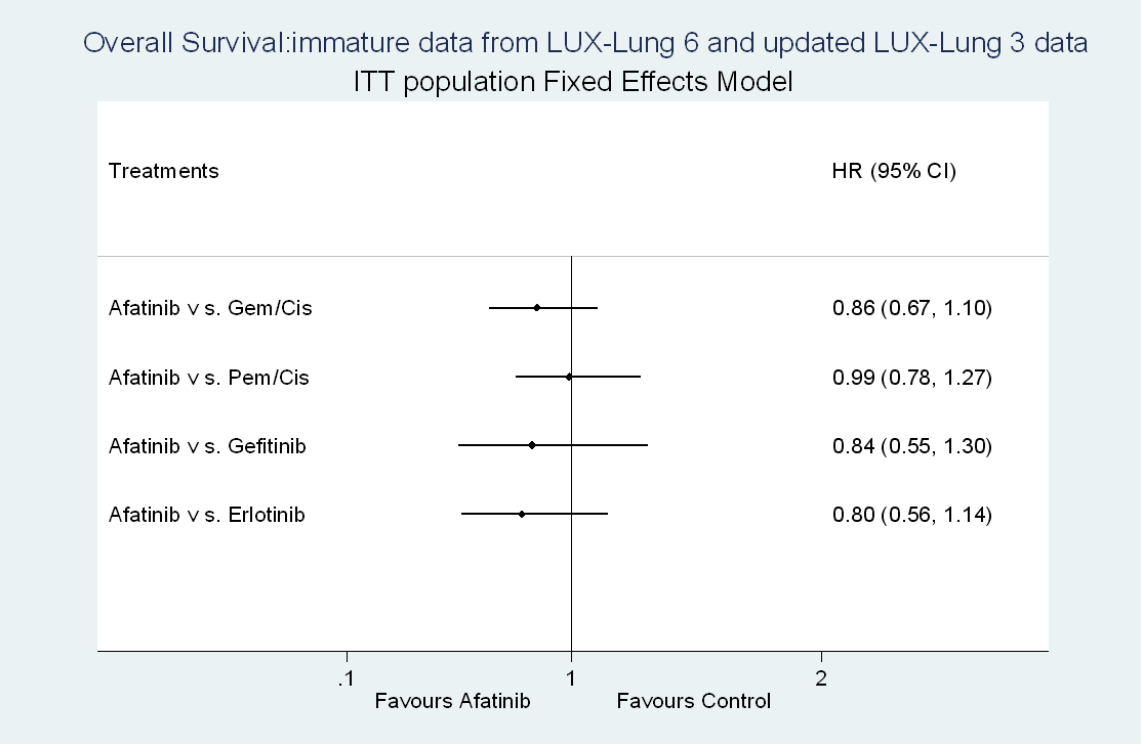


Table 4 Mixed Treatment comparison results: The probability of being the most effective treatment

Treatment	Progression free survival % probability	Overall survival % probability
Afatinib	62.6	43.3
Docetaxel / Carboplatin	0.0	1
Docetaxel / Cisplatin	0.0	1
Erlotinib	30.8	3
Gefitinib	6.5	13
Gemcitabine / Carboplatin	0.0	3
Gemcitabine / Cisplatin	0.0	0
Paclitaxel / Carboplatin	0.0	0
Paclitaxel / Cisplatin	0.0	2
Pemetraxed / Cisplatin	0.0	34
Vincristine / Cisplatin	0.0	0

Source: Manufacturers submission Tables 33 and 36 pages 115 and 118

4.6 To show the efficacy of afatinib in people who were TKI naïve but had received prior chemotherapy, the manufacturer presented data from LUX-Lung 2. LUX-Lung 2 was a multi-centre trial in the USA and Taiwan that included people with advanced EGFR positive NSCLC who had previously received chemotherapy. The total trial population was 129, of which 68 had received prior chemotherapy. There were two study arms, afatinib 40 mg and afatinib 50 mg. The people on the study were predominantly Asian (Table 5). Progression free survival and overall survival were shorter for those who had received previous treatment with chemotherapy than those who were treatment naïve (Table 5).

Table 5 Summary of efficacy results from LUX-Lung 2

	Treatment naive		Previously treated with chemotherapy	
	Afatinib 40 mg n(%)	Afatinib 50 mg n(%)	Afatinib 40 mg n(%)	Afatinib 50 mg n(%)
Total treated n (%)	23 (100)	38 (100)	7 (100)	61 (100)
Race				
Asian	18 (78.3)	30 (78.9)	6 (85.7)	58 (95.1)
Black	1 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
Caucasian	4 (17.4)	8 (21.1)	1 (14.3)	3 (4.9)
Disease control n (%)	18 (78.3)	35 (92.1)	5 (71.4)	48 (78.7)
Objective response n (%)	14 (60.9)	26 (68.4)	4 (57.1)	35 (57.4)
Median progression free survival (months)	11.9	13.8	4.5	8.3
Median overall survival (months)	23.1	NA	14.6	24.0

Source: Manufacturers submission, Table 54 Page 137.

4.7 The adverse events associated with afatinib, gefitinib and erlotinib are summarised in Table 6, as seen on the LUX-Lung 3, IPASS and EURTAC trials. LUX-Lung 3 showed that afatinib is associated with more diarrhoea, rash/acne, stomitis/muscostitis and paraonchyia than chemotherapy but less nausea, fatigue, vomiting, anaemia, leukopenia and neutropenia. Comparing the rates of adverse events between afatinib, erlotinib and gefitinib, the data presented in Table 6 suggest that afatinib is associated with more diarrhoea and rash/acne than gefitinib and erlotinib, more stomitis/muscostitis than gefitinib, but less reduced appetite and fatigue than erlotinib. These data also suggest that dose reductions were higher with afatinib than gefitinib or erlotinib. Interstitial lung disease was reported with afatinib, erlotinib and gefitinib although only in a small number of cases.

Table 6 Adverse event associated with afatinib, gefitinib and erlotinib

Adverse event (all grade)	LUX-Lung 3		IPASS		EURTAC	
	Afatinib	Cis/pem	Gefitinib	Carb/pac	Erlotinib	chemo
Diarrhoea	95%	14%	47%	Not reported	57%	
Rash/acne	89%	16%	66%		80%	
Stomitis/ muscostitis	72%	15%	17%		Not reported	
Paronychia	57%	0%	Not reported			
Reduced appetite	21%	53%			31%	
Nausea	18%	66%			Not reported	
Fatigue	18%	47%			57%	
Vomiting	17%	42%			Not reported	
Anaemia	3%	28%				
Leukopaenia	2%	19%				
Neutropenia	1%	32%				
Interstitial lung disease	3 cases	Not reported	2.6%	1.4%	1%	1%
Dose reductions	57% (38% had one, 19% had 2)	Not reported	16.1%	35.2%	21%	26%
Discontinuation	Not reported		6.9%	13.6%	6%	20%

Source: ERG report , Table 61 page 114

Evidence Review Group comments

4.8 The ERG stated that the lack of a significant OS benefit with afatinib in the LUX-Lung trials may be masked by the high rates of crossover. The ERG considered Asian and non-Asian populations to be relevant subgroups. In response to the ERG request for clarification the manufacturer provided a subgroup analysis for these subgroups using updated data from the LUX-Lung 3 trial.

[redacted]

[redacted]

Table 7 Estimated mean survival times (months) and incremental difference from treatment with afatinib vs pemetrexed/cisplatin

Endpoint	Subgroup	Afatinib	Pemetrexed/cisplatin	Difference
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

[redacted] Source: ERG report Table 10 page 33

4.9 The ERG considered the LUX-Lung 2 and 3 trials to be of good quality. They questioned the application of inclusion and exclusion criteria in searching for clinical trials in the MTC because it identified an additional 13 studies that could have been included in a mixed treatment comparison of unknown/mixed EGFR status.

4.10 The ERG considered the results of the subgroup analysis of the LUX-Lung 3 to show that the clinical effectiveness of afatinib differed according to race (Asian or non-Asian) which would also have an impact

on the results of the trials included in the mixed treatment comparison which it considered to be are unreliableand potentially misleading. The ERG stated 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 LUX-Lung 3 trial population who were predominantly of Asian origin.

4.11 The ERG also questioned whether it was appropriate to include trials of EGFR-positive populations with those with unknown/mixed EGFR status in a single mixed treatment comparison. The ERG noted that there were in differences in patient characteristics between studies of patients of EGFR-positive NSCLC and those of unknown/mixed EGFR status in relation to the proportions of men, never-smokers and patients with adenocarcinoma. The ERG also noted that the ORIGINAL mixed treatment comparison included patients with different types of non-small cell lung cancer. The ERG therefore concluded that the patient populations in the included trials are not sufficiently similar and, therefore the results generated by the manufacturer's original mixed treatment comparison are not generalisable to a UK population.

4.12 The ERG requested during the clarification stage additional sensitivity analyses on the mixed treatment comparison incorporating the following:

- the use of local investigator assessments (which had little impact on the results of the MTC)
- updated OS data (where available),
- using only data from the population of patients with EGFR activating mutations for both PFS and OS
- the impact of excluding excluding EURTAC on the above analyses.

Table 8. 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. Source: ERG report Table 17 page 47.

4.13 The ERG however noted that comparisons limited to the EGFR positive population relied primarily on data derived from the First-SIGNAL trial subgroup analysis of 42 patients to compare afatinib with gefitinib. The ERG considered that reliance on a small subgroup of patients may lead to imprecision. The ERG also noted that 5 trials were in wholly Asian populations, one study (LUX-Lung 3) was conducted in a predominantly (≥70%) Asian population and the EURTAC study was conducted solely in a European population. The ERG acknowledged that it was possible to exclude the EURTAC study (which enables the comparison of afatinib with erlotinib) from the mixed treatment comparison, but they questioned whether an analysis which only includes an Asian population can be used to inform treatment decisions for patients in the NHS.

4.14 The ERG specified that the EURTAC trial was rated as ‘average’ in the manufacturer’s quality assessment. The ERG also noted there were differences in the proportions of people who had never smoked between treatment arms, crossover after disease progression was permitted, the method used to account for missing data was not reported and there was no testing of the proportional hazards assumption. Having raised a number of issues with EURTAC, the ERG noted 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.

4.15 The ERG also noted that in all 7 of the studies of patients with EGFR-positive disease, the overall survival hazards function cross, therefore indicating the proportional hazards assumption has not been met in the mixed treatment comparison. The ERG acknowledged that this was probably due to the effect of crossover in the trials.

4.16 The ERG stated that the manufacturer's additional sensitivity analyses undertaken on the MTC had the same key limitations as the manufacturer's original mixed treatment comparison, namely they assume 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.

4.17 The ERG noted that the adverse events of special interest in the manufacturers submission were identified to be diarrhoea and rash/acne.The ERG noted that the proportion of patients with Grade 3 diarrhoea varied across studies from 5.9% (LUX-Lung 6) to 20.2% (LUX-Lung 2). It noted that the reasons for these differences were unclear but specified that they may be a chance finding or may reflect differences in the study populations in terms of age, ethnicity or dose of treatment received. The ERG noted that no Grade 4 or 5 diarrhoea adverse events were reported in any study. The ERG also noted that the proportion of patients with Grade 3 rash/acne was similar in LUX-Lung 3 and LUX-Lung 6 but slightly higher in LUX-Lung 2. It specified that the reasons for this difference were not clear but may be attributable to the higher dose of afatinib in LUX-Lung 2. The ERG noted that no Grade 4 or 5 rash/acne adverse events were reported in any study and the onset of rash/acne was only reported for LUX-Lung 3. The ERG also noted that the manufacturer also reported findings for Grade 3/4 fatigue from the mixed treatment comparison but it was not explicitly stated why this particular adverse event was reported. The ERG noted that fatigue is

known to be a relatively common adverse event in people treated with erlotinib and gefitinib.

4.18 The ERG noted that the manufacturer reported compliance rates of 87% to 99% for HRQoL questionnaires. The ERG queried if n values in the manufacturers submission for the time to deterioration in coughing, dyspnoea, and pain related items of EORTC QLQ-C30 and EORTC QLQ-L13, implied 100% response rates for these questions. The manufacturer clarified that the n values indicated the number at risk at the beginning of the study, rather than compliance. Therefore, the ERG concluded that the information provided by the manufacturer regarding compliance was insufficient.

In summary the ERG concluded that results of any MTC which includes a mix of Asian and non-Asian patients cannot produce valid survival outcomes appropriate for use in a cost-effectiveness analysis generalisable to patients in England and Wales. The ERG considered 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. The ERG further highlighted an on-going study (LUX-Lung 7) which is due to report in December 2014 on a direct comparison between afatinib and gefitinib, may shed some light on the relative clinical effectiveness of afatinib compared with erlotinib, or of afatinib compared with gefitinib, in a UK patient population.

Comments from other consultees

4.19 Professional groups stated that afatinib would be considered for people with EGFR positive lung cancer either first line alongside the other EGFR TKIs (erlotinib or gefitinib) or after erlotinib or geftinib have failed. A professional group commented that there is considerable national variation in the speed of turnaround of EGFR mutation testing. Therefore

clinical decisions may be made before an EGFR mutation result is known. In these cases if an EGFR mutation were detected after the initiation of systemic chemotherapy, a EGFR TKI (such as afatinib) would be considered as a subsequent line of treatment.

4.20 A professional group recognised the lack of evidence comparing afatinib with erlotinib or gefitinib. They noted that comparison between EGFR TKIs is not currently possible, but stated that response rates and durability are similar across EGFR TKIs, and that improved efficacy tends to come at the cost of increased side effects. They also commented that afatinib may offer a different side effect profile to gefitinib and erlotinib and noted the value of afatinib as an alternative choice to erlotinib and afatinib.

4.21 A patient group commented that although current therapies for EGFR positive NSCLC have clinical benefit, they do not provide a cure. The patient group emphasised that it was important to patients to have more treatment options. It commented that afatinib may offer benefits in improving the quality and length of life, and stated that these are important to people with EGFR positive NSCLC. The patient group also commented that as afatinib is oral, whereas chemotherapy is intravenous, it may reduce time in hospital. The patient group noted that the disadvantages of afatinib include the side effects, such as diarrhoea.

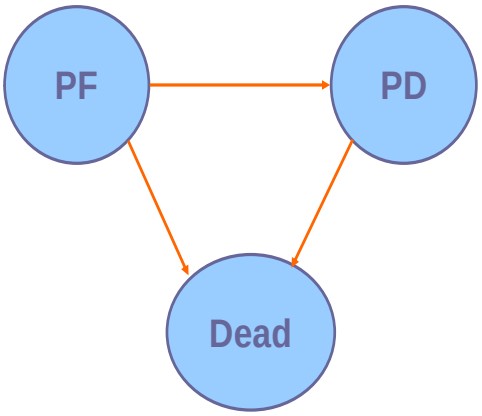
5 Cost-effectiveness evidence

5.1 The manufacturer presented a de novo disease-state cohort model consisting of 2 health states (progression-free and progressive disease (Figure 5) and a death state. The progression-free health state represented the period during which the patient’s cancer did not worsen whilst receiving active treatment. The progressive disease health state represented the period that the cancer spread. The model allowed movement from the progression-free health state to the progressive-

disease health state, or death state; or from the progressive-disease health state to the death state. The model had:

- a life time horizon of 10 years
- a cycle length of one month
- NHS / PSS perspective
- 3.5% discounting for costs and QALYs

Figure 5 Model structure



PD: progressive disease; PF: progression-free.

5.2 The manufacturer's model used the partitioned survival (also known as under the curve) method to determine the proportion of patients in each health state, for each model cycle. Data from LUX-Lung 3 and LUX-Lung 6 were used to estimate progression free survival and overall survival for afatinib in the model (Table 9). These data were extrapolated to estimate overall survival. Sensitivity analyses was conducted which used 3 types of parametric survival modelling of the clinical trial Kaplan Meier data; exponential, Weibull and Gompertz. Data from the mixed treatment comparison was used for progression free survival and overall survival of gefitinib and erlotinib (Table 9). The proportion of people in the progressive-disease state was estimated by the difference between progression-free survival and overall survival.

Table 9 Model base case inputs

Input	Detail	Source
Proportion of people in each health state	Afatinib	LUX Lung-3 LUX Lung-6
	Gefitinib and erlotinib	Mixed treatment comparison
Type and frequency of adverse events	Afatinib	LUX Lung-1 LUX Lung-3
	Gefitinib and erlotinib	Mixed treatment comparison
Utility values	Progression free	LUX-Lung-3
	Progressive disease	Chouaid et al. 2012

Source: Manufacturers submission Table 85 and 86.

5.3 The manufacturer's model included a second line of treatment in the progressive disease health state (assumed to be docetaxel in the base case) before best supportive care. In the model base case it was assumed that the time on docetaxel was the same, irrespective of the first line treatment, and this time period was based on PFS data for docetaxel from the INTEREST trial. However, a different scenario was used for sensitivity analyses in which the duration of docetaxel treatment was estimated as a proportion of the time spent in progressive disease (Table 10), and would therefore vary depending on the first line of treatment. Of note, the manufacturer's clinical expert stated that in clinical practice people are unlikely to receive a second line of treatment (see manufacturers submission page 172). The length of time on best supportive care was calculated, for each arm, by subtracting the time spent on second-line therapy from the estimated total time spent in PD.

Table 10 Time (months) spent in the progressive disease health state on docetaxel and best supportive care

		Afatinib	Erlotinib	Gefitinib
Mean total period in progressive disease		19.45	15.95	18.14
Set time period on docetaxel	Mean period on docetaxel	4.10	4.10	4.10
	Mean period on BSC	15.35	11.85	14.04
Time on docetaxel as a proportion of the total time in progressive disease	Mean period on docetaxel	3.56	2.92	3.32
	Mean period on BSC	15.89	13.03	14.82

Source: ERG report Table 28, page 67.

5.4 Adverse events are applied in the modelling for the first year only, and can occur in the progression-free or progressive disease health states. The adverse events accounted for included diarrhoea, rash/acne, fatigue, anaemia and neutropenia. The type and frequency of adverse events was estimated from LUX Lung-1 and LUX Lung-3 for afatinib, and the mixed treatment comparison for gefitinib and erlotinib. The manufacturer assumed that the number of episodes per patient, and duration of each adverse event was the same for gefitinib and erlotinib as for afatinib. The duration of adverse events were longer in the progressed disease state than the progression-free state. The disutility vales applied to each event are summarised in Table .

5.5 The utility values (see Table 11) used in the progression free health state of the manufacturer's base case model were derived from EQ-5D and EQ-VAS scores collected from the LUX-Lung trials. Utility values from the literature were used for the progressive disease health state, and for sensitivity analyses of the progression free health state. Utility values did not change over time.

Table 11 Utility and disutility values used in the manufacturer's model

Health state	Analyses		Source	Value
Progression free utility values	Base case		LUX-Lung 3	0.784
	Sensitivity analyses		Chouaid et al. 2012	0.710
			Nafees et al. 2008 (responding)	0.672
			Nafees et al. 2008 (stable)	0.653
			Nafees et al. 2008 (*weighted, assumed 50% responding 50% stable)	0.663
Progressive disease utility values	Base case	2nd line	Chouaid et al. 2012	0.73
		3rd line (BSC)	Chouaid et al. 2012	0.46
		3rd line (progression-free)	Chouaid et al. 2012	0.62
Progressive disease utility values for each treatment	Base case	Pem/cis	*	0.487
		Afatinib	*	0.517
		Erlotinib	*	0.529
		Gefitinib	*	0.521
	Sensitivity analysis (2nd line treatment duration a proportion of time in progressive disease)	Pem/cis	*	0.487
		Afatinib	*	0.509
		Erlotinib	*	0.509
		Gefitinib	*	0.509
Adverse event disutility values (relative to being progression free)	Base case	Diarrhoea (grade 3/4)	LUX-Lung 3	−0.147
		Rash/acne (grade 3/4)	LUX-Lung 3	−0.202
		Fatigue (grade 3/4)	LUX-Lung 1	−0.179
		Anaemia	Nafees et al. 2008	−0.073
		Neutropenia	Nafees et al. 2008	−0.090

Source: Manufacturers submission, Tables 84 to 86 page 189 to 190.

5.6 To estimate the costs in the model the manufacturer either used the resource used from the LUX-Lung trials, or took values from the literature (Table 11). The resource associated with disease management (progression free or progressed disease health states) and adverse events were estimated from the LUX-Lung trials, including:

- Outpatient visits (GP, specialist, nurses, occupational therapist, physiotherapist)
- Outpatient interventions (CT scan, MRI scan, surgical procedure, ultrasound, x-ray, radiotherapy)
- Unscheduled hospitalisations (unscheduled hospital stay, ICU visit, emergency room visit)
- EGFR testing

All other values were taken from the literature. The model assumes that treatment with afatinib, erlotinib or gefitinib is continuous until disease progression. Disease progression is typically assessed every 3 months by CT scan, and this cost is incorporated into the model. Afatinib, gefitinib, and erlotinib each have a patient access scheme agreed, which were accounted for in the analyses.

Table12 Costs applied to the model

Item			Cost	Source
Disease management - Progression free health state		Cost per month (same cost for all treatment arms)	£220	LUX Lung-3
Disease management - Progressive disease health state	Second line progression free	Cost per month	£362	Literature
		Afatinib (total cost)	£1,484	
		Erlotinib (total cost)		
		Gefitinib (total cost)		
	Progressive disease (best supportive care)	Cost per month	£418	LUX Lung 1
		Afatinib (total cost)	£6,410	
		Erlotinib (total cost)	£4,949	
		Gefitinib (total cost)	£5,862	
Drug costs	List price (cost per month)	Afatinib	£2,023.28	Manufacturer
		Erlotinib	£1,631.40	BNF 2011
		Gefitinib	£2,167.71	BNF 2011
		Docetaxel	£3,344	BNF 2011
	PAS price	Afatinib (28 day pack)	[redacted]	Manufacturer
		Erlotinib	Not stated	
		Gefitinib (one off fixed cost)	£12,200	NICE
Drug administration costs	Afatinib introductory administration cost (1st model cycle)		£163	Department of health
	Erlotinib – introductory administration cost (1st model cycle)		£163	Department of health
	Gefitinib	Introductory administration cost (1st model cycle)	£163	Department of health
		PAS set up cost (1st model cycle)	£34	NICE
		Monthly PAS administration cost	£70	
	Docetaxel – monthly		£302.41	Department

	administration cost		of health
Adverse events – total cost per event	Diarrhoea	[redacted]	LUX-Lung 3
	Rash/acne	[redacted]	
	Fatigue	[redacted]	LUX-Lung 1
	Anaemia	[redacted]	NICE 2009
	Neutropenia	[redacted]	

Source: Manufacturers submission Table 114, page 207

Results

5.7 The manufacturer's base case results, including PAS for each of the technologies, are presented in Table 13. The fully incremental analyses suggested erlotinib is extendedly dominated by afatinib (that is, that erlotinib has lower costs and fewer QALYs than afatinib, but the ICER for afatinib compared with erlotinib is lower than that erlotinib compared with gefitinib), Afatinib is associated with an ICER of £10,076 per QALY gained compared with erlotinib, and erlotinib was associated with an ICER of £695,000 per QALY gained compared with gefitinib. The manufacturer stated that the probability of afatinib being cost effective compared with erlotinib was 100%, at £20,000 and £30,000 per QALY, and compared with gefitinib it was 72% and 81% respectively.

Table13 Base case results, including PAS prices

Analysis		**Comparator**	**Incremental costs**	**Incremental QALYs**	**ICER**
Base case	Deterministic (pairwise)	Gefitinib	£3,113	0.17	£17,933
		Erlotinib	£1,723	0.17	£10,079
	Probabilistic (pair wise)	Gefitinib	£2,390	0.16	£15,027
		Erlotinib	£1,058	0.16	£6,671
	Deterministic (incremental)	Gefitinib	-	-	-
		Erlotinib	£1,390	0.002	£695,000 (ED)
		Afatinib	£1,723	0.171	£10,076

Source: ERG report, Table 35, page 71.

5.8 The manufacturer conducted one way sensitivity analyses of the pair wise comparisons with gefitinib and erlotinib. The main drivers were:

- the MTC-based HR for PFS
- the MTC-based HR for OS
- the cost per month for the progression free health state
- the cost per month for the best supportive care period of the progressive disease health state.

Overall the ICERs estimated for the one way sensitivity analyses ranged from £8,023 to £54,800 for afatinib compared with gefitinib, and from £7,339 to £36,718 for afatinib compared with erlotinib. As part of the one way sensitivity analyses the manufacturer looked at the impact of using different parametric survival model survival curves estimates on the ICER, and presented the impact of using Weibull model hazard ratio for comparison of afatinib with gefitinib. Using the lowest value (95% C.I HR =0.70) from the Weibull model HR (afatinib compared with pemetrexed and cisplatin) for overall survival, the ICER was £17,069 per QALY gained, and using the highest (95% C.I HR=1.31) it was £18,894 per QALY gained. Using the Weibull estimate of PFS (afatinib compared with pemetrexed and cisplatin) had more impact, using the highest value (95% C.I HR=0.82) the ICER was £30,656 per QALY gained and the lowest t (95% C.I =0.46) it was £7,135 per QALY gained.

5.9 The manufacturer conducted some scenario analyses that varied the calculation of second line treatment, varied the utility values in the progression free health state, and varied the data used in the MTC. The results are summarised in Table 14. The scenarios for second line treatment included using pemetrexed rather than docetaxel as the second line treatment, and changing the duration of second line treatment to be a proportion of the time in progressive disease, rather than a fixed duration. Using pemetrexed second line had a minimal impact on the ICER (Table 14). Applying a proportional duration of second line treatment increased the ICER to a maximum of £19,952 per

QALY gained compared with gefitinib and £15,718 per QALY gained compared with erlotinib. Applying utility values derived from the literature for the progression free health state also increased the ICER, most notably when afatinib was compared with gefitinib, which resulted in an ICER of £20,256 per QALY gained. For the comparison of afatinib with erlotinib, changing the utility values had a minimal impact on the ICER. Using only LUX-Lung 3 data in the MTC for afatinib (i.e. excluding LUX-Lung 6 which was based in Asia) had the most impact on the ICER, it increased the ICER for afatinib compared with gefitinib to £24,339, but had the opposite impact on the comparison with erlotinib, as afatinib dominated erlotinib. When only LUX-lung 3 was used, and OPTIMAL data was included, afatinib had an ICER of £15,257 per QALY gained when compared with gefitinib, and £13,013 per QALY gained when compared with erlotinib.

Table 14 Scenario analyses for afatinib compared with gefitinib or erlotinib, including PAS prices (deterministic) for afatinib compared with gefitinib and erlotinib.

Scenario analyses		**Gefitinib**	**Erlotinib**
Base case (pairwise, deterministic)		***£17,933***	***£10,079***
Second line	Pemetrexed	£17,925	£10,084
Proportional duration of second line treatment	Docetaxel	£19,904	£15,664
	Pemetrexed	£19,952	£15,718
Utility values of progressive free health state	LUCEOR data (Chouaid et al. 2012)	£19,359	£10,390
	Literature (Nafees et al. 2008)	£20,256	£10,588
Only afatinib data from LUX-Lung 3 in MTC		£24,339	Dominant
Only afatinib data from LUX-Lung 3 in MTC, with OPTIMAL data included		£15,257	£13,013

Source: ERG report, Tables 41 to 43, pages 74 and 75..

Evidence Review Group comments

5.10 The ERG considered the key flaw in the model was the progression free survival and overall survival estimates derived from the manufacturers mixed treatment comparison used in the model:

- The ERG did not consider the progression free survival and overall survival hazard ratios for afatinib compared with erlotinib and afatinib compared with gefitinib based on the mixed treatment comparison to be credible. When the estimated mean overall survival for the LUX-Lung 3 trial was compared with other first-line trials of NSCLC patients, the prognosis for people with activating EGFR mutations was considerably better [redacted] than non-squamous NSCLC patients, who had a mean life expectancy of only 15 to 20 months. The ERG also noted that LUX-Lung 3 showed that the progression free survival and overall survival was longer in the Asian than the non-Asian population.

- The ERG also disagreed with the approach taken by the manufacturer namely fitting theoretical survival models to the LUX-Lung 3 trial data. The ERG did not consider that the Weibull models generated by the manufacturer for patients receiving afatinib and pemetrexed/cisplatin accurately reflect the experience of LUX-Lung 3 patients, especially for progression free survival which has an impact on the application of hazard ratios in the manufacturer's model. The ERG therefore considered that the progression free survival results obtained from the Weibull model lacked credibility. (See figure 14 page 80 of the ERG report).

- The ERG also considered the efficacy estimates based on a specifically - Asian population could not be generalised to the UK population (See section 4.19).

The ERG identified minor issues in the manufacturer's model related to:

- **PPS;** In the model, post-progression survival (PPS) was estimated by subtracting progression free survival from overall survival. The ERG noted that after discontinuing study treatment only [redacted] of people in the afatinib arm received single agent docetaxel chemotherapy, whilst more than twice that proportion [redacted] received platinum-based chemotherapy. The ERG judged that 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.

- **Utility of second and third line treatment:** 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). The ERG noted that the treatment received by patients included in the study ares unknown. It also noted that the utility values were based on a small number of patients particularly for best supportive care where the author stressed that the numbers were too small for meaningful analysis. The ERG also noted that the utility values were noticeably higher than those published in a recent HTA report.

- **Continuity correction errors:** The ERG judged that In the manufacturer's model the time spent by patients in both the PFS and PD health states was not correctly calculated The ERG noted the resulting errors were that the cost of treatments (afatinib, and erlotinib) are underestimated by 50% of a monthly pack, health state costs were under-estimated (PF costs by 1-2% and PD costs by 7-8%) and life-years and QALYs are also under-estimated by a similar proportion.

- **Method for estimating docetaxel therapy costs'**; The ERG noted that body surface area estimate in the model were not based on a UK population and there was no accounting for the wide variation in body surface area in the population. The ERG also noted that the current EMIT price for docetaxel (£28.03) is much lower than the cost estimate used in the manufacturers model (£504.24).

- **Gefitinib PAS administration cost:** The ERG noted that in the manufacturer's model the costs associated with administering the gefitinib PAS were £34 set-up cost and a monthly administration cost of £70. However, in a previous STA considering erlotinib for the first-line treatment of locally advanced or metastatic EGFR TK mutation-positive NSCLC the prices used were a set-up cost of £70 and a monthly administration cost of £34.

- **Drug administration costs.** The ERG noted that costing afatinib, erlotinib and gefitinib in the model assumes a one-off introductory administration cost of delivering oral chemotherapy (£163). The ERG judged that costs to the NHS would occur in the form of a dispensing free from a pharmacy every time a patient received a monthly prescription. In the model, the drug administration cost for docetaxel is based on the NHS Reference Cost for the delivery of complex chemotherapy, including prolonged infusion treatment at first attendance (SB14Z) at a cost of £302.41. The ERG judged that oral medication packs are issued as part of a nurse-led out-patient visit, and that docetaxel monotherapy would be delivered as simple chemotherapy in a day-case setting.

- **Terminal care costs';** Terminal care costs are not considered in the manufacturer's model. The ERG noted that In a recent review of first-line chemotherapy for patients with NSCLC, 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. The ERG judged that inclusion of these costs is relevant when a model generates differential survival, due to the effects of discounting outcomes.

- **Adverse event costs:** The ERG judged that the cost estimates for adverse events, particularly for fatigue was underestimated in the model. It noted that a grade 3/4 adverse event would require hospitalisation and therefore the manufacturer's cost estimate of [redacted] per episode associated with that adverse event appeared to be unrealistic.

5.11 In view of the issues above, the ERG did not consider it to be appropriate to carry out an exploratory analysis using the manufacturer's

model because it judged that the survival estimates in the model lacked credibility (see section 6.10). It specified that it was not possible to incorporate alternative survival projections into the model due to the way it had been structured around the use of hazard ratios to generate survival estimates rather than using directly obtained estimates. The ERG also considered that it was also not appropriate to re-run the manufacturer's model incorporating adjustments for minor errors identified because it would give misleading credibility to the ICERs presented by the manufacturer.

5.12 The ERG carried out a cost analysis based on the assumption of the equal effectiveness of afatinib, erlotinib and gefitinib. The list price of afatinib is £2023.28 (for 28 days' supply) and that for erlotinib is £1631.53 (for 30 days' supply). With the Patient Access Scheme, the simple discount [redacted] reduces the daily cost of treatment to [redacted].

5.13 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. Median trial PFS for afatinib, erlotinib and gefitinib (from LUX-Lung 3, EURTAC and IPASS respectively) are 11.07, 9.7 and 9.5 months respectively. This means that treatment with gefitinib [redacted].

5.14 The ERG carried out an exercise to (See Appendix 10.4 of the ERG report) in order to obtain an approximate estimate of the ICER which would have been obtained if a full economic model were to be undertaken. It noted that the combination of PAS pricing and use of data for the non-Asian subgroup of LUX-Lung 3, is likely to indicate that

afatinib is cost-effective when compared to pemetrexed/cisplatin in a mainly Caucasian population of EGFR-positive patients. This analysis only utilised efficacy data from the LUX-LUNG 3 study.

Table 15 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		

Source: ERG report Table 66 Appendix 10.4

Table 16 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		

Source: ERG report Table 67 Appendix 10.4.

End-of-life considerations

The manufacturer did not put forward a case for afatinib being considered as an 'end of life' treatment.

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median overall survival on LUX-Lung 3 for the chemotherapy arm was [redacted] months (95% CI [redacted])
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	No statistically significant survival benefit was seen on LUX-Lung 3 or LUX-Lung 6

The treatment is licensed or otherwise indicated for small patient populations	The population with new advanced EGFR positive NSCLC lung cancer in England and Wales is estimated to be 1,692 based on 2010 data

6 Equality issues

6.1 A potential equality issue was raised at the scoping workshop regarding availability of timely EGFR testing to influence treatment decisions. It was concluded that this was not a relevant equality issue for this appraisal as recommendations on the use of afatinib would not be able to address this issue.

6.2 .

7 Innovation

7.1 The manufacturer stated that that afatinib was innovative because it is a selective and irreversible ErbB family blocker that inhibits EGFR, HER2 and ErbB4 receptor tyrosine kinases. It claimed that irreversible binding of an agent is believed to help extend its efficacy and delay the development of resistance, whereas targeting more than one family member of the ErbB family may improve efficacy and overcome redundancy associated with receptor crosstalk.

8 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Technology Appraisal No. 258, June 2012, 'Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation positive non-small-cell lung cancer'. Currently Review proposal in progressClinical Guideline No.121. April 2011, 'The diagnosis and treatment of lung cancer' (update of Clinical Guideline 24). Review date April 2014.

Technology Appraisal No. 192, July 2010, 'Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer'. Review proposal in progress

Technology Appraisal No. 190, June 2010, 'Pemetrexed for the maintenance treatment of non-small cell lung cancer.' Review proposal in progress.

Technology Appraisal No. 181, September 2009, 'Pemetrexed for the first-line treatment of non-small cell lung cancer'. Review proposal in progress.

Technology Appraisal No. 124, November 2007, 'Pemetrexed for the treatment of non-small-cell lung cancer'. Review date TBC.

Technology Appraisal No. 162, November 2008, 'Erlotinib for the treatment of non-small cell lung cancer'. Review proposal in progress

Guidance in development

Technology Appraisal in development, 'Pemetrexed for the maintenance treatment following induction therapy with pemetrexed and cisplatin for non-squamous non-small-cell lung cancer'. Expected date of publication December 2013.

Technology Appraisal in development, 'Erlotinib and gefitinib for the treatment of non-small-cell lung cancer following prior chemotherapy' (review of TA 162 and TA 175)'. Expected date of publication June 2014

NICE Quality Standards

- 'Lung cancer'

  http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp

NICE Pathways

- There is a NICE pathway on Lung Cancer which is available from http://pathways.nice.org.uk/pathways/lung-cancer

Appendix B: Clinical efficacy section of the draft European public assessment report [if not yet published]

[Add as a confidential appendix or add a link to the EPAR here if it is published.]