NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Erlotinib for the first line treatment of EGFR-TK mutation positive non-small-cell lung cancer

Patient Access Scheme Submission

10th October 2011

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Clinical Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Clinical Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The

‘Specification for manufacturer/sponsor submission of evidence’ provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

The patient access scheme (PAS) applies to the purchase of erlotinib (Tarceva). The PAS proposed cover all populations for which erlotinib has an EMA marketing authorization.

3.2 Please outline the rationale for developing the patient access scheme.

The patient access scheme is designed to bring the cost of erlotinib in the first line treatment of EGFR M+ mNSCLC to a level at which it can be considered cost-effective compared to the current standard of care in this setting (gefitinib).

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The PAS is a simple discount (a [redacted]% discount below the BNF62 list price of erlotinib).

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The PAS is a simple discount applied at the point of invoice. It applies to the purchase of all erlotinib, irrespective of which of its indications the erlotinib purchased is later utilised for.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

See above. The scheme is not dependent upon any criteria and is simply applied at the point of purchase.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The scheme will apply to all patients for whom erlotinib is indicated.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

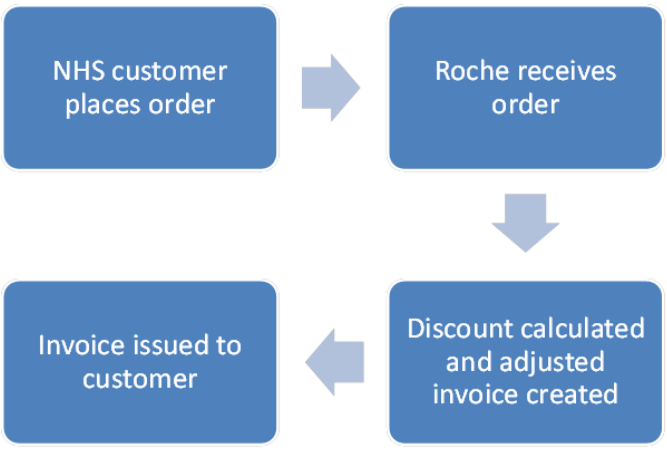
The discount will be applied at the point of invoice.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The discount will be applied at the point of invoice

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

See below:



3.10 Please provide details of the duration of the scheme.

The scheme will remain in place until the publication of the revised NICE guidance relating to erlotinib. After any review, the scheme may be withdrawn or modified or carry on in its current form depending upon the outcome of the re-appraisal.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme taking into account current legislation.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Not applicable.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

Cost effectiveness

3.14 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The PAS applies to the population considered in our primary evidence submission.

3.15 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable.

3.16 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The PAS has been applied by reducing the price of erlotinib to [redacted] % below the BNF62 list price (rather than 14.5% below BNF62 list price included in the primary evidence submission).

3.17 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

The indirect comparison of erlotinib to gefitinib utilised in the primary submission was similarly utilised for the results presented below. The base-case analysis utilised an indirect comparison of the EURTAC RCT compared to a pooling of the IPASS/First-SIGNAL/WJTOG/NEJSG RCTs (PFS HR = 0.82 {0.54, 1.26}). The use of alternative indirect comparisons was tested in sensitivity analysis.

3.18 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

The PAS is a simple discount introduced at the point of invoicing. It is therefore not subject to operational or implementation costs.

3.19 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable.

Summary results

Base-case analysis

3.20 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

Please note: The NHS currently spends around £[redacted] per annum on the use of erlotinib for indications beyond the scope of this appraisal (primarily second line mNSCLC treatment). As the [redacted]% discount proposed in support of this appraisal will apply equally across all erlotinib purchased by the NHS, NICE approval of erlotinib in the first line treatment of EGFR M+ patients will result in a saving of around [redacted] per annum on the purchase of erlotinib for its other indications. This saving equates to a saving of over £[redacted] per EGFR M+ patient given first line treatment for their mNSCLC [redacted]/418 – see section A of primary evidence submission for derivation of population figure)

This saving is not considered in the [redacted]% discount ICERs provided below.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 1: Base-case cost-effectiveness results ([redacted]% discount)

	Erlotinib	Gefitinib
Intervention cost (£)	[redacted]	£9,300
Other costs (£)	[redacted]	£6,746
Total costs (£)	[redacted]	£16,046
Difference in total costs (£)	[redacted]	
LYG	[redacted]	1.80
LYG difference	[redacted]	
QALYs	[redacted]	1.02
QALY difference	[redacted]	
ICER (£)	£21,874	

Table 2: Base-case cost-effectiveness results (14.5% discount)

	Erlotinib	Gefitinib
Intervention cost (£)	[redacted]	£9,300
Other costs (£)	[redacted]	£6,746
Total costs (£)	[redacted]	£16,046
Difference in total costs (£)	[redacted]	
LYG	[redacted]	1.80
LYG difference	[redacted]	
QALYs	[redacted]	1.02
QALY difference	[redacted]	
ICER (£)	£48,961	

Table 3: Base-case cost-effectiveness results (BNF62 List Price)

	Erlotinib	Gefitinib
Intervention cost (£)	[redacted]	£9,300
Other costs (£)	[redacted]	£6,746
Total costs (£)	[redacted]	£16,046
Difference in total costs (£)	[redacted]	
LYG	[redacted]	1.80
LYG difference	[redacted]	
QALYs	[redacted]	1.02
QALY difference	[redacted]	
ICER (£)	£74,300	

3.21 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

Table 4: Base-case incremental results – with [redacted]% discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Gefitinib	£16,046	1.796	1.015					
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,874	£21,874

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Table 5: Base-case incremental results – with 14.5% discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Gefitinib	£16,046	1.796	1.015					
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£48,961	£48,961

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 6: Base-case incremental results – BNF62 List price

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Gefitinib	£16,046	1.796	1.015					
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£74,300	£74,300

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

3.22 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Table 7: Parameters varied in deterministic sensitivity analysis (with [redacted]% discount PAS)

Parameter	Base-Case Value	Low Value	High Value		Base-Case ICER	Low Value ICER	High Value ICER
Transition Probabilities							
Monthly probability of disease progression after month 16 (erlotinib) – note: KM used before this point in time.	0.085977	-10%	+10%		£21,874	£19,232	£24,800
Monthly probability of disease progression after month 16 (gefitinib) - note: indirect PFS HR adjusted KM used before this point in time.	0.104567	-10%	+10%		£21,874	£23,915	£20,471
Monthly probability of death in PFS (both erlotinib and gefitinib)	0.014206	-10%	+10%		£21,874	£21,630	£22,124

Monthly probability of death in PD (both erlotinib and gefitinib)	0.075719	-10%	+10%	£21,874	£22,206	£21,160
Utility Values						
PFS (Stable Disease)	0.6532	0.6096 (Lower confidence interval)	0.6968 (Upper confidence interval)	£21,874	£23,235	£20,663
PFS (Response dummy variable)	0.0193	0.0065 (Lower confidence interval)	0.0321 (Upper confidence interval)	£21,874	£23,016	£20,840
Disutility of Rash	-0.0325	-0.0554 (Lower confidence interval)	-0.0095 (Upper confidence interval)	£21,874	£22,066	£21,685

Disutility of Diarrhoea	-0.0468	-0.0772, (Lower confidence interval)	-0.0164 (Upper confidence interval)	£21,874	£21,932	£21,816
PD (progression dummy variable disutility relative to PFS SD baseline)	-0.1798	-0.2223 (Lower confidence interval)	-0.1373 (Upper confidence interval)	£21,874	£21,550	£22,207
Resultant PFS Values	PFS erlotinib = 0.661 PFS gefitinib = 0.656	Gefitinib PFS utility (0.656) applied for gefitinib and erlotinib	Erlotinib PFS utility (0.661) applied for gefitinib and erlotinib	£21,874	£23,102	£22,909
Costs						
Pharmacy costs per pack of	£13	£6.63 (Lower	£19.37 (Upper	£21,874	£21,773	£21,975

erlotinib/gefitinib dispensed		confidence interval if standard error = 1/4 base case value (assumption))	confidence interval if standard error = 1/4 base case value (assumption))			
Monthly PFS BSC Cost (including monitoring)	£181.46	£92.54 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£270.38 (Upper confidence interval if standard error = 1/4 base case value (assumption))	£21,874	£20,062	£23,685
Monthly PD BSC Cost	£160.06	£81.63 (Lower confidence interval if standard error = 1/4 base case value	£238.49 (Upper confidence interval if standard error = 1/4 base case	£21,874	£22,206	£21,541

		(assumption))	value (assumption))				

Terminal Care Cost	£2,588.25	£1,320.01 (Lower confidence interval if standard error = 1/4 base case value (assumption))	£3,856.49 (Upper confidence interval if standard error = 1/4 base case value (assumption))		£21,874	£21,934	£21,813
Gefitinib per patient PAS administration cost	£70 one off cost, £35 per month on-going costs	£35 one off cost, £17.50 per month on-going costs	£140 one off cost, £70 per month on-going costs		£21,874	£24,204	£17,213
Cost of grade 3/4 Rash	£116	£59.16	£172.84		£21,874	£21,856	£21,892
Cost of grade 3/4 Diarrhoea	£867	£442.17	£1,291.83		£21,874	£21,865	£21,883
General Parameters							

Time Horizon	10 years	5 years	20 years	£21,874	£22,850	£21,863
Costs Discount Rate	3.5%	0%	6%	£21,874	£23,412	£20,869
Health Outcomes Discount Rate	3.5%	0%	6%	£21,874	£20,466	£22,869
Both Discount Rates	3.5%	0%	6%	£21,874	£21,905	£21,819

Figure 1: Tornado Diagram (with [redacted]% discount PAS)

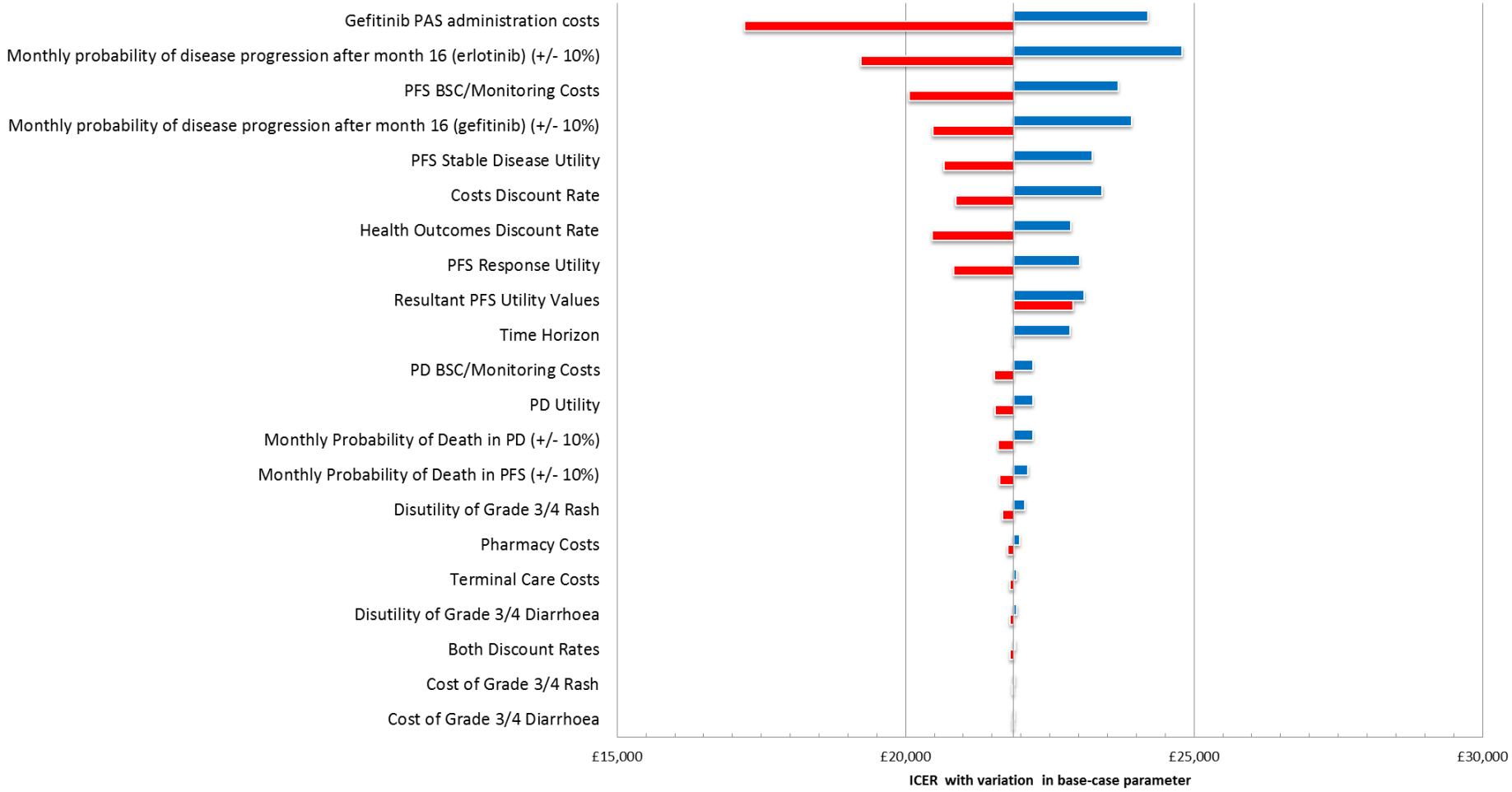


Table 8: Relative efficacy of erlotinib and gefitinib ICERs

Scenario	Description	PFS HR (erlotinib vs gefitinib)	ICER
1	Base-case (EURTAC vs Ku et al)	0.82	£21,874
2	OPTIMAL vs Ku et al	0.36	£16,552
3	Random Effects (RE) pooling (EURTAC/OPTIMAL RE pooling vs Ku et al)	0.56	£15,712
4	Fixed Effects (FE) pooling (EURTAC/OPTIMAL FE pooling vs Ku et al)	0.58	£15,800

Table 9: Proportion of patients 'activating' gefitinib PAS ICERs

Scenario	Description	ICER
1	EURTAC erlotinib 'time to last dose' curve 3 month value with indirect PFS HR applied (0.82)	£21,874
2	EURTAC erlotinib PFS curve 3 month value with indirect PFS HR applied (0.82)	£10,066
3	IPASS gefitinib PFS curve 3 month value (95%)	[redacted]
4	100% of patients 'activate' the PAS	[redacted]

Table 10: Point of transition from observed PFS KM Curve to modeled 'tail' ICERs

Scenario	Description	ICER
1	Base-Case (After Month 16)	£21,874
2	After Month 5	£21,524
3	After Month 21	£16,427
4	After Month 30	£14,826

Table 11: Point of transition from observed 'Time to last dose' erlotinib KM Curve to modeled 'tail'

Scenario	Description	ICER
1	Base-Case (After Day 300)	£21,874
2	After Day 150	£19,418
3	After Day 540	£22,335
4	After Day 600	£24,958

The above sensitivity analyses demonstrate that the base-case ICER of £21,874 (based upon an indirect comparison of EURTAC to Ku et al likely to be biased against erlotinib) is an over-estimate of the true ICER of erlotinib in this population, with an ICER of £16,500 estimated via a comparison of the OPTIMAL study and Ku et al (i.e. an indirect comparison conducted in solely those patients who are clinically comparable).

As the PAS offered will apply to all erlotinib purchased there will be sizeable 'indirect savings' (on spending on erlotinib's other indications) produced by NICE approval of erlotinib in this appraisal. These savings are not included in the economic modelling undertaken.

Budget Impact of NICE approval of erlotinib in first line EGFR M+ mNSCLC

The budget impact of NICE approval of erlotinib in the first line treatment of EGFR M+ mNSCLC under the terms of the PAS proposed (a 30% straight discount on all erlotinib sold) would be as Table 12 below.

Table 12: Budget Impact of approval (with [redacted]% discount)

Year	2012	2013	2014	2015	2016
Eligible Population	418	420	422	424	426
Erlotinib Market Share	30%	50%	60%	70%	75%
Patients Receiving Erlotinib	125.4	210	253	297	320
Direct Budget Impact	£257,811	£431,834	£520,792	£610,628	£657,516
Indirect Savings	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total Budget Impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Due to these ‘indirect savings’ NICE approval of erlotinib in the first line treatment of EGFR M+ mNSCLC patients with the [redacted]% discount proposed will result in a net saving of over £[redacted] over the next 5 years

If these savings were to be considered in the economic analyses undertaken the case for approval of erlotinib appears strong.

3.23 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Table 13: Base-case PSA results – with [redacted] % discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Gefitinib	£16,066	1.828	1.030					
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,791	£25,791

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness

Figure 2: PSA Scatter-plot erlotinib vs gefitinib (red line = £30k/QALY)

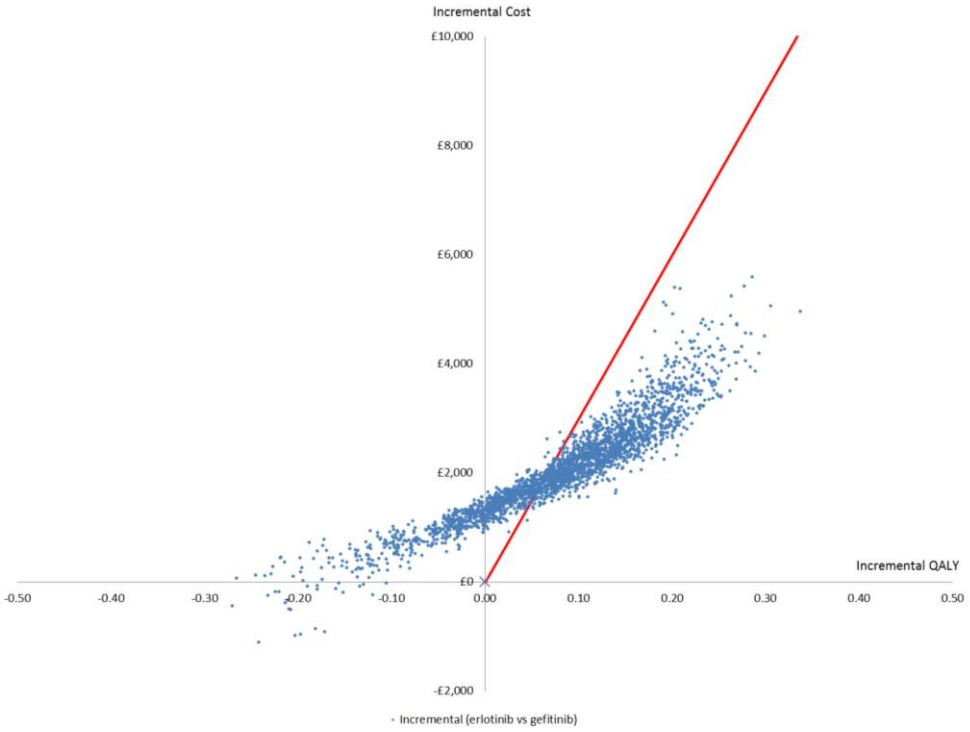
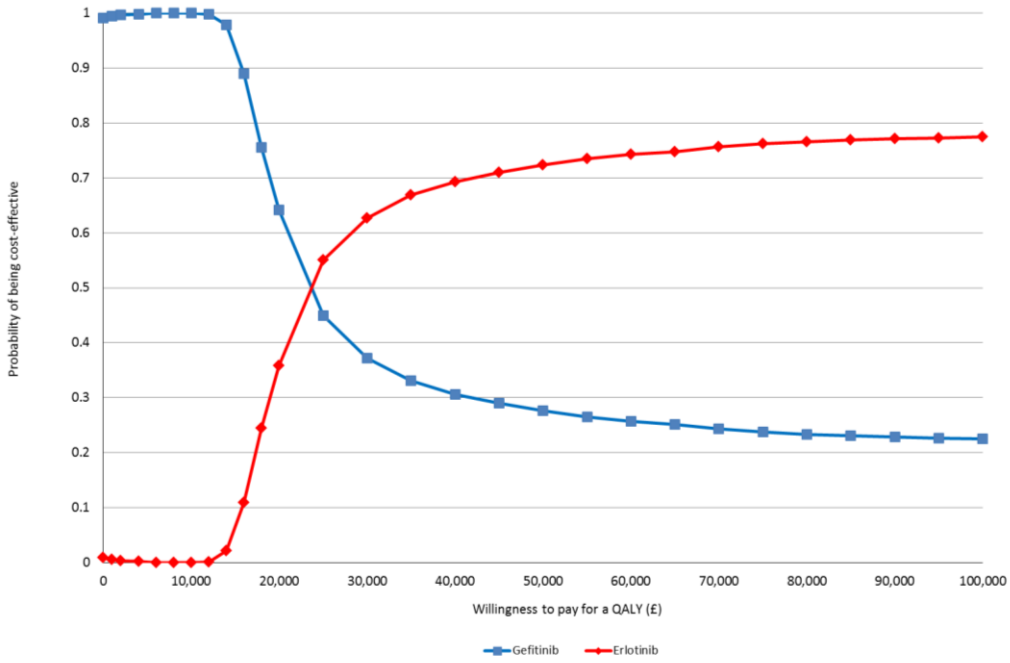


Figure 3: Cost Effectiveness Acceptability Curves



At a threshold of £20,000/QALY erlotinib would be considered cost-effective in 35.8% of simulations conducted (with gefitinib cost-effective in 64.2%).

At a threshold of £25,000/QALY erlotinib would be considered cost-effective in 55.04% of simulations (with gefitinib cost-effective in 44.96%).

At a threshold of £30,000/QALY erlotinib would be considered cost-effective in 62.76% of simulations (with gefitinib cost-effective in 37.24%).

3.24 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

See above.

3.25 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme on ICERs

3.26 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

See above.

4 Appendices

4.1 Appendix A: Additional documents

4.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Not applicable.