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LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer after previous platinum containing chemotherapy

ADDENDUM

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Table of contents

1 BACKGROUND

On 27th April 2010, the National Institute for Health and Clinical Excellence (NICE) Appraisal Committee (AC) considered the evidence for use of erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer (NSCLC) after previous platinum containing chemotherapy. On 15th June NICE issued its Appraisal Consultation Document (ACD) which stated that erlotinib monotherapy was not recommended for the maintenance treatment of patients with locally advanced or metastatic non-small-cell lung cancer with stable disease after platinum-based first-line chemotherapy.

When the original manufacturer submission (MS) was submitted to NICE in January 2010, there was considerable uncertainty about (i) the anticipated wording of the European Medicines Agency licence and (ii) whether or not pemetrexed would be recommended by NICE as a maintenance therapy for patients with NSCLC.

On 18th March 2010 the Committee for Medicinal Products for Human Use adopted a positive opinion recommending that erlotinib be indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after four cycles of standard platinum-based first-line chemotherapy.[1] Subsequently in July, 2010 the EMA approved this use of erlotinib.[2]

On 1st April, NICE recommended the use of pemetrexed as an option for the maintenance treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.[3]

As a result of both uncertainties being resolved, Roche made a successful request to NICE to submit new evidence at the ACD consultation stage for the appraisal of erlotinib as maintenance therapy, as permitted by the Single Technology Appraisal Process Guide.[4]

This document summarises an assessment by the Evidence Review Group (ERG) of the supplementary evidence submission provided by Roche.

2 SUMMARY OF SUPPLEMENTARY EVIDENCE

2.1 Submission overview

The manufacturer's supplementary evidence submission included a document providing comments on the ACD (10 pages), a new submission of clinical and cost effectiveness (>100 pages), and three cost-utility comparisons based on the results obtained from three individual EXCEL models. The main focus of the new evidence submitted was consistent with the marketing authorisation describing the use of erlotinib in patients with stable disease. Given the time constraints, the manufacturer only provided deterministic cost-effectiveness results and stated that it would not be possible to submit results from probabilistic analyses prior to the next scheduled AC meeting on 27 July 2010. In view of the volume of new evidence to be assessed by the ERG at short notice, the consideration of the new evidence was postponed to a later AC meeting which therefore allowed the manufacturer to carry out further work. On 27 August 2010, the probabilistic sensitivity analyses (PSA) for these comparisons, together with previously promised treatment cessation tables, were received.

2.2 New clinical evidence

Summary of direct evidence

The original MS provided overall clinical efficacy results for all patients as reported in the SATURN[5] trial. The supplementary clinical evidence presented by Roche includes more detailed information on this group of patients. Using *post-hoc* analyses, the manufacturer demonstrates that use of erlotinib (plus best supportive care [BSC]) leads to improved progression free survival (PFS) and overall survival (OS) compared with placebo (plus BSC) in stable disease patients with squamous and non-squamous disease (Table 1).

Table 1 Hazard ratios for the stable disease group split by histology

	N	PFS	OS
Squamous	190	0.691 [0.513 to 0.929]	0.665 [0.484 to 0.915]
Non-squamous	297	0.687 [0.541 to 0.873)	0.764 (0.586 to 0.996)

Summary of indirect evidence

The original MS carried out an indirect comparison of erlotinib versus pemetrexed in unselected patients with NSCLC using overall efficacy data from the SATURN[5] and JMEN[6] trials. In the supplementary evidence submission, the manufacturer attempts to compare erlotinib versus pemetrexed indirectly in patients with stable disease and non-squamous histology. As the manufacturer did not identify any published data describing the efficacy of pemetrexed in the stable disease/non-squamous population, the manufacturer's approach is to assume that erlotinib and pemetrexed are of equivalent efficacy and test a range of plausible relative efficacy scenarios in order to capture uncertainty around this assumption.

2.3 New economic evidence

Three economic models were created to satisfy the four cost-utility comparisons of interest:

- Stable disease: erlotinib vs placebo [model 1]
- Stable disease with squamous histology: erlotinib vs placebo [model 2]
- Stable disease with non-squamous histology: erlotinib vs placebo [model 3]
- Stable disease with non-squamous histology: erlotinib versus pemetrexed [model 3].

The results of the manufacturer's new cost-effectiveness analyses appear to demonstrate that erlotinib is cost effective compared to placebo for patients with stable disease, stable disease and squamous histology and also for patients with stable disease and non-squamous histology (ICERs range from £35,000 per quality adjusted life year (QALY) gained to £45,000 per QALY gained). These ICERs are lower than those originally presented by the manufacturer primarily due to a previous overestimation of BSC costs in the original MS.

The results of the manufacturer's indirect comparison of erlotinib vs pemetrexed in patients with stable disease and non-squamous histology show erlotinib to be less effective but also less costly than pemetrexed and that erlotinib is cost effective compared with pemetrexed.

3 STATISTICAL CRITIQUE OF CLINICAL EVIDENCE

3.1 Overview of manufacturer submission

3.1.1 Population

Following the ACD and the EMA approval of erlotinib in the stable disease group of patients with advanced NSCLC, the manufacturer submitted additional clinical evidence based primarily on *post-hoc* analyses of the SATURN[5] trial. The supplementary evidence describes three patient subgroups from the SATURN[5] trial as summarised in Table 2. The manufacturer submitted evidence for the subgroup of stable disease patients (n = 487) in accordance with the licensed indication. Of this subgroup, 235 received placebo and 252 patients received erlotinib. The stable disease subgroup was further stratified by NSCLC histology (squamous and non-squamous) and these showed no imbalance between the treatment arms (Table 2).

Table 2 Proposed population for erlotinib by the manufacturer

Population groups	**Placebo N=451**	**Erlotinib N=438**
Stable disease	235 (52.1%)	252 (57.5%)
Stable disease (Squamous)	93 (20.6%)	97 (22.2%)
Stable disease (Non-squamous)	142 (31.5%)	155 (35.4%)

3.1.2 Baseline characteristics

Demographic and other baseline characteristics for the stable disease patient subgroup in the SATURN[5] trial are presented in Table 3. The data show that baseline characteristics were reasonably balanced between the placebo and erlotinib arm in patients with stable disease as best response to first-line chemotherapy, and have a similar pattern to that observed in the primary analysis of the intention-to-treat (ITT) population.

Table 3 Summary of demographic and other base line characteristics in patients with stable disease as best response to first-line chemotherapy in the SATURN[5] trial

		Placebo N = 235	Erlotinib N = 252
Gender	Female	63 (27%)	62 (25%)
	Male	172 (73%)	190 (75%)
Age	Median	58.0	61.0
	Min-Max	30 - 81	33 - 82
Race	Oriental	35 (15%)	34 (13%)
	Non-Oriental	200 (85%)	218 (87%)
ECOG PS at baseline	0	77 (33%)	70 (28%)
	1	158 (67%)	182 (72%)
Smoking status	Current	125 (53%)	132 (52%)
	Past	62 (26%)	73 (29%)
	Never	48 (20%)	47 (19%)
Histology	Adenocarcinoma	112 (48%)	123 (49%)
	Squamous	93 (40%)	97 (38%)
	Large Cell	13 (6%)	6 (2%)
	Other	17 (7%)	26 (10%)
Stage	IV	182 (77%)	182 (72%)
	IIIB	53 (23%)	70 (28%)
Geographical regions	Africa	4 (2%)	6 (2%)
	Eastern Europe	115 (49%)	119 (47%)
	North America	12 (5%)	12 (5%)
	South East Asia	50 (21%)	54 (21%)
	Western Europe	54 (23%)	61 (24%)

3.1.3 Post-progression therapies

As was observed in the ITT population, the type and distribution of post-progression therapies administered to patients in the stable disease subgroup are not sufficiently similar to those administered to patients with NSCLC in the UK after failure of first-line chemotherapy to dismiss concerns about the generalisability of the trial to patients in the UK. As over 60% of patients in both arms received post-progression therapies (Table 4) and as administration of these therapies directly influences estimates of OS, the ERG considers that the OS benefit demonstrated in the stable disease subgroup may not be replicable in an NHS setting; it is not possible to speculate whether OS estimates would improve or worsen in a UK setting.

Table 4 Summary of post-progression treatments in patients with stable disease

	Placebo N = 235	**Erlotinib N = 252**
All therapies (excluding surgical and medical procedures)	148 (63%)	153 (61%)
Docetaxel*	67 (29%)	72 (29%)
Pemetrexed*	49 (21%)	45 (18%)
Vinorelbine*	20 (9%)	17 (7%)
Erlotinib*	35 (15%)	18 (7%)
Gefitinib*	13 (6%)	6 (2%)

*Patients may have received more than one subsequent therapy

3.1.4 Results: erlotinib vs placebo

The manufacturer presented PFS and OS results (Table 5) for the three populations described above. In the subgroup of patients with stable disease it was observed that the treatment effect was larger than for the whole population, with HRs for PFS and OS of 0.68 and OS 0.72 respectively, indicating that erlotinib was associated with statistically significant increases in PFS and OS compared to placebo. For the subgroups of stable disease patients with squamous and non-squamous disease, erlotinib was also associated with a greater PFS (HR 0.69) and OS (HR ranging from 0.67 to 0.76) than placebo (Table 5).

Although these results are based on *post-hoc* analyses, the effect observed in the subgroup of patients with stable disease can be considered of clinical relevance in this patient population with a generally poor prognosis.

Table 5 Study outcome from SATURN[5] trial for ITT, SD, and SD by histology

Endpoint Sub group	**Erlotinib**	**Placebo**	**HR (95% CI)**	**P value (Log rank)**
Primary : PFS (Weeks-median)				
Intention-to-treat (ITT)	12.3 (12.0 to 13.3)	11.1 (8.1 to 11.7)	0.71 (0.62 to 0.82)	<0.0001
Stable disease (SD)	12.1	11.3 (8.1 to 11.7)	0.68 (0.56 to 0.83)	<0.0001
Stable disease (Squamous)	NR	NR	0.69 (0.51 to 0.93)	NR
Stable disease (Non-squamous)	NR	NR	0.69 (0.54 to 0.87)	NR
Secondary OS: (Months-median)				
Intention-to-treat (ITT)	12.0 (10.6 to 13.9)	11.0 (9.9 to 12.1)	0.81 (0.70 to 0.95)	0.008
Stable disease (SD)	11.9	9.6	0.72 (0.59 to 0.89)	0.0019
Stable disease (Squamous)	NR	NR	0.67 (0.48 to 0.92)	0.0116
Stable disease (Non-squamous)	NR	NR	0.76 (0.59 to 1.00)	0.0457

ITT=intention to treat; SD=stable disease; NR=not reported

3.1.5 Results: erlotinib vs pemetrexed

The manufacturer stated that due to lack of publicly available PFS and OS evidence on patients with stable disease and non-squamous histology from the JMEN[6] trial, evidence synthesis comparing erlotinib and pemetrexed in this population was not possible. Thus, in the submitted base case the manufacturer assumed pemetrexed and erlotinib are of equivalent efficacy and then performed an exploratory sensitivity analysis using HRs for both PFS and OS of 0.9, 1.0 and 1.1 to define scenarios for potential relative efficacy (HRs) in the comparison of erlotinib to pemetrexed. However, the ERG identified that PFS and OS data for patients with stable disease and non-squamous histology were available from a previously published ERG report (Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer)[7]. As a result, the ERG was able to perform an indirect comparison between erlotinib and pemetrexed for patients with stable disease and non-squamous histology and the results of this analysis are presented in Table 6.

Table 6 Direct and indirect evidence (PFS and OS) for ITT and stable disease/non-squamous population groups in the SATURN[5] and JMEN[6] trials

Patient population	Drug	Direct evidence vs placebo		Indirect evidence: LRiG estimate	
		HR (PFS) (95% CI)	HR (OS) (95% CI)	HR (PFS) (95% CI)	HR (OS) (95% CI)
Intention-to-treat (ITT)	Erlotinib	0.71 (0.62 to 0.82)	0.81 (0.70 to 0.95)		
	Pemetrexed	0.50 (0.42 to 0.61)	0.79 (0.65 to 0.95)	0.70 (0.55 to 0.9)	0.98 (0.76 to 1.24)
Stable disease (Non-squamous)	Erlotinib	0.69 (0.54 to 0.87)	0.76 (0.59 to 1.0)		
	Pemetrexed	0.44 (0.32 to 0.61)	0.71* (0.57 to 0.89)	0.64 (0.47 to 0.89)	0.93* (0.66 to 1.3)

*estimated from SATURN and JMEN trial data

The clinical data from the two trials show that both erlotinib and pemetrexed improve PFS and OS when used as maintenance treatments in stable disease patients with non-squamous histology. The indirect comparison performed by the ERG indicates that, when comparing pemetrexed and erlotinib in patients with stable disease and non-squamous histology, the evidence yields a statistically significant PFS benefit for patients on pemetrexed; however, the difference was not statistically significant in the same population group in terms of OS.

3.1.6 Clinical evidence: ERG conclusions

The ERG considers that the clinical evidence from the SATURN[5] trial shows that use of erlotinib as a maintenance therapy in patients with stable disease and in patients with stable disease and squamous and non-squamous histology leads to statistically significant improvement in PFS compared with placebo; a similar increase in OS was identified for the stable disease/squamous population only. The ERG concludes that the pemetrexed vs erlotinib comparison yields a statistically significant PFS benefit for patients on pemetrexed; no similar increase in OS was identified Given the perceived differences in the patient populations of the two studies, use of *post-hoc* subgroup analyses, and the ERG's view that the generalisability of both trials to patients in the UK is uncertain, the ERG considers that these results should be interpreted with caution when considering maintenance treatment for patients in the UK.

4 CRITIQUE OF COST-EFFECTIVENESS EVIDENCE SUBMITTED

4.1 Overview of manufacturer submission

The manufacturer has provided three new economic models adapted from the models previously submitted. These models were created to satisfy the four cost-utility comparisons required:

- Stable disease: erlotinib vs placebo [model 1]
- Stable disease with squamous histology: erlotinib vs placebo [model 2]
- Stable disease with non-squamous histology: erlotinib vs placebo [model 3]
- Stable disease with non-squamous histology: erlotinib versus pemetrexed [model 3].

The ERG takes the view that the first of these comparisons is redundant and potentially misleading. The separate comparisons relating to the squamous and non-squamous populations encompass the whole of the stable disease population, and a combined analysis merely obscures potentially important differences in clinical effectiveness and cost-effectiveness leading to unpredictable results when combined. Therefore, only economic results generated with models 2 and 3 are discussed in this report.

The supplementary evidence submission states that the new models have incorporated the majority of the amendments made by the ERG to the original Roche stable disease model but with some important exceptions. Table 7 summarises the nine aspects of the original model which were previously revised by the ERG, together with an indication of the extent to which the manufacturer has implemented those alterations in the new models. For only four issues has the ERG approach been followed directly and appropriately (time horizon, discounting, utility values and second-line chemotherapy costs). The remaining five model changes are discussed in the following sections of the report: three cost estimates in section 4.2, and those relating to clinical effectiveness (survival gains) in subsequent sections.

Table 7 ERG model modifications and amendments made by the manufacturer in revised models

ERG modification	Manufacturer amendment in new models
Extended time horizon	15 year horizon was set as default
Discounting logic corrected	Annual discounting was implemented
Revised utility values	ERG estimates were implemented
Cost of second line chemotherapy corrected	ERG method of estimating second-line treatment costs implemented
Cost of erlotinib corrected	Manufacturer applied new estimates based on 'time to treatment cessation' data
Cost of pemetrexed corrected	Manufacturer has used a revised method to estimate monthly cost, which does not account for gender mix and differential body surface area distribution, and makes unsupported assumptions
Unit costs updated	Manufacturer corrected an error in estimating BSC monthly costs, by employing estimates used in previous STAs
ERG PFS model	Manufacturer applied ERG previous modelling approach, though this may not be appropriate with the new populations
ERG OS model	Manufacturer applied ERG previous modelling approach, though this may not be appropriate with the new populations. In particular, no attempt has been made to employ the ERG's preferred method using PFS and PPS data to derive an OS estimate

4.2 Critique of the manufacturer's amended cost estimates

4.2.1 Cost of erlotinib treatment

The original submitted model included calculations which sought to reduce the cost of erlotinib therapy on the basis of missed or reduced doses without recognising that in practice the correct currency of cost is the number of packs of tablets dispensed. In the revised model a new method has been introduced which is similar to the ERG's method (which counted packs dispensed to patients remaining progression free every 30 days), but which substitutes an alternative data source in place of PFS. A Kaplan-Meier analysis has been calculated for the time to cessation of treatment (i.e. last dose taken), which in the clinical trial tended to precede the formal date of progression where cessation of treatment was initiated by patient decision rather than by clinical assessment. These data had not previously been used in the manufacturer's model, and did not appear in the trial clinical study report (CSR) made available to the ERG.

This model amendment has the effect of reducing the mean cost of erlotinib per patient by 13.4% for the squamous population, and 9.6% for the non-squamous population. Although some uncertainty exists concerning the possible impact of different arrangements for dispensing medication and determining disease progression in normal clinical practice compared to the special circumstances of a clinical trial (in which testing and assessment occur more frequently), the ERG accepts the additional value of the new data presented and the manufacturer's revised erlotinib cost estimates.

4.2.2 Cost of pemetrexed treatment

The ERG pointed out that the manufacturer's original model failed to take account of the effect of separate distributions of body surface area (BSA) in male and female patients, leading to a small reduction in the mean estimated cost of pemetrexed treatment. The revised model uses an overall BSA distribution without distinguishing by gender, but introduces an additional unsupported modifying factor which reduces pemetrexed costs by 5%. In the absence of an adequate justification for these changes, the ERG prefers to retain its own method of estimation consistent with previous NSCLC appraisals involving pemetrexed. The resulting cost of pemetrexed treatment is thereby increased, reducing its estimated cost-effectiveness ratios compared to erlotinib and 'no treatment'.

4.2.3 Cost of best supportive care

The manufacturer has modified their approach to estimating the cost of BSC during maintenance therapy /'watch and wait' and also following disease progression, together with the cost of second-line chemotherapy, and terminal care. In this the modellers have followed the methods employed in previous pemetrexed appraisals, which appear to have been implemented accurately. This change has the effect of correcting unexpectedly high costs of supportive care in the original manufacturer's model.

4.2.4 Implementation errors

Two minor errors were detected in the revised model:

- a formula used to calculate the monthly quality adjusted life years (QALYs) for patients in PFS was amended correctly in the first month, but not copied to all other months of the analysis. This affected the placebo and pemetrexed arms, but not the erlotinib calculations; the overall effect on the model results was minor.

- the implementation of an end-of-life (terminal care) cost did not take account of the timing of death. This omission meant that the expected differential discounted costs in each treatment arm were not included in the model results; the size of the discrepancy is minor.

4.3 Critique of treatment effectiveness estimates

4.3.1 Squamous population

Progression free survival estimation (erlotinib and placebo)

In both SATURN[5] trial arms, the recorded data for PFS among the squamous cell NSCLC population indicate that no patients remained alive without disease progression at the close of the trial (i.e. the PFS data set is complete). In such situations there is no justification for resorting to projective modelling to establish the mean duration of PFS. The most appropriate and reliable measure may be derived directly from a Kaplan-Meier survival analysis. This shows the mean PFS to be 152 (95% confidence limits [CI]: 121 to 182) days for erlotinib maintenance patients, and 111 (95% CI: 82 to 140) days for the placebo comparator arm, giving a net benefit in favour of erlotinib of 41 (95% CI; 11 to 70) days.

Post-progression survival estimation (erlotinib and placebo)

Examination of the cumulative hazard trends for survival following disease progression (Figure 1) reveals that after a brief period (about 10 weeks) of common mortality risk, the two trial arms diverge, each following a steady constant hazard rate. This indicates that the most appropriate parametric function for projective modelling of post-progression survival (PPS) is an exponential survival curve. However, the recorded data for follow-up beyond disease progression continue for nearly 2 years, so the ERG decided that the most accurate and reliable basis for estimation of the mean PPS was to use the Kaplan-Meier 'area under curve' estimates up to a common maturity stage of follow-up (in this case we used Kaplan-Meier survival less than 20%, corresponding to 501 days follow-up in the erlotinib arm, and 375 days in the control arm), and then modelled projection for later times. The mean PPS estimates obtained were 294 (95% CI: 264 to 323) days for erlotinib, and 226 (95% CI: 203 to 249) days in the placebo arm, indicating a net gain in survival of 68 (95% CI: 30 to 105) days in favour of erlotinib.

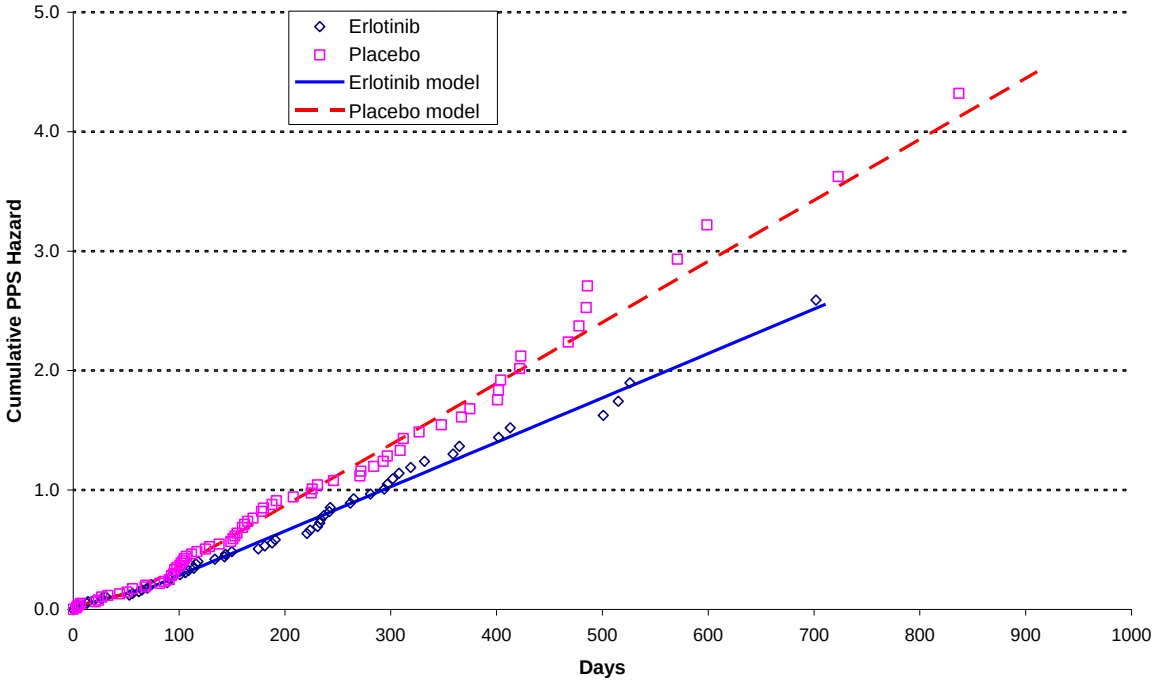

Figure 1 Cumulative hazard for PPS with exponential trend lines fitted to squamous population with stable disease in SATURN[5] trial

Overall survival estimation (erlotinib and placebo)

The estimated mean OS per patient is obtained by adding the estimated PFS to the estimated PPS adjusted to remove patients dying at or before disease progression. Table 8 summarises the results of using this preferred method of estimation, compared to the results obtained with the revised manufacturer's model. The difference in discounted QALYs gained has the effect of increasing the calculated ICER for erlotinib maintenance therapy vs placebo in the stable disease squamous population with stable disease by more than 28%.

Table 8 ERG estimates of mean OS per patient in the squamous population

	Undiscounted			**Discounted**		
	Erlotinib	**Placebo**	**Gain**	**Erlotinib**	**Placebo**	**Gain**
PFS (days)	151.7	111.1	+40.5	151.4	111.0	+40.4
PPS (days)	293.9	226.3	+67.6	284.8	226.0	+58.8
Adjusted PPS	275.8	214.1	+61.6	267.2	211.1	+56.1
OS (days)	**427.4**	**325.2**	**+102.2**	**418.6**	**322.1**	**+96.5**
QALYs	**0.6797**	**0.5105**	**+0.1691**	**0.6668**	**0.5059**	**+0.1609**
Manufacturer estimate	0.7369	0.5169	+0.2201	0.7209	0.5141	+0.2068

4.3.2 Non-squamous population

Progression free survival estimation (erlotinib and placebo)

In both SATURN[5] trial arms, the recorded data for PFS among the non-squamous cell NSCLC population indicate that no patients remained alive without disease progression at the close of the trial (i.e. the PFS data set is complete). In such situations there is no justification for resorting to projective modelling to establish the mean duration of PFS. The most appropriate and reliable measure may be derived directly from a Kaplan-Meier survival analysis. This shows the mean PFS to be 177 (95% CI: 144 to 209) days for erlotinib maintenance patients, and 115 (CI 95%: 95 to 135) days for the placebo comparator arm, giving a net benefit in favour of erlotinib of 62 (95% CI: 35 to 89) days.

Post-progression survival estimation (erlotinib and placebo)

Examination of the cumulative hazard trends for survival following disease progression (Figure 2) reveals that the two trial arms are indistinguishable from disease progression for about 600 days by which time only about 7% of cases remain in follow-up. Comparison by log-rank test indicates strongly (p=0.724) that no statistically significant difference can be detected between the erlotinib maintenance and control arms. Figure 2 also suggests strongly that a simple exponential function would be suitable for projecting beyond the trial data. This leads to an estimated mean PPS in both trial arms of 376 (95% CI: 373 to 379) days, so that there is no net benefit from PPS for either trial arm.

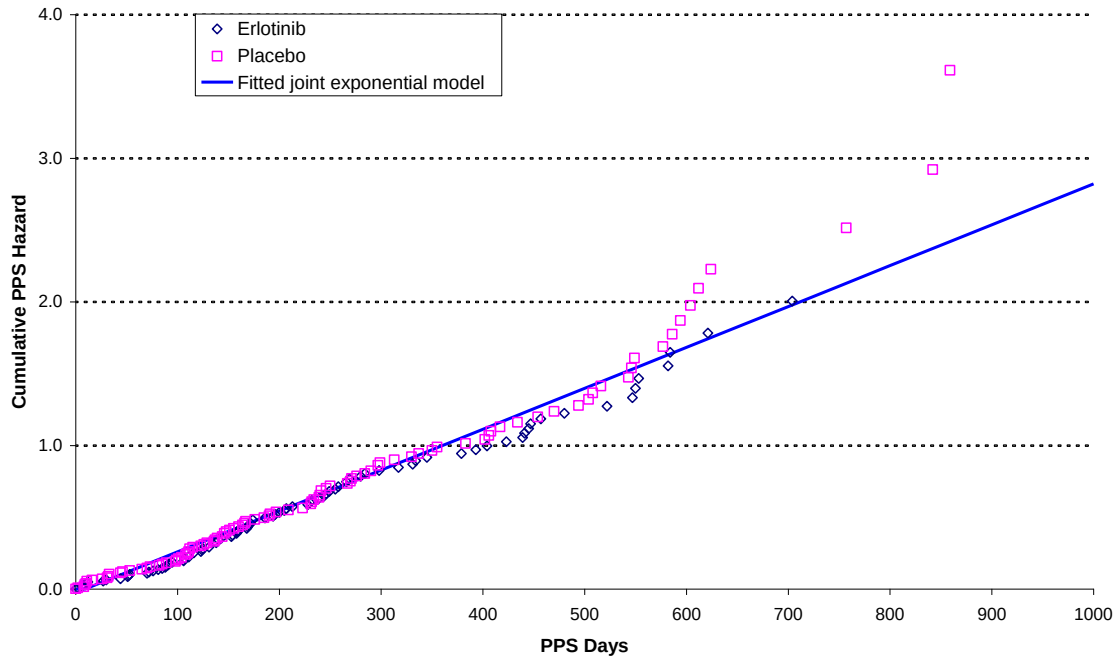

Figure 2 Cumulative hazard for PPS with joint exponential trend line fitted to non-squamous SD population in SATURN[5] trial

Overall survival estimation (erlotinib and placebo)

The estimated mean OS per patient is obtained by adding the estimated PFS to the estimated PPS adjusted to remove patients dying at or before disease progression. Table 9 summarises the results of using this preferred method of estimation, compared to the results obtained with the revised manufacturer's model. The difference in discounted QALYs gained has the effect of increasing the calculated ICER for erlotinib maintenance therapy vs placebo in the non-squamous stable disease subgroup by about 75%.

Table 9 ERG estimates of mean OS per patient in the non-squamous SD population

	Undiscounted			Discounted		
	Erlotinib	Placebo	Gain	Erlotinib	Placebo	Gain
PFS (days)	176.6	114.9	+61.7	175.8	114.7	+61.1
PPS (days)	376.2	376.2	0.0	364.5	375.8	-11.5
Adjusted PPS	354.3	349.7	+4.6	343.3	338.8	+4.5
OS (days)	**530.9**	**464.5**	**+66.4**	**519.1**	**453.5**	**+65.6**
QALYs	**0.8396**	**0.7139**	**+0.1257**	**0.8222**	**0.6979**	**+0.1243**
Manufacturer estimate	0.9157	0.6807	+0.2350	0.8826	0.6653	+0.2173

Outcome estimation (pemetrexed)

In the case of the JMEN[6] trial, information was only available for PFS and OS, so direct estimation of PPS could not be used. In this instance, the HRs for a comparison of pemetrexed vs erlotinib (Table 6) were applied to the erlotinib arm of the SATURN[5] trial and then parametric models of PFS and OS were fitted to the revised survival data. Post-progression survival was then calculated as the difference between OS and PFS. The results are shown in Table 10 for pemetrexed compared to erlotinib. It appears that the use of JMEN[6] data to inform the comparison (rather than the manufacturer's assumption of equivalent effectiveness) results in a clear advantage in favour of pemetrexed.

Table 10 ERG estimates of mean OS per patient in the non-squamous SD population

	Undiscounted			**Discounted**		
	Erlotinib	**Pemetrexed**	**Gain**	**Erlotinib**	**Pemetrexed**	**Gain**
PFS (days)	176.6	298.9	-122.3	175.8	292.9	-117.1
PPS (days)	376.2			364.5		
Adjusted PPS	354.3	286.6	+67.7	343.3	273.0	+70.3
OS (days)	**530.9**	**585.5**	**-54.6**	**519.1**	**566.0**	**-46.8**
QALYs	**0.8396**	**0.9582**	**-0.1186**	**0.8222**	**0.9277**	**-0.1055**
Manufacturer estimate	0.9157	0.9070	+0.0087	0.8826	0.8814	+0.0012

4.4 ERG revised cost-effectiveness results

4.4.1 Squamous population

Revised base-case results for the cost effectiveness of erlotinib maintenance therapy in the squamous population with stable disease are shown in Table 11, including the ERG's revised survival estimates and corrections to the manufacturer's model logic as described above. The estimated ICER is close to £45,000 per QALY gained. Pemetrexed is not indicated for this population.

Table 11 ERG estimate of the cost effectiveness of erlotinib maintenance therapy in the squamous population with stable disease compared with placebo

	Erlotinib	Placebo	Increment
Costs			
Drug acquisition	£6,644	£0	+£6,644
Drug administration	£64	£0	+£64
Adverse events	£11	£0	+£11
BSC (in PFS)	£903	£662	+£241
BSC (in PPS)	£1,405	£1,110	+£295
Second-line CTX	£4,809	£4,907	-£98
End of life	£2,525	£2,554	-£29
Total costs	£16,362	£9,233	+£7,129
Life years			
PFS	0.4145	0.3039	+0.1106
PPS	0.7315	0.5778	+0.1537
Total life-years	1.1460	0.8817	+0.2643
QALYs			
PFS	0.2791	0.2014	+0.0776
PPS	0.3877	0.3062	+0.0815
Total QALYs	0.6668	0.5077	+0.1591
ICER			**£44,812/QALY**

4.4.2 Non-squamous population

Revised base-case results for the cost effectiveness of erlotinib maintenance therapy in the non-squamous population with stable disease are shown in Table 12, including the ERG's revised survival estimates and corrections to the manufacturer's model logic as described above. For all three comparisons the estimated ICER is high (£68,000 - £84,000 per QALY gained). Pemetrexed appears to generate nearly double the additional expected benefit from erlotinib, but at more than twice the net cost to the NHS. The relative performance of the two maintenance regimens is displayed graphically in Figure 3.

Table 12 ERG estimates of the cost effectiveness of erlotinib maintenance therapy in the non-squamous population with stable disease compared to pemetrexed maintenance therapy and placebo

	Erlotinib	**Pemetrexed**	**Placebo**	**Erlotinib vs placebo**	**Pemetrexed vs placebo**	**Pemetrexed vs erlotinib**
Costs						
Drug acquisition	£7,976	£13,671	£0	+£7,976	+£13,671	+£5,695
Drug admin	£77	£2,508	£0	+£77	+£2,508	+£2,431
Adverse events	£11	£25	£0	+£11	+£25	+£14
BSC (in PFS)	£1,049	£1,748	£685	+£365	+£1,063	+£698
BSC (in PPS)	£1,805	£1,436	£1,782	+£24	-£346	-£369
2nd line CTX	£4,727	£4,727	£4,816	-£89	-£89	£0
End of life	£2,502	£2,493	£2,525	-£23	-£32	-£9
Total costs	£18,148	£26,608	£9,808	£8,340	+£16,800	+£8,460
Life years						
PFS	0.4814	0.8019	0.3141	+0.1673	+0.4878	+0.3205
PPS	0.9399	0.7476	0.9276	+0.0123	-0.1800	-0.1923
Total life-years	1.4213	1.5495	1.2417	+0.1796	+0.3078	+0.1282
QALYs						
PFS	0.3241	0.5267	0.2082	+0.1159	+0.3185	+0.2026
PPS	0.4982	0.3962	0.4916	+0.0065	-0.0954	-0.1019
Total QALYs	0.8222	0.9229	0.6998	+0.1224	+0.2231	+0.1007
ICER				**£68,120 per QALY**	**£75,299 per QALY**	**£84,029 per QALY**

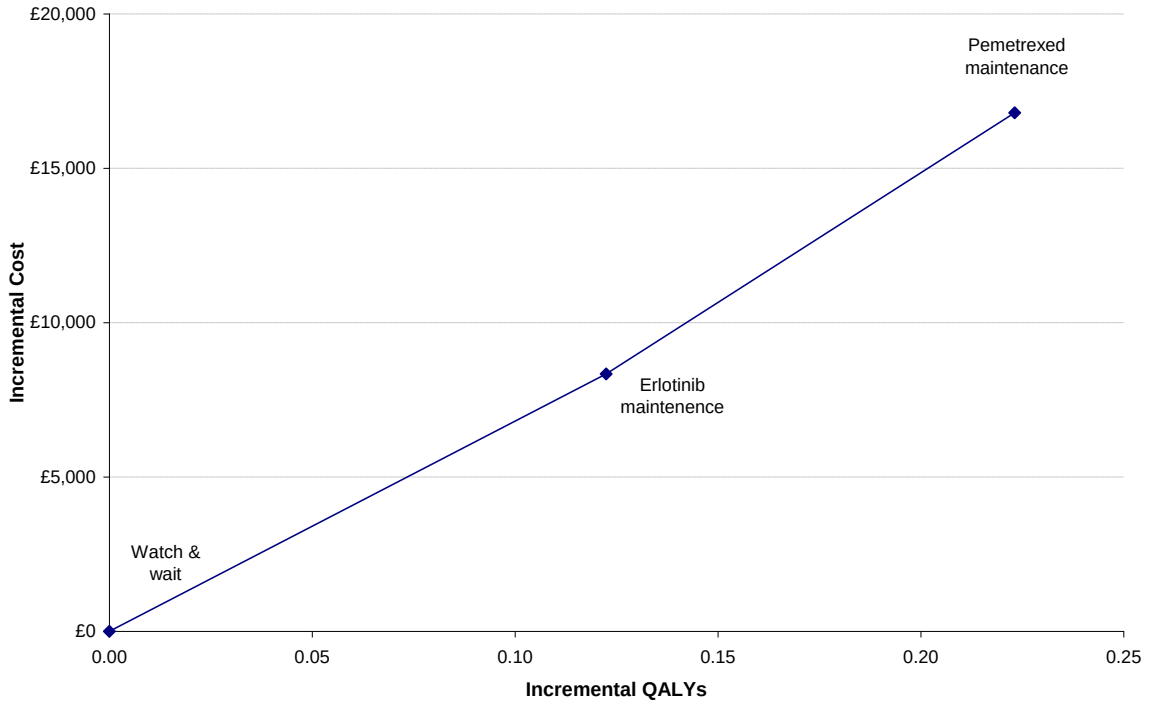

Figure 3 Relative economic performance of erlotinib and pemetrexed in the non-squamous population with stable disease

4.4.3 Cost-effectiveness evidence: ERG conclusions

In the light of the supplementary evidence submitted by the manufacturer, together with additional data provided in response to the ERG request, the ERG is of the opinion that (i) for the comparison of erlotinib vs placebo, the ICER estimated by the ERG for patients in the squamous population with stable disease is lower (£44,812 per QALY gained) than the manufacturer's original ICER for all (squamous and non-squamous) patients with stable disease (£47,743 per QALY gained); (ii) for the comparison of erlotinib vs placebo for patients in the non-squamous population with stable disease, the ICER estimated by the ERG is £68,120 per QALY gained; (iii) for the comparison of pemetrexed vs erlotinib for patients in the non-squamous population with stable disease the ICER estimated by the ERG is £84,029 per QALY gained.

4.5 End of life criteria

The manufacturer's supplementary evidence document argues that since the OS data from the SATURN[5] trial are not yet complete, there is no alternative but to estimate OS benefit by projective modelling. The manufacturer states that the ERG modelled OS gain provided by erlotinib in the stable disease population is approximately 4.2 months. However, new analysis by the ERG based on the PPS data derived from the SATURN[5] trial has reduced the ERG's best estimates of OS gain to 3.17 months (erlotinib vs placebo; squamous population with stable disease) and 2.16 months (erlotinib versus placebo; non-squamous population with SD).

4.6 Key issues

Since the original ERG report was submitted, two key issues have been resolved. Firstly, erlotinib is now licensed for use as monotherapy for maintenance treatment in patients with locally advanced or metastatic NSCLC with stable disease after four cycles of standard platinum-based first-line chemotherapy. Secondly, pemetrexed is approved by NICE as an option for the maintenance treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology if disease has not progressed immediately following platinum-based chemotherapy in combination with gemcitabine, paclitaxel or docetaxel.

However, other issues related to the appraisal of erlotinib as a maintenance therapy remain. As pointed out in the original ERG report:

Data are available from only one relevant RCT (SATURN[5]). Despite being generally well-designed, the trial exhibits several weaknesses. Of note is that, despite efforts to ensure blinding of patients and investigators, as patients in the erlotinib arm were significantly more likely to develop a rash and suffer from diarrhoea than patients in the placebo group, the extent to which patients and investigators were truly blind to treatment allocation throughout the trial is uncertain.

The randomisation technique used in the trial included stratification by six different factors. Response to treatment (e.g. stable disease) was not employed as a stratification factor. However, the manufacturer submission relies exclusively on *post-hoc* analysis of data related to this sub-group of patients. The ERG considers that the results of the *post-hoc* analyses should be considered with caution as the trial was not designed to perform this type of analysis and did not adjust for multiple testing.

The generalisability of the SATURN[5] trial to patients in England and Wales is uncertain for a number of reasons:

- Only seven patients were recruited from the UK, 75% of patients in the trial were recruited from outside of Western Europe
- The trial did not include patients who had received pemetrexed as a first-line treatment (according to the MS pemetrexed is becoming the dominant first-line treatment for patients with non-squamous NSCLC); hence the response of patients to erlotinib after treatment with pemetrexed is unknown
- Paclitaxel appears to be used as a first-line treatment for a greater proportion of patients in the trial than might otherwise be the case in clinical practice in England and Wales.[8] The impact of this when generalising to patients in England and Wales is unknown
- A number of patients in the trial received second-line therapies that are not available to patients in clinical practice in England and Wales; this may affect the magnitude of the OS benefit observed in the trial.

In addition, none of the patients in the SATURN[5] trial received pemetrexed as a first-line treatment. In the UK, pemetrexed is recommended as a first-line treatment by NICE[3] for patients with "other than squamous cell carcinoma". Currently, there is no clinical evidence to support the use of erlotinib as a maintenance therapy in patients who received pemetrexed as a first-line therapy.

5 REFERENCES

1. European Medicines Agency. Summary of opinion - Tarceva (erlotinib). London: European Medicines Agency 2010.

2. European Medicinces Agency. EPAR - Tarceva. London: European Medicines Agency 2010.

3. National Institute for Health and Clinical Excellence. Pemetrexed for the first-line treatment of non-small-cell lung cancer. 2008 [cited 2010 January]; Available from: http://www.nice.org.uk/nicemedia/pdf/TA181Guidance.pdf.

4. National Institute for Health and Clinical Excellence. Guide to the single technology (STA) process2006 September 2006.

5. Roche Ltd. Erlotinib for the 1st line maintenance treatment of non-small cell lung cancer - submission to NICE Single Technology Appraisal Process2010.

6. Ciuleanu T, Brodowicz T, Kim J, Krzakowski M, Wu Y, Bover I, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009; 374(1432-1440).

7. Greenhalgh J, McLeod C, Bagust A, Boland A, Fleeman N, Dundar Y, et al. Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC): A single technology appraisal2009 [cited 2010 20th March]: Available from: http://www.nice.org.uk/nicemedia/pdf/LungCancerPemetrexedERGReport.pdf.

8. Eli Lilly. Single Technology Appraisal - Pemetrexed in the maintenance treatment of non-small cell lung cancer. Manufacturer submission. 2009 [January]; Available from: <http://www.nice.org.uk/guidance/index.jsp?action=download&o=46610>.