Cancer Drugs Fund Review

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer [1559]

Cancer Drugs Fund update of TA416

This report was commissioned by the NIHR Systematic Reviews Programme as project number 129027

Completed 29 November 2019

DOES CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title:	Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer [ID1577] (Cancer Drug Fund update of TA416)
Produced by:	Liverpool Reviews & Implementation Group (LR*i*G)
Authors:	Sophie Beale, Research Associate, LR*i*G, University of Liverpool
	Rachel Houten, Health Economic Modeller, LR*i*G, University of Liverpool
	Angela Boland, Director, LR*i*G, University of Liverpool
	James Mahon, Director, Coldingham Analytical Services, Berwickshire
	Marty Chaplin, Medical Statistician, LR*i*G, University of Liverpool
Correspondence to:	Rachel Houten, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB
Date completed:	29 November 2019

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number 129027.

Declared competing interests of the authors: None.

Acknowledgements: The authors would like to thank Dr John Green, Consultant in Medical Oncology, The Clatterbridge Centre NHS Foundation Trust, Liverpool who provided feedback on the final version of the report.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Beale S, Houten R**,** Boland A, Mahon J, Chaplin M. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-

positive non-small cell lung cancer [ID1577]: Cancer Drugs Fund update of TA416. Liverpool Reviews and Implementation Group, University of Liverpool, 2019.

Contributions of authors:

Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Rachel Houten	Critical appraisal of the economic evidence
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
James Mahon	Critical appraisal of the economic evidence
Marty Chaplin	Critical appraisal of the statistical evidence

Table of contents

List of tables

List of figures

LIST OF ABBREVIATIONS

AC	Appraisal Committee
AE	Adverse event
AF	Acceleration factor
AUC	Area under the curve
AURA	Clinical programme of trials assessing the clinical effectiveness of osimertinib
BSA	Body surface area
CDF	Cancer Drugs Fund
CI	Confidence interval
CS	Company submission
ctDNA	circulating tumour DNA
DC	Data-cut
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EGFR (-TKI)	Epidermal growth factor receptor (tyrosine kinase inhibitor)
EGFRm+	EGFR mutation-positive
EMA	European Medicines Agency
EORTC	European Organisation for the Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions Questionnaire
ERG	Evidence Review Group
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
IMPRESS	Iressa Mutation-Positive Multicentre Treatment Beyond Progression Study
IPCW	Inverse Probability of Censoring Weighting
IPD	Individual patient data
K-M	Kaplan-Meier
MAIC	Matching-adjusted indirect comparison
NICE	National Institute of Health and Care Excellence
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressed disease
PDC	Platinum doublet chemotherapy
PF	Progression-free
PFS	Progression-free survival
PH	Proportional hazards
PHE	Public Health England
PS	Performance status
PSS	Personal and Social Services
QALY	Quality adjusted life year
RPFSTM	Rank Preserving Failure Structural Time Model
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
T790M	Secondary mutation of the EGFR
ToE	Terms of Engagement
TTD	Time to treatment discontinuation

1 EXECUTIVE SUMMARY

In October 2016, the outcome of National Institute for Health and Care Excellence (NICE) Technology Appraisal TA416 was that osimertinib was recommended as an option for use within the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) in adults whose disease had progressed after first-line treatment with an EGFR-tyrosine kinase inhibitor (TKI).

To inform TA416, the company provided evidence from the AURAext and AURA2 trials. These two single-arm trials were designed to assess the clinical effectiveness of osimertinib in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who had received treatment with an EGFR-TKI prior to recruitment. Patients in the AURAext and AURA2 studies had received between 1 and 14 prior anti-cancer treatments, including an EGFR-TKI. The data used to inform the comparison of the effectiveness of osimertinib versus platinum doublet chemotherapy (PDC) were obtained from a subgroup of patients included in the control arm of the IMPRESS trial whose tumours were identified retrospectively as having the EGFR T790M mutation. These patients had received placebo+pemetrexed+cisplatin.

The availability of final overall survival (OS) data from the AURA3 trial (osimertinib versus PDC) has triggered this review of the evidence. To inform this CDF review, as well as updated AURAext, AURA2 and AURA3 trial results, the company has also provided results from two sets of data extracted from the Systemic Anti-Cancer Therapy (SACT) dataset: (i) patients treated with osimertinib via the CDF and (ii) patients who received an EGFR-TKI as first-line therapy.

This Evidence Review Group (ERG) report focuses on the key issues outlined in the final Terms of Engagement (ToE) document issued by NICE. The ToE, although not binding, outlines NICE's expectations relating to the content of the company submission (CS) for the CDF review.

1.1 Population

The NICE Appraisal Committee's (AC) preferred population was adults with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. This matches the population recruited to the AURAext and AURA2 trials. However, the population recruited to the AURA3 trial was a subset of this population, namely patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR-TKI therapy.

The AURA3 trial population matches the population described in the company Managed Access Agreement.

1.2 Comparators

The NICE AC's preferred comparator was PDC.

The AURAext and AURA2 trials are single-arm studies. The company generated comparator data through the use of a matching-adjusted indirect comparison (MAIC). The initial step of this technique involved matching baseline characteristics of patients in the AURAext and AURA2 trials with those of patients in the comparator arm of the IMPRESS trial (placebo+pemetrexed+cisplatin).

Direct evidence for the effectiveness of osimertinib versus PDC was available from the AURA3 trial (osimertinib versus pemetrexed+carboplatin or pemetrexed+cisplatin).

1.3 Generalisability

The NICE AC concluded that the AURAext and AURA2 trials were broadly generalisable to clinical practice.

The ERG considers that whilst patient characteristics and the magnitude of key outcomes from all three AURA trials are similar, the generalisability of this evidence to clinical practice is unclear because of differences between trial and Systemic Anti-Cancer Therapy (SACT) dataset survival results, the latter being considerably lower than trial results. The reasons for the large discrepancies are unknown.

1.4 Overall survival

The NICE AC concluded that whilst it was reasonable to pool data from the AURAext and AURA2 trials, the data were too immature to robustly estimate the OS advantage of treatment with osimertinib versus PDC.

The latest pooled AURAext/AURA2 trial and AURA3 trial median OS results for patients receiving osimertinib as a second-line treatment are similar (median=26.5 months and 26.8 months respectively). Results from the AURA3 trial show that, for the comparison of treatment with osimertinib versus PDC, OS is not statistically significantly different. However, patients randomised to the PDC arm of the AURA3 trial were permitted to switch treatments after disease progression and 71% of patients randomised to the PDC arm received osimertinib in this way (i.e., crossed over). As treatment with osimertinib is not currently recommended by NICE (or available via the CDF) for use as a >second-line therapy, use of ostimertinib as a third-line treatment does not reflect current NHS practice. The company considered three

different approaches to removing the effect of crossover on OS estimates for patients randomised to receive PDC and concluded that the RPFSTM method was the most appropriate. The ERG considers that it is unclear which of these three methods would produce the most valid estimates of treatment effect and highlights the very high level of patient crossover (71%) in the AURA3 trial. The company chose to generate results using six variants of the Rank Preserving Structural Failure Time Model (RPSFTM). The hazard ratio results generated by these methods ranged from [redacted]. It is not known whether one of the RPFSTM crossover adjustment methods provides more realistic results than any of the others.

The company's AURA3 trial median crossover adjusted OS estimates for patients receiving PDC ranged from [redacted] months to [redacted] months. In contrast, median OS for patients from the IMPRESS trial who were matched with patients in the AURAext and AURA2 trials was 14.1 months and the median OS calculated from SACT data collected from NHS patients who had received initial treatment with an EGFR-TKI and went on to receive a subsequent anti-cancer treatment was 8.31 months.

1.5 Summary of key issues in clinical effectiveness evidence

The AURA3 trial provides direct evidence of the effectiveness of osimertinib versus PDC for patients who have only previously been treated with an EGFR-TKI. Survival results from the AURA3 trial support results from the pooled AURAext/2 dataset. Nearly three-quarters (71%) of patients in the PDC arm of the AURA3 trial crossed over to receive osimertinib on progression. The company considers that the RPSFTM is the most appropriate method to use to adjust for the effect of crossover. The ERG considers it is not possible to choose a 'best' method of crossover adjustment.The company has presented crossover adjusted results generated by six variants of the RPFSTM. All methods generate hazard ratios with [redacted]. It is not possible to determine which of the RPFSTM methods generates the most realistic results. The company's PDC base case median crossover adjusted OS result was more optimistic that results from the company's adjusted indirect comparison or from the SACT data (medians: [redacted]14.1 and 8.31 months respectively). These differences cast uncertainty on the generalisability of results from the three AURA trials to NHS clinical practice.

1.6 Summary of key issues in cost effectiveness evidence

Two models are included in the CDF Review CS (Model A and Model B). The basic structure of Models A and B and the model submitted as part of the TA416 CS were the same. Model A differed from that submitted as part of the TA416 CS only in that it included estimates of OS, PFS and TTD from the most up to date pooled AURAext/2 data. The key differences between Model A and Model B were that Model A was populated with OS, PFS and TTD estimates from the most up to date pooled AURAext/2 dataset whilst Model B was populated with OS, PFS and TTD estimates from the most up to date AURA3 trial data.

During TA416 the company concluded that the most likely utility estimates fell between optimistic values used by the company (derived from data collected during the AURA2 trial) and less optimistic values derived from data collected during the LUME-Lung 1 trial. Health-related quality of life data were collected as part of the AURA3 trial. Utility values derived from these data are very similar to the AURA2 values.

1.7 Summary of exploratory and sensitivity analysis undertaken by the ERG

Following discussion with the NICE technical team, the ERG created a hybrid model (Model A/B) which meets the ToE for this review better than either Model A or Model B. Model A/B has been constructed by replacing the OS, PFS and TTD data in Model A with OS, PFS, TTD data from the AURA3 trial (Model B). Using the CAA price for treatment with osimertinib and list prices for pemetrexed and cisplatin, the ERG has made four amendments to Model A/B, namely revised OS, PFS and TTD estimates (generated using AURA3 trial data) and use of the LUME-Lung 1 trial utility values. The ERG has also presented results from two scenarios:

- Scenario 1: changes to OS, PFS and TTD
- Scenario 2: changes to OS, PFS, TTD and using LUME-Lung 1 trial[1] utility values.

Model A/B base case results and results from these two scenarios are provided in the table below.

Exploratory analyses undertaken by the ERG

ERG amendment/scenario	Incremental			*ICER*	
	Cost	Life years	QALYs	£/QALY	Change from base case
A. Model A/B base case	£68,792	1.030	0.817	£84,209	
Scenario 1: R1)+R2)+R3)	£66,011	1.106	0.897	£73,565	-£10,644
Scenario 2: R1)+R2)+R3)+R4)	£66,011	1.106	0.719	£91,812	£7,602

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

1.8 End of Life

The NICE End of Life criteria are:

- treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The company's AURA3 crossover adjusted median OS estimates for patients receiving PDC ranged from [redacted] months to [redacted] months. The company's and ERG mean estimates of OS for patients receiving PDC from their modelling of OS from AURA3 trial data are [redacted] and [redacted] months respectively. The ERG therefore considers that the short life expectancy criterion is met.

A comparison of the company's AURA3 trial crossover adjusted median OS results show the difference between treatment with osimertinib and PDC to be a minimum of [redacted] months and a maximum of [redacted] months. From the company's modelling of AURA3 data, mean estimates of OS are [redacted] months for osimertinib and [redacted] months for PDC. The ERG's revised mean estimates of OS are [redacted] months for osimertinib and [redacted] months for PDC. The ERG therefore considers that the life extension criterion is met.

2 BACKGROUND

2.1 Introduction

In October 2016, osimertinib was recommended by the National Institute for Health and Care Excellence (NICE) as an option for use within the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) in adults whose disease had progressed:

- after first-line treatment with an EGFR-tyrosine kinase inhibitor (TKI) and
- if the conditions in the Managed Access Agreement (MAA)[2] for osimertinib were followed.

It is stated within the CDF review CS (Appendix 3),[3] that representatives from NHS England, NICE, Public Health England (PHE) and the company (AstraZeneca) formed a working group to agree the:

- eligibility criteria for patient access to osimertinib through the CDF
- the real-world data to be collected and analysed to support the CDF review
- CDF entry and exit dates.

The availability of final overall survival (OS) data from the AURA3 trial[3] has triggered this review of the evidence. This Evidence Review Group (ERG) report focuses on the key issues outlined in the final Terms of Engagement (ToE) document[4] issued by NICE. The ToE,[4] although not binding, outlines NICE's expectations relating to the content of the company submission (CS) for the CDF review.

2.2 Osimertinib

Key facts about osimertinib:

- Indicated for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC
- Testing to confirm the presence of the EGFR T790M mutation is necessary prior to treatment initiation
- Approval by the European Medicines Agency (EMA) for the treatment of adult patients with locally advanced or metastatic EGFR T790 mutation-positive NSCLC was granted on 17 December 2015[5]
- Available as 40mg or 80mg tablets
- The recommended dose is 80mg once a day until disease progression or unacceptable toxicity
- Available to the NHS at a discounted price via a Commercial Access Agreement (CAA).[2]

2.3 Testing for the EGFR T790M mutation in the NHS

It is necessary to confirm the presence of the EGFR T790M mutation prior to treatment with osimertinib. EGFR mutation status can be confirmed by two types of test: (i) using either tumour deoxyribonucleic acid (DNA), derived from a tissue sample, or (ii) circulating tumour DNA (ctDNA), obtained from a plasma sample. Clinical advice to the ERG is that plasma testing for T790M mutations at relapse is now widely available but concerns remain about false negative results. A number of different tests are available and the technology continues to evolve. However, in the event of a negative plasma DNA test, not all patients are suitable for rebiopsy on account of tumour location or patient fitness.

3 THE CLINICAL DECISION PROBLEM

The NICE AC's preferred clinical assumptions (as set out in the Terms of Engagement document)[4] are presented in Table 1. Further information relating to each assumption is provided in the text following the table.

Table 1 NICE Appraisal Committee's preferred clinical assumptions

Area	Summary of NICE Appraisal Committee's preferred assumptions
Population	*Adults with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.*
Comparators	*Platinum doublet chemotherapy was the most relevant comparator for this appraisal.*
Generalisability	*The trials used as the basis for evaluating the efficacy of osimertinib in people with EGFR T790M mutation-positive NSCLC that has progressed on a previous TKI were broadly generalisable to clinical practice.*
Overall survival	*Pooling the results for the two AURA trials was reasonable given that the studies were very similar regarding baseline characteristics.* *The available data were too immature to robustly estimate the overall survival advantage of osimertinib compared with platinum doublet chemotherapy.*

EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; OS=overall survival; TKI=tyrosine kinase inhibitor
Source: NICE 2018[4]

3.1 Population

Box 1 NICE Appraisal Committee's preferred assumption: population

The NICE AC considered that the population should be adults with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Source: NICE 2018[4]

The NICE AC's preferred population matches the population recruited to the AURAext and AURA2 trials.[6] However, the population recruited to the AURA3 trial was a subset of this population, namely patients with locally advanced or metastatic NSCLC whose disease had progressed after first-line EGFR-TKI therapy and who tested positive for an EGFR mutation with the T790M variant. The ERG notes that the population described in the MAA[2] is the same population as that recruited to the AURA3 trial.

The baseline characteristics of the population recruited to the AURA3 trial are similar to those of patients who were recruited to the AURAext and AURA2 trials (Table 3). The ERG highlights that:

- Clinical advice to the ERG is that patients with EGFR mutation-positive (EGFRm+) disease who are treated in the NHS are typically aged between 65 years and 70 years and the majority are of Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 1 or 2.
    - Patients participating in the AURA trials are younger (median: 62-63 years) and fitter (ECOG PS 0 or 1) than EGFRm+ patients treated in the NHS.
    - Patients participating in the IMPRESS trial are also younger (mean age of 58.1 years) and fitter (ECOG PS 0 or 1) than EGFRm+ patients treated in the NHS.
- Whilst all patients recruited to the AURA3 trial received osimertinib in the second-line setting (after an EGFR-TKI), 12.4% of patients recruited to the AURAext and AURA2 studies had received more than five lines of prior treatment. Clinical advice to the ERG is that the majority of patients treated in the NHS are not well enough to tolerate more than one or two chemotherapy treatments after a first-line EGFR-TKI.

Table 2 Baseline characteristics of patients participating in the three AURA trials

Demographic characteristic		Trial			
		Pooled AURAext/2		AURA3	
Indication		≥Second-line	Second-line	Second-line	
Treatment		Osimertinib	Osimertinib	Osimertinib	PDC
Number of patients		411	92	279	140
Age (years)	Mean (SD)	62.2 (11)	61.8 (11)	61.5 (12)	62 (12)
	Median (min-max)	63 (35-89)	60 (36-89)	62 (25-85)	63 (20-90)
	% ≥65 years	187 (46)	36 (39)	114 (41)	63 (45)
Sex n (%)	Male	132 (32)	32 (35)	107 (38)	43 (31)
	Female	279 (68)	60 (65)	172 (62)	97 (69)
Smoking n (%)	Never	284 (69)	63 (69)	189 (68)	94 (67)
	Ever	114 (28)	29 (31)	76 (27)	38 (27)
	Current	7 (2)	0 (0)	14 (5)	8 (6)
EGFR mutation n (%)	Exon 19 deletion	279 (68)	67 (73)	191 (68)	87 (62)
	L858R in exon 21	118 (29)	23 (25)	83 (30)	45 (32)
	Other	14 (3)	NR	6 (<3)	5 (3)
ECOG / WHO PS n (%)	0	152 (37)	43 (47)	103 (37)	56 (40)
	1	258 (63)	49 (53)	117 (63)	84 (60)
	2	1 (<1)	0 (0)	0 (0%)	0 (0)
	3	0 (0%)	0 (0)	0 (0%)	0 (0)
	4	0 (0%)	0 (0)	0 (0%)	0 (0)
	0–1	410 (100)	92 (100)	279 (100)	140 (100)
	2–4	1 (<1)	0 (0)	61.5 (12)	0 (0)
Metastatic at baseline n (%)		395 (96)	86 (94)	266 (95)	138 (99)
Brain metastatic at baseline n (%)		166 (40)	23 (25)	93 (33)	51 (36)
Race n (%)	White	149 (36)	36 (39)	89 (32)	45 (32)
	Asian	247 (60)	55 (60)	182 (65)	92 (66)
	Other	15 (4)	1 (1)	8 (3)	3 (2)

ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; NR=not reported; PDC=platinum doublet chemotherapy; PS=performance status; SD=standard deviation; TKI=tyrosine kinase inhibitor
Source: Company response to clarification[7]

3.2 Comparators

Box 2 Appraisal Committee's preferred assumption: comparators

The NICE AC considered that platinum doublet chemotherapy was the most relevant comparator.

Source: NICE 2018[4]

The AURAext and AURA2 trials are single-arm studies. To generate comparator data for TA416,[6] the company carried out a matching-adjusted indirect comparison (MAIC 1). This technique included matching baseline characteristics of patients recruited to the control arm

of the IMPRESS trial[8] who were identified retrospectively as having the EGFR T790M mutation with those of patients recruited to the AURAext and AURA2 trials. The IMPRESS trial was designed to compare the efficacy of gefitinib+pemetrexed+cisplatin versus placebo+pemetrexed+cisplatin (placebo+PDC). MAIC 1 included data from 129 patients recruited to the AURAext and AURA2 trials and a maximum of 61 patients recruited to the IMPRESS trial.

As part of their response[9] to the NICE Appraisal Consultation Document,[10] the company provided results from a MAIC that only included data relating to patients receiving second-line treatment (henceforth referred to as MAIC 2). Following cohort balancing, MAIC 2 included data from 92 patients treated with osimertinib and 53 patients treated with PDC. The ERG's primary concerns relating to MAIC 1[11] and MAIC 2[12] were the small numbers of patients and the immaturity of the pooled AURAext/2 data (data-cut [DC] 04).

The company has submitted MAIC 3 (an updated MAIC 2) as part of the CDF Review CS. MAIC 3 includes mature pooled AURAext/2 data (DC05, 60.9% of OS events had occurred). MAIC 2 and MAIC 3 OS results are provided in Table 3. The ERG considers that the maturity of the data renders results from MAIC 3 more credible than those from MAIC 2; however, confidence in the generalisability of the MAIC 3 results is still limited by the size of the patient populations in the intervention and comparator arms.

Table 3 Company MAIC overall survival results (adjusted)

Treatment	N	Patients with events, n (%)	Median OS (months)	Treatment effect		
				HR	95% CI	Two-sided p-value
MAIC 2						
Osimertinib	92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo+PDC	53	[redacted]	14.1			
MAIC 3						
Osimertinib	92	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo+PDC	53	[redacted]	14.1			

CI=confidence interval; n=number; HR=hazard ratio; N=number; MAIC=matching-adjusted indirect comparison; OS=overall survival; PDC=platinum doublet chemotherapy
Source: Company response to TA416 ACD (Table 1)[9] and CDF Review CS (Appendix 7, Table 4)[3]

The AURA3 trial included a comparator PDC arm. Patients included in this arm were treated with intravenous pemetrexed (500mg/m^2 of body surface area) plus either carboplatin (target area under the curve 5 [AUC5]) or cisplatin (75mg/m^2) every 3 weeks for up to six cycles. Patients without disease progression after four cycles of platinum therapy plus pemetrexed could continue maintenance pemetrexed according to the approved label. Clinical advice to the ERG is that this treatment reflects standard of care in the NHS.

3.3 Generalisability

Box 3 NICE Appraisal Committee's preferred assumption: generalisability

The NICE AC concluded that the AURAext and AURA2 trials were broadly generalisable to clinical practice.

Source: NICE 2018[4]

Clinical advice to the ERG is that results from the AURA trials are broadly generalisable to NHS clinical practice. However, the ERG considers that the generalisability of evidence from the three AURA trials to clinical practice is unclear because of differences between trial and Systemic Anti-Cancer Therapy (SACT) dataset survival results, the latter being considerably lower than might be expected. Key information about the the three AURA trials is included in the remainder of this section and details relating to the SACT data are provided in Section 3.4.1.

3.3.1 The three AURA trials

The AURAext and AURA2 trials are both single-arm trials that provide evidence for the effectiveness of osimertinib as a treatment following failure on an EGFR-TKI. Data from these two trials were used to inform TA416[6] and critiques of these two trials were included in the ERG report (dated April 2016)[11] for that appraisal. In April 2016, the ERG concluded that the AURAext and AURA2 trials were designed and conducted to a good standard, but highlighted that data from single-arm studies are difficult to interpret due to the lack of a comparator arm and may be subject to unplanned (and unrecognised) bias and confounding.[11]

Data from the AURA3 trial were not available to inform TA416[6]; however, the company has been able to provide mature data from this trial to inform this CDF review. Unlike a Single Technology Appriaisal (STA), the CDF review process does not include a full critique of new trials. However, the ERG considers that the information about the trial that has been provided by the company gives no cause to consider that the AURA3 trial has not been designed and conducted to a good standard.

The baseline characteristics of patients recruited to the AURA3 trial are very similar to those of patients participating in the AURAext and AURA2 trials (see Table 2). Key results are also very similar (see Table 4). These similarities, combined with similar adverse event (AE) incidence data (Table 5 and Table 6) suggest that results from the AURA trials are robust. The ERG highlights that the incidences of AURA3 trial AEs tend to be slightly lower than pooled AURAext/2 dataset incidence rates, perhaps reflecting the fact that patients participating in the AURA3 trial were less heavily pre-treated than most patients participating in the AURAext and AURA2 trials.

Table 4 Key results from the three AURA trials and the IMPRESS trial (MAIC 3 population)

Outcome		Trial				
		Pooled AURAext/2		IMPRESS	AURA3	
Indication		≥Second-line	Second-line	Second-line	Second-line	Second-line
Treatment		Osimertinib	Osimertinib	Placebo+ PDC	Osimertinib	PDC
Number of patients		411	92	53	279	140
ORR	Patients with responses n (%)	262/397 (66.1)	[redacted]	-	[redacted]	[redacted]
PFS	Total events n (%)	280 (68.1)	64 (69.6)	-	140 (50.2)	110 (78.6)
	Median months (95% CI)	9.9 (9.5 to 12.3)	9.7 (Not provided)	5.3	10.1 (8.3 to 12.3)	4.4 (4.2 to 5.3)
OS	Total events n (%)	271 (65.9)	[redacted]	[redacted]	188 (67.4)	93 (66.4)
	Median months (95% CI)	26.3 (24.0 to 29.1)	[redacted]	[redacted]	26.81 (23.5 to 31.5)	22.47 (20.2 to 28.8)

CDF=Cancer Drugs Fund; CS=company submission; ORR=overall response rate; OS=overall survival; PDC=platinum doublet chemotherapy; PFS=progression-free survival
Sources: Company CDF Review clarification response[7] and TA416 CS[6]

Table 5 Adverse event data from the three AURA trials (safety analysis set)

AE category	Pooled AURAext/2	AURA3	
	Osimertinib	Osimertinib	PDC
	Number (%) of patients[a]		
Sample size	411	279	136
Patients with any AE	[redacted]	[redacted]	[redacted]
CTCAE ≥Grade 3 AEs	[redacted]	[redacted]	[redacted]
SAEs	[redacted]	[redacted]	[redacted]
AE with outcome of death	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]
AEs leading to dose modification	[redacted]	[redacted]	[redacted]

[a]Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events version 4.0; MedDRA version 17.1; SAE=serious adverse event
Source: CDF Review CS

Table 6 Adverse events occurring in ≥10% of AURA3 trial patients who received osimertinib

Trial	**Pooled AURAext/2***		**AURA3****			
CTCAE grade AE	**Any grade n (%)**	**Grade≥3 n (%)**	**Any grade n (%)**	**Grade≥3 n (%)**	**Any grade n (%)**	**Grade≥3 n (%)**
Treatment	Osimertinib		Osimertinib		PDC	
Indication	≥Second-line		Second-line		Second-line	
Number of patients	411		279		136	
Diarrhoea	[redacted]	[redacted]	123 (44)	3 (1)	15 (11)	2 (1)
Rash	[redacted]	[redacted]	94 (34)	2 (1)	8 (6)	0 (0)
Dry skin	[redacted]	[redacted]	65 (23)	0 (0)	4 (6)	0 (0)
Paronychia	[redacted]	[redacted]	61 (22)	0 (0)	2 (1)	0 (0)
Decreased appetite	[redacted]	[redacted]	50 (18)	3 (1)	49 (36)	4 (3)
Cough	[redacted]	[redacted]	60 (21)	0 (0)	19 (14)	0 (0)
Nausea	[redacted]	[redacted]	45 (16)	2 (1)	67 (49)	5 (4)
Fatigue	[redacted]	[redacted]	44 (16)	3 (1)	38 (28)	1 (1)
Stomatitis	[redacted]	[redacted]	41 (15)	0 (0)	21 (15)	2 (1)
Constipation	[redacted]	[redacted]	39 (14)	0 (0)	47 (35)	0 (0)
Pruritus	[redacted]	[redacted]	35 (13)	0 (0)	6 (4)	0 (0)
Vomiting	[redacted]	[redacted]	31 (11)	1 (<1)	27 (20)	3 (2)
Back pain	[redacted]	[redacted]	29 (10)	1 (<1)	12 (9)	1 (1)
Thrombocytopenia	[redacted]	[redacted]	28 (10)	1 (<1)	27 (20)	10 (7)
Nasopharyngitis	[redacted]	[redacted]	28 (10)	0 (0)	7 (5)	0 (0)
Headache	[redacted]	[redacted]	28 (10)	0 (0)	15 (11)	0 (0)
Dyspnea	[redacted]	[redacted]	24 (9)	3 (1)	18 (13)	0 (0)
Neutropenia	[redacted]	[redacted]	22 (8)	4 (1)	31 (23)	16 (12)
Leukopenia	[redacted]	[redacted]	22 (8)	0 (0)	20 (15)	5 (4)
Anaemia	[redacted]	[redacted]	21 (8)	2 (1)	41 (30)	16 (12)
Asthenia	[redacted]	[redacted]	20 (7)	3 (1)	20 (15)	6 (4)
Pyrexia	[redacted]	[redacted]	18 (6)	0 (0)	14 (10)	0 (0)
Alanine aminotransferase elevation	[redacted]	[redacted]	18 (6)	3 (1)	15 (11)	1 (1)
Aspartate aminotransferase elevation	[redacted]	[redacted]	14 (5)	3 (1)	15 (11)	1 (1)
Malaise	[redacted]	[redacted]	11 (4)	0 (0)	14 (10)	0 (0)

*AE values published in Mok 201 [13] have been presented as they are not confidential. However, the ERG notes that that there are some discrepencies between these values and those presented in Appendix2 AURA3 CSR_AiC.pdf

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events version 4.0; N=number; PDC=platinum doublet chemotherapy

Source: *CDF Review CS (Appendix 1, Table 3.2.6) and **Mok 2017[13]

3.4 Overall survival

Box 4 NICE Appraisal Committee's preferred assumption: overall survival

- *Pooling the results for the two AURA trials was reasonable given that the studies were very similar regarding baseline characteristics*
- *The available data were too immature to robustly estimate the overall survival advantage of osimertinib compared with platinum doublet chemotherapy*

Source: NICE 2018[4]

More mature data are now available from the AURAext, AURA2 and AURA3 trials (OS results calculated after approximately two-thirds of events [deaths] had occurred). Median OS results calculated from the pooled AURAext/AURA2 trial data and AURA3 trial data are of similar magnitude (see Table 2). Results from the AURA3 trial show that, for the comparison of treatment with osimertinib versus PDC, OS is not statistically significantly different.

Patients randomised to the PDC arm of the AURA3 trial were permitted to switch treatments after disease progression and 99 patients (71%) received osimertinib in this way (i.e., crossed over). As treatment with osimertinib is not currently recommended by NICE (or available via the CDF) for use as a >second-line therapy, use of osimertinib in the third-line setting does not reflect current NHS practice. The company used statistical methods to remove the effect of crossover on OS estimates for patients randomised to receive PDC.

The company considered the strengths and weaknesses of three crossover adjustment methods (the Rank Preserving Structural Failure Time Method [RPSFTM], the Inverse Probability of Censoring Weighting [IPCW] method and the two-stage method). The company considers that the RPSFTM was the most appropriate method as the IPCW and two-stage methods may produce unreliable results due to the high proportion of patients in the PDC arm who crossed over to receive osimertinib. However, the RPSFTM relies on the assumption that the treatment effect received by switchers is the same as the treatment effect received by patients initially randomised to the experimental group. This "common treatment effect" assumption may not be valid when patients only switch after disease progression, as in the AURA3 trial. Therefore, the ERG considers that the RPSFTM may not provide a valid 'uncrossed' estimate. However, all crossover adjustment methods are subject to limitations and the ERG is not aware of a crossover adjustment method that would produce valid estimates of treatment effectiveness when a high proportion of patients cross over at disease progression.

Having identified the RPFSTM as the most appropriate approach, the company then generated RPSFTM adjusted OS results using six different approaches. The approaches

differed depending on the combination of assumptions about duration of treatment effect and method of censoring. The two different treatment effects considered were “on treatment” (osimertinib treatment effect assumed to only occur whilst on treatment) and “treatment group” (osimertinib treatment effect assumed to last until death/censoring). The three different re-censoring approaches were full recensoring (re-censoring applied in the estimation of the acceleration factor [AF] and the hazard ratio), recensoring applied in the estimation of the AF only, and no recensoring. In the company base case it was assumed that a treatment effect only occurred whilst on treatment and re-censoring was applied in the estimation of the AF only. Results from all analyses are provided in the CDF Review CS (Table 10). An examination of these results showed that Cox model hazard ratios ranged from [redacted] using the on treatment and full re-censoring approach, to [redacted] using the treatment group and no re-censoring approach. The [redacted]. In addition, whether one of the RPFSTM crossover adjustments carried out by the company provides more realistic results than the others is not known.

The company’s crossover adjusted OS estimates for patients receiving PDC ranged from [redacted], whilst median OS for patients from the IMPRESS trial who were matched (via MAIC) with patients in the AURAext and AURA2 trials was 14.1 months (CDF Review CS, Appendix 7, Table 4).

3.4.1 SACT data

The company has presented OS results from analyses of data from two SACT datasets:

- Patients receiving osimertinib for the treatment of metastatic EGFRm T790M mutation-positive NSCLC via the CDF
- Patients with a confirmed diagnosis of advanced or metastatic (Stage IIIB-IV) NSCLC, who have progressed following prior therapy with an approved EGFR-TKI agent (intervention not defined).

Osimertinib

Osimertinib was made available, via the CDF, to patients with specific characteristics (CDF Review CS, Appendix 3 [PHE report]), namely patients:

- With locally advanced or metastatic NSCLC that carried an EGFR and a T790M mutation
- Whose disease progression following first-line EGFR-TKI treatment with only one TKI and without any further systemic anti-cancer treatment
- Who had not received prior chemotherapy unless any prior neoadjuvant or adjuvant chemotherapy had been completed at least 6 months prior to starting first-line EGFR treatment
- With ECOG PS 0 or 1.

Data were collected between October 2016 and January 2019 (n=357, maximum follow-up period=28 months).

Data from the CDF Review CS (Appendix 3, Public Health England report) show that patients who received osimertinib via the CDF were on treatment for a median of 9 months (95% CI: 8.3 to 10.1). Median OS for these patients was 13.9 months (95% CI: 12.1 to 17.6 months). The ERG highlights that this period of time is [redacted] of that for patients participating in the three AURA trials. Reasons for this difference are not known. One possible contributing factor is that the NHS patients were older than those participating in the AURA trials (71.4% aged ≥60 years) and, therefore, are unlikely to have received further lines of treatment.

PDC

The SACT dataset related to patients (n=215) with the following characteristics:

- a recorded diagnosis of Stage IIIB or IV NSCLC in 2014 or 2015
- had received afatinib, erlobinib or gefitinib as their first chemotherapy regimen
- PS 0 or 1
- ≥28 days follow up.

The company provided OS results for two cohorts of patients (i) those who had (n=68/215) and (ii) those who had not (n=147/215) received a subsequent treatment.

The company assumed that the EGFR mutation status of patients' tumours was positive since they were prescribed an EGFR-TKI as a first-line treatment. However, the T790M status of patients' tumours on progression is not known. T790M status is important as results from a meta-analysis (three studies, 192 patients)[14] comparing survival of patients, with and without the T790M mutation, whose disease had progressed following treatment with an EGFR-TKI, showed that patients whose tumour tested positive for the T790M mutation may have had better OS and PFS outcomes compared with T790M naive patients. The pooled hazard ratios for OS and PFS were 0.66 (95% CI: 0.49 to 0.89, p=0.007) and 0.53 (95% CI: 0.35 to 0.79, p=0.002) respectively.

Median OS, calculated from SACT data collected from NHS patients who had received initial treatment with an EGFR-TKI and who, in the second-line setting received any subsequent anti-cancer treatment, was 8.31 months (95% CI: 7.92 to 11.17, n=68). The ERG highlights that median OS for this group of patients is [redacted] of that of patients participating in the PDC arm of the AURA3 trial. Reasons for this difference are not known.

Median OS, calculated from SACT data collected from NHS patients (n=147) who had received initial treatment with an EGFR-TKI and did not receive any subsequent anti-cancer treatment, was 2.56 months (95% CI: 2.33 to 3.19).

Table 7 Available overall survival

Data set	Line of treatment	Treatment	Number	Median OS Months (95% CI)
AURAext/2 trial (pooled)	≥Second-line	Osimertinib	411	26.3 (24.0 to 29.1)
	Second-line	Osimertinib	129	26.5 (24.0 to 31.7)
AURAext/2 trial (pooled) (MAIC 3)	Second-line	Osimertinib	92	[redacted]
IMPRESS trial (MAIC 3)	Second-line	Placebo+PDC	53	14.1
AURA3 trial	Second-line	Osimertinib	279	26.8 (23.5 to 31.5)
	Second-line	PDC	140	Unadjusted: 22.5 (20.2 to 28.8)
	Second-line	PDC	140	Company base case crossover adjusted: [redacted]
SACT data	Second-line	Osimertinib	357	13.9 (12.1 to 17.6)
	Second-line	Not defined	68 147	Treated: 8.31 (7.92 to 11.17) Untreated: 2.56 (2.33 to 3.19)

CI=confidence interval; OS=overall survival; MAIC=matching-adjusted indirect comparison; PDC=platinum doublet chemotherapy; SACT=systemic anti-cancer therapy
Source: CDF Review CS (Table 6 and Appendix 7 [Table 4])

3.5 Conclusions of the clinical effectiveness section

- The AURA3 trial provides evidence of the effectiveness of osimertinib versus PDC for patients who have only previously been treated with an EGFR-TKI
- Survival results from the AURA3 trial support results from the pooled AURAext/2 dataset
- Incidences of AURA3 trial AEs tend to be slightly lower than pooled AURAext/2 dataset incidence rates, perhaps reflecting the fact that patients participating in the AURA3 trial were less heavily pre-treated than most patients participating in the AURAext and AURA2 trials
- Nearly three-quarters (71%) of patients in the PDC arm of the AURA3 trial crossed over to receive osimertinib on progression. The company considers that the RPSFTM is the most appropriate method to use to adjust for the effect of crossover.
- The ERG considers it is not possible to choose a 'best' method of crossover adjustment.The company has presented crossover adjusted results generated by six variants of the RPFSTM. All methods generate hazard ratios with [redacted]. It is not possible to determine which of the RPFSTM methods generates the most realistic results.
- The company's PDC base case median crossover adjusted OS result was more optimistic that results from the company's adjusted indirect comparison or from the SACT data (medians: [redacted]14.1 and 8.31 months respectively). These differences cast uncertainty on the generalisability of results from the three AURA trials to NHS clinical practice.

4 THE COST EFFECTIVENESS DECISION PROBLEM

The NICE AC's preferred economic assumptions (as set out in the ToE document[4]) are presented in Table 8. Further information relating to each assumption is provided in the text following the table.

Table 8 NICE Appraisal Committee's preferred clinical assumptions

Area	Summary of the NICE AC's preferred clinical assumptions
Model structure	*The company's model structure is suitable for decision making.*
Extrapolation of overall survival	*Due to the immature data the company still had to extrapolate the overall-survival results from the clinical trials to the lifetime time horizon of the model.* *The company used a Weibull distribution for the extrapolation of both osimertinib and PDC which was not implausible.* *The committee considered using a generalised gamma distribution reasonable.* *There are several plausible overall survival extrapolation curves.* *Extrapolation of overall survival is unclear and requires further data collection.*
Utilities	*Company's base-case analysis was derived from EQ-5D-5L data collected in the AURA2 study and the modelled values were not treatment specific (that is, utility was 0.815 for progression-free disease and 0.678 for post-progression disease).* *The ERG considered the utility values from the LUME-Lung 1 study could be more reasonable (that is, 0.67 utility value for both the response and stable states and 0.64 for the progressed disease state.* *The most plausible utility values fall somewhere between those used by the company and those suggested by the ERG.*
Time to treatment discontinuation	*Time to treatment discontinuation had been included appropriately in the company's revised analysis.*
End of life	*Evidence suggested that median overall survival was in the range of 20 months for people who had not had treatment before: about 15 months for people who have been previously treated with an EGFR TKI and have the T790M mutation. The short life expectancy criterion was met.* *The committee considered that because of the immaturity of the data for osimertinib, any estimate of an overall-survival gain compared with platinum doublet chemotherapy was very uncertain.* *The committee concluded that osimertinib could plausibly meet the criteria to be considered a life-extending, end-of-life treatment. However, this should be reconsidered as more data become available.*

Source: NICE 2018[4]

4.1 Model structure

Box 5 Appraisal Committee's preferred assumption: model structure

The company's model structure is suitable for decision making.

Source: NICE 2018[4]

Two models are included in the CDF Review CS (Model A and Model B). The overall structure (i.e., the way patients move between health states) of Models A and B is the same, and replicates the structure of the model submitted as part of the TA416[6] CS. Model A differs from that submitted as part of the TA416 CS only in that it includes estimates of OS, PFS and TTD from the most up to date pooled AURAext/2 data. However, there are a number of differences between Model A and Model B (see Table 9). The key differences appear to be that Model A uses OS, PFS and TTD estimates from the most up to date pooled AURAext/2 dataset and Model B uses OS, PFS and TTD estimates from the most up to date AURA3 trial data. In addition, there are worksheet layout and parameter value differences between Model A and Model B. A more comprehensive summary of the differences between Model A and Model B compiled by the ERG is provided in Appendix A.

Table 9 Summary of key differences between Model A and Model B

	Model A	Model B
Model structure	Three-state partitioned survival model	
Population	Patients with locally advanced or metastatic EGFR-T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy, i.e., the model is relevant to patients requiring second-line or further-line treatment	Patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy, i.e., the model is relevant to patients requiring second-line
Intervention and comparators	The intervention is osimertinib and the comparator is PDC (pemetrexed+cisplatin)	
Perspective, time horizon and discounting	Perspective is that of the NHS, time horizon is set to a maximum of 15 years and cost and benefits have been discounted at a rate of 3.5%	
Modelling OS	A Weibull distribution, fitted to the latest data cut of the AURA pooled osimertinib K-M data, was used to generate OS estimates for patients receiving osimertinib. The modelling of OS for patients receiving PDC is unchanged. A Weibull distribution, fitted to data from the IMPRESS study, was used.	A log-logistic distribution, fitted to AURA3 trial osimertinib K-M data, was used to generate OS estimates for patients receiving osimertinib. This distribution was adjusted by a multiplication factor to generate OS estimates for patients receiving PDC
Modelling PFS	The company used Gompertz distributions, fitted to pooled AURAext/2 trial K-M data, and MAIC IMPRESS trial data, to generate PFS estimates for patients treated with osimertinib and PDC respectively.	A Weibull distribution, fitted to AURA3 trial osimertinib K-M data, was used to generate PFS estimates for patients receiving osimertinib. This distribution was adjusted by a multiplication factor to generate PFS estimates for patients receiving PDC.
Modelling TTD treatment	Osimertinib: AURA2 trial TTD data used directly up to 14.3 months. Estimates 14.3 months to 15 years (model time horizon) were generated using a log-logistic extrapolation. PDC: PFS estimates used up to a maximum of 4 cycles of treatment.	Osimertinib: Generalised gamma distributions were used to estimate TTD for osimertinib and PDC separately.
HRQoL	Utility values used to generate FAD ICERs per QALY gained: PF: 0.831 Stable disease: 0.751 PD: 0.715	Values derived from EQ-5D-5L data (crosswalked to EQ-5D-3L) collected as part of the AURA3 trial: PF: 0.836 Stable disease: 0.797 PD: 0.717
Resources and costs	Resource use and costs were estimated based on information from the AURAext/2 studies and the IMPRESS trial, published sources and advice from clinical and economic experts.	Resource use and costs were estimated based on information from the AURA3 study. Many of the resources used and the costs allocated to those resources differed from the resource use and cost assumptions agreed by the NICE AC prior to admission to the CDF.

AC=Appraisal Committee; CDF=Cancer Drugs Fund; DC=data cut; FAD= final appraisal determination; ICER=incremental cost effectiveness ratio; K-M=Kaplan-Meier; NSCLC=non-small cell lung cancer; PDC=platinum doublet chemotherapy; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

Using Model A, the ERG has been able to replicate the ICERs per QALY gained reported by the company in Table 17 (p33) of the CDF Review CS (cost effectiveness analyses 1-3a). Using Model B, the ERG has been able to replicate the ICERs per QALY gained reported by the company in Table 17 (p33) of the CDF Review CS (cost effectiveness analyses 4 and 4a).

The ERG considers that the direct clinical effectiveness data from the AURA3 trial (osimertinib versus PDC) form a more appropriate basis for decision making than the pooled AURAext/2 data. Both sets of data are mature and OS, PFS and TTD results are similar. The AURA3 trial has the advantage of including a relevant comparator arm. Following discussion with the NICE technical team, the ERG has created a hybrid model (Model A/B) which meets the ToE for this review[4] better than either Model A or Model B. Model A/B has been constructed by replacing the OS, PFS and TTD data in Model A with OS, PFS, TTD data from the AURA3 trial (Model B). Instructions for the creation of Model A/B are provided in Appendix B.

4.2 Overall survival

Box 6 NICE Appraisal Committee's preferred assumption: overall survival

Due to the immature data the company still had to extrapolate the overall-survival results from the clinical trials to the lifetime time horizon of the model.

The company used a Weibull distribution for the extrapolation of both osimertinib and PDC which was not implausible.

The committee considered using a generalised gamma distribution a potentially more reasonable.

There are several plausible overall survival extrapolation curves.

Extrapolation of overall survival is unclear and requires further data collection.

Source: NICE 2018[4]

The company submitted updated pooled AURAext/2 clinical effectiveness data (Model A) and the most recent data from the AURA3 trial (Model B).

The company assessed the proportionality of AURA3 trial (osimertinib versus PDC) OS hazards (see CDF Review CS, Appendix 9 for details) and concluded that there was no evidence of non-proportionality. Results from ERG analyses support the company's conclusion. The company used this conclusion to support their approach to modelling OS; they fitted a parametric curve to the AURA3 trial, crossover-adjusted, osimertinib OS K-M data and used a multiplication factor to adjust these K-M data to represent the OS of patients treated with PDC.

The company assessed the fit of six parametric distributions to the AURA3 osimertinib OS K-M data. The company concluded that none of these parametric distributions fitted the

underlying data, particularly "…the flat tail given from the observed data from ~37 months" (CDF Review CS, Appendix 9, p11). The company stated that they chose the log-logistic distribution as it provided the closest estimate to the tail of the data, and generated the most optimistic OS estimates in the longer-term. In contrast, in Model A, Weibull distributions were fitted to the osimertinib and PDC datasets.

4.3 Time to treatment discontinuation

Box 7 NICE Appraisal Committee's preferred assumption: time to treatment discontinuation

Time to treatment discontinuation had been included appropriately in the company's revised analysis.

Source: NICE 2018[4]

In Model A, for PDC, the company used their modelling of PFS based on MAIC IMPRESS trial data to estimate TTD. In Model A, for osimertinib, the company used AURA2 TTD data for 14 months and then estimated TTD with a log-logistic distribution.

The AURA3 PDC TTD estimates are almost complete and so do not require extrapolation. The AURA3 osimertinib TTD data are available up to a maximum of 52 months. In Model B, the company used generalised gamma distributions to model TTD for osimertinib and PDC.

4.4 Utilities

Box 8 NICE Appraisal Committee's preferred assumption: utilities

Company's base-case analysis were derived from EQ-5D-5L data collected in the AURA2 study and the modelled values were not treatment specific (that is, utility was 0.815 for progression-free disease and 0.678 for post-progression disease).

The ERG considered the utility values from the LUME-Lung 1 study could be more reasonable (that is, 0.67 utility value for both the response and stable states and 0.64 for the progressed disease state.

The most plausible utility values fall somewhere between those used by the company and those suggested by the ERG. The ERG considered the utility values from the LUME-Lung 1 study could be more reasonable (that is, 0.67 utility value for both the response and stable states and 0.64 for the progressed disease state.

The most plausible utility values fall somewhere between those used by the company and those suggested by the ERG.

Source: NICE 2018[4]

The company used the same utility values in Model A as were included in the TA416[6] model; the ERG used these values in Model A/B.

The utility values used in Model B were derived from EQ-5D-5L data (cross-walked to EQ-5D-3L) collected during the AURA3 trial. The values used were 0.836 for the progression-free

disease health state, 0.797 for the stable disease health state and 0.717 for the post-progression disease health state.

4.5 End of Life

Box 9 NICE Appraisal Committee's preferred assumption: end of life

Evidence suggested that median overall survival was in the range of 20 months for people who had not had treatment before: about 15 months for people who have been previously treated with an EGFR TKI and have the T790M mutation. The short life expectancy criterion was met.

The committee considered that because of the immaturity of the data for osimertinib, any estimate of an overall-survival gain compared with platinum doublet chemotherapy was very uncertain.

The committee concluded that osimertinib could plausibly meet the criteria to be considered a life-extending, end-of-life treatment. However, this should be reconsidered as more data become available.

Source: NICE 2018[4]

For the comparison of treatment with osimertinib versus PDC, the ERG discusses the NICE End of Life[15] criteria in Section 5.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company has presented results from a number of deterministic cost effectiveness analyses (see CDF Review CS, Table 17). Different combinations of study data, survival extrapolations and utility values have been used to generate cost effectiveness results. The cost effectiveness estimates from each of the company's analyses are shown in Table 10. None of these analyses generated an ICER per QALY gained below £50,000 per QALY gained.

Table 10 Company's cost effectiveness estimates

	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Cost effectiveness analysis 1: Replication of analysis that demonstrated plausible potential for cost effectiveness at CDF entry (TA416)							
Osimertinib	£81,631	3.05	1.98	£58,472	1.22	0.83	£70,776
PDC	£23,159	1.82	1.15	-	-	-	-
Model A							
Cost effectiveness analysis 2: Analysis that demonstrated plausible potential for cost effectiveness at CDF entry – incorporating updated clinical evidence (company preferred utilities)							
Osimertinib	£79,846	2.84	2.12	£56,687	1.02	0.82	£69,453
PDC	£23,159	1.83	1.30	-	-	-	-
Cost effectiveness analysis 3: New company base case, using company preferred utilities							
Osimertinib	£80,034	2.87	2.14	£56,875	1.05	0.84	£68,015
PDC	£23,159	1.83	1.30	-	-	-	-
Cost effectiveness analysis 3a: New company base case, sensitivity analysis, using ERG preferred utilities							
Osimertinib	£80,034	2.87	1.86	£56,875	1.05	0.71	£79,895
PDC	£23,159	1.83	1.15	-	-	-	-
Model B							
Cost effectiveness analysis 4: AURA 3 analysis, using company preferred utilities							
Osimertinib	£107,546	3.08	2.30	£73,155	1.03	0.82	£88,877
PDC	£34,278	2.05	1.48	-	-	-	-
Cost effectiveness analysis 4a: AURA 3 analysis, using ERG preferred utilities							
Osimertinib	£107,546	3.08	1.99	£73,155	1.03	0.70	£104,536
PDC	£34,278	2.05	1.29	-	-	-	-

CDF=Cancer Drug Fund; ICER=incremental cost-effectiveness ratio; LYG=life years gained; PDC=platinum doublet chemotherapy; QALYs=quality adjusted life year
Source: CDF Review CS, Table 17 p.33

6 EVIDENCE REVIEW GROUP ADDITIONAL ANALYSES

6.1 Model A/B base case

The ERG considers the AURA3 trial to be the most appropriate data source from which to estimate the comparative OS of osimertinib versus PDC and that the PFS and TTD data from the AURA3 trial should so be used to inform this CDF Review. The ERG considers neither Model A nor Model B are in line with the terms set out in the ToE for this review.[4] With agreement from the NICE technical team, the ERG has created a hybrid model (Model A/B) which meets the ToE for this review[4] better than either Model A or Model B.

Model A/B has been constructed by inserting AURA3 trial OS, PFS and TTD data (used in Model B) into Model A. In the company models, a mid-cycle correction was applied to TTD data; this approach means that, in the first model cycle, not all patients receive their allocated treatment and this leads to an underestimate of the cost of treatment. This minor error was corrected before generating Model A/B cost effectiveness results. All other parameters in Model A/B remain unchanged from the model used at CDF entry (Model A).

The cost effectiveness results generated by Model A/B are presented in Table 11. The mean estimates of survival generated by Model A/B are shown in Table 12.

Table 11 Cost effectiveness analysis (Model A/B)

Treatment	Total cost	Total LYG	Total QALYs	Incremental			ICER per QALY gained
				Cost	LYG	QALYs	
Osimertinib*	£92,560	3.082	2.284				
PDC	£23,769	2.052	1.468	£68,792	1.030	0.817	£84,209

ICER=incremental cost effectiveness ratio; LYG=life year gained; PAS=patient access scheme; QALY=quality adjusted life year
* Confidential discounted prices used to estimate the cost of treatment

Table 12 Mean PFS, TTD and OS in Model A/B

Treatment	PFS months (mean)	TTD months (mean)	OS months (mean)
Osimertinib	11.531	[redacted]	36.980
PDC	5.704	[redacted]	24.624

PDC=platinum doublet chemotherapy; PFS=progression-free survival; OS=overall survival; TTD=time to treatment continuation

6.2 Exploratory and sensitivity analyses undertaken by the ERG

6.2.1 Utility values

The utility estimates generated from data collected during the AURA3 trial are very similar to those generated from data collected during the AURA2 trial. The ERG TA416 report[11] includes alternative cost effectiveness results generated using utility values from the LUME-Lung 1 trial[1] (pre-progression=0.67, post-progression=0.64). The NICE AC concluded that the true utility values associated with the pre-progression and post-progression health states are likely to lie somewhere between the estimates from the AURA2 trial and the LUME-Lung 1 trial.[1] The ERG has, therefore, also generated cost effectiveness results using LUME-Lung 1 trial[1] utility values in Model A/B.

Compared with Model A/B base case, this leads to a (0.17) decrease in incremental QALYs (from 0.82 to 0.65) and no change to incremental costs, increasing the ICER per QALY gained for the comparison of osimertinib versus PDC from £84,209 to £105,693.

6.2.2 Survival and treatment costs

For OS, PFS and TTD the company has estimated parametric curves based upon AURA3 trial data. The ERG preferred approach is to use K-M data from trials directly followed by extrapolation of the K-M data after the point at which the K-M data become heavily censored and unreliable. In choosing distributions for extrapolation, cumulative hazard plots of AURA3 trial K-M data for OS, PFS and TTD for osimertinib and PDC were built (cumulative hazard plots are provided in Appendix C). In each case, a constant hazard trend (i.e., a straight line) became evident before the end of the K-M data and so it was appropriate to extrapolate the available K-M data in all cases using exponential functions.

The ERG therefore remodelled OS, PFS and TTD data for osimertinib and PDC using exponential functions. Compared with the company Model A/B base case, this approach reduces the ICER per QALY gained by £10,644.

7 IMPACT ON COST EFFECTIVENESS OF ERG ADDITIONAL ANALYSES

A summary of the impact of the ERG's amendments to Model A/B on the cost effectiveness of osimertinib versus PDC for the treatment of patients with advanced or metastatic EGFR T790M mutation-positive disease in the second-line setting after failure of an EGFR-TKI is provided in Table 13.

Using the CAA[2] price for treatment with osimertinib and list prices for pemetrexed and cisplatin, the ERG has made four amendments to Model A/B as detailed in Section 3.2. The ERG presents the results of each amendment individually in Table 13. The ERG also presents the results of two scenarios:

- Scenario 1: changes to OS, PFS and TTD
- Scenario 2: changes to OS, PFS, TTD and using LUME-Lung 1 trial[1] utility values.

Details of all Microsoft Excel revisions carried out by the ERG to Model A/B are presented in Appendix D of this ERG report.

7.1 Conclusions of the cost effectiveness section

The company's submitted ICERs per QALY gained (CDF Review CS, Table 17) ranged from £68,015 to £104,536.

The ERG's hybrid Model A/B yields a base case ICER per QALY gained of £84,209. Compared with PDC, Model A/B base case cost effectiveness results show that treatment with osimertinib generates more QALYs but at an additional cost.

Using Model A/B as the base case, the ERG's revised ICERs per QALY gained range between £73,565 and £105,693. When all of the ERG amendments are combined, the ICER per QALY gained is £91,812.

Table 13 ERG adjustments to Model A/B base case: osimertinib (Commercial Access Agreement price) versus PDC (list prices)

ERG amendment/scenario	Osimertinib			PDC			Incremental			*ICER*	
	Cost	Life years	QALYs	Cost	Life years	QALYs	Cost	Life years	QALYs	£/QALY	Change from base case
A. Model A/B base case	£92,560	3.082	2.284	£23,769	2.052	1.468	£68,792	1.030	0.817	£84,209	
R1) ERG modelling of OS	£91,003	2.808	2.089	£21,348	1.702	1.217	£69,655	1.106	0.871	£79,942	-£4,267
R2) ERG modelling of PFS	£91,130	3.082	2.311	£23,761	2.052	1.468	£67,369	1.030	0.843	£79,925	-£4,284
R3) ERG modelling of TTD	£90,321	3.082	2.284	£24,027	2.052	1.468	£66,295	1.030	0.817	£81,153	-£3,057
R4) LUME-Lung 1 utility values	£92,560	3.082	1.996	£23,769	2.052	1.345	£68,792	1.030	0.651	£105,693	£21,484
Scenario 1: R1)+R2)+R3)	£87,585	2.808	2.115	£21,575	1.702	1.218	£66,011	1.106	0.897	£73,565	-£10,644
Scenario 2: R1)+R2)+R3)+R4)	£87,585	2.808	1.830	£21,575	1.702	1.111	£66,011	1.106	0.719	£91,812	£7,602

ERG=Evidence Review Group; ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation

8 END OF LIFE

The NICE End of Life criteria[15] are:

- treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Short life expectancy

The company's AURA3 crossover adjusted median OS estimates for patients receiving PDC ranged from [redacted] months to [redacted] months. The company's mean estimate of OS for patients receiving PDC from their modelling of OS from AURA3 trial data is 24.6 months. The ERG's revised estimate of OS for patients receiving PDC produces a mean estimate of 20.4 months. The ERG therefore considers that the short life expectancy criterion is met.

Life extension

A comparison of the company's AURA3 trial crossover adjusted median OS results show the difference between treatment with osimertinib and PDC to be a minimum of [redacted] months ([redacted] months versus [redacted] months respectively) and a maximum of [redacted] months ([redacted] months versus [redacted] months respectively).

From the company's modelling of AURA3 data, mean estimates of OS are 36.9 months for osimertinib and 24.6 months for PDC.

The ERG's revised mean estimates of OS are 33.7 months for osimertinib and 20.4 months for PDC. The ERG therefore considers that the life extension criterion is met.

9 REFERENCES

1. Reck M, Kaiser R, Mellemgaard A, Douillard J, Orlov S, Krazakowski M*, et al.* Docetaxel plus nintedanib versus docetaxel plus placebo in patients iwth previously treated non-small cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncology. 2014; 15:143-55.
2. AstraZenica. Managed access agreement. Osimertinib for treating metastatic EGFR and T790M mutation-positive non-small cell lung cancer. October 2016. Available from: https://www.nice.org.uk/guidance/ta416/documents/committee-papers-3 Accessed 20 November 2019.
3. AstraZenica. Cancer Drugs Fund Review of TA416. Osimertinib for locally advanced or metastatic EGFR and T790M mutation positive non-small cell lung cancer [ID1577]. Company evidence submission. October 2019.
4. National Institute for Health and Care Excellence (NICE). Terms of engagement for CDF Review. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer (TA416). 2018.
5. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a conditional marketing authorisatioon for the medicinal product Tagrisso, intended for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) associated with a particular genetic mutation (T790M). 17 December 2015. Available from: https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-opinion-tagrisso_en.pdfAccessed Accessed 20 November 2019.
6. AstraZenica. Single Technology Appraisal. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer [ID874]. Company evidence submission. February 2016. Available from: https://www.nice.org.uk/guidance/ta416/documents/committee-papers Accessed 20 November 2019.
7. AstraZenica. Single Technology Appraisal. Osimertinib for locally advanced or metastatic EGFR and T790M mutation-positive non-small cell lung cancer [ID1577]. Response to clarification questions. November 2019. Available from: https://www.nice.org.uk/guidance/ta416/documents/committee-papers. Accessed 20 November 2019.
8. Soria J, Wu Y, Nakagawa K, Kim S, Yang J, Ahn M*, et al.* Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncology. 2015; 16:990-8.
9. AstraZenica. Single Technology Appraisal. Osimertinb for locally advanced or metastatic EGFR and T790M positive non-small cell lung cancer [ID874]. AstraZenica response to the Appraisal Consultation Document: Date: July 2016. Available from: https://www.nice.org.uk/guidance/ta416/documents/committee-papers-2 Accessed 20 November 2019.
10. National Institute for Health and Care Excellence (NICE). Appraisal Consultation Document. Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer. Issue Date: June 2016. Available from: https://www.nice.org.uk/guidance/ta416/documents/appraisal-consultation-document Accessed 20 November 2019.
11. Greenhalgh J, Mahon J, Boland A, Beale S, Krishan A, Aslam R*, et al.* Osimertinib for locally advanced or metastatic EGFR and T790M mutation-positive non-small cell lung cancer [ID874]: A Single Technology Appraisal. LRiG, University of Liverpool, 2016. 2016; Available from: https://www.nice.org.uk/guidance/ta416/documents/committee-papers Accessed 20 November 2019.
12. Liverpool Reviews and Implementation Group (LRiG). Single Technology Appraisal. Osimertinib for locally advanced or metastatic EGFR and T790M mutation positive non-small cell lung cancer [ID874]. Addendum: ERG response to issues raised in

AstraZenica response to the ACD. August 2016. Available from: https://www.nice.org.uk/guidance/ta416/documents/committee-papers-2 Accessed 20 November 2019.

13. Mok T, Wu Y-L, Ahn M-J, Garassino M, Kim H, Ramalingam S*, et al.* Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. The New England Journal of Medicine. 2017; 376:629-40.
14. Ma G, Xhang J, Jiang H, Xhang N, Yin L, Li W*, et al.* Epidermal growth factor receptor T790M mutation as a prognostic factor in EGFR-mutant non-small cell lung cancer patients that acquired resistance to EGFR tyrosine kinase inhibitors. Oncotarget. 2017.
15. National Institute for Health and Care Excellence (NICE). Appraising life-extending, end of life treatments. Available from: https://www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2 Accessed 22 November 2019.

10 APPENDICES

10.1 Appendix A: Main differences between Model A and Model B

	Model A		***Model B***	
Sheet	**Parameter**	**Value**	**Parameter**	**Value**
T790_test	ctDNA	£472	ctDNA	£472.11
	Patients needed to test	1.66	Patients needed to test	1.87
	Tissue biopsy tests performed	0.60	Tissue biopsy tests performed	0.83
	ctDNA tests performed	0.80	ctDNA tests performed	0.17
	Tissue biopsy number of tests per patient per treatment - osimertinib	1	Tissue biopsy number of tests per patient per treatment - osimertinib	1.55
	ctDNA tests number of tests per patient per treatment - osimertinib	1.33	ctDNA tests number of tests per patient per treatment - osimertinib	0.32
	Total cost of testing per patient	£1350.80	Total cost of testing per patient	£1277.30
Differences in the assumptions in the number of tests leads to a decrease in total testing costs in Model B				
Response_B	Overall response rate	67.4%	Overall response rate	70.6%
	Relative response rate versus reference treatment - osimertinib	1.00	Relative response rate versus reference treatment - osimertinib	1.00
	Relative response rate versus reference treatment - PDC	0.49	Relative response rate versus reference treatment - PDC	0.44
Response rates from AURA2 in Model A and AURA3 in Model B				
Osimertinib				
Safety_data	AEs	Number of events	AEs	Number of events
	Anaemia	2	Abdominal pain	0
	Decreased appetite	1	Anaemia	3
	Diarrhoea	2	Asthenia	2
	Dyspnoea	2	Decreased appetite	5
	Nausea	1	Epilepsy	0
	Platelet count decreased	1	Hyperglycaemia	1
	Vomiting	2	Hypokalaemia	0
			Hyponatraemia	5
			Nausea	3
			Neutropenia	2
			Neutrophil count decrease	4
			Platelet count decreased	2
			Pulmonary embolism	8
			Thrombocytopenia	1
			Vomiting	3

			White blood cell count decrease	1
PDC				
Safety_data	Anaemia	5	Abdominal pain	3
	Decreased appetite	3	Anaemia	15
	Diarrhoea	1	Asthenia	6
	Dyspnoea	3	Decreased appetite	4
	Fatigue / Asthenia	4	Epilepsy	3
	Headache	1	Hyperglycaemia	3
	Hyperglycemia	1	Hypokalaemia	3
	Nausea	6	Hyponatraemia	3
	Neutropenia	20	Nausea	5
	Stomatitis	1	Neutropenia	8
	Vomiting	3	Neutrophil count decrease	10
			Platelet count decreased	5
			Pulmonary embolism	3
			Thrombocytopenia	5
			Vomiting	3
			White blood cell count decrease	3
Adverse event rates from AURA2 in Model A and AURA3 in Model B				
N.B. The order of AEs changed (alphabetised) in this table from the order in Model A to enable clearer comparison				
Progression-free resource use (weekly)				
Costs_Dis	Follow-up OP Visit	0.184	Physician visit (surgery)	0.231
	Chest X-ray	0.130	Palliative care visit	1.000
	CT scan (chest)	0.012	Radiotherapy (brain)	0.067
	CT scan (other)	0.007	Radiotherapy (bone)	0.067
	ECG	0.020	99Tc bone scintigraphy scan	0.333
	Community Nurse Visit	0.167	Chest X-ray	0.093
	GP Surgery Visit	0.230		
	Clinical Nurse Specialist Visit	0.230		
Progression-free unit costs				
Costs_Dis	Follow-up OP Visit	£138.37	Physician visit (surgery)	£68.65
	Chest X-ray	£30.00	Palliative care visit	£87.09
	CT scan (chest)	£116.00	Radiotherapy (brain)	£129.10
	CT scan (other)	£132.00	Radiotherapy (bone)	£129.10
	ECG	£175.00	99Tc bone scintigraphy scan	£237.71
	Community Nurse Visit	£67.00	Chest X-ray	£30.74
	GP Surgery Visit	£44.00		
	Clinical Nurse Specialist Visit	£91.00		
	Total progression-free costs (weekly)	£77.44	Total progression-free costs (weekly)	£202.25

Post-progression resource use (weekly)				
Costs_Dis	Follow-up OP Visit	0.152	Physician visit (home visit)	0.500
	Chest X-ray	0.125	Palliative care visit	1.000
	CT scan (chest)	0.005	Radiotherapy (per fraction)	0.167
	CT scan (other)	0.008	Blood transfusion	0.167
	ECG	0.017	Oxygen	0.167
	Community Nurse Visit	0.167	99Tc bone scintigraphy scan	0.067
	GP Surgery Visit	0.500	X-ray	0.093
	Clinical Nurse Specialist Visit	0.230		
	Therapist Visit	0.500		
Post-progression unit costs				
Costs_Dis	Follow-up OP Visit	£138.37	Physician visit (home visit)	£115.78
	Chest X-ray	£30.00	Palliative care visit	£87.09
	CT scan (chest)	£116.00	Radiotherapy (per fraction)	£129.10
	CT scan (other)	£132.00	Blood transfusion	£199.80
	ECG	£175.00	Oxygen	£14.37
	Community Nurse Visit	£67.00	99Tc bone scintigraphy scan	£237.71
	GP Surgery Visit	£112.22	X-ray	£30.74
	Clinical Nurse Specialist Visit	£91.00		
	Therapist Visit	£44.00		
	Total post-progression costs (weekly)	£139.58	Total post- progression costs (weekly)	£220.91
Terminal- care costs one-off resource use				
Costs_Dis	Hospital	0.56	Hospital	0.56
	Hospice	0.17	Hospice	0.17
	Home	0.27	Home	3.82
Terminal-care resource use				
Costs_Dis	Hospital	£3228.37	Hospital	£3728.16
	Hospice	£4035.46	Hospice	£3728.16
	Home	£5207.80	Home	£87.09
	Total terminal care costs	£3905.35	Total terminal care costs	£3042.86
Resource use items and the costs of those items differs between the models. This results in higher costs in the pre-progression and post-progression health states in Model B and lower costs in Model A for terminal care.				
Admin costs – first visit				
Costs_Tx	Not included	Not included	Osimertinib	0.00
			PDC	£269.75
Admin costs – after first visit				
Costs_Tx	Osimertinib	£0.48	Osimertinib	0.00
	PDC	£332.50	PDC	£269.75
Small difference to osimertinib admin costs. The higher cost for an initial visit is not included in Model A				
Time spent on subsequent therapy				

Costs_SubTx	Osimertinib	16.38	Osimertinib	20.39
	Platinum doublet chemo	2.43	Platinum doublet chemo	3.38
	Pemetrexed monotherapy (exc.)	2.32	Pemetrexed monotherapy (exc.)	3.36
	Docetaxel monotherapy (exc.)	2.32	Docetaxel monotherapy (exc.)	2.44
	TKI monotherapy (exc.)	2.43		
	TKI combination therapy (exc.)	2.43		
	CO-1686 (exc.)	0.00		
	BSC (exc.)	2.43		
	Chemo monotherapy (exc.)	0.00		
Fewer subsequent therapy options in Model B, with an increase in the duration of subsequent therapy for those that are the same as in Model A				
AE costs				
Costs_AE	Anaemia	£3110.11	Abdominal pain	0.00
	Back Pain	£1679.85	Anaemia	£1002.07
	Constipation	£2367.66	Asthenia	£379.11
	Cough	0	Decreased appetite	£81.97
	Decreased appetite	£2367.66	Epilepsy	0.00
	Diarrhoea	£2411.2	Hyperglycaemia	0.00
	Dyspnoea	£1447.73	Hypokalaemia	0.00
	Fatigue / Asthenia	£3110.11	Hyponatraemia	0.00
	Febrile neutropenia	£2426.86	Nausea	£1966.24
	Headache	£1344.07	Neutropenia	£354.52
	Hyperglycemia	0	Neutrophil count decrease	0.00
	Nausea	£2245.09	Platelet count decreased	0.00
	Neutropenia	£2426.86	Pulmonary embolism	0.00
	Oedema peripheral	£1759.98	Thrombocytopenia	0.00
	Platelet count decreased	£2425.65	Vomiting	£1966.24
	Pruritus	0	White blood cell count decrease	0.00
	Rash (grouped term)	£2666.09		
	Stomatitis	£1483.11		
	Upper respiratory tract infection	0		
	Vomiting	£2245.09		
The AEs listed follow those reported in AURA2 for Model A and AURA3 for Model B. There are some differences in costs for those that are common in both models.				
N.B. The order of AEs changed (alphabetised) in this table from the order in Model A to enable clearer comparison				
Health states				
Utilities	CR/PR	0.831	CR/PR	0.836
	SD	0.751	SD	0.797
	Post-progression	0.715	Post-progression	0.717
AE disutilities				
Utilities	Anaemia	0.073	Abdominal pain	0.050

	Back Pain	0.05	Anaemia	0.073
	Constipation	0.05	Asthenia	0.073
	Cough	0.05	Decreased appetite	0.000
	Decreased appetite	0.05	Epilepsy	0.050
	Diarrhoea	0.047	Hyperglycaemia	0.050
	Dyspnoea	0.05	Hypokalaemia	0.050
	Fatigue / Asthenia	0.21	Hyponatraemia	0.050
	Febrile neutropenia	0.09	Nausea	0.048
	Headache	0.05	Neutropenia	0.090
	Hyperglycemia	0	Neutrophil count decrease	0.050
	Nausea	0.048	Platelet count decrease	0.050
	Neutropenia	0.09	Pulmonary embolism	0.050
	Oedema peripheral	0.05	Thrombocytopenia	0.050
	Platelet count decreased	0.05	Vomiting	0.048
	Pruritus	0	White blood cell count decrease	0.050
	Rash (grouped term)	0.032		
	Stomatitis	0.05		
	Upper respiratory tract infection	0		
	Vomiting	0.048		
The AEs listed follow those reported in AURA2 for Model A and AURA3 for Model B. Most of those that appear in both models have the same value, however, there are some differences between those that are common in both models.				
N.B. The order of AEs changed (alphabetised) in this table from the order in Model A to enable clearer comparison				

10.2 Appendix B: Instructions for the creation of Model A/B

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
Survival curves (OS and PFS)	Model B to model A	ClinicalData_B	Model b K7:X12 To Model a CN7:DA12	Lift the survival functions for osimertinib from the live values section of model b and paste values into the live values section of model a
	Model B to model A		Model b K35:X40 To Model a CN35:DA40	Repeat for PDC
	Model A	Survival_B	K34 & K48	Switch the choice of parametric curve to log-logistic
			S34 & S48	Switch the choice of parametric curve to Weibull
TTD	Model B	ResSurv_B	HW22:HW802	AURA3 Osi company TTD – without mid-cycle correction Copy
	Model A	Create new sheet and name in AURA3_TTD	A2	Paste values
			A1	Add label “Osi”
	Model B	ResSurv_B	IA22:IA802	AURA3 PDC company TTD – without mid-cycle correction Copy
	Model A	AURA3_TTD	B2	Paste values
			B1	Add label “PDC”
	Model A	PatFlow_B	DE13 Copy down to DE792	Osi company AURA3 TTD =’AURA3_TTD’!A2
			DD13 Copy down to DD792	PDC company AURA3 TTD =’AURA3_TTD’!B2
	Model A	Cost_calc	Model a V13 Copy down to V792	Use: =(IF(TTD_TrueFalse,(INDEX(Patflow_area,$C13,S$6+96)*IF($B13>=V$9,0,V$11)),(SUM(INDEX(Patflow_area,$C13,S$6+2),INDEX(Patflow_area,$C13,S$6+3))*IF($B13>=V$9,0,V$11)))*$D13)
Save as a new model.				

10.3 Appendix C: ERG cumulative hazard plots for OS, PFS and TTD

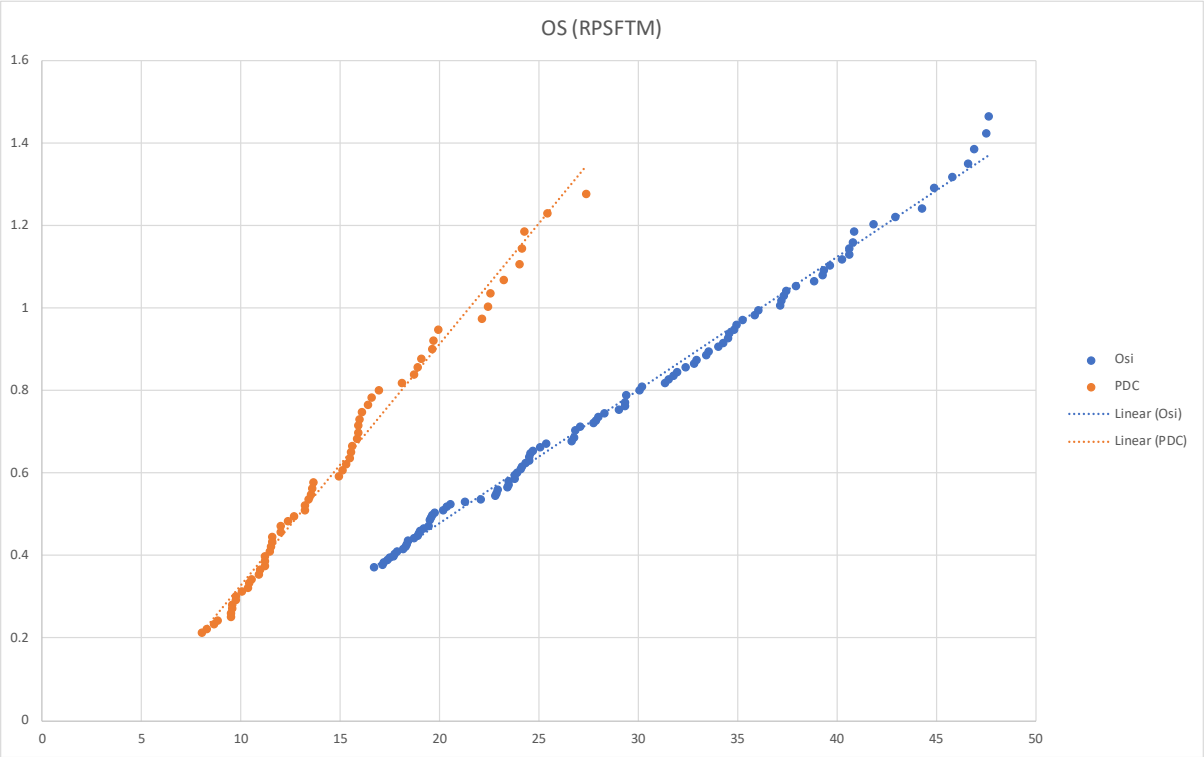

Figure 1 AURA3 OS K-M data cumulative hazard plots

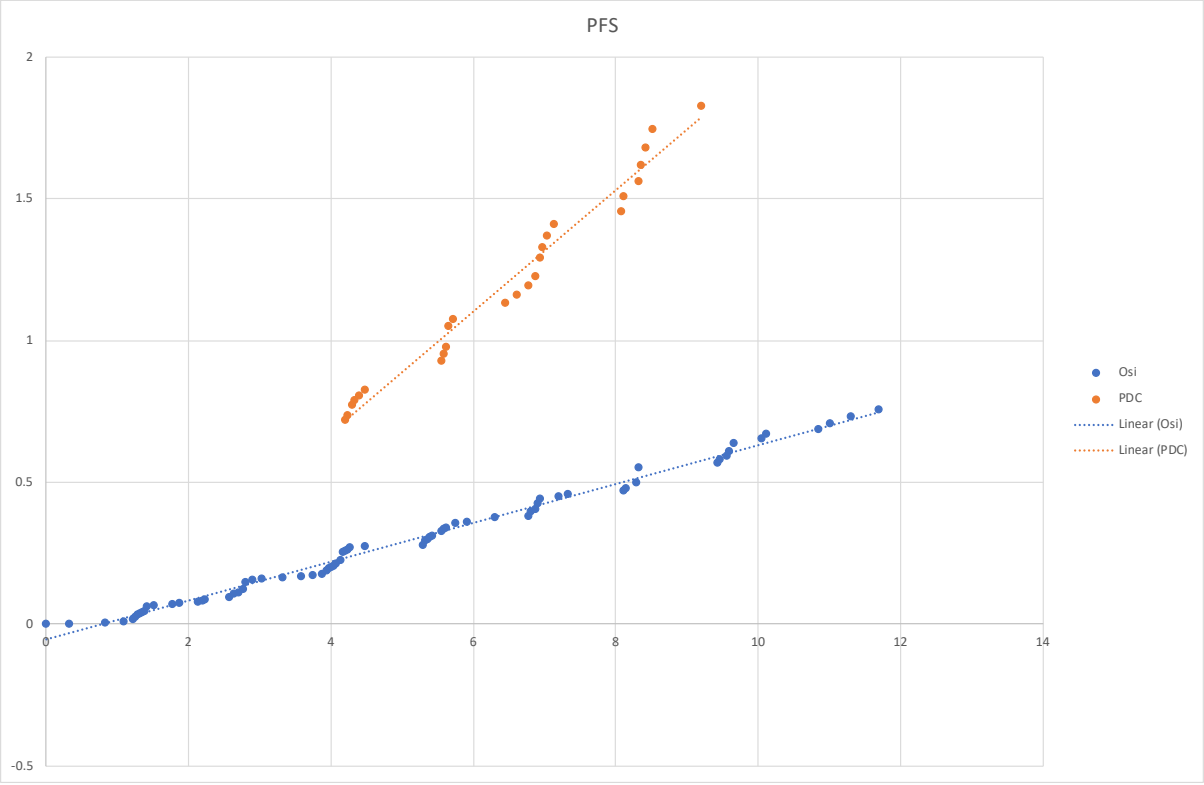

Figure 2 AURA3 PFS K-M data cumulative hazard plots

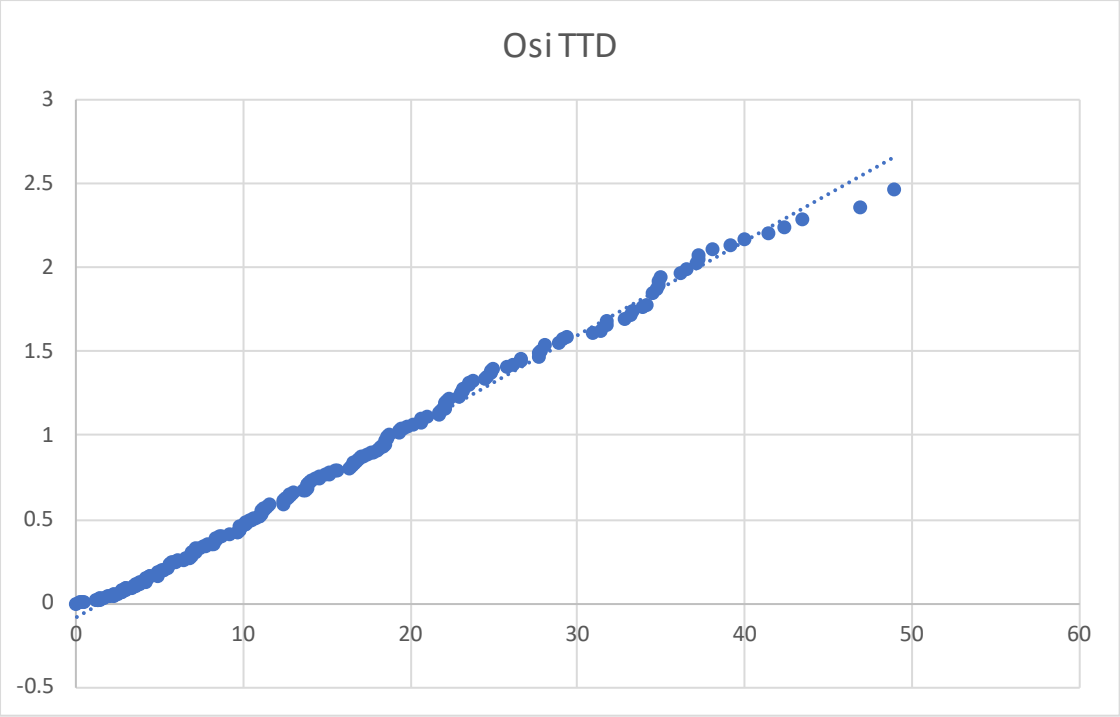

Figure 3 AURA3 TTD K-M data cumulative hazard plots

10.4 Appendix D: ERG Microsoft EXCEL revisions to Model A/B

All revisions are activated by a logic switch with:

0=unchanged

1=apply ERG modification

Logic switches are indicated by named range variables Mod_*letter* where letter = A - D.

A menu of revisions and Mod names appear below and on the 'Results' worksheet together with summary results as used to transfer to the ERG report.

Revision #	Modification name	Switch	Description
R4)	Mod_A	0	ERG suggested utility values
R2)	Mod_B	0	ERG estimates of PFS based on the AURA3 trial data
R3)	Mod_C	0	ERG estimates of TTD based on the AURA3 trial data
R1)	Mod_D	0	ERG estimates of OS based on the AURA3 trial data

Instructions for modifying the company model

1. Move all sheets from *Osi 1577_ERG additional model data (CiC).xlsx* into company model

2. Create named switches for each of the modifications mod_A to mod_D

3. For each sheet given in the 'Sheet' column below:
    - copy formulae from the 'Modified formulae' column in the table below
    - paste formulae into the cells referred to in the 'Cells' column in the table below

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
R4) Use ERG suggested utility values	Mod_A	CountryData Add modification to three utility options in this sheet	G680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.833)
			H680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.891)
			I680	Use ERG suggested utility value for pre-progression =IF(mod_A=1,0.67,0.831)
			G681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.753)
			H681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.825)
			I681	Use ERG suggested utility value for pre-progression for stable disease also =IF(mod_A=1,0.67,0.751)
			G682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,((0.751+0.679)/2))
			H682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,0.821)
			I682	Use ERG suggested utility value for post-progression =IF(mod_A=1,0.64,((0.751+0.679)/2))
			G688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.833)
			H688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.891)
			I688	Use ERG suggested utility value for pre-progression =IF(Mod_A=1,0.67,0.831)
			G689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.753)
			H689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.825)
			I689	Use ERG suggested utility value for pre-progression for stable disease also =IF(Mod_A=1,0.67,0.751)
			G690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0.67,((0.751+0.679)/2))

ERG revision number and description	Modification name	Sheet	Cells	Modified formulae
			H690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0.67,0.821)
			I690	Use ERG suggested utility value for post-progression =IF(Mod_A=1,0.67,((0.751+0.679)/2))
R2) Use ERG re-modelled PFS data from AURA3	Mod_B	ResSurv_B	E22 copy down to E802	Use AURA3 ERG re-modelled PFS for osimertinib =IF(Mod_B=1,'ERG - PFS'!A4,IF(OR(analysis_nr=1,INDEX(surv_model_nr,E$13)=1,SUM(E$17:E$20)=0),0,Survival_func(E$16:E$20,$C22)))
			G22 copy down to G802	Use AURA3 ERG re-modelled PFS for PDC =IF(Mod_B=1,'ERG - PFS'!B4,IF(OR(analysis_nr=1,INDEX(surv_model_nr,G$13)=1,SUM(G$17:G$20)=0),0,Survival_func(G$16:G$20,$C22)))
R1) Use ERG re-modelled OS data from AURA3	Mod_D	ResSurv_B	F22 copy down to F802	Use AURA3 ERG re-modelled OS for osimertinib =IF(Mod_D=1,'ERG - OS'!A3,IF(OR(analysis_nr=1,INDEX(surv_model_nr,F$13)=1,SUM(F$17:F$20)=0),0,CHOOSE(surv_param_model,Survival_func(F$16:F$20,$C22),ClinicalData_B!DV22)))
			H22 copy down to H802	Use AURA3 ERG re-modelled OS for PDC =IF(Mod_D=1,'ERG - OS'!B3,IF(OR(analysis_nr=1,INDEX(surv_model_nr,H$13)=1,SUM(H$17:H$20)=0),0,CHOOSE(surv_param_model,Survival_func(H$16:H$20,$C22),ClinicalData_B!DX22)))
R3) Use ERG re-modelled TTD data from AURA3	Mod_C	PatFlow_B	NB: PDC then OS in this sheet DE13 copy down to DE792	Use AURA3 ERG re-modelled TTD for osimertinib =IF(Mod_C=1,'ERG - TTD'!A3,'AURA3_TTD'!A2)
			DD13 copy down to DD792	Use AURA3 ERG re-modelled TTD for PDC =IF(Mod_C=1,'ERG - TTD'!B3,'AURA3_TTD'!B2)