

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

Technology appraisal guidance

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Your responsibility

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1 Recommendations

- 1.1 Afatinib is recommended as an option, within its marketing authorisation, for treating adults with locally advanced or metastatic non-small-cell lung cancer only if:
- the tumour tests positive for the epidermal growth factor receptor tyrosine kinase (EGFR-TK) mutation **and**
 - the person has not previously had an EGFR-TK inhibitor **and**
 - the manufacturer provides afatinib with the discount agreed in the patient access scheme.

2 Information about afatinib

- 2.1 Afatinib (Giotrif, Boehringer Ingelheim) is an irreversible tyrosine kinase inhibitor (TKI) that blocks the epidermal growth factor receptor (EGFR) ErbB1 and other members of the ErbB family. The ErbB family is involved in the growth, migration and metabolism of tumour cells. Afatinib has a marketing authorisation as a monotherapy 'for the treatment of EGFR TKI-naive adult patients 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 very common adverse reactions for afatinib: diarrhoea, rash/acne, blistering and dry skin conditions, pruritus, decreased appetite, nose bleed, 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 Afatinib is given orally at a recommended dosage of 40 mg once daily. The dosage may be increased to a maximum of 50 mg/day in the first 3 weeks in patients who are able to tolerate 40 mg/day without adverse reactions of greater than grade 1 severity. For patients who have more severe adverse reactions, the dose may be reduced (usually by 10 mg decrements) or treatment interrupted or discontinued. For full details see the summary of product characteristics. The NHS list price, provided by the manufacturer, is £2,023.28 per pack of 28 tablets (20 mg, 30 mg, 40 mg or 50 mg). The manufacturer stated that the 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 in which a confidential discount is applied at the point of purchase or invoice. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The manufacturer's submission

The [Appraisal Committee](#) considered evidence submitted by the manufacturer of afatinib and a review of this submission by the [Evidence Review Group](#) (ERG).

- 3.1 The clinical effectiveness data presented by the manufacturer were predominantly from 2 phase III open-label randomised controlled clinical trials. LUX-Lung 3 compared afatinib with cisplatin plus pemetrexed and LUX-Lung 6 compared afatinib with cisplatin plus gemcitabine. There was also a mixed treatment comparison that compared afatinib with erlotinib and gefitinib. LUX-Lung 3 was an international trial (ethnicity: 26% white, 72% Eastern Asian, 2.0% other) that compared afatinib (40 mg daily, n=230) with cisplatin plus pemetrexed (n=115) for patients with EGFR mutation-positive NSCLC. LUX-Lung 6 was conducted in China, Thailand and South Korea and compared afatinib (40 mg daily, n=242) with cisplatin plus gemcitabine (n=122) for patients with EGFR mutation-positive NSCLC. In both trials patients were included who had received no prior treatment with chemotherapy or EGFR-targeting drugs and adenocarcinoma was the predominant histology. The primary outcome of the clinical 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.
- 3.2 In LUX-Lung 3, there was a statistically significant increase in median progression-free survival for afatinib compared with cisplatin plus pemetrexed combination chemotherapy (11.14 months compared with 6.90 months; a gain of 4.24 months) with a hazard ratio of 0.58 (95% confidence interval [CI] 0.43 to 0.78) when assessed by independent review. When the outcome was assessed by the trial investigator, there was a statistically significant increase in median progression-free survival for afatinib compared with combination chemotherapy (11.07 months compared with 6.70 months; a gain of 4.37 months) with a hazard ratio of 0.49 (95% CI 0.37 to 0.65).
- 3.3 In LUX-Lung 6, there was a statistically significant increase in median

progression-free survival for afatinib compared with cisplatin plus gemcitabine combination chemotherapy (11.01 months compared with 5.59 months; a gain of 5.42 months) with a hazard ratio of 0.28 (95% CI 0.20 to 0.39) when assessed by independent review. When the outcome was assessed by the trial investigator, there was a statistically significant increase in median progression-free survival for afatinib compared with combination chemotherapy (13.73 months compared with 5.55 months; a gain of 8.18 months) with a hazard ratio of 0.26 (95% CI 0.19 to 0.36).

- 3.4 In LUX-Lung 3, overall survival data were not mature by the cut-off date (February 2012) for the primary analysis because 67 patients (29.1%) in the afatinib arm and 31 patients (27.0%) in the chemotherapy arm had died. The manufacturer presented the results of the updated analysis (using additional data after the February 2012 cut-off) and the results of an updated analysis submitted to the European Medicines Agency using data up to January 2013). The manufacturer stated that final analysis of overall survival will be performed when 209 patients have died. No statistically significant difference in overall survival was seen in LUX-Lung 3 or LUX-Lung 6 between afatinib and chemotherapy with hazard ratios of 1.12 (95% CI 0.73 to 1.72) and 0.95 (95% CI 0.68 to 1.33) respectively. Treatment crossover occurred in both LUX-Lung 3 (72%) and LUX-Lung 6 (80%) with most patients receiving at least 1 line of subsequent anticancer therapy after stopping the study drugs. Crossover was not accounted for when estimating overall survival. The manufacturer conducted subgroup analyses of LUX-Lung 3 and LUX-Lung 6 for pre-specified baseline characteristics such as gender, age, family origin and common EGFR mutations, which was consistent with the analysis in the intention-to-treat populations.
- 3.5 Health-related quality of life data from LUX-Lung 3 and LUX-Lung 6 were reported for the pre-specified NSCLC-related symptoms of cough, dyspnoea and pain, measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and QLQ-LC13 questionnaires. More than 87% of patients completed the questionnaires. Afatinib was associated with a statistically significant improvement in breathing, non-specific pain and chest pain, fatigue and the time to deterioration in cough, dyspnoea and pain compared with chemotherapy (cisplatin plus either pemetrexed or gemcitabine). EQ-5D (UK and Belgium) and EQ-VAS data collected during the LUX-Lung 3 clinical trial reported no statistically significant difference

in values between afatinib and chemotherapy with an absolute improvement in utility of 0.008 (UK) and 0.007 (Belgium).

- 3.6 Because there was no head-to-head randomised controlled trial comparing the effectiveness of afatinib with erlotinib or gefitinib for progression-free survival or overall survival, the manufacturer presented a mixed treatment comparison. This was based on a previous mixed treatment comparison conducted for [NICE's technology appraisal guidance on 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 and erlotinib. The studies used to populate the mixed treatment comparison were identified through systematic review. The manufacturer identified 20 randomised controlled trials, 4 of which included gefitinib (first SIGNAL trial, IPASS trial, Mitsudomi 2010, Maemondo 2010) and 1 that included erlotinib (EURTAC trial). The population of the studies included in the mixed treatment comparison was people with locally advanced or metastatic non-small cell lung cancer. However, only 7 of the trials were carried out exclusively in people with EGFR-positive disease. The manufacturer specified that the EURTAC trial was of average quality and the first SIGNAL trial only included 42 patients with EGFR-positive disease. All the trials included in the mixed treatment comparison permitted crossover after disease progression. A fixed-effects model was used to assess progression-free survival and a random-effects model was used to assess overall survival. There was no testing of the proportional hazards assumption.
- 3.7 The results of the manufacturer's mixed treatment comparison showed that there was no statistically significant difference in progression-free survival or overall survival between afatinib and gefitinib or erlotinib. Afatinib had the highest probability (62.6%) of being the most effective treatment in terms of progression-free survival gain compared with all the comparator treatments including erlotinib (30.8%) and gefitinib (6.5%). Afatinib also had the highest probability (43%) of being the most effective treatment in terms of overall survival gain compared with all the comparator treatments including erlotinib (3%) and gefitinib (13%).
- 3.8 The resulting hazard ratios from the mixed treatment comparison for the difference in median progression-free survival for afatinib were:
- 0.36 (95% CI 0.25 to 0.52) compared with gemcitabine plus cisplatin

- 0.46 (95% CI 0.32 to 0.66) compared with pemetrexed plus cisplatin
- 0.78 (95% CI 0.47 to 1.20) compared with gefitinib
- 0.91 (95% CI 0.53 to 1.50) compared with erlotinib.

3.9 The resulting hazard ratios from the mixed treatment comparison for the difference in median overall survival for afatinib were

- 0.86 (95% CI 0.67 to 1.10) compared with gemcitabine plus cisplatin
- 0.99 (95% CI 0.78 to 1.27) compared with pemetrexed plus cisplatin
- 0.84 (95% CI 0.55 to 1.30) compared with gefitinib
- 0.80 (95% CI 0.56 to 1.14) compared with erlotinib.

3.10 The manufacturer submitted evidence from the non-placebo controlled LUX-Lung 2 trial, a phase II multicentre trial conducted in the USA and Taiwan, which evaluated the safety and efficacy of afatinib in patients with locally advanced or metastatic EGFR-positive NSCLC. The patients in the study were predominantly Asian. This trial evaluated the effectiveness of afatinib in patients who had not previously received chemotherapy (n=61) and patients whose disease had progressed after 1 previous chemotherapy treatment (n=68). There were 2 study arms, afatinib 40 mg and afatinib 50 mg. The primary outcome of LUX-Lung 2 was progression-free survival, as assessed by central independent review by RECIST version 1.1. Secondary outcomes included objective response rate and median overall survival.

3.11 In LUX-Lung 2, progression-free survival was shorter in patients who had received prior chemotherapy. The median progression-free survival was 11.9 months for patients who had not had chemotherapy before and 4.5 months for patients receiving the 40 mg dose of afatinib as a second-line treatment. LUX-Lung 2 reported shorter overall survival in patients who had prior chemotherapy compared with those who had not. The median overall survival was 23.1 months for patients who had not had chemotherapy and 14.6 months for patients receiving afatinib as a second-line treatment.

3.12 LUX-Lung 3 reported higher rates of diarrhoea, rash/acne, stomatitis/mucositis

and paronychia compared with chemotherapy but less nausea, fatigue, vomiting, anaemia, leukopenia and neutropenia. The manufacturer compared the adverse reactions from the pivotal clinical trials for afatinib (LUX-Lung 3), gefitinib (IPASS) and erlotinib (EURTAC), which showed that afatinib is associated with more diarrhoea (95%) than gefitinib (47%) and erlotinib (57%), more rash/acne (89%) than gefitinib (66%) and erlotinib (80%), more stomatitis/mucositis (72%) than gefitinib (17%), but less reduced appetite (21%) than erlotinib (53%) and less fatigue (18%) than erlotinib (47%). Dose reductions were higher with afatinib (57%, LUX-Lung 3) compared with gefitinib (16.1%, IPASS) or erlotinib (21%, EURTAC).

- 3.13 The manufacturer presented a de novo disease-state cohort model consisting of 2 health states (progression-free and progressive disease) and death. The progression-free health state represented the period during which the patient's cancer did not worsen while 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 lifetime horizon of 10 years and a cycle length of 1 month, with an NHS and personal social services perspective and 3.5% discounting for costs and health effects.
- 3.14 The manufacturer's model used the partitioned survival 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, but parametric survival models based on hazard ratios produced from the mixed treatment comparison were used to project progression-free survival and overall survival over the 10-year model time horizon. The Weibull method was used to extrapolate the trial data in the base-case model to estimate progression-free survival and overall survival. Sensitivity analyses were conducted that used 2 further types of parametric survival modelling of the clinical trial Kaplan-Meier data: exponential and Gompertz. The progression-free survival and overall survival estimates for people treated with erlotinib and gefitinib were estimated by applying the mixed treatment comparison hazard ratios to the survival estimates for people treated with afatinib. Progression-free survival and overall survival were incorporated into the cost-effectiveness model by using full parametric approximation or by using

Kaplan-Meier data from the clinical trials extrapolated using parametric survival models.

3.15 Adverse reactions (diarrhoea, rash/acne, fatigue, anaemia and neutropenia) were applied in the model for the first year only, in both the progression-free and progressive disease health states. The type and frequency of adverse reactions was estimated from LUX-Lung 1 and LUX-Lung 3 for afatinib, and from the mixed treatment comparison for gefitinib and erlotinib.

3.16 In the base-case model the utility value used in the progression-free health state was 0.78 (from LUX-Lung 3) and utility values from the literature were used for the progressive disease health state (0.73 and 0.46 for second- and third-line treatment respectively). Alternative utility values derived from the literature for the progression-free health state were used in a sensitivity analysis. Utility values did not change over time.

3.17 To estimate the costs in the model, the manufacturer either used resource costs from the LUX-Lung 3 and 6 trials, or values from the literature. The resource costs associated with disease management (progression-free or progressed disease health states) and adverse reactions estimated from the LUX-Lung 3 and 6 trials included:

- 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, intensive care unit visit, emergency room visit)
- EGFR testing.

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

- 3.18 The deterministic pairwise results of the base-case analysis showed that afatinib was associated with an ICER of £10,076 per QALY gained (incremental costs £1,723, incremental QALYs 0.171) compared with erlotinib and an ICER of £17,933 per QALY gained (incremental costs £3,113, incremental QALYs 0.173) compared with gefitinib. The manufacturer stated that there was a 100% probability of afatinib being cost effective compared with erlotinib at £20,000 and £30,000 per QALY gained. Compared with gefitinib, there was a 72% and 81% probability of afatinib being cost effective at £20,000 and £30,000 per QALY gained respectively.
- 3.19 The manufacturer conducted one-way sensitivity analyses of the pairwise comparisons with gefitinib and erlotinib. The main drivers of cost effectiveness were: the mixed treatment comparison-based hazard ratios for progression-free and overall survival, the cost per month for the progression-free health state and 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 £7,135 to £54,800 per QALY gained for afatinib compared with gefitinib, and from -£10,302 to £34,970 per QALY gained for afatinib compared with erlotinib.
- 3.20 The manufacturer conducted some scenario analyses that varied the choice of second-line treatment (using pemetrexed rather than docetaxel as the second-line treatment), the duration of second-line treatment, the utility values in the progression-free health state and the studies used in the mixed treatment comparison. Using pemetrexed as second-line treatment had a minimal impact on the ICER. Applying a proportional duration of second-line treatment increased the ICER for afatinib compared with gefitinib to a maximum of £19,952 per QALY gained 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 mixed treatment comparison for afatinib (that is, 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 per QALY gained, but had the opposite effect on the comparison with erlotinib in which afatinib dominated erlotinib (that is, was cheaper and more effective).

When only LUX-Lung 3 data and data from the OPTIMAL trial of erlotinib comparing carboplatin plus gemcitabine were 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.

ERG's critique and exploratory analyses

- 3.21 The ERG stated that the lack of a significant overall survival benefit with afatinib in the LUX-Lung 3 and 6 trials may have been 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 using updated data from LUX-Lung 3, which showed that Asian patients treated with chemotherapy may have a different progression-free survival and overall survival compared with non-Asian patients. The ERG undertook exploratory analyses using the manufacturer's data and noted that the mean expected post-progression survival was different for patients treated with afatinib in the Asian subgroup than in the non-Asian subgroup. The estimated mean progression-free survival in Asian patients was 19.5 months for afatinib and 8.7 months for pemetrexed plus cisplatin and in non-Asian patients was 14.8 months for afatinib and 4.7 months for pemetrexed plus cisplatin. The estimated mean overall survival in Asian patients was 37.3 months for both afatinib and pemetrexed plus cisplatin and in non-Asian patients was 31.4 months for afatinib and 25.3 months for pemetrexed plus cisplatin.
- 3.22 The ERG considered the population of the trials included in the mixed treatment comparison in light of evidence from the subgroup analysis of LUX-Lung 3. The subgroup analysis showed that the clinical effectiveness of afatinib differed according to family origin (Asian or non-Asian). This would also have an impact on the results of the mixed treatment comparison (which included the intention-to-treat population) which the ERG considered were not useful for decision-making. 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 population who were predominantly of Asian origin.
- 3.23 The ERG questioned whether it was appropriate to include trials of EGFR mutation-positive populations with trials of unknown or mixed EGFR status

populations in a single mixed treatment comparison. The ERG noted that there were differences in patient characteristics between studies of patients of EGFR mutation-positive NSCLC and those of unknown or mixed EGFR status in relation to the proportions of men, patients who had never smoked and patients with adenocarcinoma. The ERG also noted that the original mixed treatment comparison included patients with different histological types of NSCLC. The ERG concluded that the patient populations in the included trials were not sufficiently similar and therefore the results generated by the manufacturer's original mixed treatment comparison are not generalisable to a UK population.

- 3.24 During clarification the ERG requested additional sensitivity analyses on the mixed treatment comparison to assess the impact of local investigator assessments, updated overall survival data (if available), using only data from the population of patients with EGFR activating mutations for both progression-free survival and overall survival and excluding EURTAC trial data (because it included only European patients). The resulting hazard ratios (random-effects model) for the difference in median progression-free survival for afatinib compared with gefitinib were 0.50 (95% CI 0.02 to 10.72) when assessed by independent review and 0.48 (95% CI 0.03 to 9.57) when assessed by the trial investigator. The hazard ratio for the difference in median overall survival was 0.91 (95% CI 0.07 to 12.03) for afatinib compared with gefitinib. The ERG considered that the model should be populated with data from non-Asian patients to appraise the cost effectiveness of treatments for use in England; it is only appropriate to use data that have been generated from a non-Asian population of EGFR mutation-positive patients, whether in terms of primary clinical trials or supporting evidence for use in a simple indirect comparison or mixed treatment comparison. The ERG further highlighted an ongoing study (LUX-Lung 7) which directly compares afatinib and gefitinib in people with EGFR mutation-positive advanced NSCLC and is due to report in 2015.
- 3.25 The ERG disagreed with the approach taken by the manufacturer when fitting theoretical survival models to the LUX-Lung 3 data. The ERG did not consider that the Weibull models generated by the manufacturer for patients receiving afatinib or pemetrexed plus cisplatin accurately reflected 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.

- 3.26 In view of the issues with the manufacturer's model, the ERG did not consider it appropriate to carry out an exploratory analysis using the manufacturer's model. The ERG specified that it was not possible to incorporate alternative survival projections into the model because it had been structured around the use of hazard ratios to generate survival estimates rather than using directly obtained estimates.
- 3.27 Because of the technical issues with the mixed treatment comparison, the ERG carried out an exploratory analysis to obtain an approximate estimate of the ICER for afatinib compared with combination chemotherapy. The results for the intention-to-treat population from LUX-Lung 3 showed that afatinib was associated with an ICER of £39,300 per QALY gained compared with pemetrexed plus cisplatin. The results for the non-Asian population showed that afatinib was associated with an ICER of £23,700 per QALY gained compared with pemetrexed plus cisplatin. The ERG concluded that the combination of patient access scheme pricing and use of data from the non-Asian subgroup of LUX-Lung 3 is likely to indicate that afatinib is cost effective compared with pemetrexed plus cisplatin in a predominantly white population of EGFR-positive patients.
- 3.28 The ERG also carried out a cost analysis of afatinib, erlotinib and gefitinib incorporating the patient access schemes which have been agreed by the Department of Health. Two separate analyses were undertaken, which differed with regards to the assumption of effectiveness. The first analysis assumed that patients experience the same overall survival hazard profile as experienced in the LUX-Lung 3 trial, but experience the individual progression-free survival hazard profile from the key clinical trial for each treatment (that is, IPASS for gefitinib, EURTAC for erlotinib and LUX-Lung 3 for afatinib). The second analysis assumed that patients experience both the same overall survival and progression-free survival hazard profiles as experienced in the LUX-Lung 3 trial, irrespective of treatment. Given the discounts of the patient access schemes for both afatinib and erlotinib are commercial in confidence, the results of the cost comparison cannot be presented here. The estimated cost per patient of gefitinib was £11,886 using the progression-free survival estimate from the IPASS trial and the same overall survival as afatinib, and £12,069 assuming the same overall survival and progression-free survival as afatinib.

3.29 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of afatinib, having considered evidence on the nature of epidermal growth factor receptor (EGFR) mutation-positive locally advanced or metastatic non-small-cell lung cancer (NSCLC) and the value placed on the benefits of afatinib by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

Clinical effectiveness

3.30 The Committee discussed current clinical practice for treating EGFR mutation-positive locally advanced or metastatic NSCLC. The clinical specialists highlighted that the standard first choice of treatment for NSCLC with EGFR-positive tyrosine kinase mutations was a tyrosine kinase inhibitor, which is in line with [NICE's technology appraisal guidance on erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive nsclc and gefitinib for the first-line treatment of locally advanced or metastatic nsclc](#). The Committee was also aware of evidence presented in the manufacturer's submission which stated that 99% of eligible patients receive either erlotinib or gefitinib as a first-line treatment. The Committee concluded that treatment with erlotinib and gefitinib is standard practice for most people presenting with EGFR mutation-positive locally advanced or metastatic NSCLC.

3.31 The Committee discussed the place of afatinib in the treatment pathway in relation to current clinical practice in the NHS. The Committee noted that the manufacturer's submission only presented evidence on the use of afatinib in people who have not been previously treated with a tyrosine kinase inhibitor and this was in line with afatinib's marketing authorisation. The Committee heard from the clinical specialists that if recommended, afatinib would be likely to be considered alongside erlotinib and gefitinib for locally advanced or metastatic NSCLC that had not been treated with a tyrosine kinase inhibitor. The Committee also heard from the clinical specialists that afatinib has a different adverse

reaction profile from the other tyrosine kinase inhibitors, and that patients differ in their ability to tolerate different adverse reactions. They highlighted that if afatinib was recommended, it would enable clinicians to choose the tyrosine kinase inhibitor with the adverse reaction profile best suited to the individual patient. The Committee heard from clinical specialists that the irreversible binding of afatinib to the ErbB family of receptors (compared with the reversible binding of gefitinib and erlotinib) is believed to help reduce the possibility of resistance and delay its development. Therefore, the Committee concluded that erlotinib and gefitinib were appropriate comparators and that further first-line treatment options for EGFR mutation-positive locally advanced or metastatic NSCLC would be of value to clinicians and patients.

- 3.32 The Committee discussed the clinical effectiveness evidence, focussing on the results of the LUX-Lung 3 and 6 trials which compared afatinib with pemetrexed plus cisplatin (LUX-Lung 3) and gemcitabine plus cisplatin (LUX-Lung 6). The Committee heard from the clinical specialists that the chemotherapy doublets used in these trials were regarded as best clinical practice at the time. It noted that both trials reported a statistically significant increase in median progression-free survival with afatinib compared with chemotherapy. However, no statistically significant difference in overall survival was seen in LUX-Lung 3 or LUX-Lung 6 because the data were immature and could have been confounded by treatment crossover between the treatment and control arms in both trials. Therefore, the Committee agreed that there was sufficient evidence to conclude that afatinib was clinically effective in prolonging progression-free survival but because of the immaturity of the overall survival data available, there was uncertainty about whether treatment with afatinib resulted in an overall survival benefit compared with chemotherapy.
- 3.33 The Committee considered the pre-specified subgroup analyses of the LUX-Lung 3 progression-free survival data for baseline characteristics such as gender, age, family origin and common EGFR mutations, presented by the manufacturer in response to a request from the ERG for clarification. These analyses suggested there was no statistically significant difference in progression-free survival for any subgroup with the exception of common EGFR mutations compared with other EGFR mutations. The manufacturer's exploratory data (see [section 3.21](#)) suggested that people of Asian family origin may have a better progression-free survival than non-Asian patients. The Committee also noted that approximately

one third of patients in LUX-Lung 3 were non-Asian, which represented a small number of patients and that the trial was underpowered to detect differences in progression-free survival based on ethnicity. The Committee noted that the results of a statistical test presented by the manufacturer for interaction between family origin and treatment effect were not statistically significant. However, the Committee also noted that the ERG analysis of cumulative mortality hazard in LUX-Lung 3 showed large differences in progression-free survival between the Asian and non-Asian populations both in the control and treatment arms of the trials, indicating that ethnicity may impact on the effectiveness of treatment.

- 3.34 The Committee considered whether there was any biologically plausible reason why the effectiveness of afatinib would differ according to a person's family origin. The clinical specialists stated that based on their limited use of afatinib in small numbers of patients in England, there were no physiological differences between Asian and non-Asian patients that would explain the apparent differences in the effectiveness of afatinib. They emphasised that differences in the effectiveness of afatinib in NSCLC are more likely to be determined by EGFR mutation status rather than ethnicity; patients who are EGFR mutation-positive have similar response rates regardless of ethnic background. The Committee heard from the clinical specialists that the differences in the outcomes between the Asian and non-Asian population may be explained by the different standard of care and drug regimens used at trial centres in Asian compared with non-Asian countries, some of which may be more clinically effective than other regimens. Therefore, the Committee concluded that although there was uncertainty about the underlying reason, on balance the ERG analysis showed that ethnicity had an impact on the effectiveness of afatinib, and that the effectiveness of afatinib in clinical practice in England would be best represented by clinical effectiveness data in a non-Asian group.
- 3.35 The Committee considered the evidence presented on the relative clinical effectiveness of afatinib compared with erlotinib and gefitinib. The Committee noted comments from the clinical specialists that the comparator chemotherapy regimen used in the LUX-Lung 3 trial, namely pemetrexed plus cisplatin, was considered to be more effective than the comparator chemotherapy regimens used in the erlotinib and gefitinib trials. The Committee noted that because there were no head-to-head trials comparing the clinical effectiveness of afatinib with erlotinib and gefitinib, the manufacturer presented a network meta-analysis (see

sections 3.6 to 3.9). The Committee considered the methodology of the manufacturer's network mixed treatment comparison and the critique by the ERG. The Committee considered the ERG comments that in all 7 studies that included EGFR mutation-positive patients, the overall survival curves of the treatment arms cross. This indicated that the proportional hazards assumption had not been met, that is, the relative treatment effects captured by the hazard ratios were not constant across all time points. The Committee acknowledged that if the proportional hazards assumption was violated then using hazard ratios to form a network meta-analysis is not appropriate. It also heard from the ERG that although the manufacturer's original extrapolation of progression-free survival included in the economic model matched the trial data, ERG analysis of the Weibull models generated by the manufacturer to represent survival for patients receiving afatinib or pemetrexed plus cisplatin based on non-informative censoring (when each patient has a censoring time that is statistically independent of their treatment failure time) did not accurately reflect the experience of patients in LUX-Lung 3, especially for progression-free survival. The Committee acknowledged the ERG's view that based on a visual analysis, a 2-phase exponential model was a better fit to the trial data and therefore more accurately represented survival for patients treated with afatinib compared with pemetrexed plus cisplatin over the long term. The Committee therefore concluded that the underlying methodology of the mixed treatment comparison was not sufficiently robust.

- 3.36 The Committee also noted that the manufacturer's original mixed treatment model included trials of patients with mixed or unknown EGFR mutation status as well as patients with EGFR mutation-positive disease. It acknowledged that this had been necessary to enable the manufacturer to join the network in the mixed treatment comparison to ensure all the tyrosine kinase inhibitors could be compared. However, the Committee noted the ERG comment that differences in patient characteristics between studies of patients of EGFR mutation-positive NSCLC and those of unknown or mixed EGFR mutation status (for example, in relation to the proportion of men, those who have never smoked and patients with adenocarcinoma) meant that the populations of the included trials were not sufficiently similar to be included in a mixed treatment comparison. The Committee considered the manufacturer's mixed treatment comparison that was limited to EGFR mutation-positive patients to be the most appropriate because it is in line with the marketing authorisation for afatinib and because of the widely

accepted improved prognosis of EGFR mutation-positive patients. It noted that this analysis gave a slightly improved hazard ratio for afatinib compared with erlotinib and gefitinib. The Committee noted the statements from the manufacturer that the similarity of the results of the original and EGFR mutation-positive subgroup analysis demonstrated the robustness of the mixed treatment comparison. However, it noted that there were fewer than 50 patients included from the gefitinib trial in the EGFR mutation-positive subgroup analysis.

3.37 The Committee also noted that the mixed treatment comparison of the EGFR mutation-positive subgroup included studies of predominantly Asian populations. It considered that a mixed treatment comparison for EGFR mutation-positive patients of non-Asian ethnicity would be more clinically relevant to people with NSCLC in England, but that this had not been done. The Committee noted that the European public assessment report considered the benefits of afatinib to be 'in line with the other tyrosine kinase inhibitors' and heard from the clinical specialists that based on their limited experience with small numbers of patients, afatinib has a similar efficacy to the tyrosine kinase inhibitors erlotinib and gefitinib. The Committee concluded that evidence from the mixed treatment comparison was not sufficiently robust because of the underlying methodology (violation of the proportional hazards assumption) and because it was based on a predominantly Asian population, who were not considered generalisable to the UK. The Committee concluded that on balance afatinib is likely to have similar clinical efficacy to erlotinib and gefitinib. The Committee was also aware of the LUX-Lung 7 study (due to report in 2015) which would provide more evidence on the relative clinical effectiveness of afatinib compared with gefitinib.

3.38 The Committee considered the adverse reactions experienced by patients receiving treatment for locally advanced or metastatic EGFR mutation-positive NSCLC in the pivotal clinical trials with afatinib (LUX-Lung 3) compared with erlotinib (EURTAC) and gefitinib (IPASS). It noted that the incidence of diarrhoea and rash was considerably higher with afatinib compared with erlotinib and gefitinib. The patient expert stated that patients found adverse reactions with afatinib to be more easily tolerated than the adverse effects associated with many of the chemotherapy regimens. The Committee also heard from clinical specialists that diarrhoea is easily managed by dose reduction and drugs, which is demonstrated by the low rate of discontinuation because of diarrhoea (1.3%). The Committee further noted the conclusions of the European public assessment

report that afatinib had similar toxicity to erlotinib and gefitinib. The Committee agreed that although afatinib has a higher rate of diarrhoea and rash, these were well managed in clinical practice. The Committee concluded that although afatinib has a different adverse reaction profile from erlotinib and gefitinib, overall the toxicity of the tyrosine kinase inhibitors was similar.

Cost effectiveness

- 3.39 The Committee considered the manufacturer's base-case cost-effectiveness analysis incorporating the patient access schemes for afatinib, erlotinib and gefitinib, and the ERG critique. The Committee considered the population included in the base-case model. It noted that the population in the model (that is, people with mixed EGFR status and a combination of Asian and non-Asian patients) was not relevant to clinical practice in England (that is, EGFR mutation-positive and predominantly non-Asian). It also noted that methodological issues with the mixed treatment comparison (related to the violation of the assumption of proportional hazards and the extrapolation of progression-free survival and overall survival with afatinib) have an impact on the credibility of the economic model. The Committee considered whether it was possible to model the cost effectiveness of afatinib compared with erlotinib and gefitinib based on assumptions of the same clinical efficacy (in a similar way to that in [NICE's technology appraisal guidance on erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive nsclC](#)). The Committee heard from the ERG that this was not possible because the structure of the model relies on using a single survival model formulation through a network of hazard ratios (assuming that the proportional hazard assumption applies throughout). Any attempt at modifying it would involve creating a new model. The Committee concluded that methodological issues related to the assumption of proportional hazards, the extrapolation of progression-free survival and the population of the base-case model prevented the Committee from assessing the cost effectiveness of afatinib compared with erlotinib and gefitinib based on the manufacturer's model. Therefore a most plausible ICER could not be estimated.
- 3.40 The Committee considered the exploratory cost analysis presented by the ERG in which the average daily acquisition costs of afatinib, erlotinib and gefitinib were compared and which included the patient access schemes agreed by the

Department of Health for each treatment. The Committee considered the 2 scenarios presented, firstly in which progression-free survival and overall survival were the same for all tyrosine kinase inhibitors, and secondly in which overall survival was the same but progression-free survival depended on the results of the pivotal trials. The Committee noted that the total costs, which incorporate the patient access schemes for afatinib and erlotinib have been designated as commercial in confidence and cannot be reported here. It also noted that the complexities of the patient access scheme make it difficult to assess the daily cost of gefitinib, which varies depending on the proportion of patients who stop taking gefitinib before the third pack is received. The Committee heard from the ERG that for consistency with the assumptions in the erlotinib appraisal, their analysis assumed that 5% of patients stopped taking gefitinib before the third pack and therefore did not incur any cost for gefitinib treatment. Without robust evidence on differences in the effectiveness of afatinib compared with erlotinib and gefitinib, the Committee considered the scenario based on equal progression-free survival and overall survival to be the most appropriate. It also accepted that in clinical practice the tyrosine kinase inhibitors were likely to have similar efficacy (see section 3.37). The Committee concluded that assuming progression-free survival for afatinib is equivalent to the other tyrosine kinase inhibitors, afatinib is a cost-effective use of NHS resources because it has comparable costs to erlotinib. Although the gefitinib patient access scheme makes it difficult to assess the daily acquisition cost of gefitinib, the Committee concluded that on balance afatinib was likely to have similar cost effectiveness to gefitinib. The Committee therefore concluded that afatinib could be considered an appropriate treatment alternative to erlotinib and gefitinib.

- 3.41 The Committee considered the exploratory analyses conducted by the ERG, which estimated the cost effectiveness of afatinib compared with cisplatin in combination with pemetrexed, based on the trial data, noting that these analyses did not account for crossover in the trial, and could therefore be considered conservative. Although the comparator used in this analysis was not included in the scope, the Committee considered that it provided reassurance that afatinib was likely to be a cost-effective use of NHS resources compared with the chemotherapy that was the gold standard at the time the trials for afatinib were designed (before the tyrosine kinase inhibitors became established practice). The Committee concluded that on balance, based on all the evidence considered, afatinib is considered to be a reasonable alternative treatment option compared

with erlotinib and gefitinib, in people with locally advanced or metastatic EGFR mutation-positive NSCLC that has not been previously treated with an EGFR tyrosine kinase inhibitor or chemotherapy.

- 3.42 The Committee noted that most patients with locally advanced or metastatic EGFR mutation-positive NSCLC receive a tyrosine kinase inhibitor as first-line treatment. However, the clinical specialists advised that there is regional variation in the speed of EGFR testing and that it generally takes between 1 and 3 weeks to get the results. The clinical specialists also stated that a minority of patients with aggressive disease will therefore need treatment before EGFR mutation status is confirmed and will start treatment with chemotherapy (a third generation agent plus platinum) and receive a tyrosine kinase inhibitor as second-line treatment. The Committee noted that there is only limited evidence in small numbers of patients for the effectiveness of afatinib after prior chemotherapy. However, it acknowledged that the phase II LUX-Lung 2 trial suggested that afatinib is also effective when used as second-line treatment after chemotherapy. The Committee concluded that afatinib is likely to be clinically and cost effective as a second-line treatment for the minority of patients who have received chemotherapy as first-line treatment. The Committee therefore recommended afatinib as a treatment option in line with its marketing authorisation; that is, if the person has not previously had an EGFR tyrosine kinase inhibitor.
- 3.43 The Committee considered whether afatinib should be considered as an innovative technology, given that it is another tyrosine kinase inhibitor for the treatment of EGFR mutation-positive NSCLC. The Committee noted that afatinib irreversibly binds to the ErbB family of receptors making it different, in vitro, from the tyrosine kinase inhibitors erlotinib and gefitinib (see [section 2.1](#)). The Committee heard from the clinical specialists that there is the possibility that, because of its mechanism of action, afatinib may be less likely to be associated with the development of resistance to tyrosine kinase inhibitors. However, the Committee concluded that the clinical evidence did not suggest that the mode of action for afatinib led to any significant benefit in clinical effectiveness compared with erlotinib and gefitinib. The Committee concluded that afatinib could not be considered to show significant innovation over the other tyrosine kinase inhibitors. The Committee again acknowledged the importance of the ongoing LUX-Lung 7 trial to provide further evidence on the clinical effectiveness of

afatinib compared with gefitinib.

4 Implementation

- 4.1 [Section 7 of the National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 [Chapter 2 of Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The [NHS England and NHS Improvement Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer and the healthcare professional responsible for their care thinks that afatinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Recommendations for further research

- 5.1 The Committee recognised the importance of further clinical trials comparing the effectiveness of the tyrosine kinase inhibitors (afatinib, erlotinib and gefitinib) in EGFR mutation-positive locally advanced or metastatic NSCLC. It acknowledged the relevance of the ongoing study (LUX-Lung 7) which directly compares afatinib and gefitinib in people with EGFR mutation-positive advanced NSCLC and is due to report in 2015.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each Appraisal Committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Lindsay Smith (Chair)

General Practitioner, West Coker Surgery, Somerset

Dr Andrew Black (Vice Chair)

General Practitioner, Mortimer Medical Practice, Herefordshire

Professor David Bowen

Consultant Haematologist, Leeds Teaching Hospitals NHS trust

Dr Ian Davidson

Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon

Professor of Health Economics, University of Sheffield

Dr Martin Duerden

Assistant Medical Director, Betsi Cadwaladr University Health Board, North Wales

Dr Alexander Dyker

Consultant Physician, Wolfson Unit of Clinical Pharmacology, University of Newcastle

Gillian Ells

Prescribing Advisor – Commissioning, NHS Hastings and Rother and NHS East Sussex Downs and Weald

Professor Paula Ghaneh

Professor and Honorary Consultant Surgeon, University of Liverpool

Professor Carol Haigh

Professor in Nursing, Manchester Metropolitan University

Dr Paul Hepple

General Practitioner, Muirhouse Medical Group

Professor John Hutton

Professor of Health Economics, University of York

Professor Steven Julious

Professor in Medical Statistics, University of Sheffield

Dr Tim Kinnaird

Lead Interventional Cardiologist, University Hospital of Wales, Cardiff

Dr Warren Linley

Senior Research Fellow, Centre for Health Economics and Medicines Evaluation, Bangor University

Dr Malcolm Oswald

Lay member

Professor Femi Oyebode

Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health

Dr John Radford

Director of Public Health, Rotherham Primary Care Trust and MBC

Dr Murray Smith

Associate Professor in Social Research in Medicines and Health, University of Nottingham

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Helen Tucker

Technical Lead

Eleanor Donegan

Technical Adviser

Kate Moore

Project Manager

Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by Liverpool Reviews and Implementation Group (LRiG):

- Fleeman N, Bagust A, Beale S et al. Afatinib for treating epidermal growth factor receptor mutation positive locally advanced or metastatic non-small cell lung cancer: a single technology appraisal, December 2013.

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope. Manufacturers or sponsors were also invited to make written submissions. Professional or specialist and patient or carer groups gave their expert views on afatinib by providing a written statement to the Committee. Manufacturers or sponsors, professional or specialist and patient or carer groups, and other consultees, have the opportunity to appeal against the final appraisal determination.

Manufacturers or sponsors:

- Boehringer Ingelheim

Professional or specialist and patient or carer groups:

- Roy Castle Lung Cancer Foundation
- British Thoracic Society
- Cancer Research UK
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

Other consultees:

- Department of Health
- NHS England
- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety – Northern Ireland
- Healthcare Improvement Scotland
- AstraZeneca
- Bristol-Myers Squibb
- Lilly UK
- Pfizer
- Pierre Fabre

- Roche Products
- British Thoracic Oncology Group
- Liverpool Reviews and Implementation Group
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They gave their expert personal view on afatinib by providing oral evidence to the Committee.

- Professor Michael Lind, Foundation Professor of Oncology, nominated by Boehringer Ingelheim – clinical specialist
- Dr Clive Mulatero, Consultant Medical Oncologist, nominated by Royal College of Physicians – clinical specialist
- Dr Jesme Fox, nominated by Roy Castle Lung Cancer Foundation – patient expert

Representatives from the following manufacturer or sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Boehringer Ingelheim

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