NICE National Institute for Health and Care Excellence

Rapid Review

Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer [ID3786]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

RAPID REVIEW

Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer [ID3786]

Contents:

The following documents are made available to consultees and commentators:

1. **Company PAS submission** from AstraZeneca
2. **Evidence Review Group report** prepared by Liverpool Reviews and Implementation Group (LRiG)
3. **Evidence Review Group report – factual accuracy check**
4. **NHS England submission**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer

Patient Access Scheme submission template

January 2019

1 Introduction

In acknowledgment of the introduction of the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (VPAS) the transition arrangements as set out in paragraph 3.28 states that commercial flexibilities analogous to simple confidential and complex published Patient Access Schemes will continue to operate and be available for new products using existing processes and in accordance with existing criteria and terms as set out originally in the 2014 Pharmaceutical Price Regulation Scheme (PPRS), and guidance on the National Institute for Health and Care Excellence (NICE) website. Once NHS England establishes the approach in the commercial framework as referred to in paragraph 3.26 of the VPAS (2019), any new commercial flexibilities analogous to simple confidential and complex published PAS will operate in accordance with the commercial framework.

The PPRS (2014) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2014) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) 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 a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow 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 PPRS (2014).

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

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for companies

This document is the Patient Access Scheme submission template for technology appraisals. If companies want the National Institute for Health and Care 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 NHS England.

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'
- 'Company evidence submission template' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal April 2018. The 'User guide for company evidence submission template' 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 via NICE docs: https://appraisals.nice.org.uk.

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'

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.

Osimertinib (TAGRISSO®) for untreated EGFR mutation-positive advanced or metastatic non-small cell lung cancer (NSCLC).

3.2 Please outline the rationale for developing the Patient Access Scheme.

The Patient Access Scheme has been developed to address the concerns of the Appraisal Committee regarding the likely cost-effectiveness of the technology in the licensed indication.

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price.

The patient access scheme and Commercial Access Agreement offers osimertinib at a lower fixed price per pack (which will not vary with any change to the UK list price). This patient access scheme is conditional on the lower fixed price remaining confidential and not being published in any NICE guidance. The price cannot be disclosed to any third party.

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 scheme applies to the whole licensed population for osimertinib.

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.

The scheme will apply in perpetuity, assuming continued recommendation from NICE.

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 is expected to apply to the entire licensed population for osimertinib.

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

A revised PAS (simple discount) and an additional Commercial Access Agreement has been agreed with NHS England.

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.

N/A

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

N/A

3.10 Please provide details of the duration of the scheme.

The scheme will apply in perpetuity, assuming continued recommendation from NICE.

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?

No equity or equality issues have been identified in either the PAS or during the course of the appraisal.

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

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company 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 'Company evidence submission template'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

N/A – The population in the PAS is identical to the one presented in the main submission of evidence.

4.2 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.

The features of the updated economic analysis, as agreed with the ERG and Committee in prior Appraisal Committee Meetings, are summarised in Table 1.

We note that the ERG had concerns over the treatment effect duration of osimertinib for overall survival in the original economic model, and that the Committee agreed this effect was likely to be between 3 and 5 years. Therefore, in our revised economic analyses, we have presented cost-effectiveness results for both 3- and 5-year treatment effect duration of osimertinib for overall survival.

Table 1: Features of the economic scenario analyses presented in this Addendum

Feature	Economic scenarios presented in this Addendum	Comments
Primary data source	FLAURA	
Population	FLAURA ITT – EGFR+ NSCLC patients	
Intervention	Osimertinib	
Comparator	Gefitinib	Results for gefitinib using the existing PAS are provided. Both afatinib and erlotinib are available in the NHS with confidential discounts.
Time horizon	20 years	
Discount rate	3.5%	
PFS extrapolation	Generalised gamma dependent extrapolation	
OS extrapolation	Weibull piecewise extrapolation	
Time on treatment	Mean of [redacted] months	Modelled based on TDT (parametric [Generalised gamma]) in FLAURA
OS Treatment effect duration	Scenario 1: 3 year treatment effect duration on OS Scenario 2: 5 years treatment effect duration on OS	Revised cost-effectiveness results are presented for both 3- and 5-year treatment effect duration
Utility values	Progression-free health state utility value: 0.794 Progressed disease health state utility value: 0.678	
Healthcare resource use and unit costs	Sourced from BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care	
Osimertinib patient access scheme	A revised PAS and Commercial Access Agreement has been agreed with NHS England,	

Abbreviations: BNF, British National Formulary; CMU, Commercial Medicines Unit; EQ-5D, EuroQol 5-dimension Questionnaire; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; TDT, time to treatment discontinuation or death

4.3 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.

A revised PAS and Commercial Access Agreement has been agreed with NHS England.

The existing PAS for gefitinib (£12,200 on 3rd cycle of treatment with gefitinib) has been applied in both Table 2 and 3)

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

N/A - The clinical evidence used in the economic model is identical to the one presented in the main submission of evidence.

4.5 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 3.5 of the 'User guide for company evidence submission template'.

N/A

4.6 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.

N/A – there are no additional treatment-related costs incurred by implementing the PAS.

Summary results

Base-case analysis

4.7 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.

A suggested format is shown below.

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

Table 2: Base-case cost-effectiveness results (without PAS)

	Osimertinib	Gefitinib
3-year treatment duration effect		
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	
LYG	[redacted]	[redacted]
LYG difference	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER (£)	[redacted]	
5-year treatment duration effect		
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	
LYG	[redacted]	[redacted]
LYG difference	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER (£)	[redacted]	

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

Table 3: Base-case cost-effectiveness results (with PAS)

	Osimertinib	Gefitinib
3-year treatment duration effect		
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	
LYG	[redacted]	[redacted]
LYG difference	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER (£)	[redacted]	
5-year treatment duration effect		
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	
LYG	[redacted]	[redacted]
LYG difference	[redacted]	
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	
ICER (£)	[redacted]	

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

4.8 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

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

the incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 4: Base-case incremental results – without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
3-year treatment duration effect							
Osimertinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-year treatment duration effect							
Osimertinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Table 5: Base-case incremental results – with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
3-year treatment duration effect							
Osimertinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5-year treatment duration effect							
Osimertinib	[redacted]	[redacted]	[redacted]	-	-	-	-
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company submission of evidence for the technology appraisal. Consider using tornado diagrams.

The results of the deterministic sensitivity analyses are shown as tornado diagrams in Figure 1 for the 5-year treatment effect scenario, showing the 20 parameters with the largest impact on the ICER. The key drivers of the model results are: the relative treatment effect on TDT, health state utilities for progression-free and progressed disease, the proportion of patients receiving osimertinib in second-line, in addition to the duration of second-line treatment and costs. The same key drivers were identified in the deterministic sensitivity analysis for the 3-year duration of treatment effect scenario.

Figure 1: Tornado diagram – 5-year treatment effect duration

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

A PSA using 10,000 iterations was run using the base-case settings and the probability distributions described in the original submission.

The average results of all PSA iterations showed similar results as the base-case deterministic results. The total results were similar compared to the deterministic base-case setting for both overall survival treatment duration effect scenarios.

Table 6: Average results from the probabilistic sensitivity analysis

Technologies	Total costs (£)	Total QALYs	ICER (£) incremental (QALYs)
3-year treatment duration effect			
Osimertinib	[redacted]	[redacted]	-
Gefitinib	[redacted]	[redacted]	[redacted]
5-year treatment duration effect			
Osimertinib	[redacted]	[redacted]	-
Gefitinib	[redacted]	[redacted]	[redacted]

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

The cost-effectiveness planes (CEP) versus gefitinib for both overall survival treatment duration effect scenarios are presented in **Figure 2** and **Figure 3**, showing the incremental results of all the simulations of the PSA. Osimertinib is associated with higher costs but also higher QALYs than gefitinib in all simulations.

Figure 2: Cost-effectiveness acceptability plane – 3-year treatment effect

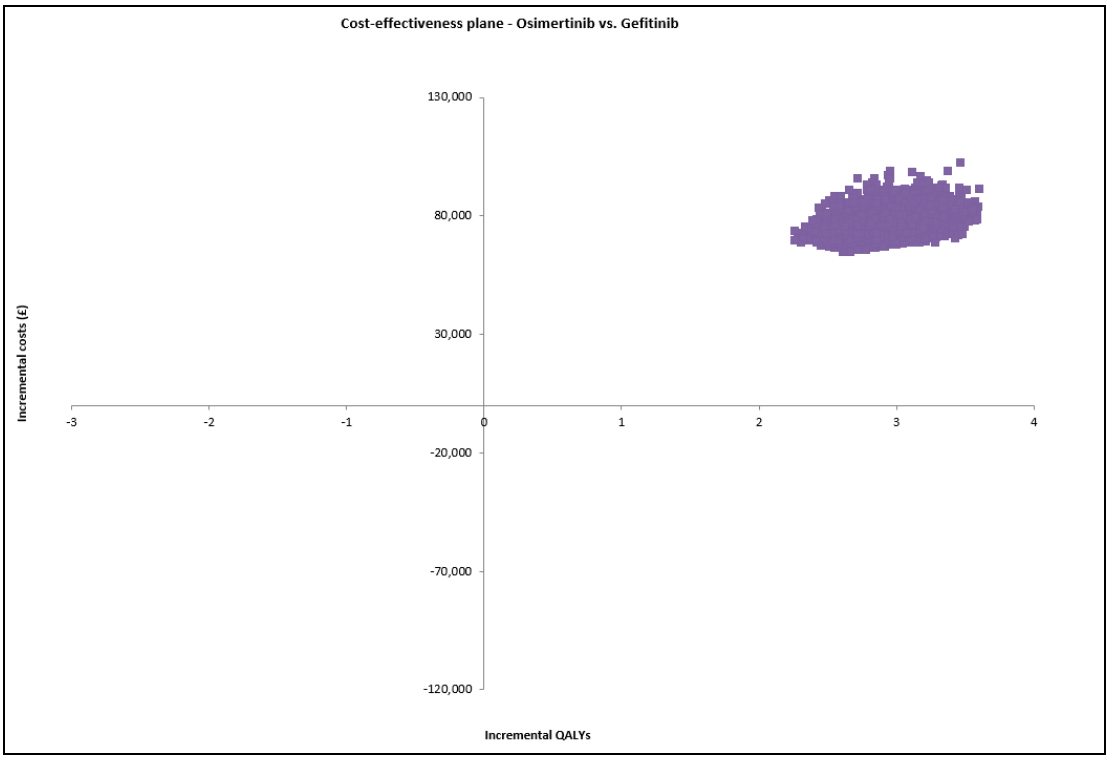
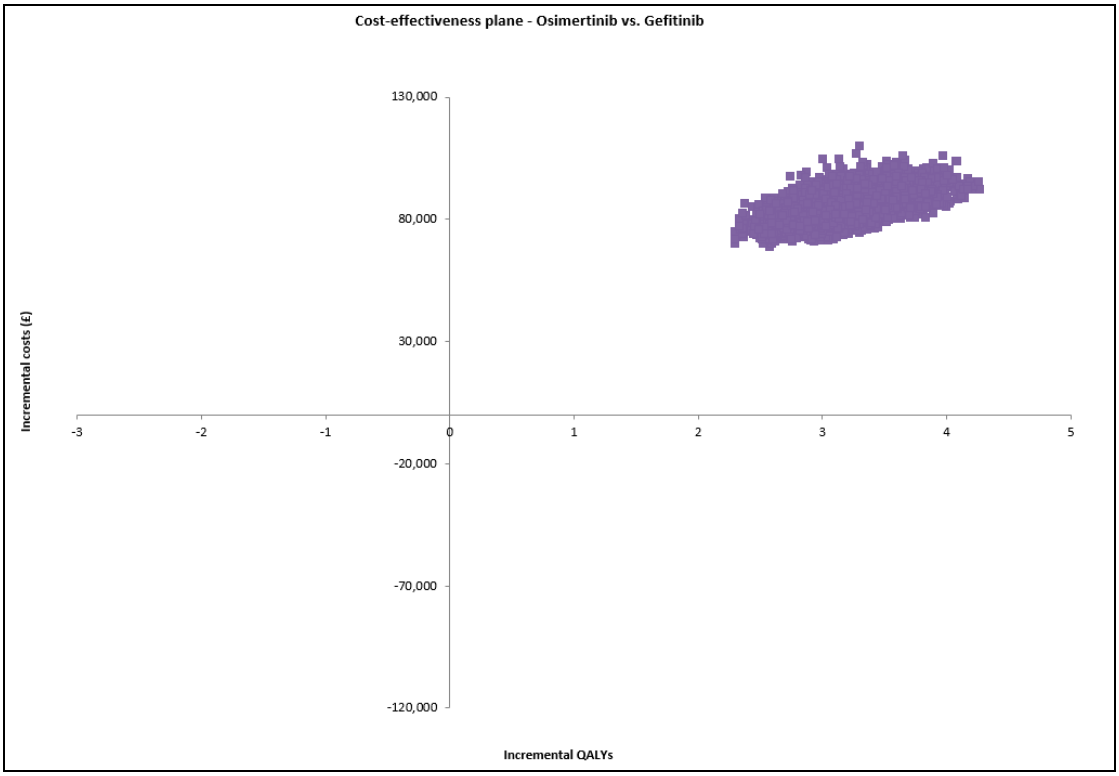


Figure 3: Cost-effectiveness acceptability plane – 5-year treatment effect



The cost-effectiveness acceptability curves (CEAC) are presented in **Figure 4** and **Figure 5**. The CEACs plot the probability that each comparator is cost-effective at a range of decision thresholds.

In the 3-year treatment effect scenario, osimertinib has a 40% probability of being cost-effective at a threshold of £30,000 and a 77% probability of being cost-effective at a threshold of £50,000. In the 5-year treatment effect scenario, osimertinib has the highest probability of being cost-effective at a threshold of £30,000 (61%) and a 90% probability of being cost-effective at a threshold of £50,000.

Figure 4: Cost-effectiveness acceptability curve – 3-year treatment effect

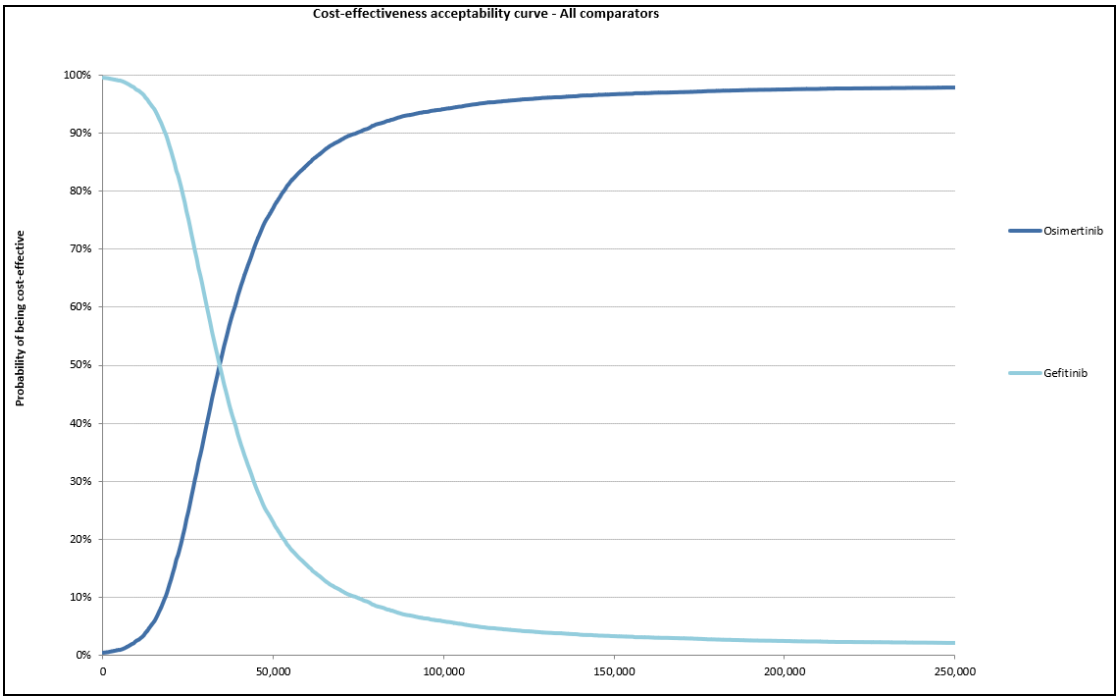
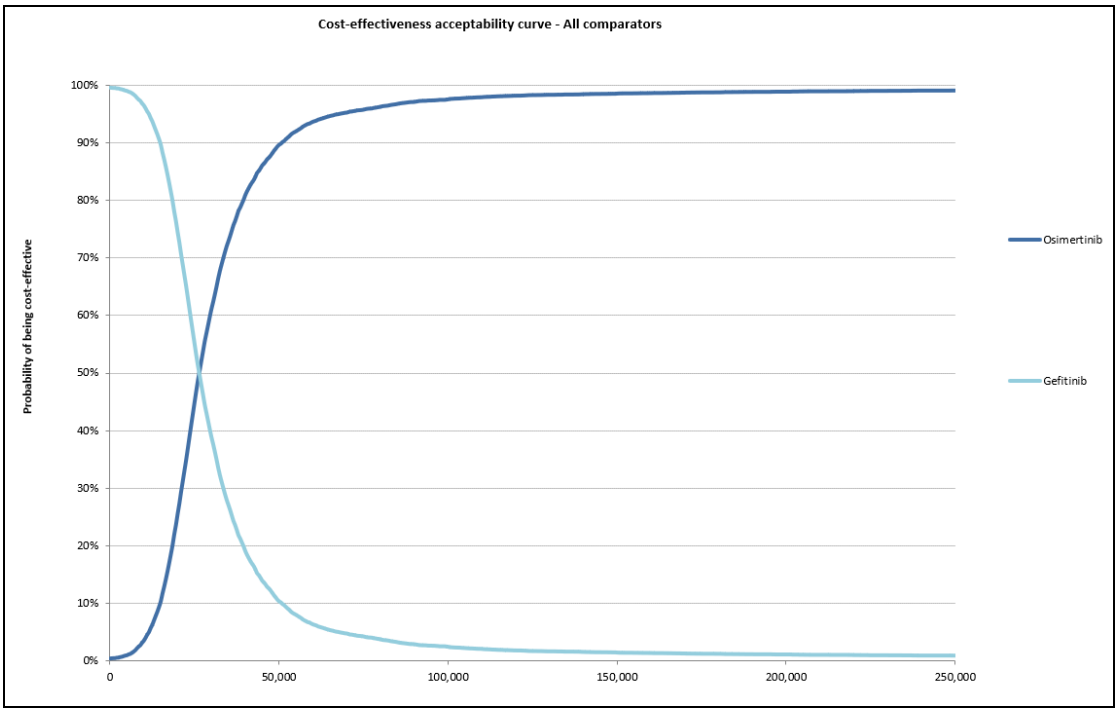


Figure 5: Cost-effectiveness acceptability curve – 5-year treatment effect



4.11 Please present scenario analysis results as described for the main company submission of evidence for the technology appraisal.

N/A

4.12 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.

N/A – clinical variables are not required for the operation of the PAS.

Impact of Patient Access Scheme on ICERs

4.13 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. 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.

Table 7: Results showing the impact of Patient Access Scheme & CAA on ICERs

	ICER for intervention versus:	
	Gefitinib	
	Without PAS	With PAS & CAA
3-year overall survival treatment effect duration	[redacted]	[redacted]
5-year overall survival treatment effect duration	[redacted]	[redacted]

PAS: Patient Access Scheme.

ERG RAPID REVIEW REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for untreated EGFR-positive non-small cell lung cancer [ID3786]

Rapid review including confidential discounted price for osimertinib and cap price for gefitinib

This report was commissioned by the NIHR Systematic Reviews Programme as project number NIHR 131771

Completed 14th July 2020

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

ALL DATA IN THIS APPENDIX ARE CONFIDENTIAL

1 INTRODUCTION

As part of the National Institute for Health and Care Excellence (NICE) Rapid Review to consider the clinical and cost effectiveness of osimertinib for treating previously untreated EGFR-positive non-small cell lung cancer, AstraZeneca (the company) provided a Patient Access Scheme (PAS) submission to NICE. The submission contained cost effectiveness results generated by an Excel based economic model that was a modified version of the model submitted for the original appraisal (TA621).

NICE asked the ERG to review the cost effectiveness results in the company PAS submission document and to check the accompanying model to ensure that:

- The PAS prices for osimertinib [redacted] had been applied appropriately
- The pairwise analyses for osimertinib versus gefitinib, afatinib, and erlotinib had been accurately calculated by the company using the Appraisal Committee's preferred assumptions (including use of specific costs and utility value for progressed disease and application of a 3-year and 5-year treatment waning effect for osimertinib).

The ERG was also asked to produce a full incremental analysis of the cost effectiveness of osimertinib versus gefitinib, afatinib and erlotinib.

After review of the company economic model that generated the cost effectiveness results presented in the PAS submission document, the ERG can confirm that the following were applied correctly in the model:

- The PAS price for osimertinib [redacted])
- Osimertinib 3-year and 5-year treatment waning effect
- Costs of the progressed disease health state and the progressed disease utility value.

The ERG highlights that the following was applied incorrectly in the model:

[redacted]

[redacted]The ERG has corrected the model for this error. In generating cost effectiveness results, the ERG has applied the relevant confidential PAS

discounts for [redacted], list prices for afatinib and erlotinib and the publicly available price cap for gefitinib.

Pairwise cost effectiveness results including a 3-year and 5-year treatment waning effect of osimertinib, following ERG corrections to the osimertinib [redacted] PAS discount, are shown in Tables 1-3. Fully incremental analyses are shown in Tables 4-5.

Table 1 Cost effectiveness results (osimertinib versus gefitinib) with PAS price for osimertinib (proposed) and price cap for gefitinib

Scenario/ERG amendment	Osimertinib			Gefitinib			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case (3-year waning)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
A1. ERG corrected base case (3-year waning)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. Company base case (5-year waning	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
B1. ERG corrected base case (5-year waning)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 2 Cost effectiveness results (osimertinib versus erlotinib) with PAS price for osimertinib (proposed) and list price for erlotinib

Scenario/ERG amendment	Osimertinib			Erlotinib			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case (3-year waning)	[redacted]	[redacted]	[redacted]	***£69,630***	***2.432***	***3.404***	[redacted]	[redacted]	[redacted]	[redacted]	
A1. ERG corrected base case (3-year waning)	[redacted]	[redacted]	[redacted]	**£59,827**	**2.432**	**3.404**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. Company base case (5-year waning	[redacted]	[redacted]	[redacted]	***£69,630***	***2.432***	***3.404***	[redacted]	[redacted]	[redacted]	[redacted]	
B1. ERG corrected base case (5-year waning)	[redacted]	[redacted]	[redacted]	**£59,827**	**2.432**	**3.404**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 3 Cost effectiveness results (osimertinib versus afatinib) with PAS price for osimertinib (proposed) and PAS price for afatinib

Scenario/ERG amendment	Osimertinib			Afatinib			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case (3-year waning)	[redacted]	[redacted]	[redacted]	***£76,984***	***2.432***	***3.404***	[redacted]	[redacted]	[redacted]	[redacted]	
A1. ERG corrected base case (3-year waning)	[redacted]	[redacted]	[redacted]	**£67,182**	**2.432**	**3.404**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. Company base case (5-year waning	[redacted]	[redacted]	[redacted]	***£76,984***	***2.432***	***3.404***	[redacted]	[redacted]	[redacted]	[redacted]	
B1. ERG corrected base case (5-year waning)	[redacted]	[redacted]	[redacted]	**£67,182**	**2.432**	**3.404**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 4 Fully incremental analysis with 3-year treatment waning effect and correct osimertinib [redacted] PAS

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER per QALY gained
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	
Erlotinib	£59,827	2.432	£11,166	0	Gefitinib dominates
Afatinib	£67,182	2.432	£18,521	0	Gefitinib dominates
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life; [redacted]

Table 5 Fully incremental analysis with 5-year treatment waning effect and correct osimertinib [redacted] PAS

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER per QALY gained
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	
Erlotinib	£59,827	2.432	£11,166	0	Gefitinib dominates
Afatinib	£67,182	2.432	£18,521	0	Gefitinib dominates
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life; [redacted]

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer [ID3786]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Wednesday 22 July** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Incorrect use of osimertinib discounts

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The ERG highlights (on page 2) that the PAS price for osimertinib [redacted] is a [redacted] discount	The corrected discount amount should read [redacted]	The agreed rebated amount as part of the CDF arrangement is [redacted]	As far as we know, this is not a factual error. The NICE team is currently considering which [redacted] price to apply in the model.
The ERG highlights (on page 2) that the following was applied incorrectly in the model: • [redacted] The ERG has corrected the model for this error. In generating cost effectiveness results, the ERG has applied the relevant confidential PAS discounts for osimertinib ([redacted], [redacted] (proposed)), list prices for afatinib and erlotinib and the publicly available price cap for gefitinib.	The outputs of the ERG's "corrected model" should be discarded as irrelevant.	The modelling approach for this appraisal needs to reflect the NICE decision problem agreed for TA621 whereby: 1. **Osimertinib subsequent treatment is included in the cost-effectiveness model, despite it being CDF-funded.** Appraisal TA621 commenced before the Jan 2019 amendment to NICE's position statement on the approach to CDF products as comparators, or in a treatment sequence. As such the appropriate modelling approach is to include osimertinib as a subsequent treatment. 2. [redacted]	As far as we know, this is not a factual error. The NICE team is currently considering which [redacted] price to apply in the model.

NHS England submission July 2020: osimertinib 1st line systemic therapy for EGFR mutated locally advanced/metastatic non small cell lung cancer

[redacted]

Patient-related issues which may not have been fully captured in the health economic analysis

1. NHS England observes that long durations of continuous therapy of TKIs are used in the treatment of EGFR-mutated NSCLC therapy and thus considers that the drug-induced chronic low grade drug toxicities (grades 1 and 2 and which are not usually incorporated into health economic analysis) have increased significance for patients. NHS England therefore believes that there are a number of reasons why the health economic analysis and modelling in this appraisal underestimate the benefits of osimertinib against the comparators of afatinib, erlotinib and gefitinib when their respective side-effects are considered:
   - osimertinib is much better tolerated than afatinib in terms of diarrhoea. Any grade diarrhoea occurs in 60% of patients with osimertinib versus 80-90% with afatinib and most of the affected patients suffer grade 1 or 2 diarrhoea)
   - osimertinib is better tolerated than erlotinib or gefitinib or afatinib in terms of skin rash (any grade rash occurs in 60% with osimertinib versus 70-80% for the 3 comparators and nearly all of the osimertinib-affected patients have grade 1 or 2 skin toxicity)
   - osimertinib therefore results in fewer clinic visits and reduced calls to specialist nurses for the side-effects of treatment to be managed when compared with afatinib, erlotinib or gefitinib.
2. The development of brain metastases occurs in at least 50% of patients with EGFR-mutated NSCLC and is associated with all or many of the very considerable morbidities of:
   - neurological impairment
   - the side-effects of long term and frequently high dose steroids
   - the inconvenience and toxicity of cerebral radiotherapy
   - reduced independence of living
   - and the inability to drive.

   These impacts on quality of life may not be captured in the utility figures in the appraisal because such patients do not usually contribute to quality of life data collection. Osimertinib crosses the blood brain barrier better than the other EGFR-targeted drugs and thus reduces the development of de novo cerebral metastases (in the FLAURA trial, the figure for osimertinib was 6% vs 15% for erlotinib/gefitinib). This difference may not have been fully captured in the modelling of quality of life.
3. The comparators erlotinib and gefitinib have to be taken on an empty stomach whereas osimertinib does not. This makes the taking of osimertinib by patients a much more convenient process. This may sound a minor issue but is one commented on by patients who have had 1st line TKI and then have 2nd line osimertinib.
4. Osimertinib via the CDF has been allowed as a 2nd line treatment in the comparator arm in this appraisal. This use is only for those patients that carry a T790M mutation in their recurrent lung cancer and diagnostic demonstration of this usually requires a bronchoscopy to gain tissue for genomic analysis. For patients progressing on erlotinib/gefitinib/afatinib,

second bronchoscopies are unpleasant procedures for patients (the 'once bitten, twice shy' effect) and in addition, such procedures are often relegated in terms of importance in diagnostic services wishing to prioritise the bronchoscopy of new patients with potential lung cancers (hence cancellations and delays of second bronchoscopies occur). The use of 1st line osimertinib removes the need for bronchoscopic biopsies at relapse. It is likely that whilst the costs of bronchoscopic biopsies will have been included in the cost-effectiveness analyses, the impact on the patients and the lung cancer diagnostic services have not.

Patient and clinician enthusiasm for 1st line osimertinib

[redacted]

[redacted]

[redacted]

[redacted]

NHS England [redacted]

July 2020