NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

- additional analyses of clinical trial data
- details of the methods and assumptions used in the indirect comparison of pemetrexed and erlotinib
- clarification of the proportion of patients estimated to receive second-line treatment and sources for the estimation
- study details such as the interim analysis plan and how patient compliance was monitored
- further information on patients who received treatment after progression had occurred, contrary to the study protocol
- details of patients with missing epidermal growth factor receptor immunohistochemistry (EGFR IHC) status and with missing Functional Assessment of Cancer Therapy - Lung (FACT-L) scores
- sources used to estimate maintenance and second-line treatment durations.

Indicative licensed indication

In March 2010, the European Medicines Agency (EMEA) issued a positive opinion recommending a variation to the marketing authorisation for erlotinib

(Tarceva, Roche) to include monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small-cell lung cancer with stable disease after 4 cycles of standard platinum-based first-line chemotherapy. The implications of this are that patients who have had a complete or partial response to first-line chemotherapy are not eligible for maintenance treatment with erlotinib. Erlotinib also has a UK marketing authorisation for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer after failure of at least one prior chemotherapy regimen.

Key issues for consideration

Clinical effectiveness

- Does the Committee consider the results of the SATURN trial to be generalisable to clinical practice in the UK?
- What is the Committee's opinion of the fact that none of the patients in the SATURN trial had first-line treatment with pemetrexed (as recommended in NICE technology appraisal guidance 181 for patients with non-squamous disease)?
- Does the Committee consider the results of the JMEN trial to be generalisable to clinical practice in the UK?
- What is the optimal place of ertlotinib in the treatment pathway for non-small-cell lung cancer (NSCLC) – is it as maintenance treatment or second-line treatment?

Cost effectiveness

- Does the Committee consider the three cost-effectiveness analyses provided by the manufacturer to be appropriate in light of the recent EMEA positive opinion for the subpopulation of patients with stable disease?
- Does the Committee consider the methods used to model progression-free survival (PFS) and overall survival to be appropriate?

- Does the Committee consider the approaches used to calculate costs of erlotinib, best supportive care and pemetrexed to be appropriate?
- Does the Committee consider the results from the manufacturer's economic models to be reliable?
- Does the Committee consider that the end-of-life criteria have been met for patients with stable disease and patients with non-squamous disease?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	(As stated in scope) Patients with advanced or metastatic (stage IIIB and IV) non-small-cell lung cancer (NSCLC) whose disease has not progressed following treatment with platinum-based first-line chemotherapy.
Intervention	(As stated in scope) Erlotinib monotherapy.
Comparators	(As stated in scope) • Best supportive care, which may include palliative radiotherapy, corticosteroids (without maintenance therapy) and watchful waiting alone. • Additionally, for patients with non-squamous NSCLC: pemetrexed monotherapy may be included as a comparator, depending on the outcome of the ongoing NICE technology appraisal 'Pemetrexed for the maintenance treatment of NSCLC'. The pemetrexed non-squamous disease subgroup analysis is provided and is considered relevant only if a positive recommendation is published for pemetrexed. Therefore it is currently marked commercial-in-confidence.
Outcomes	(As stated in scope) • Overall survival • Progression-free survival (PFS) • Tumour response rate • Adverse effects of treatment • Health-related quality of life
Economic evaluation	(As stated in scope) The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The time horizon for the economic evaluation should reflect the life expectancy of patients with NSCLC. Costs will be considered from an NHS and Personal Social Services perspective.
Subgroups to be considered	(As stated in scope) If the evidence allows, patient subgroups will be considered. These may include subgroups defined by performance status, histology (squamous or non squamous), smoking status, epidermal growth factor receptor (EGFR) mutational status, and response to first-line treatment.

1.2 Evidence Review Group comments

1.2.1 Population

The ERG considered the population in the manufacturer's decision problem, that is, patients with advanced or metastatic (stage IIIB and IV) NSCLC whose disease has not progressed following treatment with platinum-based first-line chemotherapy, to be consistent with the population in the scope of the appraisal.

1.2.2 Intervention

The ERG stated that the intervention, erlotinib is administered as a 150 mg tablet once per day. In the event that patients experience adverse reactions, most commonly rash (in 50% of patients) and diarrhoea (in 20% of patients), the dose is titrated down until symptoms are managed with the lower dose and other symptom specific treatments

1.2.3 Comparators

The ERG commented that the manufacturer considered three distinct patient groups: the whole trial population, that is, the intention-to-treat (ITT) group, patients with stable disease and patients with non-squamous disease. For the ITT and stable disease patient populations, the manufacturer appropriately compared erlotinib and placebo. For the patient population with non-squamous disease, the manufacturer compared pemetrexed with placebo because NICE is currently appraising pemetrexed as maintenance therapy for this group of patients.

1.2.4 Outcomes

The ERG considered that the outcomes included in the submission, PFS, overall survival, tumour response rates, health-related quality of life and adverse events, were consistent with the final scope issued by NICE.

1.2.5 Timeframe

The ERG stated that the manufacturer's economic model used a 5-year timeframe, which is taken to be equivalent to a life-time horizon.

1.3 Statements from professional/patient groups and nominated experts

The clinical specialists stated that there are differing opinions of the value of maintenance therapy in advanced NSCLC, but it is increasingly accepted that patients who receive second-line treatment do better than those who do not.

They commented that erlotinib has been shown to prolong life as second or third-line treatment in NSCLC compared with placebo and that it has been used as a second-line treatment since 2008 when 'Erlotinib for the treatment of non-small-cell-lung cancer' (NICE technology appraisal guidance 162) was published. The clinical specialists noted that the main adverse effects of erlotinib are skin rash and diarrhoea, which causes discontinuation of drug in a small proportion of patients.

A clinical specialist noted that maintenance therapy is best regarded as switching chemotherapy to a treatment other than the one used for induction of response, to prolong remission and overall survival. Another specialist commented that most patients with NSCLC relapse within 12 weeks of completing first-line treatment. Therefore it is arbitrary if the subsequent treatment is referred to as 'second line' or 'maintenance'.

The clinical specialists commented that subgroups of patients with non-squamous disease and patients with a mutation in the EGFR gene are most likely to benefit from an EGFR inhibitor such as erlotinib. They noted that this mutation affects about 10% of patients with NSCLC in Western populations.

The clinical specialists stated that three treatments have been considered as maintenance treatment after platinum-induced remission: docetaxel, erlotinib and pemetrexed. They noted that for patients with non-squamous NSCLC, erlotinib after induction is unlikely to be a dominant strategy over pemetrexed.

This is because pemetrexed was shown to increase survival by 5 months and erlotinib by 1 month. However, the clinical specialists also noted that pemetrexed plus cisplatin is now considered to be the optimal first-line choice for non-squamous NSCLC and it is uncertain whether further pemetrexed after this is beneficial.

The clinical specialists commented that the SATURN study reflected UK practice reasonably well and that a number of UK centres were involved. They thought that the side-effect profile of erlotinib was well established.

The clinical specialists stated that erlotinib is prescribed by oncologists in hospitals and they did not think that any extra health professional input would be required for implementation if erlotinib was recommended by NICE. They commented that the only extra resources required would be an increase in outpatient visits for patients receiving treatment and an increase in imaging tests to stop treatment continuing when the patient's disease had progressed.

There were no submissions from patients.

2 Clinical effectiveness evidence

After receipt of the final ERG report, erlotinib received a positive EMEA opinion for maintenance treatment in patients with locally advanced or metastatic non-small-cell lung cancer who have stable disease after 4 cycles of standard platinum-based first-line chemotherapy. There is also the ongoing NICE appraisal of pemetrexed as maintenance treatment for patients with non-squamous disease for which the final appraisal determination is currently in the appeal period (expected publication date May 2010). The guidance states 'Pemetrexed is recommended as an option for the maintenance treatment of locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel'. Therefore the relevant comparators for this appraisal are best supportive care for patients with squamous disease

and pemetrexed for patients with non-squamous disease, which was specified in the final scope. The manufacturer's submission included clinical and cost-effectiveness analyses for three different populations:

- the ITT population from the SATURN trial (comparing erlotinib with best supportive care)
- patients with stable disease, that is, neither a decrease or increase in tumour size (comparing erlotinib with best supportive care)
- patients with non-squamous disease (comparing erlotinib with pemetrexed).

The analyses for the stable disease subgroup include patients with squamous and non-squamous histology and the analyses for the non-squamous subgroup include patients with stable disease after first-line chemotherapy and those who had a response (partial or complete).

2.1 Clinical effectiveness in the manufacturer's submission

The key evidence for the clinical effectiveness of erlotinib comes from one randomised controlled trial (RCT) comparing erlotinib with placebo in patients with advanced or metastatic NSCLC whose disease had not progressed following platinum-based chemotherapy (SATURN).

An indirect comparison of erlotinib and pemetrexed was carried out based on data from the placebo-controlled RCT of erlotinib (SATURN) and the placebo-controlled RCT of pemetrexed (JMEN) using the placebo arms as the common comparator.

2.1.1 SATURN trial

The SATURN trial was a 12-month, phase III double-blind RCT comparing erlotinib (150 mg daily) with placebo in patients with histologically

documented, locally advanced or recurrent or metastatic (stage IIIB or stage IV) NSCLC whose disease had not progressed after 4 cycles of an acceptable, standard, platinum-based chemotherapy doublet (two chemotherapy drugs, one of which is platinum based). Patients were included if they had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and a life expectancy of at least 12 weeks.

The SATURN trial included 889 patients with a mean age of 60 years. At baseline, 31% of the patient population had an ECOG performance status of 0, 55% were current smokers, 70% had a positive epidermal growth factor receptor immunohistochemistry (EGFR IHC) status and 59% had non-squamous disease. The most common first-line treatments were gemcitabine plus carboplatin (28%), gemicitabine plus cisplatin (26%), and paclitaxel plus carboplatin (19%). Forty-four percent of the patient population had a partial or complete response to first-line treatment and 55% had stable disease after first-line treatment. Tumour response was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria and compared with baseline at the time of randomisation (after completion of induction). Stable disease was defined as no evidence of tumour shrinkage or increase in size.

The key results for the three patient populations presented in the manufacturer's submission are summarised in table 1.

Table 1 Results of the SATURN trial for ITT, stable disease and non-squamous disease populations

	ITT		Stable disease	Non-squamous disease
Median PFS (weeks)	HR: 0.71 95% CI: 0.62–0.82 P < 0.0001		HR: 0.68 95% CI: 0.56–0.83 P < 0.0001	HR: 0.68 95% CI: 0.56–0.82 P-value not stated
Median overall survival (months)	HR: 0.81 95% CI: 0.70–0.95 P = 0.0088		HR 0.72 95% CI: 0.59–0.89 P = 0.0019	HR 0.79 95% CI: 0.64–0.96 P-value not stated
Response to maintenance treatment				
Partial/complete Stable disease Progressive disease	11.9% 48.6% 35.6%	5.4% 45.4% 47.6%	Not reported	Not reported

ITT: intention to treat; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval

Overall study results (ITT population)

For the ITT population, the investigator-assessed median PFS was 12.3 weeks in the erlotinib group compared with 11.1 weeks in the placebo group (hazard ratio [HR]: 0.71; 95% confidence interval [CI] 0.62 to 0.82, p < 0.0001). Median overall survival was 12 months with erlotinib compared with 11 months in the placebo group (HR 0.81; 95% CI 0.70 to 0.95, p = 0.0088). The manufacturer's submission reported similar proportions of patients who had at least one post-study treatment in the erlotinib and placebo groups (71% and 72% respectively). However, as pointed out by the ERG, there is a discrepancy between the manufacturer's submission and the SATURN clinical study report, which reports figures of 55% and 64% respectively. The proportion of patients who had a partial or complete response after maintenance treatment was 11.9% (95% CI 9.0 to 15.3) in the erlotinib group compared with 5.4% (95% CI 3.5 to 7.9) in the placebo group (p = 0.0006). The proportion of patients who had stable disease after

maintenance treatment was similar in both treatment groups (48.6% versus 45.4%). Quality of life was assessed using the Functional Assessment of Chronic Illness Therapy - Lung (FACT-L) questionnaire. There were no statistically significant differences between the treatment arms for time to symptom progression (HR 0.91; p = 0.38), time to deterioration in trial outcome index (HR 1.06; p = 0.54), and time to deterioration in quality of life (HR 0.96; p = 0.65).

Post hoc subgroup analyses

The manufacturer conducted post hoc subgroup analyses based on histology and response to first-line treatment. These analyses showed that patients with non-squamous histology had a greater PFS benefit from erlotinib compared with placebo (HR 0.68; 95% CI 0.56 to 0.82) than patients with squamous histology (HR 0.76; 95% CI 0.60 to 0.95), although in both groups the result was statistically significant. The overall survival benefit of erlotinib was statistically significant for patients with non-squamous histology (HR 0.79; 95% CI 0.64 to 0.96) but not for patients with squamous NSCLC (HR 0.86; 95% CI 0.68 to 1.10).

Patients who had stable disease after first-line chemotherapy had a greater PFS benefit of erlotinib compared with placebo (HR 0.68; 95% CI 0.56 to 0.83, p < 0.0001) than patients who had complete or partial response (HR 0.74; 95% CI 0.60 to 0.92, p = 0.0059). Erlotinib was associated with a statistically significant overall survival benefit in patients with stable disease (HR 0.72; 95% CI 0.59 to 0.89, p = 0.0019) but not for patients who had a partial or complete response to first-line treatment (HR 0.94; 95% CI 0.74 to 1.20, p value not stated). (The data in this paragraph are academic in confidence).

Pre-planned subgroup analyses

The manufacturer conducted pre-planned subgroup analyses for a number of factors that were used for stratification during randomisation: EGFR status

(positive, negative or indeterminate), stage of disease (IIIB or IV), ECOG performance status (0 or 1); first-line chemotherapy (gemcitabine plus cisplatin or other), smoking status (never smoked, current smoker, past smoker) and geographical region (Eastern Europe, Western Europe, North America, South East Asia). Erlotinib was associated with a statistically significant benefit in both PFS and overall survival compared with placebo for patients with EGFR IHC positive tumours (HR 0.69; 95% CI 0.58 to 0.82 and HR 0.77; 95% CI 0.64 to 0.93 respectively) but not for patients with a negative EGFR IHC status (HR 0.77; 95% CI 0.51 to 1.14 and HR 0.91; 95% CI 0.59 to 1.38 respectively). For further results of the subgroup analyses see page 31–32 of the ERG report).

Adverse events

The most common adverse events in the erlotinib group were rash (49% compared with 6% in the placebo group) and diarrhoea (20% compared with 5% in the placebo group). More patients in the erlotinib group had an adverse event of any kind than in the placebo group (79% compared with 54%) and more patients in the erlotinib group had a grade 3 or 4 adverse event (25% compared with 12% in the placebo group). With regard to treatment tolerability, the proportion of patients who required dose reduction or treatment interruption was 18% in the erlotinib group and 6% in the placebo group.

2.1.2 Indirect comparison of erlotinib and pemetrexed

The manufacturer presented an indirect comparison of erlotinib and pemetrexed in patients with non-squamous disease in line with the scope. However this population included patients with stable disease at randomisation and patients who had a response to first-line treatment. Erlotinib is not licensed as maintenance treatment for patients who have a respond to first-line treatment. The JMEN study is an RCT comparing pemetrexed with placebo in patients with histologically or cytologically

confirmed stage IIIB or stage IV NSCLC who had shown no signs of progression during 4 cycles of platinum-based chemotherapy. The trial included 663 patients with a mean age of 61 years. At baseline, 39% of the patient population had an ECOG performance status of 0, 72% were current smokers, and 73% had non-squamous disease. The most common first-line treatments were cisplatin plus gemicitabine (35%), carboplatin plus paclitaxel (29%) and gemcitabine plus carboplatin (23%). Forty nine percent of the patient population had a partial or complete response to first-line treatment and 51% had stable disease after first-line treatment. A comparison of baseline characteristics of the SATURN and JMEN populations is presented in table 2.

Table 2 Baseline characteristics of patients in the SATURN and JMEN trials

	SATURN (n = 889)	JMEN (n = 663)
ECOG performance status		
0	31%	39%
1	69%	61%
Smoking status		
Never	17%	27%
Current smoker	56%	73%
Past smoker	27%	n/a
Histology		
Non-squamous	59% (525/889)	73% (481/663)
Squamous	40% (360/889)	27% (182/663)
Response to first-line treatment		
Stable disease	55% (487/889)	51% (337/663)
Partial/complete response	44% (394/889)	49% (322/663)
First line treatment		
Docetaxel plus carboplatin	3%	4%
Docetaxel plus cisplatin	5%	2%
Paclitaxel plus carboplatin	19%	29%
Paclitaxel plus cisplatin	12%	7%
Gemcitabine plus carboplatin	28%	23%
Gemcitabine plus cisplatin	26%	35%
Cisplatin plus vinorelbine	7%	0

ECOG: Eastern Cooperative Oncology Group

Only the results for patients with squamous and non-squamous disease in the JMEN and SATURN trials are presented in table 3. For results for the whole study population, see page 100 of the manufacturer's submission. In patients with non-squamous disease, median investigator-assessed PFS was 4.5 months in the pemetrexed arm compared with 2.6 months in the placebo arm (HR 0.44; 95% CI 0.36 to 0.55, p < 0.0001). Median overall survival was 15.5 and 10.3 months for the pemetrexed and placebo groups respectively (HR 0.70; 95% CI 0.56 to 0.88, p = 0.002).

Table 3 PFS and overall survival results for patients with non-squamous disease in SATURN and JMEN studies

	SATURN		JMEN	
	Non-squamous	**Squamous**	**Non-squamous**	**Squamous**
PFS (months)	PFS by treatment arm not reported HR (95% CI): 0.68 (0.56–0.83)	PFS by treatment arm not reported HR (95% CI): 0.76 (0.60–0.95)	Pemetrexed: 4.5 Placebo: 2.6 HR (95% CI): 0.44 (0.36–0.55)	Pemetrexed: 2.8 Placebo: 2.6 HR (95% CI): 0.69 (0.41–0.98)
Overall survival (months)	Erlotinib: 13.7 Placebo: 10.5 HR (95% CI): 0.79 (0.64–0.96)	OS by treatment arm not reported HR (95% CI): 0.86 (0.68–1.10)	Pemetrexed: 15.5 Placebo: 10.3 HR (95% CI): 0.70 (0.56–0.88)	Pemetrexed: 9.9 Placebo: 10.8 HR (95% CI): 1.07 (0.77–1.50)

PFS: progression-free survival; OS: overall survival; HR: hazard ratio; CI; confidence interval.

In the indirect analysis of pemetrexed compared with erlotinib in patients with non-squamous disease,

[redacted]

Pemetrexed was associated with higher rates of haematological adverse events (such as neutropenia and anaemia) and more non-haematological adverse events (such as fatigue, anorexia and nausea) than erlotinib (p-values and confidence intervals were not reported for adverse events). The

only adverse events which were higher in the erlotinib group than in the pemetrexed group were diarrhoea (18% and 5% in each group respectively) and rash (49% and 2% respectively). The rate of infection was the same with both treatments (5%). For further details of adverse event rates see table 15 of the manufacturer's submission.

The manufacturer noted that the JMEN trial did not represent UK clinical practice because:

- The trial excluded patients who received pemetrexed as first-line treatment (recommended in NICE technology appraisal guidance 181 for patients with adenocarcinoma or large-cell carcinoma in 2009).
- The baseline characteristics of patients in the JMEN and SATURN trials were different. Higher proportions of patients in the JMEN trial had never been smokers and had non-squamous disease.
- A lower proportion of patients in the JMEN trial went on to receive second-line treatment, affecting overall survival results.

2.2 Evidence Review Group comments

The ERG thought that the search strategy used by the manufacturer had been described clearly and no relevant studies were missed. It agreed with the manufacturer that the SATURN study was the only relevant study of erlotinib in patients with squamous disease, and the indirect comparison of the SATURN and JMEN studies was relevant for patients with non-squamous disease.

SATURN study

The ERG considered that the SATURN trial was generally well designed but it identified a number of potential weaknesses which are summarised below (for further information see pages 22 to 26 of the ERG report):

- Maintenance of blinding was uncertain because patients taking erlotinib were more likely to develop rash and diarrhoea.

- Protocol amendments made during the trial may have affected outcomes for patients recruited before and after the amendments, which raises concerns over the robustness of the results.

- No rationale was provided for why patients were stratified by six baseline factors during randomisation.

- Variation in approaches to tumour assessments across the large number of study sites may have affected the reliability of PFS results (despite efforts being made to maintain consistent tumour assessments).

- There was inconsistency between the reported proportion of patients who received post-progression treatments in the clinical study report (64% and 55% in the placebo and erlotinib groups respectively) and the manufacturer's submission (72% and 71% in each group respectively). Post-progression treatments have an impact on the overall survival results.

- The analyses of the populations of patients with stable disease and with non-squamous disease were post hoc. Therefore the trial was not designed to assess efficacy in these groups specifically. Additionally no adjustment was made for multiple testing, which compromises the statistical power of the study.

The ERG also questioned the generalisability of the SATURN study population to patients with NSCLC in the UK because:

- Few UK patients were included in the trial.

- The trial population was slightly younger and fitter than seen in clinical practice.

- No patients in the trial had first-line treatment with pemetrexed. Therefore there is no evidence on using erlotinib as maintenance treatment after pemetrexed. In NICE technology appraisal 181 pemetrexed is recommended for patients with 'other than squamous histology' and it is becoming a more common first-line treatment in this group.

- A greater proportion of patients had first-line treatment with paclitaxel than would in UK clinical practice.

- Some patients had post-progression treatments that are not available in the UK, which would affect overall survival results (only docitaxel and erlotinib are recommended by NICE).

The ERG noted that although the difference in median PFS of 1.2 weeks between the study groups was statistically significant, this represents a small clinical difference. This was also true for overall survival, with a statistically significant difference of 1 month in favour of erlotinib. The ERG noted that histology and response to first-line treatment were not pre-planned stratification factors in the SATURN study and that all results provided in this subgroup were from post hoc analyses.

Indirect analysis

The ERG considered that the simple indirect comparison of PFS and overall survival hazard ratios for erlotinib and pemetrexed using the JMEN and SATURN studies were appropriate because both trials shared a common placebo arm.

JMEN study

The ERG noted differences between the populations of the JMEN and SATURN trials that were highlighted in the manufacturer's submission. In the JMEN study there were higher proportions of patients who had never

smoked,and Asian patients, but smaller proportions of patients with squamous disease and patients receiving post-progression treatments. The ERG did not consider these differences in baseline characteristics to be important in relation to the relative treatment effects estimated by the indirect comparison because patients in both studies responded to treatment with placebo in the same way (that is, PFS and overall survival were similar in the placebo groups of each study). However it did consider that the generalisability of the JMEN study to UK practice is uncertain for the following reasons:

- There was a higher proportion of Asian patients, who are known to respond better to lung cancer treatments than other ethnic groups.
- There were more post-progression therapies not commonly given in the UK.
- No patients received vinorelbine or pemetrexed as first-line treatment.
- Patients received unlimited cycles of pemetrexed maintenance treatment, which is unlikely to happen in the UK.

The ERG concluded that the data from the SATURN and JMEN studies showed that both erlotinib and pemetrexed improved PFS and overall survival compared with placebo in patients with non-squamous disease. It also concluded the indirect analysis showed that pemetrexed was associated with greater benefit in PFS than erlotinib for patients with non-squamous disease, but the difference in overall survival was not statistically significant. The ERG thought that the results of this analysis should be interpreted with caution because of uncertainty over the generalisability of both trials to the UK and given the differences in the trial populations.

3 Cost effectiveness

Patient access schemes are proposed by a pharmaceutical company and referred by the Department of Health to the Patient Access Schemes Liaison

Unit (PASLU) within the Centre for Health Technology Evaluation at NICE who then provide advice on the feasibility of implementing the patient access scheme in the NHS in England and Wales.

The cost-effectiveness model submitted by the manufacturer and reviewed by the ERG includes a 14.5% reduction in the acquisition cost of erlotinib. This is based on the patient access scheme approved by the Department of Health during the appraisal of erlotinib for the second-line treatment of non-small-cell lung cancer (NICE technology appraisal guidance 162). However, the patient access scheme in NICE technology appraisal guidance 162 related to second-line use and was not for maintenance treatment. A new patient access scheme for this appraisal was submitted to the Department of Health but has not been approved at the time of writing this report. Therefore the manufacturer was asked to provide revised cost-effectiveness estimates calculated without the patient access scheme. The results of this analysis are provided at the end of the section 3.5. They have not been reviewed by the ERG.

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer's submission included three separate economic evaluations for the ITT population from the SATURN trial, patients with stable disease (including non-squamous and squamous NSCLC) who the manufacturer considered had the greatest benefit from erlotinib and patients with non-squamous disease (including patients who responded to first-line chemotherapy and those who did not respond). For the ITT and stable disease populations, erlotinib was compared with best supportive care. For patients with non-squamous disease, erlotinib was compared with pemetrexed.

In light of the recent EMEA positive opinion for erlotinib in patients with stable disease after standard platinum-based first-line chemotherapy, only the economic evaluation for patients with stable disease is relevant to the licensed

indication. However results for all populations have been presented in this report.

The manufacturer's model used an area under the curve approach with a cycle length of 1 month. The model included three health states, PFS, progressed and death. All patients were assumed to start in the PFS health state (after first-line chemotherapy) and at the end of each cycle; they could remain in PFS, move to the progressed health state or die. The progressed health state was defined as the time from first treatment relapse until death. It therefore includes the possible sequence of remission and relapse of second-line treatments as used in the respective trials (see pages 113 to 131 of the manufacturer's submission for further information).

3.2 Clinical evidence

The baseline risk of disease progression was taken from the placebo arm of the SATURN trial for the ITT and stable disease models and from the erlotinib arm of the SATURN trial for the non-squamous model. Baseline and treatment-related relative risk of disease progression were estimated separately for PFS and overall survival. For the ITT and stable disease populations, the SATURN Kaplan-Meier curves were used directly within the model to estimate progression-free survival, because most patients in the SATURN trial had progressed at the point of follow-up. For the non-squamous population, the risk of disease progression for pemetrexed compared with erlotinib was estimated by [redacted]. To estimate overall survival in each of the three populations, various parametric functions were assessed for goodness of fit to the clinical data before deciding on the final function to be used in the model.

Treatment-related adverse events were taken from the SATURN and JMEN trials. Only grade 3 and 4 adverse events with an incidence greater than 1%

were included in the model (see pages 131 to 134 of the manufacturer's submission for further information).

3.3 Utilities

Health-related quality of life for the PFS state was measured in the SATURN trial using the FACT-L questionnaire. The FACT-L scores were transformed into EQ-5D visual analogue scores, which were then transformed to EQ-5D time-trade-off scores to be consistent with the NICE reference case. Utilities for the PFS heath state were 0.685 for the stable disease and non-squamous populations and 0.695 for the ITT population. Health-related quality of life for the progressed state was not measured in the SATURN trial. Therefore the utility for the progressed state (0.47) was taken from a publication used in previous NICE technology appraisals for NSCLC (Nafees B et al. 2008).

3.4 Costs

The following costs were included in the model (see pages137 to 145 of the manufacturer's submission for further information):

- Drug costs for erlotinib and pemetrexed, including administration and hospital pharmacist time for drug preparation.
- Costs of best supportive care in the PFS and the progressed disease health states.
- Adverse events costs for erlotinib and pemetrexed.
- Post-progression treatment costs.

Drug costs

Erlotinib costs were calculated based on the list price to the NHS with a 14.5% discount in accordance with a patient access scheme implemented after the publication of NICE technology appraisal 162. Drug doses were based on the observed doses in the SATURN trial, which were calculated separately for the ITT, stable disease and non-squamous populations. Administration costs were

not included because erlotinib is given orally, but a monthly cost for drug preparation time was added (£14 per month, from the Chemotherapy Online Planning Resource Tool). The total average per-patient costs for erlotinib in the model were £6430, £6396, and £6627 for each patient population respectively.

For pemetrexed, doses were based on the doses given in the SATURN trial, using a body surface area of 1.8 m^2 (the average for patients in the JMEN trial). Additional costs for administration of intravenous infusion (£212 per cycle, from the National Schedule of Reference Costs 2007/08), drug preparation time (£37 per cycle, from the Chemotherapy Online Planning Resource Tool), and other medications needed before pemetrexed is administered (£14 per cycle) were also added. The total average per-patient cost for pemetrexed in the model was £17,853.

Best supportive care costs

The costs of best supportive care in the progression-free and progressed health states were taken from NICE technology appraisal guidance 162, which were based on expert panel consensus at the time of the appraisal and inflated using the healthcare inflation index published in the Personal Social Services Research Unit (PSSRU) Report 2009. The costs were £361 and £1089 for the progression-free and progressed health states respectively and were applied for the mean duration of time each patient spent in these health states.

Adverse event costs

The costs of the adverse events associated with erlotinib, rash and diarrhoea, were taken from NICE technology appraisal guidance 162 and inflated using the healthcare inflation index published in the PSSRU Report 2009. The total average per-patient costs for adverse events associated with erlotinib in the model were £12, £11 and £15 in the ITT, stable disease and non-squamous populations respectively. The costs of adverse events associated with

pemetrexed (neutropenia, anaemia, fatigue) were taken from the manufacturer's submission to NICE for the technology appraisal of pemetrexed as first-line maintenance treatment in 2009. The total average per-patient cost of adverse events for pemetrexed in the model was £25.

Post-progression treatment costs

Data on post-progression treatments were collected in the SATURN trial. The costs for post-progression treatments came from various sources including the 'British national formulary' (BNF) edition 58 and other NICE appraisals. Costs for treatments already included in best supportive care were excluded to avoid double counting. Average monthly post-progression treatment costs associated with erlotinib were £325, £322, and £226 per patient for the ITT, stable disease, and non-squamous populations respectively. The costs associated with placebo were £440, £483, and £413 per patient for each population respectively. Because of the lack of available data from the JMEN study, the manufacturer assumed that the post-progression treatment costs associated with pemetrexed would be the same as those for the placebo group of the SATURN study.

3.5 Results

The manufacturer's base-case results for the stable disease, non-squamous and ITT populations are reported in tables 4–6.

In the ITT population, the cost per quality-adjusted life year (QALY) gained for erlotinib compared with placebo was £55,219 (incremental cost £5706 and incremental benefit 0.103 QALYs). In the stable disease population, the cost per QALY gained for erlotinib compared with placebo was £47,743 (incremental cost £7747 and incremental benefit 0.277 QALYs). In the non-squamous population, the manufacturer presented results for pemetrexed compared with erlotinib rather than erlotinib compared with pemetrexed. The cost per QALY gained for pemetrexed compared to erlotinib was

[redacted]. The manufacturer stated that this cost-effectiveness analysis should be considered with caution because the indirect analysis showed no statistically significant difference between erlotinib and pemetrexed in overall survival.

Table 4 Base-case analysis for erlotinib versus placebo in the ITT population

	Erlotinib	Placebo	Incremental
Mean life years	1.446	1.299	0.147
Mean QALYs	0.788	0.685	0.103
Mean total cost	£25,112	£19,407	£5706
Cost per life year gained (£)	-	-	£38,896
Cost per QALY gained (£)	-	-	**£55,219**

QALY: quality-adjusted life year

Table 5 Base-case analysis for erlotinib versus placebo in the stable disease population (including patients with non-squamous and squamous disease)

	Erlotinib	Placebo	Incremental
Mean life years	1.385	1.108	0.277
Mean QALYs	0.750	0.587	0.162
Mean total cost	£24,129	£16,382	£7747
Cost per life year gained (£)	-	-	£27,968
Cost per QALY gained (£)	-	-	**£47,743**

QALY: quality-adjusted life year

Table 6 Base-case analysis for erlotinib versus pemetrexed in the non-squamous population (including patients who had a response to first line chemotherapy and patients who had stable disease)

	Erlotinib	Pemetrexed	Incremental
Mean life years	Not reported	Not reported	Not reported
Mean QALYs	[redacted]	[redacted]	[redacted]
Mean total cost	[redacted]	[redacted]	[redacted]
Cost per life year gained (£)	-	-	Not reported
Cost per QALY gained (£)	-	-	[redacted]

QALY: quality-adjusted life year

The manufacturer conducted a number of one-way sensitivity analyses (see page 159 of the manufacturer's submission and page 50 of the ERG report). For the ITT and stable disease populations, the incremental cost-effectiveness ratios (ICERs) were most sensitive to increasing and decreasing the utilities for the PFS health state by 20%. The base-case ICER for the ITT population (£55,219 per QALY gained) increased to £69,517 per QALY gained when the utilities were decreased by 20% and decreased to £45,799 per QALY gained when the utilities were increased by 20%. For the stable disease population, the base-case ICER (£47,743 per QALY gained) increased to £54,624 per QALY gained when the utilities were decreased by 20% and decreased to £42,402 per QALY gained when the utilities were increased by 20%.

For the non-squamous population, the ICERs were most sensitive to using the lower confidence intervals of the hazard ratios for overall survival ([redacted] per QALY gained compared to [redacted] in the base case), the upper confidence interval (pemetrexed was both less costly and more cost effective than erlotinib), increasing the PFS utilities by 20% ([redacted] per QALY gained) and decreasing the PFS utilities by 20% ([redacted] per QALY gained).

Probabilistic sensitivity analyses suggested that the likelihood that the ICER for erlotinib compared with placebo in the stable disease population was below £50,000 per QALY gained was 55%. There was a high degree of

certainty that pemetrexed was not cost effective compared with erlotinib in the non-squamous population.

Patient access scheme

The manufacturer provided revised ICERs calculated without the patient access scheme after completion of the ERG report.

Table 7 Revised base-case analysis with no patient access scheme for erlotinib versus placebo in the stable disease population

	Erlotinib	Placebo	Incremental
Mean life years	1.385	1.108	0.277
Mean QALYs	0.750	0.587	0.162
Mean total cost	£25,213	£16,382	£8,831
Cost per life year gained (£)	-	-	£31,881
Cost per QALY gained (£)	-	-	£54,428

QALY: quality-adjusted life year

End-of-life criteria

The manufacturer submitted end-of-life proposals for patients with non-squamous disease and stable disease. In light of the recent EMEA positive opinion for erlotinib for patients with stable NSCLC, only the proposal relating to patients with stable disease may be relevant.

The criteria for end-of-life considerations are:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- 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.
- The treatment is licensed or otherwise indicated for small patient populations.

- In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

With regard to life expectancy, the manufacturer provided one source (The National Lung Cancer Data Audit Programme, 2007) showing that the median overall survival of patients with NSCLC was 7.6 months. Data from the placebo arm of the SATURN trials showed median overall survival of 11 months. The manufacturer stated that results from the economic evaluation showed that erlotinib provided a mean extension of life of 3.3 months over placebo in patients with stable disease. There is currently no other agent available for the maintenance treatment of NSCLC in the NHS, and the total estimated number of patients in the stable disease population is 2965. The manufacturer does not state whether the criteria for life extension of at least 3 months or small patient populations are met for patients with non-squamous NSCLC.

3.6 Evidence Review Group comments

The ERG considered that in general, the manufacturer's economic evaluations met the requirements of the NICE reference case. However it identified a number of problems with the submitted models. The ERG's main criticism was that although the models used a Markov structure, they were not Markov models because movement between health states was not governed by transition probabilities. Instead parametric projection models of PFS and overall survival were used to determine how patients move between states. This means that post-progression survival estimates can take negative values and raises concerns about the reliability of the results generated.

The ERG highlighted a number of problems with the way that the costs of erlotinib, pemetrexed and post-progression treatments were calculated. For erlotinib, costs were based on the average number of patients remaining

progression free during each month. However drugs are administered at the beginning of the month to all eligible patients regardless of whether or not their disease progresses during that period. Furthermore, erlotinib costs did not account for wastage (erlotinib is administered in packs of 30 tablets which are taken at home and part-used packs would be discarded). For pemetrexed, costs were based on a mean body surface area of 1.8 m^2 (from the JMEN trial). The ERG commented that separate calculations were necessary for men and women and the effect of variation in body surface area in the population on drug wastage was not taken into account. For post-progression treatments, the total costs were estimated from the SATURN trial, converted to average monthly costs and then added to the monthly cost of best supportive care. The ERG thought this approach was problematic because many of the post-progression treatments were not recommended for use in the UK (only erlotinib and docetaxel are approved by NICE). Some patients in both arms of the SATURN trial had erlotinib post-progression although its use as maintenance therapy would normally prevent its further use as second-line treatment.

The ERG commented that the methods used to generate utilities involved a number of steps (transformation of FACT-L scores into EQ-5D visual analogue scores and then to EQ-5D scores) and it considered that each step introduced uncertainty into the values.

The ERG noted that NHS reference costs for 2008/09 have recently been released which means that some costs in the models can be updated. It noted that the discounting of costs and benefits after 1 year was done on a daily basis for the stable disease and non-squamous models rather than annually as in the NICE reference case. Lastly, the ERG identified some problems with the extrapolation of PFS and overall survival beyond the trial period in the manufacturer's economic evaluation (for further information see pages 56 to 62 of the ERG report).

3.7 Additional work undertaken by the ERG

To address the issues identified in the previous section, the ERG made a number of changes to the models. As these revisions were made to the manufacturer's model, they include costs for erlotinib based on the patient access scheme, which has not yet been accepted by the Department of Health). Changes made to the models were:

- Using an extended time horizon (the manufacturer presented results for a 5-year period but the model allowed extended time horizons up to 15 years).
- Correcting the discounting method (to annual rather than daily discounting).
- Correcting erlotinib costs (incorporating wastage into cost calculations) and pemetrexed costs (using separate dose calculations for men and women).
- Correcting post-progression treatment costs (using a fixed cost per course of post-progression chemotherapy multiplied by the proportion of progressed patients who received each treatment in SATURN, spread pro-rata over the post-progression survivors in each cycle).
- Updating unit costs based on NHS reference costs for 2008/09.
- Using alternative utility values (utilities for all health states were taken from Nafees B et al. 2008). The utilities for the PFS state used in the ERG revisions were 0.6732 for erlotinib and 0.6628 for placebo or best supportive care compared with 0.685 for both treatment arms in the manufacturer's stable disease model. The utility for the progressed health state used by the ERG was 0.53 compared with 0.47 in the manufacturer's model.
- Using alternative methods of projection modelling for PFS and overall survival. The results of this modelling suggested a slightly greater PFS benefit for erlotinib than that estimated in the manufacturer's model as well as a greater overall survival benefit (see table 9 below for results of this analysis and pages 59 and 61 of the ERG report for further information).

Table 9 Mean PFS and overall survival estimated by ERG and manufacturer for the stable disease population

Difference between erlotinib and placebo groups (months)	Manufacturer estimate using a 5 year horizon (as used in the model)	ERG estimate using a 5 year horizon	ERG estimate using a lifetime horizon (as used in ERGs revised model)
PFS	1.821	1.826	1.828
Overall survival	3.532	4.115	4.163

PFS: progression-free survival; ERG: Evidence Review Group

The results of the ERG's revisions for the stable disease population are compared with the manufacturer's base case in table 10.

Table 10 Results of the ERG revisions to the manufacturer's base case for the stable disease population

	Incremental cost	Incremental QALY	ICER
Manufacturer base case	**£7747**	**0.1623**	**£47,743**
ERG revisions			
Extended time horizon	£8230	0.1768	£46,557
Corrected discounting logic	£7790	0.1638	£47,559
Corrected erlotinib costs	£9738	0.1623	£60,012
Corrected post-progression treatment costs	£8772	0.1623	£54,061
Updated unit costs	£8046	0.1623	£49,584
Revised utilities	£7747	0.1714	£45,197
Revised PFS estimates	£7493	0.1642	£45,649
Revised OS estimates	£8132	0.1709	£47,574
ERGs revised base case	**£11,599**	**0.1955**	**£59,336**

ERG: Evidence Review Group; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; PFS: progression-free survival; OS: overall survival

In total, these revisions increased the manufacturer's base-case ICER from £47,743 to £59,336 per QALY gained for the stable disease population and from £55,219 to £63,440 per QALY gained for the ITT population. For the non-squamous population, the ICER for pemetrexed compared with erlotinib

decreased from [redacted] to £96,009 after the ERG's revisions. The major contributions to these changes were the inclusion of wastage in the acquisition cost of erlotinib, and corrections to the costs of second-line chemotherapy.

End-of-life criteria

The ERG considered that all the end-of-life criteria were met for patients with stable disease (the ERG's revisions to the modelling of overall survival in the stable disease group resulted in a higher estimated survival benefit with erlotinib than in the manufacturer's submission, 4.1 months compared with 3.3 months). However, the overall survival benefit estimated by the ERG in the patients with non-squamous disease was 2.7 months, which was less than the 3.2 months in the manufacturer's submission. Because this revised estimate is an extension to life of less than 3 months, the ERG considered that this criterion had not been met for patients with non-squamous disease.

3.8 Further considerations following premeeting briefing teleconference

The manufacturer provided separate models for the ITT and stable disease populations (comparing erlotinib with best supportive care) and for the non-squamous population (comparing erlotinib with pemetrexed). In light of the recent EMEA positive opinion for patients with stable disease, the only relevant model is the stable disease model and this analysis only compares erlotinib with best supportive care. As a result of the recent positive NICE guidance on pemetrexed as maintenance treatment for patients with non-squamous disease (currently in the appeal stage, with publication expected May 2010), pemetrexed is a valid comparator for patients with non-squamous disease. However, no clinical or cost-effectiveness data comparing erlotinib and pemetrexed in patients with stable disease who have non-squamous histology has been provided.

Erlotinib for maintenance treatment is currently being considered by the Food and Drug Administration (FDA) in the USA. The FDA initially rejected the application, however, it has since extended the review period by an additional 90 days, to April 18 2010, following the manufacturer's submission of further data in support of the application. The FDA report of the Oncologic Drugs Advisory Committee Meeting (2009) stated that the main issue concerned other available treatment options for patients in the SATURN trial. The report questioned whether treatment with single agent erlotinib or docetaxel after progression, or maintenance treatment with pemetrexed, are better options than maintenance treatment with erlotinib. The report noted that erlotinib and docetaxel have a statistically significant improvement in median survival over placebo of 2–3 months in patients with NSCLC after failure of prior chemotherapy, and pemetrexed has a 5-month improvement in median survival over placebo in a maintenance setting, compared with a 1-month improvement in the SATURN erlotinib maintenance trial.

Other key issues noted in the FDA report were:

- the weak overall survival benefit in the EGFR IHC negative subgroup (HR 0.91; 95% CI 0.59 to 1.38)
- the modest overall survival benefit in the squamous subgroup (HR 0.86; 95% CI 0.68 to 1.10)
- the lack of overall survival benefit in the EGFR mutation positive subgroup (HR 1.01; 95% CI 0.47 to 2.16) despite a beneficial effect on PFS (HR;0.10, 95% CI 0.04 to 0.25)
- concerns over the reliability of testing for EGFR status (in the SATURN erlotinib maintenance trial only 16% of patients with known EGFR IHC status were negative; whereas 47% of patients with known EGFR IHC status in an erlotinib trial in patients with advanced NSCLC after failure of at least one prior chemotherapy regimen were negative).

3.9 Equality and diversity

No equality and diversity issues were identified during scoping or in the manufacturer's submission.

4 Authors

Sally Gallaugher and Ellie Donegan, with input from the Lead Team (Darren Ashcroft, Mike Wallace and Alison Hawdale).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Liverpool Reviews and Implementation Group, University of Liverpool:

- Dickson R, Bagust A, Boland A et al. Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer (NSCLC): A Single Technology Appraisal. LRiG, The University of Liverpool, March 2009.

B Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Roche

II Professional/specialist, patient/carer and other groups:

- Clive Mulatero, Royal College of Physicians
- David Ferry, Royal Wolverhampton NHS Trust
- Andrew Nicholson, Royal Brompton and Harefield NHS Foundation Trust

C Additional references used:

Nafees B et al. (2008) Health state utilities for non-small-cell lung cancer. Health and Quality of Life Outcomes 6(84).

Food and Drug Administration (2009). Questions for the Oncologic Drugs Advisory Committee Meeting 16 December 2009. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM195716.pdf