NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Osimertinib for treating metastatic EGFR and T790M mutation-positive non-small-cell lung cancer [ID874]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

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

Premeeting briefing

Osimertinib for the treatment of locally advanced or metastatic EGFR and T790M mutation positive non-small cell lung cancer

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes analyses including a patient access scheme (PAS) submitted by the company which has not been approved by the Department of Health yet; however we expect approval before the first committee meeting,

Key issues for consideration

Clinical effectiveness

- Osimertinib is licensed for treating adults with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC. However, clinical effectiveness evidence was only available for people who have had treatment with an EGFR tyrosine kinase inhibitor. i.e. no evidence for people who have not received prior treatment.
- Evidence of the efficacy for osimertinib comes from the AURA extension and AURA 2 studies without a control group. There is no direct evidence comparing osimertinib with a relevant comparator. The company states that there is a

progression-free survival benefit of 4.4 months for osimertinib compared with platinum doublet therapy based on a naïve indirect comparison of the AURA studies and the IMPRESS trial, which provided data on the comparator, platinum doublet therapy.
    - The company also made a comparison by adjusting for baseline characteristics, [redacted]
    - The ERG noted as well as the concerns about the immature overall survival (OS) data, the adjustments made by the company [redacted]
    - Is the comparison robust?
- The AURA studies and the IMPRESS trial included people who were younger and fitter than those who would be expected to be seen in NHS clinical practice, and also very few people from the UK were included in the studies. Are these studies generalisable to clinical practice in the NHS?
- The health-related quality of life data from the AURA studies are based on relatively small numbers. Are these data reliable?
- The marketing authorisation for osimertinib is conditional upon the company submitting the clinical study report of the phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy. This is expected to report in June 2017.

Cost effectiveness

- The company only presented cost-effectiveness evidence for osimertinib in people who have received previous treatment with an EGFR tyrosine kinase inhibitor because limited data were available for people with a T790M mutation who have not received previous treatment.

- For extrapolating progression-free survival in the base case analysis, the company used a Gompertz distribution (for both osimertinib and platinum doublet therapy) and for overall survival the company used a Weibull distribution for both osimertinib and platinum doublet therapy. This resulted in a suggested overall survival gain of 10.6 months.

  - ERG considered that the overall survival projections used by the company were based on opinion and that only a progression-free survival gain of osimertinib compared with platinum doublet therapy could be supported by the evidence. Which approach is the most appropriate?

  - The ERG suggested that using time to treatment discontinuation data rather than progression-free survival data to estimate the cost of osimertinib is more appropriate since progression-free survival data underestimates the cost of osimertinib and overestimates the cost of platinum doublet therapy. Which approach is the most appropriate?

- The ERG considered that the utilities applied in the company model appeared to be implausible because they were higher in the progression-free state (0.815) than in the general population for people of the same age at the start of the model (0.80). The ERG used alternative utility values in its exploratory analysis.

- The company submission did not take into account any administration cost of osimertinib as an oral chemotherapy. The ERG believes that NHS Reference Costs for oral chemotherapy administration of osimertinib should be included.

- The company base case cost effectiveness estimate for osimertinib compared with platinum doublet therapy was £42,959 per QALY gained (including patient access scheme discount). The ERG's exploratory analyses included:

  - using time to treatment discontinuation data to estimate drug costs,

  - application of administration costs for osimertinib, alternative utility estimates, and

  - assumption of only a progression-free survival gain (no overall survival gain).

  When combined, this resulted in cost effectiveness estimates (including patient access scheme discount) of between £513,286 and £1,334,543 per QALY gained

for osimertinib compared with platinum doublet therapy. Which assumptions are the most appropriate?

- What is the Committee's view of the company's subgroup analysis of osimertinib that focused on:
    - second-line only population compared with platinum-based chemotherapy and with docetaxel monotherapy
    - third and later line population compared with docetaxel monotherapy.
- Does osimertinib meet the end-of-life criteria? The company stated that although the overall survival data were immature at the time of submission, when the most appropriate parametric curves are used to extrapolate overall survival in the economic model, a median OS gain of 12 months is observed.
    - End of life criteria stipulate that there must be sufficient evidence that the treatment offers an extension to life of at least 3 months compared with current treatment. Is this estimated overall survival gain robust enough to satisfy this criterion?
    - The company stated that for people who have had no previous treatment with an EGFR tyrosine kinase inhibitor there is currently no survival data but that it is likely that osimertinib offers an extension to life of at least 3 months in the small group of people eligible for treatment. Is the evidence sufficient?
- If osimertinib is to be considered as part of the Cancer Drugs Fund, does the Committee believe that with more mature evidence, osimertinib could be plausibly cost effective for the treating locally advanced or metastatic EGFR T790M mutation-positive NSCLC?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of osimertinib within its marketing authorisation for locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Pop.	People with locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer	As per final scope except cost-effectiveness for treatment-naïve population.	The cost-effectiveness of osimertinib is only presented for people who have received previous treatment with an EGFR TKI. For people with a T790M mutation who have not received previous treatment, there are limited data available which would allow AstraZeneca to build a robust cost effectiveness model. Therefore, apart from the clinical details provided in Section 4.15, the company submission focuses on people who received previous treatment with an EGFR TKI.	Line of treatment is not specified in the conditional EMA licence or in the final scope issued by NICE. The marketing authorisation was based on a biological assumption of effectiveness as there are no data to support the use of osimertinib in treatment-naïve patients. The evidence submitted by the company was from 2 single arm studies designed to assess the clinical effectiveness of osimertinib in people with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who

				had received treatment with an EGFR-TKI prior to recruitment
Int.	Osimertinib	As per final scope	-	-
Com.	For people who have not received previous treatment: • Afatinib • Erlotinib • Gefitinib	See comments regarding population	Patients with T790M mutated EGFR at initial diagnosis population represent approximately 1% (see Section 3) of the EGFR mutation positive population at diagnosis. The limited evidence available for this small patient group suggests a poor response to 1st generation TKIs (erlotinib/gefitinib/afatinib). The very small population, evidence of limited clinical effectiveness available from individual patient case histories with SOC and the preclinical data/biological rationale for osimertinib treatment alongside the emerging tumour response data for this patient group from the AURA study programme, was the basis of the CHMP decision to include this population within the label.	See comments above

	For people who have received previous treatment with an EGFR TKI: • Platinum doublet therapy (including pemetrexed plus carboplatin or cisplatin)	As per final scope. The base case cost-effectiveness analysis compares osimertinib with platinum doublet chemotherapy (pemetrexed plus cisplatin) for people with locally advanced or metastatic, EGFR and T790M mutation positive NSCLC who have received previous treatment with an EGFR TKI. Clinical effectiveness data for the platinum doublet chemotherapy arm were taken from a previously published Phase III trial of gefitinib plus chemotherapy versus chemotherapy in EGFRm+ NSCLC after progression on first-line gefitinib (IMPRESS).2	The expected position of osimertinib in the treatment pathway would be 2nd line following treatment with an EGFR TKI 1st line for those patients who present with the T790M mutation upon progression. This group therefore represents the vast majority of the expected population that would be eligible for treatment with osimertinib in UK clinical practice.	The ERG was aware that, for the specified population, pemetrexed+cisplatin is the most commonly used platinum doublet therapy in the NHS. The company presented comprehensive clinical effectiveness data for the unadjusted and adjusted comparison of second or further line treatment with osimertinib versus second-line platinum doublet therapy.

	For people who have received previous treatment with an EGFR TKI, and in whom platinum doublet therapy is not appropriate: • Single-agent chemotherapy including gemcitabine, paclitaxel, vinorelbine or docetaxel	As per final scope. No clinical effectiveness data were identified in the systematic review on the use of single-agent chemotherapy in people with locally advanced or metastatic, EGFR T790M mutation positive NSCLC who have received previous treatment with an EGFR TKI (Section 4.1). Furthermore, limited clinical effectiveness data were identified on the use of single-agent chemotherapy for people with locally advanced or metastatic, EGFR mutation positive NSCLC who have received previous treatment with an EGFR TKI. However, a scenario analysis was provided to compare the cost-effectiveness of osimertinib with single-agent chemotherapy for patients who have received previous treatment with an EGFR TKI and in whom platinum doublet therapy is not	AstraZeneca anticipates the proportion of patients in whom platinum doublet therapy is not appropriate as a 2nd line treatment option to be very limited based on market research. Recognising that the AURA trial programme included these patients and that many patients had failed more than 1 line of prior treatment for advanced disease, the comparison vs doublet chemotherapy from the IMPRESS trial likely represents a conservative estimate of clinical efficacy for this patient population.	See comments above. The ERG did not consider the results of the company's subgroup analyses to be informative

		appropriate (Section 5.8 of the CS).		

	For people who have received previous treatment with an EGFR TKI and chemotherapy: • Docetaxel with or without nintedanib • Nivolumab (subject to ongoing NICE appraisal) • Ramucirumab (subject to ongoing NICE appraisal) • Single-agent chemotherapy including gemcitabine, paclitaxel, vinorelbine (for those for whom treatment with docetaxel is not appropriate) • Best supportive care	No clinical effectiveness data were identified in the systematic review on the use of nintedanib (with docetaxel), nivolumab, ramucirumab and best supportive care (BSC) in people with locally advanced or metastatic, EGFR and/or T790M mutation positive NSCLC who have received previous treatment with an EGFR TKI and chemotherapy (Section 4.1). Furthermore, limited clinical effectiveness data were identified on the use of single agent chemotherapy for people with locally advanced or metastatic, EGFR mutation positive NSCLC who have received previous treatment with an EGFR TKI and chemotherapy. However, a subgroup analysis is provided to compare the cost-effectiveness of osimertinib with single-agent chemotherapy (including docetaxel) for patients who	The expected position of osimertinib in the treatment pathway would be 2nd line following treatment with an EGFR TKI 1st line for those patients who present with the T790M mutation upon progression. Upon marketing authorisation, consistent with data from the AURA programme, a pool of patients could receive osimertinib as a 3rd or 4th line treatment following EGFR TKI and chemotherapy. However, this represents a "one-off" group of patients once osimertinib is available as a 2nd line treatment for eligible patients. Within the later line group, AstraZeneca agrees that docetaxel or other single-agent chemotherapy is a relevant comparator. In relation to adding nintedanib to docetaxel, NICE TA347 specifically recommends this combination in a general lung cancer population for patients that have progressed on first-line chemotherapy. In the pivotal trial of docetaxel plus nintedanib in patients with previously treated NSCLC (LUME-Lung 1), there was no evidence presented that indicated patients were either EGFRm+ or had received prior treatment with an	See comments above. The ERG did not consider the results of the company's subgroup analyses to be informative.

		have received previous treatment with an EGFR TKI and chemotherapy (Section 5.9).	EGFR TKI.[3] Patients with EGFRm+ lung cancer will have received an EGFR TKI as their first-line treatment and any subsequent use of chemotherapy would be considered to be second-line chemotherapy. Neither ramucirumab nor nivolumab are expected to be licensed in the UK specifically for adult patients with EGFRm+ and T790M mutation positive locally advanced or metastatic NSCLC. The CHMP opinion for ramucirumab states that it is indicated in combination with docetaxel for the treatment of adult patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy. In the pivotal study of ramucirumab plus docetaxel for the second-line treatment of stage IV NSCLC (REVEL) less than 3% of patients enrolled to the study were EGFR mutation positive or had received prior EGFR TKI treatment.[4] For nivolumab, in the pivotal study CheckMate-057, the observed efficacy for overall survival in the subgroup of EGFR mutation positive patients, despite not being significant, favoured docetaxel (HR	

			1.18; 95% CI 0.69-2.00).[5] It is therefore highly unlikely that nivolumab will be considered clinically for EGFRm+ patients nor is it likely to be cost-effective versus docetaxel in a population of EGFR mutation positive patients. No information is available on the efficacy in a T790M mutation positive population. AstraZeneca does not agree that best supportive care is a relevant comparator. This was discussed in the scoping meeting and confirmed by clinical experts, that it is unlikely that patients unfit/ineligible to receive further treatment as part of their 3rd line or later care package, based on current treatment options, would be considered for treatment with osimertinib. In addition to the lack of comparative data, BSC is part of the care package offered to all locally advanced or metastatic NSCLC patients, regardless of their eligibility for systemic anticancer therapies and is captured in the cost-effectiveness analysis.	
Out.	The outcome measures to be considered include:	As per final scope	In addition, other endpoints such as tumour shrinkage, disease control	The currently available OS data from the AURAext and

	• overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life		rates and duration of response are briefly discussed as helpful to inform the discussion.	AURA2 studies (pooled) and the subgroup of patients with T790M mutations from the control arm of the IMPRESS trial are very immature (12.7% and approximately 33% respectively)

2 The technology and the treatment pathway

2.1 Osimertinib has a conditional marketing authorisation for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC). The marketing authorisation is conditional upon the company submitting the clinical study report of the phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy (expected June 2017). According to the company, the very low prevalence of T790M mutations at diagnosis means that the expected position of osimertinib in the treatment pathway would be after treatment with an EGFR tyrosine kinase inhibitor (TKI). The company stated that this group represents the vast majority of the expected population to be treated with osimertinib in UK clinical practice. A small group of patients presenting with a T790M mutation at diagnosis could receive osimertinib as a first-line treatment.

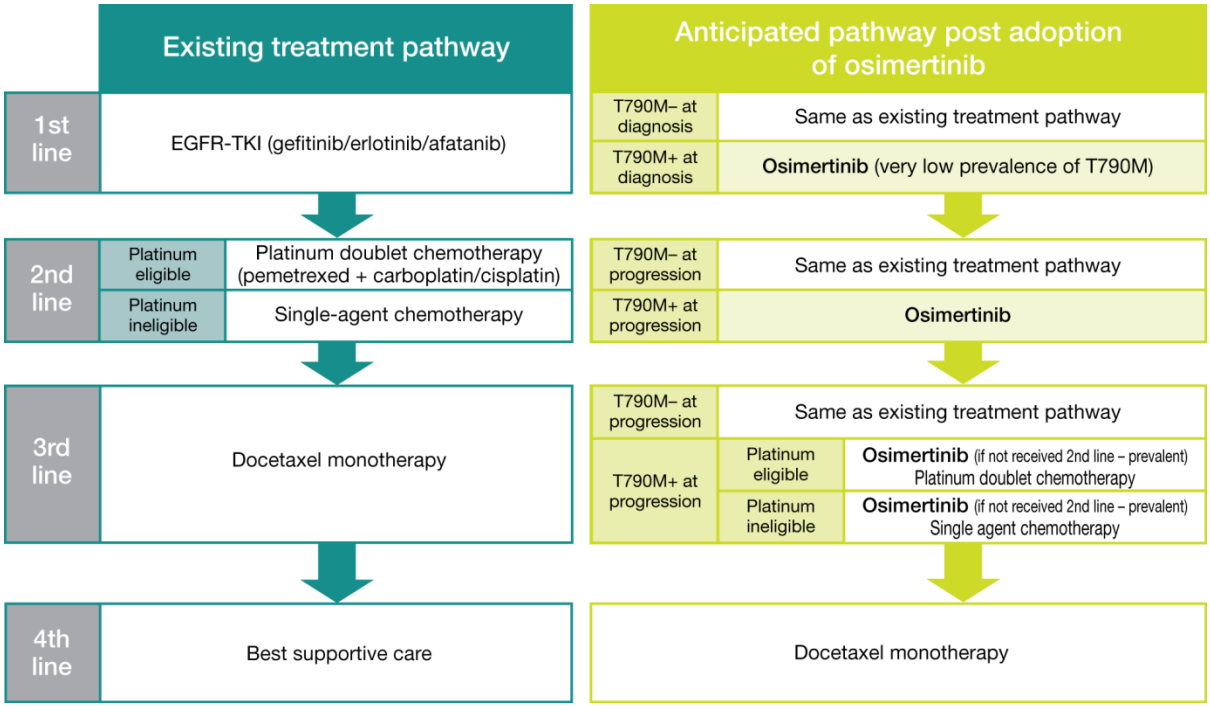
2.2 Osimertinib (previously referred to as AZD9291; Tagrisso, AstraZeneca) is a small molecule inhibitor that targets the sensitising and T790M mutant forms of the EGFR-TK. The European Medicines Agency granted the conditional marketing authorisation noting that "*Osimertinib is a new alternative before chemotherapy, with outstanding response rates. It is expected this will be translated into clinical benefit for patients, although the magnitude of such benefit in terms of OS and/or PFS remains unknown"* and that the company "*is likely to provide comprehensive clinical data at a later stage."*

2.3 The company commented that the proposed positioning of osimertinib means that people will have progressed on prior treatment with EGFR TKI who have a documented T790M mutation. Testing for the EGFR T790M mutation is not routinely carried out in the NHS either at diagnosis or after treatment failure with a first-line EGFR-TKI. The company believes that obtaining a fresh tumour specimen at disease progression to determine

T790M status for clinical adoption of osimertinib will lead to a minor change in service provision.

2.4 The company estimates that approximately 300 patients every year will be eligible for treatment with osimertinib assuming that 65% of patients who progress on an EGFR TKI receive active treatment at progression[9] alongside a T790M mutation rate of 60%. Approximately 10 patients across England and Wales would present with a T790M mutation status at diagnosis (based on a 1-6% incidence rate) and would be eligible for treatment with osimertinib first line.

Figure 1. Company's overview of current and anticipated treatment pathway
(Taken from figure 3.2 of the company submission)



2.5 For the majority of people with NSCLC, the aims of therapy are to prolong survival and improve quality of life. For people whose disease tests positive for the EGFR-TK mutation and who have not previously received treatment, NICE guidance recommends the TKIs, afatinib, erlotinib and gefitinib, as treatment options (NICE technology appraisal guidance 310, 258 and 192). Following disease progression on a TKI, pemetrexed in

combination with either cisplatin or carboplatin is used in clinical practice. For those people for whom treatment with a platinum drug is not appropriate, NICE clinical guideline 121 ‘Lung cancer’ recommends that people should be offered single agent chemotherapy with either docetaxel, gemcitabine, paclitaxel or vinorelbine. Where the disease progresses following treatment with chemotherapy, NICE clinical guideline 121 ‘Lung cancer’ recommends that docetaxel monotherapy should be offered. NICE guidance also recommends nintedanib in combination with docetaxel as an option for people with adenocarcinoma that has got worse after previous chemotherapy (NICE Technology Appraisal 347).

Table 2 Technology

	Osimertinib	Platinum doublet therapy		Docetaxel monotherapy
		Pemetrexed	Cisplatin	
Marketing authorisation	Conditional marketing authorisation: Osimertinib is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC). In section 4.2 of the SmPC it states that EGFR T790M mutation status should be determined by using a validated test method	Pemetrexed in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology	Cisplatin is intended for the treatment of advanced or metastasised non-small cell lung carcinoma	Docetaxel indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy. (Docetaxel is also indicated in combination with cisplatin is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition)
Administration method	Oral tablet (80 mg once a day until disease progression or unacceptable toxicity).	Intravenous (500mg/m^2) once every third week until disease progression	Intravenous (75 mg/m^2) once every third week until disease progression	Intravenous (75 mg/m^2) once every third week until disease progression
Cost information	NHS List Prices (not including patient access scheme discount): 80mg: £4,722.30 per pack (30 tablets) 40mg: £4,722.30 per pack (30 tablets)	£160.00 per vial , 9 vials required per administration (with waste)	£3.24 per vial, 13 vials per administration required (with waste)	£20.95 per vial, 1 vial per administration required (with waste)

	Pack price with PAS: [redacted] Treatment is continued until disease progression			

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 Clinical experts commented that people with advanced (stage IIIB or IV) lung adenocarcinoma with mutations of exon 19 or 21 of the EGFR gene (EGFRmut) are currently treated with a first line EGFR TKI such as gefitinib, erlotinib or afatinib, in accordance with NICE guidelines. All three TKIs are available within England, with local patterns of use reflecting physician preference. The experts stated that gefitinib, erlotinib or afatinib are associated with a high response rate and the median duration of response is approximately 9 to12 months together with a manageable side effect profile, and good quality of life. Experts commented that osimertinib would only be used for patients with EGFR mutation-positive lung cancer whose disease had progressed after first line EGFR TKIs. People would be required to have a repeat biopsy to demonstrate that they had developed an additional EGFR mutation, termed T790M. This occurs in around two-thirds of EGFR mutation-positive patients in this situation. On the basis of all the scenarios above, the alternative to osimertinib is chemotherapy.

3.2 Patient experts commented that people with advanced and metastatic lung cancer are in a particularly devastating situation. Even with the currently recommended options, the outlook for the majority is relatively poor. Patient experts highlighted that the availability of additional options is very important and because osimertinib is an oral therapy it has obvious benefits to patients, such as spending less time at hospital and no requirement for intravenous treatment. Osimertinib is the first therapy shown to have benefits in EGFR T790M positive NSCLC patients. As such, it represents a therapy option for a very small number of clearly defined patients

3.3 Treatment with osimertinib requires a biopsy, usually by CT-guided or bronchoscopic endobronchial ultrasound, both of which are invasive

procedures with potential complications, and there may be issues with patient acceptability. Clinical experts highlighted that there are clinical challenges in this disease area, e.g. when first line chemotherapy is started before the EGFR mutation result is known. This occurs either when the person is too unwell to wait for the mutation result, or when the result itself is delayed. In this scenario, most oncologists would continue chemotherapy whilst it remained effective, and would switch to an EGFR TKI once there was evidence of disease progression. Therefore, in these cases people would have received their EGFR TKI as a second line treatment, and when it stopped being effective, current practice would be to consider further chemotherapy, most likely a docetaxel-based regimen.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company identified no randomised controlled trials (RCTs) that provided evidence on the clinical benefits of the technology at its licensed dosage within the indication being appraised.

4.2 The company's submission did not present any evidence for osimertinib or relevant comparators for:

- people with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer who have not had previous treatment.
- people who have received previous treatment with an EGFR TKI, and in whom platinum doublet therapy is not appropriate

4.3 The main evidence supporting the company's submission was for people with EGFR and T790M mutation positive NSCLC who have progressed on a prior TKI, came from the non-randomised, non-controlled single arm AURA extension and AURA 2 studies. These studies included people with EGFR T790M mutation-positive NSCLC treated with osimertinib. The

company pooled the data from the AURAext and AURA2 studies to produce a single dataset that was subsequently used to calculate summary efficacy and safety end-points. In order to compare the efficacy of osimertinib with platinum doublet chemotherapy, the company used data from the control group of the IMPRESS clinical trial (see section 4.11).

AURA extension study

4.4 AURA extension was a continuation of the Phase I/II AURA trial. AURA was an open-label, single arm, dose-escalation, expansion and extension cohort study (n=201), which aimed to investigate the safety, tolerability, pharmacokinetics (PK), response to therapy, and AEs of osimertinib in patients with NSCLC which had progressed following treatment with an EGFR TKI.

4.5 There were two cohorts:

- people whose disease had progressed following first-line therapy with an EGFR TKI (second-line cohort; n=50), and
- people who had progressed following treatment with at least two lines of prior therapy including at least one EGFR TKI (third-line cohort; n=175).

4.6 Treatment with osimertinib was continued until disease progression, until a treatment discontinuation criterion was met, or for as long the patients were receiving clinical benefit (determined by the investigator).

AURA 2 study

4.7 The AURA2 Study is a Phase II, open-label, single-arm study (n=210) assessing the safety and efficacy of osimertinib (80 mg, orally, once daily) in patients with a confirmed diagnosis of EGFR and T790M mutation positive NSCLC (stage IIIB–IV), who have progressed following prior therapy with an approved EGFR TKI agent.

4.8 There were two cohorts:

- People with disease progression following first-line therapy with an EGFR-TKI
- people with disease progression following treatment with an EGFR-TKI and a platinum-based doublet (possibly other lines of treatment also).

4.9 In both the AURAext and AURA 2 studies, the primary efficacy endpoint was the overall response rate (ORR) according to RECIST criteria. The ORR was defined as the percentage of patients with at least 1 visit response of complete response or partial response that was confirmed at least 4 weeks later. ORR was based on blinded independent central review (BICR) of the evaluable-for-response population. Secondary outcomes included duration of response, disease control rate, tumour shrinkage, progression-free survival, overall survival and safety and tolerability.

Pooled AURA studies

4.10 Mean age of people in the AURA studies was 62.2 years and an ECOG performance status of 0 or 1. Approximately two-thirds (62.5%) of people had received prior platinum-based chemotherapy in the 2 studies. The majority of people in AURAext and AURA 2 (77.1%) received an EGFR TKI as last regimen before study entry, including 52.6% who did within 30 days of enrolment. Prior EGFR TKIs were mainly gefitinib for 58.2% of patients, erlotinib for 56.9%, and afatinib for 18.0%.

IMPRESS study

4.11 The company used results from the control group of the IMPRESS trial to provide evidence for efficacy of platinum doublet chemotherapy in people with EGFRm+ T790M mutation positive NSCLC who have progressed on a prior TKI. The IMPRESS study evaluated platinum doublet

chemotherapy in people with EGFRm+ advanced NSCLC with or without continuation of EGFR TKI therapy. People included in the IMPRESS trial had a mean age of 58.1 years and an ECOG performance status of 0 or 1.

ERG comments

4.12 The ERG considered that the AURAext and AURA2 studies were designed and conducted to a good standard. In particular, the use of blinded independent central review (BICR) in the assessment of the radiological results lends robustness to the progression-free survival outcomes. The use of a single treatment arm design means that the overall survival data from the AURAext study and AURA2 study were not affected by treatment crossover.

4.13 The ERG noted that people in the AURAext and AURA2, and those in the IMPRESS trial were younger and fitter than people with EGFR mutation-positive who are treated in the NHS

4.14 The ERG noted that there were people included in the AURAext and AURA2 studies who have received multiple EGFR-TKI treatments (up to six in the AURAext study and up to nine in the AURA2 study). Clinical advice to the ERG suggested that in NHS clinical practice, people are usually treated with only one EGFR-TKI (although a second may be offered in the case of toxicity, or if the patient is not considered to be fit enough to receive chemotherapy).

Clinical trial results

4.15 Overall response rate (ORR) based on the pooled data was calculated as the number (%) of patients with best objective response of confirmed complete response (CR) or partial response (PR) from both the AURA ext and AURA 2 studies. Results are presented in table 3.

Table 3. Summary of overall response rate from the pooled AURAext/AURA2 studies (company submission table 4.22)

Analysis set Study	N	Number of patients with confirmed response	ORR (%)	95% CI
BICR assessment of 'evaluable for response' analysis set				
AURAext	199	122	61.3	54.2 to 68.1
AURA2	199	141	70.9	64.0 to 77.1
Total	398	263	66.1	61.2 to 70.7
BICR assessment of FAS (sensitivity analysis)				
AURAext	201	122	60.7	53.6 to 67.5
AURA2	210	142	67.6	60.8 to 73.9
Total	411	264	64.2	59.4 to 68.9
Investigator assessment of FAS (sensitivity analysis)				
AURAext	201	142	70.6	63.8 to 76.8
AURA2	210	148	70.5	63.8 to 76.6
Total	411	290	70.6	65.9 to 74.9

BICR=blinded independent central review; CI=confidence interval; FAS=full analysis set: ORR=overall response rate

4.16 The company stated that at data cut off, all people in the AURA studies had been follow-up for at least 6 months. The preliminary estimate of median PFS using the pooled dataset was 9.7 months (95% CI: 8.3, NC). The results are summarised in table 4. The company highlighted that this estimated proportion was consistent across studies.

4.17 The company stated that overall survival data were still immature (12.7% of people had died in the pooled AURA dataset, and of those remaining, 72% were still on treatment). Results for survival at 3-month intervals are presented in table 4.

Table 4 Summary of progression-free survival and overall survival from AURAext and AURA 2 single arm studies (company submission table 4.27 and 4.28)

	AURAext (osimertinib 80mg) (n=201)	AURA2 (osimertinib 80mg) (n=210)	Total (osimertinib 80mg) (n=411)
Progression-free survival by BICR			
Total number of events	80	79	159
Median PFS months (95% CI)	NC (8.1 to NC)	8.6 (8.3 to 9.7)	9.7 (8.3 to NC)
Median follow-up (months)	6.9	6.7	6.8
% Progression-free at 3 months (95% CI)	81.5 (75.3 to 86.2)	84.9 (79.2 to 89.1)	83.2 (79.2 to 86.5)
% Progression-free at 6 months (95% CI)	72.0 (65.1 to 77.8)	69.7 (62.8 to 75.7)	70.9 (66.1 to 75.1)
% Progression-free at 9 months (95% CI)	54.6 (46.4 to 62.1)	47.7 (36.2 to 58.4)	51.9 (45.3 to 58.1)
Overall survival			
Total number of deaths	28	24	52
Median OS	NC	NC	NC
Survival at 3 months % (95% CI)	96.5 (92.80 to 98.32)	97.1 (93.72 to 98.70)	96.8 (94.59 to 98.14)
Survival at 6 months % (95% CI)	93.0 (88.41 to 95.77)	91.7.0 (86.97 to 94.76)	92.3 (89.27 to 94.54)
Survival at 9 months % (95% CI)	84.0 (77.49 to 88.74)	87.1 (80.83 to 91.49)	85.3 (80.85 to 88.71)
Patients in survival follow-up n (%)	168 (83.6)	181 (86.2)	349 (84.9)
Median follow-up (months)	8.3	7.0	7.4

CI=confidence interval; NC=not calculable; OS=overall survival; PFS=progression-free survival; BICR=blinded independent committee review; FAS=full analysis set

Health-related quality of life

4.18 Two patient-reported questionnaires relating to cancer symptoms were administrated (EORTC LC13 and EORTC LC30). In the AURA extension

and AURA 2 studies, assessment points were at baseline and at each clinic visit up to week 42. The company presented evidence that osimertinib had a significant, measurable and relevant impact on patients HRQoL (health-related quality of life) and symptoms. Improvements from baseline throughout all on treatment assessment time points were observed for dyspnoea, cough, chest pain, pain in arm, pain in shoulder and overall health status. Drug-related side-effects (sore mouth and diarrhoea) appeared to have minimal impact on HRQoL as reported in these studies. The patient reported outcome (PRO) data are supportive of the reported tumour response (using RECIST criteria) and suggest clinical benefit as manifested through an improvement in lung cancer symptoms and general health status improvement with osimertinib.

4.19 As part of the AURA2 study, data were also collected using the EQ-5D-5L questionnaire and the EQ-VAS (visual analogue scale). The company stated that the EQ-5D Index and VAS score showed that people on osimertinib have also a clinically significant improvement from baseline which was evident in AURA2 from 12 weeks onwards.

ERG comments

4.20 The single arm design of the AURAext and AURA 2 studies provided challenges in interpreting the results. The lack of results from a comparator arm means that it is difficult to interpret how much treatment effect can be attributed to osimertinib and may have been subject to bias and confounding. The lack of a comparator arm also meant that no direct comparison of the clinical effectiveness of osimertinib with any of the comparators listed in the final scope issued by NICE was available. The interpretation of the results of the AURAext and AURA2 studies was also hampered by the very immature survival data.

4.21 The ERG questioned the generalisability of the results from the AURAext and AURA2 studies to the population of interest who would be treated in the NHS. The patients recruited to the studies were younger and fitter

(ECOG PS 0 or 1) than similar patients seen in NHS clinical practice. Clinical advice to the ERG suggested that, typically, this population treated in the NHS are aged between 65 and 70 years and the majority have an ECOG PS of 1 or 2; whereas people in the two AURA studies had a mean age of 62 years and an ECOG PS of 0 or 1. The AURAext study was open to recruitment at two centres in the UK; however, it was not clear how many patients were recruited from the UK. The AURA2 study was not open to recruitment from UK centres.

4.22 The ERG highlighted that the lack of mature survival data was a particular difficulty in this appraisal. The OS in the pooled AURA dataset has reached only 12.7% maturity; this clearly precludes any reliable assessment of the OS benefit of treatment with osimertinib.

4.23 The ERG considered that, because the AURAext and AURA 2 studies were very similar in terms of recruitment criteria and patient baseline characteristics, it was reasonable to pool the data. The ERG also acknowledged that results generated independently using data from the two studies were similar to results generated from the pooled dataset.

4.24 The ERG cautioned that as the HRQoL data are reported separately for each study, the results are based on relatively small numbers of respondents. At baseline, the number of respondents who completed the EQ-5D-5L questionnaire and the EQ-VAS was 175; by week 36, only 30 patients completed the questionnaires.

4.25 The ERG noted that the AURA2 population baseline index score (a population with advanced or metastatic NSCLC) was higher than the UK population norm for the 55-64 years of age group. However, this difference in index score is difficult to interpret as a) there is no UK value set for the EQ-5D-5L tool and b) the UK population norms were estimated using the EQ-5D-3L tool.

Indirect comparison

4.26 The company presented an unadjusted comparison of the pooled AURA data and the single arm from the IMPRESS control group (platinum doublet therapy). The ORR for the T790M population receiving platinum doublet chemotherapy was 39% (from the IMPRESS study) compared with 64.2% observed within the osimertinib cohort from the AURA programme. The median PFS was 5.3 months for platinum doublet chemotherapy compared with 9.7 months for osimertinib. The median OS was 15.7 months for platinum doublet chemotherapy but overall survival had not been reached for osimertinib in the AURA studies.

4.27 To further evaluate the treatment effect of osimertinib monotherapy compared with platinum doublet chemotherapy, the company presented an adjusted indirect comparison of the two non-randomized individual patient data sets from the AURAext/2 studies (n=411) and the T790M subgroup of the placebo arm of the IMPRESS study (n=61), respectively. The T790M mutation positive adjusted data set was derived from the full analysis set of the:

- Pooled AURAext/2 data set that were centrally confirmed as T790M mutation positive (n=405)
- T790M mutation positive subgroup of the IMPRESS placebo arm (n=61)

4.28 The company assessed overlap of baseline characteristics between the treatment arms using propensity score matching (a statistical method that attempts to estimate the effect of a treatment, by accounting for differences in baseline characteristics). The T790M+ adjusted dataset included:

- Osimertinib arm comprising the pooled AURA data set with confirmed T790M mutation positive status with matched patients from IMPRESS placebo arm (n=287)

- Platinum doublet chemotherapy arm comprising the T790M mutation positive subgroup of the placebo arm of IMPRESS with matched patients from pooled AURA data set with confirmed T790M mutation positive status (n=51)

Table 5 Comparison of key efficacy outcomes between AURA and IMPRESS in T790M mutation positive patients (company submission tables 4.11, 4.12, 4.14)

Outcome		**AURA pooled** (n=411), Osimertinib 80mg	**IMPRESS T790M mutation positive** (n=61) (platinum doublet chemotherapy)	**Adjusted data sets**	
				Pooled AURA dataset	IMPRESS trial T790M+adjusted dataset
ORR	Total responses (%)	263* (**66.1%**, 95% CI: 61.2, 70.7)	24 (**39.3%**, 95% CI not reported**)**	179 (64.6%)	16 (34.8%)
PFS	Total events (%)	159 (**38.9%**)	51 (**83.6%)**	106 (36.9%)	42 (82.4%)
	Median [months] (95% CI)	9.7 (8.9-non-calculable)	5.3 (not reported)	9.7 (8.3 to NC)	5.3 (4.0 to 6.1)
OS	Total events (%)	52 (12.7%)	20 (32.8%)	33 (11.5)	15 (29.4)
	Median [months] (95% CI)	Not reached	15.7	NC (NC to NC)	21.7 (12.55 to NC)

CI=confidence interval; NC=not calculable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival;

4.29 The company reported that the adjusted results were consistent with the reported data for the full analysis set (n=411) from AURAext/2 (osimertinib median PFS 9.7 months; 95% CI 8.3, NC) and for the platinum doublet chemotherapy arm (n=127) of IMPRESS (5.4 months; 95% CI 4.6, 5.5).

4.30 The company stated that the PFS hazard ratio of 0.28 indicated a large, statistically significant improvement for osimertinib group compared with

the platinum doublet chemotherapy group (HR 0.280, 95% CI 0.185, 0.422; p-value < 0.0001) with median PFS of 9.7 months (95%CI 8.3, NC) for the osimertinib group compared with 5.2 months (95%CI 4.0; 6.1) in the matched platinum doublet chemotherapy cohort.

4.31 The company commented that the indirect comparison and matched adjustment of AURA compared with IMPRESS presented in the company submission should be interpreted with caution because of the heterogeneity of the data and imbalances in patient population. The company also highlighted that the retrospective analysis of IMPRESS for T790M by 'circulating tumour' DNA (ctDNA) testing was not prespecified.

ERG comments

4.32 The ERG was concerned that the clinical evidence presented by the company to support the use of osimertinib in people who have had previous treatment with an EGFR-TKI is not robust because the company had to (i) pool very immature clinical data from two single-arm studies (ii) retrospectively identify patients in the control arm of the IMPRESS trial who tested positive for the EGFR T790M mutation and (iii) carry out an unadjusted and an adjusted treatment comparison. The ERG also highlighted that the overall survival data from the pooled AURA dataset were only 12.7% mature at the time of submission and therefore no reliable long-term safety outcome data are available.

4.33 The ERG commended the company on the lengths taken to facilitate a comparison of the effectiveness of osimertinib with platinum doublet therapy, but considered that only a well-controlled, head-to-head RCT can avoid unobserved confounding. The ERG were concerned that data from single-arm, non-controlled studies (AURAext and AURA2) were compared with data from a retrospectively identified subgroup participating in a good quality placebo-controlled, double-blind RCT (IMPRESS). Furthermore, this IMPRESS subgroup only included 61 patients and OS data were only 32.8% mature. The ERG highlighted that [redacted]

[redacted]. Clinical advice to the ERG suggests that these may be important prognostic factors

4.34 The ERG noted that when testing for statistically significant differences in baseline variables, [redacted]; the rationale behind this choice is not explained. Furthermore, [redacted]

4.35 The ERG noted as well as the concerns about the immature OS data, the adjustments made by the company [redacted]

Adverse effects of treatment

4.36 The company presented an unadjusted comparison of the key safety data and noted that despite differences in the average number of lines of prior treatment, osimertinib appeared to be associated with fewer ≥ grade 3 adverse effects (AEs) compared with platinum doublet chemotherapy (29.4% vs 41.7% respectively) and with, less AEs leading to treatment discontinuation (4.1% vs 9.8% respectively). See table 6.

Table 6. Comparison of key safety data between AURA and IMPRESS (adapted from table 4.9 of the company submission)

AE category	Number (%) of patients[a]	
	AURA pooled osimertinib 80 mg	IMPRESS Control Group
Sample Size	(N=411)	(N=132)
Patients with any AE	401 (97.6)	130 (98.5)
CTCAE ≥grade 3 AEs	121 (29.4)	55 (41.7)
SAEs	83 (20.2)	28 (21.2)

Fatal SAEs	9 (2.2)	8 (6.1)
AEs leading to discontinuation	17 (4.1)	13 (9.8)
AEs leading to dose modification	81 (19.7)	NR

[a]People 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.
CTCAE = Common Terminology Criteria for Adverse Events version 4.0; MedDRA version 17.1.

4.37 The company presented data on the most common adverse events for osimertinib (see table 4.10 of the company submission) which were diarrhoea (42.3% any grade; 1.0% grade 3 or above) and rash (41.4%) any grade; 0.2% grade 3 or above). In the company's unadjusted comparison with the IMPRESS control group, the incidences of diarrhoea (14.4% any grade; 0.8% grade 3 or above) and rash (8.3% any grade; 0% grade 3 or above) were lower for platinum doublet therapy.

ERG comments

4.38 Clinical advice to the ERG is that, in NHS clinical practice, incidences of diarrhoea and fatigue can be difficult to manage, particularly in an elderly population.

5 Cost-effectiveness evidence

Model structure

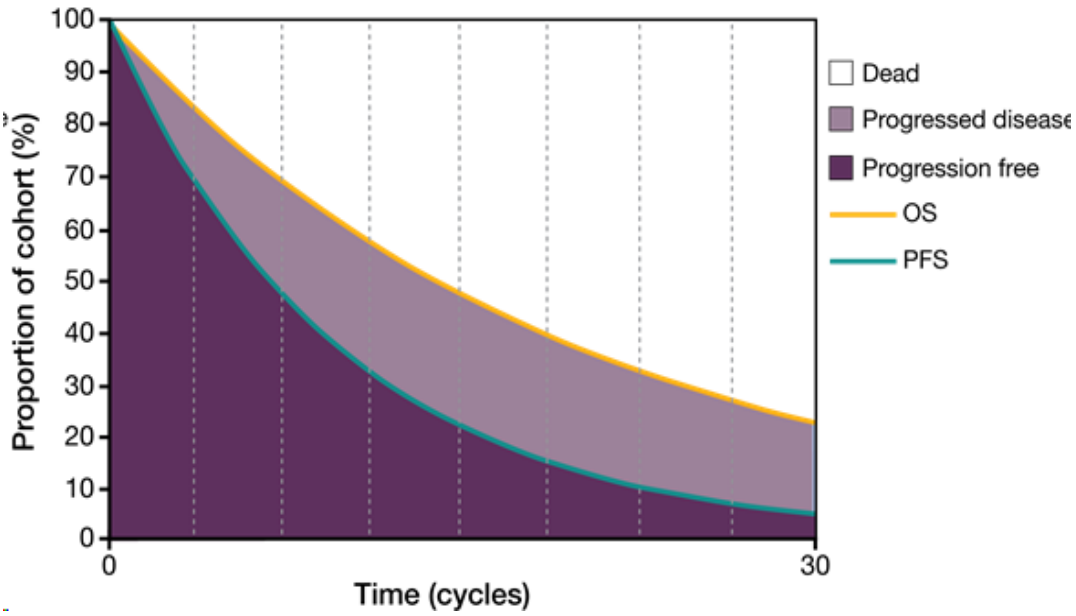
5.1 The company base case cost effectiveness analysis, compared osimertinib with platinum doublet chemotherapy (PDC – specifically, cisplatin+pemetrexed). It considered people with locally advanced or metastatic EGFR and T790M mutation positive NSCLC who have progressed on or after EGFR TKI therapy. The cost-effectiveness analysis did not consider people with locally advanced or metastatic EGFR and T790M mutation positive NSCLC who have not received prior treatment

with an EGFR TKI because of the small number of people who were treatment-naïve in the AURAext/2 studies. The model also evaluated the following subgroups from the AURA study programme and are investigated as part of the company's subgroup analysis:

- Second-line (only) - after treatment with an EGFR TKI
- People who have had treatment with both an EGFR TKI and chemotherapy

5.2 The company presented a cohort-based partitioned survival model including three health states – progression-free (PF), progressed disease (PD) and death. The model used a lifetime horizon of 15 years, a cycle length of 1 week, a mean starting age of 62.17 years and a discount rate of 3.5% for utilities and costs.

Figure 2. Company's partitioned survival analysis model structure (see figure 5.2 of the company's submission)



5.3 For osimertinib, the company used pooled data from the AURAext (n=201) and AURA2 (n=210) studies to estimate progression-free survival and overall survival. For the comparator, platinum-doublet therapy

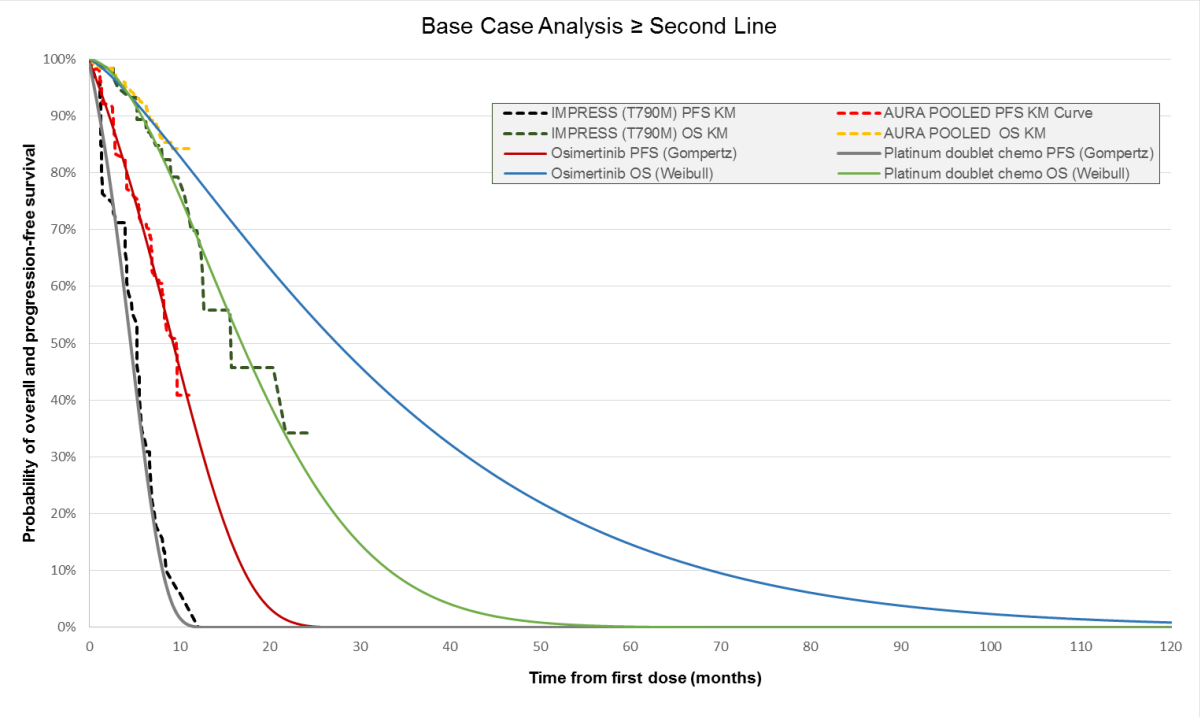
(pemetrexed plus cisplatin), Kaplan–Meier data from the IMPRESS study were used in the economic model to estimate progression-free survival and overall survival. Because of the immaturity of the data, the company used independent survival models for osimertinib and comparator treatments. The parametric model fitting was based on the clinical trial data from AURAext/2 and IMPRESS studies and then extrapolated using standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised Gamma). The company used visual inspection and statistical goodness-of-fit to assess the parametric models for progression-free survival and overall survival.

5.4 For progression-free survival, Gompertz distribution was selected for PFS in the base case analysis of the model due to having the best visual fit for both osimertinib and platinum doublet chemotherapy (see figure 3). Scenario analyses were also conducted for the Weibull and Generalised gamma distributions as they also provided a good visual fit to the non-parametric data from AURAext/2 and IMPRESS.

5.5 The company chose to use the Weibull distribution for overall survival in the base case analysis for both osimertinib and platinum doublet therapy because it appeared to be the most reasonable fit to the non-parametric OS data, based on the currently available data from AURAext/2 and IMPRESS studies. The parametric curves used in the base case analysis show that, compared with platinum doublet therapy, treatment with osimertinib results in an incremental progression-free survival gain of 4.8 months and an incremental overall survival gain of 10.6 months.

5.6 Approximately 14.8% of patients treated with osimertinib are alive at 5 years compared to 0.2% of patients on platinum doublet chemotherapy. After 10 years in the model (120 months in Figure 3), the proportion of patients alive is close to 0% for both treatments.

Figure 3 Overall survival and progression-free survival curves used in the base case analysis (company submission figure 5.7)



5.7 The company's subgroup analysis explored the use of osimertinib in second-line only and ≥third-line settings compared with platinum doublet chemotherapy and single-agent chemotherapy. Because of the immaturity of the AURA pooled data, it was assumed there was no difference in overall survival by line of treatment and therefore the data for ≥second-line was used for second-line only and ≥third-line subgroup analyses. For data on single agent chemotherapies, no survival data were identified in the company's literature review specifically for docetaxel monotherapy. The company made a simplifying assumption that docetaxel has the same clinical efficacy as pemetrexed monotherapy in the second-line only setting.

5.8 For simplicity, the parametric distributions selected by the company for the subgroup analyses were the same as those used in the base case analysis; the Gompertz distribution was used to extrapolate PFS and the Weibull distribution was used to extrapolate overall survival.

ERG comments

5.9 The ERG considered that the company's model was well constructed with no flaws in the algorithms and was straightforward to use.

5.10 In relation to the company's approach to overall survival for both osimertinib and platinum doublet therapy, which used statistical tests (AIC and BIC) as well as visual inspection of how well the curves fitted the data and clinical plausibility) the ERG considered this was broadly acceptable given the paucity of relevant survival data available, especially for osimertinib. The ERG commented that it would have been preferable to use all of the available clinical trial data before employing the statistical distribution, rather than using the company's choice of distribution over the whole time horizon. However, in this case, given that the trial data were only available for 10 months for osimertinib, the ERG considered that using actual overall survival data before using a particular distribution would not have had a significant impact on the cost effectiveness results.

5.11 The ERG noted that because the populations within the AURA studies and the IMPRESS trial appeared to be fitter than people with EGFR mutation–positive NSCLC who would be expected to be seen in clinical practice, there is doubt on the appropriateness of using these datasets to represent the UK EGFR mutation-positive population even if it was fully mature.

5.12 Therefore the ERG considered that the overall survival projections employed by the company were based on opinion rather than supported by evidence.

Model details

5.13 Resource use, costs and health state utilities were estimated based on information from the AURAext/2 studies and the IMPRESS trial, previous NICE technology appraisals, published literature and clinical experts. The following assumptions were applied in the base case analysis:

- Progression-free survival is assumed to be a predictor of treatment duration so that all patients stop primary treatment on progression
- The average treatment doses used in the model are assumed to account for dose reductions and treatment holidays
- Treatment-related adverse events, and their associated costs and disutilities, are applied as one-off events and they are resolved prior to disease progression
- Disease management costs (PF and PD) are applied as constant (rather than time-varying) costs in the respective health state
- Vial sharing (no drug wastage) is assumed for all treatment comparators in the base case
- The impact of treatment on quality of life is captured through disease progression and adverse event disutilities. In the base case analysis health state utilities are not treatment specific or dependent on response status

5.14 Health-state utilities in the model were calculated from EQ-5D-5L which were collected every 6 weeks in the AURA 2 study For the base case analysis the company did not consider it appropriate to apply treatment-specific utility values for the progression-free and post-progression states from the AURA2 and IMPRESS studies respectively. However, treatment-specific utility values from AURA2 and IMPRESS were explored in a scenario analysis. A summary of the health state utility values used in the base case analysis and subgroup analyses is presented in table 7.

Table 7 Health state utility values used in the base case analysis (table 5.15 of the company submission)

Health state	Mean utility	Standard deviation
Base case analysis (≥second-line population)		
Progression-free	0.815	0.183
Post-progression	0.678	0.314
Second-line only population		
Progression-free	0.853	0.139
Post-progression	0.726	0.319
≥Third-line population		
Progression-free	0.798	0.198
Post-progression	0.659	0.316

5.15 Utility decrements because of grade 3 or grade 4 adverse events were included in the base case analysis. These are summarised in table 8. The disutility associated with specific adverse events was assumed to last for a period of one month (i.e. 4 weekly cycles).

Table 8. Disutilities and costs associated with adverse events (from table 5.18 and 5.30 of the company submission)

Adverse event	Disutility	Cost
Diarrhoea	0.047	£431.54
Rash (grouped term)	0.032	£435.92
Nausea	0.048	£449.94
Platelet count decreased	0.05	£83.00
Fatigue/asthenia	0.073	£502.63
Oedema peripheral	0.05	£478.31
Constipation	0.05	£610.63
Cough	0.05	£365.66
Stomatitis	0.05	£0.00
Vomiting	0.048	£0.00
Anaemia	0.073	£0.00
Headache	0.05	£0.00

Adverse event	Disutility	Cost
Febrile neutropenia	0.090	£2,426.86
Neutropenia / Leucopenia / Neutrophil count decreased	0.090	£421.67
Back pain	0.05	Cost

ERG comments

5.16 The ERG considered that the utilities applied in the company model appeared to be implausible because they were higher in the progression-free state (0.815) than in the general population for people of the same age at the start of the model (0.80). While no utility values were available specifically for the population described in the company submission, the ERG considered that there were alternative utility values that might be closer to the actual values of the target population compared to the utility values used in the model.

5.17 The ERG considered that there were two studies that could possibly provide utility values closer to the real utility of the target population than those used in the company model: utility values collected during the LUME-Lung 1[65] trial and utility values reported in the Nafees study. The ERG commented that even though both these alternative sources have flaws they do provide an alternative estimation of ICERs and it is possible that they may provide a better reflection of the experience of those with advanced or metastatic NSCLC than currently available from trial data. These are explored in the ERG's analyses.

Costs

5.18 The cost of T790M testing included both the acquisition cost of the test itself plus other costs incurred during the visit for the test. Drug acquisition costs were calculated based on available formulations; pack sizes, unit costs and price per mg for each (combination of) treatment included in the

model. Dosing information was taken from the EMA label for each treatment and the drug acquisition costs were taken from the BNF for branded products. For the combination treatment 'platinum doublet chemotherapy' it was assumed that pemetrexed plus cisplatin was used. The base case analysis used patient characteristics for the whole population from AURA ext/2 while data from the second-line only and ≥third-line subgroups were used in subgroup analyses. The drug administration costs for intravenous treatments included the cost of chemotherapy infusion and premedication with dexamethasone. For all oral treatments administration costs were assumed to be £0. Tables 9 summarises the key costs included in the model.

Table 9 Costs included in the model (adapted from tables 5.21, 5.23, 5.24 of the company's submission).

Resource use	Cost applied in the model
Cost of osimertinib (per pack)	£4,722 (not including PAS)
Cost of pemetrexed (per vial)	£160
Cost of cisplatin (per vial)	£3.24
Administration cost per dose (platinum doublet chemotherapy) – first visit	£251.19
Administration cost per dose (platinum doublet chemotherapy) – subsequent visits	£326.46
Disease management costs – Progression-free state	£77.42
Disease management costs – Progressed state	£139.52
Terminal care cost	£3,905.26
EGFR T790M test costs	
Tissue biopsy (test and sample procedure)	£725 (£147 and £578)
ctDNA (plasma) - (test and sample procedure)	£472 (£147 and £325)
Admin cost for platinum doublet therapy	
Chemotherapy IV infusion – First attendance	£239.12
Dexamethasone (8mg/day for 3 days)	£6.04
Chemotherapy IV infusion – Subsequent attendances	£326.46
Dexamethasone (8mg/day for 3 days)	£6.04

ERG comments

5.19 In the 2 AURA studies, people could continue receiving osimertinib after disease progression. Therefore, the ERG highlighted that progression-free survival was not a good basis for estimating treatment cost and that time to treatment discontinuation should be used (requested during clarification step). The ERG commented that if the time to treatment discontinuation data from the two AURA studies is used to estimate the acquisition cost of osimertinib instead of the progression-free survival data, this would result in higher costs for osimertinib. The ERG included use of time to treatment discontinuation in its exploratory analyses.

5.20 The company model did not include a cost for the administration of osimertinib. Clinical advice to the ERG suggested that osimertinib is provided, on a monthly basis, in a nurse led clinic. The 2014-15 NHS Reference Cost to deliver exclusively oral chemotherapy (SB11Z, setting: "Other") is £128. The ERG noted that introducing a cost for administering osimertinib increased the total cost per patient would therefore increase the ICER for osimertinib versus PDC (see ERG exploratory analyses, section 5.32 and table 14)

Company's base-case results and sensitivity analysis

5.21 The company's base case analysis was based on the second-line or later population from AURAext/2 for osimertinib and the T790M mutation positive second-line population from the platinum doublet chemotherapy arm of the IMPRESS study. In the base case analysis including the patient access scheme discount, osimertinib generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime horizon gained compared with platinum doublet chemotherapy, resulting in an ICER of £42,959 per QALY gained.

Table 10. Company's base case results (company patient access scheme submission, table 4)

Technologies	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£) incremental (QALYs)
With inclusion of PAS					
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	£42,959
Platinum doublet chemotherapy	[redacted]	[redacted]			
Without inclusion of PAS					
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum doublet chemotherapy	[redacted]	[redacted]			

Abbreviations: Incr. – incremental; ICER - incremental cost-effectiveness ratio; PAS – patient access scheme; QALY – quality-adjusted life years;

5.22 The mean probabilistic ICER calculated from the outputs of the 10,000 simulations was £42,148 per QALY gained. The company presented a cost-effectiveness acceptability curve for osimertinib compared with platinum doublet chemotherapy (see figure 2 of the company patient access scheme submission). At a cost-effectiveness threshold of £50,000, osimertinib has a 62% probability of being cost-effective compared with platinum doublet chemotherapy.

Table 11. Company's deterministic sensitivity analysis – Osimertinib compared with platinum doublet therapy including patient access scheme discount (adapted from table 5.39 of the company's submission and section 4.9 of the patient access scheme submission)

Parameter		Parameter values			Lower value (ICER)	Upper value (ICER)
		Lower value	Base case	Upper value		
Body surface area (m²)		1.34	1.68	2.02	46,846	48,799
Discount rate	Costs	0.0%	3.5%	6.0%	46,707	49,611
	Outcomes	0.0%	3.5%	6.0%	43,323	51,073
Disease management	PF	£62	£77	£93	47,295	48,350
	PD	£112	£140	£167	46,866	48,779
	TC	£3,124	£3,905	£4,686	47,787	47,858
Drug acquisition cost: PDC		£369	£461	£554	46,847	48,798
Testing cost	ctDNA	£378	£472	£566	47,676	47,969
	Biopsy	£752	£940	£1,128	47,654	47,991
Health state utility	Osimertinib: PF	0.652	0.815	0.978	40,428	58,528
	Osimertinib: PD	0.542	0.678	0.814	37,762	65,191
	PDC: PF	0.652	0.815	0.978	44,441	51,761
	PDC: PD	0.542	0.678	0.814	40,629	58,111

PF=progression-free; PD=progressed disease; TC=terminal care; PDC=platinum doublet chemotherapy; ICER=incremental cost effectiveness ratio

ERG comments

5.23 The ERG considered that any ICER that relies on a QALY benefit that is over 90% generated by a projection is highly uncertain and that this level of uncertainty renders its use in decision-making questionable.The ERG acknowledged that treatment with osimertinib statistically significantly improved progression-free survival compared to treatment with platinum doublet therapy. However, The ERG considered that there was no clinical or statistically significant basis to support any difference in overall survival between osimertinib and platinum doublet therapy and therefore the company base case should only comprise a progression-free survival gain

for osimertinib and no overall survival gain. The ERG considered that hypothetical overall survival gains should be employed only in the company's scenario analyses and it investigated this in its exploratory analyses.

5.24 The ERG commented that even if the company's overall survival projection was accurate, the company has underestimated the acquisition costs of osimertinib because the use of PFS data, rather than time to treatment discontinuation (TTD) data, underestimated the cost of osimertinib treatment and overestimates the cost of platinum doublet therapy. In addition the ERG commented that the company submission did not take into account any administration cost of osimertinib as an oral chemotherapy. In its exploratory analyses, the ERG used time to treatment discontinuation data from the AURA studies and the IMPRESS trial and a cautious estimate of the NHS Reference Cost for oral chemotherapy administration and this resulted in substantial increases in the size of the ICER per QALY gained from the company base case.

5.25 The ERG noted that the company presented data on time spent in the progression-free survival and overall survival states, as predicted by the company model, to justify the distribution chosen to represent overall survival. The ERG acknowledged that the ratio of time in overall survival to progression-free survival predicted by the company model is similar for people treated with osimertinib (2.85) and for people treated with platinum doublet therapy (2.96). However, the reported range across the studies is large (between 2.18 and 5.38 for active treatment arms and 2.24 and 7.60 in control arms), which suggests that the relationship between overall survival and progression-free survival is complex and that there is no basis to assume that the same, or similar, OS/PFS ratios exist in this case.

5.26 The ERG highlighted that aside from concerns about the reliability of the overall survival representation of both osimertinib and platinum doublet

therapy within the company model, the ERG considered that, even if the survival data were fully mature, they would not reflect the experience of the population described in the final scope issued by NICE (see section 4.17).

Company scenarios

5.27 The following scenario analyses were presented by the company:

Survival modelling scenarios:

- used the data related to the full analysis set (rather than just the T790M population) from the platinum doublet chemotherapy arm (n=127) in the IMPRESS study
- applied other parametric distributions to the non-parametric OS data currently available from AURAext/2 and the IMPRESS T790M mutation positive population (log-logistic, Weibull, G Gamma, Gompertz and exponential). In each of these scenarios the same parametric distribution was applied to the non-parametric PFS data

Health state utility values:

- applied treatment-specific EQ-5D utility values for the progression-free and progressed disease states from the AURA2 and IMPRESS studies respectively
- A progressed disease utility decrement of -0.1798 taken from the study by Nafees *et al.* was applied because it is possible that the utility value (0.678) applied in the base case may not fully reflect the expected deterioration in a patients' HRQoL as they progress on to subsequent chemotherapy

Resource costs:

- Excluding costs of T790M mutation testing

- The company included a scenario assumption that 20.2% of patients in the osimertinib arm would have an additional 2 months of treatment post-progression. This was because in AURAext/2 there was no maximum duration of treatment as patients could continue to receive osimertinib beyond RECIST progression as long as they were benefitting clinically

- A scenario with a lowered list price (by 75%) for pemetrexed to take account of it becoming available as a generic medicine later in 2016

Table 12 Company scenario analyses for osimertinib vs platinum doublet chemotherapy including patient access scheme discount (from table 5.40 of the company submission)

Scenario	Inc. cost	Inc. QALY	ICER (£/QALY)
Base case	[redacted]	[redacted]	**42,959**
Survival modelling scenarios			
IMPRESS ITT population PFS/OS data	[redacted]	[redacted]	49,853
PFS and OS Distribution – Log Logistic (both arms)	[redacted]	[redacted]	43,299
PFS and OS Distribution – Log Normal (both arms)	[redacted]	[redacted]	31,289
PFS and OS Distribution – Weibull (both arms)	[redacted]	[redacted]	47,822
PFS and OS Distribution – G Gamma (both arms)	[redacted]	[redacted]	145,984
PFS and OS Distribution – Gompertz (both arms)	[redacted]	[redacted]	1,052,785
PFS and OS Distribution – Exponential (both arms)	[redacted]	[redacted]	43,430
Health state utility scenarios			
Treatment-specific utility values (Osimertinib – AURA2; PDC – IMPRESS)	[redacted]	[redacted]	43,125
Progressed disease utility decrement (Nafees *et al*): -0.1798 (both arms)	[redacted]	[redacted]	44,604
Resource use and costs scenarios			
Exclude T790M test costs	[redacted]	[redacted]	41,344

Treatment after RECIST progression - osimertinib	[redacted]	[redacted]	44,583
Assume Pemetrexed generic costs (75% discount)	[redacted]	[redacted]	46,015
Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio			

ERG comments

5.28 The ERG commended the company for investigating the uncertainty around the company's overall survival projections and for demonstrating how this uncertainty affects the size of the estimated ICERs. The ERG noted that this was particularly demonstrated when a Gompertz distribution was used for progression-free survival rather than a Log normal distribution resulting in large increases in the ICER.

5.29 The ERG considered that all of the distributions that were used in the survival modelling scenario analyses can, visually, be considered to provide a good fit to the available osimertinib overall survival Kaplan-Meier data. However, the ERG was not confident that any of the ICERs generated by the company model were sufficiently robust to inform decision-making.

Subgroup analyses

5.30 The company presented cost-effectiveness analyses of osimertinib in second-line only and third- and further line settings as subgroup analyses.

Table 13. Subgroup analyses including the patient access scheme discount (adapted from table 5.42, 5.43 and 5.44 of the company's patient access scheme submission)

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Osimertinib vs platinum-based chemotherapy (second-line only population)					
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	39,610

PDC	[redacted]	[redacted]			
Osimertinib vs docetaxel monotherapy (second-line only population)					
	[redacted]	[redacted]	[redacted]	[redacted]	47,358
	[redacted]	[redacted]			
Osimertinib vs docetaxel monotherapy (≥Third-line population)					
	[redacted]	[redacted]	[redacted]	[redacted]	40,900
	[redacted]	[redacted]			

ERG comments

5.31 The ERG did not identify any statistically significant difference in progression-free survival and overall survival by line of treatment for osimertinib and did not consider the evidence on single-agent chemotherapy to be convincing. As such, the ERG did not consider the results of the company's subgroup analyses to be informative.

ERG exploratory analyses

5.32 The ERG noted minor errors related to adverse event costs, discounting and the platinum doublet therapy costs per dose. However, as the impact of correcting these minor errors would only have a small impact on the size of the ICERs, the ERG did not include these minor errors in its exploratory analyses. Similarly, the testing costs for the EGFR T790M mutation were estimated to have only a small impact on the size of the ICERs and were not included in the ERG analyses.

5.33 The amendments made by the ERG to the company model are:

- use of time to treatment discontinuation data (TTD) to calculate the acquisition costs of osimertinib and platinum doublet therapy (R1)
- application of an administration cost for osimertinib (R2)
- use of health state utility values from LUME-Lung 1 study1 (R3)
- use of health state utility values from a study by Nafees (R4)
- progression-free survival gain only (i.e., equal overall survival gain for osimertinib and platinum doublet therapy) (R5).

5.34 The ERG's revised base case ICERs per QALY gained for osimertinib versus PDC, when all of the preferred revisions are combined and using the PAS price for osimertinib, range from £513,286 (Scenario G in table 14) to £1,334,543 (Scenario F) per QALY gained.

Table 14. ERG exploratory analyses including patient access scheme discount (adapted from table 43 of the ERG report)

	Osimertinib		**Platinum doublet therapy**		**Incremental**		**ICER**
Scenario	**Total cost**	**Total QALY**	**Total cost**	**Total QALY**	**costs**	**QALY**	
Company's base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£42,959***
R1) Use of time to treatment discontinuation data to cost drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,870
R2) Application of administration cost for osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,444
B. Base case + (R1:R2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£67,249**
R3) LUME-Lung 1[1] utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,459
C. Base case + (R1:R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£74,267**
R4) Nafees[2] utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£57,853
D. Base case + (R1:R2 and R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£90,531**
R5) Osimertinib generates a gain in PFS but not OS compared to PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£366,596
E. Base case + (R1:R2 and R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£648,736**
F. Base case + (R1:R3 and R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£1,334,543**
G. Base case + (R1:R2, R4:R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£513,286**

Abbreviations: Inc., incremental; QALY, Quality adjusted life year; ICER, incremental cost effectiveness ratio

Innovation

5.35 Justifications for considering osimertinib to be innovative:

- Osimertinib is a newly developed third-generation oral, irreversible EGFR TKI differing from current EGFR TKIs because it selectively targets EGFR-sensitising and T790M-resistant mutations and has higher selectivity for EGFR mutations than EGFR 'wild-type', which may improve the tolerability profile seen with first-generation TKIs
- The company does not foresee any significant and substantial health-related benefits within this patient population outside of the QALY calculation

6 End-of-life considerations

6.1 The company made a case for osimertinib to be considered as an end-of-life treatment.

Table 15. End-of-life considerations

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**For treatment-naïve population:** Current standard of care, consisting of treatment with 1st generation EGFR TKI's, reports median overall survival in the range of 20 months (21.6 months IPASS – gefitinib; 19.3 months EURTAC – erlotinib). **For people who have been previously treated with an EGFR TKI:** • The reported median overall survival in the control group of the IMPRESS trial was 17.2 months. In the subgroup of T790M mutation positive patients, the reported median OS was 15.7 months. • The other groups defined in the NICE decision problem (platinum ineligible / 3rd line)

	would be expected to have a worse life expectancy compared to a 2nd line population treated with platinum doublet chemotherapy. Treatment with single-agent chemotherapy in an EGFRm+ population reports a median overall survival in the range of 15 months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Currently, the overall survival data are immature. The OS data at the time of analysis was 11.5% maturity for osimertinib and 29.4% for the platinum doublet chemotherapy cohort. • The Kaplan–Meier risk set beyond 12 months for both osimertinib and chemotherapy in the matched, adjusted comparison is very limited (n <15 patients) leading to unstable estimates beyond this time point, especially for the estimation of medians. However, given that 68.6% of patients received osimertinib as ≥ third-line therapy the median time to PFS (9.7 months) and the Kaplan-Meier estimate of the proportion of patients alive at 6 months (92.3%; 95% CI: 89.3, 94.5), and 9 months (85.3%; 95% CI:80.9, 88.7) is consistent with a meaningful improvement over current SOC. • When the most appropriate parametric curves are used the economic model produces a median overall survival of 27.7 months for osimertinib compared with 15.7 months for current NHS standard of care (platinum doublet chemotherapy) over a lifetime horizon, resulting in a median OS gain of 12 months (see Section 5.7) • There is currently no survival data available for people receiving osimertinib as a first-line treatment. However, it is unlikely that the overall survival benefit would be smaller than that observed in the relapsed setting. Therefore, comparing the estimated medians to the observed medians in IPASS and EURTAC studies referred to above, it is highly likely that osimertinib is associated with an extension to life of at least 3 months in the small of group of patients eligible first line.

7 Equality issues

7.1 No issues raised by the company or consultees.

8 Authors

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Appendix A: Clinical efficacy section of the draft European public assessment report

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004124/WC500202024.pdf

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Osimertinib for locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of osimertinib within its marketing authorisation for locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer.

Background

Lung cancer falls into two main histological categories: around 85–90% are non-small-cell lung cancers (NSCLC) and the remainder are small-cell lung cancers. The majority of lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV). People with NSCLC can be either epidermal growth factor receptor (EGFR)-positive or EGFR-negative and those with EGFR-positive disease can receive EGFR tyrosine kinase inhibitor (EGFR-TKI) treatment. A mutation can occur at the 790 position of the EGFR, T790M, causing resistance to EGFR-TKI treatment. The T790M mutation may be present either before or after treatment with an EGFR-TKI, and accounts for approximately 50% of EGFR-TKI resistance[1].

In 2013, approximately 26,800 people were diagnosed with NSCLC in England, of whom 23% had stage III and 46% had stage IV disease[2]. Lung cancer caused 28,000 deaths in England in 2012[3]. The median survival with lung cancer (all stages) is approximately 6 months; 35% of people with lung cancer, and 14% of people with stage IV disease, survive for more than 1 year[3,4].

For the majority of people with NSCLC, the aims of therapy are to prolong survival and improve quality of life. For people whose disease tests positive for the EGFR-TK mutation and who have not previously received treatment, NICE guidance recommends the TKI afatinib, erlotinib and gefitinib as treatment options (NICE technology appraisal guidance 310, 258 and 192). Following disease progression on a TKI, pemetrexed in combination with either cisplatin or carboplatin is used in clinical practice. For those people for

[1] NIHR Horizon Scanning Centre briefing note
[2] Cancer Research, Biological therapy for lung cancer. Accessed May 2015
[3] Health and Social Care Information Centre (2014) National Lung Cancer Audit: 2013 patient cohort. Accessed June 2015.
[4] Cancer Research UK (2014) Lung cancer statistics. Accessed June 2015

whom treatment with a platinum drug is not appropriate, NICE clinical guideline 121 'Lung cancer' recommends that people should be offered single agent chemotherapy with either docetaxel, gemcitabine, paclitaxel or vinorelbine. Where the disease progresses following treatment with chemotherapy, NICE clinical guideline 121 'Lung cancer' recommends that docetaxel monotherapy should be offered. NICE guidance also recommends nintedanib in combination with docetaxel as an option for people with adenocarcinoma that has got worse after previous chemotherapy (NICE Technology Appraisal 347).

The technology

Osimertinib (previously referred to AZD9291; Tagrisso, AstraZeneca) is a small molecule inhibitor that targets the sensitising and T790M mutant forms of the EGFR-TK. It is administered orally.

Osimertinib does not currently have a marketing authorisation in the UK for treating metastatic, EGFR and T790M mutation positive NSCLC. However, the Committee for Medicinal Products for Human Use recommended granting a conditional marketing authorisation for osimertinib for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Intervention(s)	Osimertinib
Population(s)	People with locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer
Comparators	For people who have not received previous treatment: • Afatinib • Erlotinib • Gefitinib For people who have received previous treatment with an EGFR-TKI: • Platinum doublet therapy (including pemetrexed plus carboplatin or cisplatin) For people who have received previous treatment with an EGFR-TKI, and in whom platinum doublet therapy is not appropriate: • Single agent chemotherapy including gemcitabine, paclitaxel, vinorelbine or docetaxel For people who have received previous treatment with an EGFR-TKI and chemotherapy: • Docetaxel with or without nintedanib

	• Nivolumab (subject to ongoing NICE appraisal) • Ramucirumab (subject to ongoing NICE appraisal) • Single agent chemotherapy including gemcitabine, paclitaxel, vinorelbine (for those for whom treatment with docetaxel is not appropriate) • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. The use of osimertinib is conditional on the presence of the T790M mutation in the EGFR gene. The economic modelling should include the costs associated with testing for T790M mutations in people with non-small-cell lung cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of additional testing. See section 5.9 of the Guide to the Methods of Technology Appraisals.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.

Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Nintedanib for treating previously treated metastatic non-small cell lung cancer' (2015) NICE Technology Appraisal 347. Review date July 2018 'Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer' (2014) NICE Technology Appraisal 310. Review date April 2017 'Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer' (2012) NICE Technology Appraisal 258. Guidance on static list 'Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer' (2010) NICE Technology Appraisal 192. Guidance on static list Related Guidelines: Lung Cancer: The diagnosis and treatment of lung cancer (2011). NICE guideline 121. Review date March 2016. Related Quality Standards: Quality standard for lung cancer. (2012). NICE Quality Standard No. 17 http://www.nice.org.uk/guidance/qualitystandards/qualitystandards.jsp Related NICE Pathways: NICE Pathway: Lung cancer. Pathway created: Mar 2012. http://pathways.nice.org.uk/pathways/lung-cancer
Related National Policy	NHS England, Manual for prescribed specialised services, service 105: specialist cancer services (adults), Jan 2014. http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domains 1, 2, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf Department of Health (2013) Improving outcomes: a strategy for cancer, 4th annual report Department of Health (2011) Cancer commissioning services

Appendix B

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

Matrix of consultees and commentators

Consultees	**Commentators (no right to submit or appeal)**
Company • Astra Zeneca (Osimertinib) Patient/carer groups • Black Health Agency • British Lung Foundation • Cancer Black Care • Cancer Equality • Helen Rollason Cancer Charity • HAWC • Independent Cancer Patients Voice • Macmillan Cancer Support • Maggie's Centres • Marie Curie Cancer Care • Muslim Council of Britain • Roy Castle Lung Cancer Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care • UK Lung Cancer Coalition Professional groups • Association of Cancer Physicians • Association of Respiratory Nurse Specialists • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society • British Thoracic Oncology Group • British Thoracic Society • Cancer Research UK • National Lung Cancer Forum for Nurses • Primary Care Respiratory Society UK	General • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium Comparator companies • Accord healthcare (carboplatin, cisplatin, docetaxel, gemcitabine, paclitaxel) • Allergan (docetaxel, gemcitabine, paclitaxel, vinorelbine) • Boehringer ingelheim (nintedanib) • Bristol-Myers Squibb Pharmaceuticals (nivolumab) • Dr Reddy's Laboratories (docetaxel) • Eli Lilly (gemicitabine, ramucirumab) • medac GmbH (docetaxel, gemcitabine, paclitaxel, vinorelbine) • Mylan (cisplatin, gemcitabine) • Pierre Fabre (vinorelbine) • Sanofi (docetaxel)

Consultees	**Commentators (no right to submit or appeal)**
• Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society <u>Others</u> • Department of Health • NHS England • NHS Hounslow CCG • NHS Heywood, Middleton and Rochdale CCG • Welsh Government	• Sun Pharmaceuticals (carboplatin, gemcitabine) • Teva UK (carboplatin, cisplatin, docetaxel, gemcitabine, paclitaxel) • Wockhardt (carboplatin, cisplatin, paclitaxel) <u>Relevant research groups</u> • Cochrane Lung Cancer Group • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research <u>Associated Public Health Groups</u> • Public Health England • Public Health Wales

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical specialists and has the right to appeal against the Final Appraisal Determination (FAD).

All non-company consultees are invited to submit a statement[1], respond to consultations, nominate clinical specialists or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland ; other related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the *British National Formulary*.

All non-company commentators are invited to nominate clinical specialists or patient experts.

[1] Non -company consultees are invited to submit statements relevant to the group they are representing.

Company evidence submission

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Osimertinib for locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer [ID874]

Single technology appraisal (STA)

File name	Version	Contains confidential information	Date
ID874_Osimertinib_Submission OfEvidence[CIC_AIC]	1.0	Yes	19 February 2016

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Abbreviations

ACCP	American College of Chest Physicians
ACS	American Cancer Society
AIOT	Italian Association of Thoracic Oncology
BICR	Blinded Independent Central Review
BNF	British National Formulary
BOR	Best objective response
BSA	Body surface area
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMU	Commercial Medicines Unit
CR	Complete response
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events (National Institutes of Health, National Cancer Institute)
ctDNA	Circulating tumour DNA
CU	Cost utility
DALY	Disability-adjusted life year
DBL	Database lock
DCO	Data cut-off
DCR	Disease control rate
DH	Department of Health (UK)
DOR	Duration of response
DP	Decision problem
DSU	Decision Support Unit (NICE)
EAMS	Early Access to Medicines Scheme
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EGFRm+	Epidermal growth factor receptor mutation-positive

EMA	European Medicines Agency [previously EMEA]
eMIT	Electronic Marketing Information Tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D™	Euro Quality of Life – 5 Dimensions. A standardised instrument for use as a measure of health outcome
ESMO	European Society for Medical Oncology
EU	European Union
FACT-L	Functional Assessment of Cancer Therapy – Lung
FAS	Full analysis set
FDA	Food and Drug Administration (US)
GFR	Glomerular filtration rate
GLOBOCAN	Global Burden of Cancer Study
GP	General practitioner
HCHS	Hospital and Community Health Service
HE	Health economic
HR	Hazard ratio
HRQoL	Health-related quality of life
HS	Health state
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ILD	Interstitial lung disease
INN	International non-proprietary name
IPD	Individual patient data
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
IV	Intravenous
KM	Kaplan-Meier
LCS	Lung cancer subscale
LY	Life year
LYG	Life years gained
MedDRA	Medical dictionary for regulatory activities
MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MRI	Magnetic resonance imaging

MTA	Multiple Technology Appraisal
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCIN	National Cancer Intelligence Network
NCLA	National Lung Cancer Audit
NE	Not evaluable
NHS	National Health Service (UK)
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence (UK)
NPA	Negative percent agreement
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
od	Once daily
ORR	Objective response rate
OS	Overall survival
OSIM	Osimertinib
PAS	Patient Access Scheme
PAS	Prior approval supplement
PASLU	Patient Access Scheme Liaison Unit
PD	Progressive disease
PDC	Platinum doublet chemotherapy
PEM	Pemetrexed
PF	Progression free
PFS	Progression-free survival
PI	Prescribing information
PIM	Promising innovative medicine
PK	Pharmacokinetics
po	By mouth
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analysis
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality-adjusted life year

QD	Once daily
QLQ	Quality of life questionnaire
QoL	Quality of life
QTW	Once every third week
RCT	Randomized controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Standard deviation
SD	Stable disease
SEOM	Spanish Society of Medical Oncology
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single technology appraisal
T790M	A secondary point mutation that substitutes methionine for threonine at amino acid position 790
TC	Terminal care
TDP	Treatment until disease progression
TKI	Tyrosine kinase inhibitor
TL	Target lesion
TOI	Trial outcome index
ULN	Upper limit of normal
VAT	Value-added tax
WCLC	World Conference on Lung Cancer
WHO	World Health Organization
WT	Wild type

1 Executive summary

Approximately 38,000 people across the UK are diagnosed with lung cancer every year with more than 35,000 people dying from the disease annually. This accounts for 6% of all deaths in the UK making lung cancer by far the most common cause of cancer death in the UK.

These high mortality rates are the result of the aggressive nature of the disease, the typically late stage diagnosis characterised by advanced stage disease (approximately 70% of patients are stage III–IV at diagnosis) and the limited efficacy and availability of current treatment options.

The high mortality rate results in low survival rates with 1-year, 5-year and 10-year survival being approximately 32.1%, 9.5% and 4.9% in the UK, rates that are significantly lower than corresponding EU countries.[1] Resulting rates for advanced stage diagnosis are significantly worse.

Approximately 10–15% of advanced non-small cell lung cancer (NSCLC) patients harbour certain mutations in the epidermal growth factor receptor (EGFR) gene at diagnosis. For these patients, targeted EGFR tyrosine kinase inhibitors (EGFR TKI) such as gefitinib, erlotinib and afatinib have been approved for routine use and become standard of care as a first-line treatment option in these patients. Unfortunately, despite high objective tumour response, patients will ultimately progress on these treatments with the average time to progression being between 10–14 months. For patients whose disease progresses, treatment options are very limited and their prognosis is dismal (median overall survival substantially below 24 months). Upon progression, patients are currently treated with a platinum-based doublet chemotherapy; however, the efficacy of chemotherapy in this setting is moderate with response rates of approximately 20 to 30% at the cost of significant systemic toxicity. Beyond second-line, there is a limited range of treatments available with even further reduced efficacy (objective response rates typically not more than 10%) and often with significant toxicity.

Based on genomic analysis it is now known that in 50–60% of patients, the progression on a first-line EGFR TKI is characterised by an acquired secondary EGFR kinase domain mutation labelled T790M (denoting an amino acid substitution at position 790 of threonine with methionine), causing resistance to the first-line EGFR TKI.

There is, therefore, a clear and substantial unmet need for a further targeted treatment option that improves progression-free survival (PFS) and overall survival (OS), and has

greater tolerability compared with currently available treatments that mainly consist of systemic cytotoxic chemotherapy. For patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC, osimertinib meets this need.

Osimertinib represents a first-in-class novel treatment option specifically targeting T790M mutations. It is a TKI and an irreversible inhibitor of EGFRs harbouring sensitising-mutations (EGFRm) and TKI-resistance mutation T790M. The structural design of osimertinib has also been selected to reduce the affinity for the wild type EGF receptor that is expressed on many epithelial tissues, the interdiction of which results in the signature EGFR toxicities observed with first generation EGFR TKIs (eg in advanced NSCLC) and antibodies targeting EGFR (eg in advanced CRC and SCCHN). The unmet need of patients diagnosed with EGFRm+ T790M mutation positive NSCLC was recognised by UK regulators with osimertinib granted Promising Innovative Medicine (PIM) designation by the MHRA on 5 August 2015 and a subsequent Early Access to Medicines Scheme (EAMS) scheme approved allowing osimertinib to be made available to approximately NHS 25 patients before EU marketing authorisation.

1.1 Statement of decision problem

Table 1.1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer	As per final scope except cost-effectiveness for treatment-naïve population.	The cost-effectiveness of osimertinib is only presented for patients who have received previous treatment with an EGFR TKI. For patients with a T790M mutation who have not received previous treatment, there are limited data available which would allow AstraZeneca to build a robust cost effectiveness model. Therefore, apart from the clinical details provided in Section 4.15, this submission focuses on people who received previous treatment with an EGFR TKI.
Intervention	Osimertinib	As per final scope	
Comparator (s)	For people who have not received previous treatment:	See comments regarding population	See comments regarding population. Patients with T790M mutated EGFR at initial diagnosis population represent

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Afatinib Erlotinib Gefitinib		approximately 1% (see Section 3) of the EGFR mutation positive population at diagnosis. The limited evidence available for this small patient group suggests a poor response to 1st generation TKIs (erlotinib/gefinitinb/ afatanib). The very small population, evidence of limited clinical effectiveness available from individual patient case histories with SOC and the preclinical data/biological rationale for osimertinib treatment alongside the emerging tumour response data for this patient group from the AURA study programme, was the basis of the CHMP decision to include this population within the label.
	For people who have received previous treatment with an EGFR TKI:	As per final scope. The base case cost-effectiveness analysis compares osimertinib with	The expected position of osimertinib in the treatment pathway would be 2nd line following treatment with an EGFR TKI 1st line for those patients who present

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Platinum doublet therapy (including pemetrexed plus carboplatin or cisplatin)	platinum doublet chemotherapy (pemetrexed plus cisplatin) for people with locally advanced or metastatic, EGFR and T790M mutation positive NSCLC who have received previous treatment with an EGFR TKI. Clinical effectiveness data for the platinum doublet chemotherapy arm were taken from a previously published Phase III trial of gefitinib plus chemotherapy versus chemotherapy in EGFRm+ NSCLC after progression on first-line gefitinib (IMPRESS).[2]	with the T790M mutation upon progression. This group therefore represents the vast majority of the expected population that would be eligible for treatment with osimertinib in UK clinical practice.
	For people who have received previous treatment with an EGFR TKI, and in whom platinum doublet therapy is not appropriate: Single-agent chemotherapy including gemcitabine, paclitaxel, vinorelbine or	As per final scope. No clinical effectiveness data were identified in the systematic review on the use of single-agent chemotherapy in people with locally advanced or metastatic, EGFR T790M mutation positive NSCLC who have received	AstraZeneca anticipates the proportion of patients in whom platinum doublet therapy is not appropriate as a 2nd line treatment option to be very limited based on market research. Recognising that the AURA trial

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	docetaxel	previous treatment with an EGFR TKI (Section 4.1). Furthermore, limited clinical effectiveness data were identified on the use of single-agent chemotherapy for people with locally advanced or metastatic, EGFR mutation positive NSCLC who have received previous treatment with an EGFR TKI. However, a scenario analysis is provided to compare the cost-effectiveness of osimertinib with single-agent chemotherapy for patients who have received previous treatment with an EGFR TKI and in whom platinum doublet therapy is not appropriate (Section 5.8).	programme included these patients and that many patients had failed more than 1 line of prior treatment for advanced disease, the comparison vs doublet chemotherapy from the IMPRESS trial likely represents a conservative estimate of clinical efficacy for this patient population.
	For people who have received previous treatment with an EGFR TKI and chemotherapy:	No clinical effectiveness data were identified in the systematic review on the use of nintedanib (with	The expected position of osimertinib in the treatment pathway would be 2nd line following treatment with an EGFR TKI

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	Docetaxel with or without nintedanib Nivolumab (subject to ongoing NICE appraisal) Ramucirumab (subject to ongoing NICE appraisal) Single-agent chemotherapy including gemcitabine, paclitaxel, vinorelbine (for those for whom treatment with docetaxel is not appropriate) Best supportive care	docetaxel), nivolumab, ramucirumab and best supportive care (BSC) in people with locally advanced or metastatic, EGFR and/or T790M mutation positive NSCLC who have received previous treatment with an EGFR TKI and chemotherapy (Section 4.1). Furthermore, limited clinical effectiveness data were identified on the use of single agent chemotherapy for people with locally advanced or metastatic, EGFR mutation positive NSCLC who have received previous treatment with an EGFR TKI and chemotherapy. However, a subgroup analysis is provided to compare the cost-effectiveness of osimertinib with single-agent chemotherapy (including docetaxel) for patients who have received previous	1st line for those patients who present with the T790M mutation upon progression. Upon marketing authorisation, consistent with data from the AURA programme, a pool of patients could receive osimertinib as a 3rd or 4th line treatment following EGFR TKI and chemotherapy. However, this represents a "one-off" group of patients once osimertinib is available as a 2nd line treatment for eligible patients. Within the later line group, AstraZeneca agrees that docetaxel or other single-agent chemotherapy is a relevant comparator. In relation to adding nintedanib to docetaxel, NICE TA347 specifically recommends this combination in a general lung cancer population for

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		treatment with an EGFR TKI and chemotherapy (Section 5.9).	patients that have progressed on first-line chemotherapy. In the pivotal trial of docetaxel plus nintedanib in patients with previously treated NSCLC (LUME-Lung 1), there was no evidence presented that indicated patients were either EGFRm+ or had received prior treatment with an EGFR TKI.[3] Patients with EGFRm+ lung cancer will have received an EGFR TKI as their first-line treatment and any subsequent use of chemotherapy would be considered to be second-line chemotherapy. Neither ramucirumab nor nivolumab are expected to be licensed in the UK specifically for adult patients with EGFRm+ and T790M mutation positive locally advanced or metastatic NSCLC. The CHMP opinion for ramucirumab states that it is indicated in combination with docetaxel for the treatment of adult

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			patients with locally advanced or metastatic NSCLC with disease progression after platinum-based chemotherapy. In the pivotal study of ramucirumab plus docetaxel for the second-line treatment of stage IV NSCLC (REVEL) less than 3% of patients enrolled to the study were EGFR mutation positive or had received prior EGFR TKI treatment.[4] For nivolumab, in the pivotal study CheckMate-057, the observed efficacy for overall survival in the subgroup of EGFR mutation positive patients, despite not being significant, favoured docetaxel (HR 1.18; 95% CI 0.69-2.00).[5] It is therefore highly unlikely that nivolumab will be considered clinically for EGFRm+ patients nor is it likely to be cost-effective versus docetaxel in a population of EGFR mutation positive

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			patients. No information is available on the efficacy in a T790M mutation positive population. AstraZeneca does not agree that best supportive care is a relevant comparator. This was discussed in the scoping meeting and confirmed by clinical experts, that it is unlikely that patients unfit/ineligible to receive further treatment as part of their 3rd line or later care package, based on current treatment options, would be considered for treatment with osimertinib. In addition to the lack of comparative data, BSC is part of the care package offered to all locally advanced or metastatic NSCLC patients, regardless of their eligibility for systemic anticancer therapies and is captured in the cost-effectiveness analysis.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: overall survival progression-free survival response rate adverse effects of treatment health-related quality of life	As per final scope	In addition, other endpoints such as tumour shrinkage, disease control rates and duration of response are briefly discussed as helpful to inform the discussion.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs	As per final scope	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. The use of osimertinib is conditional on the presence of the T790M mutation in the EGFR gene. The economic modelling should include the costs associated with testing for T790M mutations in people with non-small cell lung cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of additional testing. See Section 5.9 of the Guide to the Methods of Technology Appraisals.		
Subgroups to be	Not specified and not applicable	There are no subgroups to be	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
considered		considered on top of the distinct populations specified in the comparator section.	
Special considerations including issues related to equity or equality	Not specified and not applicable		

1.2 Description of the technology being appraised

Table 1.2: Technology being appraised

UK approved name and brand name	• Brand name: TAGRISSO™ • INN name: osimertinib
Marketing authorisation/CE mark status	• Conditional marketing authorisation was granted on 5 February 2016
Indications and any restriction(s) as described in the summary of product characteristics	• TAGRISSO is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC
Method of administration and dosage	• The recommended dose is 80 mg osimertinib once a day until disease progression or unacceptable toxicity. This medicinal product is for oral use. The tablet should be swallowed whole with water and it should not be crushed, split or chewed

[redacted]

1.3 Summary of the clinical effectiveness analysis

The clinical efficacy and safety of osimertinib as a treatment for NSCLC is currently being investigated through the AURA clinical programme, which is comprised of three key studies assessing its efficacy and safety in patients with advanced NSCLC, EGFRm+ with T790M mutation positive status, and who have progressed on or after an EGFR TKI treatment.

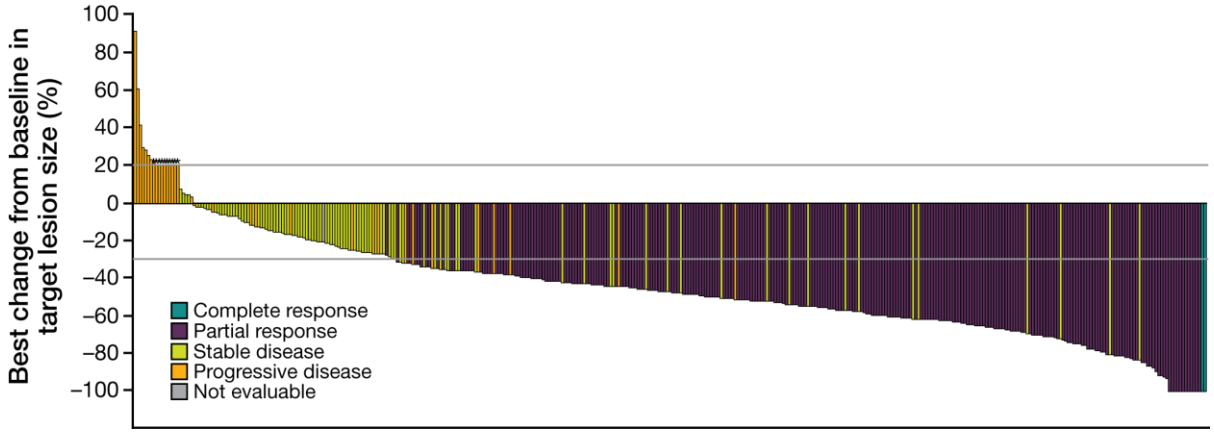
The data set which was the basis of the EU marketing authorisation (the first ever EU PRIME designated approval) consists of data from 411 patients from the Phase II AURA extension and AURA2 studies. The data cut off (DCO) for the submitted analyses was 1 May 2015.

AURA extension and AURA2 were prospectively planned to provide replication of the data: both had almost identical designs with regard to patient population, study conduct, dose and formulation, and outcome measures. Efficacy data are presented individually as well as pooled to increase the precision of the estimate for clinical outcomes in the licensed indication. The primary efficacy analysis of ORR (including BOR) was based on blinded independent central review (BICR) of the evaluable-for-response population. Sensitivity analyses of RECIST outcomes were performed based on investigator and BICR assessments in the Full Analysis Set (FAS) population.

In the 411 patients included in the FAS the median age at study entry was 63 years (range: 35 to 89 years), approximately two-thirds of patients (67.9%) were female and 60.1% were of Asian origin; the remainder were mainly white (36.2%). Approximately three-quarters of patients (71.5%) were never smokers. The majority of patients had metastatic NSCLC (96.1%), adenocarcinoma histology (96.1%), and had a WHO performance status of 1 (62.8%). At baseline 83.0% of patients had visceral metastases with one-third of patients (39.2%) diagnosed at study entry with brain metastases. The majority of patients were heavily pre-treated: 68.4% had received at least 2 prior treatment regimens and 45.5% had received 3 or more prior lines of therapy with approximately two-third (62.5%) of patients had received prior platinum-based chemotherapy.

Osimertinib is associated with high objective response rates. ORR in the primary analysis was 61.3% and 70.9% in AURAext and AURA2, respectively. In the pooled analysis, as of the DCO, 263 of 398 patients with measurable disease at baseline had confirmed objective responses to osimertinib (ORR: 66.1%, 95% CI: 61.2, 70.7). Corresponding high response rates were observed across all subgroups, ranging from 58.9% to 71.45% with analysis by line of therapy reporting an ORR of 66.9% (95% CI: 57.9, 75.1) for osimertinib as second-line treatment and 65.7% (95% CI: 59.7, 71.3) for patients receiving osimertinib as ≥ third-line treatment (see Figure 1.1).

Figure 1.1: Target lesion size, best percentage change from baseline by central review – total, waterfall plot (evaluable response analysis set)



Best percentage change in target lesion size was the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
* represented imputed values: if it was known that the patient had died, had new lesions or progression of non-target lesions, had withdrawn due to PD and had no evaluable target lesion (before or at progression) assessments, best change was imputed as 20%.
RECIST version 1.1.
Source: see Figure 2.5.3.1 from pooled efficacy figures in Module 5.3.5.3 Supportive efficacy data.

At DCO, all patients had the opportunity of having at least 6 months of radiological follow-up. The preliminary estimate of median PFS in the FAS based on assessments by BICR (38.7% maturity) was 9.7 months (95% CI: 8.3, NC). Based on BICR assessment, of the 411 EGFR T790M mutation-positive patients in the FAS, 159 (38.7%) had either progressed (142 patients, 34.5%) or died (17 patients, 4.1%). The Kaplan-Meier estimated probability of being alive and progression-free was 70.9% (95% CI: 66.1, 75.1) at 6 months. This estimated proportion was consistent across studies.

At DCO, median follow-up for OS was 7.4 months with overall survival data still immature. Of the 411 EGFR T790M mutation-positive patients in the FAS, 52 had died (12.7%); 349 patients (84.9%) were ongoing on survival follow-up, of whom 296 (72.0%) were still on treatment. The Kaplan-Meier estimate of the proportion of patients alive at 6 months was 92.3% (89.3, 94.5).

Based on analyses from the AURAext and AURA 2 studies, osimertinib has a significant, measurable and relevant impact on patients HRQOL (health-related quality of life) and symptoms. Improvements from baseline throughout all on treatment assessment time points were observed for dyspnoea, cough, chest pain, pain in arm, pain in shoulder and overall health status. Drug-related side-effects (sore mouth and diarrhoea) appeared to have minimal impact on HRQoL as reported in these studies. The PRO data are supportive of the reported tumour response (using RECIST criteria) and suggest clinical benefit as manifested

through an improvement in lung cancer symptoms and general health status improvement with osimertinib.

Relative effectiveness

Randomized controlled data directly comparing the efficacy of osimertinib versus platinum doublet chemotherapy will be available through the AURA3 Study which is [redacted]

In order to provide an estimate of the relative efficacy of osimertinib compared with current standard of care in patients progressing after 1st line EGFRm TKI treatment, results from the AURAext and AURA2 studies were compared against the control group of the IMPRESS study. The IMPRESS study is a recently completed and reported 2nd line study evaluating platinum doublet chemotherapy (the main comparator for this appraisal – see Section 1.1) in EGRFm+ advanced NSCLC patients with or without continuation of EGFR TKI therapy. As the IMPRESS trial was an AstraZeneca trial, access to the individual patient level data (IPD) and tumour analysis to confirm T790M mutation status, enabled a comparison in the population referred to in the decision problem. AstraZeneca was able to conduct a robust comparative analysis in a well matched patient population in the absence of results from a direct head-to-head clinical trial. Furthermore, common assessment criteria for objective response rates/ radiological progression, use of independent central review and adherence to current regulatory standards ensure methodological consistency between the studies which is important in any cross trial comparison. Two approaches were taken for such a comparison: (a) comparative analysis of the IMPRESS study by T790M status and (b) a full matched analysis adjusting for differences in important clinical baseline characteristics.

(a) Unadjusted comparison of T790M cohorts

Results based of the T790M mutation positive control group of the IMPRESS trial, providing the best available evidence for efficacy of platinum doublet chemotherapy in 2nd line, EGFRm+ relapsed patients after progression on 1st generation TKI. The ORR for the T790M population receiving platinum doublet chemotherapy was 39% vs 64.2% observed within the osimertinib cohort from the AURA programme. The median PFS was 5.3 months for platinum doublet chemotherapy compared with 9.7 months for osimertinib. The median OS was 15.7 months for platinum doublet chemotherapy, clearly less than 24-month criterion for End of Life qualification by NICE. No OS assessment is currently available from the AURA programme as the follow up is too immature for estimation.

Table 1.3: Comparison of key efficacy outcomes between AURA and IMPRESS in T790M mutation positive patients

Outcome		AURA pooled [REFs]	IMPRESS T790M mutation positive
Indication		≥Second-line	Second-line
Treatment		Osimertinib 80 mg	Placebo (platinum doublet chemotherapy)
Number of patients		411	61
ORR	Total responses (%)	263* (66.1%, 95% CI: 61.2, 70.7)	24 (39.3%)
PFS	Total events (%)	159 (38.9%)	51 (83.6%)
	Median (95% CI)	9.7m (8.9-NC)	5.3m (NR)
OS	Total events (%)	52 (12.7%)	20 (32.8%)
	Median (95% CI)	Not reached	15.7m

* Out of 398 patients with measurable disease at baseline

The safety data from AURA extension and AURA2, supported by consistent data from AURA Phase I, indicate that osimertinib 80 mg has an acceptable safety and tolerability profile in terms of the type, frequency and severity of events, for use in the proposed indication. Osimertinib's well tolerated profile is reflected in the very low discontinuation rate observed in the two single-arm trials. In the pooled osimertinib analysis only 4.1% of patients discontinued treatment due to an AE. Despite differences in the average number of lines of prior treatment, osimertinib appeared to be associated with less ≥ grade 3 AEs compared to platinum doublet chemotherapy (29.4% vs 41.7% respectively) and with, less AEs leading to treatment discontinuation (4.1% vs 9.8% respectively).

Table 1.4: Comparison of key safety data between AURA and IMPRESS

AE category	Number (%) of patients[a]	
	AURA pooled osimertinib 80 mg	IMPRESS Control Group
Sample Size	(N=411)	(N=132)
Patients with any AE	401 (97.6)	130 (98.5)
CTCAE ≥grade 3 AEs	121 (29.4)	55 (41.7)
SAEs	83 (20.2)	28 (21.2)
Fatal SAEs	9 (2.2)	8 (6.1)
AEs leading to discontinuation	17 (4.1)	13 (9.8)
AEs leading to dose modification	81 (19.7)	NR

[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.
CTCAE = Common Terminology Criteria for Adverse Events version 4.0; MedDRA version 17.1.

(b) Cohort comparison adjusting for baseline covariates

The treatment effect of osimertinib monotherapy was further compared with platinum doublet chemotherapy using an adjusted indirect comparison of the two non-randomized individual patient data sets from the AURAext/2 studies (N=411) and the T790M subgroup of the placebo arm of the IMPRESS study (N=60), respectively. The unadjusted comparison of efficacy results between the AURA pooled data and IMPRESS T790M mutation positive control group is likely to be a conservative analysis for a number of reasons:

- The IMPRESS control group consisted of second-line only patients whereas in AURA, over two-third of patients (68.4%) had received at least 2 lines of therapy prior to enrolment, making it a more refractory population
- The IMPRESS control group was younger compared to the AURA pooled population with a mean age of 55.8 years vs 62.2 years
- Patients in the IMPRESS control group were selected for a good response on previous EGFR TKI (at least 4 months). This was not part of the inclusion criteria of AURA
- Brain metastases at baseline were present in 40% of patients in AURA as compared to 34% in IMPRESS. It is well documented that patients with brain metastases have a worse prognosis than patients with metastatic disease with no brain involvement

The imbalance between IMPRESS and AURA in terms of patient characteristics may impact conclusions drawn from such a side by side comparison. In an attempt to reduce bias in a non-randomized efficacy comparison, using patient level data, estimated propensity score methods were used to balance the non-equivalent AURAext/2 and IMPRESS cohorts on common observable variables (presented in Section 4.10).

Overall, the PFS results from this analysis indicate a large treatment effect with the hazard ratio of 0.28 statistically significant improvement for the osimertinib group compared with the platinum doublet chemotherapy group (HR 0.280, 95% CI 0.185, 0.422; *p*-value < 0.0001). Median PFS was 9.7 months (95%CI 8.3, NC) for the osimertinib group compared with 5.2 months (95%CI 4.0; 6.1) in the matched chemotherapy cohort. Analysis by logistic regression (with treatment as a factor and propensity score as a covariate) indicated a significant difference in the odds of objective response between osimertinib and doublet

chemotherapy [odds ratio: 4.76 (95% CI 2.21, 10.26; *p*-value < 0.001)]. Analysis of OS using Cox proportional hazards model indicated an overall hazard ratio of 1.022 with wide 95% confidence intervals (95% CI 0.387, 2.696). This result likely represents the immature nature of such a comparison. For the adjusted cohort the data maturity at the time of the OS analysis was 11.5% for osimertinib and 29.4% for platinum doublet chemotherapy with the KM risk set beyond 12 months limited to less than 15 patients for both groups leading to unstable estimates beyond this time point.

Results of the adjusted indirect comparison confirm that the conclusion drawn from the unadjusted comparison do not appear to overestimate the clinical effect of osimertinib compared with doublet chemotherapy.

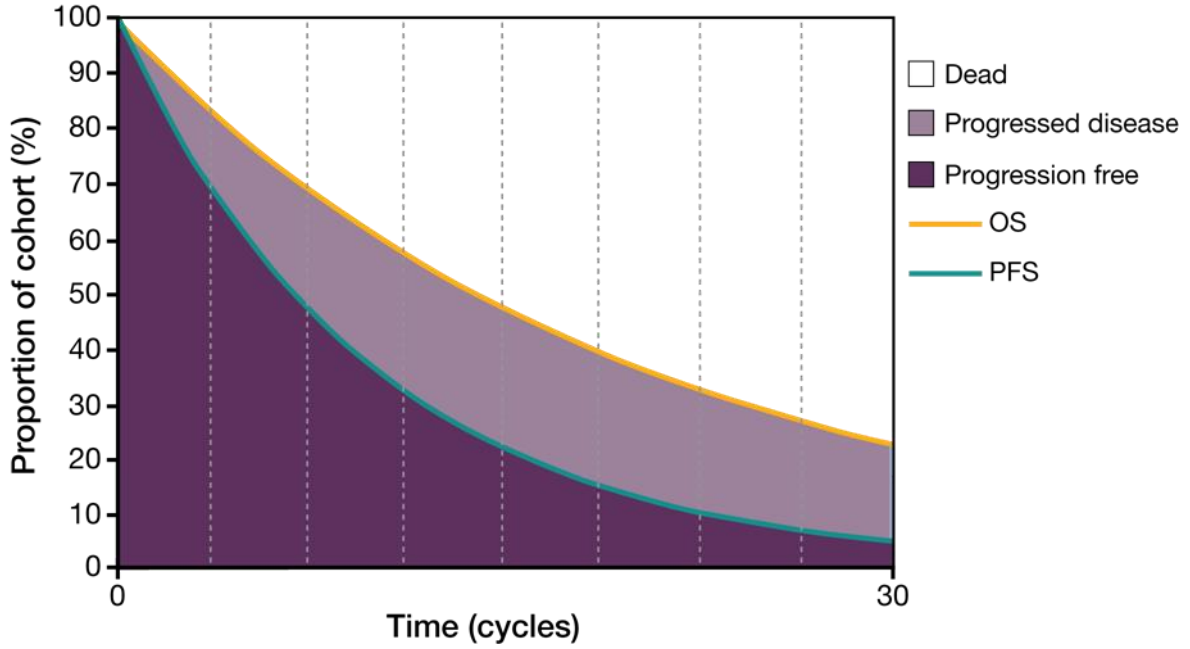
It should be noted that due to technical limitations, in this analysis not all imbalances were adjusted for including the number of prior lines of therapy and presence of brain metastases. Comparison of both these parameters would suggest that any conclusions were conservative with respect to the osimertinib treatment effect.

Collectively, these data provide clear evidence of the clinical benefit of osimertinib 80 mg in pre-treated patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. Osimertinib represents a step change over available therapies on clinically significant endpoints.

1.4 Summary of the cost-effectiveness analysis

A *de novo* three-state partitioned survival model compared osimertinib versus platinum doublet chemotherapy in EGFR T790M mutation positive advanced/metastatic NSCLC patients who have progressed on or after EGFR TKI therapy with or without additional anticancer regimens (≥ 2nd line treatment). For both costs and health benefits (applied discount rate of 3.5% was used), the base case time horizon was lifetime (set to a maximum of 15 years) and a cycle length of one week set to accurately calculate differences between the two treatment regimens.

Figure 1.2: Cost-effectiveness model structure



PFS and OS survival data was modelled using parametric best fits and extrapolated a life time horizon. Osimertinib PFS and OS data was modelled from the most recent available data analysis of pooled AURAext/AURA 2. Platinum doublet chemotherapy survival data was selected from an EGFR and T790M mutation positive population in IMPRESS matching the population referred to in the decision problem. Treatment with osimertinib was assumed until disease progression whereas platinum doublet chemotherapy was for a maximum of 6 cycles. The choice of survival extrapolation was based on NICE Decision Support Unit (DSU) guidance for both PFS and OS.

In the base case analysis, PFS was modelled using the Gompertz function as based on visual inspection and statistical goodness-of-fit, it provided the most clinically plausible distribution to the observed Kaplan-Meier data, in particular for the comparative arm where more mature data was available. The resulting median PFS values for each treatment arm in the health-economic model are consistent with the observed median values from the Kaplan-Meier data as well as the reported medians from the adjusted indirect comparison.

In the base case analysis, OS was modelled using the Weibull function as it had a good fit based on visual inspection and statistical goodness-of-fit for IMPRESS. For AURA, it also represented the most conservative and clinically plausible scenario with other distributions generating OS estimates lacking face validity. Therefore, the Weibull distribution was chosen as it produced the most reasonable fit to the non-parametric OS data based on the currently available data. In the absence of mature OS data for osimertinib, an attempt to validate the modelled OS results through an analysis comparing the median/mean PFS and OS

estimates alongside available HR for other products in a similar treatment setting was performed.

The results from the base case analysis are summarised in Table 1.5, where the Gompertz distribution and Weibull distribution were used to extrapolate PFS and OS, respectively.

There are a number of limitations in the current version of the cost-effectiveness analysis which should be noted:

- OS survival data from AURA ext/2 is currently immature (13%). The more immature the data, the more uncertainty there is in any extrapolated estimate of OS. Sensitivity analysis is undertaken to show how different fits and resulting OS estimates impact on the results.

- Given that AURAext and AURA2 are both single arm studies, there is no controlled comparative clinical data for osimertinib and the platinum doublet chemotherapy arm. Despite this, results from the adjusted indirect comparison suggest that this is unlikely to bias the results of the cost-effectiveness analysis in favour of osimertinib.

Despite some of the limitations in the current data set, the presented cost-effectiveness analysis demonstrates that osimertinib is a cost-effective treatment option for patients with EGFR and T790M mutation positive aNSCLC who have progressed on treatment with an EGFR TKI:

- The IPD and tumour analysis for T790M mutation status of the IMPRESS control group allow for a robust non-randomized comparison between very similar populations

- The imbalance in patient characteristics between IMPRESS and AURA suggest a bias in favour of platinum doublet chemotherapy

- The adjusted indirect comparison between AURA and IMPRESS resulted in a statistically significant treatment effect on PFS with an unprecedented HR of 0.274

- Additional data available throughout 2016 and 2017 will allow further assessment of the treatment effect of osimertinib in the population of interest

Table 1.5: Base case cost-effectiveness results (with and without inclusion of PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
With inclusion of PAS							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,959
Platinum doublet chemotherapy	[redacted]	[redacted]	[redacted]				
Without inclusion of PAS							
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum doublet chemotherapy	[redacted]	[redacted]	[redacted]				

2 The technology

2.1 Description of the technology

Brand name: TAGRISSO™ film-coated tablets (80 mg and 40 mg)

UK approved name (INN): osimertinib

Therapeutic class: Osimertinib falls under the class of antineoplastic agents, protein kinase inhibitors. The ATC code is L01XE35.

Mechanism of action: Osimertinib is a Tyrosine Kinase Inhibitor (TKI). It is an irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harbouring sensitising-mutations (EGFRm) and TKI-resistance mutation T790M.

2.2 Marketing authorisation/CE marking and health technology assessment

Marketing authorisation

Following an accelerated central regulatory procedure, the European Commission granted a conditional marketing authorisation for the medicinal product TAGRISSO™ (AZD9291, osimertinib) 80 mg once daily on 3 February 2016 for the treatment of adult patients with locally advanced or metastatic EGFR T790M non-small cell lung cancer (NSCLC), irrespective of previous treatment with an EGFR tyrosine kinase inhibitor.

TAGRISSO is the first new medicine to be approved under the European Commission's expedited process

The summary of product characteristics (SmPC),[6] provided in appendix, states the following therapeutic indication:

TAGRISSO is indicated for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Contraindications

Section 4.3 of the SmPC[6] contains the following contraindications:

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SmPC

- St. John's wort should not be used together with TAGRISSO (see Section 4.5 of the SmPC)

Product availability

AstraZeneca anticipates making the product available across England and Wales as of 01 April 2016.

EMA regulatory assessment

The European Public Assessment Report (EPAR)) was published on February 17 2016.[7]

The marketing authorisation is conditional on AstraZeneca providing the final results and safety analysis of the Phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy by 30 June 2017, in order to further confirm the efficacy and safety of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. In the Summary of Opinion available on the EMA website, it is furthermore highlighted that:

"A conditional marketing authorisation is granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. The marketing authorisation holder is likely to provide comprehensive clinical data at a later stage."

On clinical efficacy, the EMA stated that: *"the high antitumor activity shown by osimertinib in the two Phase II studies carried out is considered of clinical value. Osimertinib is a new alternative before chemotherapy, with outstanding response rates. It is expected this will be translated into clinical benefit for patients, although the magnitude of such benefit in terms of OS and/or PFS remains unknown."*

Regarding safety, the EMA concluded that overall, the osimertinib safety profile was as expected for a population of patients with advanced NSCLC treated with an EGFR TKI agent with an improved margin of selectivity against wild-type EGFR. The most commonly reported AEs being low-grade gastrointestinal disturbances (primarily diarrhoea) and skin effects (mainly rash, acne, and dry skin) which are consistent with some degree of inhibition of wild-type EGFR. In total, 2.9% (35/1221) of patients have reported ILD or suspected ILD-like events. The EMA further noted that that *"the lack of comparator in the studies hampers to properly contextualise the tolerability and toxicity. The long-term safety profile is not totally*

known. Nevertheless, despite these uncertainties, the overall safety profile of osimertinib is considered acceptable and manageable, with a likely better tolerability than the traditional chemotherapy."

Regulatory assessment outside of Europe

Outside of Europe, on 13 November 2015, the US Food and Drug Administration (FDA) granted an accelerated approval to osimertinib for patients with advanced EGFR T790M mutation-positive NSCLC following progression on a prior EGFR TKI. This approval followed Fast Track, Breakthrough and Priority Review status by the FDA. Given this rapid development and approval under the FDA's accelerated program, a full indication for osimertinib is contingent on findings from confirmatory studies. The exact wording of the FDA label is:

TAGRISSO is a kinase inhibitor indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.[8]

Regulatory submissions in other geographies are currently ongoing.

Other health technology assessment in the UK

AstraZeneca is planning to make a submission to the Scottish Medicines Consortium (SMC) early 2016. Exact timelines will be provided to NICE once the SMC Secretariat has scheduled the submission. AstraZeneca is currently in discussions with All Wales Medicines Strategy Group (AWMSG) whether an appraisal ahead of the outcome of the NICE STA process is within scope.

2.3 Administration and costs of the technology

Table 2.1: Costs of the technology being appraised[6]

Pharmaceutical formulation	Film-coated tablets	
Acquisition cost (excluding VAT) *	NHS List Price 80mg: £ 4,722.30 per pack consisting of 30 film-coated tablets corresponding to 30 days' supply NHS List Price 40mg: £ 4,722.30 per pack consisting of 30 film-coated tablets corresponding to 30 days' supply 	This reflects the list price submitted and approved by the Department of Health
Method of administration	This medicinal product is for oral use. The tablet should be swallowed whole with water and it should not be crushed, split or chewed If the patient is unable to swallow the tablet, the tablet may first be dispersed in 50 mL of non-carbonated water. It should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed. No other liquids should be added If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15 mL for the initial dispersion and 15 mL for the residue rinses. The resulting 30 mL of liquid should be administered as per the nasogastric tube manufacturer's instructions with appropriate water flushes. The dispersion and residues should be administered within 30 minutes of the addition of the tablets to water	
Doses **Dosing frequency**	The recommended dose is 80 mg osimertinib once a day until disease progression or unacceptable toxicity If a dose of TAGRISSO is missed, the dose should be made up unless the next dose is due within 12 hours TAGRISSO can be taken with or without food at the same time each day	
Average length/cost of a course of treatment	Treatment is continued until disease progression so there is no common average course of treatment and there is significant variation in treatment duration between individual patients	
Anticipated average interval between courses of treatments	Not applicable Patients are treated continuously until disease progression	
Anticipated number of repeat courses of treatments	Although not specified within the licence, it is anticipated that patients will receive only one course of treatment with osimertinib	
Dose adjustments	Dose adjustments Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to 40 mg taken once daily. Further details on dose adjustments are provided within the SmPC Section 4.2	

Anticipated care setting	Specialist cancer centres SmPC Section 4.2 confirms: Treatment with TAGRISSO should be initiated by a physician experienced in the use of anticancer therapies
* Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented	

2.4 Changes in service provision and management

Treatment with osimertinib must be initiated and supervised by physicians experienced in the treatment of cancer. In the UK, hospital oncology units already have the staffing and infrastructure needed for the administration of cancer treatments. It is anticipated that the administration of osimertinib would utilise this existing NHS infrastructure.

Due to osimertinib being an oral treatment administered as a once-a-day tablet, the administration is significantly easier compared to intravenously administered cytotoxic chemotherapy. This represents a significant benefit to patients but also has a positive impact on NHS resources. This is accounted for in the economic modelling presented in Section 5.

The main additional resource use to the NHS is associated with the identification of patients eligible for osimertinib.

As referenced in the decision problem, the proposed positioning of osimertinib requires patients to have progressed on a prior EGFR TKI with a documented T790M mutation. There are two key issues to address with respect to the potential expansion of service provision related to identification of eligible patients:

- acquisition of tumour specimens from patients at progression
- assessment of tumour specimens for T790M mutation

Since EGFR mutation status is determined in up to 90% of UK patients with treatment naïve NSCLC,[9] the pathway for acquisition, handling and testing of tissue, in addition to mechanisms for reporting of results, is well established.

Furthermore, in 2015 there were 95 laboratories enrolled with UK NEQAS and validated to conduct EGFR mutation testing, of which 28 were UK based. While country specific data have not been published, 88% of the labs in the scheme were able to detect T790M mutations using existing platforms ([redacted]). As such, AstraZeneca asserts that T790M mutations are already routinely identified and therefore no

additional equipment, reagent or manpower costs are associated with assessment of tumour specimens beyond the incremental increase in testing volumes.

The situation regarding acquisition of tumour specimens will require a change in pathway, if not a change in provision *per se*. Outside of academic centres, tissue biopsy at disease progression following resistance to EGFR TKI therapy is not routine, since clinical utility of tumour genotyping in this population is not established. Within leading teaching centres, tumour samples at progression are frequently taken on research protocols or to confirm histological changes such as transformation to SCLC.

There are a number of parameters by which optimal choice of sample can be measured, including biological, technical, clinical and practical aspects.

The predominant biological challenge with assessing tissue specimens is the phenomenon of tumour heterogeneity and the subsequent risk of evaluating a biopsy that is not representative of the overall tumour burden. There may also be a choice of lesion to biopsy, including the primary tumour, local and distant metastases. At present, there is a paucity of data to inform the optimal selection of lesions for biopsy.

The issue of tumour heterogeneity is mitigated when evaluating circulating tumour DNA from plasma, however not all tumours shed DNA to the same extent and tumour size and location may be important factors.

Technically, there are relatively few limitations to tissue based testing and molecular pathology labs are highly experienced in handling FFPE or frozen tissue samples. The most frequently observed challenge is assay failure due to poor quality samples with low tumour cell content or exhaustion of small samples during histopathology work-up.

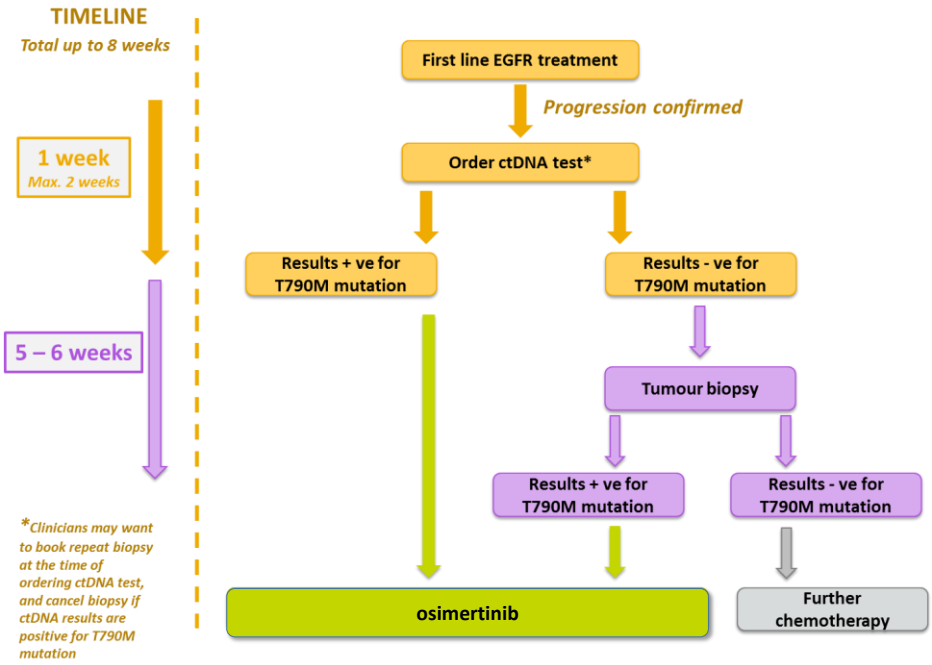
Labs are increasingly accustomed to performing tests on circulating free DNA (largely due to the growth in circulating free foetal DNA testing) however relatively few are currently testing circulating tumour DNA (ctDNA) from cancer patients. When compared to tissue, assay sensitivity from plasma samples is typically lower (resulting in a higher false negative rate), and while this may be related to underlying biology factors, a tissue sample should be sought for a patient whose is reported as T790M negative from plasma.

Clinically, it follows that later line metastatic NSCLC patients have poorer performance status and a reduced willingness to undergo tissue biopsy when compared to those in first-line, particularly if a test from a blood sample is readily available. While low in absolute terms, the frequency of complications arising from invasive tissue acquisition procedures is

estimated to be significantly higher than for blood draw, and these complications may include pneumothorax, infection and bleeds.

From a practical perspective, the tissue pathway is well established in the UK – at least in the first-line setting – which may be advantageous in the short-term. However, the clinical the advantages of plasma sample acquisition (i.e. phlebotomy) carries the advantages of lower cost and greater speed. Some feasibility studies may be required to validate the pre-analytical steps of the plasma processing pathway and these are expected to commence in Q2 2016 , (eg International Quality Network for Pathology), along with a quality assurance scheme run by a consortium that includes UK NEQAS. Balancing the relative merits and disadvantages of tissue and plasma-based testing, and based on feedback from advisory board meetings, it is anticipated that the optimal testing pathway for the UK will be as shown in Figure 2.1.

Figure 2.1: Anticipated optimal testing pathway for T790M mutation status[10]



There are a number of soon to be available treatments that would require acquisition of fresh tissue at progression to molecularly characterize the tumour an inform treatment decisions. Therefore, AstraZeneca believes that the acquisition of a fresh tumour specimen at disease progression to determine T790M status for clinical adoption of osimertinib will be a part contributor to a minor change in service provision. In parallel, it is though that a modest increase in EGFR mutation testing volume will occur, in the subset of patients who have previously been identified as having EGFR TKI sensitising mutations and equating to an approximate 10% increase in patients tested for EGFR mutations today.

2.5 Innovation

Osimertinib was granted a Promising Innovative Medicine (PIM) designation by the MHRA on 5 August 2015 and a subsequent MHRA positive scientific opinion was issued under the Early Access to Medicines Scheme (EAMS) on 7 December 2015 with enrolment open to newly diagnosed patients from that date up to the marketing authorisation received earlier this month. The MHRA stated the following rationale on giving osimertinib a positive EAMS opinion:

"EGFR T790M mutation-positive lung cancer is a life threatening disease. Patients with this condition have very limited treatment options, reduced life expectancy and there is an urgent need for more therapies. In clinical studies, osimertinib was able to slow or shrink the cancer in these patients. Other currently available treatments have limited activity. The MHRA has considered the benefits of osimertinib in this difficult to treat condition and concluded that the benefits are greater than the risks."

Although TK inhibitors are considered standard of care in the first-line setting for patients with EGFRm+ NSCLC approximately 60% of these will become resistant due to the T790M mutation.

Osimertinib is a newly developed third-generation oral, irreversible EGFR TKI differing from current EGFR TKIs:

Selectively targets EGFR-sensitising and T790M-resistant mutations

Higher selectivity for EGFR mutations than EGFR WT, which may improve the tolerability profile seen with first-generation TKIs

We do not foresee any significant and substantial health-related benefits within this patient population outside of the QALY calculation.

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview

Lung cancer is the most common cancer worldwide and the leading cause of cancer death worldwide with estimated annual death toll of 1.59 million people.[11,12] The two main types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) – NSCLC accounts for approximately 85% of all lung cancers.[13] Most patients are diagnosed with NSCLC only at an advanced stage where symptoms of weight loss, bone pain, headaches, anaemia, and paraneoplastic syndromes can be detected in preliminary diagnosis.[13,14] The majority of lung cancer cases are diagnosed when patients have either locally advanced or distant metastatic disease, a stage that is not amenable to curative surgery. Even when NSCLC is detected early, the 5-year survival rate is considerably lower than with many other cancers.[11] Patients diagnosed with stage III NSCLC can expect a 5-year survival rate of 5–15%, whereas the corresponding figure for those with stage III colon cancer is more than 70%. If patients have distant metastases (stage IV NSCLC), 5-year survival is only around 1%.

Within the UK, approximately 38,000 people are diagnosed with lung cancer every year of which NSCLC accounts for 88%. Also in the UK, most patients in are diagnosed at an advanced stage (stage III or IV) of the disease.[15]

Advanced NSCLC (aNSCLC) is further divided in to subtypes depending on the molecular profile and predominant oncogenic driver of the tumour. One of these is aNSCLC with an epidermal growth factor receptor sensitising mutation (EGFRm+). The prevalence of EGFR mutations in NSCLC varies according to the different histological subtypes and patient ethnicity. As such, direct comparisons between subgroups of NSCLC cases are not appropriate. In a Caucasian aNSCLC population, EGFR mutations account for approximately 10% all aNSCLC cases.[7]

EGFR mutation status has emerged as a key predictive biomarker in aNSCLC correlating with sensitivity to an EGFR TKI.

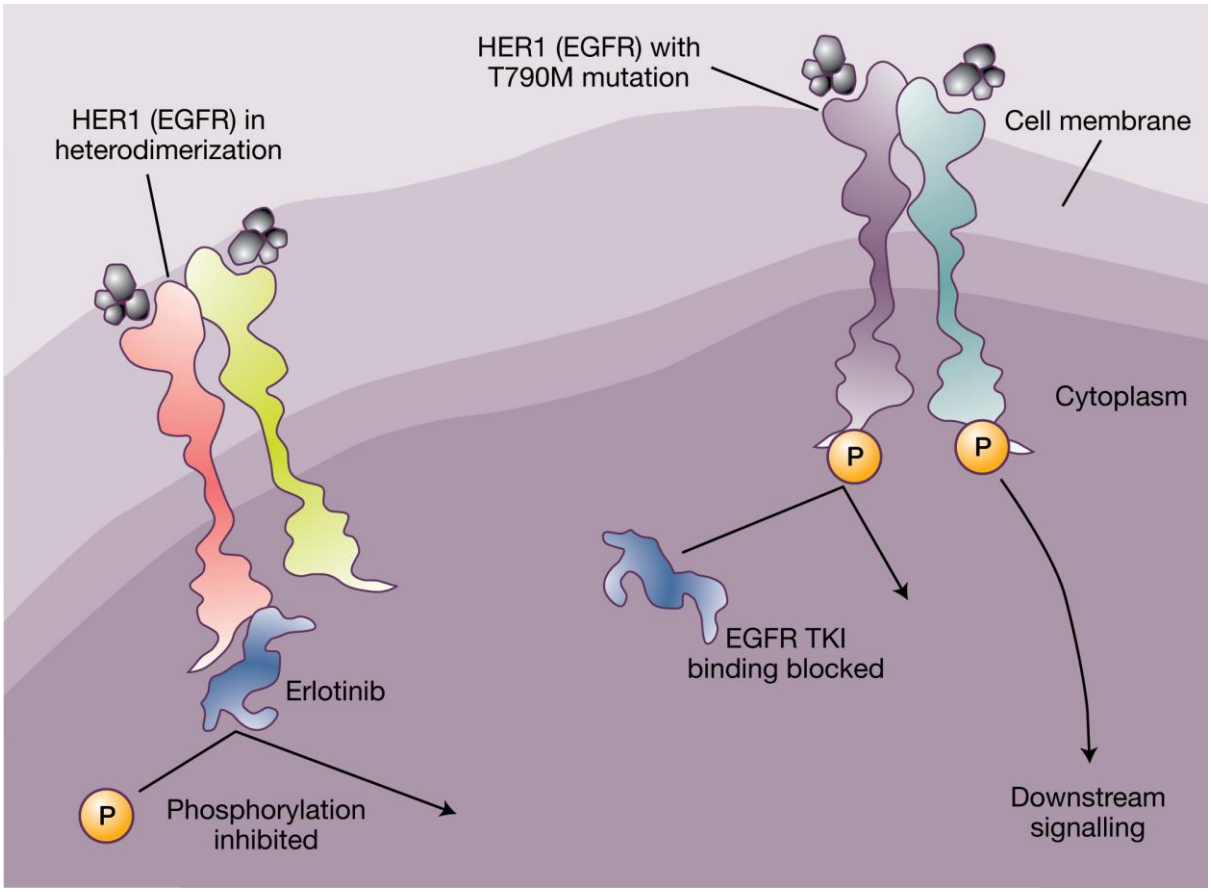
In tumours with EGFRm+, the EGF receptor is permanently activated, so that the EGFR signalling pathway is always switched on, driving tumour growth. These tumours have a different biology to tumours without such mutations (i.e. EGFRm-), as they are addicted to signalling via the EGFR-signalling pathway for growth and survival. EGFR TKIs, such as

gefitinib, have a high affinity for mutant activated EGFR, and have been shown to block signalling and inhibit tumour growth.[16] Specifically, the presence of activating EGFR exon 19 deletion or exon 21 L858R mutations is predictive of treatment benefit from therapy with an EGFR TKI. Clinical guidelines recommend routine testing for EGFR mutations before selecting first-line therapy for aNSCLC.[17–19]

Most advanced NSCLC tumours initially respond to EGFR TKIs, but subsequently develop resistance to therapy on average after 10–14 months after commencing treatment.[20–26] This can be either due to secondary mutations or via activation of bypass signalling pathways (c-Met amplification).[27,28]

The most common mechanism of acquired resistance to EGFR TKI therapy in patients with advanced EGFRm+ NSCLC is an amino acid substitution at position 790 in EGFR from a threonine to a methionine (T790M). T790M mutations account for 50–60% of all cases of acquired resistance[27–30] Secondary T790M mutations are believed to confer resistance to currently approved EGFR TKIs by two potential mechanisms. The first is through steric hindrance, in which a change to the spatial structure of the receptor reduces binding of these EGFR TKIs to it. The second potential mechanism is increased binding affinity of EGFR for adenosine triphosphate (ATP), which reduces the potency of reversible EGFR TKIs (Figure 3.1).

Figure 3.1: T790M mutation in EGFR[31]



In general, T790M mutations are classified as *de novo* (primary) or acquired after TKI treatment (secondary mutations).[24] T790M is rarely detected in EGFR TKI untreated tumours with reports in literature ranging between 0.5% and 6%.[23,32–34] The majority of patients acquire resistance to front line EGFR-targeted TKIs due to T790M as a result of selective pressure during treatment.[35] In findings from the AURA study in patients who progressed following an EGFR TKI prevalence of the T790M mutation was 67% (83/131) with no difference between Asian and Caucasian patients.[36]

The prognostic role of T790M mutation is not fully understood. In an population unselected for the T790M mutation, it has been shown that patients on doublet chemotherapy will progress in 5.4 months.[23] However, until recently, no data has been available to demonstrate the effect that the presence of the T790M mutation has on long-term outcomes. The most recent and robust dataset is from the IMPRESS study. Median PFS was consistent, PFS 5.3 months and 5.4 months for T790M mutation positive and T790M mutation negative patients respectively when diagnosed with a ctDNA test. The OS KM plots between the T790M mutation positive and negative control group of IMPRESS showed a degree of separation from 12 months onwards (see Section 4.11).

3.2 Burden of illness

3.2.1 Societal Impact

It should come as no surprise that lung cancer places a huge burden on societies in terms of disability and premature mortality, as well as impact on direct health service costs, drug expenditure and the indirect costs related to lost production. Lung cancer is the most common cause of cancer death in the UK, accounting for more than 1 in 5 cancer deaths. In 2004, lung cancer was the leading cause of cancer-related lost life years and disability with 22.8 million LYs and 23.1 million DALYs lost worldwide.[37] This accounted for 15.7% of all LYs lost due to cancer.[38] In Europe, 3.2 million DALYs are lost per year due to lung cancer.[39] In 2012, 35,371 deaths from lung cancer across the UK were recorded.[40]

The annual direct cost to the EU healthcare systems due to lung cancer was 3.35 billion Euro in 2012.[39] In addition, lung cancer accounts for a total of 1.8 million DALYs lost per year.[39] The average DALY lost is estimated to cost 350,000 Euro per patient.[39] The direct cost per case is estimated at 11,473 Euro in 2011 values. The indirect costs of lung cancer have not been quantified.

In the UK, costs associated with lung cancer exceed the cost of all other cancer types and were calculated to be approximately €2.17 billion during 2009 out of which €1.2 billion and €56 million were associated with lung cancer mortality and morbidity respectively.[41]

For the year 2013-2014, hospital admissions in England associated to lung cancer (ICD-10 C34) reached 88,350 and accounted for 108,216 completed consultant episodes and 282,717 bed days.[15]

3.2.2 Impact on patients and care givers

Most NSCLC patients experience multiple symptoms;[42] the majority of metastatic patients (79% to 81%) endure three or more symptoms.[43,44] NSCLC symptoms directly affect physical functioning and mental wellbeing. This has a direct impact on patients' HRQoL, which is significantly reduced amongst patients with early disease stages.[45]

A preference study conducted in lung cancer cases showed that patients would prefer chemotherapy as opposed to BSC if the former only improved symptoms but had no impact on survival.[46] This study highlights patient preference for treatments that reduce the burden of symptoms which could directly improve HRQoL. Chemotherapy is furthermore associated with acute, potentially life-threatening side-effects and serious longer term toxicities. Chemotherapy-treated patients require frequent clinic visits for intravenous administration,

intensive specialist care, administration of concomitant medications and a mandatory pre-medication period prior to chemotherapy initiation.

NSCLC can cause a burden for people who provide informal care for patients due, to its direct psychological impact. As the disease progresses, informal care givers may also experience an economic burden due to time out of work as a direct or indirect result of providing daily care for NSCLC patients.[47]

3.3 Clinical pathway and proposed use of the technology

3.3.1 Treatment evolution

The treatment options available for NSCLC over the last 30 years have gradually improved resulting to improved median OS. Patients enrolling in clinical trials prior to 1990 experienced a median OS of approximately 6 months.[48,49] Additional research in the early 2000s elucidated a better understanding of the role of *EGFR* mutations, resulting in the discovery of reversible first-generation TKIs. Patients with aNSCLC harbouring EGFR mutations sensitive to TKIs could now be treated with these agents upon failure of chemotherapy.

More recent developments have provided the necessary evidence for 1st line usage of 1st generation TKIs (gefitinib, erlotinib).[17,25] There are no controlled randomized clinical trials (RCTs) studying the OS benefit of TKIs versus chemotherapy used as first- or second-line treatment for aNSCLC that are not confounded by subsequent cross-over to a TKI in the chemotherapy control arm. Conducting such trials would be unethical due to the proved superior efficacy of these agents. TKIs treatment and EGFRm+ testing have been approved in many countries since resulting in an improved median life expectancy for patients of approximately 20-24 months from the point of initial diagnosis.[21,25,50–53]

As explained in Section 3.2, despite the improved median life expectancy that 1st generation TKI treatments offer, patients often develop resistance within the first 12 months of administration. A better molecular understanding of the mechanisms underlying the development of resistance led to the development of the 2nd generation irreversible TKIs (afatinib). In approximately 60% of patients developing TKI resistance, this is due to an additional amino acid substitution, known as T790M in the EGFR due to a single DNA base substitution in the EGFR gene. The mutated EGRFm+ protein carries a threonine amino acid

instead of methionine amino acid in the position 790 of the original protein. This renders the tumour cells insensitive to the 1st generation TKIs.[54]

Second-generation TKIs (such as afatinib), which were not specifically designed for T790M, have been developed and tested against T790M patients but failed to improve the overall response rates.[55] Osimertinib, the treatment under consideration, has been specifically developed to target the T790M mutation. It employs an irreversible inhibiting mechanism by formation of covalent bonds with the mutated protein.[54]

3.3.2 Current clinical pathway

In an unselected population, platinum-based doublet chemotherapy is recognised as the most effective chemotherapy in first-line treatment.[19,56] This is in line with NICE CG121 stating that: *"Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status" and that: "Chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug (carboplatin or cisplatin)."*[57] The guideline also highlights that: *"patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy".* In addition, NICE TA181 recommends pemetrexed as a possible 1st line treatment option for locally advanced or metastatic NSCLC.[58] NICE TA192, TA258 and TA310 recommend the use of gefitinib, erlotinib or afatinib respectively as first-line treatment options for patients harbouring an EGFR mutation.[59–61]

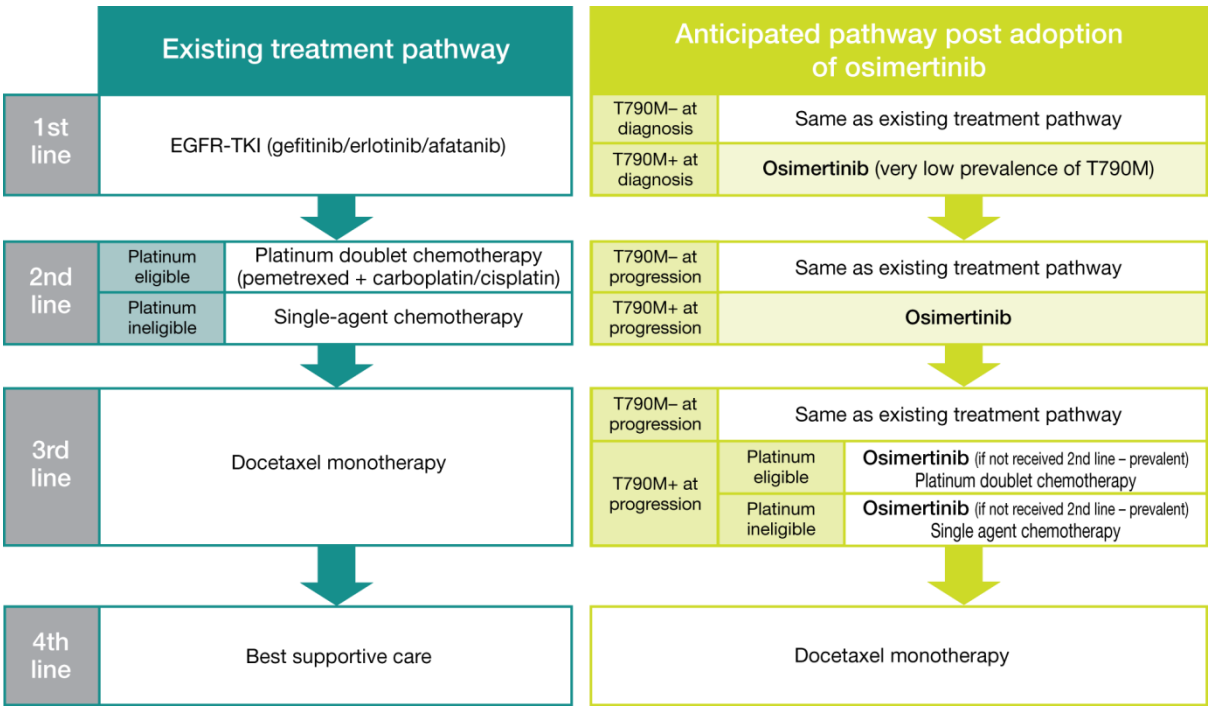
Therefore, platinum doublet chemotherapy is also the most effective currently available option for EGFRm+ patients who progress after treatment with an EGFR TKI. In second-line, pemetrexed plus cisplatin/carboplatin was recommended as the current SoC by regulators.[62] This can therefore be considered the standard of care treatment second line in EGFRm+ patients who have progressed on an EGFR TKI first line. No other regimen either as monotherapy or in combination has been specifically approved in this setting nor has shown superior efficacy. The efficacy of chemotherapy in a previously treated population of patients with aNSCLC has been studied widely resulting in poor outcomes with median PFS in the range of 2-3 months across studies.[63]

In an unselected population, NICE CG121 states that: *"Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy."* Therefore, docetaxel monotherapy is also the most effective currently available 3rd line treatment option for EGFRm+ patients who progress after treatment with an EGFR TKI and subsequent progression on platinum doublet chemotherapy.

3.3.3 Osimertinib in the clinical pathway

Osimertinib is a potent, oral, selective, irreversible inhibitor of the EGFR mutation (TKI-sensitising) and resistant T790M mutation (TKI-resistance conferring mutation), for the treatment of adult patients with locally advanced or metastatic EGFR T790M NSCLC, irrespective of previous treatment with an EGFR TKI. However, as a result of the very low prevalence of T790M mutations at diagnosis (Section 3.1), the expected position of osimertinib in the treatment pathway would be 2nd line following treatment with an EGFR TKI 1st line. This group represents the vast majority of the expected population to be treated with osimertinib in UK clinical practice. In addition, a small group of patients presenting with a T790M mutation at diagnosis could receive osimertinib as a first-line treatment (Section 4.14). Upon marketing authorisation, a pool of prevalent patients (currently 2nd line) could receive osimertinib as a 3rd line treatment following EGFR TKI and chemotherapy. However, it should be clear that this represents a one-off group of patients as osimertinib becomes the standard of care in the second line setting. This is illustrated in Figure 3.2.

Figure 3.2: Overview of current and anticipated treatment pathway



3.4 Life expectancy and number of eligible patients for treatment with osimertinib

3.4.1 Life expectancy

In the UK, 5-year lung cancer survival rates fall well below the European average (9% vs 13%) and are lower than survival rates in other Western European countries such as Austria (16.7%), Germany (15.6%) and France (13.8%).[64] The 5-year survival rate for patients diagnosed with stage IIIB NSCLC is very low at 7-9% and an even worse prognosis is associated with stage IV (distant metastases) of the disease (5-year survival equal to 1%).[65]

For EGFRm+ positive patients treated with a first-line EGFR TKI, median overall survival is approximately 20 months according to data from the IPASS and EURTAC studies presented in Table 3.1. It should be noted that the likely OS benefit in each study was confounded due to a large number of patients (>60% in each study) in the control group receiving subsequent active treatment with an EGFR TKI.

Table 3.1: OS data for aNSCLC, EGFR mutation positive patients treated with first-line EGFR TKI

Name of trial	Population of interest	Line of therapy	Treatment arm	OS
EURTAC[66]	EGFR mutation positive, treatment naive	1st	Erlotinib	22.9 months
			Chemotherapy*	19.6 months
IPASS[50]	EGFR mutation positive, treatment naive	1st	Gefitinib	21.6 months
			Chemotherapy**	21.9 months

* Platinum agent (cisplatin or carboplatin) plus a second drug (docetaxel or gemcitabine)
** carboplatin/ paclitaxel

At disease progression and for patients who develop EGFR TKI resistance, median OS is approximately 17 months according to the IMPRESS trial. The IMPRESS results provide the most robust estimate of median overall survival in EGFRm+ patients who receive platinum doublet chemotherapy as a 2nd line treatment option after progression on an EGFR TKI.. The life expectancy for the population under consideration therefore falls well short of 24 months. Note, the IMPRESS patient population only included patients with a good performance on first generation EGFR TKI and therefore might overestimate the actual survival in the overall population.

3.4.2 Eligible patients for treatment with osimertinib

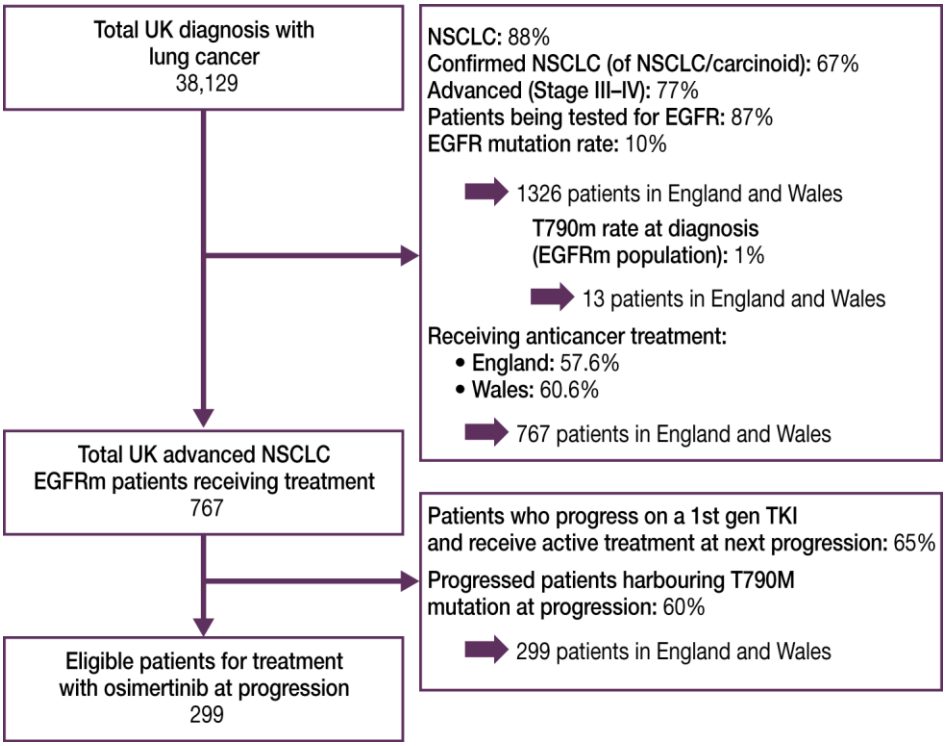
As shown in Figure 3.3, the total number of UK people diagnosed with lung cancer in 2015 was 38,129.[15] After taking into consideration:

- Incidence of NSCLC (88%)[15]
- Incidence of confirmed NSCCL (67%)[15]
- Incidence of advanced disease (77%)[15]
- Proportion of patients being tested for EGFR mutation status (87%)[67]
- Incidence of EGFR mutation (10%)[7]

The resulting pool of patients with EGFRm+ aNSCLC at diagnosis is approximately 1,326 across England and Wales out of which 767 will receive anticancer treatment.[15] Assuming that approximately 65% of patients who progress on an EGFR TKI receive active treatment at progression[9] alongside a T790M mutation rate of 60%,[27–30] results in approximately 300 patients every year being eligible for treatment with osimertinib.

The incidence rate of T790M mutation positive NSCLC at diagnosis is 1–6% (see Section 3.1). As this is currently not routinely tested for and unlikely to change in the near future, we anticipate that approximately 10 patients across England and Wales would present with a T790M mutation status at diagnosis and would be eligible for treatment with osimertinib first line.

Figure 3.3: Osimertinib eligible patient pool for England and Wales



3.5 NICE guidance for locally advanced or metastatic, EGFR and T790M mutation positive NSCLC patients

There is currently no published guidance specific to EGFR and T790M mutation positive, advanced or metastatic NSCLC. Such patients are initially treated with a TKI agent:

- Afatinib; NICE technology appraisal guidance 310[61]
- Erlotinib; NICE technology appraisal guidance 258[60]
- Gefitinib; NICE technology appraisal guidance 192[59]

At disease progression following treatment with a TKI agent, pemetrexed combined with either cisplatin or carboplatin is used in current clinical practice.[68] NICE clinical guideline 121 for lung cancer recommends that people intolerable of platinum doublet chemotherapy should be offered single-agent chemotherapy with a third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine).[57] NICE technology appraisal 374 recommends the use of nintedanib plus docetaxel for those patients that do not respond to prior chemotherapy.[69]

3.6 Other guidelines

In the US, the major clinical practice guidelines are issued by NCCN, ASCO, ACS, and ACCP. In addition, ACR has summarised the recommendations pertaining to non-surgical treatment of NSCLC patients. In Europe, the major guidelines are those issued by ESMO, AIOT, NICE, German Respiratory Society and the German Cancer Society, SEOM, and SIGN. The only Japanese guideline identified was published in 2003 and updated in 2005; little information could be identified.

All agencies stratify recommendations according to EFGRm status (positive, negative/ unknown). None of the current treatment guidelines acknowledge the development of resistance in first-generation TKIs due to T790M mutation positive.

US guidelines for EGFRm+ tumours:

- For patients with confirmed diagnosis of tumours harbouring EGFRm+, USA-based treatment guidelines recommend use of a first-generation TKI as first-line treatment
- Most of the second-line treatment recommendations in USA-based guidelines involve use of erlotinib, gefitinib or erlotinib in combination with platinum chemotherapy if metastases other than brain have occurred[70]
- Additional treatment options in second line include docetaxel and pemetrexed
- Following the FDA approval of osimertinib in November 2015, the NCCN guidelines were updated recommending osimertinib as a treatment option for EGFR T790M mutation positive NSCLC following treatment with an EGFR TKI

European guidelines for EGFRm+ tumours:

- ESMO guidelines, aligned with NICE, recommend erlotinib and gefitinib as first-line TKIs. It recommends that second-line treatment options should only include 1st generation TKIs if patients were not previously treated with one. This is recommended also for stage IV patients
- Guidelines specific to Germany, Italy and Spain recommend gefitinib as first and second-line treatment for patients with EGFRm+ but again are not mutation specific.

US guidelines for EGFRm- or EGFRm unknown tumours

- First-line treatment options recommended in US-based guidelines include singlet chemotherapy such as cisplatin, carboplatin, paclitaxel, docetaxel, vinorelbine,

etoposide, pemetrexed, and gemcitabine; or doublet therapy (often platinum-based combinations)

- Use of first-generation TKIs is not recommended for unselected patients
- Second-line treatment options recommended by NCCN for ECOG scores of 0-2 are docetaxel, erlotinib, gemcitabine, BSC or pemetrexed. For patients with ECOG scores of 3–4, treatment with erlotinib or gefitinb is recommended if tumors become EGFR-positive, otherwise BSC
- ASCO recommends erlotinib or gefitinib in third line for patients who have not previously received either drug

<u>European guidelines for EGFRm- or EGFRm unknown tumours</u>

- ESMO recommends the use of platinum-based doublet chemotherapy as first line.
- The second-line therapies recommended by ESMO are docetaxel and pemetrexed. Erlotinib is also recommended if ECOG score is 0–2, or for ECOG 0–3 after progression on second-line treatment

All the US and EU guidelines have recommended EGFR TKIs for either first- or second- line therapy for advanced/metastatic EGFR mutation-positive NSCLC. NCCN guidelines have already been updated recommending osimertinib for patients with T790M. Erlotinib, gefitinib, BSC, or participation in a clinical trial are the only recommended third-line treatment approaches, but erlotinib or gefitinib are only recommended for patients who have not received these agents in an earlier line of therapy. There are no licensed targeted treatments for use in patients that have progressed on an EGFR TKI.

3.7 Issues relevant to current clinical practice

There is a significant, unmet clinical need for new treatment options in patients that have developed resistance to an EGFR TKI. Current treatment options, limited to cytotoxic chemotherapy, are characterised by low response rates and poor tolerability.

3.8 Equality

AstraZeneca does not anticipate the use of this technology to result in any equality issues.

4 Clinical effectiveness

Treatment of people who have received previous treatment with an EGFR TKI

The clinical efficacy and safety of osimertinib in patients with aNSCLC with disease progression following prior therapy with an EGFR TKI is being investigated through the AURA clinical programme, compromising three key studies in patients with EGFRm+ and T790M mutation positive aNSCLC who have progressed on or after an EGFR TKI treatment:

- AURA extension
- AURA2
- AURA3

Both the AURA extension (AURAext) and AURA2 were single-arm studies. Therefore, in order to compare the efficacy of osimertinib with platinum doublet chemotherapy, this submission also describes the results of the IMPRESS clinical trial. This Phase III RCT compared the efficacy of gefitinib in combination with platinum-based chemotherapy versus chemotherapy alone in patients with EGFRm+ NSCLC who had progressed on or after EGFR TKI treatment. The control group of this trial represents the only robust evidence for EGFRm+ patients treated with chemotherapy. As this was an AstraZeneca clinical trial, by using the IPD, AstraZeneca was able to retrospectively test archival tumor biopsies to identify the patients whose progression in the control arm was driven by the emergence of the T790M mutation.

All studies are described in more detail in Section 4.11.

First-line treatment in the presence of a T790M mutation

The marketing authorization of osimertinib also includes the treatment of patients who have not previously received an EGFR TKI treatment but present with a T790M mutation upon diagnosis. This population represents a very small proportion of EGFRm+ patients upon diagnosis with literature estimates ranging between 1% and 6% (see Section 2.1). Despite very limited data on patients with a *de novo* T790M mutation from the AURA expansion study, the CHMP recommended use in all lines of treatment based on the underlying presence of the T790M mutation being the biological driver for the disease. More details on this population are provided in Section 4.15.

As limited evidence is available regarding this population, the remainder of this section focuses on the significantly larger clinically relevant group of patients who have been previously treated with an EGFR TKI.

4.1 Identification and selection of relevant studies

Search strategy

A systematic search of the literature was undertaken to identify RCTs investigating the efficacy and safety of osimertinib, alongside comparators, in the treatment of advanced or metastatic NSCLC for EGFR and T790M mutation positive patients failing treatment with a TKI. This formed part of a broader search for evidence to support the cost-effectiveness analysis and decision problem. Due to lack of data the search was broadened to include studies that focused on advanced or metastatic NSCLC and EGFR mutation positive patients irrespective of their T790M mutation status.

The search strategy was designed to capture articles studying a broad advanced NSCLC patient population (Appendix A1.1). The EGFR and/or T790M mutation positive and resistant (to prior TKI treatment) populations were depicted through the screening process in order to align with the NICE decision problem for this STA, as stated in Section 1.1. The population of interest could be either the total study population or a subgroup. For completeness and due to lack of data, literature was searched broadly resulting in an extensive range of comparators that are included in the eligibility criteria (Table 4.3) and search strategy (Appendix A1.1). In line with the decision problem, only a group of these comparators can be considered relevant for this submission, including:

- Afatinib
- Erlotinib
- Gefitinib
- Platinum doublet therapy (including pemetrexed plus carboplatin or cisplatin)
- Single-agent chemotherapy including gemcitabine, paclitaxel, vinorelbine or docetaxel
- Docetaxel with or without nintedanib

- Nivolumab
- Ramucirumab

A randomized control trial was defined as any trial with at least two arms where the intervention or comparator could be osmertinib or any of the UK comparators (Appendix A1.1). Trials were included irrespective of blinding status. The RCT publications had to provide data on efficacy and safety for each arm and, if available, on HRQoL. However, given the limited availability of RCT data, single-arm trials, non-randomized trials and observational studies were also considered for review (Appendix A1.1).

Searches of the electronic databases (Table 4.1) and relevant conference proceedings (Table 4.2) were facilitated in January 2016; conferences were searched for the last 4 years (2012, 2013, 2014 and 2015).

Table 4.1: Summary of data sources for the systematic review

Search strategy component	Sources	Date limits
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies (CADTH, 2014; IQWiG, 2008; NICE, 2015d; NICE, 2015e)	MEDLINE® MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL)	Database inception to 4 January 2016

Abbreviations: Embase® = Excerpta Medica Database; HTA = Health Technology Assessment; MEDLINE® = Medical Literature Analysis and Retrieval System Online

Table 4.2: Conferences searched for the systematic review and the service provider used

Conference	Dates	Website
American Society of Clinical Oncology (ASCO)	2012	http://meetinglibrary.asco.org/subcategories/2012%20ASCO%20Annual%20Meeting
	2013	http://meetinglibrary.asco.org/subcategories/2013%20ASCO%20Annual%20Meeting
	2014	http://meetinglibrary.asco.org/subcategories/2014%20ASCO%20Annual%20Meeting
	2015	http://meetinglibrary.asco.org/subcategories/2015%20ASCO%20Annual%20Meeting
European Society for Medical Oncology (ESMO)	2012	http://www.esmo.org/Conferences/Past-Conferences/ESMO-2012-Congress
	2013	http://www.esmo.org/Conferences/Past-Conferences/European-Cancer-Congress-2013
	2014	http://www.esmo.org/Conferences/Past-Conferences/ESMO-2014-Congress
	2015	http://www.europeancancercongress.org/Scientific-Programme/Abstract-search
World Conference on Lung Cancer (WCLC)*	2013	http://www.2013worldlungcancer.org/
	2015	http://wclc2015.iaslc.org/wp-content/uploads/2015/09/WCLC-2015-Abstract-Book1.pdf

* WCLC is held every 2 years. Abbreviations: Embase® = Excerpta Medica Database; HTA = Health Technology Assessment; MEDLINE® = Medical Literature Analysis and Retrieval System Online

This work follows the framework specified by the Cochrane collaboration and NICE. Full details on the literature search strategy and the search strings used are presented inside Appendix A1.1.

Study selection

All references retrieved through the database searches were exported in Reference Manager 12 and duplicated before being exported to an excel spreadsheet. At an initial stage, citations identified through the searches were abstract and title screened for inclusion by two independent reviewers and conflicts were resolved by a third one. Similarly, the full text of articles considered relevant at abstract/title screening was reviewed and those meeting the inclusion criteria were considered for data extraction. In either of the aforementioned screening stages, excluded publications were disregarded.

Searches were limited to evidence published between 2004–2016 and only articles published in the English language were considered.

Eligibility criteria used in the clinical systematic review are listed in Table 4.3, including the additional step to restrict to patients with advanced NSCLC.

Table 4.3: Eligibility criteria used in clinical search strategy

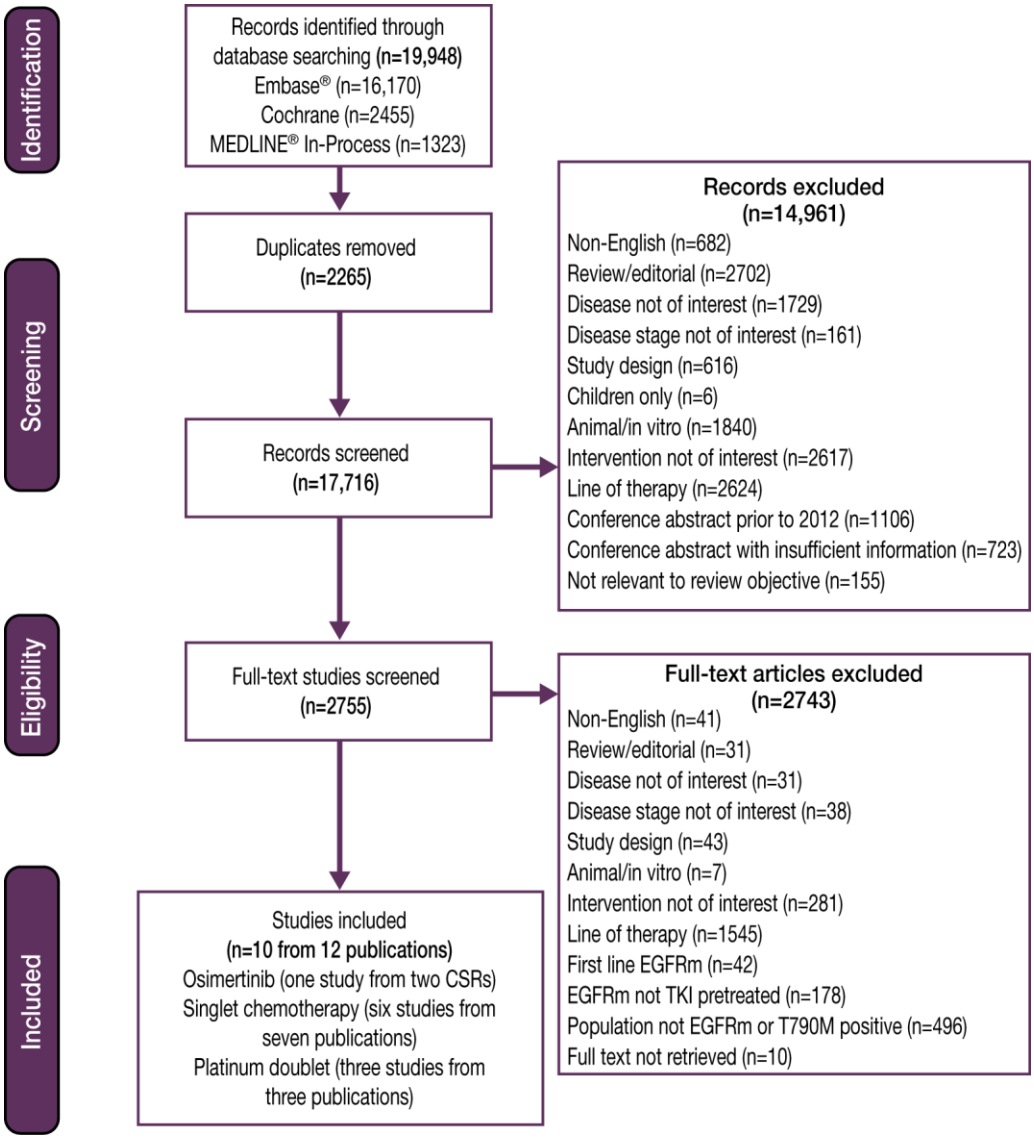
	Criteria	Rationale
Inclusion criteria	Population Age: adults (≥18 years) Sex: any Race: any Disease: advanced or metastatic NSCLC patients with acquired EGFR and/or T790M mutation Line of therapy: all patients with at least one prior EGFR TKI therapy	The patient population has been restricted to match that stated in the NICE decision problem for osimertinib in the treatment of previously EGFR TKI treated advanced or metastatic, EGFR and/or T790M mutation non-small cell lung cancer.
	Intervention Osimertinib (AZD9291)	Intervention was defined by the NICE decision problem for treatment of previously EGFR TKI treated locally advanced or metastatic, EGFR and/or T790M mutation non-small cell lung cancer.
	Comparators* Second- or further-line of therapy using: including: Afatinib Bevacizumab Carboplatin Ceritinib Cisplatin Crizotinib Docetaxel Erlotinib Gefitinib Gemcitabine Methotrexate Paclitaxel Pemetrexed Vinorelbine Nintedanib Ipilimumab Axitinib Nivolumab Cetuximab Rociletinib Icotinib Ramucirumab	All comparators defined by the NICE decision problem for treatment with osimertinib previously EGFR TKI treated locally advanced or metastatic, EGFR and/or T790M mutation non-small cell lung cancer were included in the search. All comparators were included in the systematic review to retrieve complete evidence.

	Criteria	Rationale
	Outcome measures Efficacy outcomes (ORR, DCR, PFS, OS, DOR, tumour shrinkage) Safety outcomes (Adverse reactions, treatment discontinuations) HRQoL	To explore availability of data appropriate to support this NICE decision.
	Study design All randomized controlled clinical trials (RCTs irrespective of blinding status) Single arm trials Non-randomized controlled trials Observational studies(retrospective analysis, prospective studies, cohort studies, case control studies, longitudinal studies)	RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of interventions. Considering the limited RCT evidence, additional study designs such as single-arm trials, non-randomized trials and observational studies were also included in this review.
	Restrictions Language: Only studies with the full-text published in English language were included Publication timeframe for literature searches: Database inception to 4 January 2016 Publication timeframe for conference searching ASCO: 2012, 2013, 2014 and 2015 ESMO: 2012, 2013, 2014 and 2015 WCLC: 2013 and 2015	The restriction would not limit results substantially due to data availability in English language. Studies that are presented at conferences are usually published in journals within 3 years.
Exclusion criteria	Excluded population Patients without a locally advanced or metastatic NSCLC Patients with a locally advanced or metastatic NSCLC where EGFR or T790M mutation status was negative or unclear Children or adolescents (< 18 years of age) Mixed patient population studies where subgroup data for adult patients are not reported Treatment-naïve patients who have not received any prior therapy Patients receiving first-line therapy Studies enrolling patients receiving first- or further-line therapy with no subgroup data for patients receiving further-line therapy	This study population was not relevant to the decision problem. For treatment-naïve patients who present with a T790M mutation upon diagnosis, please see Section 4.15 for further details.

	Criteria	Rationale
	Excluded interventions/comparators Studies not assessing any of the included interventions Studies where interventions are administered for the treatment of AEs Studies investigating the role of radiotherapy, chemo-radiotherapy or surgery Studies assessing interventions used to control the symptoms of the disease such as erythropoietin to treat anaemia, antibiotics to treat infections and various types of pain medication Studies assessing adjuvant or neoadjuvant therapy	These interventions are not relevant to the decision problem.
	Excluded outcomes Outcomes other than those of interest	Such outcomes would not adequately inform the decision problem.
	Excluded study designs Case studies and case reports Cross-sectional studies Review, letters to the editors and editorials	The design of such studies was not relevant to the decision problem.
	Restrictions Non-English studies Studies published beyond 12 past years	Non- English studies could not be translated due to limited time and resources. Due to the fast growing disease landscape, studies prior to 12 years would not study treatments or populations of interest .
Further selection of key comparators	Study comparators were further restricted to include studies assessing: Following treatment with an EGFR TKI inhibitor: Platinum doublet therapy (pemetrexed plus carboplatin or cisplatin) Single agent chemotherapy including gemcitabine, paclitaxel, vinorelbine (for those for whom treatment with a platinum therapy is not appropriate) Following two prior treatments, an EGFR TKI inhibitor and chemotherapy: Docetaxel with or without nintedanib Single agent chemotherapy including gemcitabine, paclitaxel, vinorelbine (for those for whom treatment with docetaxel is not appropriate)	Comparators were restricted in line with the NICE decision problem and the marketing authorisation for osimertinib.

A Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram showing the number of studies included and excluded at each stage of the systematic review is presented in Figure 4.1.

Figure 4.1: PRISMA flow diagram of the systematic review process



As shown in the PRISMA flow diagram, the clinical systematic review identified 10 studies (including the AURA Phase I/II cohort study)[71] that met the inclusion criteria of the review. It should be noted that hereafter and throughout the clinical effectiveness section, instead of the published data limited to the Phase I/II cohort study we refer to the unpublished AURAext/2 pooled data cohort (n=411) which was used as the basis of the EU regulatory submission for osimertinib and was therefore not identified in the systematic review.

The systematic review used broad inclusion criteria to allow the identification of all studies that might be relevant to NICE's decision problem. Of the 10 studies included in the review, only one study was in T790M mutation positive patients (AURAext/2) and the other nine studies were in EGFR mutation positive patients.

Of the 10 studies assessing treatments relevant to the decision problem, six were assessing single-agent chemotherapies, three in second-line setting, two in third-line and one in the ≥second-line setting. The other three studies assessed platinum doublet combinations, all in the second-line only setting. The pooled analysis of AURAext/2 provided data for osimertinib in the ≥second-line setting as well as for second-only and ≥third-line subgroups (see Section 4.11 for further details).

Six studies were retrospective observational studies with often small patient numbers and differences in patient populations compared to the AURA Pooled data set. Also definitions of progression and other endpoints are generally not consistent with those of prospective studies. These studies were, therefore, not considered as the most appropriate basis for comparison against the AURA pooled data set in the basecase economic analysis.

Out of the remaining three prospective studies (excluding AURA), the Kasahara 2015[72] and Halmos 2015 studies[73] respectively enrolled 35 and 17 EGFRm+ patients, making it a too small population for a robust comparison.

Therefore the IMPRESS Study, a Phase III RCT with a control group of 132 patients provides the most suitable evidence providing efficacy and safety results on the comparators referred to in the decision problem. Furthermore, the IMPRESS Study is the only study with results by T790M mutation status due to it being an AstraZeneca Study with resulting access to the IPD.

A brief overview of the 4 prospective studies identified in the review is presented in Table 4.4. Baseline characteristics of the patients included in these studies are provided in Appendix A1.2. A detailed critical appraisal of the studies identified in the systematic review is provided in Appendix A1.3.

A summary of key results in terms of ORR, PFS and OS from the studies identified in the systematic review is provided in Table 4.5.

Table 4.4: Summary of studies reporting data for previously EGFR TKI-treated EGFR and/or T790M mutation positive locally advanced or metastatic NSCLC population

Trial ID (Acronym)	Primary author, year (reference)	Design	Location	Intervention/ comparators (n)	Duration	Patient population
NR	Tseng 2014	Retrospective observational study	Two medical centres of Taiwan	Cisplatin/Carboplatin + Pemetrexed(61)	Survival data were followed up until the end of November 2013	• Histologically or cytologically confirmed and inoperable lung adenocarcinoma. • Patients with known EGFR mutations and clinically measurable disease were included. • Patients were excluded if they have incomplete data records, or received other treatments, such as radiotherapy, concurrently. • Patients with only evaluable lesions were excluded. • No prior history of other chemotherapies. • No other active malignancy.
NEJ002 trial	Miyauchi 2015	Retrospective observational study	Japan	Cisplatin/Carboplatin + Pemetrexed (11)	NR	• Age ≤ 75 years. • Advanced NSCLC harbouring activating EGFR mutations (excluding the resistant EGFR mutation T790M). • ECOG PS 0 or 1 • No history of chemotherapy. • Patients who received second-line platinum based chemotherapy were included. • Patients who did not receive second-line treatment or received EGFR TKI, or a non-platinum-based regimen were excluded from the analysis.
NR	Park 2015	Retrospective observational study	Korea	Pemetrexed (37) Platinum doublet (46)	January 2006 to April 2014	• Patients with activating EGFR mutations consisting of microdeletion in exon 19 or an L858R point mutation in exon 21 were included. • Patients who received first-line therapy with palliative EGFR TKI (gefitinib or erlotinib) were included. • Patients were included if they failed first-line EGFR TKI treatment. • Documented Epidermal Growth Factor

						Receptor (EGFR) positive disease. • Karnofsky PS ≥70%. • Patients progressing or relapsing after treatment with EGFR tyrosine kinase inhibitors. • Adequate bone marrow, hepatic and renal functions. • Patients were excluded if they received prior systemic chemotherapy or immunotherapy for NSCLC
NR	Halmos 2015	RCT	7 institutions in USA	Pemetrexed or docetaxel (17) Erlotinib + pemetrexed or docetaxel (14)	NR	• Age ≥18 years. • Patients with stage IIIB (with pleural effusion) or stage IV non-small cell lung cancer • Patients were included if their disease progressed after at least twelve weeks of erlotinib treatment. • ECOG PS 0-2 • Patients with life expectancy of at least 12 weeks were included. • Patients with adequate hematologic, hepatic and renal functions were included. • Patients with history of more than one prior cytotoxic chemotherapy regimen for relapsed or metastatic disease (not including erlotinib) and any prior EGFR inhibitor (beside erlotinib) were excluded • Patients with known or suspected clinically active brain metastases were not included.
NR	Zhou 2014	Retrospective observational study	China	Pemetrexed (61)	March 2010 to March 2014	• Patients with advanced EGFR mutation-positive lung cancer • Patients with prior treatment with gemcitabine and cisplatin (GP) chemotherapy, one type of EGFR TKI therapy were reviewed. • Patients with a third-line application of pemetrexed alone or in combination with bevacizumab were reviewed
NR	Kasahara 2015	RCT	Japan	Docetaxel (17) Ramucirumab + Docetaxel (18)	Enrolment: 16 months; Follow-up: 4 months	• Patients with stage IV NSCLC. • Patients with all NSCLC histology's were included • Age ≥20 years.

						• Patients with disease progression following platinum-based first-line therapy • ECOG PS 0 or 1 • Adequate organ function • Measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST) V1.1 • Patients with life expectancy of ≥3 months were included. • Patients with untreated central nervous system metastases (treated asymptomatic brain metastases eligible) were excluded. • Patients with major blood vessel invasion or significant intratumor cavitation as defined by computed tomography or magnetic resonance imaging scanning were excluded
IMPRESS trial	Soria 2015	RCT	71 centres in 11 countries in Europe (France, Germany, Hungary, Italy, Russia, and Spain) and the Asia-Pacific region (China, Hong Kong, Japan, South Korea, and Taiwan)	Cisplatin + Pemetrexed (132) Gefitinib + cisplatin + Pemetrexed (133)	Median duration of follow-up for the primary analysis of progression-free survival was 11·2 months (IQR 8·0–15·0)	• Patients with confirmed activating EGFR mutation who had achieved a complete or partial response for longer than 4 months or durable stable disease for at least 6 months on first-line gefitinib treatment and had subsequently developed radiological disease progression • Cytologically or histologically confirmed chemotherapy-naive advanced NSCLC were included • Age ≥20 years in Japan. • WHO PS 0 or 1 • Patients with life expectancy of at least 12 weeks were included. • Patients with NSCLC of predominantly squamous cell histology and a history of interstitial lung disease were excluded. • Patients with any other coexisting malignancies diagnosed within the past 5 years (excluding basal cell carcinoma, cervical cancer in situ, or completely resected intramucosal gastric cancer), or treatment with another investigational drug 4 weeks or less before random allocation were excluded
NR	Wu 2010	Retrospective	Taiwan	Gemcitabine (13)	January 2004	• Patients with stage IIIB or IV NSCLC

		observational study			and July 2008	• Pre-treated with gefitinib between January 2004 to July 2008 • Receiving at least 1 subsequent line therapy after failure of previous gefitinib treatment
NR	Kim 2013	Retrospective observational study	Unclear	Pemetrexed (41)	Unclear	• Patients with EGFR-mutant stage IV adenocarcinoma • Progressed during gefitinb treatment
AURA 2/AURA extension	AURA 2/AURA extension	Single arm	44 study centres in Canada, Hong Kong, Italy, Japan, South Korea, Spain, Taiwan and USA	osimertinib (411)	2014-ongoing	• Confirmed diagnosis of EGFRm locally advanced or metastatic NSCLC (stage IIIB–IV) • Patients should be progressed following prior • therapy with an approved EGFR TKI agent • A mandatory biopsy was required for central testing of T790M mutation

Table 4.5: Summary of outcomes for identified prospective studies in previously EGFR TKI-treated EGFR and or T790M mutation positive locally advanced or metastatic NSCLC population

Trial ID (Acronym)	Study Design	Primary author, year (reference)	Treatment arm	Line of therapy	EGFRm+ Number of PTS (in population of interest)	ORR % (n)	OS Median [95%CI] (Range) (months)	PFS Median [95%CI] (Range) (months)
IMPRESS trial	Ph III RCT	Soria 2015	Cisplatin + Pemetrexed	Second-line	132	34.1% (45)	17.2 [15.6-NR]	5.4 [4.6-5.5]
AURAext/2	Ph I/II open-label	AURA 2/AURA extension	Osimertinib	Second- or further line	411	66.1 (263)[#]	–	9.7 [8.3-NR]
NR	Ph II RCT	Halmos 2015	Pemetrexed or docetaxel	Second-line	17	-	–	5.85*
NR	RCT	Kasahara 2015	Ramucirumab+Docetaxel (DR) or Docetaxel (D)	Third-line	DR:18 D:17	DR:44% (18) D:41% (7)	–	DR:5.7 [3.9-9.9] D:4.4 [2.9-9.9]

*Estimated from reported KM curve; [#]evaluable N=398; ORR: Objective response rate; OS: Overall survival: PFS: Progression-free survival

4.2 List of relevant randomized controlled trials

No RCTs were identified that provide evidence on the clinical benefits of the technology at its licensed dosage within the indication being appraised. Therefore, Sections 4.3 to 4.9 have been omitted from this submission.

A confirmatory Phase III RCT, AURA3, is currently ongoing. This trial is event driven [redacted]. It is designed to compare the efficacy and safety of osimertinib versus platinum-based doublet chemotherapy in patients with EGFRm+ and T790M mutation positive aNSCLC whose disease has progressed following prior therapy with an EGFR TKI. As results are not yet available, this study will not be described in further detail within the main submission. For more details on the design of this study, please see Section 4.14.

The relevant evidence underpinning this submission consists of data from 3 separate clinical trials. These are described in detail in Section 4.11. We recommend to review the evidence presented in 4.11 before reading Section 4.10 describing the indirect treatment comparison.

4.10 Indirect and mixed treatment comparisons

As described in the introduction to Section 4, the main focus of this submission and presented cost-effectiveness analysis is the comparison of osimertinib to platinum doublet chemotherapy in patients who have been previously treated with an EGFR TKI. Results from the control group in the IMPRESS trial provide the most robust evidence base for the clinical effectiveness and safety of platinum doublet chemotherapy in this population (Section 4.1).

To this purpose, the pooled AURA clinical study results, described in full detail in Section 4.11, have been compared to the results of the control group in the IMPRESS trial, consisting of second-line EGFR mutation positive patients receiving platinum doublet chemotherapy following progression on a first-line TKI.

As the IMPRESS trial was an AstraZeneca trial, access to the IPD and tumour analysis to confirm T790M mutation status, allowed the comparison in the population referred to in the decision problem. This section therefore provides a discussion on the comparison of both study populations, a simple unadjusted comparison of clinical trial results as well as the results of an adjusted indirect comparison in order to control for differences in baseline characteristics.

4.10.1 Comparison of study populations

4.10.1.1 Study inclusion criteria

The inclusion criteria of the AURA extension and AURA2 studies are similar to those of IMPRESS and are presented in Table 4.6. Key differences include prior treatment history, prior treatment response to EGFR TKI and applied methods to identify baseline T790M mutation status.

In the AURA pooled population, 68.4% of patients had received at least 2 prior treatment regimens and 45.5% had received 3 or more prior lines of therapy prior to initiating treatment with osimertinib. The AURA pooled population is therefore more refractory in nature as compared to the IMPRESS control group where all patients had received only 1 prior line of therapy prior to receiving study drug.

In the AURA pooled population, 66.7% of patients had received an EGFR TKI as last therapy prior to study entry, compared to 100% of patients in the IMPRESS population. In AURA, the duration of the most recent prior EGFR TKI therapy was ≥6 months in 69.1% of patients. For IMPRESS, one of the inclusion criteria was a minimum duration on first-line gefitinib of at least 4 months for patients achieving CR or PR. In addition, prior to enrolment in IMPRESS, patients needed to demonstrate prior objective clinical benefit (PR, CR or durable SD >6 months after initiation of first-line gefitinib).

These differences between the AURA and IMPRESS populations might have had a prognostic effect favouring the IMPRESS T790M mutation positive control group as it was a second-line only population, which had less previous treatment and was selected for good performance on previous EGFR TKI.

Table 4.6: Comparison of inclusion criteria in AURAext/AURA2 versus IMPRESS

Parameter	AURAext/AURA2 Pooled Osimertinib 2L =129 Osimertinib 3L+= 282	IMPRESS Iressa + Pem/Cis (N=133) Placebo + Pem/Cis (N=132)
NSCLC	• Locally advanced and metastatic	• Locally advanced and metastatic
Prior Treatment History	• 1st line EGFR TKI (2L) • EGFR TKI + additional therapies (3L+)	• 1st line gefitinib (2L)
Prior treatment response to EGFR TKI	• No specific requirements	• Prior objective clinical benefit (PR, CR or durable SD >6 months after initiation of first-line gefitinib) • Minimum duration on first-line gefitinib treatment of 4 months for patients achieving CR or PR
Baseline sensitising EGFRm status	• Positive by local test for enrolment • Results reported by central test	• Positive by local test for enrolment
Baseline T790M status (tissue)	• T790M mutation positive by tissue (central test)	
Baseline T790M status (plasma)	• Determined by Roche Cobas	• Determined by BEAMing digital PCR
Disease Progression on Prior EGFR TKI	• Radiological documentation of disease progression while on a previous continuous treatment with an EGFR TKI e.g. gefitinib or erlotinib • Documented radiological progression on the last treatment	• Radiological documentation of disease progression while on continuous treatment with first-line gefitinib within 4 weeks prior to randomization into the study
Brain Metastases	• Allowed if asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment	• Allowed if stable without steroid for at least 10 days within 4 weeks of randomization into the study.
WHO Performance Status	• 0 and 1	• 0 and 1
Baseline medical status	• Excluded prior ILD • Criteria for adequate bone marrow reserve/organ function • Specific exclusion for cardiac criteria	• Excluded prior ILD • Criteria for adequate bone marrow reserve/organ function
Predominant Races Enrolled	• Asian and White	• Asian and White
RECIST Assessment	• Measurable disease at BL • RECIST Every 6 weeks • Investigator assessment (sensitivity) – including DoR • Independent assessment (primary) – including DOR	• Measurable disease at BL • RECIST every 6 weeks • Investigator assessment (primary) • Independent assessment (sensitivity)

4.10.1.2 Patient demographics

Overall, patient demographics were well balanced between the AURA pooled dataset and IMPRESS T790M mutation positive control group (Table 4.7). Key differences were age and the presence of brain metastases at baseline.

The IMPRESS T790M mutation positive control population was significantly younger compared to the AURA pooled population with a mean age of 55.8 years compared to 62.2

years; 16.4% of patients were aged ≥65 years compared to 45.5% in the AURA pooled population.

Furthermore, less patients presented with brain metastases at baseline [21 (35%)] as compared to the pooled AURA dataset [166 (40.4%)].

Both these imbalances might have had a prognostic effect favouring the IMPRESS T790M mutation positive control group.

Table 4.7: Overview of baseline characteristics across AURA and IMPRESS

Demographic characteristic		AURA pooled[74,75]	IMPRESS all-comers	IMPRESS T790M mutation positive
Indication		≥Second-line	Second-line	Second-line
Treatment		Osimertinib 80 mg	Placebo (platinum doublet chemotherapy)	Placebo (platinum doublet chemotherapy)
Number of patients		411	132	61
Age (years)	Mean (SD)	62.2 (10.76)	57 (11.25)	55.8 (10.20)
	Median (min-max)	63 (35-89)	58 (35-79)	55 (38-79)
	% ≥65 years	187 (45.5%)	34 (25.8%)	10 (16.4%)
Sex	Male	132 (32.1%)	48 (36.4%)	23 (37.7%)
	Female	279 (67.9%)	84 (63.6%)	38 (62.3%)
Smoking	Never	284 (69.1%)	91 (69.0%)	39 (65.0%)
	Ever	114 (27.7%)	NR	NR
	Current	7 (1.7%)	NR	NR
EGFR mutation	Exon 19 deletion	279 (67.9%)	86 (65.2%)	43 (71.7%)
	L858R in exon 21	118 (28.7%)	42 (31.8%)	17 (28.3%)
	Other	14 (3.4%)	NR	NR
ECOG / WHO performance system	0	152 (37.0%)	53 (40.0%)	22 (36.1%)
	1	258 (62.8%)	79 (60.0%)	39 (63.9%)
	2	1 (0.2%)	0 (0%)	0 (0%)
	3	0 (0%)	0 (0%)	0 (0%)
	4	0 (0%)	0 (0%)	0 (0%)
	0–1	410 (99.8%)	132 (100%)	61 (100%)
	2–4	1 (0.2%)	0 (0%)	0 (0%)
Metastatic at baseline		395 (96.1%)	119 (90.0%)	58 (95.1%)
Brain metastatic at baseline		166 (40.4%)	31 (23.0%)	21 (34.4%)

4.10.2 Unadjusted comparison of study results

4.10.2.1 Clinical effectiveness

The response rate observed within the AURA pooled dataset (ORR 64.2%) was significantly higher compared to the IMPRESS control group (ORR 34.1%) and IMPRESS T790M mutation positive control group (ORR 39.3%). This translated into a median PFS of 9.7 months in AURA compared to 5.3 months in the IMPRESS T790M mutation positive control group.

Table 4.8: Overview of key efficacy outcomes across AURA and IMPRESS

Outcome		AURA pooled[74,75]	IMPRESS all-comers	IMPRESS T790M mutation positive
Indication		≥Second-line	Second-line	Second-line
Treatment		Osimertinib 80 mg	Placebo (platinum doublet chemotherapy)	Placebo (platinum doublet chemotherapy)
Number of patients		411	132	61
ORR	Total responses (%)	264 (66.1%)	45 (34.1%)	24 (39.3%)
PFS	Total events (%)	159 (38.9%)	107 (81.1%)	51 (83.6%)
	Median (95% CI)	9.7m (8.9-NC)	5.4m (4.6-5.5)	5.3m (NR)
OS	Total events (%)	52 (12.7%)	37 (28%)	20 (32.8%)
	Median (95% CI)	Not reached	17.2m (15.6-NC)	15.7m (NR)

Presence and development of brain metastases

Presence of brain metastases is a strongly negative prognostic factor for outcome in NSCLC. Therefore, effective strategies to prevent their development or to control existing brain metastases are desirable to meet an area of significant need for lung cancer patients. In both murine and simian preclinical models, it has been shown that osimertinib crosses the blood-brain barrier, in contrast to other EGFR TKIs.[76] Preliminary clinical data support these findings.[77,78]

In an EGFR mutation positive population, the 1- and 2-year cumulative risk of CNS progression was 7% and 19% respectively, in patients treated with gefitinib or erlotinib, significantly lower rates than observed in historical data for chemo.[79]

Furthermore, post hoc analyses of the IMPRESS study may shed light on the proportion of second-line EGFRm+ patients who, based on the absence or presence of brain/CNS metastases on study entry, went on to progress due to growth or emergence of brain

metastases. Although populations were not perfectly analogous, indirect comparisons with the pooled Phase II AURA data provide directional evidence.

Specifically, of patients with baseline brain metastases, 57.9% (11/24) of patients who progressed on the control arm (platinum doublet) of IMPRESS did so in brain/CNS compared with 33.8% (23/161) of the same population in AURA. For patients without baseline brain metastases these numbers were 8.9% (7/79) and 4.1% (3/74) respectively, hinting at a potential brain/CNS protective effect of osimertinib compared to chemotherapy. The validity of this hypothesis will be confirmed robustly in AURA3.

4.10.2.2 Safety

The safety data from AURA extension and AURA2, supported by consistent data from AURA Phase I, indicate that osimertinib 80 mg has an acceptable safety and tolerability profile in terms of the type, frequency and severity of events, for use in the proposed indication. Osimertinib's well tolerated profile is reflected in the very low discontinuation rate observed in the two single-arm trials. In the pooled osimertinib analysis only 4.1% of patients discontinued treatment due to an AE. Despite differences in the average number of lines of prior treatment, osimertinib appeared to be associated with less ≥ grade 3 AEs compared to platinum doublet chemotherapy (29.4% vs 41.7% respectively) and with, less AEs leading to treatment discontinuation (4.1% vs 9.8% respectively).

Table 4.9: Comparison of key safety data between AURA and IMPRESS

AE category	Number (%) of patients[a]	
	AURA pooled osimertinib 80 mg	IMPRESS Control Group
Sample Size	(N=411)	(N=132)
Patients with any AE	401 (97.6)	130 (98.5)
CTCAE ≥grade 3 AEs	121 (29.4)	55 (41.7)
SAEs	83 (20.2)	28 (21.2)
Fatal SAEs	9 (2.2)	8 (6.1)
AEs leading to discontinuation	17 (4.1)	13 (9.8)
AEs leading to dose modification	81 (19.7)	NR

[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.
CTCAE = Common Terminology Criteria for Adverse Events version 4.0; MedDRA version 17.1.

Table 4.10: Overview of the most common adverse events (occurring in ≥10% of patients in the pooled dataset of AURA extension and AURA2 or IMPRESS)

	Osimertinib ≥Second line		Platinum doublet chemotherapy	
Sample size (n)	N=411		n=132	
	Any AE N (%)	Gr≥3 N (%)	Any AE N (%)	Gr≥3 N (%)
Diarrhoea	174 (42.3)	4 (1.0)	19 (14.4)	1 (0.8)
Rash	170 (41.4)	1 (0.2)	11 (8.3)	0
Dry skin	95 (23.1)	0	8 (6.1)	0
Paronychia	72 (17.5)	0	1 (0.8)	0
Nausea	69 (16.8)	2 (0.5)	81 (61.4)	6 (4.5)
Decreased appetite	65 (15.8)	3 (0.7)	45 (34.1)	3 (2.3)
Constipation	62 (15.1)	1 (0.2)	35 (26.5)	0
Cough	57 (13.9)	1 (0.2)	15 (11.4)	0
Fatigue	57 (13.9)	2 (0.5)	23 (17.4)	0
Pruritus	57 (13.9)	0	7 (5.3)	0
Back pain	52 (12.7)	3 (0.7)	14 (10.6)	0
Stomatitis	49 (11.9)	0	5 (3.8)	1 (0.8)
Platelet count decreased	47 (11.4)	2 (0.5)	3 (2.3)	0
Headache	42 (10.2)	1 (0.2)	19 (14.4)	1 (0.8)
Anaemia	40 (9.7)	6 (1.4)	33 (25.0)	5 (3.8)
Vomiting	39 (9.5)	2 (0.5)	44 (33.3)	3 (2.3)
Asthenia	31 (7.5)	3 (0.7)	30 (22.7)	4 (3.0)
Neutrophil count decreased	25 (6.1)	7 (1.7)	22 (16.7)	10 (7.6)
Pyrexia	22 (5.4)	0	14 (10.6)	0
Neutropenia	17 (4.1)	2 (0.5)	28 (21.2)	7 (5.3)
Leucopenia	12 (2.9)	3 (0.7)	22 (16.7)	3 (2.3)

4.10.3 Adjusted indirect comparison of osimertinib compared with platinum doublet chemotherapy

4.10.3.1 Introduction

The treatment effect of osimertinib monotherapy compared with platinum doublet chemotherapy was assessed using an adjusted indirect comparison of the two non-randomized individual patient data sets from the AURAext/2 studies (N=411) and the T790M subgroup of the placebo arm of the IMPRESS study (N=60), respectively.

In an attempt to reduce bias in a non-randomized efficacy comparison, estimated propensity score (PS) methods were used to balance the non-equivalent AURAext/2 and IMPRESS cohorts on common observable variables.

4.10.3.2 Overall analysis design/methodology

Patients who had tested positive for EGFR and T790M mutations from AURAext/2 were matched with patients who tested positive for EGFR and T790M mutations and randomized to the placebo arm of IMPRESS based on baseline demographic and disease characteristics. Patients without a match were dropped (trimmed) from the analysis. For the retained cohort, the treatment effect of osimertinib versus platinum doublet chemotherapy was assessed for key efficacy and safety endpoints using standard statistical methods with inclusion of an additional covariate (termed propensity score) to adjust for remaining baseline differences between the two osimertinib and platinum doublet chemotherapy treatment groups.

Prior to analysis of endpoints, differences between baseline demographic and disease characteristics were accounted for by a three-step process of adjustment, termed cohort balancing, as follows:

(i) selection of baseline variables that were statistically significantly different between groups (based on a *p*-value < 0.2);

(ii) generation of a propensity score to represent aggregated differences in variables selected and trimming of the data set by removal of patients for which there was no similar PS in the alternative group and;

(iii) incorporation of propensity score as covariate in analysis of treatment effect of osimertinib for each endpoint to adjust for remaining differences between the two groups.

The estimated propensity score was defined as the conditional probability that a patient will be treated with osimertinib or platinum doublet chemotherapy given the observed pre-treatment baseline variables. For example, if two patients have the same probability of receiving osimertinib i.e. 0.50 this means that both patients had a 50% chance of receiving osimertinib and if one did and one did not actually receive osimertinib, then, in the absence of strong confounding effects from one or more unobservable variables, these two subjects may be considered as “randomly” assigned to each treatment group in the sense of being equally likely to be treated with osimertinib or platinum doublet chemotherapy.

The resultant adjustment was assumed to be a proxy for randomization and thus enable an unbiased comparison between osimertinib and platinum doublet chemotherapy using IPD from the AURAext/2 studies and IMPRESS, respectively.

The final baseline demographic and disease characteristics variables that were used in the regression model used to estimate propensity scores and the final trimmed dataset included age, ethnicity, baseline target lesion size and smoking history. However, it was not feasible to include variables that were directly associated with the line of treatment, including number of previous EGFR TKIs, in the model.

Once each patient had a propensity score estimate, an attempt was made to balance the cohorts using appropriate applications of the estimated propensity scores. The primary analysis of progression-free survival (PFS) was then conducted on the balanced cohort. The same methodology was used to analyse other secondary endpoints, including objective response rate (ORR), disease control rate (DCR), and overall survival (OS). Full details of the methods used to derive the adjusted, balanced cohorts for both treatment arms are provided in the accompanying technical report.[80]

4.10.3.3 Patient population

The FAS from the pooled AURAext/2 data set (n=411) and the placebo (platinum doublet chemotherapy) arm from IMPRESS (n=127, following exclusion of patients from France) was used as the starting point for selection of patients for inclusion in the analysis.

A T790M mutation positive adj data set was derived from the FAS of the:

- Pooled AURAext/2 data set that were centrally confirmed as T790M mutation positive (n=405)
- T790M mutation positive subgroup of the IMPRESS placebo arm (n=60)

Following assessment of overlap between the two arms in baseline demographic and disease characteristics, patients that did not have a match according to their propensity score were excluded to produce the *T790M+adj* set. The *T790M+adj* set included:

- **Osimertinib arm** comprising the pooled AURA data set with confirmed T790M mutation positive status with matched patients from IMPRESS placebo arm (n=287)
- **Platinum doublet chemotherapy arm** comprising the T790M mutation positive subgroup of the placebo arm of IMPRESS with matched patients from pooled AURA data set with confirmed T790M mutation positive status (n=51)

4.10.3.4 Results

(i) Primary outcome – PFS

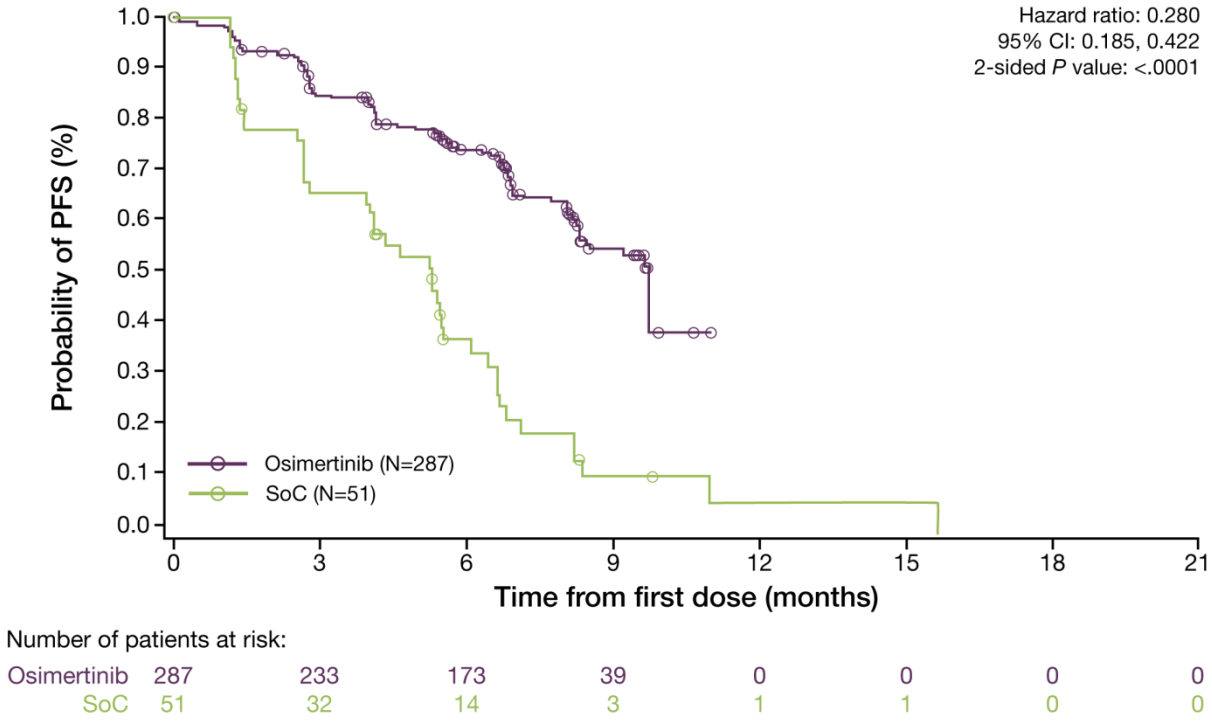
Analysis of PFS using a Cox proportional hazards model (with treatment as a factor and propensity score as a covariate) is presented in Table 4.11 based on independent central review for the *T790M+adj* dataset.

Overall, the PFS results indicate a large treatment effect with the hazard ratio of 0.28 showing a statistically significant improvement for osimertinib group compared with the platinum doublet chemotherapy group (HR 0.280, 95% CI 0.185, 0.422 *p*-value<0.0001).
Median PFS was 9.7 months (95%CI 8.3, NC) for the osimertinib group compared with 5.2 months (95%CI 4.0; 6.1) in the matched platinum doublet chemotherapy cohort. A KM plot for the primary calculated RECIST-defined PFS is presented in Figure 4.2. These data indicate that the treatment effect associated with osimertinib is consistent over time.

Table 4.11: Summary of primary analysis of PFS: *T790M+adj* set

		Number (%) of patients with events	Median PFS (months) 95% CI	Treatment effect (Osimertinib vs PDC)		
Treatment	**N**			**Hazard ratio**	**95% CI**	**2 sided *p*-value**
Osimertinib	287	106 (36.9)	9.7 (8.3, NC)	0.280	0.185, 0.422	<0.0001
Platinum doublet chemotherapy	51	42 (82.4)	5.3 (4.0, 6.1)			

Figure 4.2: Kaplan-Meier plot of PFS: *T790M+adj* set



These data are consistent with the reported data for the FAS (n=411) from AURAext/2 (osimertinib median PFS 9.7 months; 95% CI 8.3, NC) and for the platinum doublet chemotherapy arm (n=127) of IMPRESS (5.4 months; 95% CI 4.6, 5.5).

(ii) Secondary efficacy variables – objective response rate (ORR)

The response rate was calculated for each treatment for the *T790M+adj* set evaluable for response (defined as all patients who had received at least one dose of treatment and had measurable disease at baseline according to the ICR or baseline imaging data). The response rate was calculated for each treatment based on the percentage of patients who had a best objective response (according to RECIST) of CR or PR.

The analysis of ORR by logistic regression (with treatment as a factor and propensity score as a covariate) is summarised in Table 4.12. These data indicate that osimertinib has a significant improvement in ORR (64.6% patients) compared with platinum doublet chemotherapy (34.8% patients). The calculated odds ratio for this difference was 4.76 (95% CI 2.21, 10.26; *p*-value<0.001).

Table 4.12: Objective response rate, logistic regression (*T790M+adj* set Evaluable for Response)

		Number (%) of patients with response	Treatment effect (Osimertinib vs PDC)		
Treatment	**N**		**Odds ratio**	**95% CI**	**2 sided *p*-value**
Osimertinib	277	179 (64.6)	4.76	2.21, 10.26	<0.0001
Platinum doublet chemotherapy	46	16 (34.8)			

(iii) Secondary efficacy variables – disease control rate (DCR)

The DCR analysis was performed by logistic regression (with treatment as a factor and propensity score as a covariate) for the *T790M+adj* set (evaluable for response set) and is presented in Table 4.13.

Patients treated with osimertinib had a statistically significant improvement in DCR compared with the platinum doublet chemotherapy group (92.1% in the osimertinib group and 76.1% in the SoC group) with an odds ratio of 4.39 (95% CI 1.71, 11.28; *p*-value =0.002).

Table 4.13: Secondary analysis of DCR (*T790M+adj* set Evaluable for Response)

		Number (%) of patients with response	Treatment effect (Osimertinib vs PDC)		
Treatment	**N**		**Odds ratio**	**95% CI**	**2 sided *p*-value**
Osimertinib	277	255 (92.1)	4.39	1.71, 11.28	0.002
Platinum doublet chemotherapy	46	35 (76.1)			

(iv) Secondary efficacy variables – overall survival (OS)

The analysis of OS was performed at the time of PFS analysis (for AURAex and AURA2 and IMPRESS) for the *T790M+adj* set by a Cox proportional hazards model based on independent central review and is presented in Table 4.14.

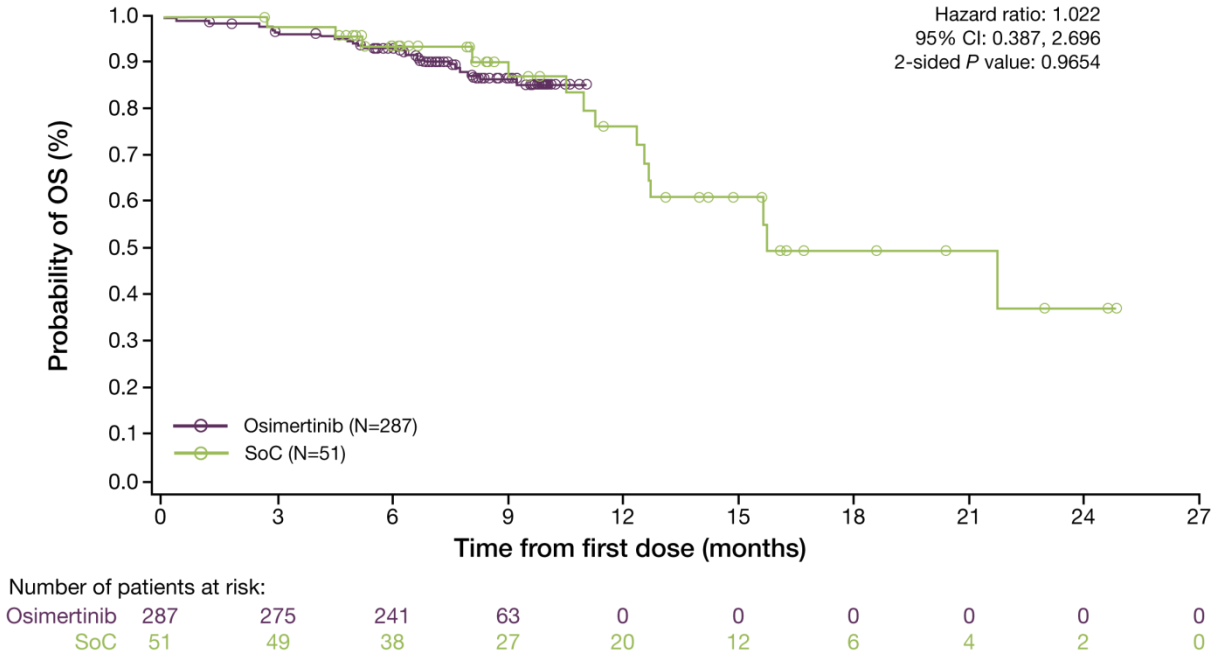
Caution should be exercised when interpreting the adjusted results of the OS in light of the immaturity of the OS data available at the time of analysis (Osimertinib 11.5% maturity and platinum doublet chemotherapy 29.4% maturity). For both groups the KM risk set beyond 12 months is very limited (n <15 patients) leading to unstable estimates beyond this time point, especially for the estimation of median OS.

The overall hazard ratio for OS for osimertinib compared with platinum doublet chemotherapy in this analysis was 1.022 with wide 95% confidence intervals (95% CI 0.387, 2.696) likely representing the immature nature of this comparison.

Table 4.14: Analysis of overall survival at time of progression-free survival analysis: *T790M+adj* set

		Number (%) of patients with events	Median OS (months) 95% CI	Treatment effect (Osimertinib vs PDC)		
Treatment	**N**			**Hazard ratio**	**95% CI**	**2 sided *p*-value**
Osimertinib	287	33 (11.5)	NC* (NC, NC)	1.022	0.387, 2.696	0.9654
Platinum doublet chemotherapy	51	15 (29.4)	21.7 (12.55, NC)			

Figure 4.3: Kaplan-Meier plot of OS: *T790M+adj* set



4.10.3.5 Conclusions from the adjusted indirect comparison

Overall, the results from the matched adjusted indirect treatment comparison indicate a large treatment effect. The PFS hazard ratio of 0.28 indicates a large, statistically significant improvement for osimertinib group compared with the platinum doublet chemotherapy group (HR 0.280, 95% CI 0.185, 0.422; p-value < 0.0001) with median PFS of 9.7 months (95%CI 8.3, NC) for the osimertinib group compared with 5.2 months (95%CI 4.0; 6.1) in the matched platinum doublet chemotherapy cohort. Analysis by logistic regression (with treatment as a factor and propensity score as a covariate) indicate a significant difference in the odds of objective response between osimertinib and platinum doublet chemotherapy [odds ratio: 4.76 (95% CI 2.21, 10.26; p-value < 0.001). Immaturity of OS data (OS data maturity at DCO: 11.5% for osimertinib and 29.4% for platinum doublet chemotherapy) with the KM risk set beyond 12 months limited to less than 15 patients for both groups indicate that it is likely too early to estimate treatment differences on this outcome using this method.

The results of the adjusted indirect comparison confirm that the conclusion drawn from the unadjusted comparison do not appear to overestimate the clinical effect of osimertinib compared with doublet chemotherapy.

4.11 Non-randomized and non-controlled evidence

As stated previously, there are currently no results of RCT's directly evaluating the efficacy of osimertinib compared to any of the comparators stated in the decision problem. In patients with EGFRm+ T790M mutation positive NSCLC who have progressed on a prior TKI, the studies evaluating osimertinib are the AURA extension and AURA2 studies. For patients receiving platinum doublet chemotherapy, the control group of the IMPRESS study provides evidence in the population referred to in the decision problem. Each of these studies is described below separately. An indirect comparison is presented in Section 4.10.

4.11.1 AURA/AURA2

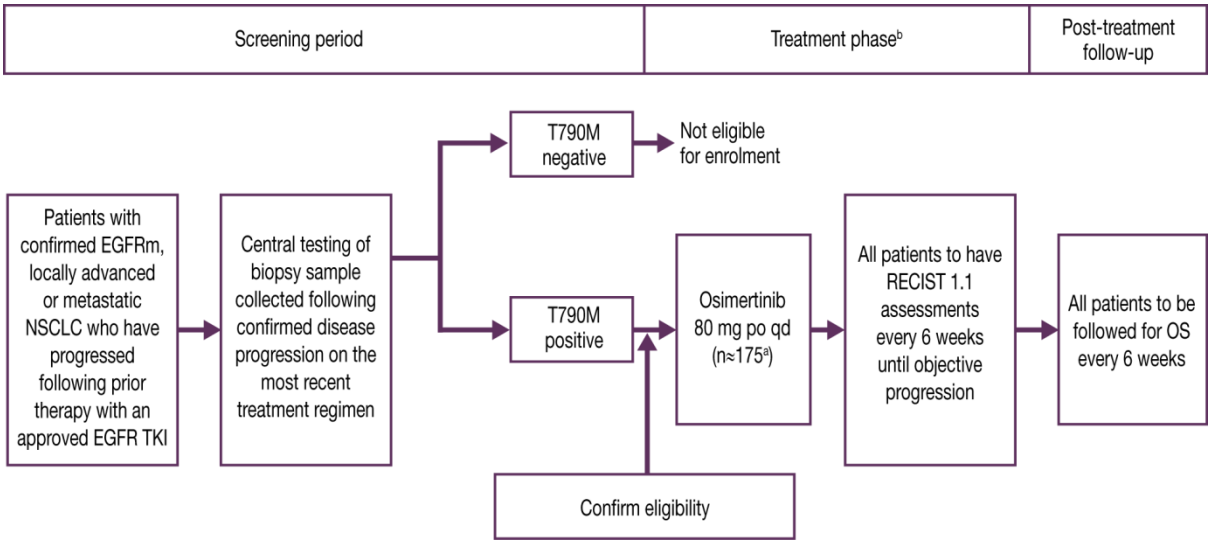
4.11.1.1 Study methodology

Trial design

AURA extension

AURA is a Phase I/II, open-label, dose-escalation, expansion and extension cohort study, which aimed to investigate the safety, tolerability, pharmacokinetics (PK), response to therapy, and AEs of osimertinib in patients with aNSCLC progressing following treatment with an EGFR TKI.[71] This section describes AURAext, the Phase II extension study, relevant to the decision problem. The dose studied (80 mg once daily) was determined in the Phase I dose-escalation phase (not described in this dossier).

Figure 4.4: AURA extension study flow chart



The study design is shown in Figure 4.4. There were two cohorts: patients whose disease had progressed following first-line therapy with an EGFR TKI (second-line cohort; n=50), and patients who had progressed following treatment with at least two lines of prior therapy including at least one EGFR TKI (third-line cohort; n=175).

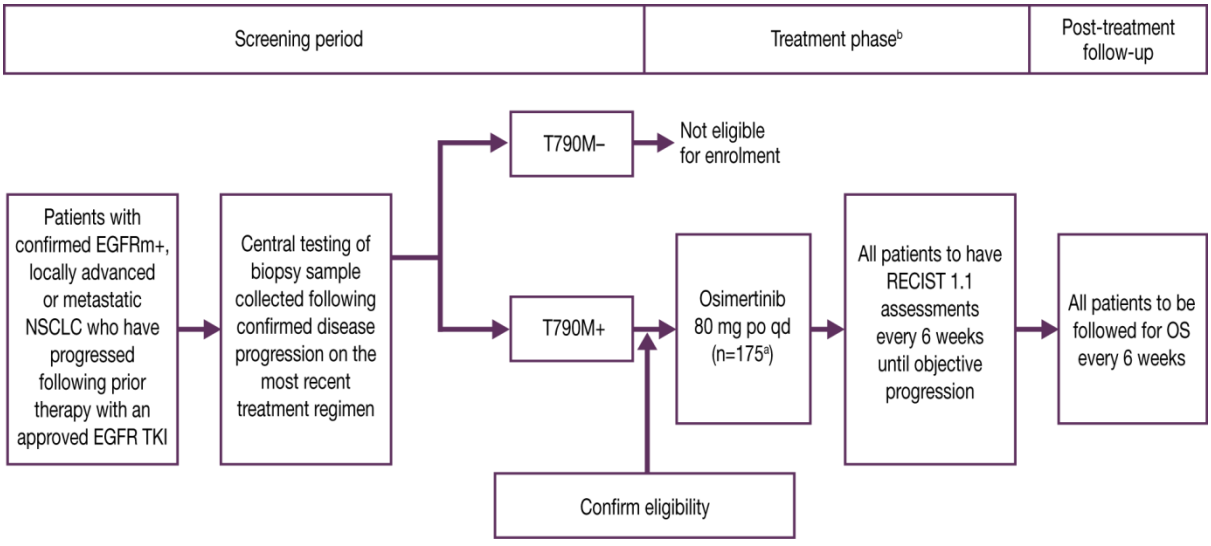
Patients continued to receive osimertinib until objective disease progression (according to RECIST 1.1), until a treatment discontinuation criterion was met, or for as long they were receiving clinical benefit in the opinion of the investigator. Patients who discontinued study treatment for reasons other than disease progression continued tumour assessments until progression as per study protocol.

The full analysis set was defined as all patients who received at least one dose of osimertinib. The evaluable for response analysis set was defined as patients who received at least one dose of osimertinib and had measurable disease at baseline according to independent review of baseline imaging data. ORR, the primary endpoint, was analysed in the evaluable for response analysis population. Subgroup analyses were conducted using the two treatment cohorts to determine any differences in response between the two groups.

AURA2

The AURA2 Study is a Phase II, open-label, single-arm study assessing the safety and efficacy of osimertinib (80 mg, orally, once daily) in patients with a confirmed diagnosis of EGFRm+ and T790M mutation positive NSCLC (stage IIIB–IV), who have progressed following prior therapy with an approved EGFR TKI agent.

Figure 4.5: AURA2 study flow chart



The study was composed of three phases: screening, treatment, and post-treatment follow-up (Figure 4.5).

Study treatment was osimertinib 80 mg once daily. A reduced dose of 40 mg could be used following AEs. Patients were to continue on study treatment for as long as they continued to show clinical benefit as judged by the investigator, and in the absence of discontinuation criteria. If a patient continued to receive treatment with osimertinib beyond RECIST 1.1 defined progression they had to continue to follow the Treatment visit schedule and assessments excluding study-specific RECIST 1.1 response assessments. Assessment took place every 6 weeks (±7days).

The full analysis set was defined as all patients who received at least one dose of osimertinib. The evaluable for response analysis set was defined as patients who received at least one dose of osimertinib and had measurable disease at baseline according to independent review of baseline imaging data. ORR, the primary endpoint, was analysed in the evaluable for response analysis population. Subgroup analyses were conducted using the two treatment cohorts to determine any differences in response between the two groups.

Eligibility criteria

The key inclusion and exclusion criteria used in both studies are described below (Table 4.15 and Table 4.16). If applicable, differences between both studies are highlighted.

Table 4.15: AURA extension and AURA2 key inclusion criteria

Key inclusion criteria

1. Male or female at least 18 years in age (20 years in Japan);
2. Histological or cytological confirmation of the diagnosis of NSCLC;
3. *Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy* (**AURA2** only);
4. All patients had to have documented radiological progression on the last treatment administered prior to enrolling in the study (previous treatment with EGFR TKI and possibly other lines of therapy). In **AURA2**, this criterion was further defined as follows: radiological documentation of disease progression *either following first-line EGFR TKI treatment but no further treatment OR following prior therapy with an EGFR TKI and a platinum-based doublet chemotherapy*.
5. *Confirmation that the tumour harboured an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, and L861Q)* (mandatory in **AURA2**); in **AURA extension**, this criterion could be omitted if the patient had *experienced clinical benefit from EGFR TKI according to the Jackman criteria (Jackman et al 2010) followed by systemic objective progression (RECIST or WHO) while on continuous treatment with EGFR TKI*;
6. Central confirmation of the tumour T790M mutation-positive status from a biopsy sample taken after confirmation of disease progression on the most recent treatment regimen;
7. WHO performance status of 0-1;
8. At least 1 lesion, not previously irradiated and not chosen for biopsy during the study screening period, that could be accurately measured at baseline with computerised tomography (CT) or magnetic resonance imaging (MRI), which was suitable for accurate repeated measurements;
9. Females of child-bearing potential had to use adequate contraceptive measures, not to breast-feed, and to have a negative pregnancy test prior to the start of dosing;
10. Male patients had to be willing to use barrier contraception, ie, condoms;
11. *Patients from Japan were to be willing to remain in hospital from the first dosing day until Day 1 of Cycle 2* (**AURA extension** only);
12. For inclusion in the optional genetic research study, patients had to provide separate consent for genetic research.

Table 4.16: AURA extension and AURA2 key exclusion criteria

Key exclusion criteria

1) Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study sites);

2) Treatment with any of the following:

   a) An EGFR TKI (eg, erlotinib, gefitinib, afatinib) within 8 days or approximately 5 half-lives, whichever was the longer, of the first dose of osimertinib;

   b) Any cytotoxic chemotherapy, investigational agents or other anticancer drugs (in **AURA extension** only: *for the treatment of advanced NSCLC*) from a previous treatment regimen or clinical study within 14 days of the first dose of osimertinib;

   c) Previous treatment with osimertinib *or* (in **AURA2** only) *with a third-generation EGFR TKI (eg, CO-1686);*

   d) Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of osimertinib;

   e) *Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of* osimertinib (in **AURA extension** only), with the exception of patients receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which had to be completed within 4 weeks of the first dose of osimertinib;

   f) Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of osimertinib) medications or herbal supplements known to be potent inhibitors of cytochrome P450 (CYP) 2C8 and potent inhibitors or inducers of CYP3A4;

   g) (In **AURA2** only) *Treatment with an investigational drug within 5 half-lives of the compound*;

3) Any unresolved toxicities from prior therapy greater than grade 1 in the CTCAE at the time of starting osimertinib, with the exception of alopecia and grade 2 prior-platinum-therapy-related neuropathy;

4) Spinal cord compression or brain metastases unless asymptomatic, stable, and not requiring steroids for at least 4 weeks prior to start of osimertinib treatment;

5) Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which, in the Investigator's opinion, made it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol; or active infection including hepatitis B, hepatitis C, and human immunodeficiency virus. Screening for chronic conditions was not required;

6) Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib;

7) Any of the following cardiac criteria:

   a) Mean resting QTc >470 msec, obtained from 3 electrocardiograms (ECGs);

   b) Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, eg, complete left bundle branch block, third-degree heart block, second-degree heart block, or PR interval >250 msec;

   c) Any factors that increased the risk of QTc prolongation or risk of arrhythmic events;

8) Past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD;

9) Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

   a) Absolute neutrophil count <1.5 x 10^9/L;

   b) Platelet count <100 x 10^9/L;

   c) Haemoglobin <90 g/L;

   d) Alanine aminotransferase >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases;

   e) Aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases;

   f) Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinaemia) or liver metastases;

   g) Creatinine >1.5 times ULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance was only required when creatinine >1.5 times ULN;

10) History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib;

11) Women who were breast-feeding;

12) Judgement by the Investigator that the patient should not participate in the study if the patient was unlikely to comply with study procedures, restrictions and requirements

Clinical trial settings

AURA extension

The first patient started treatment on 14 May 2014 and the last patient started treatment on 21 October 2014. The DCO for this report was 01 May 2015.

The study was open for enrolment at 46 study centres in Japan (16), the USA (7), South Korea (4), Australia (3), France (3), Germany (3), Spain (3), Italy (3), Taiwan (2) and the UK (2). Patients were screened and recruited at 40 centres in 10 countries; 50.7% of patients were from Asia, 20.4% from North America, and 28.9% from Europe and the rest of world.

AURA2

The first patient started treatment on 13 June 2014 and the last patient started treatment on 27 October 2014. The DCO for this report was 01 May 2015.

The study was open for enrolment at 44 study centres in Canada (3), Hong Kong (2), Italy (5), Japan (14), South Korea (3), Spain (6), Taiwan (2) and the USA (9);51.9% of patients were from Asia, 31.9% were from North America and 16.2% were from Europe and rest of world.

Trial drugs and concomitant medication

The recommended osimertinib oral daily dose of 80 mg was selected from a review of all available safety, tolerability, PK, and efficacy data from AURA Phase I.

Patients (with the exception of patients with insulin-dependent diabetes) had to fast for ≥1 hour prior to taking a dose to ≥2 hours after dosing. Water was permitted during this fasting period.

Patients continued on treatment with osimertinib until RECIST v1.1-defined progression or until a treatment discontinuation criterion was met. There was no maximum duration of treatment as patients could continue to receive osimertinib beyond RECIST v1.1-defined progression as long as they continued to show clinical benefit, as judged by the investigator.

Overall, the concomitant medications received by patients during this study were as expected for an advanced NSCLC patient population and were not considered to have impacted the study results.

Study objectives

AURA extension

Primary objective: To investigate the safety, tolerability, and efficacy (ORR) of osimertinib when given orally to patients with locally advanced or metastatic NSCLC who had progressed following prior therapy with an EGFR TKI agent.

Key secondary objectives: To obtain additional assessments of the anti-tumour activity of osimertinib by evaluation of DoR, DCR, tumour shrinkage, PFS, using RECIST v1.1 as assessed by blinded independent central review (BICR) of radiological information, and OS; and to characterise the pharmacokinetics of osimertinib and its metabolites (AZ5104 and AZ7550) after multiple oral doses.

AURA2

Primary objective: To investigate the efficacy (ORR by BICR) of orally administered osimertinib.

Key secondary objectives: To further assess the efficacy of osimertinib in terms of DoR, DCR, tumour shrinkage, and PFS as assessed by BICR; to investigate the safety and tolerability profile of osimertinib and to characterise the pharmacokinetics of osimertinib and its metabolites; to investigate the effect of osimertinib on QTc interval after oral dosing to NSCLC patients.

Study outcomes

Primary endpoint

In both studies, the primary efficacy endpoint variable was the ORR according to RECIST 1.1 by BICR using the evaluable for response analysis set.

The ORR was defined as the percentage of patients with at least 1 visit response of CR or PR that was confirmed at least 4 weeks later (ie, a best objective response [BOR] of complete responses [CR] or partial response [PR]). Data obtained up until progression, or the last evaluable assessment in the absence of progression, were included in the assessment of ORR. However, any CR or PR that occurred after a further anticancer therapy was received was not included in the numerator of the ORR calculation. Assessment were carried out every 6 weeks. For each patient, the BICR defined the overall visit response as CR, PR, stable disease (SD), progressive disease (PD) or not evaluable (NE) and the relevant scan dates for each time point (ie, for visits where response or progression was or was not identified).

From the investigators' review of the imaging scans, the RECIST tumour response data were used to determine each patient's visit response for target lesions (TLs), NTLs and new lesions. Patients with brain metastases, asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment, were included in the study; any brain metastases present at baseline were recorded as NTL. Sensitivity analyses of ORR were performed using the investigators' assessments of RECIST and the concordance between

the ORR as assessed by BICR and as assessed by the investigator summarised using those patients evaluable for response by both investigator and BICR.

Patients with brain metastases (which had to be asymptomatic, stable and not requiring steroids for at least 4 weeks prior to the start of study treatment) were included in the study; any brain metastases present at baseline were recorded as non-target lesions (NTLs).

Secondary endpoints

Duration of response (DoR)

The DoR was defined as the time from the date of first documented response, (that is subsequently confirmed) until the date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response was defined as the latest of the dates contributing towards the first visit response of PR or CR. This outcome is not relevant to the decision problem and will therefore not be discussed in further detail.

Disease control rate

The DCR was defined as the percentage of patients who had a BOR of CR or PR or SD for at least 6 weeks (allowing for a 1-week visit window).

Tumour shrinkage

Tumour size is the sum of the longest diameters of the TLs. The best percentage change in tumour size from baseline was determined for each patient, ie, the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction from baseline based on all post-baseline assessments prior to progression or the start of subsequent anticancer therapy. Although not specified in the decision problem, tumour shrinkage and burden provides further insight in disease status upon progression and will be discussed in more detail.

Progression-free survival

The PFS was defined as the time from date of first dose until the date of objective disease progression as defined by RECIST or death (by any cause in the absence of progression) regardless of whether the patient withdrew from osimertinib therapy or received another anticancer therapy prior to progression.

Overall survival

Overall survival was defined as the time from the date of first dose until death due to any cause.

Safety and tolerability

Safety and tolerability of osimertinib, as assessed by number and severity of adverse events as recorded on the case report form, clinical chemistry, haematology, urinalysis, vital signs, physical examination, weight, ECG and WHO Performance status.

Exploratory endpoints

To assess the impact of osimertinib on patients' disease-related symptoms and HRQoL, the following PROs were collected:

- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30)
- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13)
- AURA2 also collected EQ-5D-5L data alongside the administration of the EORTC QLQ-C30

4.11.1.2 Statistical analyses and definition of study groups

Sample size

AURA extension

The primary endpoint of this Phase II extension part of the AURA study was ORR. The extension phase was to recruit approximately 175 patients with EGFR T790M mutation positive advanced NSCLC, whose disease had progressed following either 1 prior therapy with an EGFR TKI (2nd-line; no additional lines of therapy, n=50) or following treatment with at least 2 lines of prior therapy including at least 1 EGFR TKI and potentially other anticancer therapies (≥3rd-line, n=125).

With 175 patients, the precision of the estimation of ORR in the overall study population would be within ±8% (e.g. ORR 40%, 95% CI: 33.0%, 47.4%). The precision of the estimation of ORR would be within ±13% in the 50 patient cohort who have only received previous TKI treatment and within ±9% in the 125 patient cohort who have received previous TKI treatment and other anticancer therapy. The study also provided an adequate number of

patients in which to assess the safety and tolerability of osimertinib; if zero events were observed in the 175 patients, there would be 95% confidence (2 sided) that the true event rate was less than 2.2%.

AURA2

The primary endpoint of this study was ORR. The study was to recruit approximately 175 patients with EGFR T790M mutation positive locally advanced NSCLC or metastatic NSCLC whose disease had progressed following either 1 prior therapy with an EGFR TKI (2nd-line, n=50) or following treatment with both EGFR TKI and a platinum-based doublet chemotherapy (patients may have also received additional lines of treatment; ≥3rd-line, n=125).

With 175 patients, the precision of the estimation of ORR in the overall study population would be within ±8% (eg. ORR 40%, 95% CI 33.0%, 47.4%). The precision of the estimation of ORR would be within ±13% in the cohort who have only received previous TKI treatment and within ±9% in the cohort who have received previous TKI treatment and other anticancer therapy. The study also provided an adequate number of patients in which to assess the safety and tolerability of osimertinib; if zero events were observed in the 175 patients, there would be 95% confidence (2 sided) that the true event rate was less than 2.2%.

Randomization and blinding

Not applicable since both studies were not randomized and were single-arm and open-label studies.

Statistical methods

Descriptive statistics were used for all variables. Continuous variables were summarised by the number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables were summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages were calculated based on the full analysis set (FAS). The FAS was defined as all patients enrolled who received at least 1 dose of study treatment. Summaries of demography and all safety data summaries and analyses were produced based on the FAS.

The following efficacy analyses were conducted in the FAS:

- PFS by BICR
- Sensitivity analysis of ORR and best objective response (BOR) by BICR

- Investigator RECIST outcomes
- QoL

The evaluable for response analysis set was defined as all patients who received at least one dose of study treatment and had measurable disease at baseline according to the BICR of baseline imaging data.

The primary analysis of ORR, BOR, DoR, DCR and tumour shrinkage by BICR were produced based on the evaluable for response analysis set (patients evaluable for response by BICR).

Primary endpoint

The primary analysis of ORR was presented together with 95% exact (Clopper-Pearson) confidence interval (CI) by study and overall. Overall ORR based on the pooled data was calculated as the number (%) of patients with best objective response of confirmed CR or PR from both studies.

The similar analysis of ORR was also presented by treatment cohort (2nd- versus ≥3rd-line) and overall. The ORR in each treatment cohort based on the pooled data was calculated as the number (%) of patients with best objective response of confirmed CR or PR from each treatment cohort across two studies.

Secondary endpoints

In both studies the secondary outcomes variables were DoR, DCR, tumour shrinkage and PFS, according to RECIST 1.1 using assessments performed by a BICR. A further secondary variable was OS.

Duration of response (DoR)

If the response was not confirmed, it was not included. If a patient did not progress following a response, then their DoR used the PFS censoring time. DoR (months) in responding patients based on the BICR will be summarised using the median and 95% CI. The median will be calculated using the Kaplan-Meier method. The number and percentage of responding patients remaining in response at >3; >6; >9; >12 months will be summarised. The above analyses will be presented by study and overall. For overall DoR, the responding patients from both studies will be included in the analyses. A Kaplan-Meier plot will be presented for overall pooled population. The similar analysis of DoR will be presented by treatment cohort and overall. For DoR in each treatment cohort, the responding patients

from each treatment cohort across two studies will be included in the analyses. A Kaplan-Meier plot was presented for each treatment cohort.

Tumour shrinkage

To assess the depth of tumour shrinkage, the proportion of patients who achieved >30%, >50% and >75% reduction in TL tumour size was summarised descriptively. The percentage change in TL tumour size from baseline was summarised using descriptive statistics and presented for each visit.

The best percentage change from baseline in TL tumour size was summarised descriptively and presented graphically using waterfall plots. In the following situations where patients' best percentage change data would have been missing, the value of +20% was imputed:

- If a patient had no post-baseline assessments and had died
- If a patient had new lesions or progression of NTLs
- If a patient had withdrawn due to disease progression and had no evaluable TL data before or at progression

Progression-free survival

PFS was displayed using a Kaplan-Meier plot for the overall pooled population. The total number of events, median PFS (calculated from the Kaplan-Meier plot, with 95% CIs), and the percentage PFS at 3, 6, 12 and 18 months was summarised by study and overall. Similar analyses of PFS were presented by treatment cohort and overall. A Kaplan-Meier plot was presented for each treatment cohort.

Overall survival

Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

<u>Sensitivity analysis</u>

Sensitivity analyses of ORR, DCR, DoR, tumour shrinkage and PFS using the investigators assessment of RECIST were performed in an analogous manner to those using the BICR described above.

The concordance between ORR as assessed by BICR and by investigator was presented by study and overall based on the FAS.

Subgroup analysis

The consistency of the ORR and DoR by BICR across the following key subgroups was also evaluated based on pooled data across two studies. The analysis of ORR together with 95% exact (Clopper-Pearson) CI was presented by treatment cohort and overall within each category of the key subgroups. DoR (months) in responding patients based on the BICR was summarised using the median and 95% CI by treatment cohort and overall within each category of the key subgroups. The median was calculated using the Kaplan-Meier method. Kaplan-Meier plots were presented for DoR within each category of the key subgroups for the overall pooled population to ensure that the median estimates within subgroups are not over-interpreted in these potentially small subgroups where the data may be limited and not mature at the primary analysis.

- Patients who received EGFR TKI as last treatment prior to study start (further split into whether EGFR TKI was <30 days or ≥30 days prior to first dose of osimertinib) and those whose treatment prior to study start was not an EGFR TKI
- Ethnicity (Asian versus Non-Asian)
- Gender (Male versus Female)
- Age at screening (<65 versus ≥65)
- Mutation status prior to start of study (Exon 19 deletion/L858R/Other)
- Duration of most recent prior EGFR TKI (<6 months versus ≥6 months)
- Smoking history
- Brain metastases at entry
- Patients with T790M mutation positive detected in their baseline plasma sample (ctDNA) and patients that are T790M- by the plasma test
- Region (North America/Asia/Europe and rest of world)

Forest plots of ORR by BICR for the above defined subgroups are constructed for each treatment cohort and overall.

Interim analyses

There were no formal interim analyses planned for this study, but 2 DCO points were planned at approximately 3 months and 8 months after the last patient had been enrolled. This report covers analyses from the 8-month DCO corresponding to May 2015. The final database will be locked at the end of the study, at 12 to 24 months after the last patient was enrolled.

4.11.1.3 Participant flow and baseline characteristics

Participant flow

A total of 873 patients signed informed consent and started screening in AURA extension and AURA2. Of these 873 patients, 462 (52.9%) failed screening, mainly because the EGFR T790M mutation-positive status of their tumours was not confirmed by central testing. The second most frequent reason for screening failure (19/462 screening failures across studies [4.1%]) was a WHO performance status greater than 1; each of the other reasons for screening failure occurred in less than 1% of all screened patients in the pooled population.

A total of 411 patients were assigned to treatment with osimertinib 80 mg tablet and all received at least 1 dose of study drug.

The 411 patients in the pooled population (201 from AURA extension and 210 from AURA2) consisted of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who had progressed on or after EGFR TKI therapy. Of the 411 patients, 129 (31.4%) received osimertinib as second-line therapy and 282 (68.6%) as ≥third-line therapy.

As of the DCO, 349/411 patients (84.9%) were ongoing in the studies, including 296 patients (72.0%) who were still receiving treatment with osimertinib. A total of 115 patients (28.0%) discontinued treatment with osimertinib: 75 patients (18.2%) due to objective disease progression, 22 patients (5.4%) due to AEs, 3 patients (0.7%) per patient decision, and 15 patients (3.6%) for other reasons. Of the 62 patients (15.1%) no longer ongoing in the study, 52 (12.7%) had died.

In line with the protocols, following RECIST progression as assessed by the investigator, patients could either continue to receive osimertinib, or discontinue osimertinib and receive other anticancer therapies. They continued to be followed in the study in order to collect anticancer therapies received and OS. Although RECIST data beyond progression was collected only in AURA2 (and not in AURA extension), patients continued to be followed by investigator-based RECIST assessment beyond RECIST progression in both studies.

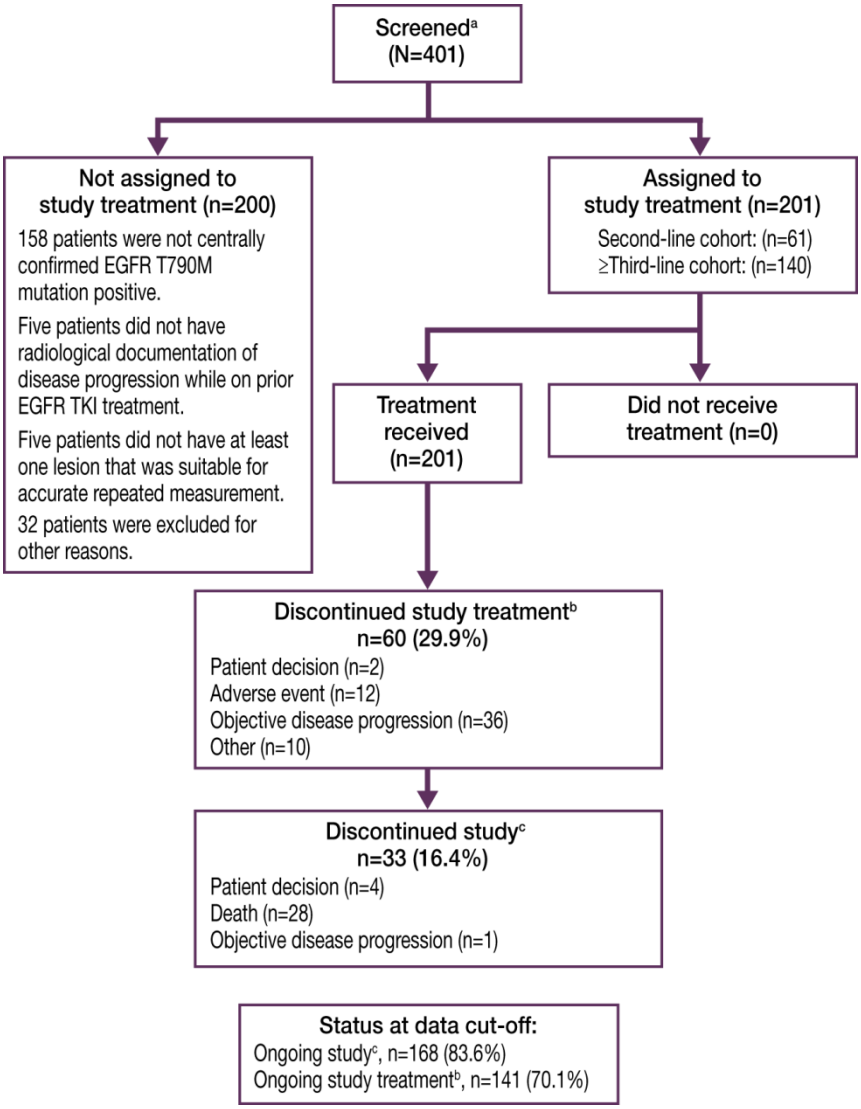
After radiological progression (as assessed by the investigator), 139 of the 158 patients with progressive disease (PD) were alive, of whom 83 (59.7%) continued to receive osimertinib for at least 7 days. Fifty-seven of the 139 patients (41.0%) received other anticancer therapies after progression.

Among the 83 patients who continued osimertinib therapy for at least 7 days after radiological progression, the median duration of treatment with osimertinib after progression was 1.6 months (range: 0.4 to 8.4). Thirty-nine of the 83 patients subsequently discontinued osimertinib treatment before the DCO: 27 due to objective disease progression, 5 due to AEs, 2 per patient decision, and 5 due to other reasons (see Table 2.9.2.2S in pooled efficacy tables in Module 5.3.5.3 Supportive efficacy data). The 2 studies were similar with regard to patient disposition.

AURA extension

The patient flow for the AURA extension study is illustrated in the CONSORT diagram shown in Figure 4.6.

Figure 4.6: AURAext CONSORT diagram



[a] Informed consent received. Patients could have had more than 1 reason for not being assigned to treatment and hence would be counted more than once.
[b] Percentages were calculated from the number of patients who received treatment.
[c] Percentages were calculated from the number of patients who were assigned to treatment.

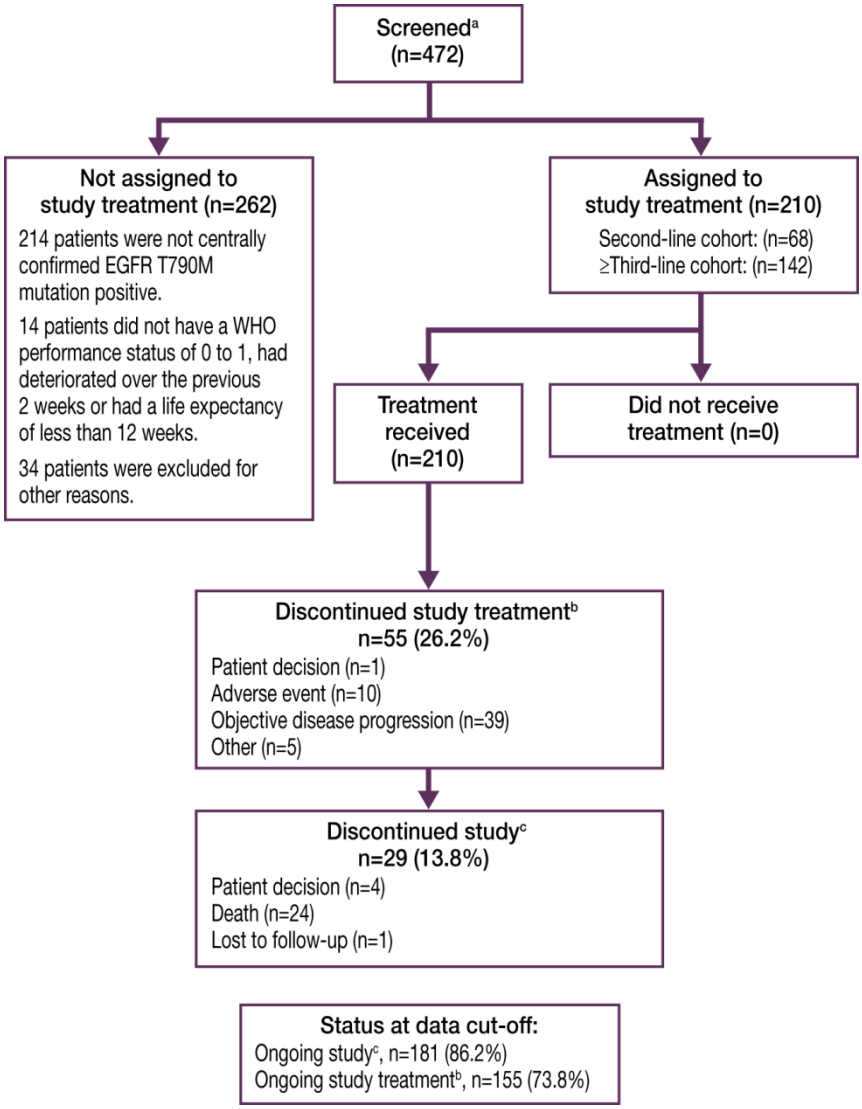
Abbreviations: EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor

In AURAext, 19 were patients identified as having protocol deviations for review; 5 did not fulfil eligibility criteria, 9 protocol-required procedures were not adhered to, and 5 other reasons.

AURA2

The patient flow for the AURA2 study is illustrated in the CONSORT diagram shown in Figure 4.7.

Figure 4.7: AURA2 CONSORT diagram



[a] Informed consent received. Patients could have had more than 1 reason for not being assigned to treatment and hence would be counted more than once.
[b] Percentages were calculated from the number of patients who received treatment.
[c] Percentages were calculated from the number of patients who were assigned to treatment.
Abbreviations: AE, adverse event; Excl, exclusion criterion; Incl, inclusion criterion.
Source: Table 11.1.1.

In AURA2, 25 patients were identified as having protocol deviations for review; 12 did not fulfil eligibility criteria, 6 protocol-required procedures were not adhered to, and 5 other reasons. Of these deviations, there were 7 patients in the ≥3rd-line cohort who received 2 or more prior treatment regimens but did not have a platinum-containing doublet regimen as treatment for advanced NSCLC, as required in inclusion criterion 5. Two other protocol deviations were considered important protocol deviations with the potential to impact the

primary assessment of efficacy as two patients had their tumour assessment performed more than 28 days before first dose

There were only two amendments, the first one was made prior to the start of patient recruitment (01 April 2014) and the second one after the start of patient recruitment (24 September 2014). None of the amendments was considered as major.

Baseline characteristics

Patient demographics

The median age at study entry was 63 years (range: 35 to 89 years); 54 patients (13.1%) were ≥75 years old (Table 4.18). Approximately two-thirds of patients (67.9%) were female and 60.1% were of Asian racial origin; the remainder were mainly white (36.2%).

Approximately three-quarters of patients (71.5%) were never smokers; the remainder were mostly former smokers (26.8%), with only 7 patients (1.7%) who were current smokers.

Demographic characteristics were similar across studies (AURA extension and AURA2) and lines of therapy (Table 4.17). These characteristics were consistent with those of an advanced EGFRm patient population.

Table 4.17: Demographic characteristics by study (FAS)

		AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
Age (years)	n	201	210	411
	Mean	61.4	62.9	62.2
	SD	10.58	10.91	10.76
	Median	62.0	64.0	63.0
	Min	37	35	35
	Max	89	88	89
Age group (years) n (%)	<50	30 (14.9)	20 (9.5)	50 (12.2)
	≥50-<65	86 (42.8)	88 (41.9)	174 (42.3)
	≥65-<75	64 (31.8)	69 (32.9)	133 (32.4)
	≥75	21 (10.4)	33 (15.7)	54 (13.1)
	Total	201 (100)	210 (100)	411 (100)
Sex n (%)	Male	68 (33.8)	64 (30.5)	132 (32.1)
	Female	133 (66.2)	146 (69.5)	279 (67.9)
	Total	201 (100)	210 (100)	411 (100)
Race n (%)	White	76 (38.2)	72 (34.3)	148 (36.2)
	Black or African American	1 (0.5)	3 (1.4)	4 (1.0)
	Asian	114 (57.3)	132 (62.9)	246 (60.1)
	Native Hawaiian or other Pacific Islander	0	1 (0.5)	1 (0.2)
	Other	4 (2.0)	2 (1.0)	6 (1.5)
	Not Reported	4 (2.0)	0	4 (1.0)
	Total	199 (100)	210 (100)	409 (100)
Ethnic group n (%)	Hispanic or Latino	16 (8.0)	5 (2.5)	21 (5.2)
	African-American	1 (0.5)	0	1 (0.2)
	Asian (other than Chinese and Japanese)	45 (22.4)	35 (17.2)	80 (19.8)
	Chinese	30 (14.9)	51 (25.0)	81 (20.0)
	Japanese	35 (17.4)	46 (22.5)	81 (20.0)
	Other	74 (36.8)	67 (32.8)	141 (34.8)
	Total	201 (100)	204 (100)	405 (100)

Source: Table 1.4.1 in pooled efficacy tables in Module 5.3.5.3 Supportive efficacy data.

Disease characteristics

EGFR and T790M mutational status

Patients were assigned to treatment on the basis of central laboratory confirmation that their tumours were T790M mutation-positive. Central testing was performed using cobas® EGFR mutation test on a tissue sample taken after progression on the most recent line of therapy. All but 4 of the 411 dosed patients (all in AURA extension) had tumours with centrally-confirmed T790M mutation-positive status. The presence of a T790M mutation was not confirmed centrally for 4 patients in AURA extension (3 had T790M mutation-negative tumours by central testing, and 1 patient had insufficient tissue to perform the central test).

Per protocol, patients also had to have local confirmation that their tumours were carrying an EGFR sensitising mutation to be assigned to treatment; central testing of EGFR sensitising mutations was not mandatory per the inclusion/exclusion criteria. However, central testing of

EGFR mutations by cobas central test was performed at the time of T790M testing. Based on central testing, the most common EGFR sensitising mutations were exon 19 deletion (67.9%) and L858R (28.7%) (Table 4.19). Two patients, 1 in each of the 2 studies, had both exon 19 deletion and L858R, which were grouped under exon 19 deletion for the purpose of subgroup analyses. Subgroup analyses based on EGFRm are presented based on central testing results.

NSCLC characteristics

Disease characteristics of the pre-treated patients with EGFR T790M mutation positive NSCLC in the pooled population were representative of a locally-advanced or metastatic pre-treated EGFR mutation-positive NSCLC population and of the patient population intended for treatment with osimertinib (Table 4.18):

- The majority of patients had metastatic NSCLC (96.1%), adenocarcinoma histology (96.1%), and had a WHO performance status of 1 (62.8%)
- The median tumour burden at entry, based on the sum of the longest diameters for target lesions at baseline per BICR, was 51.0 mm (range: 10–229 mm)
- The majority of patients (83.0%) had visceral metastases. In addition, 46.7% had bone metastases)
- Approximately one-third of patients (39.2%) had brain metastases A greater proportion of patients in the ≥third-line treatment cohort (44.3%) had brain metastases compared to the second- line cohort (27.9%). Brain metastases were considered to be NTLs for the purpose of RECIST assessment

Table 4.18: Disease characteristics at baseline by study (FAS)

	Number (%) of patients		
	AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
WHO performance status			
0 (Normal activity)	68 (33.8)	84 (40.0)	152 (37.0)
1 (Restricted activity)	132 (65.7)	126 (60.0)	258 (62.8)
2 (In bed less than or equal to 50% of the time)	1 (0.5)	0	1 (0.2)
Histology type			
Squamous cell carcinoma (NOS)	0	2 (1.0)	2 (0.5)
Adenocarcinoma (NOS)	171 (85.1)	170 (81.0)	341 (83.0)
Adenocarcinoma: acinar	11 (5.5)	10 (4.8)	21 (5.1)
Adenocarcinoma: papillary	10 (5.0)	17 (8.1)	27 (6.6)
Adenocarcinoma: bronchiolo-alveolar	3 (1.5)	1 (0.5)	4 (1.0)
Adenocarcinoma: solid with mucous formation	0	2 (1.0)	2 (0.5)
Adenosquamous carcinoma	1 (0.5)	1 (0.5)	2 (0.5)
Other	5 (2.5)	7 (3.3)	12 (2.9)
EGFR mutations by cobas® central test[d]			
T790M	197 (98.0)	208 (99.0)[d]	405 (98.5)[d]
Exon 19 deletion	142 (70.6)	137 (65.2)	279 (67.9)
L858R	51 (25.4)	67 (31.9)	118 (28.7)
G719X	4 (2.0)	4 (1.9)	8 (1.9)
S768I	3 (1.5)	3 (1.4)	6 (1.5)
Exon 20 insertion	2 (1.0)	1 (0.5)	3 (0.7)
T790M only[d]	5 (2.5)	1 (0.5)	6 (1.5)
Overall disease classification			
Metastatic[a]	197 (98.0)	198 (94.3)	395 (96.1)
Locally advanced[b]	4 (2.0)	12 (5.7)	16 (3.9)
Brain metastases[c]	74 (36.8)	87 (41.4)	161 (39.2)
Visceral metastases[c]	173 (86.1)	168 (80.0)	341 (83.0)
Baseline sum of target lesions (mm)			
n	199	199	398
Mean	60.7	59.7	60.2
SD	37.08	40.57	38.82
Median	52.0	49.3	51.0
Min	12	10	10
Max	229	218	229
Baseline sum of target lesions tumour size category (mm)			
< 40	65 (32.3)	68 (32.4)	133 (32.4)
40 - 79	86 (42.8)	90 (42.9)	176 (42.8)
80 - 119	31 (15.4)	26 (12.4)	57 (13.9)
≥ 120	17 (8.5)	15 (7.1)	32 (7.8)

[a] Metastatic disease - Patient has any metastatic site of disease.

NSCLC characteristics

The majority of patients were heavily pre-treated: 68.4% had received at least 2 prior treatment regimens and 45.5% had received 3 or more prior lines of therapy (Table 4.20).

The median number of prior therapies, including 1 EGFR TKI and any other prior treatment for advanced NSCLC, was 2 (range: 1 to 14).

Per protocol, all patients entering the studies had received treatment with at least 1 prior EGFR TKI. The median number of prior EGFR TKI regimens was 1 (range: 1–9) (Table 4.20).

Approximately two-third (62.5%) of patients had received prior platinum-based chemotherapy. Prior EGFR TKIs were mainly gefitinib for 58.2% of patients, erlotinib for 56.9%, and afatinib for 18.0%. The majority of patients (77.1%) received an EGFR TKI as last regimen before study entry, including 52.6% who did within 30 days of enrolment. The duration of the most recent EGFR TKI therapy, which could continue after objective RECIST progression was documented per protocol, was ≥6 months in 77.4% of patients.

Among the 129 second-line patients whose only prior therapy was an EGFR TKI, 49.6% had received gefitinib, 46.5% had received erlotinib, and 3.1% received afatinib; 1 patient (0.8%) had received another EGFR TKI (dacomitinib)

Of the 282 patients in the ≥third-line cohort :

- The vast majority (91.1%) had received prior platinum-containing doublet chemotherapy

- Prior EGFR TKIs were mostly gefitinib (62.1%), erlotinib (61.7%), and afatinib (24.8%). Approximately 41% of patients received more than 1 prior TKI as illustrated in Table 4.21. Two-third of the ≥third-line patients (66.7%) had received an EGFR TKI as last therapy prior to study entry. The duration of the most recent prior EGFR TKI therapy was ≥6 months in 69.1% of patients

- 41.5% had received other anticancer therapies besides EGFR TKI or platinum-based chemotherapy, which included, but were not limited to, gemcitabine, paclitaxel, vinorelbine, docetaxel, sunitinib, and novel investigational products such as AUY922 and LY2875359. In addition, 48.7% of patients overall had received at least one course of prior radiotherapy), including 38.8% of second-line patients and 53.2% of ≥third-line patients). Previous NSCLC therapies were similar across studies.

Table 4.19: Number of previous anti-cancer treatment regiments at baseline (FAS)

	Number (%) of patients		
Number of regimens	AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
1	61 (30.3)	69 (32.9)	130 (31.6)
2	49 (24.4)	45 (21.4)	94 (22.9)
3	33 (16.4)	38 (18.1)	71 (17.3)
4	22 (10.9)	22 (10.5)	44 (10.7)
5	14 (7.0)	7 (3.3)	21 (5.1)
> 5	22 (10.9)	29 (13.8)	51 (12.4)
n	201	210	411
Mean	2.8	3.0	2.9
SD	1.92	2.43	2.20
Median	2.0	2.0	2.0
Min	1	1	1
Max	11	14	14

Patients in the unknown category were not included in the calculation of n or the associated summary statistics.
Source: Table 1.1 in pooled safety tables in Module 5.3.5.3 Supportive safety data.

Table 4.20: Number of previous EGFR TKI regimens at baseline (FAS)

	Number (%) of patients		
Number of regimens	AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
1	111 (55.2)	131 (62.4)	242 (58.9)
2	47 (23.4)	42 (20.0)	89 (21.7)
3	33 (16.4)	18 (8.6)	51 (12.4)
4	7 (3.5)	9 (4.3)	16 (3.9)
5	2 (1.0)	4 (1.9)	6 (1.5)
> 5	1 (0.5)	6 (2.9)	7 (1.7)
n	201	210	411
Mean	1.7	1.8	1.7
SD	0.98	1.34	1.18
Median	1.0	1.0	1.0
Min	1	1	1
Max	6	9	9

Patients in the unknown category were not included in the calculation of n or the associated summary statistics.
Patients might have received more than one prior regimen.
Source: Table 1.2 in pooled safety tables in Module 5.3.5.3 Supportive safety data.

4.11.1.4 Quality assessment of clinical studies

The quality of the AURAext and AURA2 studies was assessed using the Down and Black's checklist.[81] The results are described in Table 4.21.

Table 4.21: Quality Assessment of the AURAext and AURA2 studies

Downs and Black Checklist[81]	AURAext	AURA2
Reporting		
Q1: Aim clearly described	Yes	Yes
Q2: Outcomes clearly described	Yes	Yes
Q3: Patients characteristics clearly described	Yes	Yes
Q4: Interventions clearly described	Yes	Yes
Q5: Principal confounders clearly described	Yes	Yes
Q6: Main findings clearly described	Yes	Yes
Q7: Random variability for the main outcome provided	Yes	Yes
Q8: Adverse events reported	Yes	Yes
Q9: Lost to follow up reported	Yes	Yes
Q10: Actual *p*-value reported	No	No
External validity and bias		
Q11: Sample asked to participate representative of the population	Yes	Yes
Q12: Sample agreed to participate representative of the population	Yes	Yes
Q13: Staff participating representative of the patient's environment	Yes	Yes
Q14: Attempt to blind participants	No	No
Q15: Attempt to blind assessors	Yes	Yes
Q16: Data dredging results stated clearly	Yes	Yes
Q17: Analysis adjusted for length of follow up	Yes	Yes
Q18: Appropriate statistics	Yes	Yes
Q19: Reliable compliance	Yes	Yes
Q20: Accurate outcome measures	Yes	Yes
Statistical bias and power		
Q21: Same population	Yes	Yes
Q22: Participants recruited at the same time	Yes	Yes
Q23: Randomized?	No	No
Q24: Adequate allocation concealment?	UTD	UTD
Q25: Adequate adjustment for confounders?	UTD	UTD
Q26: Loss of follow up reported?	Yes	Yes

UTD: Unable to Determine

4.11.1.5 Clinical effectiveness

This section focuses on results from the pooled data from AURA extension and AURA2 as of the DCO date of 1 May 2015. Any differences between individual studies are noted. This pooled data also forms the basis for the active treatment arm in the health economic analysis presented in Section 5. The rationale for pooling is based on both studies having very similar designs in terms of the patient population, conduct and outcome measures as previously described. They also included a well-defined, molecularly characterised patient population based on ensuring all patients were confirmed as EGFR T790M mutation positive based on central testing.

Detailed individual study results are provided within the Clinical Study Reports of each individual study.[82,83]

Objective response rates

Osimertinib is associated with high objective response rates. The primary efficacy analysis of ORR (including BOR) was based on BICR of the evaluable-for-response population. Sensitivity analyses of RECIST outcomes were performed based on investigator and BICR assessments in the FAS population.

As of the DCO, the primary analysis of the pooled confirmed ORR was 66.1% (95% CI: 61.2, 70.7) (Table 4.22). Of the 398 patients with measurable disease at baseline based on BICR assessment, 263 had confirmed objective responses to osimertinib: 2 patients (0.5%) had a BOR of CR and 261 (65.6%) had a BOR of PR.

Table 4.22: Summary of overall response rate by BICR (evaluable-for-response set and FAS) and investigator (FAS) assessments from the pooled studies

Analysis set Study	N	No. of patients with confirmed response[a]	ORR (%)	95% CI
BICR assessment of evaluable-for-response analysis set (primary efficacy analysis)				
AURA Extension AZD9291 80 mg	199	122	61.3	54.2, 68.1
AURA2 AZD9291 80 mg	199	141	70.9	64.0, 77.1
Total AZD9291 80 mg	398	263	66.1	61.2, 70.7
BICR assessment of FAS (sensitivity analysis)				
AURA Extension AZD9291 80 mg	201	122	60.7	53.6, 67.5
AURA2 AZD9291 80 mg	210	142	67.6	60.8, 73.9
Total AZD9291 80 mg	411	264	64.2	59.4, 68.9
Investigator assessment of FAS (sensitivity analysis)				
AURA Extension AZD9291 80 mg	201	142	70.6	63.8, 76.8
AURA2 AZD9291 80 mg	210	148	70.5	63.8, 76.6
Total AZD9291 80 mg	411	290	70.6	65.9, 74.9

BICR = blinded independent central review; FAS = full analysis set; ORR = objective response rate;
[a] Responses excluded unconfirmed responses.
Objective response rate was defined as the number (%) of patients with at least one visit response of CR or PR that was confirmed at least 4 weeks later.
The CIs were calculated using Clopper-Pearson exact method for binomial proportions.
Of note, by protocol and by BICR charter, brain metastases were considered to be non-target lesions. Therefore, in line with RECIST v1.1, brain metastases were not measured and were only assessed qualitatively at the time points specified in the protocols.
Source: see Tables 2.1.1.1, 2.1.1.2, and 2.1.1.4 from pooled efficacy tables in Module 5.3.5.3 Supportive efficacy data.

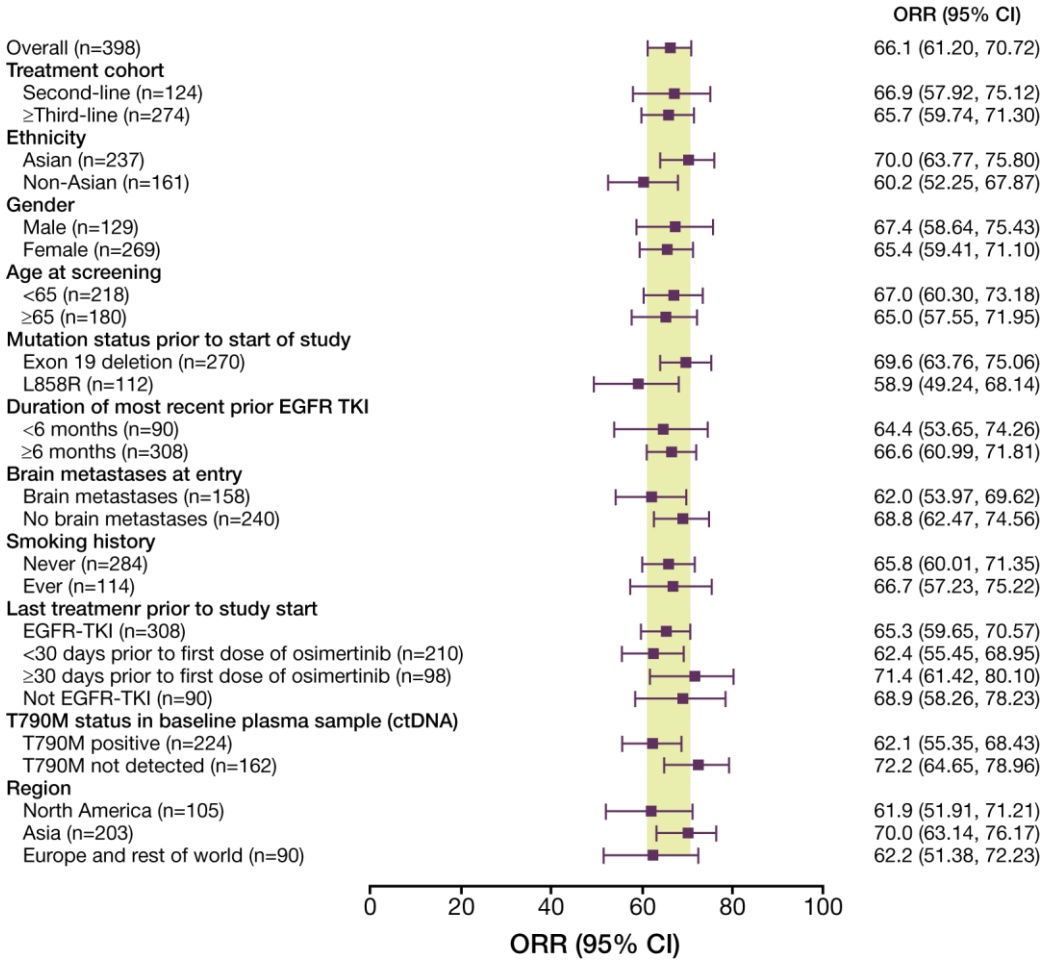
Table 4.23: Best objective response (BOR) by central review by study (evaluable for response analysis set) from the pooled studies

		Number (%) of patients		
Response status	Best objective response	AURA Extension AZD9291 80 mg (N=199)	AURA2 AZD9291 80 mg (N=199)	Total AZD9291 80 mg (N=398)
Response	Total	122 (61.3)	141 (70.9)	263 (66.1)
	Complete response[a]	0	2 (1.0)	2 (0.5)
	Partial response[a]	122 (61.3)	139 (69.8)	261 (65.6)
Non-response	Total	77 (38.7)	58 (29.1)	135 (33.9)
	Stable disease ≥6 weeks[b]	58 (29.1)	41 (20.6)	99 (24.9)
	Unconfirmed partial response[c]	14 (7.0)	12 (6.0)	26 (6.5)
	Stable disease	44 (22.1)	29 (14.6)	73 (18.3)
	Progression	19 (9.5)	15 (7.5)	34 (8.5)
	Unconfirmed partial response[c]	1 (0.5)	0	1 (0.3)
	RECIST progression	13 (6.5)	12 (6.0)	25 (6.3)
	Early death	5 (2.5)	3 (1.5)	8 (2.0)
	Not evaluable	0	2 (1.0)	2 (0.5)
	No evaluable follow-up assessments	0	1 (0.5)	1 (0.3)
	Unconfirmed partial response[c]	0	1 (0.5)	1 (0.3)

[a] Responses required confirmation after 4 weeks.
[b] SD ≥ 6 weeks included RECIST visit window (±7 days).
[c] PR or CR achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.
RECIST version 1.1.
Source: see Table 2.2.1.1 from pooled efficacy data in Module 5.3.5.3 Supportive efficacy data.

ORR by BICR in the evaluable for response population confirmed high ORRs, ranging from 58.9% to 72.2% across all subgroups (Figure 4.8) including by line of therapy [second-line patients (66.9%; 95% CI: 57.9, 75.1) and ≥third-line patients (65.7%; 95% CI: 59.7, 71.3)].

Figure 4.8: Objective responses rate (ORR) by central review, Forest plot, by subgroup (evaluable for response analysis set)



Objective response rate (ORR) and 95% CI.
The CIs are calculated using Clopper-Pearson exact method for binomial proportions.
Dashed vertical lines represent the 95% confidence interval for the overall ORR.
Source: see Figure 2.1.4.1R from pooled efficacy figures in Module 5.3.5.3 Supportive efficacy data.

Duration of response

The median DoR based on BICR assessment had not been reached yet (22.8% maturity); however, the lower limit of the 95% CI was 8.3 months. Of 263 patients with confirmed objective responses by BICR at the time of DCO, 60 had subsequently progressed or died:

- Of the 263 responders, 203 (77.2%) had ongoing responses at the time of DCO, with DoR ranging from 1.3 months to 9.7 months

Based on a Kaplan-Meier analysis, 94.9% (95% CI: 91.3, 97.0) of responding patients were estimated to have a DoR >3 months, 78.4% (95% CI: 72.1, 83.5) a DoR >6 months, and

55.3 (95% CI: 40.6, 67.8) a DoR >9 months. The median DoR based on investigator assessment (27.6% maturity) was 8.5 months (95% CI: 8.5, NC).

Disease control rates

In the pooled population, the DCR (defined as CR + PR + SD ≥6 weeks) was 91.0% (95% CI: 87.7, 93.6), with similar DCR across studies (Table 4.24). This comprised 2 patients (0.5%) with confirmed CR, 261 patients (65.6%) with confirmed PR, and 99 patients (24.9%) with SD ≥6 weeks. Results were similar in the FAS based on investigator assessment and on BICR assessment (Table 4.24) and across lines of therapy.

Table 4.24: Summary of disease control rate (DCR) by BICR and investigator assessments

Analysis set Study	N	No. of patients with disease control	DCR (%)	95% CI
BICR assessment of evaluable-for-response set				
AURA Extension AZD9291 80 mg	199	180	90.5	85.5, 94.2
AURA2 AZD9291 80 mg	199	182	91.5	86.7, 94.9
Total AZD9291 80 mg	398	362	91.0	87.7, 93.6
BICR assessment of FAS				
AURA Extension AZD9291 80 mg	201	182	90.5	85.6, 94.2
AURA2 AZD9291 80 mg	210	192	91.4	86.8, 94.8
Total AZD9291 80 mg	411	374	91.0	87.8, 93.6
Investigator assessment of FAS				
AURA Extension AZD9291 80 mg	201	188	93.5	89.2, 96.5
AURA2 AZD9291 80 mg	210	197	93.8	89.7, 96.7
Total AZD9291 80 mg	411	385	93.7	90.9, 95.8

Disease control = best objective response of confirmed complete response, confirmed partial response or stable disease ≥6 weeks.
The CIs were calculated using Clopper-Pearson exact method for binomial proportions.
RECIST version 1.1.
Source: see Tables 2.4.1.1, 2.4.1.2, and 2.4.1.3 from pooled efficacy tables in Module 5.3.5.3 Supportive efficacy data.

Tumour shrinkage

The median best percentage change from baseline in TL size by BICR in the evaluable-for-response population was −47.6% (minimum: −100%; maximum: +90.8%) (Table 4.25 and Figure 4.9). The mean best percentage change from baseline was −45.0% (SD: 28.0). Tumour shrinkage pattern was similar across studies.

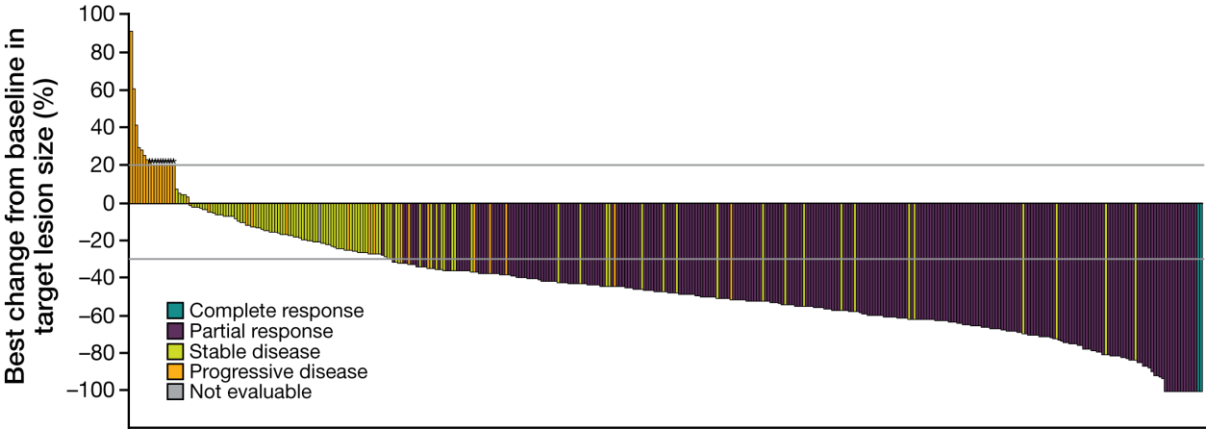
Table 4.25: Best percentage change from baseline in target lesion size by central review by study (evaluable response analysis set)

Statistic	AURA Extension AZD9291 80 mg (N=199)	AURA2 AZD9291 80 mg (N=199)	Total AZD9291 80 mg (N=398)
n	199	198	397
Mean	-41.09	-48.94	-45.01
SD	24.705	30.539	28.010
Min	-100.0	-100.0	-100.0
Median	-44.30	-52.15	-47.60
Max	25.0	90.8	90.8

Best change in target lesion size was the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
n was the number of patients with at least one post baseline RECIST target lesion assessment scan.
Any changes in target lesion size that were imputed (rules defined in SAP) were included.
A negative change denoted a reduction in target lesion size.
SD=Standard Deviation.
RECIST version 1.1.
Source: see Table 2.5.1.1 from pooled efficacy tables in Module 5.3.5.3 Supportive efficacy tables.

In each study, evidence of tumour shrinkage was generally documented at the first scheduled follow-up RECIST scan, at Week 6±1 week).

Figure 4.9: Target lesion size, best percentage change from baseline by central review – total, waterfall plot (evaluable response analysis set)

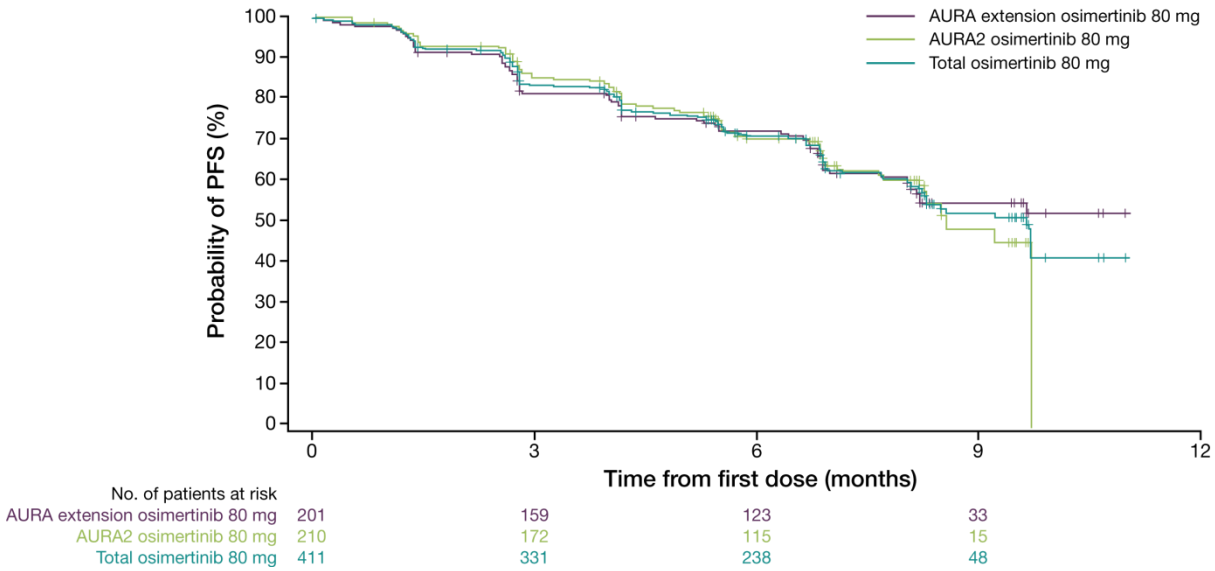


Best percentage change in target lesion size was the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
* represented imputed values: if it was known that the patient had died, had new lesions or progression of non-target lesions, had withdrawn due to PD and had no evaluable target lesion (before or at progression) assessments, best change was imputed as 20%.
RECIST version 1.1.
Source: see Figure 2.5.3.1 from pooled efficacy figures in Module 5.3.5.3 Supportive efficacy data.

Progression-free survival

At DCO, all patients had the opportunity of having at least 6 months of radiological follow-up. The preliminary estimate of median PFS in the FAS based on assessments by BICR (38.7% maturity) was 9.7 months (95% CI: 8.3, NC) (Figure 4.8).

Figure 4.8: Progression-free survival by central review by study and total, Kaplan-Meier plot (FAS)



Based on BICR assessment, of the 411 EGFR T790M mutation-positive patients in the FAS, 159 (38.7%) either progressed (142 patients, 34.5%) or died (17 patients, 4.1%) (Table 4.26). Of the remaining 252 patients (61.3%), 248 remained alive and progression-free at the time of analysis (60.3%) and 4 (1.0%) had withdrawn consent (Table 4.27). Based on follow-up at DCO, the Kaplan-Meier estimated probability of being alive and progression-free based on BICR assessment was 83.2% (95% CI: 79.2, 86.5) at 3 months, 70.9% (95% CI: 66.1, 75.1) at 6 months, and 51.9% (95% CI: 45.3, 58.1) at 9 months (Table 4.27). This estimated proportion was consistent across studies.

Table 4.26: Progression status at time of data cut-off by central review by study (FAS)

Progression status	Type of event	Number (%) of patients: AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
Progression[a]	Total	80 (39.8)	79 (37.6)	159 (38.7)
	RECIST progression	73 (36.3)	69 (32.9)	142 (34.5)
	Target Lesions[c]	21 (10.4)	34 (16.2)	55 (13.4)
	Non Target Lesions[c]	44 (21.9)	36 (17.1)	80 (19.5)
	New Lesions[c]	41 (20.4)	46 (21.9)	87 (21.2)
	Death[b]	7 (3.5)	10 (4.8)	17 (4.1)
No progression	Total	121 (60.2)	131 (62.4)	252 (61.3)
	Censored RECIST progression or death[d]	0	0	0
	Progression free at time of analysis[e]	120 (59.7)	128 (61.0)	248 (60.3)
	Lost to follow-up[f]	0	0	0
	Withdrawn consent[f]	1 (0.5)	3 (1.4)	4 (1.0)
	Discontinued study[f]	0	0	0

[a] Only included progression events that occurred within 19 weeks of the last evaluable assessment.
[b] Death in the absence of RECIST progression.
[c] Target Lesions, Non Target Lesions and New Lesions were not necessarily mutually exclusive categories.
[d] Included patients, known to be alive, with no evaluable baseline RECIST assessment (censored at day 0).
[e] Patients at last evaluable RECIST assessment.
RECIST version 1.1.
Source: see Table 2.6.1.3 from pooled efficacy tables in Module 5.3.5.3 Supportive efficacy data.

Table 4.27: Progression-free survival by BICR by study (FAS)

	AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
Median PFS based on BICR of FAS			
Total number of events[a]	80	79	159
Median progression free survival (months)[b]	NC	8.6	9.7
95% CI for median progression free survival	8.1, NC	8.3, 9.7	8.3, NC
Progression free at 3 months (%)	81.5	84.9	83.2
95% CI for PFS at 3 months	75.3, 86.2	79.2, 89.1	79.2, 86.5
Progression free at 6 months (%)	72.0	69.7	70.9
95% CI for PFS at 6 months	65.1, 77.8	62.8, 75.7	66.1, 75.1
Progression free at 9 months (%)	54.6	47.7	51.9
95% CI for PFS at 9 months	46.4, 62.1	36.2, 58.4	45.3, 58.1
Median follow-up for PFS (Months)	6.9	6.7	6.8

Kaplan-Meier survival models were fitted to PFS as well by line of therapy (2nd line and ≥3rd line).

Overall survival

At DCO, median follow-up for OS was 7.4 months (Table 4.28 and Figure 4.11). Overall survival data were still immature. Of the 411 EGFR T790M mutation-positive patients in the FAS by BICR, 52 had died (12.7%); 349 patients (84.9%) were ongoing on survival follow-up, of whom 296 (72.0%) were still on treatment (see Section 4.11.1.3).

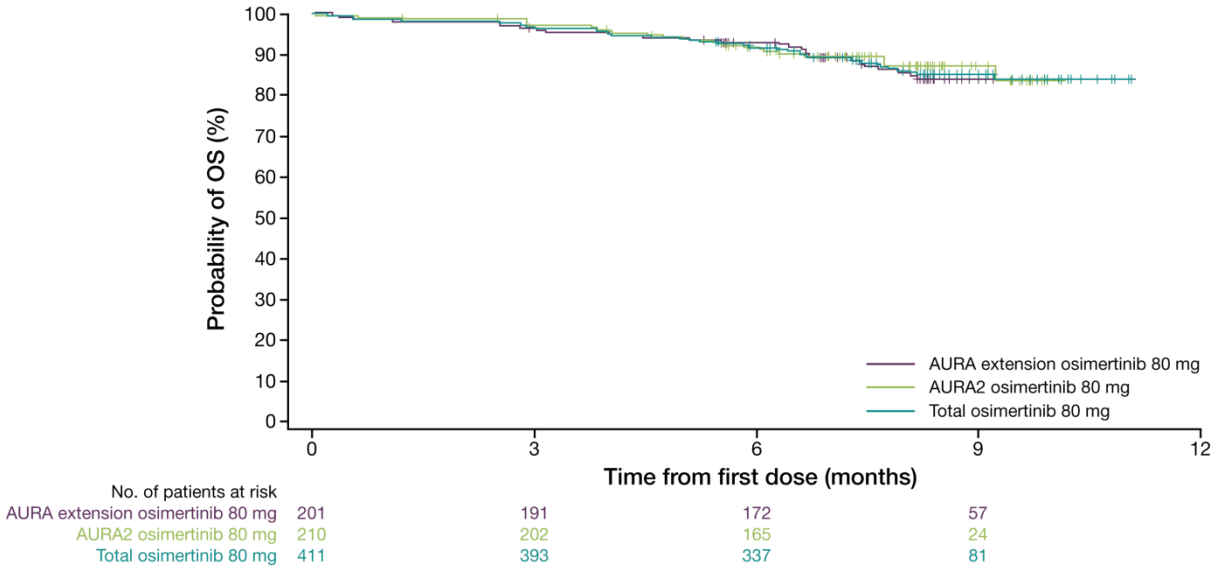
The Kaplan-Meier estimate of the proportion of patients alive based on BICR assessment of the FAS was 96.8% (95% CI: 94.6, 98.1) at 3 months, 92.3% (89.3, 94.5) at 6 months, and 85.3% (80.9, 88.7) at 9 months (Table 4.28).

Table 4.28: Survival status at the time of data cut-off and median overall survival by study (FAS)

	Number (%) of patients		
Status	**AURA Extension AZD9291 80 mg (N=201)**	**AURA2 AZD9291 80 mg (N=210)**	**Total AZD9291 80 mg (N=411)**
Death	28 (13.9)	24 (11.4)	52 (12.7)
Still in survival follow up[a]	168 (83.6)	181 (86.2)	349 (84.9)
Terminated prior to death[b]	5 (2.5)	5 (2.4)	10 (2.4)
Voluntary Discontinuation by Subject	4 (2.0)	4 (1.9)	8 (1.9)
Subject Lost to Follow-up	0	1 (0.5)	1 (0.2)
Other	1 (0.5)	0	1 (0.2)
Total number of deaths	28	24	52
Median Overall survival (months)c	NC	NC	NC
95% CI for Median overall survival	NC, NC	NC, NC	NC, NC
Survival at 3 months (%)	96.5	97.1	96.8
95% CI for survival at 3 months	92.80, 98.32	93.72, 98.70	94.59, 98.14
Survival at 6 months (%)	93.0	91.7	92.3
95% CI for survival at 6 months	88.41, 95.77	86.97, 94.76	89.27, 94.54
Survival at 9 months (%)	84.0	87.1	85.3
95% CI for survival at 9 months	77.49, 88.74	80.83, 91.49	80.85, 88.71
Median follow-up for overall survival (months)	8.3	7.0	7.4

[a] Included patients known to be alive at data cut-off.
[b] Included patients with unknown survival status or patients who were lost to follow-up.
[c] Calculated using the Kaplan-Meier technique.
Source: Tables 2.7.1.1. and 2.7.1.2 in pooled efficacy tables in Module 5.3.5.3 Supportive efficacy tables.

Figure 4.11: Overall survival by central review by study and total, Kaplan-Meier plot (FAS)



Health-related quality of life (HRQoL)

In AURA extension and AURA2, two patient-reported questionnaires relating to cancer symptoms were administrated (EORTC LC13 and EORTC LC30). In AURA extension, a paper-based questionnaire administered at clinical visits was used, while in AURA2, patients completed the questionnaires on an electronic hand-held device. As the method of administration differed, the PRO data across the two studies were not pooled. Data are presented below as summaries; no formal statistical testing applied.

The PRO compliance across both validated questionnaires (EORTC QLQ-LC13 and EORTC QLQ-C30) was high (>90% for the first 6 months in AURA extension and >70% for the first 6 months in AURA2). Data were evaluated by comparing baseline scores to scores up to Week 42. Patients were categorised according to whether they had improved, remained stable or deteriorated in their symptoms according to pre-defined criteria. No major differences were noted in PROs between the second-line and ≥third-line therapy cohorts in the early stages of the treatment up to 6 months.

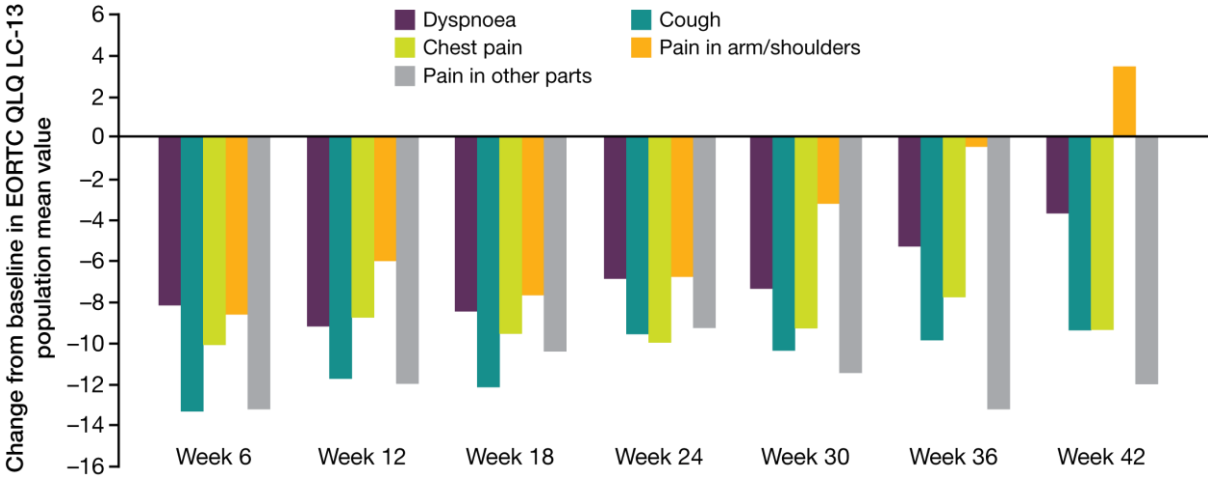
Patients who participated in the studies were representative of the patient population when compared to a reference group of 1262 unselected NSCLC patients. Consistent with the underlying disease, the most severe symptoms at baseline in both studies were generally cough, dyspnoea, pain, and fatigue. Following treatment with osimertinib, changes in lung cancer symptoms paralleled RECIST-based efficacy results, with fewer symptoms and

higher quality-of-life scores, as well as reduction in pain medications, on treatment compared to baseline.

AURA extension

- A clinically meaningful improvement from baseline in the EORTC QLQ LC-13 population mean value was noted in dyspnoea, cough, and all three pain items (ie, pain in chest, pain in arm/shoulder, pain in other parts of body) (Figure 4.12). The percentage of patients meeting clinical worsening criteria over the course of treatment was low. Starting at Week 6 (first follow-up time point), at each time point, 35% to 45% of patients reported clinically relevant improvement in dyspnoea, 31% to 39% in cough, 28% to 33% in chest pain, 17% to 28% in pain in arm/shoulder, and 36% to 39% in pain in other parts of the body. Conversely, a clinically meaningful worsening in the population mean value was noted for sore mouth at Week 12; this change generally remained over the follow-up time points. Starting at Week 12, 19% to 27% of patients reported a worsening in sore mouth, with the remainder reporting stability or improvement

Figure 4.12: Symptom Improvement in AURAext – change from baseline



- Data for the cancer-specific quality-of-life instrument (EORTC QLQ-C30) showed therapeutic benefit from treatment as evidenced by consistent positive responses on the symptomatic domains and the broader quality-of-life domains up to Week 42. A clinically significant improvement in overall global health status domain was evident from Week 12 to Week 30 with 44% to 48% patients reporting clinically meaningful improvement in overall health status. A clinically meaningful increase in diarrhoea was reported by 37% of the patients at Week 6 and 26% at Week 30; however, a

clinically meaningful increase in the population mean value was noted only at Week 6. This however is in line with the osimertinib safety profile

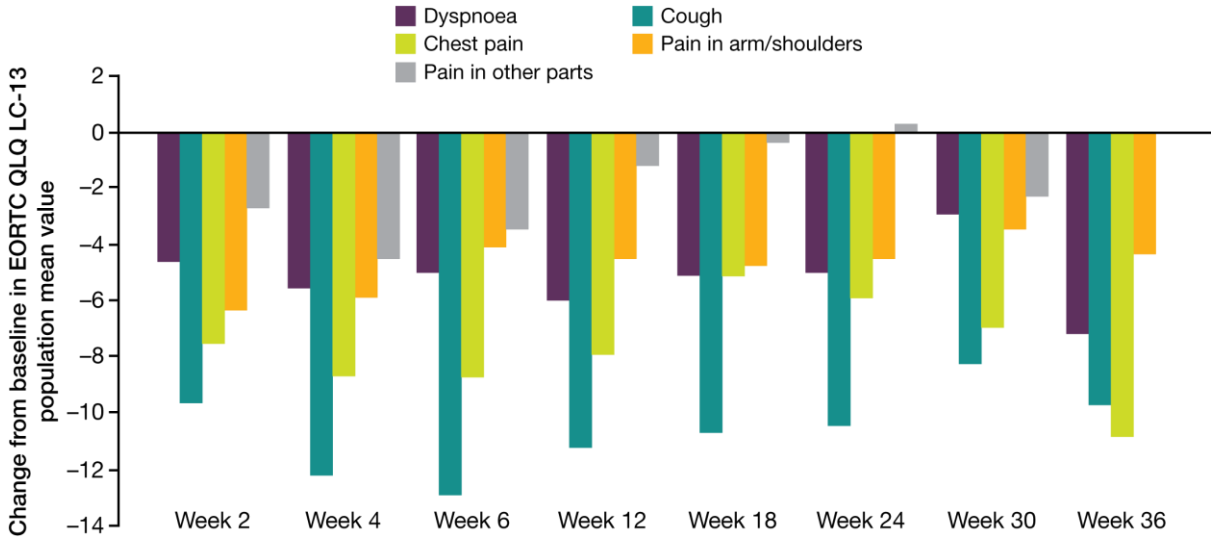
- Six months after starting treatment with osimertinib, the majority of patients (62%) had not experienced worsening of key lung cancer symptoms of dyspnoea, cough, and pain.

AURA2

In AURA2, patient-reported outcome data showed a very rapid onset of improvement in key lung cancer-related symptoms, pain medication, and HRQoL, which was sustained at most of the follow-up time points to Week 24 and sometimes beyond.

- Over the course of treatment, patients had an improvement from baseline in cough, chest pain, dyspnoea, and pain in the arm and shoulder, as shown by consistent and sustained mean decreases on all key symptom data collected in EORTC QLQ-LC13 at specific time points (Figure 4.13). The mean changes met the lower threshold of the published criteria for clinically relevant improvements (ie, a decrease in ≥5 points) in all key lung cancer symptoms as well as pain medication. The percentage of patients meeting clinical worsening criteria over the course of treatment was low. The onset to clinically meaningful improvement was very rapid, starting at Week 1 for chest pain, Week 2 for cough and pain in the arm and shoulder, Week 4 for dyspnoea, and Week 5 for pain medication, and it was sustained during most of the follow-up time points to Week 24 and sometimes beyond. From Week 2/4 through Week 36, 31% to 40% of patients reported improvement in cough, 20% to 31% improvement in chest pain, and 25% to 39% improvement in dyspnoea. The same trend in early improvement was observed for pain in arm/shoulder but did not consistently meet the clinically relevant cut-off; 23% to 29% of patients reported improvements from Week 6 through Week 36 for pain in arm/shoulder

Figure 4.13: Symptom Improvement in AURA2 – change from baseline



- Data for cancer-specific EORTC QLQ-C30 showed therapeutic benefit from treatment, as evidenced by consistent positive responses on the symptomatic items and the broader QoL items up to Week 30. There was a consistent improvement in overall global health status throughout the treatment period although mean data did not meet criteria for clinical meaningful improvement. Patients also reported sustained clinically meaningful improvements in social functioning for the first 24 weeks, with 38% to 44% of patients reporting an improvement. A clinically meaningful improvement was observed at Weeks 6, 18 and 24 for appetite loss (29% to 34% of patients); at Weeks 12 and 18 for insomnia (34% to 35%); and at Week 18 for fatigue (49.6%). While a clinically meaningful worsening was reported in diarrhoea for 30% of the patients at Week 6, no clinically meaningful increase in the population mean value was noted throughout the treatment period.

- The analyses of time to symptom deterioration for key lung cancer symptoms (dyspnoea, pain items, and cough) showed that the biggest therapeutic benefits were for cough and pain in the chest on the EORTC QLQ-LC13. Based on EORTC QLQ-C30, time to symptom deterioration analyses in the key symptomatic domains showed that therapeutic benefit rates were slightly higher for pain and dyspnoea.

AURA2 also collected EQ-5D-5L data alongside the administration of the EORTC QLQ-C30. The EQ-5D Index and VAS score show that patients on osimertinib have also a clinically significant improvement from baseline (MID for cancer =>7.5 on VAS, and 0.1 on HUI score[84] which is evident in AURA2 from 12 weeks onwards.

Table 4.29: EQ-5D-5L index score for AURA2 for FAS

	Total (N=210)			2L (N=68)			≥3L (N=142)		
	n	mean	SD	n	mean	SD	n	mean	SD
Baseline	175	0.745	0.2380	55	0.742	0.2563	120	0.746	0.2302
Week 6	146	0.819	0.1646	47	0.846	0.1451	99	0.807	0.1723
Week 12	136	0.841	0.1753	44	0.863	0.1361	92	0.830	0.1910
Week 18	122	0.822	0.2044	40	0.848	0.2257	82	0.809	0.1934
Week 24	116	0.813	0.2587	35	0.873	0.1473	81	0.787	0.2910
Week 30	73	0.803	0.2709	22	0.884	0.1337	51	0.768	0.3065
Week 36	30	0.805	0.2657	9	0.875	0.1638	21	0.775	0.2973
Week 42	4	0.660	0.5361	1	1.000		3	0.547	0.5951
At discontinuation	5	0.489	0.5159	2	0.760	0.0516	3	0.309	0.6399
28-day follow up visit	9	0.548	0.4846	2	0.396	0.1916	7	0.592	0.5450
Post IP follow up visit	4	0.578	0.1364	1	0.558		3	0.585	0.1663

Baseline is defined as last evaluable assessment prior to the first dose date. This table summarises all EQ-5D-5L assessments at baseline, then every 6 weeks thereafter until progression , or until the data cut off for the primary analysis, at discontinuation of study treatment visit and 28 days post last dose.
Only patients who have a baseline EQ-5D-5L assessment are included.EQ-5D index scores range from 0 (dead) to 1 (full health).
SD = standard deviation.

Table 4.30: EQ-VAS scores for AURA2 for FAS

	Total (N=210)			2L (N=68)			≥3L (N=142)		
	n	mean	SD	n	mean	SD	N	mean	SD
Baseline	175	65.0	20.33	55	62.8	22.02	120	66.0	19.52
Week 6	149	72.2	17.59	49	72.6	17.85	100	72.0	17.55
Week 12	139	73.9	17.16	46	74.5	17.29	93	73.6	17.19
Week 18	124	72.8	18.06	41	75.4	16.84	83	71.5	18.60
Week 24	118	74.6	18.83	36	78.6	14.09	82	72.9	20.40
Week 30	75	74.4	18.46	23	77.6	15.37	52	73.0	19.64
Week 36	32	73.9	18.65	10	75.8	20.02	22	73.1	18.42
Week 42	4	69.0	26.12	1	97.0	-	3	59.7	22.37
At discontinuation	8	52.4	23.78	4	53.8	11.41	4	51.0	34.42
28-day follow up visit	9	43.6	23.31	2	35.0	8.49	7	46.0	26.10
Post IP follow up visit	4	56.5	21.30	1	35.0	-	3	63.7	19.30

Source: Table 11.2.2.10 EQ-5D-5L Question 6.
Baseline is defined as last evaluable assessment prior to the first dose date. This table summarises all EQ-5D-5L assessments at baseline, then every 6 weeks thereafter until progression, or until the data cut off for the primary analysis, at discontinuation of study treatment visit and 28 days post last dose. Only patients who have a baseline EQ-5D-5L assessment are included. The EQ-Visual analogue scale (VAS) scores range from 0 (worst imaginable health) to 100 (best imaginable health). EQ-5D dimension scores (Questions 1-5) in Table 11.2.2.11. SD = standard deviation. Program: \\wilbtia\wilbtia02\AZ AZD5160C00002\Trunk\TLF\T11020210 Executed: 09JUL2015 23:18 Data Extraction Date: 01MAY2015

These PRO data are supportive of the reported RECIST efficacy data and suggest clinical benefit as manifested through an improvement in lung cancer symptoms with administration of osimertinib.

4.11.2 IMPRESS

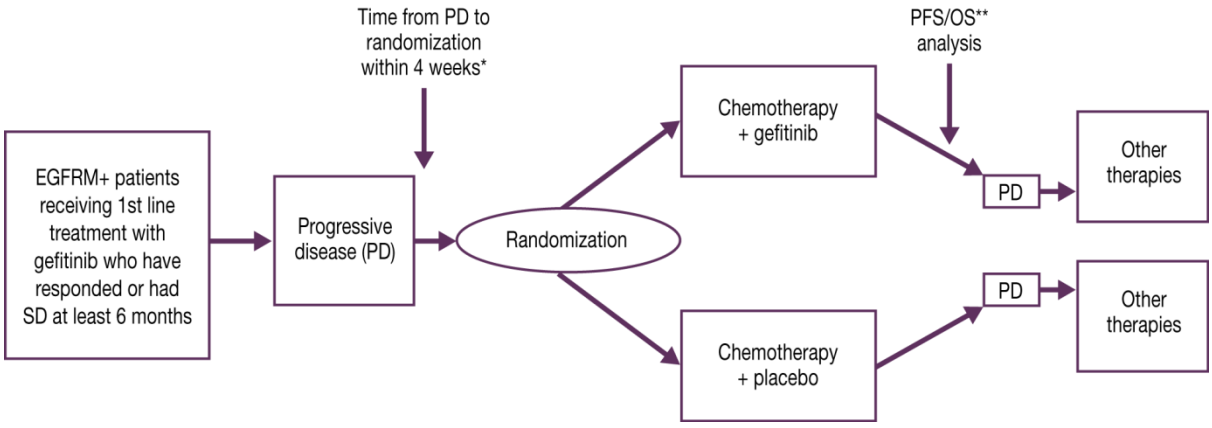
4.11.2.1 Study methodology

Trial design

IMPRESS was a double blind, placebo-controlled, parallel, multi-centre study to assess the efficacy and safety of continuing gefitinib (250 mg, orally once daily) in addition to chemotherapy (cisplatin plus pemetrexed, maximum 6 cycles, intravenously on Day 1 of each cycle) versus chemotherapy alone in patients who had EGFRM+ locally advanced or metastatic NSCLC and had progressed on first-line gefitinib.

The study design is shown in Figure 4.14.

Figure 4.14: Flow chart of IMPRESS study design



*PD based on radiological evaluation, using modified Jackman's criteria to define patients with 'aquired resistance' to prior gefitinib.
**Primary DCO for analysis estimated to occur 11 months following the last patient randomized (approximately 190 PFS events, 125 OS events). After primary PFS, patients were followed up until final DCO (70% OS maturity).

Approximately 250 patients with locally advanced or metastatic EGFRm+ NSCLC who had received gefitinib as first-line treatment were planned to be randomized in the study. Eligible patients for the study had to have received a minimum duration of 4 months first-line gefitinib and had to have either responded (CR or PR) (at least 4 months) or achieved a durable SD (at least 6 months) on their first-line gefitinib treatment and subsequently developed radiological disease progression (as assessed by the investigator according to principles outlined in Response Evaluation Criteria in Solid Tumors [RECIST], Version 1.1).

Eligibility criteria

The key inclusion and exclusion are described below (Table 4.31 and Table 4.32).

Table 4.31: IMPRESS key inclusion criteria

Key Inclusion Criteria

- Provision of informed consent prior to any study specific procedures
- Male or female patients aged 18 years or older (for Japan only- male or female patients aged 20 years or older)
- Cytological or histological confirmation of NSCLC other than predominantly squamous cell histology with an activating EGFR tyrosine kinase (TK) mutation as determined locally
- 'Acquired resistance' on first-line gefitinib as defined by the following clinical endpoints:
    - Radiological documentation of disease progression while on continuous treatment with first-line gefitinib within 4 weeks prior to randomization into the study:
        - Evidence of central nervous system (CNS) recurrence only while on first-line gefitinib was not considered a sign of developing 'acquired resistance' and therefore those patients were not eligible for the study.
        - Evidence of CNS recurrence with other systematic progression while on first-line gefitinib was considered 'acquired resistance.' Those patients were eligible if CNS lesion was treated with surgery and/or radiation, if applicable, and stable without steroid for at least 10 days within 4 weeks of randomization into the study.
    - Prior objective clinical benefit defined by either partial or complete radiological response or durable SD (>6 months) after initiation of first-line gefitinib
    - Minimum duration on first-line gefitinib treatment of 4 months for patients achieving CR or PR
- World Health Organization (WHO) performance status 0, 1
- Life expectancy of at least 12 weeks or longer
- Patients suitable to start cisplatin plus pemetrexed combination chemotherapy
- At least 1 lesion, not previously irradiated, that could be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes having short axis ≥15 mm) with computed tomography (CT) or magnetic resonance imaging (MRI) and which was suitable for accurate repeated measurements.

Table 4.32: IMPRESS key exclusion criteria

Key Exclusion Criteria

- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study centre)
- Previous enrolment or randomization in the present study
- Prior chemotherapy or other systemic anticancer treatment (excluding gefitinib):
    - Adjuvant/neoadjuvant treatment with an EGFR TKI was not allowed.
    - Adjuvant/neoadjuvant treatment with chemotherapy was allowed if it was completed more than 6 months prior to first-line gefitinib treatment.
    - Palliative bone radiotherapy had to be completed at least 2 weeks before start of study treatment with no persistent radiation toxicity (Protocol Amendment 3, Section 5.8.1).
- Past medical history of interstitial lung disease (ILD), drug-induced interstitial disease, radiation pneumonitis which required steroid treatment or any evidence of clinically active ILD
- Neutrophils <1.5×109/L or platelets <100×109/L
- Serum bilirubin >1.5×the upper limit of normal (ULN)
- Creatinine clearance <45 mL/min (or <60 mL/min as required by local prescribing information for cisplatin in France, Italy, Hong Kong and Hungary) as calculated by either Cockcroft-Gault formula, 24-hour urine collection, ethylenediaminetetraacetic acid scan or other validated methods (Protocol Amendment 1, Section 5.8.1)
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5×ULN in the absence of liver metastases, or >5×ULN in the presence of liver metastases
- As judged by the investigator, any evidence of severe uncontrolled systemic disease (eg, unstable or uncompensated respiratory, cardiac, renal or hepatic disease)
- Treatment with an investigational drug within 4 weeks before randomization first-line gefitinib received via a clinical study or other access programme was allowed)
- Other co-existing malignancies or malignancies diagnosed within the last 5 years, with the exception of basal cell carcinoma or cervical cancer in-situ or completely resected intra-mucosal gastric cancer
- Patients who were breast feeding and women of childbearing potential who did not comply with the following:
    - Use of an effective primary method of contraception combined with a male condom to avoid pregnancy throughout the study and for up to 4 weeks after the study in such manner that the risk of pregnancy was minimised.
    - Had a negative pregnancy test.

Clinical trial settings

The first patient was randomized into the study on 29 March 2012; the last patient was randomized on 20 December 2013. The primary DCO for the study occurred on 05 May 2014. An attempt was made to contact all patients prior to the primary DCO to confirm survival status.

As planned the study was conducted in Europe and the Asia-Pacific region including Japan. A total of 265 EGFRm+ patients with locally advanced or metastatic NSCLC, who had progressed after first-line gefitinib treatment, were enrolled at 61 centres in 11 countries. The following number of patients was recruited from 11 countries in the study: China (118 [44.5%] patients), France (9 [3.4%] patients), Germany (6 [2.3%] patients), Hong Kong (5 [1.9%] patients), Hungary (4 [1.5%] patients), Italy (16 [6.0%] patients), Japan (23 [8.7%] patients), Russia (2 [0.8%] patients), Korea (42 [15.8%] patients), Spain (22 [8.3%] patients) and Taiwan (18 [6.8%] patients).

Quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures.

AstraZeneca's quality assurance and quality control procedures provide reassurance that the clinical study programme was carried out in accordance with GCP guidelines. AstraZeneca undertakes a GCP audit programme to ensure compliance with its procedures and to assess the adequacy of its quality control measures. Audits, by a Global Quality Assurance group operating independently of the study monitors and in accordance with documented policies and procedures, are directed towards all aspects of the clinical study process and its associated documentation.

Trial drugs and concomitant medication

Study treatment

Eligible patients were randomized in a 1:1 ratio to the following treatment groups:

- Gefitinib 250 mg once daily in addition to cisplatin plus pemetrexed combination chemotherapy; or
- Matching placebo to gefitinib 250 mg once daily in addition to cisplatin plus pemetrexed combination chemotherapy.

Investigational product

Eligible patients received either gefitinib 250 mg or matching placebo once daily continuously from Visit 2 (start of study treatment) until criterion for discontinuation was met. Gefitinib or matching placebo tablets were to be taken about the same time each day. It was preferred that gefitinib or matching placebo was taken in the morning either before meal or with meal. On Day 1 of each cycle of chemotherapy, patients had to wait to take their gefitinib or matching placebo until after the blood sample was collected. If a patient inadvertently did not take the dose of the study drug in the morning, he or she could take that day's dose any time up to 22:00 hours on the same day. If a patient missed the scheduled dose, that missed dose was not to be made up, and he or she had to take the next scheduled dose. The missed dose was documented in the appropriate eCRF. The dose of study drug could be repeated if vomiting occurred within 30 minutes of taking the study drug. Post randomization gefitinib toxicity was managed by dose interruptions to allow recovery from AEs or for improvement to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade 1. Previous studies allowed up to 14 days dose interruption; however, in order to support management of toxicity that patients could experience due to combination of gefitinib- and pemetrexed-based chemotherapy, and to fit in with the visit schedule, if required, interruptions were allowed up to a maximum of 3 weeks on each occasion.

Patients, who could not tolerate the combination of chemotherapy plus randomized treatment (gefitinib or placebo) due to repeated CTCAE grade 3 to 4 toxicity, could discontinue the randomized treatment (gefitinib or placebo). In these cases, requests for further use of randomized treatment after completion of chemotherapy was required to be discussed with an AstraZeneca representative for agreement on management. As all patients had tolerated at least 6 months of gefitinib treatment prior to randomization, it was expected that patients could continue randomized treatment (gefitinib or placebo) once chemotherapy was completed.

Additional study treatment – chemotherapy

All eligible patients received cisplatin plus pemetrexed combination chemotherapy as additional study treatment, administered along with either gefitinib 250 mg or matching placebo. Chemotherapy and associated premedication was managed by the investigator as per local prescribing information. Although local prescribing guidelines were followed, the recommended dose of pemetrexed was 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each cycle. The recommended

dose of cisplatin was 75 mg/m^2 BSA infused over 2 hours approximately 30 minutes after completion of the pemetrexed infusion on the first day of each cycle. After receiving a maximum of 6 cycles of cisplatin plus pemetrexed chemotherapy, patients continued on blinded gefitinib or matching placebo until progression. Pemetrexed maintenance was not allowed after completion of chemotherapy. The investigator sites were required to locally purchase the accepted standard brand of available and commonly used cisplatin plus pemetrexed combination chemotherapy.

Pre-study treatment for cancer

Prior chemotherapy or other systemic anticancer treatment (excluding gefitinib) was not allowed except adjuvant/neoadjuvant treatment completed at least 6 months prior to first-line gefitinib treatment. Palliative bone radiotherapy was required to be completed at least 2 weeks before the start of study treatment with no persistent radiation toxicity.

Concomitant anticancer medication

No additional systemic anticancer treatment could be used prior to discontinuation of study treatment. Bisphosphonates for treatment of bone pain or hypercalcaemia were allowed during study treatment. Palliative radiotherapy for painful bone metastases or to other non-pulmonary metastatic site was allowed during study treatment and there was no need to discontinue study treatment.

Other medication considered necessary for the patient's safety and well-being could be given at the discretion of the investigators.

Study objectives

Primary objective: The primary objective of the study was to evaluate PFS in patients who had 'acquired resistance' to first-line gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.

Key secondary objectives:

- To evaluate OS in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.
- To evaluate ORR and disease control rate (DCR) in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy compared with cisplatin plus pemetrexed

combination chemotherapy alone

- To evaluate symptoms and HRQoL as measured by the Functional Assessment of Cancer Therapy - Lung (FACT-L) questionnaire in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone

Safety objective: The safety objective of the study was to evaluate the safety and tolerability in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone.

Exploratory objectives:

- To investigate biomarkers in samples from patients who had 'acquired resistance' to gefitinib to ascertain if there are any biomarkers that differentiate for a relative treatment effect, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone. Biomarker analysis could include EGFR mutations (including T790M), c-Met amplification and other exploratory biomarkers

- To collect utilities assessed by Euro Quality of Life-5 Dimensions (EQ-5D) questionnaire to support health technology assessment and health economic modelling in patients who had 'acquired resistance' to gefitinib, comparing continuing gefitinib in addition to cisplatin plus pemetrexed combination chemotherapy versus cisplatin plus pemetrexed combination chemotherapy alone

Study outcomes

Primary endpoint

The primary efficacy outcome variable of this study was PFS, defined as the time from randomization until objective disease progression as detailed in RECIST or death (by any cause in the absence of progression) regardless of subsequent treatment.

The primary analysis of PFS was based on RECIST results programmatically determined from the tumour assessments recorded in the eCRF as collected via the investigator (ie, site data from individual TLs, from the investigator overall assessment of NTLs, and from new lesion data). Patients having signs of clinical progression were assessed via RECIST for

objective disease progression. The PFS time was derived based on scan/assessment dates and not based on visit dates. Central review of scans provided data for a sensitivity analysis of PFS. in addition, agreement between the site assessment and central review was also assessed.

Patients, who had not progressed or died at the time of the statistical analysis, were censored at the latest date of the TL/NTL assessment from their last evaluable RECIST assessment (ie, last assessment had to have a visit response of CR, PR or SD for censoring in the absence of progression). However, if the patient had progressed or died after 2 or more missed visits, the patient was censored at the time of the latest evaluable RECIST assessment. If the duration between two assessments due to missing visits was more than 14 weeks (98 days), then the patient was regarded as having missed two or more visits. If the patient had no evaluable visits or did not have baseline data, the patient was censored at 0 days unless they died within two visits of baseline.

Secondary endpoints

Overall survival (OS)

Overall survival was defined as the time from the date of randomization until death due to any cause. Any patient not known to be dead at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

Once the date of DCO (primary as well as final) was determined, efforts were made to ensure that survival status was determined in all patients. If survival status could not be determined by the time of DCO, then the last date the patient was known to be alive was calculated from the latest assessment date of all data modules (except the visit module) on the database before the DCO; however, if the patient was known to be alive or had died after the DCO, then the patient was censored for OS on the date of the DCO.

Objective response rate (ORR)

The ORR rate was defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression or last evaluable assessment, in the absence of progression were included in the assessment of ORR. This was irrespective of whether or not patients discontinued treatment or received a subsequent therapy prior to progression. The denominator included all patients in the full analysis set (FAS).

Similar to PFS, objective tumour response was calculated using a programming algorithm (ie, based on data from individual TLs, from the investigator's overall assessment of NTLs, and from new lesion data). This calculation ensured consistency with the derivation of PFS.

Disease control rate (DCR)

Disease control rate was defined as the percentage of patients who achieved disease control at 6 weeks following randomization. Disease control at 6 weeks was defined as a best objective response of CR, PR or SD ≥6 weeks. If a patient experienced a CR/PR very shortly after starting treatment but then progressed or became NE by 6 weeks, then they were not included as having disease control at 6 weeks.

Symptoms and health-related quality of life (HRQoL)

Data on symptoms and HRQoL were assessed using the FACT-L questionnaire. Functional Assessment of Cancer Therapy - Lung has been validated with respect to its psychometric properties and sensitivity to clinical changes.[85,86] This questionnaire has been used in many clinical studies in patients with advanced lung cancer, including previous AstraZeneca studies, and is considered appropriate, valid, and sensitive to clinical changes in this study population.

FACT-L domain (subscales) scores:

The FACT-L questionnaire contains 35 questions covering 5 subscales (domains) as follows:

Physical well-being (PWB)

Functional well-being (FWB)

Social/family well-being (SWB)

Emotional well-being (EWB) and

Lung Cancer Subscale (LCS)

Each subscale consists of up to 7 HRQoL questions and the patients provided a score to individual questions ranging from 0 to 4.

FACT-L derived scores:

Using the above specific subscales, the following scores were derived:

- FACT-L total score: The overall score for the FACT-L questionnaire which was the sum of the PWB, FWB, SWB, EWB and LCS domain scores
- 7-Item LCS total score

- Trial Outcome Index (TOI): This score was calculated using the sum of all the individual questions comprising the PWB, FWB and LCS. The TOI score measures improvement in patient-reported functionality. The TOI focused primarily on physically oriented problems in cancer and so should be directly correlated with signs and symptoms and AEs

Euro Quality of Life-5 Dimension (EQ-5D)

The EQ-5D questionnaire was used to assess utilities to support health technology assessment and health economic modelling in patients. The EQ-5D questionnaire is a standardised measure of health status, developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal. It consists of the EQ-5D descriptive system (comprising 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) plus an overall rating of health status measured on a Visual Analogue Scale. The information can be converted into a single index value of health status, generally ranging from 0 (representing a health state of being dead) to 1 (representing a health state of full health). For each EuroQoL health state, there exists corresponding valuations that would be used for health economic calculations (refer to Dolan 1997 for methods for calculating responses into utilities). In addition to the time points specified prior to progression, the EQ-5D questionnaire was to be completed at the post-progression follow-up visits until the time of the PFS DCO.

Exploratory variables

Exploratory biomarkers could be analysed for patients who had evaluable tumour samples. The proposed exploratory biomarker analyses would help ascertain the key molecular subtypes which could predict for a relative treatment effect. Such analyses could include, but were not limited to the following:

The EGFR mutation status could be detected from the original diagnostic tumour samples recorded in the eCRF.

Tumour samples could be analysed for T790M, c-Met amplification and EGFR amplification.

Blood samples could be analysed for EGFR mutation status.

4.11.2.2 Statistical analyses and definition of study groups

Sample size

The sample size for this study was selected to be consistent with the research hypothesis. The study was designed to have 190 PFS events based on 90% power to demonstrate superiority of gefitinib in combination with cisplatin plus pemetrexed combination chemotherapy versus chemotherapy alone at a 2-sided 5% significance level assuming an HR of 0.63. It was expected that 250 patients were needed to be randomized to achieve the 190 PFS events (ie, 75% PFS maturity).

At the time of the PFS analysis it was estimated that there would be approximately 125 OS events (ie, 50% OS maturity). The recruitment was estimated to take 2 years and follow-up would be around 11 months giving a total study time around 35 months to primary DCO.

Randomization and blinding

Within 28 days of documented radiological progression on first-line treatment with gefitinib (the date of scan confirming progression), eligible patients were randomized in a 1:1 ratio using Interactive Web Response System or Interactive Voice Response System to receive either blinded gefitinib or blinded placebo (identical gefitinib and placebo tablets).

Statistical methods

A comprehensive SAP was prepared before database lock (DBL) and analysis. The statistical analysis was carried out by Phastar (2 Heathfield Terrace, London, W4 4JE), using SAS® software Version 9.1.3 or higher (SAS Institute Inc, Cary, North Carolina).

In this study, 2 DCOs were planned: the primary DCO for primary PFS analysis and the final DCO for final OS analysis. The primary PFS analysis took place when approximately 190 progression events had occurred and 75% PFS maturity was observed. At the time of the primary PFS analysis, OS was also analysed and it was estimated that there would be 125 OS events (ie, approximately 50% had died). The final DCO is planned when approximately 175 deaths occur (ie, 70% OS maturity is observed).

In this study for each endpoint there was 1 comparison of interest, namely gefitinib 250 mg in addition to cisplatin and pemetrexed combination chemotherapy versus matching placebo in addition to cisplatin and pemetrexed combination chemotherapy. RECIST results were determined programmatically from investigator's assessment (site data). In addition, a sensitivity analysis was performed based on independent blinded review assessments. All statistical tests were performed at a 2-sided 5% significance level unless otherwise stated.

No adjustment was made for the multiplicity variables as the secondary outcome variables were used to support the primary outcome variable.

Primary outcome

The primary analysis compared the PFS between treatment groups using a Cox proportional hazards model that included terms for treatment and age (<65, ≥65 years), and prior response to gefitinib (SD versus PR and CR combined). The hazard ratio (HR) (gefitinib: placebo) was estimated together with its 95% confidence interval (CI) and *p*-value. Confidence intervals were profile-likelihood intervals. The progression status of patients at the time of primary analysis was summarised and included the number (%) of patients who had a progression event included within the primary analysis, along with the type of progression event (ie, RECIST progression or death). Progression-free survival was summarised for each group using median (in months). The proportion of patients that were event free at 4, 6, and 8 months was also presented by treatment. The reasons that patients were censored within the primary analysis were also presented. Progression-free status was displayed graphically using Kaplan-Meier (KM) plots by treatment.

Several sensitivity analyses for PFS were performed. For more details please see the CSR.

The consistency of treatment effect for PFS between subgroups was assessed for each of the following subgroups:

- Region (Asia, European Union)
- Time from progression to randomization (≤2 weeks, >2weeks)
- Smoking history (never versus current/former)
- Prior response to gefitinib (SD versus PR and CR combined)
- Exon 19 deletion (present, absent/unknown)
- L858R mutation (present, absent/unknown)
- Age (<65 years, ≥65 years)
- Gender (male, female)
- Disease stage at diagnosis (1=locally advanced versus 0=metastatic, 'other')
- Time to progression for initial gefitinib (≤10 months, >10 months)

- Site of disease at baseline (brain/CNS, non-brain/CNS)
- WHO performance status (0=normal activity, 1=restricted activity)

The Exon 19 deletion and L858R mutation would be analysed as 2 independent subgroups (Exon 19 or L858R). A global interaction test was performed to test the overall strength of evidence for consistency of treatment effect for PFS over all these subgroups. If the global interaction test was found to be statistically significant ($p<0.1$) an attempt to determine the cause and type of interaction was made. In addition, the treatment effect in each of the subgroups was investigated by a Cox proportional hazards model. The model was adjusted for treatment, factor (for the subgroup of interest) and treatment-by-factor interaction term. The treatment effect (HR) and 95% Cis for each level of the factor was obtained from this single model. The HR and associated 2-sided 95% CIs were summarised and presented on a Forest plot, along with the overall primary analysis results. If there were less than 20 events in a subgroup, the relationship between that subgroup and PFS was not formally analysed. In this case, only descriptive summaries were provided.

Secondary outcomes

Overall survival

The analysis set for OS was the FAS. The first OS analysis took place at the same time as the PFS analysis (at which time it was expected that the OS data would have reached 50% maturity). A second and final analysis of OS (using the same methodology) would take place when approximately 175 deaths occur. The analysis of OS compared the OS between treatment groups using proportional hazards model adjusted for adjusted for age (<65 years, ≥65 years) and prior response to gefitinib. The HR (gefitinib: placebo) was estimated together with its 95% CI and *p*-value. Confidence intervals were profile likelihood intervals. A KM plot of OS was presented and the median survival time from the KM curve was presented. The median OS, 9-, 12-, and 18-month rates were also presented.

Objective response rate

The ORR was summarised for all patients in the FAS. The response rate was calculated for each randomized treatment based on the percentage of patients who had a best objective response (according to RECIST) of CR or PR. Objective tumour response was compared between the randomized treatment groups using a logistic regression model. The model allowed for the effect of randomized treatment and the same covariates as used in the analysis of PFS. The odds ratio for treatment (gefitinib: placebo) was estimated from the model along with its associated 95% CI and *p*-value. The *p*-value was based on twice the

change in log-likelihood resulting from the addition of a treatment factor to a model containing the covariates detailed above. Confidence intervals were profile likelihood intervals. If the number of responses was low (<20), then alternative analyses such as Fisher's exact test were to be considered.

Disease control rate

The DCR was summarised in patients included in the FAS and was analysed using the same methodology as ORR.

Health-related quality of life

The change from baseline was summarised for each of the FACT-L total score, TOI and LCS by randomized treatment, for each week that HRQoL was assessed and where there were 20 or more patients with available data across the 2 treatment groups. The mean change from baseline and 95% CI at each of these weeks were also plotted for each treatment group separately. The number and percentage of patients with each of the best overall responses were presented for each treatment group. The reasons for the other best overall response category could be explored if there was an imbalance between the 2 treatment groups. The HRQoL improvement rates (for FACT-L total score, TOI and LCS) were summarised descriptively by treatment groups and analysed using the same methodology as ORR. The improvement rate was calculated for each randomized treatment group based on the percentage of patients who had a best overall response of improved. The analysis of the TOI improvement rates was regarded as the primary analysis of the FACT-L questionnaire with the other outcomes (LCS and Total FACT-L) as supportive. The time to worsening data were analysed using a proportional hazards model including terms for treatment received and the covariates as defined for PFS. The HR along with its 95% CI and *p*-value were presented. The KM curves for time to worsening were also plotted. The median was presented, in addition to the number of patients who worsened by 3 and 6 weeks.

4.11.2.3 Participant flow and baseline characteristics

Participant flow

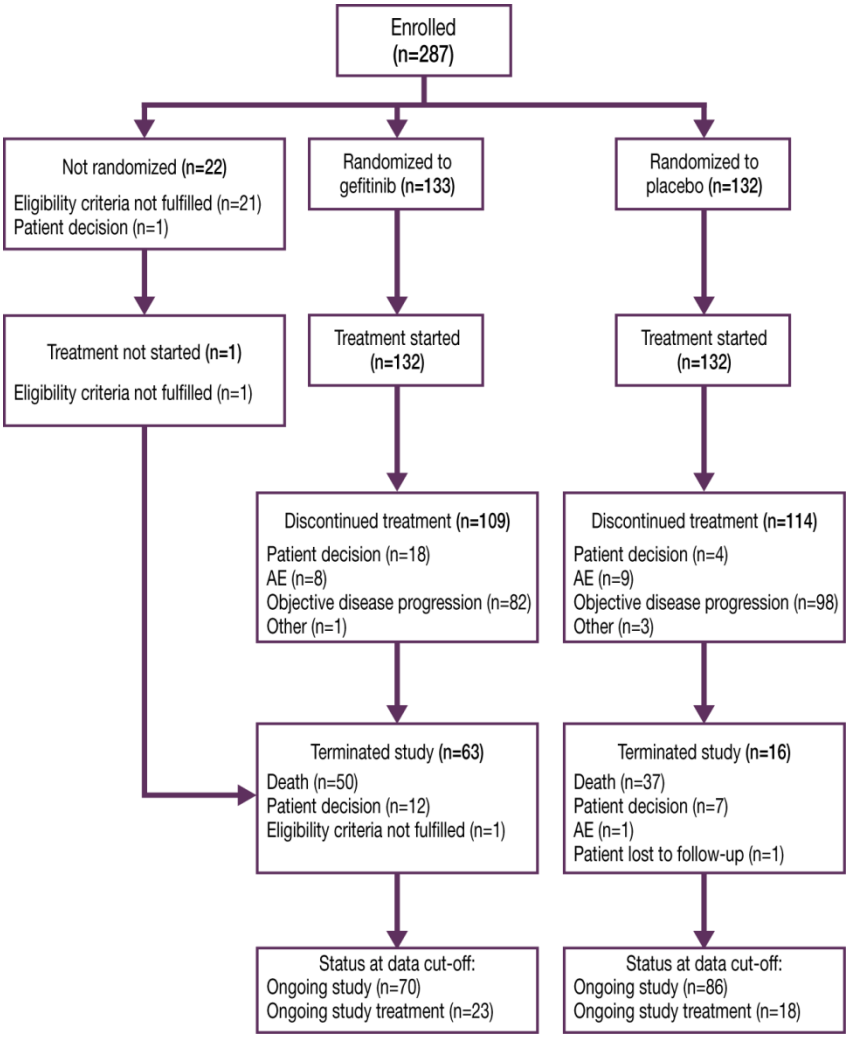
A total of 265 (100.0%) patients were randomized: 133 patients to the gefitinib group and 132 patients to the placebo group (Figure 4.15). The first patient was randomized into the study on 29 March 2012; the last patient was randomized on 20 December 2013. The primary DCO for the study occurred on 05 May 2014. An attempt was made to contact all patients prior to the primary DCO to confirm survival status.

A similar number of patients in the gefitinib group (109 [82.0%] patients) discontinued study treatment compared with the placebo group (114 [86.4%] patients). The proportion of patients discontinuing the study treatment due to disease progression was lower in the gefitinib group (82 [61.7%] patients) compared with the placebo group (98 [74.2%] patients). Other than progression of disease, common reasons for discontinuing the study treatment included: patient decision (18 [13.5%] and 4 [3.0%] patients in the gefitinib and placebo treatment groups, respectively) and AE (8 [6.0%] and 9 [6.8%] patients in the gefitinib and placebo treatment groups, respectively).

At primary DCO for PFS, 63 (47.4%) patients in the gefitinib group and 46 (34.8%) patients in the placebo group had terminated the study. The most common reason for termination from the study in both the gefitinib and placebo groups was death (50 [37.6%] and 37 [28.0%] patients in the gefitinib and placebo groups, respectively), followed by-patient decision (12 [9.0%] and 7 [5.3%] patients in the gefitinib and placebo groups, respectively). All other reasons for study termination were not reported in >1 [0.8%] patient.

At primary DCO, 156 (58.9%) patients were continuing in the study (70 [52.6%] and 86 [65.2%] patients in the gefitinib and placebo groups, respectively), and a higher number of patients in the gefitinib group (23 [17.3%]) were still receiving the study treatment compared with the placebo group (18 [13.6%]).

Figure 4.15: Patient disposition (all patients)



Overall, 47 important protocol deviations were reported in the study (28 and 19 in the gefitinib and placebo groups, respectively). Few patients in either treatment group reported at least 1 important protocol deviation: 16 (12.0%) patients in the gefitinib group and 12 (9.1%) patients in the placebo group. Important protocol deviations were generally balanced between treatment groups. The most common important deviation observed in both treatment groups was ‘other protocol deviation’ (15 [11.3%] and 12 [9.1%] patients in the gefitinib and placebo groups, respectively). In the ‘other protocol deviation’ category, the most common reason for deviation was ‘patient experienced RECIST progression but was not withdrawn from the study’ (eight patients in the gefitinib group and nine patients in the placebo group).

The number and type of protocol deviations did not raise any particular concern about the overall conduct and quality of the study and did not have any impact on the interpretation of primary or secondary results.

Baseline characteristics

Patient demographics

Overall 94 (35.5%) males and 171 (64.5%) females with median age of 59 years (range 33 to 79 years) were randomized in the study (Table 4.33). Overall, there were more patients ≥65 years in the gefitinib group (43 [32.3%] patients) compared with placebo group (34 [25.8%] patients). The majority of the patients were Asian (206 [77.7%] patients).

Table 4.33: IMPRESS demographic characteristics by study (FAS)

Demographic characteristic		Number (%) of patients		
		Gefitinib 250 mg N=133	Placebo N=132	Total N=265
Age (years)	n	133	132	265
	Mean	59.3	57.0	58.1
	SD	10.63	11.25	10.98
	Median	60.0	58.0	59.0
	Min	33	35	33
	Max	79	79	79
Age group (years), n (%)	<65	90 (67.7)	98 (74.2)	188 (70.9)
	≥65	43 (32.3)	34 (25.8)	77 (29.1)
	Total	133 (100.0)	132 (100.0)	265 (100.0)
Sex, n (%)	Male	46 (34.6)	48 (36.4)	94 (35.5)
	Female	87 (65.4)	84 (63.6)	171 (64.5)
	Total	133 (100.0)	132 (100.0)	265 (100.0)
Race, n (%)	White	29 (21.8)	29 (22.0)	58 (21.0)
	Black or African American	0	1 (0.8)	1 (0.4)
	Asian	104 (78.2)	102 (77.3)	206 (77.7)
	Total	133 (100.0)	132 (100.0)	265 (100.0)
Ethnic group, n (%)	Hispanic or Latino	4 (3.0)	5 (3.8)	9 (3.4)
	African	0	1 (0.8)	1 (0.4)
	Asian (other than Chinese and Japanese)	21 (15.8)	21 (15.9)	42 (15.8)
	Chinese	71 (53.4)	70 (53.0)	141 (53.2)
	Japanese	12 (9.0)	11 (8.3)	23 (8.7)
	Caucasian	7 (5.3)	11 (8.3)	18 (6.8)
	European	3 (2.3)	2 (1.5)	5 (1.9)
	Not applicable	15 (11.3)	11 (8.3)	26 (9.8)
	Total	133 (100.0)	132 (100.0)	265 (100.0)

Disease characteristics

Baseline characteristics were representative of the target population of patients with EGFRm+ locally advanced or metastatic NSCLC and were generally well balanced between

the 2 treatment groups. At baseline, a similar number of patients in both treatment groups had abnormalities in their physical examination results (66 [49.6%] and 60 [45.5%] patients in the gefitinib and placebo groups, respectively). Most common abnormalities in both treatment groups were reported in the skin (38 [28.6%] and 39 [29.5%] patients in the gefitinib and placebo groups, respectively) and respiratory systems (14 [10.5] and 18 [13.6%] patients in the gefitinib and placebo groups, respectively).

The time from disease progression to randomization was similar between the 2 treatment groups with a higher percentage of patients having >2 weeks from disease progression to randomization (87 [65.4%] and 79 [59.8%] patients in the gefitinib and placebo groups, respectively).

The time to progression for initial gefitinib treatment was similar in both treatment groups and approximately 60% of patients had first-line Iressa/gefitinib >10 months from progression (81 [60.9%] and 74 [56.1%] patients in the gefitinib and placebo groups, respectively). Overall, the majority of patients had never smoked (88 [66.2%] and 91 [68.9%] patients in the gefitinib and placebo treatment groups, respectively) and 44 (33.1%) and 41 (31.1%) patients in the gefitinib and placebo treatment groups, respectively, were former smokers; 1 (0.4%) patient was a current smoker (gefitinib group).

At baseline, a higher percentage of patients in the placebo group (75.7%) had a prior response to gefitinib compared with patients in the gefitinib group (68.4%).

There were slightly less patients in the gefitinib group (4 [3.0%] patients with CR and 87 [65.4%] patients with PR) who had prior response compared with placebo group (2 [1.5%] patients with CR and 98 [74.2%] patients with PR).

There were slightly less patients in the placebo group (31 [23.5%]) with brain metastases at baseline compared to the gefitinib group (44 [33.1%]).

Table 4.34: Key demographic and baseline characteristics

	Number (%) of patients	
	Gefitinib 250 mg N=133	**Placebo N=132**
≥65 years[a]	43 (32.3)	34 (25.8)
Mean age (range), years	59.3 (33-79)	57.0 (35-79)
Female	87 (65.4)	84 (63.6)
WHO performance status		
Normal activity (0)	55 (41.4)	53 (40.2)
Restricted activity (1)	78 (58.6)	79 (59.8)
Time from progression to randomisation		
>2 weeks	87 (65.4%)	79 (59.8%)
≤2 weeks	46 (34.6%)	53 (40.2%)
Time to progression for initial Iressa treatment		
≤10 months	52 (39.1%)	58 (43.9%)
>10 months	81 (60.9%)	74 (56.1%)
Never smoked	88 (66.2)	91 (68.9)
Adeno histology	126 (94.8)	131 (99.2)
Metastatic disease (initial diagnosis)	120 (90.2)	119 (90.2)
Metastatic disease (baseline)	124 (93.2)	119 (90.2)
Brain metastases at baseline	44 (33.1)	31 (23.5)
Prior response to gefitinib[a]	91 (68.4)	100 (75.7)
Exon 19 deletion	85 (63.9)	86 (65.2)
L858R	40 (30.1)	42 (31.8)

[a] Covariates in the Cox model.
Abbreviation: WHO, World Health Organization

Baseline characteristics by T790M status

As discussed in Section 4.11.2.1, an exploratory analysis for biomarkers by T790M mutation status was part of the CSP.

Table 4.35: Demographic characteristics for subjects with positive or negative T790M mutations

		Number (%) of patients				
		Gefitinib 250 mg		Placebo		Total (N=247)
		T790M mutation positive (N=81)	T790M mutation negative (N=46)	T790M mutation positive (N=61)	T790M mutation negative (N=59)	
Age, years	Mean	57.8	61.5	55.8	58.5	58.2
	SD	10.82	9.97	10.20	12.39	11.02
	Median	57.0	62.0	55.0	63.0	59.0
	Min	33	33	38	35	33
	Max	78	78	79	78	79
Age group, n (%)	<65 years	57 (70.4)	29 (63.0)	51 (83.6)	37 (62.7)	174 (70.4)
	≥65 years	24 (29.6)	17 (37.0)	10 (16.4)	22 (37.3)	73 (29.6)
Sex, n (%)	Male	31 (38.3)	13 (28.3)	23 (37.7)	18 (30.5)	85 (34.4)
	Female	50 (61.7)	33 (71.7)	38 (62.3)	41 (69.5)	162 (65.6)
Race, n (%)	White	18 (22.2)	10 (21.7)	12 (19.7)	15 (25.4)	55 (22.3)
	Black or African American	0	0	1 (1.6)	0	1 (0.4)
	Asian	63 (77.8)	36 (78.3)	48 (78.7)	44 (74.6)	191 (77.3)
Ethnic group, n (%)	Hispanic or Latino	3 (3.7)	1 (2.2)	2 (3.3)	3 (5.1)	9 (3.6)
	African	0	0	1 (1.6)	0	1 (0.4)
	Asian (other than Chinese or Japanese)	16 (19.8)	5 (10.9)	13 (21.3)	8 (13.6)	42 (17.0)
	Chinese	41 (50.6)	25 (54.3)	30 (49.2)	30 (50.8)	126 (51.0)
	Japanese	6 (7.4)	6 (13.0)	5 (8.2)	6 (10.2)	23 (9.3)
	Caucasian	5 (6.2)	2 (4.3)	4 (6.6)	6 (10.2)	17 (6.9)
	European	2 (2.5)	1 (2.2)	1 (1.6)	0	4 (1.6)
	Not applicable	8 (9.9)	6 (13.0)	5 (8.2)	6 (10.2)	25 (10.1)
Histological type	Cannot be determined	1 (1.2)	0	0	0	1 (0.4)
	Adenocarcinoma (NOS)	69 (85.2)	44 (95.7)	59 (96.7)	56 (94.9)	228 (92.3)
	Adenocarcinoma: bronchioloalveolar	5 (6.2)	2 (4.3)	1 (1.6)	3 (5.1)	11 (4.5)
	Large cell carcinoma	2 (2.5)	0	0	0	2 (0.8)
	Adenosquamous carcinoma	1 (1.2)	0	1 (1.6)	0	2 (0.8)
	Carcinoma of lungs	1 (1.2)	0	0	0	1 (0.4)

		Number (%) of patients				
		Gefitinib 250 mg		Placebo		Total (N=247)
		T790M mutation positive (N=81)	T790M mutation negative (N=46)	T790M mutation positive (N=61)	T790M mutation negative (N=59)	
	NSCLC	1 (1.2)	0	0	0	1 (0.4)
	Sarcomatoid	1 (1.2)	0	0	0	1 (0.4)
WHO performance status	0: Normal activity	33 (40.7)	19 (41.3)	22 (36.1)	24 (40.7)	98 (39.7)
	1: Restricted activity	48 (59.3)	27 (58.7)	39 (63.9)	35 (59.3)	149 (60.3)
	2: In bed ≤50% of the time	0	0	0	0	0
	3: In bed >50% of the time	0	0	0	0	0
	4: 100% bedridden	0	0	0	0	0
	Missing	0	0	0	0	0
Overall disease classification	Metastatic*	76 (93.8)	42 (91.3)	58 (95.1)	50 (84.7)	226 (91.5)
	Locally advanced†	4 (4.9)	3 (6.5)	3 (4.9)	8 (13.6)	18 (7.3)
	Missing	1 (1.2)	1 (2.2)	0	1 (1.7)	3 (1.2)

IMPRESS results were analysed by T790M status. It was found that 142 patients (54% across both arms) tested positive at baseline for T790M and 105 patients tested negative (46%). In the doublet chemotherapy group it was found that 61 patients (55%) tested positive and (45%) tested negative. For 14 patients across both arms, the T790M status was unknown. These T790M prevalence figures, across the two arms, above are in line with published sources (50–60%) (Section 3).

Also within the T790M mutation positive cohort, more patients in the placebo group (21 [34.4%] had brain metastases at baseline compared to the gefinitib treatment arm.

4.11.2.4 Quality assessment of clinical studies

A detailed critical appraisal of the IMPRESS study was conducted, using the minimum criteria recommended by NICE for the quality assessment (based on Centre for Reviews and Dissemination's guidance), Jadad score,[87] and allocation concealment grade (Grade A: adequate; Grade B: uncertain; Grade C: inadequate; Grade D: no allocation concealment attempted). Details of the critical appraisal of IMPRESS are presented in Table 4.36.

Table 4.36: Quality assessment of the IMPRESS study[2]

JADAD score	4
Allocation concealment grade	A
Was randomization carried out appropriately	Low risk; the patients were assigned to treatment arms via central block randomization in a 1:1 ratio using interactive web response system or inter active voice response system during the first visit (initial screening)
Were the groups similar at the outset of the study in terms of prognostic factors?	Low risk; The baseline characteristics between the two treatment arms were well balanced
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low risk; This was a double-blind study. All study investigators and participants were masked to treatment allocation. To ensure masking of study investigators and participants, all gefitinib and placebo packaging was identical. Apart from safety reasons, nobody was allowed access to the randomization scheme or study results until completion of the randomized treatment period to minimise any potential bias in data handling and to safeguard the integrity of the masking of study investigators.
Were there any unexpected imbalances in drop-outs between groups?	Low risk; study withdrawals were adequately reported and incorporated in the patient flow diagram
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk; the authors measured all outcomes as reported in the protocol (NCT01544179)
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low risk; The safety and efficacy analysis was performed using mITT and ITT population respectively

4.11.2.5 Clinical effectiveness

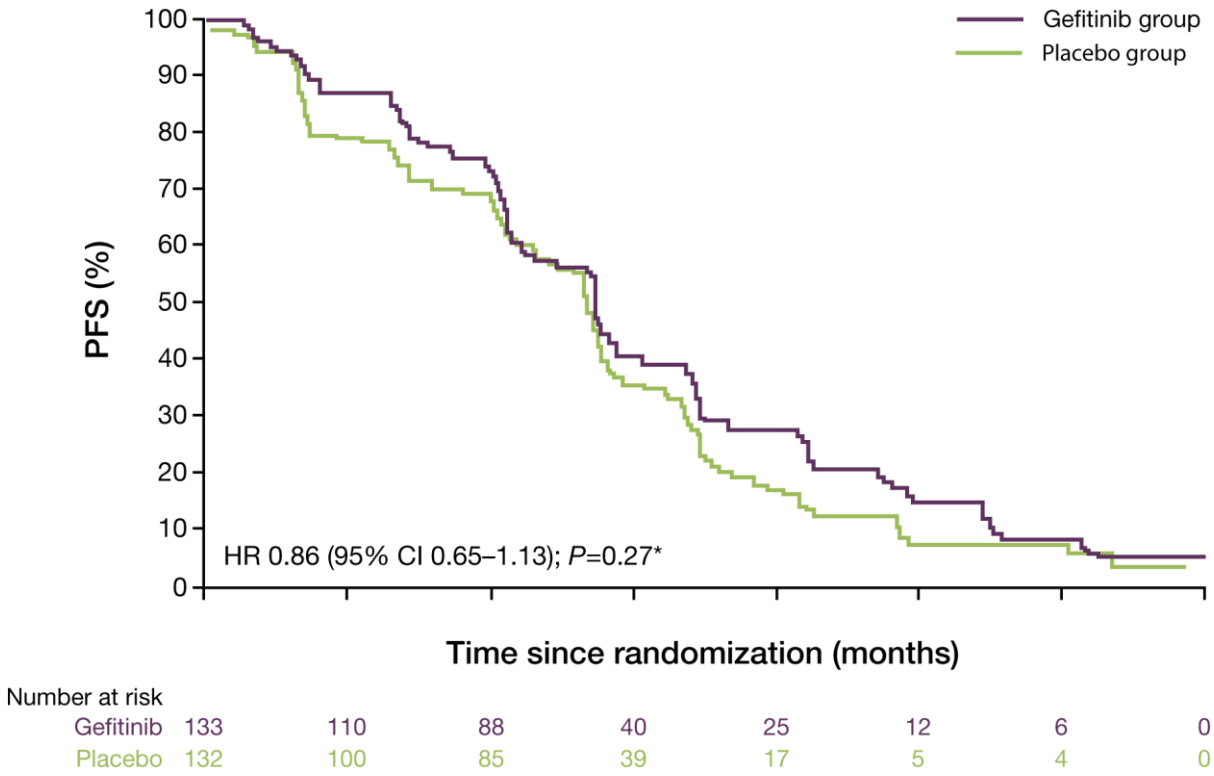
This section describes results from the IMPRESS clinical trial as of the DCO date of 5 May 2015. This data forms the basis for the comparative treatment arm in the health economic analysis presented in Section 5. In order to match the population defined in the decision problem, an exploratory ctDNA biomarker analysis was performed to evaluate the detection rate of the T790M resistance mutation following first-line gefitinib failure (upon entry into IMPRESS) and more importantly to study the IMPRESS primary outcome according to T790M patient subgroups. This was possible as for 98% of patients (n=261), baseline plasma samples were available for analysis, subsequently tested for T790M mutation status by ctDNA BEAMing. Results are first described for the overall population before discussing results by T790M status.

Progression-free survival

In accordance with the CSP and SAP, the primary analysis of PFS was to be performed once at least 190 PFS events had accrued in the FAS population (the primary DCO) (DCO date: 05 May 2014). The analysis was conducted as planned based on a total of 205 progressions (77.4% maturity).

The PFS HR based on site-read (investigator assessment) data demonstrated a numerical advantage for gefitinib but the difference did not demonstrate statistically significant improvement in the gefitinib group relative to the placebo group (HR 0.86, 95% CI 0.65 to1.13, *p*-value =0.273) as illustrated in Figure 4.16. Median PFS was 5.4 months (95% CI 4.5 to 5.7 months) in the gefitinib group compared with 5.4 months (95% CI 4.6 to 5.5 months) in the placebo group. In general, the KM plots did not cross and the treatment effect appeared consistent over time.

Figure 4.16: IMPRESS Kaplan-Meier plot of PFS by investigator assessment[2]



The proportion of patients progression free at 4 months and 6 months was similar in the gefitinib and placebo groups and at 8 months was slightly higher in the gefitinib group (28.2% patients, 95% CI 19.8 to 37.1) compared with the placebo group (17.3% patients, 95% CI 10.9 to 25.1) (Table 4.37).

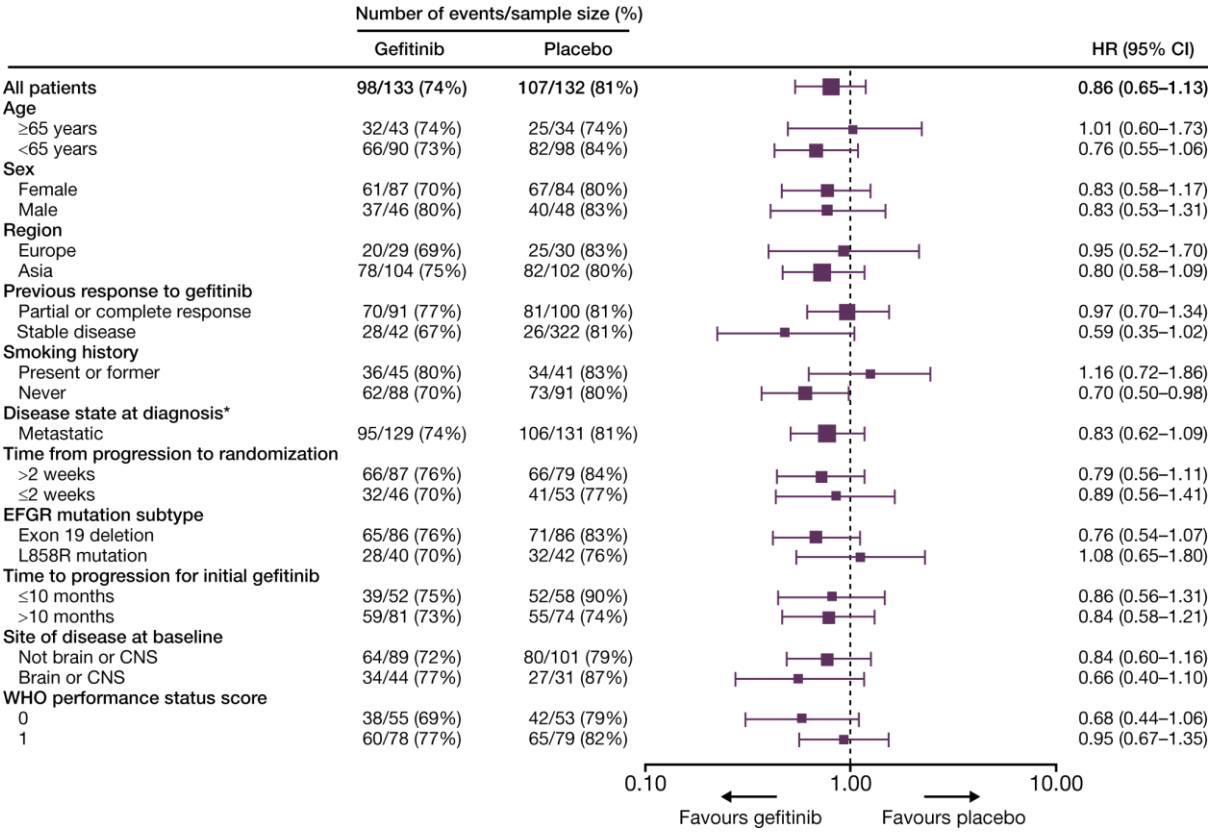
Table 4.37: IMPRESS median PFS and landmark analysis (FAS)

	Gefitinib 250 mg (N=133)	Placebo (N=132)
Total number of events[a]	98	107
Median PFS (months)[b]	5.4	5.4
95% CI for median PFS	4.5, 5.7	4.6, 5.5
PFS at 4 months (%)	73.5	67.8
95% CI for PFS at 4 months (%)	64.8, 80.4	59.0, 75.2
PFS at 6 months (%)	40.8	36.0
95% CI for PFS at 6 months (%)	31.5, 49.8	27.4, 44.6
PFS at 8 months (%)	28.2	17.3
95% CI for PFS at 8 months (%)	19.8, 37.1	10.9, 25.1

[a] Progression events that did not occur within 14 weeks of the last evaluable assessment (or randomisation) were censored and therefore excluded in the number of events.
[b] Calculated using the Kaplan-Meier technique.
Progression included death in the absence of RECIST progression.
Abbreviations: CI, confidence interval; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors (Version 1.1).

The subgroup analysis of PFS in the FAS population is presented in the Forest plot for PFS in Figure 4.17. The PFS subgroup analysis was generally consistent with the overall PFS results. Significant interactions were observed the following subgroups: region (HR was lower for Asia [HR=0.80] versus Europe [HR=0.95]), smoking history (HR was lower for never smokers [HR=0.70] versus current or former smokers [HR=1.16]), Exon 19 deletion mutations (HR was lower for Exon 19 deletion present [HR=0.76] versus Exon 19 deletion absent or unknown [HR=0.97]) and WHO performance status (HR was lower for WHO performance status=0 [HR=0.68] versus WHO performance status=1 [HR=0.95]); these interactions were quantitative in nature.

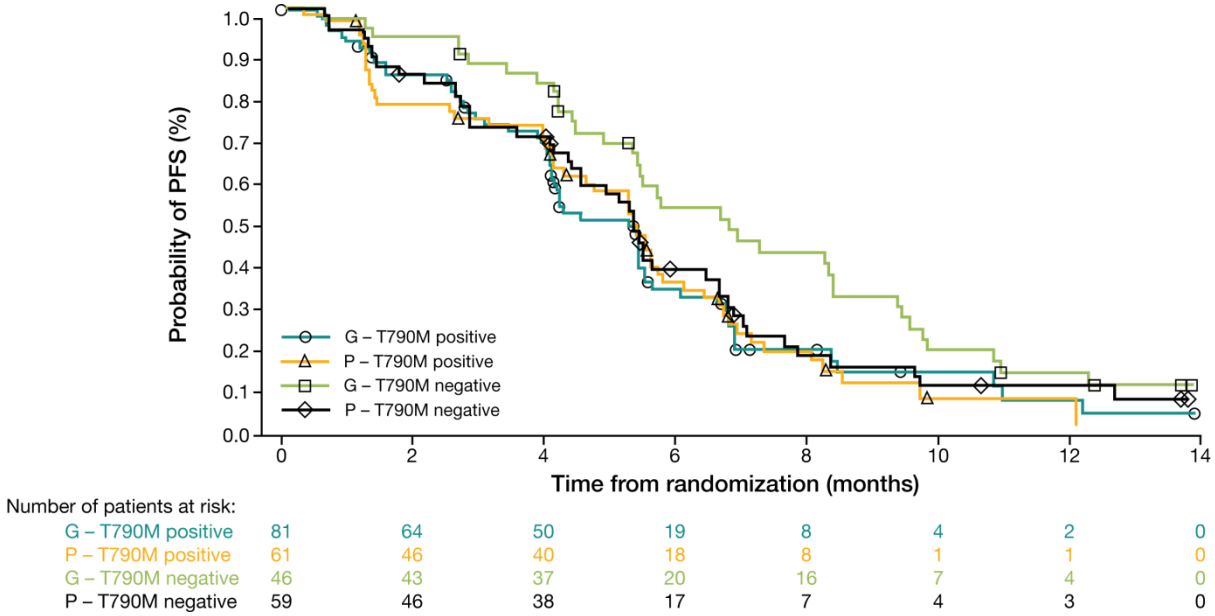
Figure 4.17: Forest plot of progression-free survival subgroup analyses in IMPRESS[2]



Results by T790M status

Within the control group, median PFS was 5.3 months in the T790M mutation positive group (51/61, 83.6% maturity) compared with 5.4 months in the T790M mutation negative group (46/59, 78% maturity).

Figure 4.18: Progression-free survival by plasma biomarker status, Kaplan-Meier plot (full analysis set)



As can be seen in Figure 4.18, though not significant, a treatment effect with gefitinib was observed in the subgroup of T790M mutation negative patients. This supports the underlying biologic hypothesis that in patients with T790M mutation negative status, the absence of the mutation results in the tumour still being partially sensitive to 1st generation TKIs (HR 0.67; 95% CI 0.43 to 1.03; *p*-value=0.0745). In the T790M mutation positive group, no gefitinib treatment effect was observed (HR 0.97; 95%CI 0.67 to 1.42; *p*-value=0.8829).

Overall survival

The primary analysis of OS was performed at the time of PFS analysis in the FAS population by Cox proportional hazards model. At the DCO for the primary analysis of this study, 87 patient deaths had occurred (87/265, 33% maturity). Follow-up of patients in this study is ongoing and the final analysis is planned when approximately 175 death events have occurred. [redacted].The number of patients still in survival follow-up was higher in the placebo group (86 [65.2%] patients) compared with the gefitinib group (70 [52.6%] patients).

Analysis of OS at primary DCO revealed that OS was statistically significantly lower in the gefitinib group compared with the placebo group (HR 1.62; 95% CI 1.05 to 2.52; *p*-value=0.029) (Table 4.38). Median overall survival was 17.2 months (95% CI 15.6 to not reached) in the placebo group versus 14.8 months (10.4 to 19.0) in the gefitinib group.[2]

Table 4.38: Primary analysis of overall survival at time of progression-free survival analysis (FAS)

Randomised treatment	N	Number (%) of patients with events	Treatment effect (Gefitinib vs Placebo) Hazard ratio	95% CI	2-sided p-value
Gefitinib 250 mg	133	50 (37.6)	1.62	1.05, 2.52	0.029
Placebo	132	37 (28.0)			

The analysis was performed using a Cox proportional hazards model with factors for treatment, age (<65, ≥65) and prior response to gefitinib (SD, PR and CR combined).
A hazard ratio <1 favoured gefitinib.
CI was calculated using profile likelihood.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

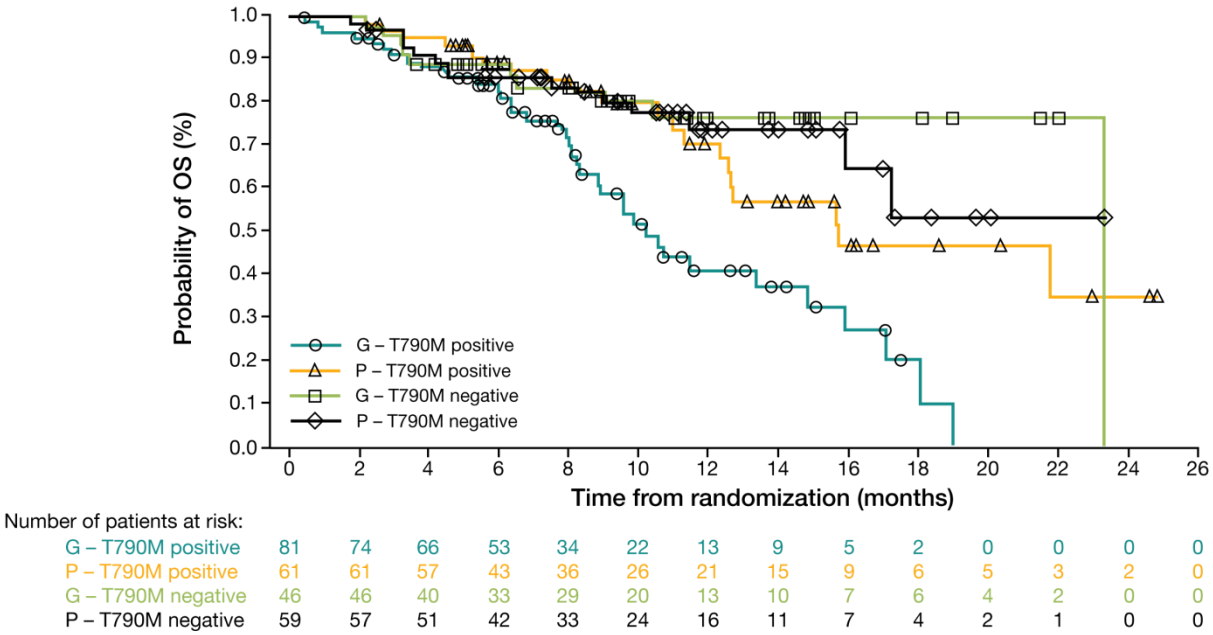
Further anticancer therapy post treatment discontinuation

At the time of DCO, 61 (45.9%) patients in the gefitinib group and 72 (54.5%) patients in the placebo group had received further anticancer therapy post discontinuation of study drug. A total of 57 (42.9%) and 68 (51.5%) patients in the gefitinib and placebo groups, respectively received subsequent cancer therapy after progression and 3 (2.3%) and 2 (1.5%) patients in the gefitinib and placebo groups, respectively received subsequent cancer therapy before progression.

Results by T790M status

At the time of DCO, 20 (32.8%) out of 61 patients within the T790M mutation positive control group had an event compared to 14 (23.7%) out of 59 patients in the T790M mutation negative control group. The KM plots did show a separation between the T790M mutation positive and negative control group (Figure 4.19). Median overall survival in the T790M mutation positive control group was 15.7 months.

Figure 4.19: Overall survival by plasma biomarker status, Kaplan-Meier plot (full analysis set)[2,75]



Objective response rates

The response rate was calculated for each randomized treatment based on the percentage of patients who had a best objective response (according to RECIST) of CR or PR. The analysis of ORR by logistic regression in the FAS population based on site-read (investigator assessment) data is summarised in Table 4.39.

Objective response rate was similar in the gefitinib (31.6% patients) and placebo (34.1% patients) groups (odds ratio 0.92, 95% CI 0.55 to 1.55, *p*-value=0.760).

Table 4.39: Objective response rate, logistic regression (full analysis set)[2,75]

Randomised treatment	N	Number (%) of patients with response	Treatment effect (Gefitinib vs Placebo) Odds ratio	95% CI	2-sided p-value
Gefitinib 250 mg	133	42 (31.6)	0.92	0.55, 1.55	0.760
Placebo	132	45 (34.1)			

The analysis was performed using a logistic regression model with factors for treatment, age (<65, ≥65) and prior response to gefitinib (SD, PR and CR combined).
An odds ratio >1 favours gefitinib.
Abbreviations: CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.

Results by T790M status

At the time of DCO, 24 (39.3%) out of 61 patients within the T790M mutation positive control group had response compared to 16 (27.1%) out of 59 patients in the T790M mutation negative control group.

Disease control rates

The DCR analysis was performed by logistic regression in the FAS. Patients in the gefitinib group had a small numerical advantage compared with the placebo group but this difference did not reach statistical significance (84.2% in the gefitinib group and 78.8% in the placebo group) (odds ratio 1.39, 95% CI 0.74 to 2.62, *p*-value=0.308).

Healthcare-related quality of life

In general, FACT-L total score, TOI and LCS and scores remained relatively stable over time and were broadly similar between treatment groups. As these results are not relevant to the decision problem or allow a comparison versus the AURA pooled data, they will not be discussed in more detail.

Euro Quality of Life-5 Dimension scores (EQ-5D-3L)

The EQ-5D-3L scores summarised in the EFQoL population (a subset of the FAS population with a baseline HRQoL assessment and at least 1 post-baseline HRQoL assessment) are presented in Table 4.40 below. In general, both the compliance rate for completion of and the evaluability rate of the EQ-5D questionnaires were similar in the gefitinib and placebo groups.

Table 4.40: Summary of EQ-5D-3L VAS Scores over time from IMPRESS

	Gefitinib (n=124)			Platinum doublet chemo (n=129)		
Timepoint	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Baseline	123	74.6	19.1	128	74.4	19.7
Week 3	118	72.7	21.4	123	74.6	19.4
Week 6	106	72.9	19.5	103	75.8	16.3
Week 9	98	75.4	19.8	95	72.9	18.5
Week 12	93	75.9	18.1	82	76.4	14.9
Week 15	85	74.1	19.8	77	78.0	15.0
Week 18	76	77.8	18.5	70	77.8	14.1
Week 24	45	78.8	16.5	43	76.1	20.2
Week 30	31	77.8	21.2	29	82.3	14.5
Week 36	23	82.4	18.7	16	80.5	14.4
Week 42	13	80.2	21.7	10	83.9	16.7
Week 48	8	84.8	13.9	5	80.0	23.5
Week 54	4	84.0	17.4	2	87.5	10.6
Week 60	3	74.3	18.3	2	90	7.1
Discontinued	73	66.0	23.9	85	70.1	20.1
Post-Prog FU 1	32	71.7	20.1	40	71.5	20.2
Post-Prog FU 2	22	71.7	19.6	27	75.3	15.6
Post-Prog FU 3	13	75.2	21.8	21	75.8	14.6
Post-Prog FU 4	7	74.4	19.0	11	83.8	9.6
Post-Prog FU 5	3	72.3	23.6	10	79.0	29.2
Post-Prog FU 6	4	77.8	13.0	6	74.2	12.0
Post-Prog FU 7	2	57.0	32.5	3	78.3	7.6
Post-Prog FU 8	1	80.0	NC	2	70.0	14.1
Post-Prog FU 9	0	NC	NC	2	65.0	7.1
Post-Prog FU 10	0	NC	NC	1	90.0	NC
Post-Prog FU 11	0	NC	NC	1	90.0	NC

FU – follow-up; NC – non-calculable

4.12 Adverse reactions

The safety data from AURA extension and AURA2, supported by consistent data from AURA Phase I, indicate that osimertinib 80 mg has an acceptable safety and tolerability profile in terms of the type, frequency and severity of events, for use in the proposed indication. Osimertinib's well tolerated profile is reflected in the very low discontinuation rate observed in the two single-arm trials. In the pooled analysis only 4.1% of patients discontinued treatment due to an AE.

This section describes the safety assessment of the AURA pooled data and IMPRESS study separately. A comparison is presented in Section 4.10.

4.12.1 AURA extension and AURA2 safety assessment

The safety assessment was limited to the population of enrolled patients who received at least one dose of study drug (the safety population) which is also the defined full analysis set (FAS). Adverse events and SAEs were collected from the time of informed consent, throughout the treatment period and including the safety follow-up period (defined as 28 days after study drug was discontinued).

Given the almost identical study designs of AURA extension and AURA2, safety data were pooled to provide increased sensitivity and precision towards the evaluation of the safety and tolerability profile of osimertinib in the proposed indication, compared to each individual trial using the same testing methodology. Data from AURA Phase I are presented as additional information towards the primary safety assessment provided by the Phase II pooled dataset.

The median total treatment duration was longer in the AURA extension study than in AURA2 due to an earlier recruitment period (8.2 months versus 7.4 months).

At the time of DCO for these clinical studies, 01 May 2015, 296 patients (72.0%) in the Phase II studies remained on study drug treatment (141 patients (70.1%) in AURA extension, and 155 patients [73.8%] in AURA2) so exposure will increase with longer follow up. The majority of common AEs (ie, rash, diarrhoea) occur within the first few weeks of treatment.

Adverse events

In the pooled analysis of the Phase II studies, the majority of patients (68.1%) experienced AEs of mild (Grade 1: 30.4%) to moderate (Grade 2: 37.7%) severity. The most commonly reported EGFR-associated AEs by Medical Dictionary for Regulatory Activities [MedDRA] were diarrhoea, rash, dry skin and paronychia; these AEs were mostly mild to moderate in severity.

In 86.4% (355/411) of patients, AEs were considered to be possibly causally related to osimertinib by the investigator.

Dose interruptions, dose reductions and treatment discontinuations with osimertinib 80 mg due to AEs were reported for 18.7%, 4.4%, and 5.6% of patients respectively; the mean and median relative dose intensity (RDI) was 97.7% and 100.0% respectively.

Table 4.41: Categories of adverse events: Number (%) of patients who had at least one adverse event in any category (FAS)

AE category	Number (%) of patients[a]		
	AURAext Osmertinib 80 mg	AURA2 Osmertinib 80 mg	Total Osmertinib 80 mg
Sample Size	(N=201)	(N=210)	(N=411)
Patients with any AE	198 (98.5)	203 (96.7)	401 (97.6)
CTCAE ≥grade 3 AEs	60 (29.9)	61 (29.0)	121 (29.4)
SAEs	41 (20.4)	42 (20.0)	83 (20.2)
Fatal SAEs	4 (2.0)	5 (2.4)	9 (2.2)
AEs leading to discontinuation	9 (4.5)	8 (3.8)	17 (4.1)
AEs leading to dose modification	40 (20.4)	41 (19.5)	81 (19.7)

[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.
CTCAE = Common Terminology Criteria for Adverse Events version 4.0; MedDRA version 17.1.

The most common AEs reported with osmertinib were consistent across AURA extension and AURA2 and in line with the expected profile of an EGFR TKI (Table 4.41). AEs of decreased appetite, fatigue, and nausea occurred at an incidence of >10% (Table 4.42) but were mostly mild in nature and non-serious.

Severe AEs (CTCAE ≥Grade 3) were reported for 29.4% (121/411) of patients and were considered by the investigator to be possibly causally related to osimertinib in 11.7% (48/411) of patients.

Table 4.42: Most common adverse events (those occurring in ≥10% of patients in the pooled dataset of AURA extension and AURA2 (Full analysis set)

Patients with an AE	AURA Ext N=201 n (%)		AURA2 N=210 n (%)		Total N=411 n (%)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3	Any Gr	Gr ≥3
AEs by preferred term, occurring in ≥10% of patients overall						
Diarrhea	93 (46.3)	2 (1.0)	81 (38.6)	2 (1.0)	174 (42.3)	4 (1.0)
Rashes and acnes (grouped terms)	81 (40.3)	1 (0.5)	87 (41.4)	1 (0.5)	170 (41.4)	2 (0.5)
Dry skin	43 (21.4)	0	52 (24.8)	0	95 (23.1)	0
Paronychia	40 (19.9)	0	32 (15.2)	0	72 (17.5)	0
Nausea	35 (17.4)	2 (1.0)	34 (16.2)	0	69 (16.8)	2 (0.5)
Decreased appetite	36 (17.9)	2 (1.0)	29 (13.8)	1 (0.5)	65 (15.8)	3 (0.7)
Constipation	30 (14.9)	1 (0.5)	32 (15.2)	1 (0.5)	62 (15.1)	1 (0.2)
Cough	32 (15.9)	0	25 (11.9)	1 (0.5)	57 (13.9)	1 (0.2)
Fatigue	25 (12.4)	2 (1.0)	32 (15.2)	0	57 (13.9)	2 (0.5)
Pruritus	25 (12.4)	0	32 (15.2)	0	57 (13.9)	0
Back pain	27 (13.4)	1 (0.5)	25 (11.9)	2 (1.0)	52 (12.7)	3 (0.7)
Stomatitis	27 (13.4)	0	22 (10.5)	0	49 (11.9)	0
Platelet count decreased	27 (13.4)	1 (0.5)	20 (9.5)	1 (0.5)	47 (11.4)	2 (0.5)
Headache	22 (10.9)	0	20 (9.5)	1 (0.5)	42 (10.2)	1 (0.2)

Gr, grade

4.12.2 IMPRESS safety assessment

The proportion of patients reporting any AE (95.5% gefitinib and 98.5% placebo), any AE of CTCAE grade 3 or higher (44.7% gefitinib and 41.7% placebo) and any AE leading to discontinuation of study drug (7.6% gefitinib and 9.8% placebo) was similar in both the gefitinib and placebo groups.

The proportion of patients reporting any SAE (including events with an outcome of death) was slightly higher in the gefitinib group (gefitinib 28.0% versus placebo 21.2%) and any SAE leading to discontinuation of study drug was slightly higher in the placebo group (gefitinib 3.0% versus placebo 8.3%). Adverse events leading to death were reported in 5 (3.8%) patients in the gefitinib group and 8 (6.1%) patients in the placebo group. No other significant AEs were identified for this study.

The most common AEs in both treatment groups were nausea (64.4% in the gefitinib group and 61.4% in the placebo group); decreased appetite (49.2% in the gefitinib group and

34.1% in the placebo group) and vomiting (41.7% in the gefitinib group and 33.3% in the placebo group) (Table 4.43).

Table 4.43: Adverse events; most common (frequency of >10%) (Safety analysis set)

MedDRA preferred term	Number (%) of patients[a]	
	Gefitinib 250 mg (N=132)	Placebo (N=132)
Patients with any AE	126 (95.5)	130 (98.5)
Nausea	85 (64.4)	81 (61.4)
Decreased appetite	65 (49.2)	45 (34.1)
Vomiting	55 (41.7)	44 (33.3)
Anaemia	42 (31.8)	33 (25.0)
Constipation	34 (25.8)	35 (26.5)
Diarrhoea	44 (33.3)	19 (14.4)
Neutropenia	29 (22.0)	28 (21.2)
Fatigue	28 (21.2)	23 (17.4)
Leucopenia	27 (20.5)	22 (16.7)
Asthenia	15 (11.4)	30 (22.7)
Neutrophil count decreased	16 (12.1)	22 (16.7)
Pyrexia	22 (16.7)	14 (10.6)
Cough	18 (13.6)	15 (11.4)
White blood cell count decreased	17 (12.9)	13 (9.8)
Headache	10 (7.6)	19 (14.4)
Dyspnoea	16 (12.1)	10 (7.6)
Back pain	11 (8.3)	14 (10.6)
Rash	14 (10.6)	11 (8.3)
Stomatitis	14 (10.6)	5 (3.8)

[a] Number (%) of patients with AEs, sorted in decreasing frequency of preferred term (sorted by total column).
Most common was defined as a total frequency of >10% (in any treatment group).
Included AEs with an onset date on or after the date of the first dose and up to and including 30 days following the date of last dose of study medication.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities (Version 17.0).
Source: Table 11.3.2.3.

The proportion of patients reporting any AE causally related to study drug only was higher in the gefitinib arm (47 [35.6%] patients) compared with placebo group (32 [24.2%] patients). The proportion of patients reporting any AE causally related to chemotherapy only was similar in the gefitinib group (109 [82.6%] patients) and the placebo group (111 [84.1%] patients). The proportion of patients reporting any AE causally related to both study drug and chemotherapy was the same in the gefitinib and placebo groups (30 [22.7%] patients).

Overall, 59 (44.7%) patients in the gefitinib group and 55 (41.7%) patients in the placebo group had at least 1 AE of CTCAE grade 3 or higher (Table 4.44). Overall, the incidence of most frequently reported AEs (occurring in >5% patients) of CTCAE grade 3 or higher was similar in the gefitinib and placebo groups and the majority of events were haematology-related events.

Table 4.44: Adverse events of CTCAE grade 3 or higher; most common (frequency of >5%) (Safety analysis set)

	Number (%) of patients[a]	
MedDRA preferred term	Gefitinib 250 mg (N=132)	Placebo (N=132)
Patients with AE of CTCAE grade 3 or higher	59 (44.7)	55 (41.7)
Neutrophil count decreased	8 (6.1)	10 (7.6)
Anaemia	11 (8.3)	5 (3.8)
Neutropenia	9 (6.8)	7 (5.3)
White blood cell count decreased	7 (5.3)	2 (1.5)

[a] Number (%) of patients with AEs of CTCAE grade 3 or higher, sorted in decreasing frequency of preferred term (sorted by total column).
Most common was defined as a total frequency of >5% (in any treatment group).
Included AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of study medication.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities (Version 17.0).
Source: Table 11.3.2.4.3.

The proportion of patients with dose interruptions in the gefitinib group (11 [8.3%] patients) was similar to the placebo group (9 [6.8%] patients) and the majority of these patients had 1 interruption (6 [4.5%] and 7 [5.3%] patients in the gefitinib and placebo groups, respectively). Dose interruptions in chemotherapy were reported in 5 (3.8%) patients in the gefitinib group and 2 (1.5%) patients in the placebo group; all of these patients had only 1 interruption.

Overall, 14 (10.6%) patients in the gefitinib group and 9 (6.8%) patients in the placebo group had their dose of chemotherapy reduced during the study; the majority of these patients experienced 1 dose reduction. Dose reductions in chemotherapy due to AEs were similar in both treatment groups (6 [4.5%] and 7 [5.3%] patients in the gefitinib and placebo arms, respectively) and dose reductions in chemotherapy due to other reasons were higher in the gefitinib group (9 [6.8%] patients) compared with the placebo group (2 [1.5%] patients).

4.13 Interpretation of clinical effectiveness and safety evidence

Following treatment with an EGFR TKI, current treatment options for patients with locally advanced or metastatic EGFR and T790M mutation positive NSCLC have a dire prognosis. At this time, there are no approved therapies that specifically target the acquired T790M TKI-resistance conferring mutation. Current treatment options are limited to cytotoxic chemotherapy, associated with modest efficacy and poor tolerability. Even with platinum based doublet chemotherapy, the current standard of care for 2nd line treatment following progression after an EGFR TKI, less than 30% of patients achieve an objective response, median progression free survival is less than 6 months and median survival is approximately 18 months. Clinical benefit associated with single agent chemotherapy as 3rd line treatment is even more limited with poor tolerability. While the available literature does not report the median duration of response for single-agent chemotherapy, the response rate is low (approximately 10%) and median PFS is between 2 and 3 months. Re-challenge with an EGFR TKI similarly offers low response rates and short median PFS.

Osimertinib has ben designed specifically to bind to the ATP binding pocket of the mutated EGF receptor regardless of the absence or presence of the T790M mutation. The chemical structure has also been selected to minimise unwanted side effects typically seen with oterh EGFR TKIs by ensuring that binding to EGF wild type receptors in the skin and on other epitheilial tissues as well as cross binding to insulin growth factor receptor are minised at therapeutic doses. The AURA clinical trial programme demonstrates that osimertinib has a superior clinical efficacy and tolerability compared to current standard of care; and represents a step change in the management of locally advanced or metastatic NSCLC by replacing cytotoxic chemotherapy as the treatment of choice for EGFR and T790M mutation positive patients post progression on an EGFR TKI. Osimertinib offers a targeted treatment option in an easy once-a-day oral formulation. It has demonstrated unprecendeted response rates (over 60%) and long progression free treatment period (median PFS of approximately 10 months) in an advanced NSCLC population. Importantly, similar response rates and PFS estimates are observed whether given as 2nd line therapy immediately after progression of 1st line EGFR TKI or as a 3rd line option after both EGFR TKI and chemotherapy. Data from over 400 patients demonstrate excellent tolerability and evidence of symptom alleviation during treatment and support a very positive benefit risk profile for this treatment over existing therapeutic options.

Strength of the current evidence base

Patients with locally advanced or metastatic EGFR and T790M mutation positive NSCLC represent a small patient population with significant unmet need. The AURA studies presented here provide compelling data on a total of 411 patients (201 from AURA extension and 210 from AURA2) treated with the licensed dose of osimertinib 80 mg tablet. The 411 patients in the pooled population consisted of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who had progressed on or after EGFR TKI therapy. Of the 411 patients, 129 (31.4%) received osimertinib as second-line therapy and 282 (68.6%) as ≥ third-line therapy. The 2 studies were conducted with rigorous monitoring and oversight according to current regulatory standards. Eligibility required central confirmation of the tumour T790M mutation-positive status from a biopsy sample taken after confirmation of disease progression on the most recent treatment regimen. In both studies, the primary efficacy endpoint variable was the ORR according to RECIST 1.1 by blinded independent central review (BICR) using the evaluable for response analysis set.

The use of a BICR to ensure a consistent and objective measure of RECIST response, the consistency of clinical outcome measures between the 2 studies and the magnitude of benefit compared indirectly with other studies in similar patients provides compelling evidence regarding the benefit of this treatment. The rigorous matched adjusted comparison provided provides further compelling evidence regarding the benefit of osimertinib compared directly to doublet platinum chemotherapy, the current standard of care in the UK. Having access to IPD of IMPRESS trial allows for a robust non-randomized comparison in the population referred to in the decision problem. Using the IPD the comparator cohort is well matched for baseline characteristics and importantly, the AURA and IMPRESS studies used similar monitoring, oversight (BICR), testing standards and trial assessment schedules that provide increased confidence in the validity of the matched indirect comparison. The treatment effect in the matched adjustment confirms the unadjusted side by side comparison of AURA and IMPRESS clinical trial results and indicates that the clinical effect of osimertinib previously unseen when compared with the large body of evidence in 2nd/3rd line setting of advanced NSCLC.

Limitations of the current evidence base

Consistent with the accelerated approval (EU PRIME designation) for osimertinib a number of limitations in the current evidence exist:

- Low data maturity in the AURA studies due to limited follow up. The first patient started treatment on 14 May 2014 and the last patient started treatment on 21

October 2014. The first patient in the AURA 2 study started treatment on 13 June 2014 and the last patient started treatment on 27 October 2014. The DCO for both studies for this report was 1 May 2015. Patients in the AURA extension and AURA2 studies are still being followed for clinical assessments with many remaining on treatment. More mature evidence of these event-driven trials will become available throughout the next 12 months. A mature overall survival analysis of IMPRESS is also expected to become available throughout 2016.

- While confidence regarding the analyses of the primary endpoints of ORR, secondary endpoints of PFS and safety/tolerability assessments can be considered high, caution should be exercised when interpreting the results of the OS analyses. The OS data are very immature at the time of analysis (Osimertinib 11.5% maturity and platinum doublet chemotherapy 29.4% maturity). Consequently in the matched adjusted comparison in both groups the KM risk set beyond 12 months is very limited (n <15 patients) leading to unstable estimates beyond this time point, especially for the estimation of medians.

- Lack of a formal randomized clinical trial. AURA3 a phase III, confirmatory RCT comparing osimertinib with platinum-based doublet chemotherapy (AURA3) is ongoing. This study is likely to report in the next 12 months but data are not expected to become available during the appraisal.

The indirect comparison and matched adjustment of AURA versus IMPRESS presented in Section 4.10 should be interpreted with caution in light of the heterogeneity of the data and imbalances in patient population. In additional, the retrospective analysis of IMPRESS for T790M by ctDNA BEAMing was not prespecified.

There is limited evidence available on the efficacy of treatment options other than platinum doublet chemotherapy in EGFRm+ patients previously treated with an EGFR TKI.

Table 4.45: End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	**For treatment-naïve patients:** • Current standard of care, consisting of treatment with 1st generation EGFR TKI's, reports median overall survival in the range of 20 months (21.6 months IPASS – gefitinib; 19.3 months EURTAC – erlotinib). The primary analysis of overall survival in the LUX-LUNG 7 trial (afatinib) is planned for 2016.

Criterion	Data available
	For patients who have been previously treated with an EGFR TKI: • The T790M subgroup of the control group of the IMPRESS trial, described in Section 4.11, provides the most relevant evidence for life expectancy in patients receiving platinum doublet chemotherapy as a second-line treatment. • The reported median overall survival in the control group of the IMPRESS trial was 17.2 months. In the subgroup of T790M mutation positive patients, the reported median OS was 15.7 months. • The other groups defined in the NICE decision problem (platinum ineligible / 3rd line) would be expected to have a worse life expectancy compared to a 2nd line population treated with platinum doublet chemotherapy. Treatment with single-agent chemotherapy in an EGFRm+ population reports a median overall survival in the range of 15 months.[88] **AstraZeneca therefore believes this criteria is met for the full population included of the licensed indication.**
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	• Currently, the overall survival data are immature. The OS data at the time of analysis was 11.5% maturity for osimertinib and 29.4% for the platinum doublet chemotherapy cohort. • The KM risk set beyond 12 months for both osimertinib and chemotherapy in the matched, adjusted comparison is very limited (n <15 patients) leading to unstable estimates beyond this time point, especially for the estimation of medians. However, given that 68.6% of patients received osimertinib as ≥ third-line therapy the median time to PFS (9.7 months) and the Kaplan-Meier estimate of the proportion of patients alive at 6 months (92.3%; 95% CI: 89.3, 94.5), and 9 months (85.3%; 95% CI:80.9, 88.7) is consistent with a meaningful improvement over current SOC. • When the most appropriate parametric curves are used the economic model produces a median overall survival of 27.7 months for osimertinib compared with 15.7 months for current NHS standard of care (platinum doublet chemotherapy) over a lifetime horizon, resulting in a median OS gain of 12 months (see Section 5.7) • There is currently no survival data available for people receiving osimertinib as a first-line treatment. However, it is unlikely that the overall survival benefit would be smaller than that observed in the relapsed setting. Therefore, comparing the estimated medians to the observed medians in IPASS and EURTAC studies referred to above, it is highly likely that osimertinib is associated with an extension to life of at least 3 months in the small of group of patients eligible first line. **AstraZeneca therefore believes this criteria is met for the full population included of the licensed indication.**

Criterion	Data available
The treatment is licensed or otherwise indicated for small patient populations	• As discussed in Section 3, AstraZeneca expects the number of eligible patients to be treated with osimertinib in the licensed indication to be approximately 300 patients per year. This is based on assumptions sourced from the National Lung Cancer Audit alongside published literature. **AstraZeneca therefore believes this criteria is met for the full population included of the licensed indication.**

4.14 Ongoing studies

The AURA extension and AURA2 studies are still ongoing and potential more mature evidence of these event-driven trials will become available throughout the next 12 months. In addition, interim results from the Phase III, open-label confirmatory RCT comparing osimertinib with platinum-based doublet chemotherapy (AURA3) is likely to report in the next 12 months and therefore are not expected to become available during the appraisal. [redacted]

4.15 De novo T790M population

As discussed in the introduction to this section, the population within scope of the original decision problem (December 2015) referred to patients with locally advanced or metastatic, EGFR and T790M mutation positive, NSCLC who had failed prior treatment with an EGFR TKI agent. This population reflected the participants of the AURA clinical programme (AURA extension, AURA2 and AURA3).

In December 2015, although no clinical studies have been conducted in this setting, the CHMP recommended a broad indication for osimertinib in patients with T790M mutation, including the first-line treatment in the presence of the mutation. In its recommendation, the CHMP expects osimertinib to be effective in first-line treatment in the very small group of patients in which this mutation is prevalent first line (Section 3). This led to the change in the expected marketing authorisation now including first-line treatment as well.

Due to the lack of available data, AstraZeneca is not in a position to present an economic evaluation for treatment within this setting. However, the prevalence of the T790M mutation first line and the limited available evidence are described in more detail below.

4.15.1 Incidence of T790M mutations first line

It is expected that the use of osimertinib in first line will be limited because of the low prevalence of this mutation in patients not previously exposed to EGFR TKI therapies (Section 3).

AstraZeneca therefore estimates that approximately 13 patients would be eligible for treatment with osimertinib as a first-line therapy across England and Wales every year.

4.15.2 Clinical efficacy of osimertinib in treatment-naïve patients

AURA Phase 1 Clinical Data

Within the AURA Phase 1 clinical trial, 5 treatment-naïve patients with a T790M mutation positive status received osimertinib as a first-line therapy.

Rationale by CHMP

In its recommendation, the CHMP provided the following rationale for including the treatment-naïve population within the now approved indication:

"From a mechanistic point of view, there is no foreseen impact of previous treatment on the expected benefit from treatment with osimertinib in patients with T790M mutation. Nevertheless, the consequence of moving the chemotherapy to 2nd-line is unknown in terms of life expectancy. As explained by Yun et al[89] substitution of threonine 790 with methionine (T790M) has been thought to cause resistance by steric interference with binding of TKIs, including gefitinib and erlotinib. Osimertinib is therefore considered the optimal treatment alternative over available EGFR TKI therapies in patients with advanced EGFR positive NSCLC in the presence of T790M, regardless of the line of therapy.

Taking as a reference the most recent study of chemotherapy in first line in EGFR mutation positive patients, the LUX-Lung 3 study (afatinib vs cisplatin plus pemetrexed chemotherapy) it can be observed that the ORR for chemotherapy was 23% and 44% (independent and investigator assessment respectively) with a median duration of response of 5.5 months. In the EURTAC study, the best overall response rate for chemotherapy was 10.5%, whereas in the IPASS study, ORR for chemotherapy was 47% (EGFR+). In all of them the use of TKIs offered better results in response rate and PFS. It is therefore reasonable to expect that osimertinib in first line treatment of patients with T790M mutation will have a higher activity than chemotherapy as well. But in the worst case scenario, where osimertinib had a similar efficacy than chemotherapy, the better safety profile of this drug would make it a more suitable treatment option."

Systematic literature review

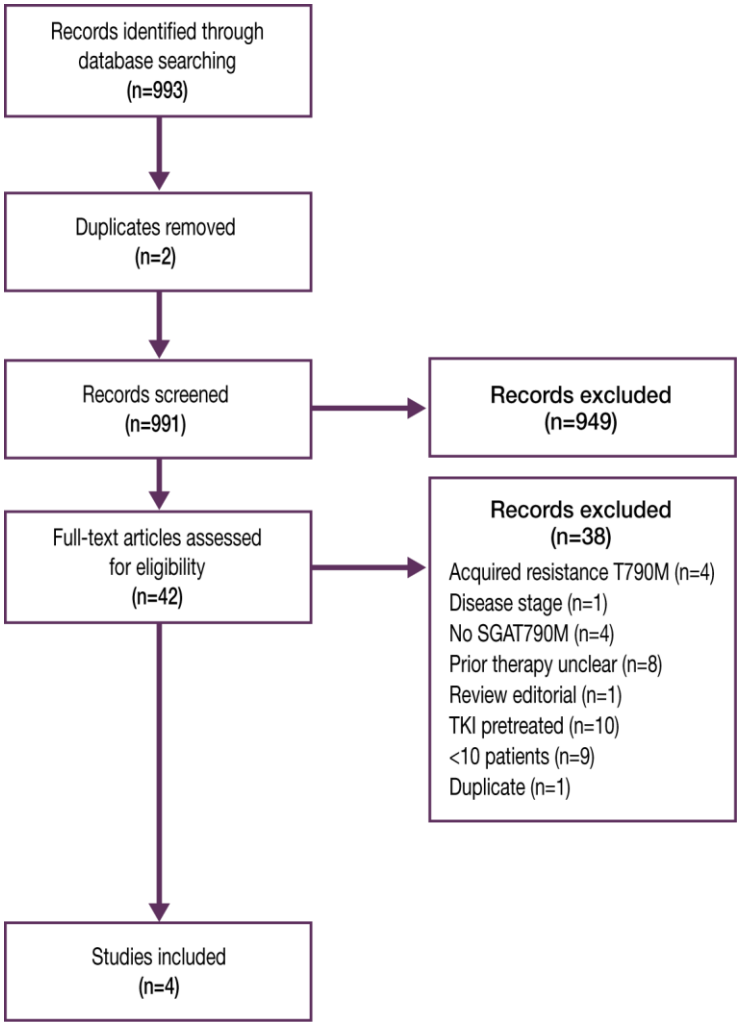
For the population previously treated with an EGFR TKI, a systematic review was conducted (Section 4.1). After going through the screening stages, in line with the exclusion criteria (Table 4.46) but focusing on T790M mutation positive status, none of the 19,948 retrieved studies were flagged as appropriate. In addition, an additional literature search was conducted, in accordance to the broadened UK license for osimertinib, relevant to treatment naïve, locally advanced or metastatic, EGFR and T790M mutation positive NSCLC patients. 993 articles were obtained of which two were excluded as duplicates (Figure 4.20). Finally, after applying pre-specified eligibility criteria (Table 4.46:), four studies were included for qualitative analysis (three full publications and one abstract) (Figure 4.20).

Table 4.46: Eligibility criteria for the *de novo* population systematic review

	Criteria	**Rationale**
Inclusion criteria	Population Age: adults (≥18 years) Sex: any Race: any Disease: advanced or metastatic NSCLC patients with *de novo* T790M mutation Line of therapy: all patients without any prior EGFR TKI	The patient population has been restricted to match that stated in the NICE decision problem for osimertinib in the treatment of previously EGFR TKI untreated advanced or metastatic, *De novo* T790M mutation non-small cell lung cancer.
	Intervention Osimertinib (AZD9291)	Intervention was defined by the NICE decision problem for the treatment of previously EGFR TKI untreated advanced or metastatic, *De novo* T790M mutation non-small cell lung cancer.
	Comparators* No restriction	All comparators defined by the NICE decision problem for treatment with osimertinib previously EGFR TKI untreated locally advanced or metastatic, *De novo* T790M mutation non-small cell lung cancer were included in the search. All comparators were included in the systematic review to retrieve complete evidence
	Study design All randomized controlled clinical trials (RCTs irrespective of blinding status) Single arm trials Non-randomized controlled trials Observational studies(retrospective analysis, prospective studies, cohort studies, case control studies, longitudinal studies)	RCTs are the gold standard of clinical evidence, minimising the risk of confounding and allowing the comparison of the relative efficacy of interventions. Considering the limited RCT evidence, additional study designs such as single-arm trials, non-randomized trials and observational studies were also included in this review.
	Language Only studies with the full-text published in English language were included	The restriction would not limit results substantially due to data availability in English language.

	Criteria	Rationale
	Publication timeframe for literature searches Database inception to 04 January 2016 Publication timeframe for conference searching ASCO: 2012, 2013, 2014 and 2015 ESMO: 2012, 2013, 2014 and 2015 WCLC: 2013 and 2015	Studies that are presented at conferences are usually published in journals within 3 years.
Exclusion criteria	Excluded population Patients without a locally advanced or metastatic NSCLC Patients with a locally advanced or metastatic NSCLC where T790M mutation status was negative or unclear Children or adolescents (< 18 years of age) Mixed patient population studies where subgroup data for adult patients are not reported EGFR TKI treated patients Studies enrolling patients *De novo* and acquired T790M mutation with no subgroup data for patients with *De novo* T790M	This study population was not relevant to the decision problem.
	Excluded interventions/comparators Studies not assessing any of the included interventions Studies where interventions are administered for the treatment of AEs Studies investigating the role of radiotherapy, chemo-radiotherapy or surgery Studies assessing interventions used to control the symptoms of the disease such as erythropoietin to treat anaemia, antibiotics to treat infections and various types of pain medication Studies assessing adjuvant or neoadjuvant therapy	These interventions are not relevant to the decision problem.
	Excluded study designs Case studies and case reports Cross-sectional studies Review, letters to the editors and editorials	The design of such studies was not relevant to the decision problem.
Further selection of key comparators	Study comparators were further restricted to include studies assessing: Platinum doublet therapy (pemetrexed plus carboplatin or cisplatin) Single agent chemotherapy including gemcitabine, paclitaxel, vinorelbine (for those for whom treatment with a platinum therapy is not appropriate) Docetaxel with or without nintedanib Single agent chemotherapy including gemcitabine, paclitaxel, vinorelbine (for those for whom treatment with docetaxel is not appropriate)	Comparators were restricted in line with the NICE decision problem and the anticipated new marketing authorisation for osimertinib

Figure 4.20: PRISMA flow diagram of studies focusing on the *de novo* population identified in the systematic literature review



A study by Costa et al based on the EURTAC trial (NCT00446225)[90] was one of the studies that met the inclusion criteria for the broadened license population. EURTAC is a randomized, Phase III trial comparing erlotinib to chemotherapy in treatment naïve, advanced NSCLC, EGFR mutation positive patients. The aim of this study was to evaluate the impact of pre-treatment EGFR T790M in 95 EURTAC trial participants with available tumour specimens. The mutation was detected in 62 (65.25%) out of the 95 subjects for which PFS was 9.7 months (95% CI 6.9–21.9) in the erlotinib vs 6 months (95%CI 4.1–7.7) in the chemotherapy arm. No T790M mutation positive patients reached complete response while partial response was reached by 16 (47.06%) vs four (14.29%) in the erlotinib and chemotherapy group respectively.

The study by Lee *et al*[91] was also identified as relevant, aiming to search for clinical markers associated with sporadic pre-treatment of EGFR T790M mutations. Pre-treatment tumour

samples (n=124) from the National Cancer Hospital of Korea (Goyang) were collected from EGFR mutation positive patients treated between January 2009 and August 2011. The T790M mutation was detected in 35 (25%) patients, out of which those having an EGFR TKI as first-line treatment presented a TTP equal to 6 months. The same subgroup reached a median OS of 35.9 months. Similarly, Rosell R *et al*[92] studied 129 erlotinib-treated, advanced NSCLC, EGFR mutation positive patients in order to verify that PFS can be influenced both by the EGFR T790M status and by components of DNA repair pathways. The T790M mutation was detected in 45 (35%) out of the 129 patients of which 21 received first-line erlotinib and presented a PFS of 8 (95% CI 3.5-12.5) months.

LUX-lung 3 is a Phase III, open label, randomized trial comparing first-line afatinib with cisplatin plus pemetrexed chemotherapy in patients with advanced lung adenocarcinoma and proven EGFR mutations. Yang JCH *et al*, 2015[93] was an abstract of the trial focusing on results of 37 patients with uncommon EGFR mutations. T790M mutations were present in 13 (35%) of the total population of which 11 were treated with afatinib and presented a PFS within the range of 0.3–11 months. Partial response was observed in one patient, stable disease in seven and progressive disease in three afatinib-treated patients. Results for the cisplatin/pemetrexed arm (n=2) showed PFS ranged between 2.6–6.7 months, with one patient achieving partial response and one with stable disease.

5 Cost-effectiveness

- A *de novo* cost-utility analysis was undertaken to assess the cost-effectiveness of osimertinib patients with locally advanced or metastatic EGFR and T790M mutation positive NSCLC who have progressed on or after EGFR TKI therapy
- The economic model used a standard three health state (progression-free, progressed disease or death) cohort-based partitioned survival approach to determine the proportion of patients in each health state. This model structure has been routinely used in previous NICE submissions in advanced NSCLC and oncology.
- A time horizon of 15 years (equivalent to lifetime) was applied to ensure that of all relevant costs and outcomes were captured, a discount rate of 3.5% was applied to costs and outcomes and an NHS and PSS perspective was used. Therefore, the economic analysis was consistent with the NICE reference case
- In line with the NICE decision problem, the base case analysis compares osimertinib with platinum doublet chemotherapy in patients who have received previous treatment with an EGFR TKI
- As the osimertinib clinical efficacy data were based on a pooled analysis of two single arm studies (AURAext and AURA2), robust comparative efficacy data for the platinum doublet chemotherapy arm were obtained from a trial of EGFR mutation positive patients who had received previous EGFR TKI therapy (IMPRESS)
- Clinical efficacy, resource use, costs and health state utilities were estimated based on information from the AURAext/2 studies and the IMPRESS trial, previous NICE technology appraisals, published literature and clinical experts. Health-state utilities in the model were calculated from EQ-5D collected in AURA2
- In the base case analysis, OS was modelled based on the Weibull parametric distribution and PFS on the Gompertz distribution as these provide the most clinically plausible fit to the observed data currently available from the pooled AURAext/2 data and IMPRESS
- The base case ICER was [redacted] per QALY gained for osimertinib compared with platinum doublet chemotherapy
- Sensitivity analyses suggest that results of the model are most sensitive to the parametric curve used to extrapolate the currently available OS data. However, when compared with previously published studies of targeted therapies for advanced NSCLC, the modelled survival estimates do not appear to be biased in favour of osimertinib

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

A systematic literature review was conducted to identify evidence to support the cost-effectiveness model for osimertinib which focuses on patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC who have progressed on or after EGFR TKI therapy. A single review was carried out to identify studies reporting economic evaluations as well as resource use and costs. The primary objective of the economic review was to assess the cost-effectiveness associated with pharmacological interventions for the treatment of patients with advanced/metastatic NSCLC harbouring EGFR mutations and/or T790M mutations with acquired resistance of an EGFR TKI.

However, due to lack of data for EGFR T790M mutation positive NSCLC patients, the scope of the review was extended to include the following patient populations with advanced/metastatic NSCLC:

a) Patients harbouring EGFR and/or T790M mutations following prior a therapy (not restricted to TKI)

b) Patients with unknown EGFR and T790M mutation status following treatment failure with an EGFR TKI

The literature was searched in biomedical electronic literature databases recommended by HTA agencies including NICE.[94,95] MEDLINE® In-process was searched to ensure that non-indexed citations were retrieved. The full list of databases that were searched is presented in Table 5.1.

Table 5.1: Data sources for the economic systematic review

1. Search strategy component	2. Sources	3. Date limits
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies	MEDLINE® MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL) Cochrane National Health Service Economic Evaluation Database (NHS EED) EconLit®	01 JAN 2004 to 21 JAN 2016
Conference proceedings	HTA International	2012–2016
	International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	
	European Society for Medical Oncology	
	American Society of Clinical Oncology	

The search strategy is presented separately in Appendix A2.1. During the abstract and title screening, articles passed on to full text revision according to predefined inclusion/exclusion criteria. All citations meeting the inclusion criteria after the second stage of full text screening were extracted. The screened and extracted articles were independently verified and validated by a second reviewer.

The inclusion/exclusion criteria for the systematic review are summarised in Table 5.2. The range of comparators included in the search is broader than the scope of the decision problem, to enable a complete review of the available literature. Within the scope of this appraisal, only UK-specific comparators are discussed. The final list of included studies is presented in Table 5.3.

Table 5.2: Inclusion/exclusion criteria for the economic review

	Economic evaluations	Rationale
Patient population (P)	Age: adults aged ≥18 years Gender: any Race: any Disease: patients with advanced/metastatic NSCLC who are EGFR and/or T790M mutant and who have failed at least one EGFR TKI ± other anticancer regimens	The patient population of interest to the review comprised of adult patients with advanced/metastatic NSCLC of any race and gender because NSCLC can occur at any age but is most common in adults aged between 40 years and 70 years.[96] Therefore, studies focusing solely on children and adolescents were not included in this review
Intervention (I)	osimertinib	This is the intervention of interest within the decision problem
Comparator (C)	Any pharmacological intervention Placebo Best supportive care	The searches for economic review were not restricted to any interventions in order to collate all available published economic evidence in patients with advanced/metastatic NSCLC harbouring EGFR/T790M mutations following prior therapy
Outcome (O)	Studies were not be excluded based on the reported outcomes	The aim of the review was to identify relevant economic evaluations that also reported costs
Study design 1 (S1)*	All economic evaluation studies based on models Cost-effectiveness analysis Cost-utility analysis Cost-minimisation analysis Cost-benefit analyses Budget impact models Resource use studies Cost/economic burden of illness	The aim of the review was to identify relevant economic evaluations that also reported costs
Study design 2 (S2)*	Randomized controlled trials Database studies Prospective observational studies Retrospective observational studies	The aim of the review was to identify relevant studies that reported quality of life data
Line of therapy	Second- or further-line of therapy	This is the relevant line of treatment
Search timeframe	2004 to 2016	This period was deemed relevant to reflect models that are representative of the current NSCLC landscape
Language	Only studies with the full-text published in English language were included	It is expected that the majority of evidence in this disease area will be available in the English language
Exclusion criteria	Reviews, letter to the editors, and editorials Case studies/case series Case reports Cross-sectional studies	The design of such studies was not relevant to the decision problem These are generally smaller studies with higher risk of bias, hence excluded
	Studies investigating the role of radiotherapy, chemo-radiotherapy, hormonal therapy, or surgery only were	Only pharmacological interventions (chemotherapies and targeted therapies) were considered as relevant comparators

	Economic evaluations	Rationale
	excluded Studies investigating the role of maintenance/consolidation therapy after surgery were also excluded Adjuvant or neo-adjuvant therapy were excluded No subgroup analysis	for osimertinib Studies that included children and adults and did not provide subgroup analysis for the adult populations Studies which enrol a mixed population of stage I, II, IIIa, and stage IIIb/IV NSCLC and did not provide subgroup analysis for the disease stage IIIb/IV

5.1.2 Description of identified studies

The literature search identified 2,330 articles for abstract screening of which 16 were duplicates and were excluded. Following the first review of the abstracts, 24 potentially relevant references were identified and full-text reviewed for more detailed evaluation (Figure 5.1).

Following detailed examination of the full-text publications, only one study published as a conference proceeding was conducted in the primary population of interest. In order to explore more evidence relevant to the review question, the primary inclusion criteria was relaxed to include the following patient populations with locally advanced or metastatic NSCLC:

a) One study included adult EGFRm+ patients with advanced/metastatic NSCLC who had failed at least one EGFR TKI[97]

b) Patients harbouring EGFR mutations following prior therapy (not restricted to EGFR TKI): two studies[98,99]

c) Patients with unknown EGFR and T790M mutation status following treatment failure with an EGFR TKI: two studies[100,101]

Data mining across different HTA sources retrieved no substantial evidence in the primary population of interest to the review. Therefore, a final set of five studies relevant to the economic review objective were included and extracted. Further details are provided in Table 5.3.

A quality assessment for each of the cost-effectiveness studies is presented in Appendix 2.2.

Figure 5.1: Identification of economic evaluation identified in the systematic literature review

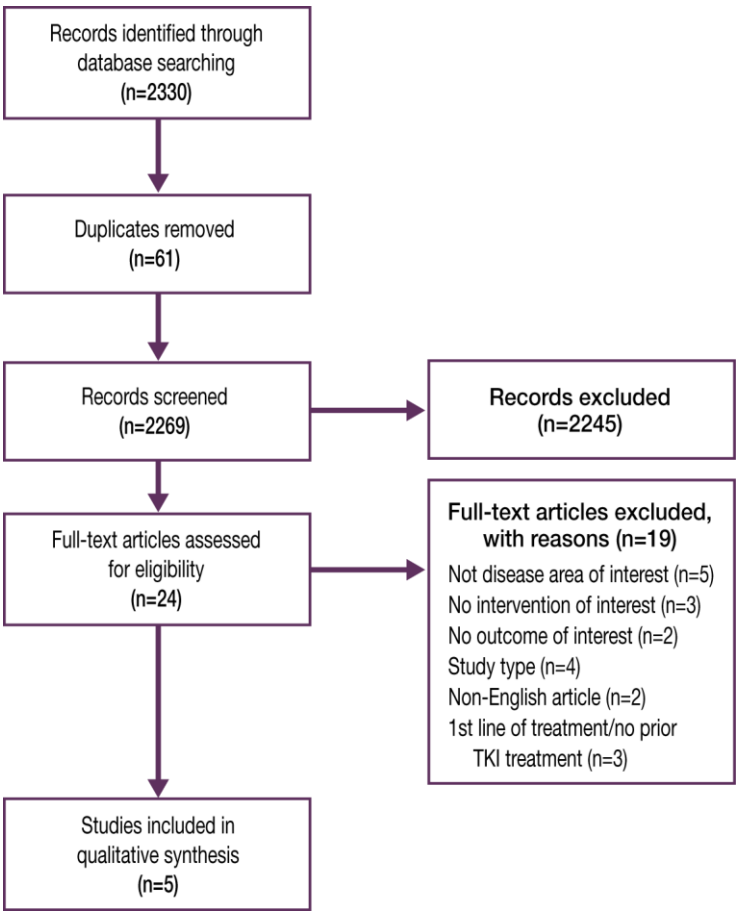


Table 5.3: Summary of published cost-effectiveness studies

Author	Mean age ±SD in years	Disease stage	Line of therapy	Treatments being compared	Evaluation type, cost year	Perspective	Model design	QALYs	Total costs	ICER
Carlson 2009	60 years	Advanced (stage IIIB/IV)	Second-line and further	EGFR protein expression or gene copy number testing vs. standard care with erlotinib	CUA Cost year: 2006	US societal perspective	Decision analytic model	–		–
Horgan 2011	NR	Advanced or metastatic	Second-line and further	Gefitinib vs docetaxel	Cost consequence analysis Cost year: 2008	The Canadian public healthcare system perspective	Markov model	–	Total costs: Gefitinib vs Docetaxel ($13,407 vs $8246) Net incremental costs: $5161	–
Chouaid 2013	78.2 ± 4.4	Stage IIIB/ IV	Second-line	First-line erlotinib followed by chemotherapy on progression vs the reverse strategy	CEA Cost year: 2011	Third-party payer perspective	NR	First-line erlotinib followed by chemotherapy on progression vs reverse strategy: 0.33 +/- 0.33 vs 0.35 +/- 0.34	First-line erlotinib followed by chemotherapy on progression vs reverse strategy: €15,233 ± 15,310 vs €15,363 ± 11,346	First-line erlotinib followed by chemotherapy on progression vs reverse strategy: €47,381/QALY vs €44,350/QALY
Chouaid 2012	Mean age = 76 ± 5 years	Stage IIIb/IV	Second-line	First-line erlotinib followed by chemotherapy on progression vs the reverse strategy	CEA Cost year: 2011	The French healthcare system	Monte Carlo simulation	First-line erlotinib followed by chemotherapy on progression vs reverse strategy: 0.51 ± 0.44 vs 0.52 ± 0.41	First-line erlotinib followed by chemotherapy on progression vs reverse strategy:	Reverse strategy/ erlotinib followed by chemotherapy: €395,400/ QALY

Author	Mean age ±SD in years	Disease stage	Line of therapy	Treatments being compared	Evaluation type, cost year	Perspective	Model design	QALYs	Total costs	ICER
									€27,734 ± 19,801 vs €31,688 ± 22,693	
Patel 2014	NR	Stage III/IV	Second-line	Doublet chemotherapy at first-line therapy followed either by erlotinib or docetaxel; erlotinib at first-line followed by second-line docetaxel*	CEA Cost year: NR	UK NHS	Markov model	–	Current scenario vs revised scenario: £17,560,205 vs £19,433,873 Incremental costs: £1,873,667	–

*The study compared two scenarios: a current scenario (in which a cohort of NSCLC patients received doublet chemotherapy at first-line therapy, followed either by erlotinib or docetaxel at second-line) and a revised scenario (in which all EGFR TK mutation positive patients received erlotinib at first-line followed by second-line docetaxel, and all mutation negative patients received doublet chemotherapy followed by either docetaxel or erlotinib)
CEA Cost-Effectiveness Analysis; CU = Cost-Utility; ICER = Incremental Cost-effectiveness Ratio; NHS = National Health Service; NSCLC = Non-Small Cell Lung Cancer; NR = Not Reported; QALY = Quality-Adjusted Life Year

5.2 De novo analysis

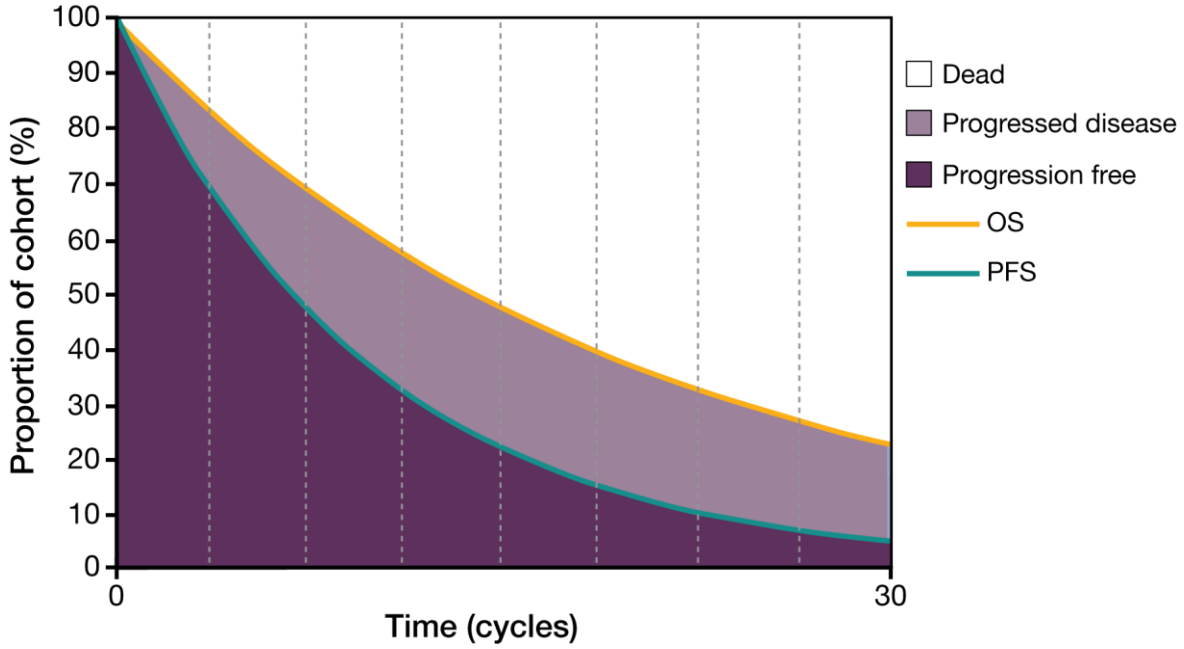
5.2.1 Patient population

The economic evaluation considers patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC who have progressed on or after EGFR TKI therapy, which is consistent with the patient population included in the AURAext/2 trials used to support the EU marketing authorisation for osimertinib. Although the EU label has been expanded to include patients with locally advanced or metastatic EGFR and T790M mutation positive NSCLC who have not received prior treatment with an EGFR TKI, the cost-effectiveness analysis does not consider this patient population due to the small number of treatment-naïve patients available for analysis from AURAext/2 (see Section 4.15).

5.2.2 Model structure

A cohort-based partitioned survival model including three health states – progression-free (PF), progressed disease (PD) and death – was developed in Microsoft Excel. Within the partitioned survival model, the state occupancy of the simulated cohort is estimated by extrapolating the cumulative survival probability of PFS and OS to a lifetime horizon, and using the curves to estimate the proportion who are alive and have not progressed (% on PFS curve), those who have died (1 - % on OS curve) and those who are alive but have experienced disease progression (% on OS curve minus % on PFS curve), at each time point of the simulation (see Figure 5.2).

Figure 5.2: Partitioned survival analysis model structure



Within the framework of the partitioned survival model, it is assumed that the health states (progression-free, progressed disease and death) represent the key sequence of events that patients may experience over the course of their treatment for NSCLC (progression of disease and death), with the additional assumption that these events are progressive, mutually exclusive, and irreversible (e.g. a patient who experiences disease progression and enters the progressed disease state of the model, cannot recover their progression-free status, and return to the progression-free state). This assumption is consistent with the definitions of PFS and OS from clinical trials, and the approaches used in previous NICE HTA submissions in aNSCLC and other advanced cancers.

In line with the NICE reference case, the model adopts an NHS/PSS perspective and includes the resource use and costs associated with disease management, treatment acquisition, administration and adverse events as well as T790M mutation testing. In order to fully capture the benefits of osimertinib and comparator treatments, a lifetime time horizon is used in the base case analysis. The timeframe of the model is dependent on the OS data and stops when <1% of the population remain alive. As a result, the maximum length of the time horizon in the model is 15 years.

Costs and health-state utility values are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. The cycle length is 1 week to facilitate comparability with other treatments as a 1-week cycle length is the single common denominator of treatment frequency for most chemotherapy regimens. The model

calculates mid-cycle estimates in each health state by taking the average between the number of patients present at the beginning of the cycle and the number of patients at the end of the cycle. This prevents underestimation of costs and QALYs. In line with the NICE reference case, an annual discount rate of 3.5% is applied to costs and outcomes (Table 5.4).

Table 5.4: Features of the *de novo* analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (maximum 15 years)	NICE reference case[102]
Cycle length	1 week	Provides better accuracy and more exact estimates compared to longer cycle length
Starting age	62.17 years	Based on average age of patients in AURAext/2
Half-cycle correction	Yes	Mitigates bias due to cycle length
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case
Discount rate of 3.5% for utilities and costs	Yes	NICE reference case
Perspective (NHS/PSS)	Yes	NICE reference case
PSS, personal social services; QALYs, quality-adjusted life years		

5.2.3 Intervention technology and comparators

For the base case analysis the model is populated for ≥second-line treatment patients following treatment with an EGFR TKI from the AURA ext/2 programme. The model is also populated for the following subgroups from the AURA programme that are investigated as part of additional subgroup analyses:

- Second-line (only) patients after treatment with an EGFR TKI
- ≥Third-line patients after treatment with both an EGFR TKI and chemotherapy

In the base case analysis, osimertinib is compared with platinum doublet chemotherapy (pemetrexed + cisplatin) in line with the decision problem. In subgroup analyses osimertinib is compared with:

- Platinum doublet chemotherapy in patients who have received previous treatment with an EGFR TKI (second-line only)

- Single-agent chemotherapy (docetaxel) in patients who have received previous treatment with an EGFR TKI and in whom platinum doublet therapy is not appropriate (second-line only)
- Single-agent chemotherapy (docetaxel) in patients who have received previous treatment with both an EGFR TKI and chemotherapy (≥third-line)

As discussed in the decision problem (see Section 1.1), it was not considered appropriate or feasible to compare the cost effectiveness of osimertinib with nivolumab, ramucirumab or best supportive care in patients who have received previous treatment with both an EGFR TKI and chemotherapy.

5.3 Clinical parameters and variables

5.3.1 Overview of the clinical data

As summarised in Section 1.3, the clinical efficacy and safety of osimertinib as a treatment for NSCLC is currently being investigated through the AURA clinical programme which comprises three key studies assessing its efficacy and safety in patients with advanced or metastatic EGFR T790M NSCLC. Patient-level data were obtained from one additional trial by AstraZeneca (IMPRESS), which provides robust comparative efficacy data for the platinum doublet chemotherapy comparator. In addition, a systematic literature review was carried out to identify published survival data for the other comparators. In cases where individual patient data (IPD) were missing, the published KM curves were digitised and re-estimated using a method suggested by Guyot *et al*.[103]

5.3.2 Published literature (single-agent chemotherapies)

As described in Section 4.1, the systematic literature review identified eight studies (in addition to AURAext/2 and IMPRESS) that met the inclusion criteria (see Table 5.5) for possible comparator treatments in locally advanced or metastatic NSCLC patients who have progressed on prior EGFR TKI treatment. Since IPD is available to enable a comparison with platinum doublet chemotherapy (from the IMPRESS study), only studies including single-agent chemotherapies in second-line only and ≥third-line settings were of interest. The first filter, therefore, excluded all studies that did not include a single-agent chemotherapy arm [Tseng 2014; Miyauchi 2015].[104,105] Of the six studies that included single-agent chemotherapy,[73,88,106,107] one study did not include PFS or OS outcomes [Kim 2015],[108] one study did not include PFS [Wu 2010],[106] one study did not provide OS data [Kasahara 2015],[72] one study did not provide OS data for the EGFRm+ population [Halmos 2015],[73] three studies did not present the complete KM data needed to adequately re-estimate the

IPD of high quality [Wu 2010; Zhou 2014; Halmos 2015],[73,106,107] and one only included ≥second-line patients [Halmos 2015].[73] The study by Zhou *et al* was considered for inclusion for the ≥third-line setting, as its only immediate drawback was the lack of complete KM data, However, due to its retrospective study design, it was believed that the time from when progression free or overall survival was measured in the study had a significant impact on the survival estimates, and therefore this study was not considered further as a relevant alternative to the prospective, randomized trials.

Therefore, only one study[88] was included in the analysis for the second-line only setting. In addition, one additional study was identified[109] outside of the systematic literature review that included single-agent chemotherapy in a ≥third-line setting with complete KM data. The reason the study was not included in the original systematic literature review was because no central EGFR mutation testing was performed, instead a clinically enriched EGFR inclusion criterion was used. This was considered to be a suitable proxy and therefore included in the subgroup analysis for a ≥third-line setting.

Table 5.5: Summary of clinical trials relevant for inclusion in the economic model

Publication	Included?	Rationale
Tseng 2014	No	- Only doublet chemotherapy
Miyauchi 2015	No	- Only doublet chemotherapy
Park 2015	Yes	+ Second-line + Single-agent chemotherapy + Complete KM data to re-estimate IPD
Halmos 2015	No	- ≥Second-line + Singlet chemotherapy - Low-quality KM data to adequately re-estimate IPD - OS data only available for all-comers (only 70% EGFRm)
Zhou 2014	No	+ ≥Third-line + Single-agent chemotherapy - Low quality KM data to adequately re-estimate IPD - Retrospective study design
Kasahara 2015	No	+ ≥Third-line + Single-agent chemotherapy - No overall survival
Wu 2010	No	+ Single-agent chemotherapy - No overall survival - Low-quality KM data to adequately re-estimate IPD
Kim 2013	No	+ Single-agent chemotherapy - No PFS/OS reported
Schuler 2015*	Yes	+ ≥Third-line + Singlet chemotherapy + Complete KM data to re-estimate IPD - No central EGFR testing

* Not identified in clinical systematic review

Park 2015

The study by Park *et al* was a retrospective cohort study of 314 patients with EGFRM positive NSCLC who had received prior treatment with an EGFR TKI.[88] It included a subgroup of 37 patients receiving pemetrexed, compared to 46 patients receiving non-pemetrexed-based platinum doublet chemotherapy. The platinum doublet chemotherapy arm is not comparable to the IMPRESS placebo arm because the patients in the IMPRESS trial received pemetrexed plus cisplatin, and thus the published hazard ratios cannot be included without making an assumption that these treatments are equivalent. A notable difference between AURA ext/2 and Park *et al* is that the latter is not specific to T790M patients. However, the study was included to be used in the scenario analysis to inform the comparison of osimertinib with single-agent chemotherapy in patients who have received

previous treatment with an EGFR TKI and in whom platinum doublet therapy is not appropriate in a second-line only setting.

Schuler 2015

The study by Schuler *et al* was based on the LUX-Lung 5 trial, which included 202 patients who had failed treatment with at least one EGFR TKI and chemotherapy.[109] Patients were not centrally tested for EGFR mutations prior to randomization, but had to achieve ≥12 weeks of clinical benefit on afatinib monotherapy to be included, after which they were randomized to afatinib plus paclitaxel or investigator's choice of single-agent chemotherapy. A notable difference between AURA ext/2 and Schuler *et al* is that the latter study was not specific to T790M mutation positive patients and documentation of EGFR mutation status was not mandatory prior to study entry. However, a significant proportion (61.8%) of patients fulfilled the higher clinical enrichment criteria (defined as complete or partial response to prior EGFR TKI or ≥48 weeks' treatment with prior EGFR TKI). The single-agent chemotherapy arm of the study consisted of 68 patients and was used in a subgroup analysis to inform the comparison of osimertinib with single-agent chemotherapy in the ≥third-line setting.

5.3.3 Patient characteristics of included studies

Table 5.6 summarises the baseline patient characteristics in the data used to assess the clinical efficacy of osimertinib, platinum doublet chemotherapy, and pemetrexed/docetaxel in the economic evaluation. Patients who participated in the IMPRESS study and were based in France were excluded (n=5) from the analysis dataset due to patient consent at the time of analysis not covering use of the IPD outside of the study agreed within the patient consent form. Subsequent information from a formally translated ICF in the meantime has informed us that French patients could be included for analysis although it is anticipated that including these additional 5 patients (including one with confirmed T790M mutation positive status) will have a minor impact on the results obtained from the IMPRESS study. Both the all-comer (n=127) and T790M mutation positive (n=60) populations from the IMPRESS trial are presented. The proportion of males is slightly higher in the study by Schuler *et al*. The population in Park *et al* is slightly older, with relatively more females and a larger proportion of higher ECOG performance scores. The AURA pooled population has a higher proportion of patient with brain metastasis at baseline. The IMPRESS all-comer population has a younger population and a lower proportion of patients with brain metastases at baseline compared with AURAext/2. The main difference in the study by Schuler *et al* is that no central EGFR testing was performed.

Table 5.6: Summary of patient characteristics of studies included in the economic evaluation

Demographic characteristic		AURA pooled[74,75]			IMPRESS all-comers	IMPRESS T790M mutation positive	Park 2015[88]	Schuler 2015[109]
Indication		Second-line	≥Third-line	≥Second-line	Second-line	Second-line	Second-line	≥Third-line
Treatment		Osimertinib 80 mg	Osimertinib 80 mg	Osimertinib 80 mg	Placebo (platinum doublet chemotherapy)	Placebo (platinum doublet chemotherapy)	Pemetrexed	Chemotherapy*
Number of patients		129	282	411	127	60	37	68
Age (years)	Mean (SD)	63.3 (11.0), 40.3-88.5	61.7 (10.6), 36-84	62.2 (10.76), 35-89	57 (11.28)	56 (10.28)	NR (NR)	NR
	Median (min-max)	62.8 (NR)	63.3 (NR)	63 (NR)	58 (35-79)	55 (38-79)	67 (45-85)	60.5
	% ≥65 years	61 (47.3%)	156 (55.3%)	187 (45.5%)	32 (25.2%)	10 (16.7%)	NR	NR
Sex	Male	44 (34.1%)	88 (31.2%)	132 (32.1%)	48 (37.8%)	23 (38.3%)	9 (24.3%)	34 (50%)
	Female	85 (65.9%)	194 (68.8%)	279 (67.9%)	79 (62.2%)	37 (61.7%)	28 (75.7%)	34 (50%)
Smoking	Never	93 (72.1%)	201 (71.3%)	284 (69.1%)	86 (67.7%)	39 (65.0%)	NR	37 (54.4%)
	Ever	36 (27.9%)	74 (28.7%)	114 (27.7%)	NR	NR	NR	31 (45.6%)
	Current	0 (0.0%)	7 (2.5%)	7 (1.7%)	NR	NR	6 (16.2%)	21 (30.9%)
EGFR mutation	Exon 19 deletion	89 (69.0%)	190 (67.4%)	279 (67.9%)	83 (65.4%)	43 (71.7%)	25 (67.6%)	NR**
	L858R in exon 21	36 (27.9%)	82 (29.1%)	118 (28.7%)	40 (31.5%)	17 (28.3%)	12 (32.4%)	NR**
	Other	4 (3.1%)	10 (3.5%)	14 (3.4%)	NR	NR	0 (0%)	NR**
ECOG/ WHO performance system	0	54 (41.9%)	98 (34.8%)	152 (37.0%)	49 (38.6%)	21 (35.0%)	NR	14 (20.6%)
	1	75 (58.1%)	183 (64.9%)	258 (62.8%)	78 (61.4%)	39 (65.0%)	NR	46 67.6%)
	2	0 (0%)	1 (0.3%)	1 (0.2%)	0 (0%)	0 (0%)	NR	8 (11.8%)
	3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NR	NR

Demographic characteristic		AURA pooled[74,75]			IMPRESS all-comers	IMPRESS T790M mutation positive	Park 2015[88]	Schuler 2015[109]
	4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NR	NR
	0-1	129 (100%)	281 (99.7%)	410 (99.8%)	127 (100%)	60 (100%)	32 (86.5%)	NR
	2-4	0 (0%)	1 (0.3%)	1 (0.2%)	0 (0%)	0 (0%)	5 (13.5%)	NR
Metastatic at baseline		123 (95.4%)	272 (96.5%)	395 (96.1%)	114 (89.8%)	55 (91.7%)	NR	NR
Brain metastatic at baseline		40 (31.0%)	126 (44.7%)	166 (40.4%)	30 (23.6%)	21 (35.0%)	11 (29.7%)	NR

*Paclitaxel (35.0%), docetaxel (15.0%), pemetrexed (26.7%), vinorelbine (8.3%), gemcitabine (6.7%), carboplatin (1.7%), non-protocol defined chemotherapy (6.7%). ** EGFR clinically enriched criteria (no central testing)
GP, gemcitabine and cisplatin; TKI, tyrosine kinase inhibitor

5.3.4 Disease progression and overall survival model inputs

Osimertinib – AURAext/2 pooled data

The AURAext/2 pooled data used in the model were based on data from the cut-off date of 1 May 2015 (CTD-2) including all patients enrolled to the study who received at least one dose of the investigational product (FAS). There were 201 patients in the full analysis set in AURA extension and 210 patients in the full analysis set in AURA2.[74]

As described in Section 4.10, the PFS survival data were 39% mature and the OS survival data were 13% mature at the time of data cut-off. The non-parametric analyses for PFS and OS from the AURAext/2 pooled study are summarised in Table 5.7 and the Kaplan-Meier (KM) curves are presented in Section 4.10. As part of the subgroup analyses for second-line only and ≥third-line settings the PFS data were censored ≤7 months resulting in the total number of events as presented in Table 5.7. This was done on the basis that the KM curves for the second-line only and ≥third-line populations intersected at approximately 7 months, leading to the PFS curve for the ≥third-line population lying slightly above that of the second-line only population after this point (see Appendix A4.1 for more information).

Table 5.7: Summary of AURA ext/2 pooled non-parametric analysis

		≥Second-line (base case)	Second-line	≥Third-line
Number of patients (N)		411	129	282
Progression-free survival	159	159	50	109
	Median PFS (months) & 95% CI*	9.7 (8.3, NC)	8.3 (7.7, NC)	NC (8.3, NC)
Progression-free survival (censored at ≤7 months)	Total number of events	–	43	96
	Median PFS (months) & 95% CI*	–	NC (NC, NC)	NC (NC, NC)
Overall survival	Total number of events	52	13	39
	Median OS (months) & 95% CI*	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)

*Calculated using the Kaplan-Meier technique; NC – not calculable

Platinum doublet chemotherapy – IMPRESS data

The original KM data for platinum doublet chemotherapy collected in the IMPRESS study (PFS and OS) were included for the parametric analyses to be applied in the economic model. There were 132 patients in the IMPRESS platinum doublet chemotherapy arm who received at least one dose of the investigational product (full analysis set), and 127 patients included in the final analysis set (following exclusion of 5 patients based in France). Of these

127 patients, 60 patients were T790M mutation positive and included for the parametric analyses for the base case analysis. The non-parametric PFS and OS data for both patient groups (all-comers and T790M mutation positive) are summarised in Table 5.8 and the KM curves are presented in Appendix A4.2. There is little difference in median PFS between all-comers and T790M mutation positive patients; however for OS the median durations (17.2 months and 15.7 months for all-comers and T790M mutation positive patients, respectively) suggest that T790M mutation positive patients have a slightly worse prognosis.

Table 5.8: Summary of IMPRESS non-parametric analysis

		Platinum doublet chemotherapy, all-comers	**Platinum doublet chemotherapy, T790M mutation positive patients**
Number of patients (N)		127	60
Progression-free survival	Total number of events	98	48
	Median PFS (months) & 95% CI*	4.6 (4.1, 5.4)	5.3 (4.0, 5.5)
Overall survival	Total number of events	37	20
	Median OS (months) & 95% CI*	17.2 (12.7, NC)	15.7 (12.4, NC)

*Calculated using the Kaplan-Meier technique/based on digitised graphs
NC: not calculable

Single-agent chemotherapies – Park 2015 and Schuler 2015 data

PFS and OS KM data for the pemetrexed monotherapy arm the study by Park *et al* was digitised and parameterised for inclusion in the economic model (for the second-line only subgroup analysis). Similarly, PFS and OS data for the chemotherapy arm in the study by Schuler *et al* (PFS and OS) were digitised and parameterised for inclusion in the model (for the ≥3L subgroup analysis only). The original KM curves from the studies with an illustrative overlay of the parametric curves are presented in Appendix A4.3.

In the study by Park *et al*, there were 37 patients in the pemetrexed monotherapy arm included in the analysis resulting in a median PFS of 4.2 months, and median OS of 15.1 months.

Since no survival data was identified in the literature review specifically for docetaxel monotherapy, a simplifying assumption was made that docetaxel has the same clinical efficacy as pemetrexed monotherapy in the second-line only setting. The non-parametric analyses of PFS and OS from the study by Park *et al* are summarised in Table 5.9 and the KM curves are presented in Appendix A4.3.

Table 5.9: Summary of Park 2015 non-parametric analysis

		Single-agent chemotherapy
Number of patients (N)		37
Progression-free survival	Total number of events	34
	Median PFS (months) & 95% CI*	4.2 (2.9, 6.2)
Overall survival	Total number of events	20
	Median OS (months) & 95% CI*	15.1 (9.7, 26.0)

*Calculated using the Kaplan-Meier technique

In the study by Schuler *et al*, there were 68 patients in the chemotherapy arm included in the analysis, resulting in a median PFS of 2.8 months and median OS of 12.2 months. The study by Schuler *et al* is relevant only to the subgroup analysis for ≥third-line setting and, as noted previously, applies different EGFR inclusion criteria where no central testing was performed.

Since no survival data were identified in the literature specifically for docetaxel monotherapy, a simplifying assumption was made that all single-agent chemotherapies have the same efficacy in the ≥third-line setting. In addition, the study by Schuler *et al* included a mix of single-agent chemotherapies, depending on the investigators choice. The non-parametric analyses of PFS and OS from the study by Schuler *et al* are summarised in Table 5.10 and the KM curves are presented in Appendix A4.3.

Table 5.10: Summary of Schuler 2015 non-parametric analysis

		Single-agent chemotherapy
Number of patients (N)		68
Progression-free survival	Total number of events	54
	Median PFS (months) & 95% CI*	2.8 months
Overall survival	Total number of events	46
	Median OS (months) & 95% CI*	12.2 months

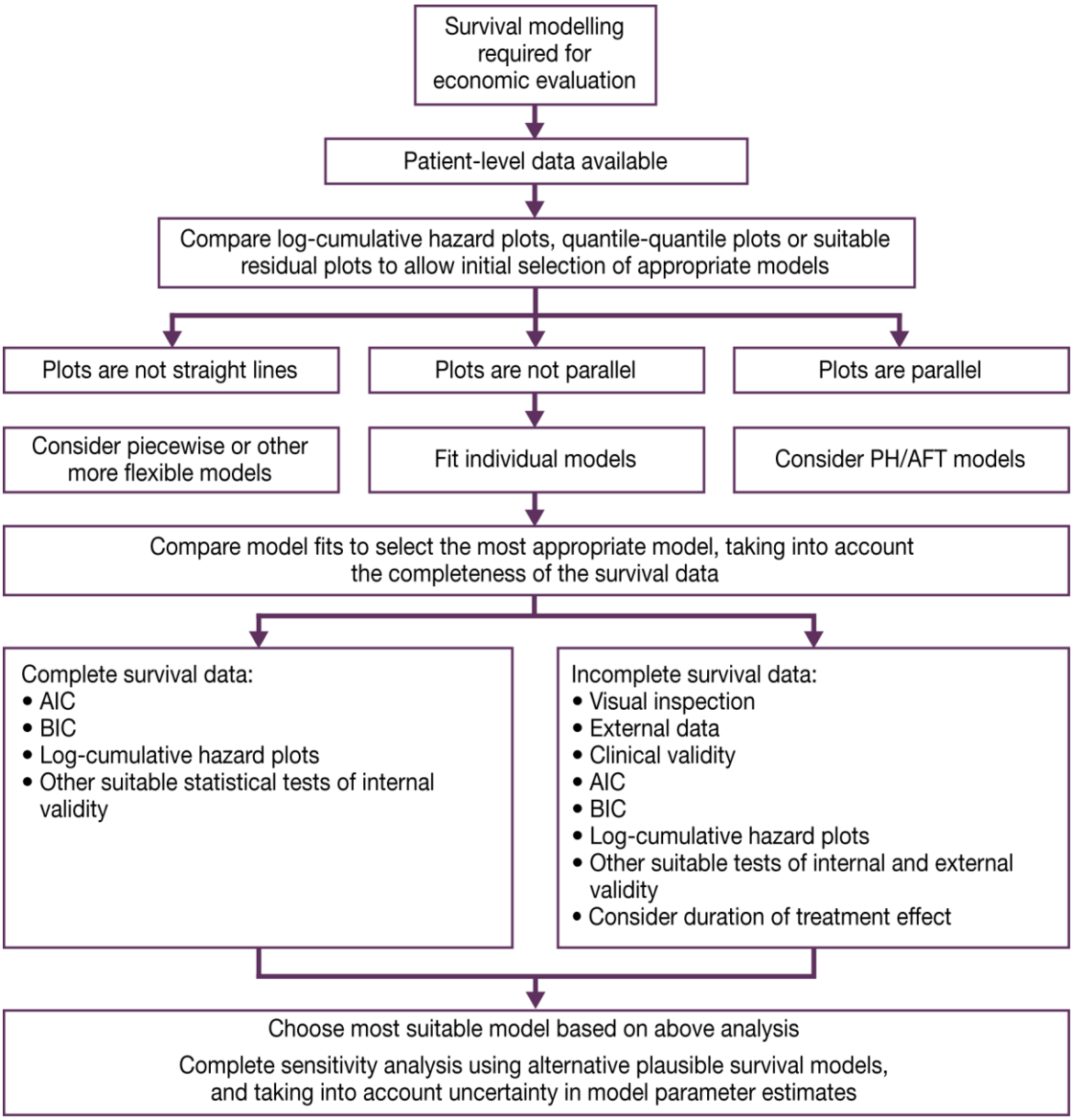
*Calculated using the Kaplan-Meier technique

5.3.5 Parametric survival models – base case analysis

In line with the decision problem, the base case analysis focuses on a comparison of osimertinib with platinum doublet chemotherapy in the ≥second-line setting based on data from the AURAext/2 pooled study and the T790M mutation positive control arm of the

IMPRESS study. Standard guidance for fitting and selecting survival functions was used and a full step-wise description of the statistical analysis based on the NICE DSU guidance is provided in Figure 5.3. Due to the immaturity of the survival data currently available from AURAext/2, the assumption of proportional hazards is difficult to test. The current analysis therefore uses independent survival models for osimertinib and comparator treatments. The parametric model fitting is based on the clinical data presented in Section 4 extrapolated using standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised Gamma). Visual inspection and statistical goodness-of-fit was used to assess the parametric models for PFS and OS.

Figure 5.3: Survival model selection process recommended by NICE DSU[110]

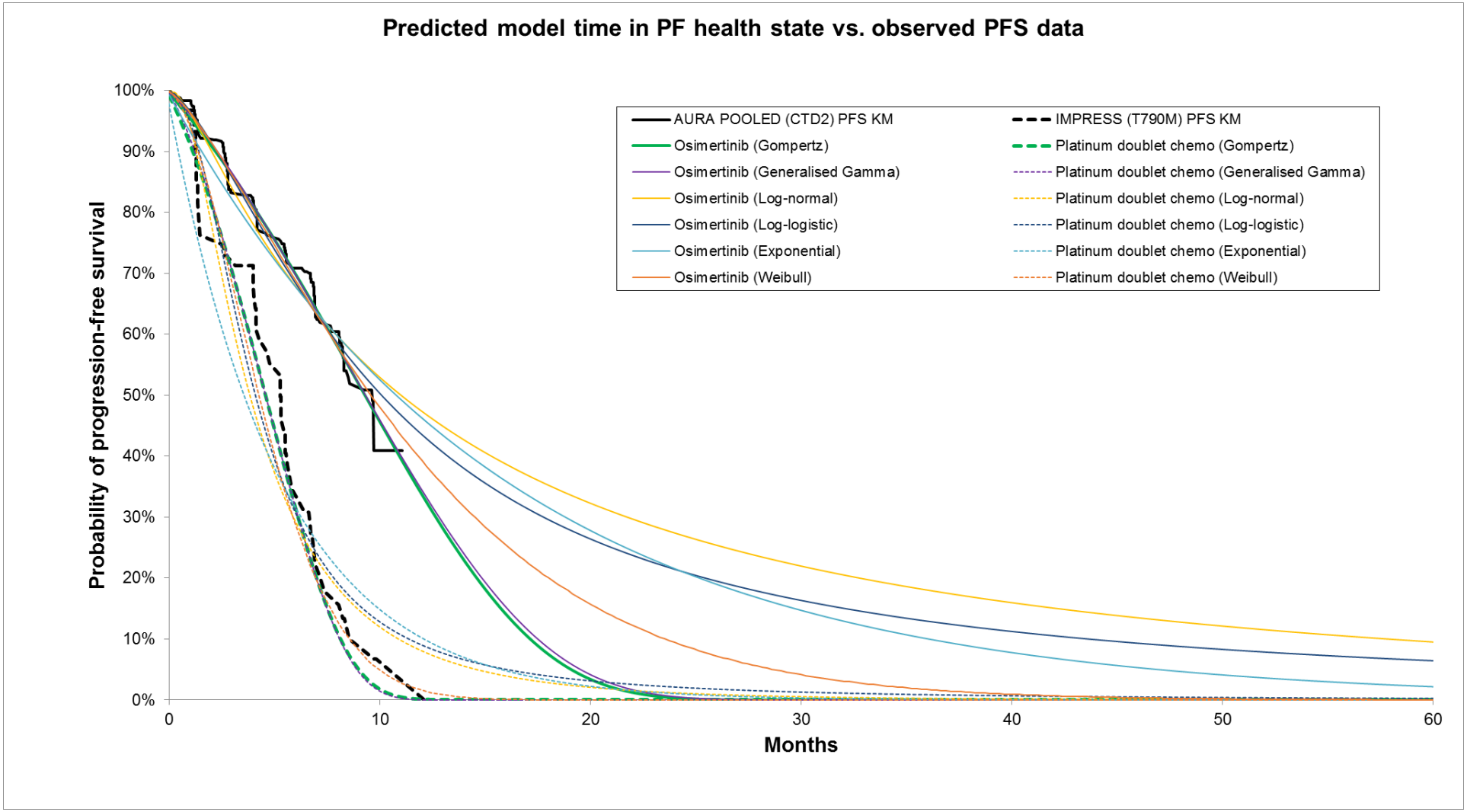


5.3.6 Visual inspection

The KM data and extrapolated parametric survival models for osimertinib, platinum doublet chemotherapy, and pemetrexed are presented in Appendix A5. Table 5.11 and Table 5.12 summarise the results of the parametric analyses and compare them against the non-parametric data. Figure 5.4, Figure 5.5 and Figure 5.6 present the overlaid modelled parametric curves to the non-parametric PFS and OS KM plots for osimertinib and platinum doublet chemotherapy for all candidate survival functions. Overall, the following results were observed:

- The Weibull, Gompertz, and Generalised gamma models for PFS result in similar extrapolated estimates for platinum doublet chemotherapy. Based on IMPRESS (T790M mutation positive population), all standard parametric distributions tend to slightly underestimate the median PFS and PFS at 4 months, but PFS at 6 months and 8 months are overestimated. Overall, the Gompertz, Weibull and generalised gamma distributions appear to provide the most adequate estimates of PFS
- For osimertinib PFS, the Weibull model appears to provide the best fit. The median PFS extrapolated from the Weibull distribution is 9.69 months which compares well with a median of 9.7 months observed in the AURAext/2 pooled data. The Gompertz distribution also provided a good fit to the observed AURAext/2 PFS data

Figure 5.4: Predicted model time in PF health state for all parametric distributions compared with observed PFS data



- For platinum doublet chemotherapy (IMPRESS T790M mutation positive population), all standard parametric distributions included in the analysis tend to overestimate both the median OS and OS at 18 months, although OS at 9 months and 12 months show a reasonable fit compared with the non-parametric data. The log-logistic and Weibull parametric models appear to have the best fit. The Weibull distribution has a good fit throughout the observed data whilst the log-logistic has a slightly better fit at the last data point (~24 months)
- At the latest data cut-off (May 2015) median OS has not been reached in the AURAext/2 data set. Therefore, the extrapolated estimates are subject to a degree of uncertainty with median OS varying between 17.5 months (Gompertz) and 63.9 months (log-normal). In an attempt to validate the extrapolation of the AURAext/2 pooled data, KM data from the AURA Phase I dose expansion study[71], consisting of n=182 patients with centrally-tested EGFR T790M mutation positive status, were compared with the extrapolated curves from AURAext/2 pooled data. Although the follow-up period available for the Phase I study is longer, it has still not reached median OS (11% data maturity at May 2015 data cut-off).

Figure 5.5: Kaplan-Meier data and extrapolation of parametric distributions for osimertinib OS (20 months follow-up)

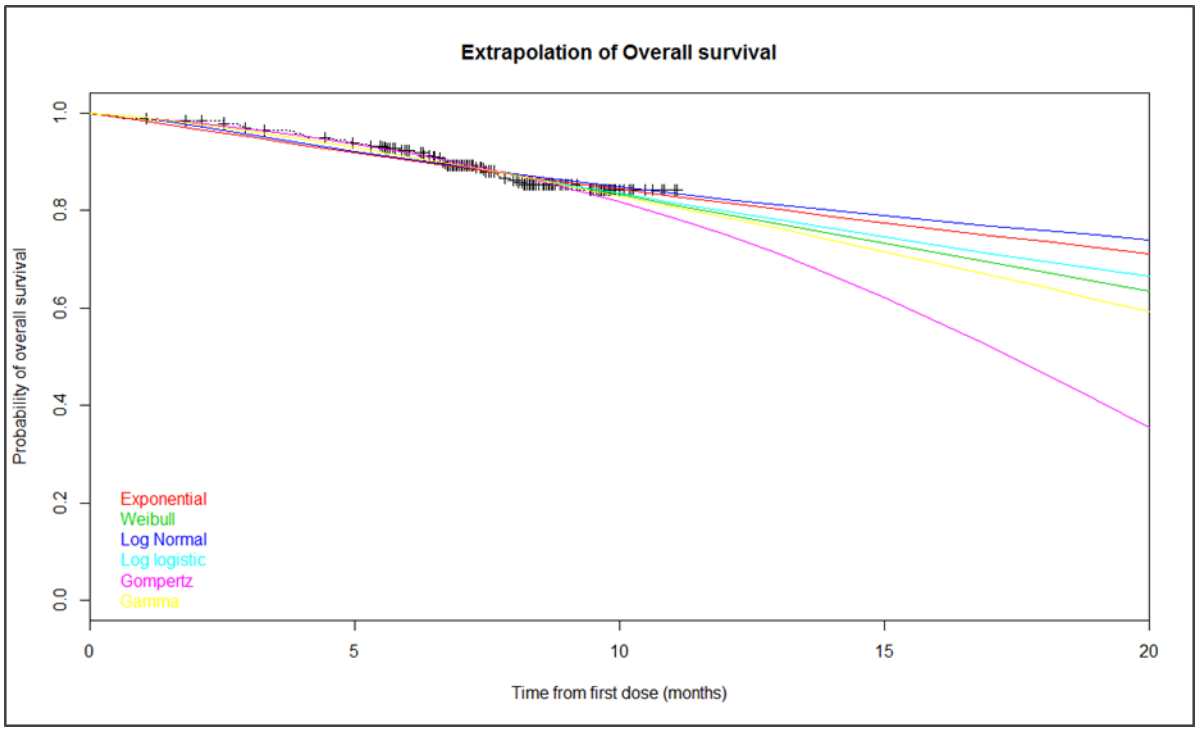


Figure 5.6: Predicted model alive (OS) for all parametric distributions compared with observed OS data

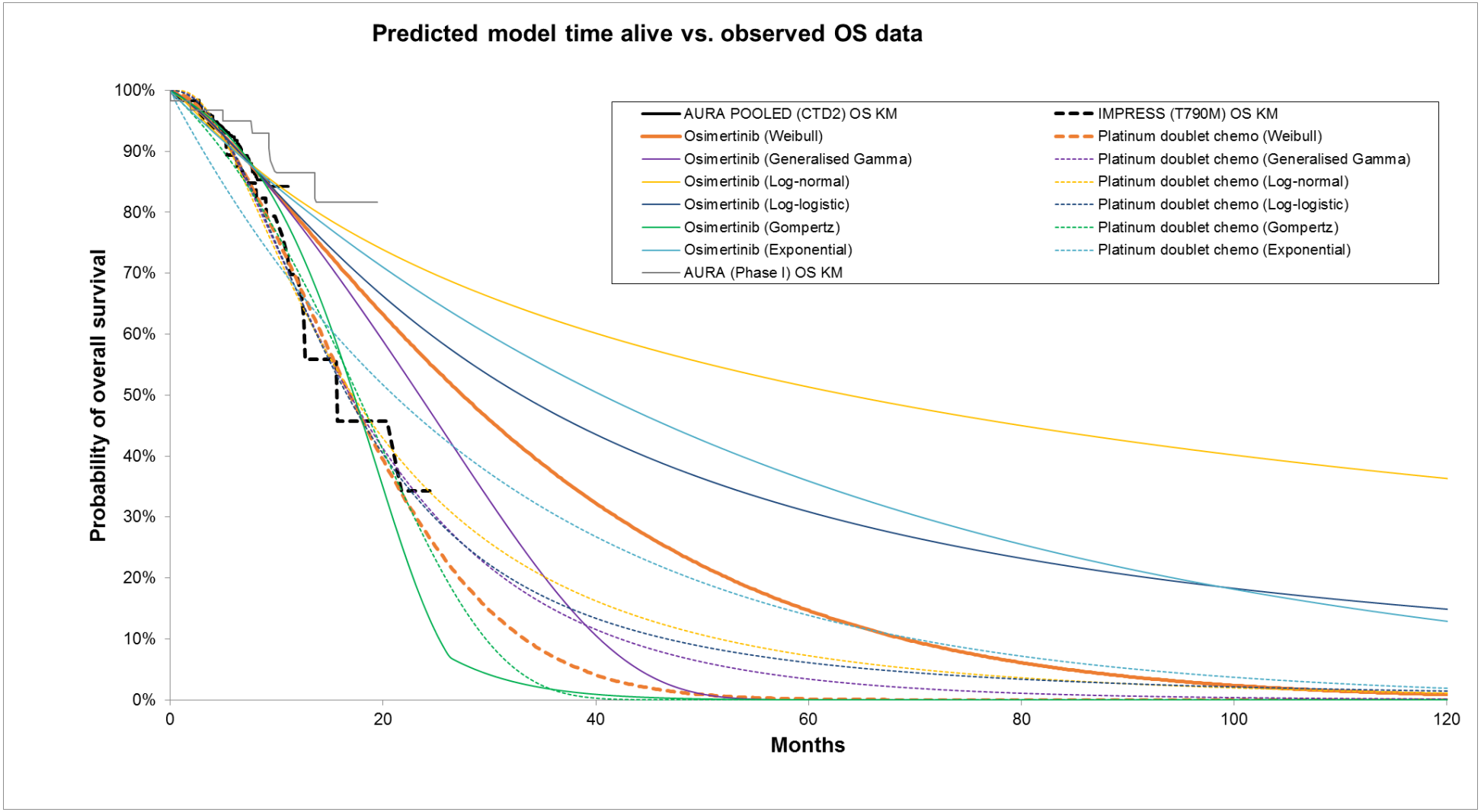


Table 5.11: Median duration (in months) of the parametric survival models in the AURAext/2 pooled and IMPRESS (T790M mutation positive population) studies

	PFS		OS	
	PDC	**Osimertinib**	**PDC**	**Osimertinib**
Exponential	3.69	10.85	21.00	40.62
Weibull	4.38	9.69	17.08	27.69
Gompertz	4.62	9.46	17.77	17.31
Log-logistic	4.15	10.15	16.85	33.23
Log-normal	3.90	11.08	17.31	63.92
Gen gamma	4.62	9.46	17.08	23.54
Non-parametric data	**5.3**	**9.7**	**15.7**	**NC**

NC: not calculable, PDC: platinum doublet chemotherapy

Table 5.12: Survival rate at various time-points of the parametric survival models applied to the IMPRESS (T790M mutation positive population) study

	PFS			OS			
	4 months	**6 months**	**8 months**	**9 months**	**12 months**	**18 months**	**24 months**
Exponential	46.7%	31.6%	22.3%	74.1%	67.2%	55.2%	45.3%
Weibull	54.8%	28.8%	13.8%	79.6%	68.5%	46.1%	27.6%
Gompertz	58.5%	31.4%	12.1%	79.5%	70.2%	48.5%	26.1%
Log-logistic	52.4%	30.8%	20.0%	78.5%	66.6%	45.8%	31.4%
Log-normal	49.0%	29.3%	19.1%	77.1%	65.9%	47.7%	34.8%
Generalised gamma	58.7%	31.6%	12.0%	78.0%	66.6%	46.6%	32.0%
Non-parametric data	**66.0%**	**32.8%**	**15.6%**	**79.3%**	**69.8%**	**45.7%**	**34.3%**

5.3.7 Statistical goodness-of-fit

Table 5.13 summarises Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) for the PFS and OS estimates. Although caution should be taken in interpreting the goodness of fit statistics based on the currently available survival data from AURAext/2, the following conclusions can be made:

- Based on the AIC and BIC of the PFS curves, the Weibull distribution had the best fit for osimertinib and second best fit for platinum doublet chemotherapy, whilst Gompertz had the best fit for platinum doublet chemotherapy and second best fit for osimertinib

- The goodness-of-fit for the OS curves is not as conclusive and differs between the studies. Whilst the log-logistic (#1) and log-normal (#2) distributions have the best fit for platinum doublet chemotherapy they represent the poorest fit for osimertinib. The scenario is almost reversed for the Gompertz distribution which has the best statistical fit for osimertinib but does not rank high for platinum doublet chemotherapy. The Weibull distribution provides a relatively adequate goodness-of-fit for platinum doublet chemotherapy and osimertinib

Table 5.13: Goodness-of-fit statistics for PFS and OS for platinum doublet chemotherapy from the control arm of the IMPRESS (T790M) and osimertinib from AURAext/2

	PFS				OS			
	PDC		Osimertinib		PDC		Osimertinib	
	AIC (#)	BIC (#)	AIC (#)	BIC (#)	AIC (#)	BIC (#)	AIC (#)	BIC (#)
Exponential	258.3 (6)	260.4 (6)	1195.9 (5)	1200.0 (5)	178.6 (6)	180.7 (6)	529.5 (5)	533.6 (2)
Weibull	242.7 (3)	246.9 (2)	**1183.0 (1)**	**1191.1 (1)**	172.4 (3)	176.5 (3)	527.9 (2)	535.9 (3)
Gompertz	**241.5 (1)**	**245.7 (1)**	1184.2 (2)	1192.3 (2)	175.4 (5)	179.5 (4)	**525.0 (1)**	**533.0 (1)**
Log-logistic	250.8 (5)	255.0 (5)	1185.5 (4)	1193.6 (3)	**171.7 (1)**	**175.9 (1)**	528.5 (3)	536.5 (4)
Log-normal	250.7 (4)	254.9 (4)	1197.0 (6)	1205.1 (6)	171.9 (2)	176.1 (2)	536.5 (6)	544.5 (6)
Gen gamma	242.4 (2)	248.6 (3)	1184.6 (3)	1196.7 (4)	173.71 (4)	179.99 (5)	529.3 (4)	541.4 (5)

5.3.8 Parametric survival model selection

In accordance with NICE DSU guidelines, the same parametric models were selected for both treatment arms.[110] Given the immaturity of the AURA pooled data, especially for OS, the IMPRESS data were believed to be more reliable in the selection of parametric models. More specifically:

- **PFS:** The Gompertz distribution was selected for PFS in the base case analysis of the model due to having the best visual fit for both osimertinib and platinum doublet chemotherapy. Scenario analyses were also conducted for the Weibull and Generalised gamma distributions as they also provided a good visual fit to the non-parametric data from AURAext/2 and IMPRESS
- **OS:** The Weibull distribution was selected for OS in the base case analysis. Although the Gompertz distribution provides the best statistical fit for the AURAext/2 pooled data, it does not for IMPRESS (T790M mutation positive). Furthermore, due to the steep curve, it generates OS estimates that are clinically implausible and lack face validity, resulting in a median OS estimates slightly in favour of platinum-based chemotherapy despite much lower median PFS estimates compared with osimertinib. Similarly, the generalised gamma distribution produces a clinically implausible scenario where the OS curves for osimertinib and platinum doublet chemotherapy intersect at around 40 months. Whilst the log-logistic and log-normal distributions provide the best statistical fit to the IMPRESS (T790M) OS data, they have a poorer fit to the AURA pooled data, generating OS estimates that lack face validity. Therefore, the Weibull distribution appears to produce the most reasonable fit to the non-parametric OS data, based on the currently available data from AURAext/2 and IMPRESS (T790M)

Figure 5.7 presents the Gompertz and Weibull survival functions used in the base case compared with the observed data from the trials. Approximately 14.8% of patients treated with osimertinib are alive at 5 years compared to 0.2% of patients on platinum doublet chemotherapy. After 10 years in the model (120 months in Figure 5.7), the proportion of patients alive is close to 0% for both treatments

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Figure 5.7: Overall and progression-free survival curves used in the base case analysis

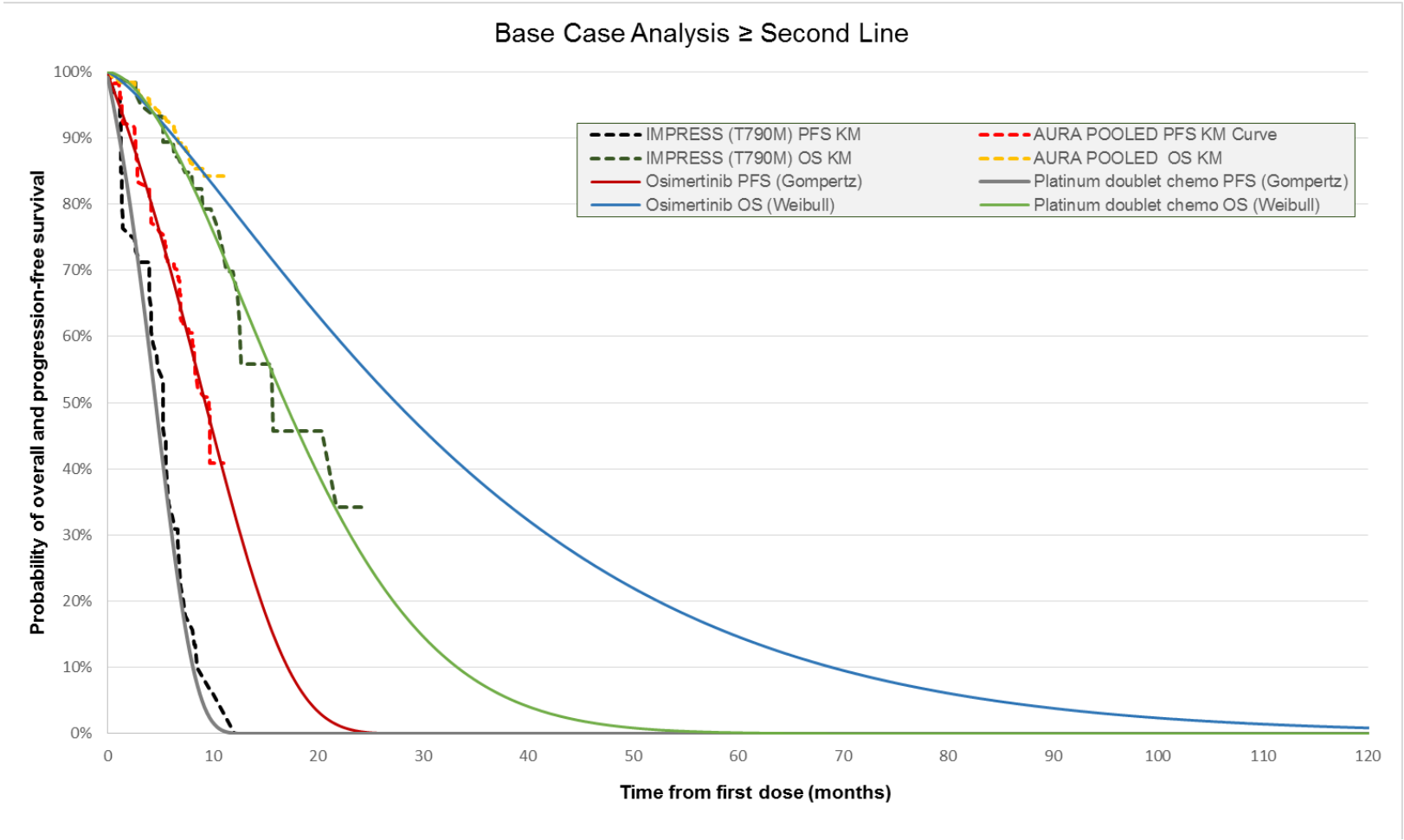
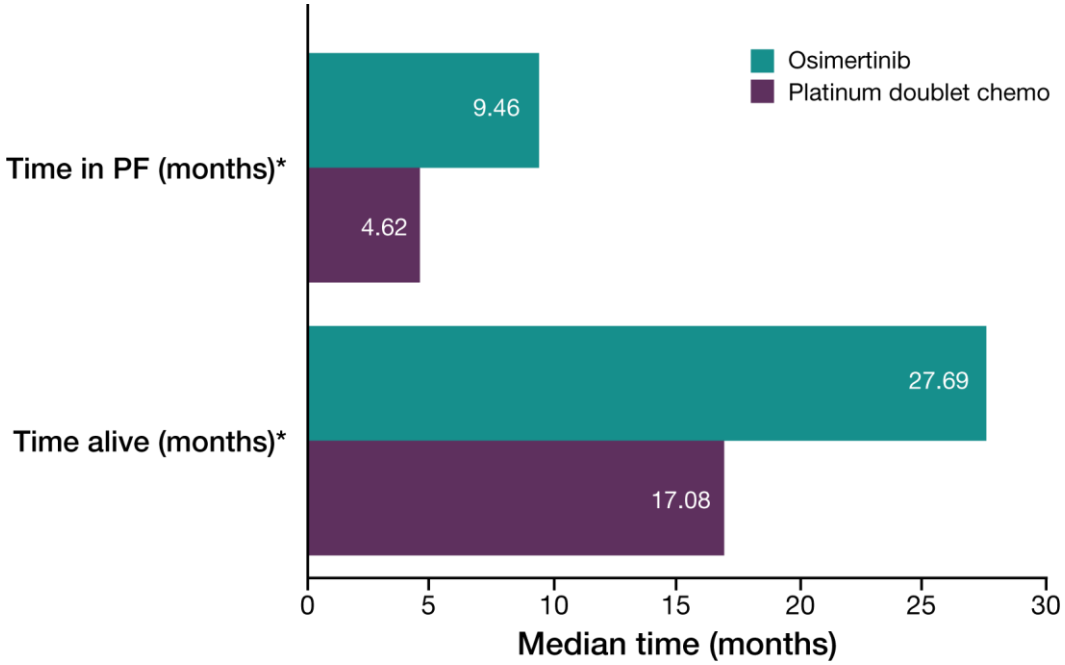


Figure 5.8 presents the median PFS and OS for osimertinib and platinum doublet chemotherapy showing an incremental PFS gain of 4.8 months and an incremental OS gain of 10.6 months for osimertinib compared with platinum doublet chemotherapy.

Figure 5.8: Median duration of the parametric distributions used in the base case analysis



* Undiscounted results

5.3.9 Parametric survival models – subgroup analysis

In order to address the other comparisons described in the decision problem, subgroup analysis explores the use of osimertinib in second-line only and ≥third-line compared with platinum doublet chemotherapy and single-agent chemotherapy. All graphs and tables used for visual and statistical inspection can be found in the Appendices A5 and A6. Due to immaturity of the AURAext/2 pooled data and low numbers at risk (especially in ≥third-line) it was assumed there was no difference in OS by line of treatment so that the OS data for ≥second-line was used for second-line only and ≥third-line subgroup analyses. In addition, extrapolation of the AURAext/2 pooled PFS data was based on the partial dataset (censored at ≤7 months).

In the second-line setting, the AURAext/2 pooled second-line PFS (≤7 months) and ≥second-line OS was used for osimertinib; the IMPRESS all-comers (placebo) was used for platinum doublet chemotherapy; and, Park *et al* pemetrexed arm was used for all single-agent chemotherapies.[75,88,111] In the ≥third-line setting, the AURA pooled ≥third-line PFS (≤7

months) and ≥second-line OS was used for osimertinib; and, Schuler *et al* chemotherapy arm was used for all single-agent chemotherapies.[109,111]

For simplicity, the parametric distributions selected for these subgroup analyses were equivalent to those used in the base case analysis; the Gompertz distribution was used to extrapolate PFS and the Weibull distribution was used to extrapolate OS. This is justified on the basis that much of the data from these subgroups provide similar parametric model fits to those generated in the base case analysis or even use the same data.

5.3.10 Safety

Adverse events were included in the model to account for the potential cost and quality of life burden of experiencing events whilst on treatment. The incidence rates for osimertinib were sourced from the AURA pooled study and data for platinum doublet chemotherapy was derived from IMPRESS. Due to the relatively small number of adverse events in the T790M mutation positive patients in IMPRESS, it was decided to use the AE incidence rates from the IMPRESS ITT control arm (n=132) in order to provide a more robust estimate. The incidence rates for the other comparators were taken from the HTA study by Brown *et al*.[112] Due to data limitations it was not possible to apply an indirect comparison of adverse event data. Therefore, it is possible that differences between treatments may partially be driven by differences in patient characteristics as well as follow-up periods in the respective studies. The incidence rates for osimertinib and platinum doublet chemotherapy are potentially dependent on the time of data cut-off, as patients still in PF might experience an AE after the data cut-off date; however, advice from UK clinical experts verified that almost all AEs would occur within the first 6 months of treatment and therefore the timing of data cut-off is unlikely to have a large impact on the model outcomes.

The incidence rates are reported in Table 5.14. The following criteria were applied:

- Adverse events occurring in ≥10% of the population in either treatment were selected for inclusion in the model
- For these AEs, the incidence rate of grade ≥3 events, according to the Common Terminology Criteria for Adverse Events (CTCAE) was applied
- There was insufficient information on event rates causally related to treatment with single-agent chemotherapy in the published literature, therefore a conservative decision was made to consider any adverse event for both osimertinib and platinum doublet chemotherapy

Table 5.14: Incidence rates of adverse events used in the model

	Osimertinib[82,83]			Platinum doublet chemotherapy[2]	Docetaxel[112]
	Second-line	≥Third-line	≥Second-line		
Sample size (n)	n=129	n=282	n=411	n=132	n=100 (assumed)
Diarrhoea	1.6%	0.7%	1.0%	0.8%	6.4%
Rash	0.0%	0.2%	0.2%	–	
Nausea	0.0%	0.7%	0.5%	4.5%	10.2%
Decreased appetite	0.8%	0.7%	0.7%	2.3%	–
Platelet count decreased	0.0%	0.5%	0.5%	–	–
Fatigue/asthenia	0.2%	1.0%	1.2%	3.0%	9.0%
Oedema peripheral	0.0%	0.2%	0.2%	–	–
Constipation	0.0%	0.4%	0.2%	–	–
Cough	0.0%	0.4%	0.2%	–	–
Stomatitis	–	–	–	0.8%	–
Vomiting	0.8%	0.4%	0.5%	2.3%	10.2%
Anaemia	0.0%	2.1%	1.5%	3.8%	–
Headache	0.0%	0.4%	0.2%	0.8%	–
Febrile neutropenia	–	–	–	–	2.9%
Neutropenia / Leucopenia / Neutrophil count decreased	0.0%	2.9%	2.9%	15.2%	62.1%
Back pain	0.0%	0.7%	0.7%	–	–

Adverse events were applied as one-off events for one cycle at the start of the simulation. An alternative approach is to convert the events into weekly rates and apply throughout the time on treatment. The benefits of using the one-off event approach are: (1) it already incorporates the time aspect since costs and disutilities are defined as one event, and (2) the rates derived from trial data are based on the full trial population and by applying a one-off event in the first cycle, the adverse events rates are applied to the full model population which should reflect more closely the results from the clinical trials. In contrast, when using weekly rates throughout the model, as patients are allowed to progress, adverse events are likely to be underestimated compared with results reported in the clinical trial.

The drawback with the one-off event approach is that, since all costs and disutilities are assumed to occur within one cycle, they are not discounted properly. However, the model does not apply inter-year discounting (in line with NICE methods guide); therefore to the extent that the effects of adverse events are shorter than 1 year, the results are not affected.

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

The AURA2 study included EQ-5D-5L collected every 6 weeks, making it possible to derive utility values directly from the trial data.[82] An EQ-5D index score was calculated for each subject and visit. To date an EQ-5D-5L tariff has not been formally published or recommended by NICE, therefore the EQ-5D-5L crosswalk index values for the UK were applied.[113]

The average EQ-5D utility values were calculated by averaging the EQ-5D index score for each subject in the full analysis set, and then calculating the average value across all subjects within each health state. The utility value for PF was calculated by including all post-baseline records up to the day before progression. For patients who did not progress, all post-baseline records were used. The utility value for PD was calculated by only including patients on or after the day of progression.

The utility values are presented in Table 5.15 for the base case analysis (≥second-line population), as well as for the second-line only and ≥third-line populations, which were used in subgroup analyses (see Section 5.9).

Table 5.15: Average EQ-5D-5L utility values for progression-free and progressed disease states from AURA2 study

Health state	n	Mean utility	Standard deviation
Base case analysis (≥second-line population)			
Progression-free	158	0.815	0.183
Post-progression	39	0.678	0.314
Second-line only population			
Progression-free	50	0.853	0.139
Post-progression	11	0.726	0.319
≥Third-line population			
Progression-free	108	0.798	0.198
Post-progression	28	0.659	0.316

In addition, the IMPRESS study collected EQ-5D-3L data in a similar manner to the AURA2 study and index scores were calculated using a similar approach. The values calculated for the placebo arm (pemetrexed plus cisplatin) of this study are summarised in Table 5.16.

Table 5.16: Average EQ-5D-3L index value from IMPRESS (placebo arm)

Health state	n	Mean utility	Standard deviation
Progression-free	117	0.779	0.210
Post-progression	88	0.679	0.271

For the base case analysis it was not considered appropriate to apply treatment-specific utility values for the PF and PD states from the AURA2 and IMPRESS studies respectively. As described previously, the AURA2 study includes a ≥second-line EGFR and T790M mutation positive population while the IMPRESS study includes a second-line only EGFR-M positive population. Although it was possible to estimate mean EQ-5D-5L utility values for the second-line only population from AURA2, these values are associated with a greater degree of uncertainty given the small patient numbers available for analysis, especially for the progressed disease state. Similarly, the AURA2 study collected the 5-level version of the EQ-5D instrument whereas the IMPRESS collected the 3-level version which may further limit the comparability of the utility values derived from both studies. However, treatment-specific utility values from AURA2 and IMPRESS were applied in scenario analysis. The utility values used in the base case analysis are presented in Table 5.17.

Overall, the mean utility values estimated from the AURA2 study and applied in the cost-effectiveness analysis are comparable to EQ-5D utility estimates obtained from previous studies of targeted therapies for locally advanced or metastatic NSCLC. For example, the PROFILE 1007 RCT of crizotinib versus chemotherapy in previously treated patients with ALK-positive aNSCLC produced a mean EQ-5D-3L utility value of 0.82 for patients on crizotinib treatment.[114] Similarly, the LUX-Lung 3 trial of afatinib for the first-line treatment of EGFR-M positive locally advanced or metastatic NSCLC produced a mean EQ-5D utility value of 0.784 for patients in the progression-free phase.[115]

In addition, the use of utility values calculate from the AURA2 study via the EQ-5D-5L instrument is in line with the NICE reference case and, because it utilises patient-level data for a patient population specific to the decision problem, thus making it directly relevant to the cost-effectiveness analysis.

Table 5.17: Health-state utility values used in the base case analysis

Health state	Utility value	Source
Progression-free	0.815	AURA2
Post-progression	0.678	AURA2
Death	0.000	By definition

5.4.2 Health-related quality-of-life studies

A systematic literature review was conducted to identify HRQoL and utility studies relevant to the decision problem and using the inclusion and exclusion criteria defined in Table 5.2 and the search strategy presented in Appendix A3.1. Similar to the clinical and economic literature reviews, due to lack of published data for EGFR and T790M mutation positive NSCLC, the relevant population was not limited to T790M mutation status and was expanded to include all EGFR mutation positive patients with locally advanced or metastatic NSCLC that have failed treatment with an EGFR TKI. 594 potentially relevant studies were identified from the database searches and were considered for abstract screening during which 63 were marked as appropriate and 41 duplicate records were excluded by two independent reviewers. Following full text screening none of the 63 articles were characterised as suitable to inform the decision problem of this submission.

5.4.3 Adverse reactions

In addition to the health state utility values, utility decrements due to grade 3 or grade 4 adverse events were included in the model base case analysis. The disutility associated with specific adverse events was assumed to last for a period of one month (i.e. 4 weekly cycles). Disutilities associated with adverse events were either taken from a study by Nafees *et al*[116] which has been used to estimate health-state utility values and AE disutilities in previous NSCLC HTA submissions to NICE or based on assumptions used previously. The AE disutilities used in the model are presented in Table 5.18.

Table 5.18: Disutilities associated with adverse events

Adverse event	Disutility	Source
Diarrhoea	0.047	Nafees 2008[116]
Rash (grouped term)	0.032	Nafees 2008
Nausea	0.048	Nafees 2008
Platelet count decreased	0.05	Assumption – based on Nintedanib NICE Appraisal[117]
Fatigue/asthenia	0.073	Nafees 2008
Oedema peripheral	0.05	Assumption
Constipation	0.05	Assumption
Cough	0.05	Assumption
Stomatitis	0.05	Assumption
Vomiting	0.048	Nafees 2008
Anaemia	0.073	Assumed to be same as fatigue/ asthenia event
Headache	0.05	Assumption
Febrile neutropenia	0.090	Nafees 2008
Neutropenia / Leucopenia / Neutrophil count decreased	0.090	Nafees 2008
Back pain	0.05	Assumption

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

A systematic review was conducted to identify studies reporting costs and healthcare resource use (Section 5.1) using the inclusion and exclusion criteria defined in Table 5.2 and the search strategy presented in Appendix A2.1. Only one of the studies identified was UK-based[97] and, because this was a conference abstract, limited information was provided on the resource use and cost estimates used.

Therefore, in addition to the systematic literature review, the NICE website was searched to identify any relevant, recently published HTA submissions of second-line treatment for locally advanced or metastatic NSCLC. The results of this search identified the following potentially relevant HTA submissions:

- NICE (2015). Erlotinib and gefitinib for treating non-small cell lung cancer that has progressed after prior chemotherapy (NICE TA374)[118]
- NICE (2015). Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small cell lung cancer (NICE TA347)[117]
- NICE (2013). Crizotinib for previously treated non-small cell lung cancer associated with an anaplastic lymphoma kinase fusion gene (NICE TA296)[119]

5.5.2 Intervention and comparators' costs and resource use

T790M testing costs – Osimertinib

Diagnostic strategies are only included in the model for cost purposes since the decision rule assumes that only identified T790M mutation positive patients are treated with osimertinib. The model includes four possible testing strategies: (i) tissue biopsy; (ii) ctDNA (plasma) test followed by tissue biopsy in patients identified as T790M negative by ctDNA (plasma); (iii) ctDNA (plasma) alone and (iv) tissue biopsy followed by ctDNA (plasma). In the base case analysis only the first two testing strategies are considered: it is assumed that 20% of patients undergo tissue biopsy alone and 80% undergo ctDNA (plasma) followed by tissue biopsy (see Section 2).

An underlying T790M incidence (*T790i*) is used in the model where each test has an associated T790M test performance, expressed as sensitivity (*SE*) and specificity (*SP*). To

estimate the true positives (*TP*), false positives (*FP*), true negatives (*TN*), and false negatives (*FN*), the following four calculations for first-level tests (*t1*) were used:

$$t1_{TP} = T790_i * t1_{SE} \qquad t1_{FP} = (1 - T790_i) * (1 - t1_{SP})$$

$$t1_{TN} = (1 - T790_i) * t1_{SP} \qquad t1_{FN} = T790_i * (1 - t1_{SE})$$

In addition, the following four calculations for sequential tests (*t2*) were used:

$$t2_{TP} = t1_{FN} * t2_{SE} \qquad t2_{FP} = t1_{TN} * (1 - t2_{SP})$$

$$t2_{TN} = t1_{TN} * t2_{SP} \qquad t2_{FN} = t1_{FN} * (1 - t2_{SE})$$

The T790M incidence and T790M test performance used in the calculations are presented in Table 5.19.

Table 5.19: T790M incidence and test sensitivity/specificity

Model inputs	**Incidence**		**Source**
Underlying T790M incidence	60%		[28,30]
	Sensitivity	**Specificity**	
Tissue biopsy	88.3%	97.3%	[120]
ctDNA	80.0%	94.9%	Assumption (unpublished results)
Tissue biopsy followed by ctDNA	88.3%	97.3%	Assumed same as first-level test
ctDNA followed by tissue biopsy	80.0%	94.9%	Assumed same as first-level test

Using the calculations and model inputs as presented above gives the outputs for each diagnostic strategy as presented in Table 5.20. The eligible T790M mutation positive patients in the model are the false positives and true positives. The number needed to test (1/(FP+TP)) represents the number of patients that needs to be tested within each strategy in order to identify one patient with the T790M mutation and thus eligible for osimertinib treatment.

Table 5.20: T790M diagnostic strategy outputs

	T790M mutation negative		T790M mutation positive		# patients needed to test	# tissue biopsies per patient	# ctDNA (plasma) per patient
	TN	FP	TP	FN			
1: tissue biopsy	38.9%	1.1%	53.0%	7.0%	1.85	1.00	0.00
2: ctDNA (plasma)	38.0%	2.0%	48.0%	12.0%	2.00	0.00	1.00
3: ctDNA followed by tissue biopsy	36.9%	3.1%	58.6%	1.4%	1.62	0.50	1.00
4: tissue biopsy followed by ctDNA (plasma)	36.9%	3.1%	58.6%	1.4%	1.62	1.00	0.46
Weighted average used in model*	37.3%	2.7%	57.5%	2.5%	1.66	0.60	0.80

*Based on the distribution of diagnostic strategies

Overall, based on these data, the combination of diagnostic strategies and positive rates result in an overall positive detection rate of 60.1% (i.e. for every 1.66 patients tested, one patient is identified as T790M mutation positive and eligible for osimertinib treatment). The model also assumes that the same diagnostic strategies, incidence, and test performance apply in second-line only and ≥third-line patients.

The cost of T790M testing includes the acquisition cost of the test itself plus other costs incurred during the visit for the test. Table 5.21 summarises the resource use and costs of testing applied in the model.

Table 5.21: T790M test costs

Resource	Tissue biopsy	ctDNA	Source/Comment
Test cost	£147	£147	Tissue biopsy: based on cost of cobas EGFR Test [NICE 2013][121] ctDNA: assumed to be same as tissue biopsy
Sample procedure	£578	£325	Tissue biopsy: £578 NHS Ref Costs: DZ70Z Endobronchial Ultrasound Examination of Mediastinum [NHS 2015][122] ctDNA: assumption
Total cost	£725	£472	Total costs applied in the model

Drug acquisition costs – initial treatment

Drug acquisition costs were calculated based on available formulations; pack sizes, unit costs and price per mg for each (combination of) treatment included in the model. The

dosing information was taken from the EMA label for each treatment and the drug acquisition costs were taken from the BNF for branded products[123,124] and the NHS Commercial Medicines Unit (CMU) through the Electronic Marketing Information Tool (eMIT) for generic products.[124] The vial sizes used for intravenous (IV) treatments in the base case analysis were those resulting in the lowest monthly acquisition cost, assuming no wastage (i.e. vial sharing is assumed).

For the combination treatment 'platinum doublet chemotherapy' it was assumed that pemetrexed plus cisplatin was used. The dosages for IV chemotherapy treatments included in the model were based on average patient characteristics from the AURA ext/2 studies in terms of body weight, body surface area (BSA) and glomerular filtration rate (GFR) which are summarised in Table 5.22. The base case analysis uses patient characteristics for the whole population from AURA ext/2 while data from the second-line only and ≥third-line subgroups are used in subgroup analyses.

Table 5.22: Patient characteristics used to inform chemotherapy acquisition costs in the model

Parameter		≥Second-line (base case)	Second-line	≥Third-line	Source/comment
Starting age (years)		62.2	63.3	61.7	Weighted average of AURA (Extension) and AURA2 (i.e. AURA pooled). Gender-specific data unavailable[82,83]
Proportion females		67.9%	65.9%	68.8%	
Average body weight	Female	61.6 kg	63.7 kg	60.7 kg	
	Male	61.6 kg	63.7 kg	60.7 kg	
Average body height	Female	161.8 cm	162.3 cm	161.6 cm	
	Male	161.8 cm	162.3 cm	161.6 cm	
Average BSA	Female	1.68 m^2	1.71 m^2	1.67 m^2	Calculated based on average height and weight using the Gehan and George formula (0.0235*(height^0.42246)*(weight^0.51456)[125]
	Male	1.68 m^2	1.71 m^2	1.67 m^2	
Average GFR	Female	150 ml/min	150 ml/min	150 ml/min	Using Calvert formula (target AUC x GFR +25 ml/min) and max allowed GFR estimate (125 ml/min for patients with normal renal function)[126]
	Male	150 ml/min	150 ml/min	150 ml/min	

In the base case analysis, treatment duration for osimertinib was assumed to be 'treatment until progression' (i.e. the time patients spend in the progression-free health state). In AURAext/2 patients were continued on osimertinib treatment until RECIST v1.1-defined progression or until a criterion for study discontinuation was met. There was no maximum

duration of treatment as patients could continue to receive osimertinib beyond RECISt progression as long as they were benefitting clinically, as determined by investigators. The dose per administration was calculated as the 80 mg dose multiplied with the overall compliance to osimertinib treatment. A compliance rate of 98.6% was derived from the AURAext/2 pooled data by taking the 'mean months of actual treatment duration' / 'mean months of total treatment duration', where actual treatment duration includes dose interruptions.[111]

Table 5.23 summarises the treatment dosing, administration and drug acquisition costs for the treatments included in the model.

Table 5.23: Treatment dosing, administration and drug acquisition costs used in the model

		Osimertinib	Platinum doublet chemotherapy		Docetaxel monotherapy
			Pemetrexed	Cisplatin	
Label information	Admin method	Oral	IV	IV	IV
	Dose per admin	78.9 mg*	500 mg/m^2	75 mg/m^2	75 mg/m^2
	IV minutes per admin	0	10	120	60
	Admin frequency	QD	QTW	QTW	QTW
	Treatment duration	TDP	TDP or maximum 6 doses	TDP or maximum 6 doses	TDP or maximum 4 doses
Package information	Formulation	80 mg	100 mg	1 mg	20 mg/ml
	Pack size	30	1	10	7
	Price	£4722	£160.00	£3.24	£20.95
Dosing used in model	Required dose	80 mg	840 mg/m^2	126 mg/m^2	126 mg/m^2
	Vials/caps per admin (with waste)	1.00	9.00	13.00	1.00
	Vials/caps per admin (without waste)	1.00	8.40	12.59	0.90

Source: BNF 2015; eMIT (accessed January 2016); IV: Intravenous; QD: once daily; QTW; once every third week; TDP: treatment until disease progression

5.5.3 Drug administration costs

The drug administration costs for IV treatments include the cost of chemotherapy infusion and premedication with dexamethasone. For all oral treatments administration costs were assumed to be £0. The administration usage was based on the EMA label information for

each treatment. The costs and resource use values used in the model are summarised in Table 5.24. Administration costs are applied to all patients on treatment.

Table 5.24: Unit costs, resource use and total administration costs used in the model (per administration)

Treatment	Cost item	Unit cost (£)	Sum (£)	Source
Osimertinib	–	–	£0.00	–
Platinum doublet chemotherapy	Chemotherapy IV infusion – First attendance	£239.12	£245.16	NHS Ref Costs 2015; DH 2011[122,124]
	Dexamethasone (premedication – 8 mg per day for 3 days)	£6.04		
	Chemotherapy IV infusion – Subsequent attendances	£326.46	£332.50	
	Dexamethasone (premedication – 8 mg per day for 3 days)	£6.04		
Docetaxel monotherapy	Chemotherapy IV infusion – First attendance	£239.12	£251.19	
	Dexamethasone (premedication – 16 mg per day for 3 days)	£12.07		
	Chemotherapy IV infusion – Subsequent attendances	£326.46	£338.53	
	Dexamethasone (premedication – 16 mg per day for 3 days)	£12.07		

Drug monitoring costs

Costs related to drug monitoring were based on the EMA label information for each treatment and the costs of laboratory tests were taken from NHS Reference Costs 2014–2015.[122] Since no frequency data were given in the EMA label information, this data was taken from the nintedanib NICE submission.[117] The frequency of monitoring tests were only available for pemetrexed and erlotinib and were thus assumed to be the same for all other chemotherapies or oral treatments. Table 5.25 summarises the monitoring costs used in the model. Monitoring costs are applied weekly to all patients whilst on treatment.

Table 5.25: Unit costs, resource use and total weekly monitoring costs used in the model

Treatment	Cost item	Numbers per week	Unit cost (£)	Sum (£)
Osimertinib	–	–	–	£0.00
Platinum doublet chemotherapy	Liver function test	0.153	£7.0	£4.61
	Renal function test	0.153	£10.0	
	Complete blood count	0.667	£3.0	
Docetaxel	Complete blood count	0.667	£3.0	£2.0

Subsequent treatment costs

The model includes the cost of treatments following discontinuation from the primary treatment for patients in the progressed disease state. It is anticipated that osimertinib will alter the clinical treatment pathway following progression on first-line EGFR TKI therapy by delaying treatment with current standard of care. In other words, upon progression, patients treated with osimertinib will subsequently be treated first with platinum doublet chemotherapy and then with single-agent chemotherapy (pemetrexed or docetaxel). In line with this, upon progression patients on platinum doublet chemotherapy as primary treatment will move onto single-agent chemotherapy and those on single-agent chemotherapy will receive best supportive care. The cost of subsequent treatments was calculated using the following steps:

- The data from AURA ext/2 were immature at the time of analysis and, on the basis of clinical expert validation, were not believed to represent current UK clinical practice. Therefore, the distribution of patients across subsequent treatments for each primary treatment, as presented in Table 5.26, was based on UK clinical expert opinion
- In the absence of alternative data, the duration of all subsequent treatments (>second-line) was assumed to be the same as the modelled duration in primary treatment. After subsequent treatment, patients either stop treatment or die with no additional costs incurred

The monthly cost of subsequent treatments was assumed to be the sum of the monthly drug acquisition, administration, and monitoring costs. This was multiplied by the distribution of subsequent treatments used for each treatment in the model. The resulting total costs of subsequent treatment are presented in Table 5.26 for the base case analysis (≥second-line population).

The cost of subsequent treatment was applied as a one-off cost for all patients entering the PD health state. Due to the nature of a partitioned survival model it is not possible to accurately account for patients who enter the PD health state and die in the same cycle. As a proxy, the difference in PD patients between two weekly cycles was used. This method may slightly underestimate the subsequent treatment costs in the model and therefore favours treatments with a higher cost of subsequent treatment. However, the overall impact on the total costs of subsequent treatment is minimised by the short cycle length (weekly) used in the model.

Table 5.26: Distribution and costs of subsequent treatment according to primary treatment

To ↓	From →	Osimertinib	Platinum doublet chemotherapy	Docetaxel
Base case analysis (≥ 2nd-line) and 2nd-line only subgroup				
Platinum doublet chemotherapy		80%	0%	0%
Docetaxel monotherapy		50%	50%	15%
Best supportive care		70%	50%	85%
Total		200%*	100%	100%
≥ 3rd-line subgroup				
Platinum doublet chemotherapy		0%	N/A	0%
Docetaxel monotherapy		50%	N/A	15%
Best supportive care		50%	N/A	85%
Total		100%	N/A	100%
Total cost per patient on subsequent treatment (≥second-line)		£7,304	£609	£183

*Note that total proportion for osimertinib is 200% in 2L or ≥2L setting to reflect that patients will have two subsequent treatments following progression on osimertinib treatment

5.5.4 Health-state unit costs and resource use

Disease management costs in the model are split into progression-free and progressed disease health state costs per weekly cycle, as well as one-off costs of end-of-life/terminal care. The disease management costs are thus health state-specific, and not treatment-specific. For the progression-free and progressed health states, resource use data were taken from the HTA study of first-line chemotherapy for locally advanced or metastatic NSCLC by Brown *et al*[112] and subsequently used by the Assessment Group for the recent NICE MTA of erlotinib and gefitinib for treating patients with NSCLC whose disease has progressed following prior chemotherapy [NICE TA374].[118] The costs were taken from NHS Reference Costs 2014–2015[122] and Unit Costs of Health and Social Care[127] and are summarised in Table 5.27 and Table 5.28.

Table 5.27: Progression-free health state resource use and costs

Cost item	Annual resource use	Weekly resource use	Unit cost	Source/Notes[112]
Outpatient visit	9.61	0.184	£138.37	Code 800 clinical oncology (Consultant led follow-up attendance, non-admitted, face to face)[122] [NHS 2015]
Chest X-ray	6.79	0.130	£30.00	Code DAPF – direct access plain film [NHS 2015]
CT scan (chest)	0.62	0.012	£116.00	Code RD24Z – CT Scan (2 areas with contrast) [NHS 2015]
CT scan (other)	0.35	0.007	£132.00	Code RD26Z – CT Scan (3 areas with contrast) [NHS 2015]
ECG	1.04	0.020	£175.00	Code EY51Z – Electrocardiogram Monitoring or Stress testing – Clinical Oncology 800 [NHS 2015]
Community nurse visit	8.70	0.167	£67.00	Cost per hour spent on home visits (including qualification)[127] [PSSRU 2015]
GP home visit	12.0	0.230	£112.22	Cost per surgery visit (11.7 minutes, including direct care staff) [PSSRU 2015]
Clinical nurse specialist	12.0	0.230	£91.00	Cost per contact hour (including qualification) [PSSRU 2015]
Total weekly cost (sum)			**£77.42**	–

Table 5.28: Progressed health state resource use and costs

Cost item	Annual resource use	Weekly resource use	Unit cost	Source/Notes[112]
Outpatient visit	7.91	0.152	£138.37	Code 800 clinical oncology (Consultant led follow-up attendance, non-admitted, face to face) [NHS 2015][122]
Chest X-ray	6.50	0.125	£30.00	Code DAPF – direct access plain film [NHS 2015]
CT scan (chest)	0.24	0.005	£116.00	Code RD24Z – CT Scan (2 areas with contrast) [NHS 2015]
CT scan (other)	0.42	0.008	£132.00	Code RD26Z – CT Scan (3 areas with contrast) [NHS 2015]
ECG	0.88	0.017	£175.00	Code EY51Z – Electrocardiogram Monitoring or Stress testing - Clinical Oncology 800 [NHS 2015]
Community nurse visit	8.70	0.167	£67.00	Cost per hour spent on home visits (including qualification) [PSSRU 2015][127]
GP home visit	26.09	0.500	£112.22	Cost per home visit (23.4 minutes, including travel time); inflated to 2014/15 using HCHS Index [PSSRU 2012][128]
Clinical nurse specialist	12.00	0.230	£91.00	Cost per contact hour (including qualification) [PSSRU 2015]
Therapist visit	26.09	0.500	£44.00	Cost per hour (including training) [PSSRU 2015]
Total weekly cost (sum)			**£139.52**	–

The model also includes the one-off costs associated with end-of-life/terminal care. Resource use for end-of-life/terminal care was also based on information taken from the HTA study by Brown *et al*[112] which provides resource use for the time spent either in hospital, hospice, or at home. Costs were taken from NHS Reference Costs 2014–2015[122] and Unit Costs of Health and Social Care.[127] The overall weighted end-of-life care cost is shown in Table 5.29.

Table 5.29: End-of-life/terminal care costs (one-off)

Resource	% of patients in each care setting	Number required	Unit costs (£)	Source/Notes[112]
Hospital	55.8%	1 + 0.84 excess bed days	£3,228.37	Codes DZ17L-DZ17U (Respiratory Neoplasms Non-elective Inpatient (long stay) – weighted average [NHS 2015]
Hospice	16.9%	1	£4,035.46	Hospice costs assumed to be 25% greater than hospital costs
Home	27.3%	GP home visits (7); Community nurse visits (28); Macmillan nurse (50)	£5,207.80	Cost per home visit (23.4 minutes, including travel time); inflated to 2014/15 using HCHS Index [PSSRU 2102] Cost per hour spent on home visits (including qualification) [PSSRU 2015] Macmillan nurse assumed to be 66% of cost of community nurse
Total cost			**£3,905.26**	Calculation

5.5.5 Adverse reaction unit costs and resource use

Adverse events were entered in the model as one-off events. This means that the incidence data used is for the whole treatment period and the unit costs are per event. The unit costs for each adverse event were based on various sources, as summarised in Table 5.30.

Table 5.30: Cost of adverse events

Adverse event	Cost	Source/comment
Diarrhoea	£431.54	NHS Reference Costs 2014–15 FZ36G-FZ36Q Gastrointestinal Infections with Multiple Interventions – Non-elective short stay (Weighted Average) [NHS 2015][122]
Rash (grouped term)	£435.92	NHS Reference Costs 2014–15 JD07A-JD07K Skin Disorders with Interventions – Non-elective short stay (Weighted Average) [NHS 2015]
Nausea/vomiting	£449.94	NHS Reference Costs 2014–15 FZ91A-FZ91M Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions – Non-elective short stay (Weighted Average) [NHS 2015]
Decreased appetite	£83.00	NHS Reference Costs 2014–15 Assumed one outpatient dietician visit [NHS 2015]
Platelet count decreased	£502.63	NHS Reference Costs 2014–15 SA12G-SA12K Thrombocytopenia – Non-elective short stay (Weighted Average) [NHS 2015]
Neutropenia / Leucopenia / Neutrophil count decreased	£478.31	NHS Reference Costs 2014–15 SA35A-SA35E Agranulocytosis – Non-elective short stay (Weighted Average) [NHS 2015]
Fatigue/asthenia/anaemia	£610.63	NHS Reference Costs 2014–15 SA01G-SA01K Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia – non-elective short stay (Weighted Average) [NHS 2015]
Oedema peripheral	£365.66	NHS Reference Costs 2014–15 WH10A-WH10B Unspecified Oedema – Non-elective short stay (Weighted Average) [NHS 2015]
Constipation	£0.00	Assumed to be zero cost
Cough	£0.00	Assumed to be zero cost
Stomatitis	£0.00	Assumed to be zero cost – as per ipilimumab TA319 NICE submission [NICE 2014][129]
Headache	£0.00	Assumed to be zero cost – as per ipilimumab TA319 NICE submission [NICE 2014]
Febrile neutropenia	£2,426.86	NHS Reference Costs 2014–15 SA35A-SA35E Agranulocytosis – Non-elective long stay (Weighted Average) [NHS 2015]
Back pain	£421.67	NHS Reference Costs 2014–-15 HC32H-HC32K: Low Back Pain Without Interventions – Non-elective short stay (Weighted Average) [NHS 2015]

5.6 Summary of base case de novo analysis inputs and assumptions

5.6.1 Summary of base case de novo analysis inputs

Details of all of the values used in the economic model are provided in Appendix A7. A summary of the key variables used in the model is presented in Table 5.31.

Table 5.31: Summary of variables applied in the economic model (base case analysis)

Area	Variable	Value	Reference to section in submission
Model settings/ patient characteristics	Time horizon	15 years	5.2
	Model cycle length	1 week	
	Starting age	62.17 years	
	Discount rate	3.5%	
	Average body weight (kg)	61.59 kg	5.5
	Body surface area	1.68 m^2	5.5
Clinical efficacy data	Overall survival – osimertinib (≥second-line)	Distribution: Weibull Shape: [redacted] Scale: [redacted]	5.3
	Progression-free survival - Osimertinib (≥second-line)	Distribution: Gompertz Shape: [redacted] Scale: [redacted]	
	Overall survival – Platinum doublet chemotherapy (second-line, T790M+)	Distribution: Weibull Shape: [redacted] Scale: [redacted]	
	Progression-free survival – Platinum doublet chemotherapy (second-line, T790M+)	Distribution: Gompertz Shape: [redacted] Scale: [redacted]	
Resource use and costs	Cost of osimertinib (per pack)	£4,722	5.5
	Cost of pemetrexed (per vial)	£160	
	Cost of cisplatin (per vial)	£3.24	
	Administration cost per dose (platinum doublet chemotherapy) – first visit	£251.19	
	Administration cost per dose (platinum doublet chemotherapy) – subsequent visits	£326.46	
	Disease management costs – Progression-free state	£77.42	
	Disease management costs – Progressed state	£139.52	
	Terminal care cost	£3,905.26	
Utility values	PFS	0.815	5.4
	PD	0.678	

5.6.2 Assumptions

The key assumptions applied in the base case analysis are described below:

- The base case analysis is for ≥second-line patients. Currently, differences by line of treatment in the OS data for osimertinib are not considered to be robust due to immaturity of the data (13% for OS). Therefore, the OS data for ≥second-line was used in the subgroup analysis (second-line only and ≥3 third-line) as well. The PFS data was more mature (39%) and differences by line of treatment were therefore used in subgroup analysis (second-line only and ≥third-line)
- The efficacy data for osimertinib and platinum doublet chemotherapy is specific to T790M mutation positive patients. However, the data for docetaxel in second-line is based on a study on EGFR mutation positive patients who received pemetrexed (Park *et al*). It was therefore assumed that both single-agent chemotherapies (pemetrexed and docetaxel) have the same efficacy in a second-line setting. Similarly, the clinical literature review did not identify studies for docetaxel in ≥third-line in the target population and the data used is based on a study which includes various single-agent chemotherapies [Schuler 2015]
- The AE rates for osimertinib (EGFR and T790M mutation positive patients) and platinum doublet chemotherapy (EGFR mutation positive patients) are based on unadjusted trial data. Due to the small number of T790M mutation positive patients in IMPRESS, it was not possible to estimate adverse event rates in this subset of the EGFR population. The adverse event rates for the other comparators are taken from aggregated data identified in the literature review. Events with >10% incidence were selected for inclusion and the incidence of ≥3 grade events was applied

In addition, the following assumptions were applied in the base case analysis:

- A year in the model is assumed to consist of 52 weekly cycles, and thus, each month is 4.33 weeks long
- Progression-free survival is assumed to be a predictor of treatment duration so that all patients stop primary treatment on progression
- The average treatment doses used in the model are assumed to account for dose reductions and treatment holidays
- Treatment-related adverse events, and their associated costs and disutilities, are applied as one-off events and they are resolved prior to disease progression

- Disease management costs (PF and PD) are applied as constant (rather than time-varying) costs in the respective health state
- Vial sharing (no drug wastage) is assumed for all treatment comparators in the base case
- The impact of treatment on quality of life is captured through disease progression and adverse event disutilities. In the base case analysis health state utilities are not treatment specific or dependent on response status

5.7 Base case results

5.7.1 Base case incremental cost-effectiveness analysis results

Total costs, Life years gained (LYG), QALYs and incremental cost per QALY for osimertinib versus platinum doublet chemotherapy are presented in Table 5.32. As described previously, the base case analysis is based on the ≥second-line population from AURAext/2 for osimertinib and the T790M mutation positive second-line population from the platinum doublet chemotherapy arm of the IMPRESS study. The Weibull distribution was used to extrapolate OS and the Gompertz distribution was used to extrapolate PFS in the base case analysis. In the base case analysis, osimertinib generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime horizon gained compared with platinum doublet chemotherapy, resulting in an ICER of [redacted] per QALY gained.

Table 5.32: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incr LYG	Incr QALYs	ICER (£) incremental (QALYs)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum doublet chemotherapy	[redacted]	[redacted]	[redacted]				

5.7.2 Clinical outcomes from the model

Treatment with osimertinib is associated with a life expectancy of [redacted] years ([redacted] months) compared with [redacted] years ([redacted] months) when patients receive platinum doublet chemotherapy. The proportion of patients alive at 1 and 2 years is [redacted] and [redacted] for those treated with osimertinib compared with [redacted] and [redacted] for those treated with platinum doublet chemotherapy.

The predicted mean and median time to disease progression, time in progressed disease and time alive for each arm of the simulation are summarised in Table 5.33. The predicted mean and median time to disease progression are [redacted] and 9.46 months for osimertinib, compared with [redacted] and 4.62 months for platinum doublet chemotherapy. These estimates are slightly below the observed results from the relevant AURAext/2 pooled trial data (median PFS 9.7 months) and the IMPRESS T790M mutation positive population (median PFS 5.3 months).

The predicted mean and median time to death are [redacted] and 27.69 months for osimertinib, compared with [redacted] and 17.08 months for platinum doublet chemotherapy. The median OS estimate for platinum doublet chemotherapy is similar to the observed IMPRESS T790M mutation positive population (median OS 17.2 months). However, it is not possible to fully validate the estimated survival for osimertinib until more mature data become available from the AURAext/2 studies.

Table 5.33: Survival outcomes; time (mean and median) spent in health states, undiscounted

	Time in PFS (months)		Time in PD (months)		Time alive (months)	
Treatment	**Mean**	**Median**	**Mean**	**Median**	**Mean**	**Median**
Osimertinib	[redacted]	9.462	[redacted]	18.231	[redacted]	27.692
PDC	[redacted]	4.615	[redacted]	12.462	[redacted]	17.077

5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Table 5.34 summarises the breakdown of QALYs for each health state over the model time horizon in the base case analysis. Treatment with osimertinib is associated with more QALYs in pre-progression and post-progression compared with platinum doublet chemotherapy. Disutilities associated with adverse events are also estimated to be lower for osimertinib compared with platinum doublet chemotherapy.

Table 5.34: Summary of QALY gain by health state

Health state	QALY intervention (osimertinib)	QALY comparator (PDC)	Incremental QALYs	% absolute incremental QALYs
PF	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]
AE disutility	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

PDC: platinum doublet chemotherapy

Table 5.35 summarises the breakdown of costs in the base case analysis. The largest contributor to the total costs in the osimertinib arm is the drug acquisition cost, accounting for [redacted] of the total costs, whilst the largest proportion of costs for platinum doublet chemotherapy are the disease management costs. In the osimertinib arm, the cost of T790M mutation testing represents [redacted] of the total costs. Treatment with osimertinib is associated with higher absolute disease costs compared with platinum doublet chemotherapy, which is largely driven by patients surviving longer on osimertinib treatment. For the same reason, and given that two subsequent treatments are considered in the base case analysis, the cost of subsequent treatment is also higher for osimertinib. All other sources of costs are higher in the platinum doublet chemotherapy arm.

Table 5.35: Summary of costs by health state

Health state	Cost intervention (osimertinib)	Cost comparator (PDC)	Incremental costs	% absolute increment
Disease management: PF	[redacted]	[redacted]	[redacted]	[redacted]
Disease management: PD	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]
Treatment acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Administration and monitoring	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
T790M testing	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

In order to undertake the probabilistic sensitivity analysis (PSA), parameters in the model were assigned a probability distribution, reflecting both the central estimate (mean) of that parameter, its variance (standard error) and the anticipated shape of the data around its mean. Table 5.36 presents the probabilistic distributions applied in the model. Appendix A7 presents a summary of all parameters used in the model, along with the variation of the parameter used in the PSA.

Table 5.36: List of parameters and distributions included in the probabilistic sensitivity analysis

Parameter	Distribution	Comment
Survival functions	Cholesky decomposition	Decomposition of a Hermitian, positive-definite matrix into the product of a lower triangular matrix and its conjugate transpose
Adverse event rates (incidence)	Beta	Bounded between 0 and 1
Resource use (costs)	Gamma	Bounded between 0 and infinity, and skewed
Number of T790M tests	Gamma	Bounded between 0 and infinity, and skewed
Distribution of subsequent treatments	Dirichlet distribution	Normalized sum of independent gamma variables
Duration of subsequent treatment	Log-normal	Bounded between 0 and infinity, and skewed
Health state utilities	Beta	Bounded between 0 and 1
Adverse event disutilities	Log-normal	Bounded between 0 and infinity, and skewed

The PSA was run for 10,000 iterations for the base case analysis (osimertinib compared with platinum doublet chemotherapy). Results from the PSA are presented in Table 5.37. The probabilistic ICER is [redacted] per QALY gained which compares with [redacted] in the deterministic analysis (a less than 3% difference in the ICER).

Table 5.37: Average results based on the probabilistic sensitivity analysis (10,000 iterations)

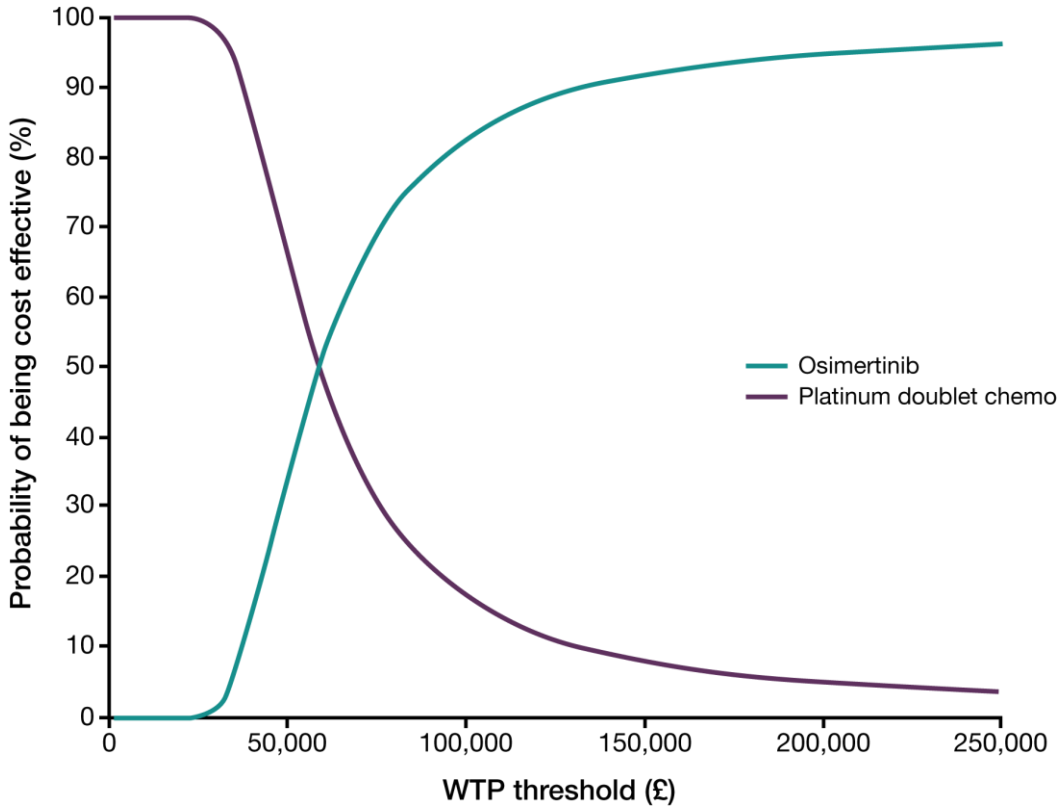
Treatment	Total costs	QALYs	Incremental Costs (£)	Incremental QALYs	ICER per QALY gained
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]			

The cost-effectiveness plane and cost-effectiveness acceptability curve for osimertinib compared with platinum doublet chemotherapy are presented in Figure 5.9 and Figure 5.10 respectively. At a cost-effectiveness threshold of £50,000, osimertinib has a 35% probability of being cost-effective compared with platinum doublet chemotherapy.

Figure 5.9: Cost-effectiveness plane for osimertinib vs platinum doublet chemotherapy

[Figure Removed]

Figure 5.10: Cost-effectiveness acceptability curve for osimertinib vs platinum doublet chemotherapy



5.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis was conducted by varying key model parameters by +/- 20% around the mean values applied in the base case analysis (see Table 5.38). The results of the analysis and the Tornado diagram are presented in Table 5.39 and Figure 5.11, respectively.

The tornado diagram shows that the ICER is most sensitive to the utility values used in the model, particularly for the progressed disease state. The discount rate for outcomes is also a key driver of the model results, given the long period over which outcomes occur and the importance of the health state utility values.

Table 5.38: Deterministic sensitivity analysis parameters

Parameter		Parameter values			Reference
		Lower value	Base case	Upper value	
Body surface area (m²)		1.34	1.68	2.02	Assume -/+20%
Discount rate	Costs	0.0%	3.5%	6.0%	Fixed 0% to 6%
	Outcomes	0.0%	3.5%	6.0%	Fixed 0% to 6%
Disease management	PF	£62	£77	£93	Assume -/+20%
	PD	£112	£140	£167	Assume -/+20%
	TC	£3,124	£3,905	£4,686	Assume -/+20%
Drug acquisition cost: PDC		£369	£461	£554	Assume -/+20%
Drug acquisition cost: Docetaxel		£5	£6	£8	Assume -/+20%
Testing cost	ctDNA	£378	£472	£566	Assume -/+20%
	Biopsy	£580	£725	£870	Assume -/+20%
Health state utility	Osimertinib: PF	0.652	0.815	0.978	Assume -/+20%
	Osimertinib: PD	0.542	0.678	0.814	Assume -/+20%
	PDC: PF	0.652	0.815	0.978	Assume -/+20%
	PDC: PD	0.542	0.678	0.814	Assume -/+20%

PF: Progression free; PD: Progressed disease; PDC: Platinum doublet chemotherapy; TC: Terminal care

Table 5.39: Results of deterministic sensitivity analysis – osimertinib vs platinum doublet chemotherapy

Parameter		Parameter values			Lower value (ICER)	Upper value (ICER)
		Lower value	Base case	Upper value		
Body surface area (m²)		1.34	1.68	2.02	[redacted]	[redacted]
Discount rate	Costs	0.0%	3.5%	6.0%	[redacted]	[redacted]
	Outcomes	0.0%	3.5%	6.0%	[redacted]	[redacted]
Disease management	PF	£62	£77	£93	[redacted]	[redacted]
	PD	£112	£140	£167	[redacted]	[redacted]
	TC	£3,124	£3,905	£4,686	[redacted]	[redacted]
Drug acquisition cost: PDC		£369	£461	£554	[redacted]	[redacted]
Drug acquisition cost: Docetaxel		£5	£6	£8	[redacted]	[redacted]
Testing cost	ctDNA	£378	£472	£566	[redacted]	[redacted]
	Biopsy	£752	£940	£1,128	[redacted]	[redacted]
Health state utility	Osimertinib: PF	0.652	0.815	0.978	[redacted]	[redacted]
	Osimertinib: PD	0.542	0.678	0.814	[redacted]	[redacted]
	PDC: PF	0.652	0.815	0.978	[redacted]	[redacted]
	PDC: PD	0.542	0.678	0.814	[redacted]	[redacted]

Figure 5.11: Tornado diagram – osimertinib vs platinum doublet chemotherapy

[Figure Removed]

5.8.3 Scenario analysis

(i) Survival modelling

IMPRESS all-comer population

A scenario analysis was conducted to assess the impact of using the data related to the full analysis set from the platinum doublet chemotherapy arm (n=127) in the IMPRESS study. This included survival data (PFS and OS), based on fitting parametric curves to the full population data. Similar to the T790M mutation positive population used in the base case analysis, the Gompertz distribution provided the best visual fit to non-parametric PFS data and the Weibull distribution provided the best visual fit to non-parametric OS data. All other model input parameters for the IMPRESS all-comer population were equivalent to those used for the T790M mutation positive population.

The results of this analysis showed that the platinum doublet chemotherapy arm IMPRESS all-comer population achieved better outcomes than the T790M mutation positive population in terms of overall survival and consequently higher total QALYs. This reflects the clinical data available from IMPRESS, which shows slightly better outcomes in the all-comer population in terms of median OS (17.2 months vs 15.7 months). Overall, the ICER for osimertinib compared with platinum doublet chemotherapy increased to [redacted] per QALY gained in this scenario.

Parametric survival distributions – OS and PFS

Given the uncertainty around the modelled OS estimates for osimertinib from the limited OS data currently available from the pooled AURAext/2 studies, scenario analyses were conducted to assess the impact of applying the other parametric distributions to the non-parametric OS data currently available from AURAext/2 and the IMPRESS T790M mutation positive population. In each of these scenarios the same parametric distribution was applied to the non-parametric PFS data.

(a) Log-logistic

When the log-logistic distribution was fitted to the non-parametric OS and PFS data it resulted in approximately 7% of patients in the osimertinib arm still alive and on treatment (in the PF state) at 5 years follow-up and approximately 15% still alive at 10 years follow-up, which may not be clinical plausible given the immaturity of the survival data. This consequently results in incremental costs of [redacted] and incremental QALYs of [redacted] for osimertinib compared with platinum doublet chemotherapy. However, the ICER of [redacted] per QALY gained is very similar to the base case analysis.

(b) Log-normal

Similar to the log-logistic distribution, the log-normal distribution resulted in approximately 10% of patients in the osimertinib arm still alive and on treatment (in the PF state) at 5 years follow-up and 36% still alive at 10 years follow-up, resulting in a median overall survival of approximately 64 months (5.3 years) for patients treated with osimertinib. This scenario consequently results in very high incremental costs of [redacted] and incremental QALYs of [redacted] for osimertinib compared with platinum doublet chemotherapy. This scenario also results in a lower ICER of [redacted] per QALY gained.

(c) Weibull

When the Weibull distribution was fitted to both the non-parametric PFS and OS data, this scenario results in an overall survival gain for osimertinib that is identical to the base case analysis but results in higher incremental costs for osimertinib compared with platinum doublet chemotherapy. This scenario results in an ICER of [redacted] per QALY gained.

(d) Generalised gamma

When the Generalised gamma distribution was fitted to the non-parametric OS and PFS data it resulted in a clinically implausible situation where the extrapolated OS curves for the two treatment arms intersected at approximately 40 months follow-up (see Figure 5.6). This scenario results in a projected mean survival gain of only [redacted] months and a mean QALY gain of only [redacted] for osimertinib compared with platinum doublet chemotherapy. Consequently, the ICER increases to [redacted] per QALY gained in this scenario.

(e) Gompertz

Similar to the Generalised Gamma distribution, the Gompertz distribution results in a clinically implausible situation where the extrapolated OS curves for the two treatment arms intersect at approximately 20 months follow-up. This scenario results in a mean overall survival difference in favour of the platinum doublet chemotherapy of [redacted] months despite the same parametric distribution resulting in a mean PF gain of approximately [redacted] months for osimertinib compared with platinum doublet chemotherapy. Consequently, the ICER increases to just over [redacted] per QALY gained in this scenario.

(f) Exponential

The results of fitting the exponential distribution to the non-parametric PFS and OS data produces similar results to the results obtained when fitting the Log-logistic and log-normal

distributions. In this scenario, the model estimates that approximately 13% of patients treated with osimertinib are still alive at 10 years follow-up. Overall, the ICER of [redacted] is very similar to the base case analysis

(ii) Health state utility values

Treatment-specific utility values

As described in Section 5.4, it was possible to estimate treatment-specific EQ-5D utility values for the progression-free and progressed disease states from the AURA2 and IMPRESS studies respectively. It should be noted that, when these utility values were applied in the model, additional treatment-specific disutilities associated with adverse events were not included as it is assumed that these are already captured in the treatment-specific utility values. In this scenario the ICER for osimertinib compared with platinum doublet chemotherapy increased slightly to [redacted] per QALY gained.

Progressed disease utility values

As described in Section 5.4, utility values for the progressed disease state were calculated by only including patients on or after the day of progression. Therefore, it is possible that the utility value (0.678) applied in the base case may not fully reflect the expected deterioration in a patients' HRQoL as they progress on to subsequent chemotherapy (which is associated with greater toxicity) and eventually to palliative care and death. However, this issue is common across all economic models in advanced cancer that adopt a similar simple partitioned model structure and require a single utility value to be applied across the entire duration that a patient spends in the progressed disease state. Furthermore, HRQoL data including the EQ-5D instrument are often not collected in a clinical trial once the patient has experienced disease progression. To explore the impact of applying a lower utility value for the progressed disease state in the model, a utility decrement of -0.1798 taken from the study by Nafees *et al*[116] was applied when patients moved from progression-free to progressed disease. This resulted in a lower utility value of 0.635 applied to the progressed disease state. Overall, this scenario resulted in a slightly higher ICER of [redacted] per QALY gained for osimertinib compared with platinum doublet chemotherapy.

(iii) Resource use and costs

Excluding costs of T790M mutation testing

A scenario analysis was conducted that excluded the cost of T790M mutation testing in line with the decision problem. This scenario resulted in a slightly lower ICER of [redacted] per QALY gained for osimertinib compared with platinum doublet chemotherapy.

Treatment post-progression – osimertinib

As described in Section 5.5, in AURAext/2 there was no maximum duration of treatment as patients could continue to receive osimertinib beyond RECIST progression as long as they were benefitting clinically, as determined by investigators. In AURAext/2, 83 patients (20.2%) continued osimertinib treatment beyond RECIST progression and the median duration of treatment with osimertinib after progression for these patients was 1.6 months.[82,83] To assess the impact of treatment beyond progression in the model, it was assumed that 20.2% of patients in the osimertinib arm would have an additional 2 months of treatment post-progression. This results in a total additional cost of [redacted] per patient treated with osimertinib after progression, which was applied simply as a one-off cost at the start of the model (and thus does not account for timing or discounting associated with treatment after disease progression). This scenario resulted in a slightly higher ICER of [redacted] per QALY gained for osimertinib compared with platinum doublet chemotherapy.

Pemetrexed generic cost

It is anticipated that pemetrexed will become available in generic form during 2016 as the patent is due for expiry sometime in 2016. Therefore, a scenario was conducted which lowered the list price of pemetrexed by 75%, resulting in a price of £40 per 100 mg vial. This scenario resulted in a slightly higher ICER of [redacted] per QALY gained for osimertinib compared with platinum doublet chemotherapy.

Table 5.40: Results of scenario analyses for osimertinib vs platinum doublet chemotherapy

Scenario	Total cost (£) Osimertinib	Total cost (£) PDC	Total QALYs Osimertinib	Total QALYs PDC	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(i) Survival modelling							
IMPRESS ITT population PFS/OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS and OS Distribution – Log Logistic (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS and OS Distribution – Log Normal (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS and OS Distribution – Weibull (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS and OS Distribution – G Gamma (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS and OS Distribution – Gompertz (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS and OS Distribution – Exponential (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(ii) Health state utility values							
Treatment-specific utility values (Osimertinib – AURA2; PDC – IMPRESS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD Utility decrement (Nafees *et al*): -0.1798 (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
(iii) Resource use and costs							
Exclude T790M test costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment after RECIST progression - osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume Pemetrexed generic costs (75% discount)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5.9 Subgroup analysis

The cost-effectiveness of osimertinib in second-line only and ≥third-line was explored in subgroup analyses in order to address as far as possible the relevant comparisons listed in the decision problem. Osimertinib was compared against appropriate treatment comparators (platinum doublet chemotherapy and docetaxel), creating three scenarios as specified in Table 5.41, with the corresponding source of survival data used. In addition, the following parameters were dependent on the line of treatment:

- Patient demographics (see Table 5.22 Section 5.5)
- Survival data (see Section 5.3)
- Safety (see Table 5.14 Section 5.3)
- Subsequent treatments (see Table 5.22 Section 5.5)

Table 5.41: Subgroup analyses conducted

Subgroup analysis	Scenario
Second-line setting vs PDC	IMPRESS T790M subgroup in second-line
Second-line setting vs docetaxel monotherapy	Singlet chemotherapy in second-line (Park 2015)[88]
≥Third-line setting vs single-agent chemotherapy	Singlet chemotherapy in ≥third-line (Schuler 2015)[109]

Second-line only population

Osimertinib versus platinum-based chemotherapy

The results of this subgroup analysis, which utilises data specific to the second-line only population from AURAext/2 (n=129), are presented in Table 5.42. Compared with the base case analysis, this subgroup analysis produced a lower ICER of [redacted] per QALY gained for osimertinib compared with platinum-based chemotherapy. An additional scenario analysis was conducted for the second-line only population by applying the health-state utility values from AURA2 to both treatment arms for the second-line only population (PF = 0.853; PD = 0.726). This scenario analysis resulted in slightly higher incremental QALYs of [redacted] for osimertinib compared with platinum-based chemotherapy and consequently a slightly lower ICER of [redacted] per QALY gained.

Table 5.42: Subgroup analysis – osimertinib vs platinum-based chemotherapy (second-line only population)

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]			

Osimertinib versus docetaxel monotherapy

This scenario analysis considers a comparison where patients who have progressed on first-line EGFR TKI treatment are not eligible for platinum-containing treatment regimen (in line with the decision problem). This scenario utilises survival data for the ≥second-line population from AURAext/2 for osimertinib and data from the Park 2015 study for single-agent chemotherapy (docextaxel). Compared with the base case analysis, this subgroup analysis produced a higher ICER of [redacted] per QALY gained for osimertinib compared with single-agent chemotherapy. An additional scenario analysis was conducted for this comparison by applying the health-state utility values from AURA2 for the second-line only population. This scenario analysis resulted in slightly higher incremental QALYs of [redacted] for osimertinib compared with single-agent chemotherapy and consequently a slightly lower ICER of [redacted] per QALY gained.

Table 5.43: Subgroup analysis – osimertinib vs docetaxel monotherapy (second-line only population)

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]			

≥Third-line population: osimertinib versus single-agent chemotherapy

This scenario analysis considers a scenario where patients have received previous treatment with both an EGFR TKI and chemotherapy (in line with the decision problem). This scenario utilises data specific to the ≥third-line population from AURAext/2 for osimertinib (n=282) and data from the Schuler 2015 study for single-agent chemotherapy (docextaxel). Compared with the base case analysis, this subgroup analysis produced a lower ICER of [redacted] per QALY gained for osimertinib compared with single-agent chemotherapy. An additional scenario analysis was conducted for this comparison by applying the health-state

utility values from AURA2 for the ≥third-line population (PF = 0.798; PD = 0.659). This scenario analysis resulted in slightly lower incremental QALYs of [redacted] for osimertinib compared with single-agent chemotherapy and consequently a slightly higher ICER of [redacted] per QALY gained.

Table 5.44: Subgroup analysis – osimertinib vs docetaxel monotherapy (≥Third-line population)

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]			

5.10 Validation

5.10.1 Validation of *de novo* cost-effectiveness analysis

The predicted model outcomes for the base case analysis were compared to the observed IMPRESS, and AURAext/2 pooled data to confirm that the model behaves as expected and produces survival curves similar to the observed data. The PFS and OS curves in Figure 5.12 and Figure 5.13 indicate that the model accurately predicts the time in progression-free and the time alive.

Figure 5.12: Predicted model time in PF health state vs observed PFS data

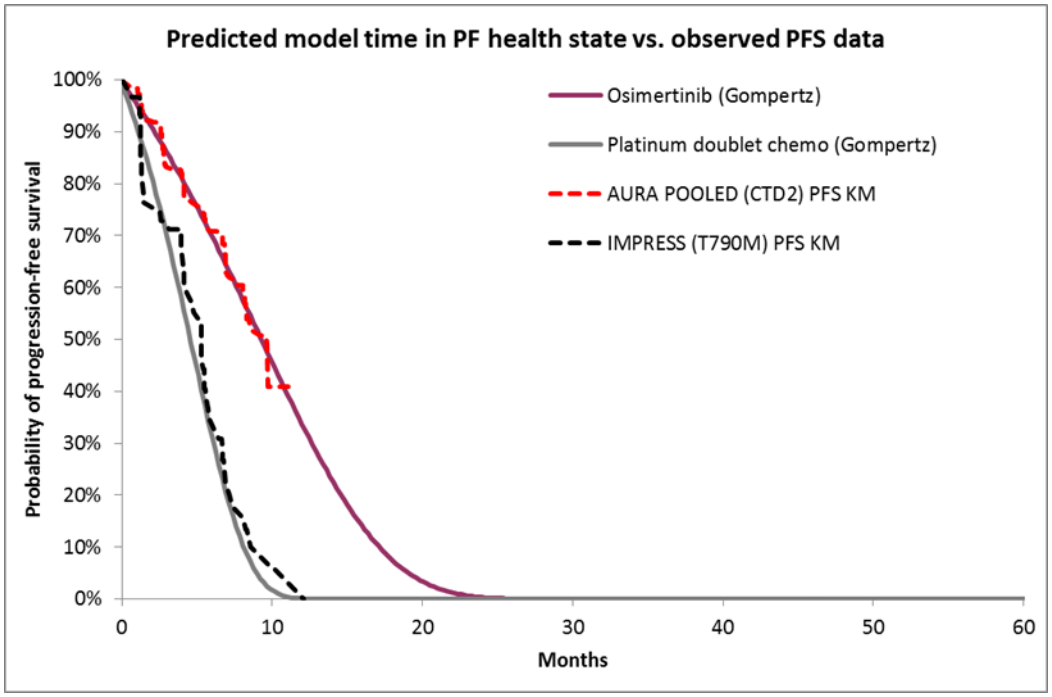


Figure 5.13: Predicted model time alive vs observed data

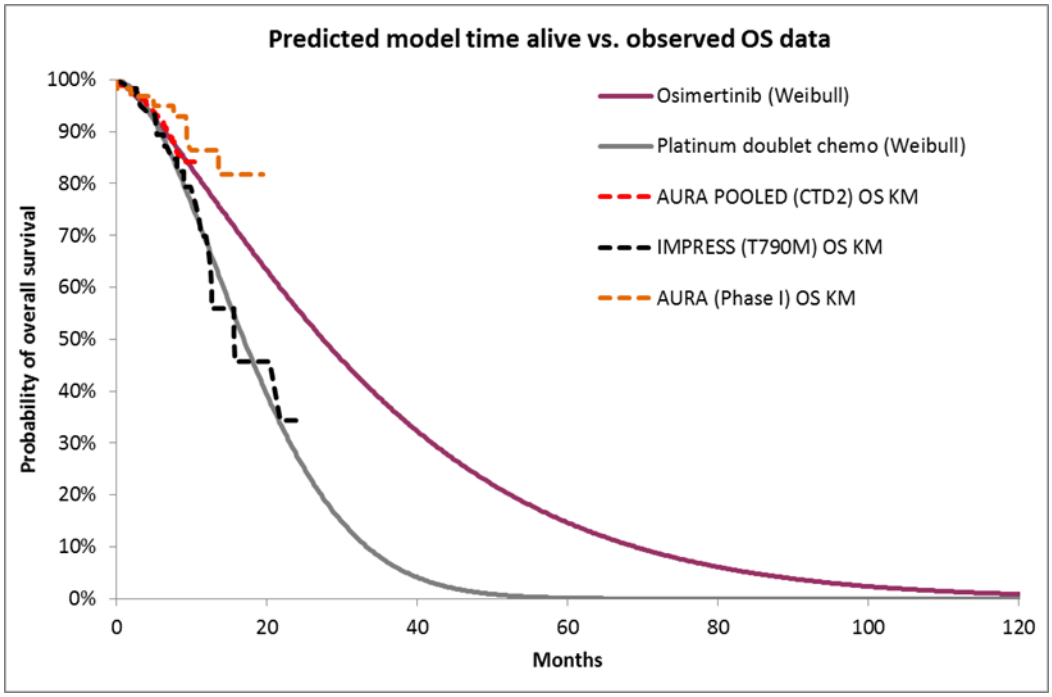


Table 5.45 and Table 5.46 present the long-term predicted model outcomes. These are not possible to verify without external long-term data. However, at this point it can be concluded that the model outcomes for the base case analysis generate survival estimates that are clinically plausible:

- After 2 years the proportion of patients progression free is 0% for both treatments
- The survival rate at 10 years is approximately 0% for platinum doublet chemotherapy and only 0.9% in the osimertinib arm
- 14.8% of patients in the osimertinib arm and 0.2% in the platinum doublet chemotherapy arm are still alive after 5 years in the model

Table 5.45: Predicted proportion of patients in PF health state

	Time from model entry				
	Month 3	**Month 6**	**Month 12**	**Month 18**	**Month 24**
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	0.0%
Platinum doublet chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	0.0%

Table 5.46: Predicted proportion of patients alive

	Time from model entry				
	Month 3	**Month 6**	**Month 12**	**Month 60**	**Month 120**
Osimertinib	96.1%	90.8%	79.0%	14.8%	0.9%
Platinum doublet chemotherapy	96.7%	89.4%	68.5%	0.2%	0.0%

As limited long term data are available from the AURAext/2 trials a meaningful comparison of osimertinib OS data from the trial with the model estimates is impossible beyond 12 months. Therefore, to provide further validation of the projected survival estimates in the base case analysis we analysed the relationship between PFS and OS from other trials in advanced NSCLC patients in an attempt to see if our model estimated a ratio of OS to PFS that could be considered clinically plausible.

We evaluated first line and ≥second-line line phase 3 studies in advanced NSCLC, including products appraised by NICE (see Table 5.47). This analysis was conducted by examining the ratio between the reported median PFS and median OS estimates. For example, a reported median PFS of 12 months and a reported median OS estimate of 24 months would elicit an OS:PFS ratio for that specific treatment arm of 2.0. Results were tabulated by line of therapy (first line studies and ≥ second-line studies). For active treatment arms the OS:PFS ratio was between 2.10 and 5.30. Excluding the nivolumab trial due to the emerging evidence that PFS and survival curves for immuno-oncology may have different characteristics, the range is 2.10 to 3.71 with some evidence that the ratio is higher in the more refractory setting. Observed ratios in the control groups of these studies appear to be slightly larger than those observed in the active arms, with ratios ranging from 2.21 to 7.61, again with some evidence for higher ratios in the ≥ second-line setting. This effect is largely explained by the very rapid progression in the control groups of many of these trials alongside crossover to active study drug post progression.

For osimertinib the median OS:PFS ratio of 2.85 predicted in the base case analysis (27.60 months OS vs 9.70 months PFS) is consistent with the results of the active arm in other recent studies of novel lung cancer therapies. This provides confidence that the model has

generated survival estimates that is consistent with the relationship between PFS and OS that has been established through the large body of evidence in the advanced NSCLC setting.

Comparing the ratios between the IMPRESS T790M mutation positive group used as a control group in our comparison, the observed ratio is 2.96, which is higher than the ratio for the AURA pooled data, and provides further confidence that the modelled estimates in the base case analysis are unlikely to be biased in favour of osimertinib.

Table 5.47: Validation of modelled PFS and OS estimates with previously published studies in advanced NSCLC

Trial	Active Arm	Control Group	Population	Active Arm			Control Arm		
				Median PFS	Median OS	OS/PFS Ratio	Median PFS	Median OS	OS/PFS Ratio
First Line Studies									
LUX-Lung 3[130]	Afatanib	Platinum doublet (pemetrexed+cisplatin)	1L EGFRm+ aNSCLC	11.10[13] 1	28.20	2.54	6.90	28.20	4.09
EURTAC[66]	Erlotinib	Cisplatin + docetaxel/gemcitabine	1L EGFRm+ aNSCLC	9.70[25]	22.90	2.36	5.20	19.60	3.77
IPASS[50]	Gefitinib	Carboplatin + paclitaxel	1L EGFRm+ aNSCLC	9.50	21.60	2.27	6.30	21.90	3.48
NR	Pemetrexed + cisplatin	Gemcitabine + cisplatin	1L NSCLC (Adeno & large cell carcinoma)	5.30	11.80	2.23	4.70	10.40	2.21
LUX-Lung 6[130]	Afatanib	Cisplatin plus gemcitabine CT	1L EGFRm+ aNSCLC	11.00[13] 2	23.10	2.10	5.60	23.50	4.20
2L+ Studies									
CheckMate 057	Nivolumab	Docetaxel	≥2L NSCLC post platinum-doublet	2.30	12.20	5.30	4.20	9.40	2.24
LUME-Lung 1	Nintedanib + docetaxel	Docetaxel	2L NSCLC	3.40	12.60	3.71	2.70	10.30	3.81
AURA ext/2	Osimertinib[a]	N/A	≥2L EGFRm+ T790M aNSCLC	9.70	27.60	**2.85**			
IMPRESS	Gefitinib + platinum doublet CT	Platinum doublet	2L EGFRm+ aNSCLC	5.40	14.80	2.74	5.40	17.20	3.19
IMPRESS	N/A	Platinum doublet in T790M mutation +ve[c]	2L EGFRm+ T790M aNSCLC				5.30	15.70	2.96
PROFILE 1007	Crizotinib	Docetaxel/pemetrexed	Previously treated ALK+ NSCLC	7.70	20.30	2.64	3.00	22.80	7.60
REVEL	Ramucirumab + docetaxel	Placebo + Docetaxel	2L NSCLC post 1L platinum CT	4.50	10.50	2.33	3.00	9.10	3.03
NR	Afatinib + paclitaxel	Single-agent CT by investigator choice	≥3L post initial disease control on erlotinib/gefitinib followed by paclitaxel	5.60	12.20	2.18	2.80	12.20	4.36

[a] Osimertinib median OS is estimated from CE extrapolation
[b] Numbers likely to have been confounded due to crossover

5.11 Interpretation and conclusions of economic evidence

(i) Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

This is the first economic evaluation undertaken for osimertinib for patients with EGFR and T790M mutation positive locally advanced or metastatic NSCLC who have received previous treatment with an EGFR TKI. Therefore, it is not possible to compare the results presented here with previously published analyses.

(*ii) Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?*

The economic evaluation focuses on EGFR and T790M mutation positive patients with locally advanced or metastatic NSCLC who have received previous EGFR TKI therapy. This covers the vast majority of patients who are likely to use the technology in clinical practice in England; that is, following treatment failure on first-line EGFR TKI treatment.

(iii) How relevant (generalisable) is the analysis to clinical practice in England
The analysis is likely to be directly applicable to clinical practice in England because:

- The patient population in AURAext/2 and the economic evaluation is reflective of patients with locally advanced or metastatic NSCLC and thus the clinical outcomes of PFS and OS are likely to be applicable to the patient population in England
- The economic model structure is in line with other models in advanced cancer including previous NSCLC HTA submissions to NICE
- Resource use and costs were taken from UK-based sources and previous NICE technology appraisals and have been validated by UK-based clinicians

(iv) What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Due to the immaturity of the PFS and OS data for osimertinib currently available from AURAext/2, the extrapolated survival estimates are subject to uncertainty.

Given that AURA and AURA2 are both single arm studies, there is no controlled comparative clinical data for osimertinib and the platinum doublet chemotherapy. Although the model is

based on a unadjusted comparison with data from the IMPRESS study, we have shown (in Section 4.10.3) that this is unlikely to bias the results of the cost-effectiveness analysis in favour of osimertinib.

Despite the only available clinical data for osimertinib being from two single arm studies, we have attempted to generate a robust and clinically appropriate clinical comparator by identifying a subgroup of patients in the IMPRESS study who are T790M mutation positive.

(v) What further analyses could be carried out to enhance the robustness or completeness of the results?

As described in Section 4.14 a confirmatory Phase III RCT, AURA3, is currently ongoing. This trial is event driven and anticipated to report in 2017. It is designed to compare the efficacy and safety of osimertinib versus platinum-based doublet chemotherapy in patients with EGFRm+ and T790M mutation positive aNSCLC whose disease has progressed following prior therapy with an EGFR TKI. The data from this Phase III study will be able to address uncertainty around the comparative efficacy of osimertinib with platinum-based chemotherapy (the most relevant comparator to the decision problem).

6 Assessment of factors relevant to the NHS and other parties

6.1 Number of people eligible for treatment in England

The estimated number of incident and prevalent patients eligible for osimertinib treatment following progression on an EGFR TKI is based on Section 3.4.2 and summarised in Table 6.1. The prevalent pool of patients is based on those patients currently living with locally advanced or metastatic NSCLC who may be eligible for osimertinib upon marketing authorisation or later. As the rate of identified T790M mutations is estimated to be approximately 1% in treatment-naïve EGFRm positive patients[7], the estimated patient numbers and net budget impact of osimertinib in this patient population is expected to be negligible.

Table 6.1: Eligible population for osimertinib in England

Population	Proportion of patients	Number of patients (Incident)	Number of patients (Prevalent)	References
Lung cancer diagnosis	–	31,393	25,276	National Lung Cancer Audit (NCLA) Annual Report 2015; Cancer Research UK
Confirmed NSCLC	59%	18,447	14,853	NCLA 2015
Patients with stage III/IV NSCLC	77%	14,204	11,437	National Cancer Intelligence Network. Stage Breakdown by CCG 2013 (link is external). London: NCIN; 2015
Patients tested for EGFR mutation	87%	12,372	9,961	National Lung Cancer Audit (NCLA) Annual Report 2014
Patients with EGFR mutation	10%	1,237	996	AZ Internal Research
Patients receiving 1st-line anticancer treatment	58%	713	574	NCLA 2015
Patients who progress on 1st-line EGFR TKI and receive active treatment	Incident: 65% Prevalent: 50%	463	287	AZ Internal Research
Patients who harbour T790M mutation at progression	60%	278	172	Yu 2013[28]; Pao 2005[30]

6.2 Assumptions made about current treatment options and associated costs

The budget impact analysis makes the simplifying assumption that the incremental costs of a scenario with osimertinib compared with a scenario without osimertinib is limited to active second-line treatment and that following second-line treatment all patients would move to best supportive care (BSC) and thus incur no further treatment costs. Assumptions about the mean duration of second-line treatment were based on the available clinical trial data; pooled data from AURA ext/2 and the IMPRESS study[75,82,83] or the summary of product characteristics for docetaxel. The costs of single-agent chemotherapy is based on docetaxel montherapy were based on the summary of product characteristics which states that treatment. The costs of osimertinib treatment includes the costs of T790M testing required to identify patients eligible for treatment after progression on first-line EGFR TKI treatment. The costs of platinum-based and single-agent chemotherapy includes the costs of IV administration while it was assumed that BSC was not associated with any treatment costs. Further details are shown in Table 6.2.

Table 6.2: Duration of treatment and treatment costs

Comparator	Mean duration of treatment (months)	Costs of treatment	Total treatment costs
Osimertinib	[redacted]	£4,722.30 per month £1,351 per patient identified as T790M mutation positive	[redacted]
Pemetrexed plus cisplatin	3.2	PEM – £160 per 100 mg vial CIS – £3.24 per 1 mg/10 ml vial £263.26 1st admin £338.53 subsequent admin	£7,662
Docetaxel	2.8 (4 x 3-weekly cycles)	£20.95 per 140mg/7ml vial £263.26 1st admin £338.53 subsequent admin	£1,114
BSC	N/A	N/A	£0

6.3 Assumptions about market share in England

The current market share for available treatments following disease progression on first-line EGFR TKI are presented in Table 6.3 and represents the 'scenario without osimertinib'. Although the majority of patients (95%) would be expected to be treated with platinum doublet chemotherapy upon disease progression, a small proportion would be ineligible to receive platinum doublet chemotherapy and would instead receive single-agent chemotherapy. Based on internal projections, it is estimated that the uptake of osimertinib will reach 80% by year 4 (Table 6.4). Due to limited forecasts, the market share projection

for year 5 is assumed to be the same as for year 4. For patients not treated with osimertinib in the 'scenario without osimertinib', the distribution is assumed to be equivalent to the distribution in the 'scenario with osimertinib' for years 1–5.

Table 6.3: Market share analysis – scenario without osimertinib

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Osimertinib	0%	0%	0%	0%	0%
Pemetrexed plus cisplatin	95%	95%	95%	95%	95%
Docetaxel	5%	5%	5%	5%	5%
Total	100%	100%	100%	100%	100%

Table 6.4: Market share analysis – scenario with osimertinib

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Osimertinib	35%	50%	70%	80%	80%
Pemetrexed plus cisplatin	62%	47%	28%	19%	19%
Docetaxel	3%	3%	2%	1%	1%
Total	100%	100%	100%	100%	100%

6.4 Estimated annual budget impact on the NHS in England

The budget impact is estimated as the number of patients and associated costs for treating those patients according to the assumed market share and expected uptake of osimertinib in a scenario without (Table 6.5) and with osimertinib (Table 6.6). It should be noted that the estimated prevalent population eligible for osimertinib treatment (n=172) is divided equally between the first 2 years in which treatment with osimertinib is available. The results of this analysis show that the net cumulative budget impact of introducing osimertinib for patients who have received prior EGFR TKI treatment from 2016–2020 is approximately [redacted] (Table 6.7).

Table 6.5: Patient numbers and total costs in scenario without osimertinib

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Patients					
Osimertinib	–	–	–	–	–
Pemetrexed plus cisplatin	346	346	264	264	264
Docetaxel	18	18	14	14	14
Total patients	364	364	278	278	278
Total costs					
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed plus cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6.6: Patient numbers and total costs in scenario with osimertinib

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Patients					
Osimertinib	127	182	195	222	222
Pemetrexed plus cisplatin	225	173	79	53	53
Docetaxel	12	9	4	3	3
Total patients	364	364	378	278	278
Total costs					
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pemetrexed plus cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6.7: Summary of budget impact

	Y1 (2016)	Y2 (2017)	Y3 (2018)	Y4 (2019)	Y5 (2020)
Scenario without osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario with osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative cost impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Single technology appraisal

Osimertinib for treating metastatic EGFR and T790M mutation-positive non-small-cell lung cancer [ID874]

Dear Wim,

The Evidence Review Group, Liverpool Reviews and Implementation Group (LRiG), and the technical team at NICE have looked at the submission received on 19 February 2016 from AstraZeneca. In general they consider that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **24 March 2016**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial in confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Ahmed Elsada, Technical Lead (ahmed.elsada@nice.org.uk). Any procedural questions should be addressed to Kate Moore, Project Manager (kate.moore@nice.org.uk).

Yours sincerely

Helen Knight
Associate Director – Appraisals,
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **Priority question**. Please describe in more detail the method that has been used to pool:

   a. The time-to-event outcomes (progression-free survival [PFS], overall survival [OS] and duration of response [DoR]) from the AURAext and AURA2 studies.

   b. All other outcomes (objective response rate [ORR], best objective response [BOR] and disease control rate [DCR]) from the AURAext and AURA2 studies.

A2. **Priority question**. In Section 1.2 of the company's technical report, the company refers to a list of documents. Please provide document '*CTD2 5.3.5.3 Supportive Tables and Figures and Statistical Analysis Plan for the Summary of Clinical Efficacy'.*

A3. **Priority question**. Please provide the Statistical Analysis Plans for the AURAext, AURA2 and IMPRESS studies.

A4. **Priority question**. In the report entitled '*D5160C0000a Adjusted Indirect Comparison of osimertinib vs Standard of Car*e' the authors mention (page 3) that they have not adjusted for multiple testing of multiple subgroups and endpoints. Please explain why multiple testing of endpoints was not adjusted for. Please repeat the analyses described in Section 4.10.3.4 of the company's submission adjusting for multiple testing of endpoints, and present the results for each comparison.

A5. **Priority question**. It is not clear to the ERG how the company pooled the data from the AURAext and the AURA2 studies and compared these data with data from patients with T790M mutation-positive non-small-cell lung cancer (NSCLC) in the control arm of the IMPRESS trial. Please perform sensitivity analyses to show that the methods used were robust. Three steps should be undertaken:

   a. Treat the AURAext and AURA2 trials separately (i.e. no pooling), then carry out the propensity score (PS) analysis that has been proposed by the company (page 80 of the company's submission), and then pool the treatment effects.

   b. Please randomly select half of the patients with T790M mutation-positive NSCLC from the IMPRESS trial, then match them to patients in the AURAext trial. The remaining patients with T790M mutation-positive NSCLC from the IMPRESS trial should be matched to patients in the AURA2 trial before carrying out a meta-analysis.

   c. Please repeat this process at least 1000 times and assess how often the p value is statistically significant. Alternatively, the company may use permutation tests to

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show how robust their findings are. Whichever method is used, please provide details of results.

A6. **Priority question**. The company states on page 149 of its submission that 'in general the PFS K-M curves from the IMPRESS trial do not cross' (see Figure 4.16). However, the ERG considers that the curves do cross. Please provide the results of the analyses undertaken (e.g. cumulative hazard plot) based on which the company concluded that the proportional hazards assumption is valid?

A7. Please reproduce Table 4.7 (page 76 of the company's submission) for patients receiving second-line, third-line and fourth- and subsequent-line treatment in the pooled data set of AURA.

A8. The results for the subgroup analyses are presented in Figures 4.8 and 4.17 in the company's submission for the pooled dataset of AURA, and the IMPRESS trial respectively. Please provide the p values for the tests for interaction for all subgroup analyses for ORR and PFS.

A9. Please reproduce Figure 4.8 (page 114 of the company's submission) for the population with T790M mutation-positive NSCLC in the IMPRESS trial who have received doublet chemotherapy (n=61).

A10. Please complete the table below with the number of patients who died whilst on different lines of study treatment for the following populations: all patients in the IMPRESS trial who received platinum doublet chemotherapy (n=132), patients in the IMPRESS trial with T790M mutation-positive NSCLC who have received doublet chemotherapy (n=61), patients in AURAext, patients in AURA2, and the pooled populations from AURA (second-line, ≥second line and ≥third-line).

	IMPRESS (n=132)	IMPRESS (n=61)	AURAext	AURA2	AURA pooled
Second line					
≥ Second line					
≥ Third line					

A11. The authors of the IMPRESS publication in Lancet Oncology (Soria et al., 2015) state that the IMPRESS trial OS data are immature. Please comment on the degree to which the published data are immature, and clarify whether there is a planned update of results expected soon (including outcomes for the subgroup of patients with T790M mutation-positive NSCLC)? If so, please will you provide us with these data?

A12. Please indicate when the results from the next planned analysis of the AURA pooled data will be available.

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Section B: Clarification on cost effectiveness data

B1. **Priority request: Kaplan-Meier (K-M) data.** Please provide the K-M analyses listed in 'a' to 'e' below for the following populations: all patients in the IMPRESS trial who received platinum doublet chemotherapy (n=132); patients in the IMPRESS trial with T790M mutation-positive NSCLC who have received platinum doublet chemotherapy (n=61); patients in AURAext, patients in AURA2; and the pooled populations from AURA (second-line, ≥second line and ≥third-line for all three AURA datasets).

a. Time to death from any cause (OS) K-M analysis stratified by treatment arm.
b. Time to disease progression or death (PFS) K-M analysis based on investigator assessment, stratified by treatment arm.
c. Time from disease progression by investigator assessment to death from any cause (PPS) K-M analysis.
d. Time to study treatment discontinuation K-M analysis.
e. Time from study treatment discontinuation to death.

Format: Please present analysis outputs using the format of the sample table shown below. Please provide these data in a .xcl or .csv file.

Censoring: Please censor lost to follow-up and patients who withdrew from the study at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off i.e. not when last known to be alive (OS/post-progression survival [PPS]), and not at the date when the tumour was last assessed (PFS).

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Sample table: Example of output (SAS) required from specified Kaplan-Meier analyses - The LIFETEST Procedure

Product-Limit Survival Estimates						
DAYS		**Survival**	**Failure**	**Survival Standard Error**	**Number Failed**	**Number Left**
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		……	……	……	…	…
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

Section C: Textual clarifications and additional points

C1. In Figure 4.1 (page 66 of the company's submission):

a. 19,948 records were identified and 2265 duplicates were removed. The number screened is expected to be 17,683. However, in Figure 4.1 the number screened is 17,716. Please clarify.

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b. 723 conference abstracts were excluded for having insufficient information. Please clarify what criteria were used to decide whether or not the information given in an abstract was insufficient.

c. 10 full text articles were not retrieved. Please give the reasons for not retrieving these articles.

C2. Please provide a full legend for Table 4.18 (page 108 of the company's submission) and explain superscripts b, c and d.

C3. There are 2 documents referred to in the company's submission that were not included in the CD containing the company references. Please provide the following documents:

a. AstraZeneca. Market Research report. *Data on file* 2015

b. AstraZeneca. Advisory board. *Data on file* 2015

Section D: Marking of confidential information

D1. We note that section 4.10.3 of the company's submission (pages 79–86) about the adjusted indirect comparison of osimertinib with platinum doublet chemotherapy is entirely marked as academic-in-confidence. These analyses are expected to form part of the appraisal committee's considerations, and NICE does not agree that they can be wholly designated confidential. We therefore request that you to reconsider all restrictions relating to these data. As a minimum, a description of the methods and results of the indirect comparisons (eg in the form of an abstract) must be made available for public disclosure.

Response to Clarification Questions

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Osimertinib for locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer [ID874]

Single technology appraisal (STA)

File name	Version	Contains confidential information	Date
ID874_Osimertinib_Clarification Questions_AZResponse [CIC_AIC]	1.0	Yes	24 March 2016

AstraZeneca UK Ltd
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Section A: Clarification on effectiveness data

A1. Priority question. Please describe in more detail the method that has been used to pool:

a) The time-to-event outcomes (progression-free survival [PFS], overall survival [OS] and duration of response [DoR]) from the AURAext and AURA2 studies.
b) All other outcomes (objective response rate [ORR], best objective response [BOR] and disease control rate [DCR]) from the AURAext and AURA2 studies.

Description of Pooling

Data sets for AURAext and AURA2 were merged to produce a single data set from which efficacy and safety end-points were calculated. Results of analysis of end-points were not pooled.

For the AURAext and AURA2 studies separately, each patient had analysis variables generated to allow for the analysis to be conducted at the study level. These variables were pre-defined in the Statistical Analysis Plans (SAPs) and are identical for both studies. These analysis variables were created at a patient level within each study to allow for the individual study analysis to be conducted.

At the time of pooling the 2 studies, new datasets were created at a patient level by using a unique patient identification number and 'stacking' the patients from AURAext on to new datasets containing the AURA2 patients. These new datasets contained all 411 patients and the required variables for analysis. No new analysis variables were created.

The analysis of the pooled data was then conducted as defined in the SAP using each patient's data. Results of the analysis from the two individual studies were not pooled. The data was pooled at a patient level for AURAext and AURA2 and new analysis was conducted (as predefined in the SAP).

Description of derivation of efficacy endpoints

For time-to-event outcomes (PFS, OS and DoR), the methodology was a Kaplan-Meier estimate of the survival function to allow us to take into account the fact that some patients have not experienced the event of interest (censoring). For the DoR,

the same methodology was used, but the analysis was only conducted on those patients who experienced a RECIST confirmed response (complete or partial response). Patients were censored in this analysis if the response had not ended (so the patient had not progressed or died).

Regarding the primary endpoint, overall response rate (ORR), the number of patients experiencing a confirmed RECIST response of CR or PR (complete response or partial response) was divided by the total population (either the evaluable for response population when considering the independent reviewer assigned response, or the full analysis set when considering the investigator assigned response) multiplied by 100 [ie number of patients with a confirmed response of CR or PR / number of patients in the population * 100]. An exact 95% confidence interval using the Clopper-Pearson methodology was also produced.

Regarding the disease control rate (DCR), the same methodology was used for the overall response rate but included in the numerator the patients who experienced a best overall response of stable disease.

Best objective response (BoR) was calculated based on the overall visit response from each RECIST assessment. It is the best response a patient has had following start of treatment but prior to starting any subsequent anti-cancer therapy and prior to RECIST progression or the last evaluable assessment in the absence of RECIST progression and subsequent anti-cancer therapy. Categorisation of BoR was based on RECIST using the following response categories: complete response (CR), partial response (PR), stable disease (SD), progression of disease (PD) and not evaluable (NE). BoR was determined programmatically based on RECIST from the overall visit response at each visit including all data up until the first progression, the start of any subsequent cancer therapy or the last evaluable assessment in the absence of progression. For determination of a best response of SD, the earliest of the dates contributing towards a particular overall visit assessment was used. SD was recorded at least 6 weeks after starting treatment. For patients who died with no evaluable RECIST assessments, if the death occurred ≤6 weeks after starting treatment, then BoR was assigned to the progression (PD) category. For patients who died with no evaluable RECIST assessments, if the death occurs >6 weeks after starting treatment then BoR was assigned to the NE category. The number of

patients with a best response in each of the RECIST categories was then summarised.

A2. Priority question. In Section 1.2 of the company's technical report, the company refers to a list of documents. Please provide document '*CTD2 5.3.5.3 Supportive Tables and Figures and Statistical Analysis Plan for the Summary of Clinical Efficacy'.*

This document is provided in attachment to this response.

A3. Priority question. Please provide the Statistical Analysis Plans for the AURAext, AURA2 and IMPRESS studies.

The Statistical Analysis Plans for all studies are provided in attachment to this response.

A4. Priority question. In the report entitled 'D5160C0000a Adjusted Indirect Comparison of osimertinib vs Standard of Care' the authors mention (page 3) that they have not adjusted for multiple testing of multiple subgroups and endpoints. Please explain why multiple testing of endpoints was not adjusted for. Please repeat the analyses described in Section 4.10.3.4 of the company's submission adjusting for multiple testing of endpoints, and present the results for each comparison.

The adjusted indirect comparison of osimertinib vs. the platinum doublet chemotherapy arm from the IMPRESS study is an exploratory analysis with the objective to gauge the efficacy benefit of osimertinib compared with the standard of care, given the osimertinib studies were single-arm.

Osimerinib produced a profound, statistically significant improvement in key efficacy endpoints relative to platinum doublet chemotherapy (Table 1), as follows:

- PFS: osimertinib 9.7 months versus 5.3 months, HR=0.280, p-value<0.0001;
- ORR: osimertinib 64.6% versus 34.8%, OR=4.76, p-value<0.001;
- DCR: osimertinib 92.1% versus 76.1%, OR=4.39, p-value=0.002.

There were no predefined hypothesis and the objective was not to prove or disprove any hypothesis by the use of p-values. The interest was to gauge any trends in treatment differences with the use of parameter estimates and confidence intervals. Therefore, we did not consider it appropriate to adjust for multiple testing to counteract the increased risk of a false positive result for an indirect comparison of

non-randomised data with no pre-specified testing of efficacy endpoints. Hence no adjustment for multiplicity was applied. However, if we were to retrospectively apply an approach to control the family-wise error rate at 0.05 (2-sided), the interpretation would not change, as illustrated below. A Bonferroni correction (Bland & Altman, 1995) is a conservative method and is free of dependence and distributional assumptions. The method equally divides the alpha between all of the comparisons, as such:

$$\alpha_k = \frac{\bar{\alpha}}{k}$$

where k is the number of comparisons, $\bar{\alpha}$ is the family-wise error rate and α_k is the alpha level assigned to each k comparison. AstraZeneca considered 4 comparisons and a family-wise error rate of 0.05. Therefore the adjusted alpha level would be 0.05 / 4 = 0.0125 (2-sided).

The table below presents the p-values from the report for the 4 efficacy analysis (pg2/3). The p-values for PFS, ORR and DCR are all less than the adjusted significance level of 0.0125. The p-value for OS is larger than 0.0125. However it is also larger than 0.05, and hence the interpretation of the data has not changed by applying a conservative adjustment to the alpha level. As stated in the original submission, caution should be taken when interpreting the adjusted results of the OS in light of the immaturity of the OS data available at the time of analysis (Osimertinib 11.5% maturity and platinum doublet chemotherapy 29.4% maturity). For both groups the KM risk set beyond 12 months is very limited (n <15 patients) leading to unstable estimates beyond this time point, especially for the estimation of median OS.

Endpoint	Result	p-value

PFS	osimertinib demonstrated an improvement in median PFS: 9.7 months versus 5.3 months for platinum doublet chemotherapy; HR 0.280, 95% CI 0.1855 to 0.422	<0.0001
ORR (confirmed for the evaluable-for-response population)	osimertinib demonstrated an improvement in ORR: 64.6% versus 34.8% for platinum doublet chemotherapy; OR 4.76, 95% CI 2.21 to 10.26	<0.001
DCR	osimertinib demonstrated an improvement in DCR: 92.1% versus 76.1% for platinum doublet chemotherapy; OR 4.39, 95% CI 1.71 to 11.28	0.002
OS	median OS for osimertinib was not calculable, median OS for platinum doublet chemotherapy was 21.7 months (95% CI 12.55, NC). Kaplan-Meier plots were overlapping for the two groups; HR 1.022, 95% CI 0.387 to 2.696	0.9654

The overall hazard ratio for OS for osimertinib compared with platinum doublet chemotherapy in this analysis was 1.022 with wide 95% confidence intervals (95% CI 0.387, 2.696) likely representing the immature nature of this comparison.

Table 1: Adjusted Indirect Comparison of osimertinib vs Standard of Care – p-values by endpoint

A5. Priority question. It is not clear to the ERG how the company pooled the data from the AURAext and the AURA2 studies and compared these data with data from patients with T790M mutation-positive non-small-cell lung cancer (NSCLC) in the control arm of the IMPRESS trial. Please perform sensitivity analyses to show that the methods used were robust. Three steps should be undertaken:

a. Treat the AURAext and AURA2 trials separately (i.e. no pooling), then carry out the propensity score (PS) analysis that has been proposed by the company (page 80 of the company's submission), and then pool the treatment effects.

b. Please randomly select half of the patients with T790M mutation-positive NSCLC from the IMPRESS trial, then match them to patients in the AURAext trial. The remaining patients with T790M mutation-positive NSCLC from the IMPRESS trial should be matched to patients in the AURA2 trial before carrying out a meta-analysis.

c. Please repeat this process at least 1000 times and assess how often the p value is statistically significant. Alternatively, the company may use permutation tests to show how robust their findings are. Whichever method is used, please provide details of results.

(i) Clarification on how data from AURAext and AURA2 studies were pooled

As described in our main submission (see Tables 4.15 and 4.16, pp.89-92), the inclusion/exclusion criteria for the AURAext and AURA2 studies were almost identical. Similarly, due the almost identical study designs, patient populations (ie, similar inclusion criteria, and similar proportion of second-line and ≥third-line patients), study conduct, dose regimen and formulation (80 mg tablet), and outcome measures (eg same schedule of radiological assessments) of AURAext and AURA2, efficacy data were pooled to increase the precision of the estimate of the ORR in the proposed indication compared to each individual trial, using the same testing methodology. This was reflected in the prospective plan to pool the efficacy and safety data, which is included in both US and EU labels.

A summary of the main differences between AURAext and AURA2 protocols and conduct relevant to the efficacy analysis is provided in Table 2.

Table 2: Summary of main differences between AURA extension and AURA2 protocols and study conduct

Parameters	AURA extension	AURA2	Impact
Study design	Eligible patients were those with advanced NSCLC who progressed following therapy with an EGFR-TKI ± additional drug treatment regimens	Two cohorts of pretreated patients were predefined in the inclusion criteria: (i) Second-line (ie, had received 1 EGFR-TKI only and no other treatment) (ii) ≥Third-line (ie, had received 1 EGFR-TKI and at least 1 regimen of platinum-based doublet chemotherapy)	The percentages of patients who received prior platinum-based chemotherapy were similar in both studies (60.7% in AURA extension and 64.3% in AURA2)
Inclusion criteria	Patients had to fulfil one of 2 conditions: (i) Either they had a confirmed EGFR mutation known to be associated with EGFR TKI sensitivity (G719X, exon 19 deletion, L858R, L861Q) or (ii) they had experienced clinical benefit from EGFR-TKI according to Jackman criteria followed by objective progression while on continuous treatment with EGFR-TKI.	The 2 cohorts of 2nd-line and ≥3rd-line patients were pre-defined as above. Jackman criteria were not used[a]. All patients had to have central confirmation of EGFR mutation to be enrolled.	The presence of an EGFR mutation known to be associated with TKI sensitivity was confirmed centrally in 98.0% of patients in AURA extension.
Exclusion criteria	Prior treatment with a third-generation EGFRTKI (eg, CO-1686) not stipulated as exclusionary	Patients excluded if they had prior treatment with a third-generation EGFRTKI (eg, CO-1686)	Only 2 patients in AURA extension had prior treatment with a third generation EGFR-TKI (CO-1686).

Comparative analysis of baseline demographics and disease characteristics of AURAext and AURA2 are shown in Table 3. Following merging of the data sets (AURAext, AURA2 and IMPRESS), p-values were generated to compare baseline characteristics from the two studies. For categorical variables these were based on the Chi-Square test or Fishers exact test (if 50% or more of the cells have expected counts of less than 5) and for continuous variables, p-values were based on a T-test or on the Wilcoxon rank-sum test if normality assumption was violated (Shapiro-Wilk test).

Seven baseline characteristics had a nominal p value < 0.05 (region, time from recent progression to start of treatment, ethnicity, smoking history, never smoker,

respiratory status at baseline, TNM classification – primary tumour, and AJCC stage classification). AstraZeneca believes that the two studies are largely comparable and appropriate to pool given both the similar inclusion/exclusion criteria and the results from this baseline comparison. Therefore, it was considered appropriate to compare pooled AURAext/2 efficacy and safety outcomes in an adjusted indirect comparison with the platinum-based chemotherapy arm of the IMPRESS study.

Table 3: Baseline characteristics of patients in AURA extension and AURA2

Variable	AURAEXT	AURA2	Std. Diff.	p-value
Total number of patients	197 (100.0%)	208 (100.0%)		
Age cont (N)	197	208	-0.112	0.2590
mean, sd	61.57 (10.53)	62.78 (10.91)		
median	62.00	63.50		
min, max	37.00, 89.00	35.00, 88.00		
Age categories 1 (n, %)				0.2367
<50	29 (14.7%)	20 (9.6%)	0.157	
>=50-<65	84 (42.6%)	88 (42.3%)	0.007	
>=65-<75	63 (32.0%)	67 (32.2%)	-0.005	
>=75	21 (10.7%)	33 (15.9%)	-0.154	
Age categories 2 (n, %)				0.2720
<65	113 (57.4%)	108 (51.9%)	0.109	
>=65	84 (42.6%)	100 (48.1%)	-0.109	
Gender (n, %)				0.5559
F	131 (66.5%)	144 (69.2%)	-0.059	
M	66 (33.5%)	64 (30.8%)	0.059	
Region (n, %)				0.0004
Asia	102 (51.8%)	107 (51.4%)	0.007	
Europe	45 (22.8%)	34 (16.3%)	0.164	
North America	40 (20.3%)	67 (32.2%)	-0.273	
ROW	10 (5.1%)	0 (0.0%)	0.327	
Weight [kg] (N)	197	207	0.031	0.6155
mean, sd	61.66 (13.68)	61.24 (14.02)		
median	60.00	59.00		
min, max	33.00, 122.00	35.00, 106.00		
Weight imputed [kg] (N)	197	208	0.031	0.6225
mean, sd	61.66 (13.68)	61.24 (13.98)		
median	60.00	59.50		
min, max	33.00, 122.00	35.00, 106.00		
Height [cm] (N)	197	201	0.074	0.3145
mean, sd	162.16 (9.34)	161.43 (10.27)		
median	162.00	160.00		
min, max	135.00, 188.00	141.00, 185.00		
Height imputed [cm] (N)	197	208	0.074	0.3255
mean, sd	162.16 (9.34)	161.44 (10.09)		
median	162.00	160.50		
min, max	135.00, 188.00	141.00, 185.00		
Time from recent progression to start of treatment (N)	197	208	-0.148	0.0207
mean, sd	73.09 (63.22)	83.05 (71.25)		
median	58.00	64.00		
min, max	21.00, 527.00	22.00, 568.00		
Body mass index [kg/m2] (N)	197	201	0.012	0.9944
mean, sd	23.33 (4.16)	23.28 (4.01)		
median	22.74	22.77		
min, max	14.86, 42.21	15.18, 40.54		
Body mass index imputed [kg/m2] (N)	197	208	0.012	0.9374
mean, sd	23.33 (4.16)	23.28 (3.94)		
median	22.74	22.87		
min, max	14.86, 42.21	15.18, 40.54		
Ethnicity (n, %)				0.0027

Variable	AURAEXT	AURA2	Std. Diff.	p-value
AFRICAN-AMERICAN	1 (0.5%)	0 (0.0%)	0.101	
ASIAN (OTHER THAN CHINESE AND JAPANESE)	45 (22.8%)	35 (16.8%)	0.151	
CHINESE	30 (15.2%)	50 (24.0%)	-0.223	
HISPANIC OR LATINO	16 (8.1%)	5 (2.4%)	0.258	
JAPANESE	35 (17.8%)	45 (21.6%)	-0.097	
MISSING	0 (0.0%)	6 (2.9%)	-0.244	
NOT APPLICABLE	0 (0.0%)	0 (0.0%)		
OTHER	70 (35.5%)	67 (32.2%)	0.070	
Treatment Line (n, %)				0.5520
2L	59 (29.9%)	68 (32.7%)	-0.059	
>=3L	138 (70.1%)	140 (67.3%)	0.059	
Number of prior regimens at baseline (n, %)				0.5897
1	59 (29.9%)	69 (33.2%)	-0.069	
2	47 (23.9%)	45 (21.6%)	0.053	
3	33 (16.8%)	38 (18.3%)	-0.040	
4	22 (11.2%)	22 (10.6%)	0.019	
5	14 (7.1%)	7 (3.4%)	0.169	
>5	22 (11.2%)	27 (13.0%)	-0.056	
Number of previous EGFR TKIs (n, %)				0.0861
1	109 (55.3%)	131 (63.0%)	-0.156	
2	45 (22.8%)	42 (20.2%)	0.065	
3	33 (16.8%)	18 (8.7%)	0.245	
4	7 (3.6%)	8 (3.8%)	-0.016	
5	2 (1.0%)	4 (1.9%)	-0.076	
>5	1 (0.5%)	5 (2.4%)	-0.159	
Number of pack years (N)	63	49	0.000	0.9368
mean, sd	20.00 (17.98)	20.00 (16.85)		
median	15.00	15.00		
min, max	0.00, 80.00	0.00, 53.00		
Baseline target lesion size (N)	195	197	0.029	0.4550
mean, sd	60.93 (37.24)	59.80 (40.76)		
median	52.00	49.30		
min, max	11.80, 229.40	10.40, 218.40		
Baseline target lesion size imputed (N)	197	208	0.030	0.6136
mean, sd	60.91 (37.05)	59.76 (39.66)		
median	52.50	51.00		
min, max	11.80, 229.40	10.40, 218.40		
Previous EGFR TKI Gefitinib regimen	116 (58.9%)	121 (58.2%)	0.014	0.8847
Previous EGFR TKI Erlotinib regimen	113 (57.4%)	116 (55.8%)	0.032	0.7468
Previous EGFR TKI Afatinib regimen	34 (17.3%)	37 (17.8%)	-0.014	0.8886
Previous EGFR TKI Dacomitinib regimen	4 (2.0%)	2 (1.0%)	0.088	0.4382
Previous EGFR TKI Afatinib + cetuximab regimen	4 (2.0%)	3 (1.4%)	0.045	0.7176
Previous EGFR TKI Other regimen	5 (2.5%)	2 (1.0%)	0.120	0.2730
Previous platinum-containing doublet therapy	122 (61.9%)	133 (63.9%)	-0.042	0.6749
Previous platinum-containing doublet plus bevacizumab therapy	25 (12.7%)	24 (11.5%)	0.035	0.7224
Smoking history: Never smoker	132 (67.0%)	158 (76.0%)	-0.199	0.0457
Smoking pack year history [0=Never, 1=Ever with PYs<30, 2=Ever with PYs>=30 (n, %)				0.1358
0	132 (67.0%)	158 (76.0%)	-0.199	
1	47 (23.9%)	36 (17.3%)	0.163	
2	18 (9.1%)	14 (6.7%)	0.089	
WHO Performance status (n, %)				0.2226
0	66 (33.5%)	84 (40.4%)	-0.143	
1	130 (66.0%)	124 (59.6%)	0.132	
2	1 (0.5%)	0 (0.0%)	0.101	
Overall disease classification Metastatic	193 (98.0%)	196 (94.2%)	0.194	0.0535
Exon 19 deletion present [vs. absent/unknown]	140 (71.1%)	137 (65.9%)	0.112	0.2605
L858R mutation present [vs. absent/unknown]	50 (25.4%)	67 (32.2%)	-0.151	0.1295
EGFR Mutation by cobas central plasma test T790M present [vs. absent/unknown]	197 (100.0%)	208 (100.0%)		
Site of disease at baseline: brain/CNS	73 (37.1%)	86 (41.3%)	-0.088	0.3768
BRAIN/CNS	68 (34.5%)	81 (38.9%)	-0.092	0.3561
PLEURAL EFFUSION	76 (38.6%)	70 (33.7%)	0.103	0.3022

Variable	AURAEXT	AURA2	Std. Diff.	p-value
RESPIRATORY	146 (74.1%)	134 (64.4%)	0.211	0.0349
HEPATIC [INCLUDING GALL BLADDER]	64 (32.5%)	55 (26.4%)	0.133	0.1819
SKIN/SOFT TISSUE	7 (3.6%)	9 (4.3%)	-0.040	0.6895
BONE AND LOCOMOTOR	101 (51.3%)	89 (42.8%)	0.171	0.0874
LYMPH NODES	104 (52.8%)	109 (52.4%)	0.008	0.9377
PERICARDIAL EFFUSION	6 (3.0%)	9 (4.3%)	-0.068	0.4950
OTHER METASTATIC SITES	51 (25.9%)	45 (21.6%)	0.100	0.3144
Prior radiotherapy	102 (51.8%)	96 (46.2%)	0.113	0.2579
EGFR TKI	197 (100.0%)	208 (100.0%)		
TNM Classification- Distant Metastases [1=M0,2=M1,3=MX] (n, %)				0.1111
1	30 (15.7%)	39 (19.5%)	-0.100	
2	157 (82.2%)	150 (75.0%)	0.176	
3	4 (2.1%)	11 (5.5%)	-0.179	
Missing values	6	8		
TNM Classification- Primary Tumour [1=T0,2=T1,3=T2,4=T3,5=T4,6=TX] (n, %)				0.0016
1	1 (0.5%)	0 (0.0%)	0.103	
2	27 (14.1%)	44 (22.3%)	-0.214	
3	54 (28.3%)	77 (39.1%)	-0.230	
4	23 (12.0%)	14 (7.1%)	0.168	
5	70 (36.6%)	41 (20.8%)	0.355	
6	16 (8.4%)	21 (10.7%)	-0.078	
Missing values	6	11		
TNM Classification- Regional Lymph Nodes [1=N0,2=N1,3=N2,4=N3,5=N4,6=NX] (n, %)				0.2710
1	61 (31.9%)	46 (23.1%)	0.198	
2	14 (7.3%)	18 (9.0%)	-0.063	
3	46 (24.1%)	61 (30.7%)	-0.148	
4	52 (27.2%)	51 (25.6%)	0.036	
5	0 (0.0%)	0 (0.0%)		
6	18 (9.4%)	23 (11.6%)	-0.070	
Missing values	6	9		
AJCC Stage Classification [1=IA,2=IB,3=IIA,4=IIB,5=IIIA,6=IIIB,7=IV] (n, %)				0.0259
1	3 (1.5%)	6 (2.9%)	-0.094	
2	11 (5.6%)	9 (4.4%)	0.056	
3	1 (0.5%)	5 (2.4%)	-0.160	
4	2 (1.0%)	1 (0.5%)	0.061	
5	5 (2.5%)	21 (10.2%)	-0.318	
6	9 (4.6%)	10 (4.9%)	-0.013	
7	166 (84.3%)	154 (74.8%)	0.237	
Missing values	0	2		
Mutation Status [1=Exon 19 deletion,2=L858R mutation,3=Unknown] (n, %)				0.2298
1	140 (71.1%)	137 (65.9%)	0.112	
2	49 (24.9%)	66 (31.7%)	-0.153	
3	8 (4.1%)	5 (2.4%)	0.094	
Ethnic Group [1=Asian,2=Non-Asian,3=Not applicable] (n, %)				0.2464
1	115 (58.4%)	131 (63.0%)	-0.094	
2	80 (40.6%)	77 (37.0%)	0.074	
3	2 (1.0%)	0 (0.0%)	0.143	

For both of the individual AURAext and AURA2 studies, each patient had analysis variables generated to allow for the analysis to be conduct at the study level. These variables were pre-defined in the Statistical Analysis Plans (provided in response to clarification question A3) and are identical for the two studies. These analysis

variables were created at a patient level within each study to allow for the individual study analysis to be conducted.

Pooling of study data was achieved by merging the data sets, whilst retaining study and anonymised study identifiers and ensuring derived variables where derived identically across the three studies. New datasets were created at a patient level by using a unique patient identification number and 'stacking' the patients from AURAext on to new datasets containing the AURA2 patients. These new datasets contained all 411 patients and the required variables for analysis. No new analysis variables were created.

The analysis of the pooled data was then conducted as defined in the SAPs using each individual patient's data. We wish to clarify that results of the analysis from the 2 individual studies were not pooled. The data were pooled at a patient level for AURAext and AURA2 and new analysis was conducted (as predefined in the SAP)

(ii) Adjusted indirect comparison methodology

As described in our main submission (see section 4.10.3, pp.79-86), in addition to a simple comparison between the AURAext/2 and IMPRESS studies, the efficacy and safety of osimertinib compared with platinum doublet chemotherapy (PDC) was assessed using an adjusted indirect comparison of patients with a confirmed T790M mutation by central testing from the AURAext/2 studies (N=405) and confirmed T790M mutation by plasma from the placebo-chemotherapy arm of IMPRESS (N=60), respectively. As stated in the main submission, differences between the AURAext/2 and IMPRESS populations are likely to have had a prognostic effect favouring the IMPRESS T790M mutation positive control group. The IMPRESS study included a second-line only population, which had therefore received less previous treatment and was also selected for good performance on previous EGFR TKI, which cannot be adjusted for in an adjusted indirect comparison.

Prior to analysis of endpoints, differences between baseline (i.e. pre-randomisation) demographic and disease characteristics using the same baseline variables (observed and derived identically) that were amenable to adjustment using this

approach, were accounted for by a three-step process of adjustment, termed cohort balancing, as follows:

1. Analysis of statistical differences between baseline variables, selection of variables with p-value <0.2.

2. Generation of a propensity score (PS) to represent aggregated differences in variables selected and trimming of the data set by removal of patients for which there was no similar PS in the alternative group.

    a. The PS was generated using a logistic regression as follows: *For [PS=1 | Baseline], 1=osimertinib arm and 0= PDC arm, conditional on the baseline variables selected in the prior step.*

    b. The range in PS for inclusion of patients in the analysis was defined as the lowest from the osimertinib arm and the highest of the PDC arm. The range of overlap in PS between the two groups was 0.2808396422 to 0.986685555. Individual patients with a PS outside of this range were not included in the analysis of endpoints.

3. Incorporation of PS as covariate in the analysis of treatment comparison of osimertinib with PDC for each endpoint to adjust for remaining differences between the two groups.

Analysis of treatment effects of osimertinib compared with PDC for efficacy, quality of life and adverse events were performed by standard statistical techniques for event rates and time to event.

Following cohort balancing, sample sizes for the two groups were: osimertinib, N=287; PDC, N=51. Due to the relatively small sample size for the PDC group, we believe that it would be inappropriate to split the sample size further, as suggested by the ERG (A5 b & c) as this would risk biasing the decision on significance of a difference in outcome being driven by reduction in the sample size rather than the magnitude of the difference within the sample of eligible subjects included in the comparison of osimertinib versus PDC. Furthermore, it should be noted that, based on the available literature on the clinical efficacy of second-line chemotherapy

regimens for EGFR-M positive NSCLC, it is highly unlikely that the results from the IMPRESS study provide a conservative estimate of the relative clinical efficacy for platinum doublet chemotherapy. However, a comparison of efficacy outcomes PFS and ORR from AURA extension and AURA2 with the PDC group from IMPRESS is described below.

(iii) Results of adjusted indirect comparison from the individual AURAext and AURA2 studies

In response to clarification question A3 (a) and in order to assess the consistency of the treatment effect for each individual study with the overall pooled data, we have repeated the analyses described in our main submission for the two primary efficacy endpoints of PFS and ORR with platinum doublet chemotherapy separately for the AURAext and AURA2 studies. The PFS analysis by independent central review was performed using a Cox proportional hazards model with treatment as a factor and estimated propensity score as a covariate. The ORR analysis was performed using logistic regression with treatment as a factor and estimated propensity score as a covariate. A summary of these PFS and ORR results, along with the results from the original analysis of the pooled data presented in our main submission, are shown in Tables 4 and 5 respectively. Figures 1 and 2 also present the K-M survival plots for the PFS analysis based on the individual AURAext and AURA2 studies.

Overall, these analyses indicate that the treatment effect for osimertinib compared with platinum doublet chemotherapy in terms of PFS and ORR for both of the individual AURAext and AURA2 studies is consistent with the pooled results. [redacted].

Table 4: Summary of PFS analysis for AURAext and AURA2 studies

Treatment	N	Number (%) of patients with events	Median PFS (months) 95% CI	Treatment Effect (osimertinib vs PDC)		
				Hazard Ratio	95% CI	2 sided p-value
AURAext/2 Pooled						
Osimertinib	N=287	106 (36.9)	9.7	0.280	0.185, 0.422	<.0001
PDC	N=51	42 (82.4)	5.3			
[redacted]						

NC= Not calculable; PDC = Platinum doublet chemotherapy

Table 5: Summary of ORR analysis for AURAext and AURA2 studies

Treatment	N	*Number (%) of patients with response*	Treatment Effect (osimertinib vs PDC)		
			Odds ratio	95% CI	2 sided p-value
AURAext/2 Pooled					
Osimertinib	N=277	179 (64.6)	4.76	2.21, 10.26	<0.0001
PDC	N=46	16 (34.8)			
[redacted]					

Figure 1. Kaplan-Meier plot of PFS: AURAext versus IMPRESS

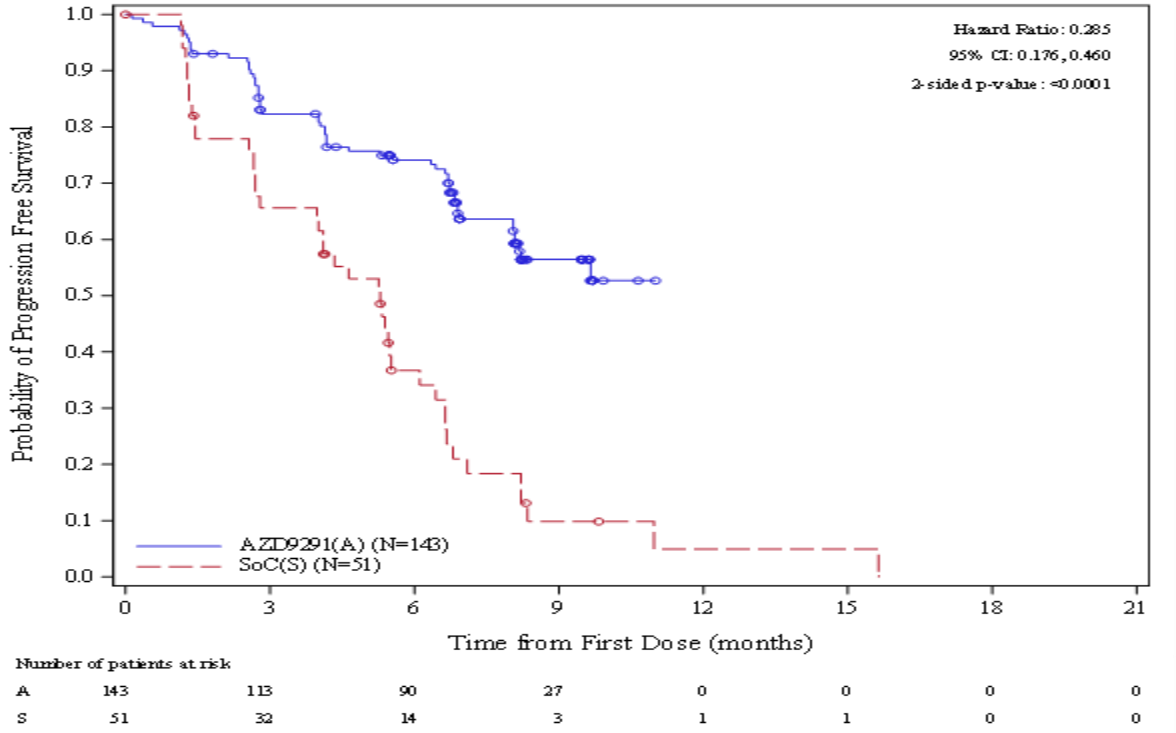
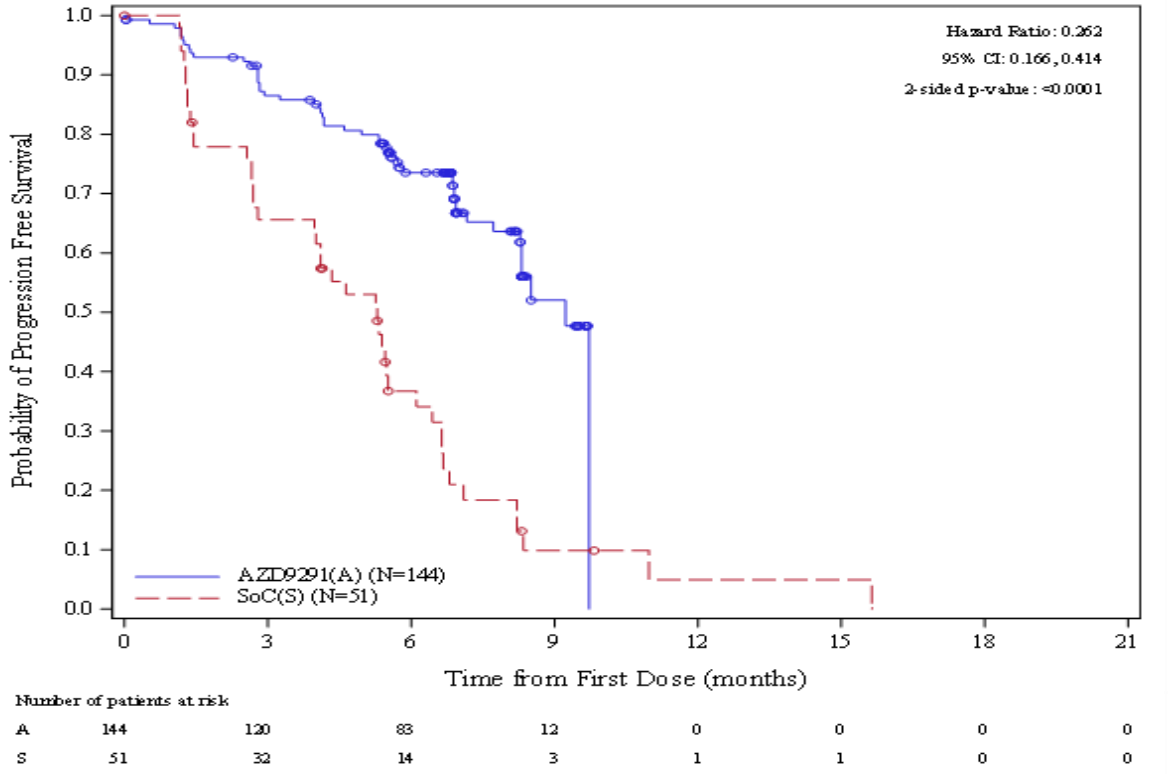


Figure 2. Kaplan-Meier plot of PFS: AURA2 versus IMPRESS



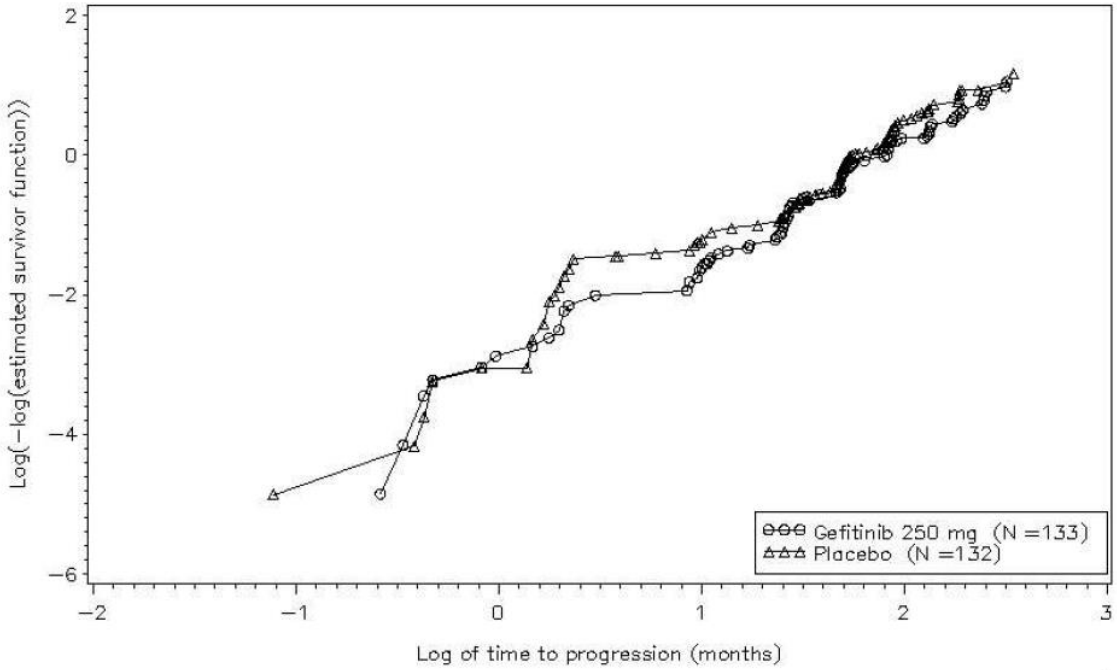
A6. Priority question. The company states on page 149 of its submission that 'in general the PFS K-M curves from the IMPRESS trial do not cross' (see Figure 4.16). However, the ERG considers that the curves do cross. Please provide the results of the analyses undertaken (e.g. cumulative hazard plot) based on which the company concluded that the proportional hazards assumption is valid?

The company is uncertain as to the relevance of the question on the current submission, given that the PFS K-M curves being referenced are the active (Iressa+Chemotherapy) and control (Placebo+Chemotherapy) arms from the IMPRESS study.

However, the company acknowledges the comment and would like to provide the following further information. Whilst in general the PFS K-M do not cross, the curves do touch and slightly cross over around the PFS median.

In according with the SAP, the assumption of Proportional hazards was tested firstly by examining plots of complementary log log (event times) versus log (time) (see Figure 3).

Figure 3: Plot of complementary log – log (event) versus log (time) – site read (Full Analysis Set)



Since the lines are not parallel, this raised a concern about the assumption of proportional hazards and subsequently a time dependent covariate was fitted to the Cox Proportional hazards model to assess the extent to which this represents random variation. The p value for the test of non proportional hazards was 0.565,

suggesting there was insufficient evidence of non-proportionality. (Reference : Table 11.2.1.14 Test for non-proportional hazards for progression free survival (full analysis set) IRESSA IMPRESS) . This leads to the conclusion that in general, the PFS K-M do not cross.

A7. Please reproduce Table 4.7 (page 76 of the company's submission) for patients receiving second-line, third-line and fourth- and subsequent-line treatment in the pooled data set of AURA.

Please see Table 6 below.

Conclusion – Baseline characteristics are generally consistent for patients receiving Tagrisso as 2nd, 3rd, 4th and >=5th lines with the exception of the increase in metastatic and brain metastatic disease increasing as the line of receiving treatment increases.

Table 6: Baseline characteristics in pooled AURAext/2 data-set by line of therapy

	Number (%) of patients				
	Second-line[a] (N=129)	Third-line[b] (N=95)	Fourth-line[b] (N=71)	≥ Fifth-line[b] (N=116)	Total (N=411)
Age (years)					
Mean (SD)	63.3 (11.05)	[redacted]	[redacted]	[redacted]	62.2 (10.76)
Median (min-max)	62.0 (36-89)	[redacted]	[redacted]	[redacted]	63.0 (35-89)
≥65 n (%)	61 (47.3)	[redacted]	[redacted]	[redacted]	187 (45.5)
Sex					
Female	85 (65.9)	[redacted]	[redacted]	[redacted]	279 (67.9)
Male	44 (34.1)	[redacted]	[redacted]	[redacted]	132 (32.1)
Smoking					
Never	93 (72.1)	[redacted]	[redacted]	[redacted]	294 (71.5)
Current	0	[redacted]	[redacted]	[redacted]	7 (1.7)
Former	36 (27.9)	[redacted]	[redacted]	[redacted]	110 (26.8)
EGFR mutations by cobas® central test					
T790M	127 (98.4)	[redacted]	[redacted]	[redacted]	405 (98.5)
Exon 19 deletion	89 (69.0)	[redacted]	[redacted]	[redacted]	279 (67.9)
L858R	36 (27.9)	[redacted]	[redacted]	[redacted]	118 (28.7)
Other[c]	5 (3.9)	[redacted]	[redacted]	[redacted]	14 (3.4)
WHO performance status					
0 (Normal activity)	54 (41.9)	[redacted]	[redacted]	[redacted]	152 (37.0)
1 (Restricted activity)	75 (58.1)	[redacted]	[redacted]	[redacted]	258 (62.8)
2 (In bed less than or equal to 50% of the time)	0	[redacted]	[redacted]	[redacted]	1 (0.2)
0-1	129 (100)	[redacted]	[redacted]	[redacted]	410 (99.8)
2-4	0	[redacted]	[redacted]	[redacted]	1 (0.2)

	Number (%) of patients				
	Second-line[a] (N=129)	Third-line[b] (N=95)	Fourth-line[b] (N=71)	≥ Fifth-line[b] (N=116)	Total (N=411)
Metastatic at baseline	123 (95.3)	[redacted]	[redacted]	[redacted]	395 (96.1)
Brain metastatic at baseline	40 (31.0)	[redacted]	[redacted]	[redacted]	166 (40.4)

[a] Second-line is determined by cohort.
[b] Determined by number of previous anti-cancer treatment regimens at baseline.
[c] Other mutations are G719X, S768I and Exon 20 insertion.

A8. The results for the subgroup analyses are presented in Figures 4.8 and 4.17 in the company's submission for the pooled dataset of AURA, and the IMPRESS trial respectively. Please provide the p values for the tests for interaction for all subgroup analyses for ORR and PFS.

AstraZeneca has provided the p-value for the test of differences between the levels of a subgroup (e.g. the differences between males and females for the gender subgroup) for the pooled dataset of AURA and the placebo-chemotherapy arm of the IMPRESS trial. This is to answer the question specifically about prognostic differences between the levels of a subgroup. Please note that it is not a treatment interaction test, as there is only one treatment group for the AURA pooled dataset (all patients received osimertinib) and we have only assessed prognostic differences for the subgroups within the platinum doublet chemotherapy arm of the IMPRESS trial.

[redacted]

Table 7: AURA Pooled dataset - Objective response rate (ORR) by central review by subgroup

Subgroup		ORR (95% CI)	Odds Ratio (95% CI)	2-sided p-value
Overall (n=398)		66.1 (61.20, 70.72)		
Treatment cohort	Second-line (n=124)	66.9 (57.92, 75.12)	1.06 (0.67, 1.66)	[redacted]
	>= Third-line (n=274)	65.7 (59.74, 71.30)		
Ethnicity	Asian (n=237)	70.0 (63.77, 75.80)	1.54 (1.01, 2.35)	[redacted]
	Non-Asian (n=161)	60.2 (52.25, 67.87)		
Gender	Male (n=129)	67.4 (58.64, 75.43)	1.09 (0.70, 1.71)	[redacted]
	Female (n=269)	65.4 (59.41, 71.10)		
Age at screening	<65 (n=218)	67.0 (60.30, 73.18)	1.09 (0.72, 1.66)	[redacted]
	>=65 (n=180)	65.0 (57.55, 71.95)		
Mutation status prior to start of study	Exon 19 deletion (n=270)	69.6 (63.76, 75.06)	1.60 (1.01, 2.52)	[redacted]
	L858R (n=112)	58.9 (49.24, 68.14)		
Duration of most recent prior EGFR TKI	<6 months (n=90)	64.4 (53.65, 74.26)	0.91 (0.56, 1.49)	[redacted]
	>=6 months (n=308)	66.6 (60.99, 71.81)		
Brain metastases at entry	Brain metastases (n=158)	62.0 (53.97, 69.62)	0.74 (0.49, 1.13)	[redacted]
	No brain metastases (n=240)	68.8 (62.47, 74.56)		

Subgroup		ORR (95% CI)	Odds Ratio (95% CI)	2-sided p-value
Smoking history	Never (n=284)	65.8 (60.01, 71.35)	0.96 (0.61, 1.53)	[redacted]
	Ever (n=114)	66.7 (57.23, 75.22)		
Last treatment prior to study start	EGFR-TKI (n=308)	65.3 (59.65, 70.57)	0.85 (0.51, 1.40)	[redacted]
	<30 days prior to first dose of AZD9291 (n=210)	62.4 (55.45, 68.95)	0.75 (0.44, 1.27)	[redacted]
	>=30 days prior to first dose of AZD9291 (n=98)	71.4 (61.42, 80.10)	1.13 (0.60, 2.11)	[redacted]
	Not EGFR-TKI (n=90)	68.9 (58.26, 78.23)		
T790M status in baseline plasma sample (ctDNA)	T790M positive (n=224)	62.1 (55.35, 68.43)	0.63 (0.41, 0.97)	[redacted]
	T790M not detected (n=162)	72.2 (64.65, 78.96)		
Region	North America (n=105)	61.9 (51.91, 71.21)	0.99 (0.55, 1.76)	[redacted]
	Asia (n=203)	70.0 (63.14, 76.17)	1.41 (0.84, 2.38)	[redacted]
	Europe and rest of world (n=90)	62.2 (51.38, 72.23)		

Table 8: IMPRESS Placebo Group - Progression free survival by central review by subgroup

Primary analysis		Number (%) of patients with events [a]	HR (95% CI)	2-sided p-value
Overall (n=127)		98 (77.2%)		
Age	<65 (n=95)	73 (76.8%)	1.08 (0.69, 1.71)	[redacted]
	>= 65 (n=32)	25 (78.1%)		
Gender	Male (n=48)	34 (70.8%)	1.10 (0.73, 1.67)	[redacted]
	Female (n=79)	64 (81.0%)		
Region	Asia (n=102)	78 (76.5%)	0.91 (0.56, 1.49)	[redacted]
	Europe (n=25)	20 (80.0%)		
Prior response to gefitinib	Partial or complete response (n=97)	78 (80.4%)	0.76 (0.47, 1.25)	[redacted]
	Stable disease (n=30)	20 (66.7%)		
Smoking history	Never (n=86)	67 (77.9%)	0.79 (0.51, 1.21)	[redacted]
	Present or former (n=41)	31 (75.6%)		
Disease state at diagnosis	Metastatic (n=114)	90 (78.9%)		
Time from progression to randomisation	>2 weeks (n=76)	60 (78.9%)	0.93 (0.62, 1.40)	[redacted]
	<= 2 weeks (n=51)	38 (74.5%)		
EGFR mutation subtype	Exon 19 deletion (n=83)	71 (85.5%)	0.55 (0.34, 0.89)	[redacted]
	L858R (n=38)	22 (57.9%)		

Primary analysis		Number (%) of patients with events [a]	HR (95% CI)	2-sided p-value
Time to progression for initial gefitinib	<= 10 months (n=56)	46 (82.1%)	0.79 (0.53, 1.19)	[redacted]
	>= 10 months (n=71)	52 (73.2%)		
Site of disease at baseline	Not brain or CNS (n=97)	73 (75.3%)	1.89 (1.19, 2.99)	[redacted]
	Brain or CNS (n=30)	25 (83.3%)		
WHO performance status score	0 (n=49)	35 (71.4%)	1.00 (0.66, 1.51)	[redacted]
	1 (n=78)	63 (80.8%)		

A9. Please reproduce Figure 4.8 (page 114 of the company's submission) for the population with T790M mutation-positive NSCLC in the IMPRESS trial who have received doublet chemotherapy (n=61).

As requested, figure 4 below provides the Objective Response Rate (ORR) by central review for subgroups of the population with T790M mutation-positive NSCLC in the IMPRESS trial who have received doublet chemotherapy.

Note, there were n=59 patients who tested positive for T790M, had evaluable disease at baseline for independent assessment and were not from France*.
(*Patients who participated in the IMPRESS study and were based in France were excluded from this analysis due to the interpretation of the patient consent at the time of this analysis.)

Figure 4 Objective response rate (ORR) by central review, Forest plot, by subgroup (evaluable for response analysis set)

[Figure Removed]

A10. Please complete the table below with the number of patients who died whilst on different lines of study treatment for the following populations: all patients in the IMPRESS trial who received platinum doublet chemotherapy (n=132), patients in the IMPRESS trial with T790M mutation-positive NSCLC who have received doublet chemotherapy (n=61), patients in AURAext, patients in AURA2, and the pooled populations from AURA (second-line, ≥second line and ≥third-line).

Table 9: Number of patients who died whilst on different lines of study treatment

	IMPRESS (n=132)	IMPRESS T790M (n=61)	AURAext (n=201)	AURA2 (n=210)	AURA pooled (n=411)
Second line	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ Second line			[redacted]	[redacted]	[redacted]
≥ Third line			[redacted]	[redacted]	[redacted]
[redacted]					

A11. The authors of the IMPRESS publication in Lancet Oncology (Soria et al., 2015) state that the IMPRESS trial OS data are immature. Please comment on the degree to which the published data are immature, and clarify whether there is a planned update of results expected soon (including outcomes for the subgroup of patients with T790M mutation-positive NSCLC)? If so, please will you provide us with these data?

[redacted]

A12. Please indicate when the results from the next planned analysis of the AURA pooled data will be available.

[redacted]

Section B: Clarification on cost effectiveness data

B1. **Priority request: Kaplan-Meier (K-M) data.** Please provide the K-M analyses listed in 'a' to 'e' below for the following populations: all patients in the IMPRESS trial who received platinum doublet chemotherapy (n=132); patients in the IMPRESS trial with T790M mutation-positive NSCLC who have received platinum doublet chemotherapy (n=61); patients in AURAext, patients in AURA2; and the pooled populations from AURA (second-line, ≥second line and ≥third-line for all three AURA datasets).

a. Time to death from any cause (OS) K-M analysis stratified by treatment arm.
b. Time to disease progression or death (PFS) K-M analysis based on investigator assessment, stratified by treatment arm.
c. Time from disease progression by investigator assessment to death from any cause (PPS) K-M analysis.
d. Time to study treatment discontinuation K-M analysis.
e. Time from study treatment discontinuation to death.

Format: Please present analysis outputs using the format of the sample table shown below. Please provide these data in a .xcl or .csv file.

Censoring: Please censor lost to follow-up and patients who withdrew from the study at the date recorded. Patients alive and still at risk of the target event at the date of data cut-off should be censored at the date of data cut-off i.e. not when last known to be alive (OS/post-progression survival [PPS]), and not at the date when the tumour was last assessed (PFS).

AstraZeneca have conducted K-M analyses (see attached) for the following outcomes for the following populations: all patients in the IMPRESS trial who received platinum doublet chemotherapy (n=132); patients in the IMPRESS trial with T790M mutation-positive NSCLC who have received platinum doublet chemotherapy (n=61); patients in AURAext, patients in AURA2; and the pooled populations from AURA (second-line, ≥second line and ≥third-line for all three AURA datasets):

a. Time to death from any cause (OS)
b. Time to disease progression or death (PFS) by central review
d. Time to study treatment discontinuation

These K-M analyses can be found in the attached file.

However, as (i) time from disease progression by investigator assessment to death from any cause (PPS) and (ii) time from study treatment discontinuation to death were not pre-specified outcomes from any of the AURAext/2 or IMPRESS studies, we have not conducted the relevant K-M analyses for these outcomes. Furthermore, we believe that there are likely to be significant issues with the interpretation of these time-to-event outcomes due to the immaturity of currently available data and the high level of censoring of patients in the post-progression period from AURAext/2.

Patient Numbers

Table 10 below provides the number of patients included in each analysis. Note, there were n=127 patients in the populations of IMPRESS trial who received platinum doublet chemotherapy and n=60 patients in the IMPRESS trial who tested positive for T790M and were not based in France*.

Censoring

The analyses have been performed using the censoring methodology as pre-defined in the SAP and in line with analyses submitted to health authorities and global reimbursement agencies. We have censored at the point last known to be alive (OS/post-progression survival [PPS]), or at the date when the tumour was last assessed (PFS) rather than the date of data cut-off as this approach fairly assumes knowledge to the point until we no longer have it. If there is a time gap between the last known date to be alive and the data cut-off date then censoring at the data cut-off date would assume that we have knowledge of the patient up to this time point and may contribute to influencing the KM estimates. Furthermore, given the pattern of censoring between the AURAext/2 and IMPRESS studies, it is likely that the conventional censoring approach could be considered conservative, resulting in K-M analyses in favour of the platinum doublet chemotherapy arm of IMPRESS. The use of a later time point (such as DCO) in the alternative censoring approach will elevate the osimertinib risk set compared with censoring at the last point known to be alive. The impact on the estimate of the probability of the event at that timepoint will in effect be lower due to the larger number of patients at risk. As there is more censoring in the AURAext/2 studies this will likely “push up” the K-M line relative to the platinum chemotherapy arm in the IMPRESS study.

Definitions

The footnotes of Table 10 also provide the full definitions of the time to event variables. Note that the time to event variables use Independent assessment (not Investigator assessment) as this was the primary endpoint of the AURA Phase II studies and for consistency we have used Independent assessment for the analyses using the IRESSA IMPRESS populations. This is also in line with the approach taken for the adjusted indirect comparison and the time-to-event data applied in the cost effectiveness model.

Table 10: Numbers of patients included in each analysis

Analysis	a. OS	b. PFS	d. TTD
AURA Extension	201	201	201
AURA Extension (2nd line)	61	61	61
AURA Extension (≥3rd line)	140	140	140
AURA2	210	210	210
AURA2 (2nd line)	68	68	68
AURA2 (≥3rd line)	142	142	142
AURA Ph II Pooled	411	411	411
AURA Ph II Pooled (2nd line)	129	129	129
AURA Ph II Pooled (≥3rd line)	282	282	282
IRESSA IMPRESS Doublet Chemotherapy	127	129	127
IRESSA IMPRESS Doublet Chemotherapy T790M Positive	60	60	60

Key

a. OS Time from start of treatment to death from any cause
   - all patients in the full analysis set

b. PFS Time from start of treatment to disease progression or death based on **independent** RECIST assessment
   - all patients in the full analysis set

d. TTD Time from start of treatment to study treatment discontinuation (discontinuation of chemotherapy).

- all patients in the full analysis set

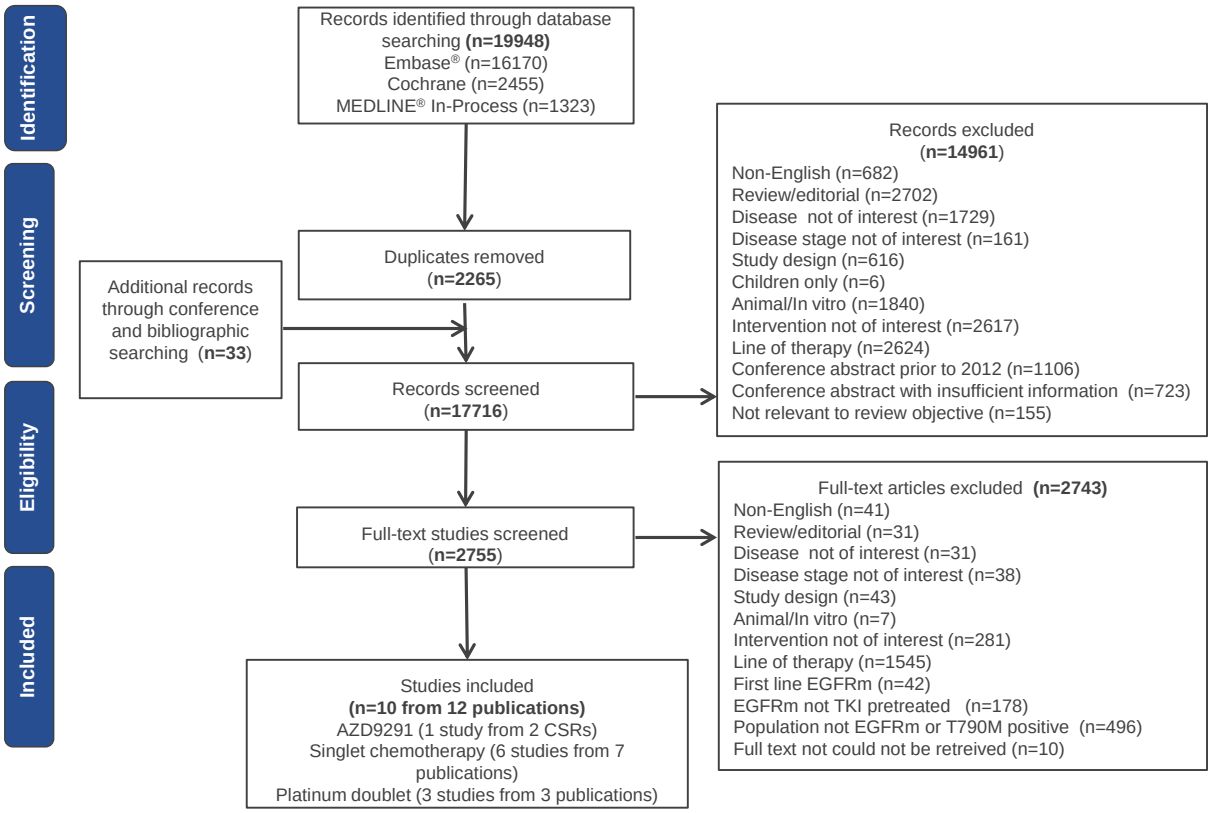
Section C: Textual clarifications and additional points

C1. In Figure 4.1 (page 66 of the company's submission):

a. 19,948 records were identified and 2265 duplicates were removed. The number screened is expected to be 17,683. However, in Figure 4.1 the number screened is 17,716. Please clarify.

33 records were identified through conference and bibliographic searching. Therefore, the number of records screened is 19,948+33 = 19,941-2265=17,716. The corrected trial flow is provided below in Figure 5.

Figure 5: Updated PRISMA flow diagram of the systematic review process



b. 723 conference abstracts were excluded for having insufficient information. Please clarify what criteria were used to decide whether or not the information given in an abstract was insufficient.

Criteria (in line with review criteria)

Disease stage: Locally advanced or metastatic NSCLC

Conference abstracts were excluded, where information regarding disease stage was unclear

Population: Adults

Conference abstracts were excluded, where information regarding study population age was unclear

Line of therapy: Second or further line

Conference abstracts were excluded, where information regarding study treatment line was unclear

Prior treatment: EGFR-TKI

Conference abstracts were excluded, where information regarding prior TKI treatment was unclear

Mutation: EGFRm or T790M positive mutation

Conference abstracts were excluded, where information regarding mutation status (EGFRm or T790M) was unclear

c. 10 full text articles were not retrieved. Please give the reasons for not retrieving these articles.

Full text publications of these studies were not available. Also, based on a review of the title and abstract none of these articles were considered to be relevant to the decision problem for osimertinib.

C2. Please provide a full legend for Table 4.18 (page 108 of the company's submission) and explain superscripts b, c and d.

[a] Metastatic disease - Patient has any metastatic site of disease.

[b] Locally advanced - Patient had only locally advanced sites of disease.

[c] Brain and Visceral Metastases were determined programmatically from baseline data.

[d] EGFR mutation identified by the cobas® EGFR central test (by biopsy taken after confirmation of disease progression on the most recent treatment regimen). Two patients in study AURA2 (E4304208 was a screen failure and was then rescreened, and entered the study as E4304211; E7401221 was a screen failure and was then rescreened and entered the study as E7401244) had mutation data collected under the initial screening information, which were not included in the current output.

Source: Table 1.7.1 from pooled efficacy tables in Module 5.3.5.3 Supportive efficacy data

C3. There are 2 documents referred to in the company's submission that were not included in the CD containing the company references. Please provide the following documents:

a. AstraZeneca. Market Research report. *Data on file* 2015

b. AstraZeneca. Advisory board. *Data on file* 2015

Both documents have been provided in attachment to this submission.

Section D: Marking of confidential information

D1. We note that section 4.10.3 of the company's submission (pages 79–86) about the adjusted indirect comparison of osimertinib with platinum doublet chemotherapy is entirely marked as academic-in-confidence. These analyses are expected to form part of the appraisal committee's considerations, and NICE does not agree that they can be wholly designated confidential. We therefore request that you to reconsider all restrictions relating to these data. As a minimum, a description of the methods and results of the indirect comparisons (eg in the form of an abstract) must be made available for public disclosure.

In order to ensure that the appraisal process is as transparent as possible, AstraZeneca is willing to lift the confidentiality marking in section 4.10.3 of our main submission (pp.79-86), which summarises the methods and results from the adjusted indirect comparison of osimertinib with platinum doublet chemotherapy. We have enclosed a revised submission document with the confidentiality marking lifted from this section. However, we wish to stress that full details of the adjusted indirect comparison contained within the supporting technical report [Adjusted Indirect Comparison of osimertinib vs Standard of Care (D5160C0000a)] must remain academic-in-confidence at this stage of the appraisal process.

Submission from Roy Castle Lung Cancer Foundation, for consideration by NICE, in their review of Osimertinib, EGFR and T790M positive [ID874]

Submitting Organisation

Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research, tobacco control initiatives and work in lung cancer patient care (information, support and advocacy activity).

The Foundation has contact with patients/carers through its UK wide network of over 50 monthly Lung Cancer Patient Support Groups, online Forums and its Lung Cancer Information Helpline.

Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 10%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of non small cell lung cancer (nsclc).

General Points

1. For patients with advanced or metastatic nsclc, cure is not a treatment option. In this scenario, improving quality of life and even small extensions in duration of life are of considerable significance to the individual and their family.

2. As overall outcomes for this patient population remain poor, the availability of new therapy choices are of key importance.

3. The importance of 'end of life' therapies. When considering the cost of treatment, it is not appropriate, for example, to give the same weighting to the final six months of life, as to all other six months of life. It is important for this to be part of any numeric equation, which is looking at cost and quality of life. This point is of crucial importance to patients and relatives in this situation

4. Improvement in symptoms. Patients with advanced or metastatic non small cell lung cancer are often debilitated with multiple and distressing symptoms. Symptoms such as breathlessness are very difficult to manage clinically. Therapies with anti-tumour activity often provide the best option for symptom relief.

This Product

1. Very targeted population.

T790M is a point mutation in the EGFR gene that is associated with resistance to EGFR kinase inhibitors like Erlotinib and Gefitinib. We understand that more than half of patients whose disease progresses after treatment with an EGFR inhibitor develop the T790M mutation. T790M is rarely (<5%) found in untreated EGFR-mutated tumours. This therapy therefore represents a targeted treatment option, providing benefit to a clearly defined small segment of non small cell lung cancer.

2. Oral Preparation
   Oral therapy has obvious benefits to patients, in spending less time at hospital and in not requiring intravenous cannulation for treatment.

3. Side effect profile
   In the anecdotal patient experience reported to us, Osimertinib is reasonably well tolerated – in particular, when compared with current standard cytotoxic therapy for nsclc. Common side effects include diarrhoea, rash, dry skin and nail toxicity. More rarely, serious adverse events noted - interstitial lung disease (2.7%) and cardiac toxicity.

4. Response
   We do not have any information or trial data for this therapy, beyond that which is published and publicly available. Patients with advanced/metastatic nsclc are a group with significant unmet medical need. We note two clinical studies (AURA and AURA2) in 411 patients with EGFR T790M mutation positive lung cancer, whose tumour had grown on prior therapy. The objective response rate (ORR) with Osimertinib was around two thirds (61%).

5. As noted above, even relatively small benefits can be disproportionately large for patients.

Our observations come from a combination of one-to-one discussion with lung cancer patients, published research and our patient information helpline.

In summary

Patients with advanced and metastatic lung cancer are in a particularly devastating situation. Even with the currently recommended options, the outlook for the majority is relatively poor. It is for this reason that the availability of additional options is very important.

Osimertinib is the first therapy shown to have benefits in EGFR T790M positive nsclc patients. As such, it represents a therapy option, for a very small number of clearly defined patients.

[redacted], **RCLCF.**

February 2016.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Thoracic Society
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? xx
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Osimertinib STA [redacted] Comments

Osmertinib will be a welcomed addition to the management strategies for the small proportion of patients with an EGFR positive advanced NSCLC, and another step forward in personalised medicine. Early phase data for this medication is extremely promising and randomised controlled trial data is awaited. As with all TKI therapies it is a highly desirable treatment compared to platinum doublet chemotherapy or docetaxel in terms of side effects and quality of life.

Some considerations for the STA:

Some patients are identified as harbouring the T790M mutation at presentation - ie at first biopsy. Will this appraisal consider the role of Osimertinib as first line TKI treatment in such patients?

The comparators should include ongoing TKI treatment - in the event of disease progression on first line treatment with afatinib, gefitinib or erlotinib there is the option of continuing TKI therapy (there may only be mild progression and the patient may not suitable for chemotherapy & continuing the TKI may still offer some control - ie lessen the speed of progression).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

When considering costs effectiveness & the additional costs for T790M testing - it should be noted that rebiopsy of disease at the point of progression on TKI therapy could be considered standard care as histological transformation to small cell carcinoma has been demonstrated in a small proportion of patients. The costs should therefore be for the EGFR testing and not include the biopsy procedure, as the EGFR testing is the only additional test relevant to Osmertinib.

What are the quality assurance processes for T790M testing centres and what are the guidelines for the handling and processing of pathological samples by local trusts prior to sending to testing centres to ensure a high proportion of successful testing and thus, ensure equality if access to this treatment?

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must

include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: NLCFN

Your position in the organisation: [redacted]

Brief description of the organisation: Charity Forum representing Lung CNS and patients. Current membership >300 Lung CNS. Actively engaged in promoting lung cancer patient issues and research to ensure best care available across UK

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: none

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

n/a

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Stablitly or reduction in disease, good quality of life through treatment

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Patient report easier to tolerate, less side effects. Reduced hospital visits means more time to enjoy good quality of life

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

All above

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

none

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

none

Please list any concerns patients or carers have about the treatment being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Elderly or those with other co mordibities were other treatment options are not available

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not able to comment

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment

as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes

If yes, please explain what makes it significantly different from other treatments for the condition.

Administration of oral medication instead on intravenous

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

-
-
-
-
-

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

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To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] **on behalf of:**

Name of your organisation: NCRI-RCP-ACP-RCR

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

The NCRI-RCP-ACP-RCR are grateful for the opportunity to respond to the above consultation. In doing so we would like to endorse the response submitted by the British Thoracic Society. We have also liaised with our clinical experts and would like to make the following comments.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Background

Lung cancer is one of the most common cancers in the UK with over 44 thousand new cases being diagnosed each year. In 2012, there were 35 400 deaths from lung cancer, a statistic that demonstrates how very poor the prognosis is for these patients1 (http://www.cancerresearchuk.org/cancer-info/cancerstats/types/lung). Lung cancer is the most common cause of cancer mortality in the UK, accounting for more than a fifth of all cancer deaths and constitutes almost a quarter (24%) of all male deaths from cancer and is also the most common cause of cancer death in women (21%).

The majority of patients with non-small cell lung cancer (NSCLC) present with advanced disease and although treatment rates vary across the UK, only of 55% of patients who have good performance status (PS 0-1) receive first line chemotherapy2 (http://www.hscic.gov.uk/lung) with around 25% of all patients diagnosed undergoing any systemic treatment.

Epidermal growth factor receptor (EGFR) activating mutations were first identified in patients with NSCLC who experienced impressive responses to EGFR tyrosine kinase inhibitors (TKIs) in 20043. Activating mutations are present in 10-30%4-6 of non-squamous NSCLC (in the UK the prevalence is around 10%) and are more common in particular sub-groups of patients eg patients who have never smoked or are ex light smokers.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

The 1st line treatment of choice for this group of patients is an EGFR TKI (gefitinib, erlotinib or afatinib7-9) and compared to chemotherapy, EGFR TKI's demonstrate improved response rates, progression free survival (PFS) time and quality of life, although it has been difficult directly demonstrate an overall survival benefit due to cross over in the clinical trials. Most patients tolerate treatment well and the median duration of therapy is 9-10 months, however, resistance to therapy is inevitable and further treatment is necessary.

Studies have shown that there are a number of mechanisms of resistance to EGFR TKI's including:

- Development of T790M (approx 50-60%)
- Small cell transformation (3-6%)
- Met amplification (5%)
- BRAF (1%)
- HER-2 (1-10%)
- PIK3CA (1-5%)
- MAPK1 (1-3%)
- Other (30-35%)[10]

Targeting the mechanism of resistance is a compelling avenue for research in this group of patients in order to improve outcomes and avoid the toxicity of chemotherapy.
T790M mutation in exon 20 of the EGFR gene is the most common mechanism of acquired resistance and, is consequently, an important target for drug development. There are several molecules in an advanced stage of clinical development in this field, which have demonstrated very promising results, including osimertinib (AZD9291), rocelitinib and HM61713.

Clinical Practice

Clinical practice for patients with NSCLC and an EGFR activating mutation is consistent across the NHS in England: the standard 1st line treatment is with an EFGR TKI (Gefitinib TA192, Erlotinib TA 258 or Afatinib TA310) and 2nd line treatment is with platinum doublet chemotherapy. This is usually with cisplatin or carboplatin combined with pemetrexed, as almost all patients with EGFR mutations have non-squamous histology. If patients are not fit enough to receive platinum doublet chemotherapy, then single agent treatment with gemcitabine or vinorelbine is an option. If patients complete 4 cycles of cisplatin and pemetrexed and remain PS 0-1, with at least stable disease as response to therapy, they may continue maintenance pemetrexed 3 weekly until disease progression or significant toxicity occurs (accessed via the Cancer Drug Fund).

If a patient does not have an EGFR mutation result available prior to initiation of treatment (either due to a delay in obtaining the result, insufficient biopsy material or a technical failure of the assay) then it is possible that the patient may receive chemotherapy as a first line treatment with the EGFR TKI therapy being displaced to

2nd line. This would be an infrequent scenario as most treating centres in England will have results available prior to commencing systemic therapy.
The only potential NICE approved 2nd line chemotherapy (3rd line systemic treatment) for this group of patients is docetaxel.

One of the biggest challenges facing clinicians and patients, when the EGFR TKI stops working, is determining what the mechanism of acquired resistance is, which most often involves a repeat biopsy. This is an area of evolving practice as repeat biopsies carry a variety of risks (eg, pneumothorax, bleeding, no tissue obtained) and there may be limited capacity within existing NHS systems to provide this service. However there is a compelling reason to consider a further invasive procedure: the result will influence the next treatment step, eg. if there is a transformation to small cell histology then a different type of chemotherapy would be the treatment of choice, if a T790M mutation is identified the patient may be suitable for a new targeted agent (currently within the context of a clinical trial) or if no actionable mutation or change in histology is identified then treatment may be with standard docetaxel chemotherapy. At present repeat biopsies are not consistently offered to patients in all hospitals, but increasingly this will be considered to be the standard approach to care for this selected group of patients, providing the individual is fit for further therapy. The larger centres in England have already adopted this approach and internationally it is regarded as the appropriate patient pathway.

The Technology

The “AURA” phase 1 study of AZD9291 (osimertinib)11 reported on outcomes of 253 patients with advanced NSCLC who received AZD9291 in doses of 20mg to 240mg once daily, after radiologically documented disease progression, following previous treatment with an EGFR TKI. Patients were recruited in 33 sites across the world, including the UK, and 80% of patients had also received previous chemotherapy. The study included dose-escalation cohorts and dose-expansion cohorts. In the expansion cohorts tumour biopsies were required for central determination of T790M status.

The treatment was remarkably well tolerated with no dose limiting toxicities documented in the dose escalation cohorts. In the 5 expansion cohorts 222 patients were treated and the most common toxicities documented were:

- Diarrhoea (2% grade 3 or worse)
- Rash (1% grade 3 or worse)
- Nausea (<0.5% grade 3 or worse)
- Reduced appetite (1% grade 3 or worse)

There were also 6 cases of pneumonitis which led to drug discontinuation and 11 cases of prolongation of QT interval which did not require intervention.

Among the 127 patients with confirmed T790M positive disease, the response rate was 61% (95% CI 52% to 70%). The median PFS in this group of patients was 9.6 months (95% CI 8.3 months to not reached).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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The study has generated enormous excitement from the lung cancer community as it represents a major advance it the treatment of this disease. Expected response rates to second line chemotherapy are around 10%, and so the response rate of 61% and the PFS time of 9.6 months demonstrated in this study (which are more in keeping with what we might hope to see in an effective 1st line lung cancer treatment) were impressive. Furthermore, the adverse event reporting from this study, and UK clinical experience, suggest that the technology is very well tolerated and is associated with less of the typical EGFR related side effects (rash and diarrhoea) than is experienced with the 1st and 2nd generation EGFR TKIs.

The toxicity profile is significantly more tolerable than chemotherapy.

The AURA 2 phase 2 expansion study was reported by Yang at the 15th WLCC in Denver in September 2015 and results were consistent with the published phase 1 study previously reported.

The FDA and EMEA have licensed AZD9291 (osimertinib) via an acelerated approval pathway on the basis of the results from phase 1 and 2 data.

AURA 3 is the ongoing Phase III, randomised study of AZD9291 versus platinum-based doublet chemotherapy for patients with locally advanced or metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and whose tumours harbour a T790M mutation, which has completed recruitment of 410 patients. The study will provide valuable head to head data on AZD9291 compared to chemotherapy and presentation of data is eagerly awaited (anticipated later in 2016).

The FLAURA study is approaching the end of recruitment and is examining the role of AZD9291 compared to Gefitinib in the 1st line treatment of patients with locally advanced or metastatic NSCLC with EGFR activating mutations.

Where is the technology used?

The technology is used in secondary care and administered through oncology out-patient clinics. No chemotherapy suite attendance is required.

Guidelines

At present the NCCN guidelines version 4.201611 recommend osimertininb (AZD9291) for patients for with T790M mutations after progression on 1st line EFGR TKI.
ESMO and ASCO guidelines have not yet been updated.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology

be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

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If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The main advantages of the technology under appraisal are:

1. AZD9291 (osimertinib) provides a well-tolerated effective treatment for T790M positive NSCLC following previous therapy with an EGFR TKI.
2. The response rate is 61% (95% CI 52% to 70%) and the median PFS is 9.6 months (95% CI 8.3 months to not reached) which compares favourably to standard chemotherapy.
3. The treatment is remarkably well tolerated with no dose limiting toxicities documented in the dose escalation cohorts and <3% grade 3 or worse adverse events.

The main disadvantages of the technology under appraisal are:

1. The need for T790M assessment of tumour – the most sensitive means of determining whether T790M is the mechanism of acqiured resitance is by repeat tumour biopsy. Assessment for presence of T790M by blood test, although possible, is less sensitive.
2. The possible additional cost burden to the NHS compared to chemotherapy.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must

include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

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Implementation issues

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If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The majority of NSCLC patients with EGFR activating mutations who receive 2nd line treatment in the UK receive 4 cycles of platinum pemetrexed chemotherapy, which may be followed by pemetrexed maintenance therapy. For patients with T790M mutation, oral therapy (osimertinib, AZD9291) would remove the need for chemotherapy suite attendance (saving chair time for each patient on the chemotherapy suite of approximately 3-6 hours, every 3 weeks for 4 cycles, followed by 30 minutes every 3 weeks until disease progression).

This group of patients would also usually have an outpatient appointment and routine blood tests every 3 weeks whilst on chemotherapy and the frequency of these visits would reduce to every 4 weeks on osimertinib (AZD9291). Radiological assessments (CT scans) would continue as standard of care every 2-3 months.

The reduced burden of toxicity from osimertinib (AZD9291) compared to standard chemotherapy would mean less prescription of supportive medication such as:

- Antibiotics
- Antiemetics
- Blood products

- Growth factors

Perhaps most importantly, there will be a reduced incidence of hospital admissions to treat chemotherapy associated toxicity, with consequent improvement in quality of life for patients.
Overall patients are likely to be on treatment longer than chemotherapy and so there may be some increased burden on oncology out-patient clinics.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

There are no equality issues identified.

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Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: ROYAL COLLEGE OF PATHOLOGISTS
Are you (tick all that apply):

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- **SPECIALIST ADVISOR TO RCPATH FOR LUNG PATHOLOGY, I REPRESENT PATHOLOGISTS WHO WOULD DEAL WITH THE BIOPSIES FOR DIAGNOSING LUNG CANCER AND HELP WRITE NATIONAL GUIDELINES FOR DATASETS AND HANDLING OF TISSUE**

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The main issue for pathologists in relation to treatment with this kind of drug is the cost of undertaking additional molecular testing for the T790M mutation.

The cost of this test needs to be defined - and accounted for along with the cost of the drug - it will have to be found within budgets on a regional basis, which should be reflected in the cost analyses. Also, a percentage will likely require a re-biopsy, which is an additional cost factor.

Pathologists/molecular laboratories will likely charge for the test in the same way as they do for EGFR mutations.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for previously treated locally advanced or metastatic, EGFR and T790M mutation positive non-small-cell lung cancer [ID874]

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Osimertinib for treating metastatic EGFR and T790M mutation-positive non-small-cell lung cancer [ID874]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Dr Thomas Newsom-Davis

Name of your organisation: Chelsea and Westminster Hospital, London

Are you (tick all that apply):

- ✓ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ✓ a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- \- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- \- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

I have no links to declare

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Patients with advanced (stage IIIB or IV) lung adenocarcinoma with mutations of exon 19 or 21 of the EGFR gene ($EGFR^{mut}$) are currently treated with a first line EGFR tyrosine kinase inhibitor (TKI) such as gefitinib, erlotinib or afatinib, according to NICE guidelines. All three TKIs are available within England, with local patterns of use reflecting physician preference. These agents are associated with a high response rate, manageable side effect profile, and good quality of life. The median duration of response is 9-12 months.

When $EGFR^{mut}$ cancer progresses on 1^{st} line EGFR TKI, patients are switched to platinum-based chemotherapy, usually pemetrexed and cisplatin. This is often effective in regaining control of the patient's disease, although is associated with significantly greater toxicities than EGFR TKIs as well as 3-weekly day-case attendances. There is some variation in the exact chemotherapy used, but the impact on the patient is broadly the same. Switching to another EGFR TKI is not recognised as standard practice or supported by NICE.

The scenario above reflects the great majority of clinical practice, is supported by international clinical guidelines (ESMO, ASCO), and there is consensus amongst oncologists.

One variation is the not un-common situation where a patient is started on first line chemotherapy before the EGFR mutation result is known. This occurs either when the patient it too unwell to wait for the mutation result, or when the result itself is delayed. In this scenario, most oncologists would continue chemotherapy whilst it remained effective, and would switch to an EGFR TKI once there was evidence of disease progression. Therefore such patients would have received their EGFR TKI as a second line treatment, and when it stopped being effective, current practice would be to consider further chemotherapy, most likely a docetaxel-based regimen.

Osimertinib would only be used for patients with $EGFR^{mut}$ lung cancer whose disease had progressed after first line EGFR TKI. Patients would be required to have a repeat biopsy to demonstrate that had had developed an additional EGFR mutation, termed T790M. This occurs in around two-thirds of $EGFR^{mut}$ patients in this situation. On the basis of all the scenarios above, the alternative to Osimertinib is chemotherapy.

There are no subgroups of patients who have a different prognosis from the typical patient, nor are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology.

Osimertinib would be used exclusively within oncology units and centres of secondary care, as part of lung cancer clinics. Patients would already be treated by the multi-disciplinary team and this would continue, however patients on oral medications such as Osimertinib typically require fewer outpatient appointments, less specialist nurse and oncologist input, fewer day-case attendance, no 'chemotherapy chair-time', and fewer acute attendances and inpatient admissions.

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Single Technology Appraisal (STA)

Osimertinib is not yet available outside of the EAMS (now closed).
Osimertinib is not included in NICE, ESMO or ASCO guidelines.

The advantages and disadvantages of the technology

Direct clinical trials (e.g. AURA3) comparing osimertinib to chemotherapy are underway, but have not reported yet. However having treated patients with Osimertinib as part of that trial and as part of compassionate access programs, and based on single-arm studies of osimertinib, my views on the relative advantages and disadvantages are below.

Advantages:
The clinical activity of Osimertinib is impressive given the clinical setting and compared to chemotherapy, with a high response rate (59%) and good medican progression free survival (12.4 months).

Osimertinib is associated with a more favourable side effect profile than chemotherapy. The principal symptoms are rash and diarrhoea, which are usually mild and easy to control. Other side effects such as pneumonitis and prolonged QT interval are rare. In contrast, platinum-based chemotherapy is associated with greater side effects including fatigue, nausea, vomiting, appetite loss, nephrotoxicity, neurotoxicity and rash. The chances of severe treatment-related toxicities and associated inpatient admission much lower with Osimertinib than with chemotherapy.

Osimertinib is an oral medication (compared to IV chemotherapy) and as much is more convenient for the patient. It is given once every 4-weeks, as opposed to 3-weekly chemotherapy, meaning fewer outpatient attendances. No routine day-case procedures or admissions would be required.

The consequence of this means that patients on Osimertinib are more likely to maintain their good quality of life. One should also recognise the psychological advantage of keeping on an outpatient oral medication, and not yet requiring chemotherapy.

Disadvantages:
Only patients with T790M mutations are eligible for Osimertinib. Furthermore patients are required to undergo a repeat biopsy to demonstrate this. Currently this would either be CT-guided or bronchoscopic/EBUS, both of which are invasive procedures with their own complications, and there may be issues with patient acceptability. There is also an additional delay when molecular analysis is undertaken, meaning that starting Osimertinib is a more complex, costly, and slower process than starting chemotherapy.

Osimertinib is contra-indicated in patients with previous pneumonitis, which may further limit the number of patients eligible for it.

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Single Technology Appraisal (STA)

Osimertinib is continued until disease progression and so patients may find being on continuous therapy difficult, and it may restrict their lifestyle. However I have not come across this issue with Osimertinib, perhaps reflecting its good tolerability.

My clinical experience of Osimertinib reflects the published AURA clinical trials. The majority of patients respond to treatment, side effects are usually fewer than those from the previous EGFR TKI they have been on, and quality of life is good. I have not used the drug for long enough or in enough patients to establish whether the real-life progression-free survival matches that of the clinical trials.

As in all clinical trials, the patient groups included in the published data are of very good performance status. Real-life patient populations may have a poorer performance status. However $EGFR^{mut}$ patients are typically younger, fitter and have fewer co-morbidities that the general lung cancer population anyway and so in this respect the clinical trials are reasonably representative of expected real-life clinics.

Due to the nature of the clinical trials conducted and published, the rapid development and accelerated approval of Osimertinib, mature data of all outcomes measures is not yet available. The most important metrics (response rate, progression free survival, toxicities) are known. Others (e.g. overall survival, formal quality of life assessment) are not. The latter will be important to know, but their absence should not prevent evaluation of Osimertinib's efficacy. Showing overall survival advantage may not be possible, given the likelihood of cross-over of subsequent therapies.

Side effects of Osimertinib are usually mild and drug well tolerated. This is critical in advanced lung cancer where treatments are not curative and so quality of life is key. The ability of patients to continue an oral medication which is unlikely to cause severe side effects is of great value.

I am not aware of any toxicities that are not described in the literature so far.

Equality and Diversity

I do not think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Any additional sources of evidence

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Single Technology Appraisal (STA)

None, apart from the published and widely available clinical trial data.

Implementation issues

Approval by NICE for Osimertinib would not have any impact on oncology clinics, chemotherapy waiting times or chemotherapy unit work-load, since it is an outpatient oral treatment.

There would be an increased demand for CT- and bronchoscopic/EBUS-biopsies, and subsequent molecular testing, however the overall number of $EGFR^{mut}$ patients is low and I do not foresee any of these resulting in any adverse effect on patient care as a result of dramatically increased workloads. The development of $EGFR^{mut}$ testing from serum (not yet widely available) would mitigate this issue anyway.

Agreement for molecular analysis of repeat biopsies from $EGFR^{mut}$ patients would need to be agreed by commissioners.

STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for locally advanced or metastatic EGFR and T790M mutation-positive non-small cell lung cancer [ID874]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/121/09

26th April 2016

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Osimertinib for locally advanced or metastatic EGFR and T790M mutation-positive non-small cell lung cancer [ID874]

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Declared competing interests of the authors: None

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

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Contributions of authors:

Greenhalgh J	Project lead, critique of the clinical evidence, drafted the clinical results section and supervised the final report
Mahon J	Checking and validation of the economic model and critique
Boland A	Critical appraisal of the clinical and economic evidence
Beale S	Critical appraisal of the clinical and economic evidence
Krishan A	Critical appraisal of the statistical evidence
Aslam RW	Project administration, critique of the clinical evidence, drafted the clinical results section
Kotas E	Cross-check of the company submission search strategy
Banks L	Critical appraisal of the company submission
Green J	Clinical advice and critical appraisal of the clinical evidence

All authors read and commented on draft versions of the ERG report.

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike Information Criterion
AURA	Clinical programme of trials assessing the clinical effectiveness of osimertinib
BIC	Bayesian Information Criterion
BICR	blinded independent central review
BOR	best overall response
BSA	body surface area
BSC	best supportive care
CI	confidence interval
CR	complete response
CS	company submission
CSR	clinical study report
ctDNA	circulating tumour DNA
DCR	disease control rate
DoR	duration of response
EAMS	Early Access to Medicines Scheme
ECOG	Eastern Cooperative Oncology Group
EGFR (-TKI)	epidermal growth factor receptor (tyrosine kinase inhibitor)
EGFRm+	epidermal growth factor receptor mutation-positive
EMA	European Medicines Agency
EORTC	European Organisation for the Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life - 5 Dimensions Questionnaire
ERG	Evidence Review Group
FACT-L	Functional Assessment of Cancer Therapy – Lung
FAS	full analysis set
GLOBOCAN	Global Burden of Cancer Study
HR	hazard ratio
HRQoL	health related quality of life
ICER	incremental cost effectiveness ratio
IMPRESS	Iressa Mutation-Positive Multicentre Treatment Beyond Progression Study
IPD	individual patient data
K-M	Kaplan-Meier
MHRA	Medicine and Healthcare Regulatory Agency
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressed disease
PDC	platinum doublet chemotherapy
PF	progression free
PFS	progression-free survival
PH	proportional hazards
PPS	post-progression survival
PR	partial response
PS	performance score
PSA	probabilistic sensitivity analysis
PSS	Personal and Social Services
PTDS	post-treatment discontinuation survival
QALY	quality adjusted life year
RCT	randomised controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SmPC	summary of product characteristics
T790M	A secondary mutation of the EGFR
TTD	time to treatment discontinuation

1 SUMMARY

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by AstraZeneca UK Ltd to support the use of osimertinib (Tagrisso®) for locally advanced or metastatic epidermal growth factor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC).

Osimertinib is licensed in Europe for the treatment of adults with locally advanced or metastatic EGFR T790M NSCLC. The European Medicines Agency (EMA) granted osimertinib a conditional marketing authorisation on 3rd February 2016. The marketing authorisation is conditional on AstraZeneca providing the final results of an ongoing phase III randomised controlled trial (RCT), AURA3, to the EMA by 30th June 2017.

The clinical evidence presented in the company submission (CS) comes from three main sources: AURAext and AURA2 (both single-arm studies) and the IMPRESS trial (a double-blind placebo-controlled RCT). Data from the two AURA studies provide evidence for the clinical effectiveness of osimertinib. The IMPRESS trial was designed to compare the efficacy of gefitinib+pemetrexed+cisplatin versus placebo+pemetrexed+cisplatin; in this trial, the placebo+pemetrexed+cisplatin combination is labelled as platinum doublet chemotherapy (PDC). The outcomes from a small subgroup of patients (n=max 61) recruited to the control arm of the IMPRESS trial, who were identified retrospectively as having the EGFR T790M mutation, are compared to the outcomes calculated from the pooled AURA dataset.

1.1 Critique of the decision problem in the company submission

Intervention

The intervention specified in the final scope issued by NICE and discussed in the CS is osimertinib. Osimertinib is administered at a dose of 80mg once daily. It is available as 40mg or 80mg film-coated tablets.

Line of treatment is not specified in the conditional EMA licence or in the final scope issued by NICE. The EMA's decision to grant a licence for all treatment lines was based on a biological assumption of effectiveness as there are no data to support the use of osimertinib in treatment-naïve patients. The company expects that, in NHS clinical practice, osimertinib will mainly be used as a second-line treatment after failure of a first-line EGFR tyrosine kinase inhibitor (EGFR-TKI). The company estimates that, if recommended by NICE,

approximately 300 patients per year in England will be eligible for treatment with osimertinib. This estimate includes patients at all lines of treatment.

It is stipulated in the summary of product characteristics (SmPC) for osimertinib that treatment should only be initiated after the patient's EGFR T790M mutation status is positively confirmed using a validated test method. EGFR testing after first-line treatment to establish the presence or absence of the EGFR T790M mutation is feasible in the NHS as the infrastructure is in place. However testing at this point in the treatment pathway is not currently standard practice in the NHS.

Population

The population described in the final scope issued by NICE is people with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. This is the same as the population described in the conditional licence for osimertinib issued by the EMA.

The clinical evidence describing osimertinib submitted by the company is derived from two single-arm studies (AURAext and AURA2). These studies 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.

Comparators

There are 13 comparators listed in the final scope issued by NICE; these vary by line of treatment. The company presents comprehensive clinical effectiveness data for the unadjusted and adjusted comparison of second or further line treatment with osimertinib versus second-line PDC (specifically, placebo+pemetrexed+cisplatin).

The data used to inform the PDC comparison were obtained from the subgroup of patients (n=61) included in the control arm of the IMPRESS trial whose tumours were identified retrospectively as having the EGFR T790M mutation. Comparisons between outcomes for the selected patients from the IMPRESS trial and patients in the pooled AURA dataset were made using two approaches, a simple unadjusted comparison and an adjusted comparison. The adjusted comparison involved adjustments to control for differences in baseline characteristics between the populations in the two datasets.

The company has assumed that treatment with pemetrexed+cisplatin can be used to represent all PDC treatments, i.e. vinorelbine, gemcitabine, docetaxel or paclitaxel in combination with cisplatin or carboplatin. The ERG is aware that, for the specified

population, pemetrexed+cisplatin is the most commonly used PDC in the NHS. The company also assumes that the efficacy of docetaxel monotherapy in patients untested for EGFR T790M mutations can be used to represent the efficacy data associated with any single-agent chemotherapy for the second-, third-line and further treatment of patients with tumours exhibiting EGFR T790M mutations.

Outcomes

Clinical evidence is presented in the CS for all five outcomes specified in the final scope issued by NICE: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), adverse events (AEs) and health-related quality of life (HRQoL). The currently available OS data from the AURAext and AURA2 studies (pooled) and the subgroup of patients with T790M mutations from the control arm of the IMPRESS trial are very immature (12.7% and approximately 33% respectively).

Other considerations

No subgroups were specified in the final scope issued by NICE in addition to the distinct populations specified in the comparator section. The company has submitted a Patient Access Scheme (PAS) proposal to the Department of Health.

Equality and End of Life considerations

The company has not identified any equality issues. However, the company has presented a case for osimertinib to be assessed against the NICE End of Life criteria.

1.2 Summary of clinical effectiveness evidence submitted by the company

Direct evidence

The company conducted a broad literature search and did not identify any RCTs other than the ongoing phase III AURA3 trial. The results of the AURA3 trial are expected to be available in 2017.

The company has presented results from two single-arm studies, the phase I/II AURAext study and the phase II AURA2 study. The company combines the data from these two studies in a pooled analysis. Results from the pooled AURA dataset (n=411) demonstrate that treatment with osimertinib yields an ORR of 66.1% (95% CI: 61.2 to 70.7), a finding that is consistent across all subgroups tested. Median PFS is 9.7 months (95% CI: 8.3 to not calculable). Results for OS were not available due to the immaturity of the data. The most commonly reported AEs (all grades) were diarrhoea (42.3%) and rashes and acne (41.4%). Grade 3 or 4 AEs included respiratory disorders (13%), infections (6%), investigations

(5.8%) and blood disorders (5%, AURA2). The HRQoL data collected during the AURAext and AURA2 studies suggest that osimertinib has a significant, measurable and relevant impact on patients' HRQoL and symptoms.

Unadjusted and adjusted comparisons evidence

Two comparisons, (unadjusted and adjusted), were carried out to compare the effectiveness of osimertinib with that of PDC.

The unadjusted comparison of osimertinib with PDC yields a statistically significantly higher ORR for osimertinib (66.1% versus 39.3%). The comparison of PFS also demonstrates a statistically significant difference of 4.4 months (9.7 months [95% CI 8.9 to not calculable] versus 5.3 months) in favour of osimertinib. Median OS was not reached for osimertinib and was 15.7 months for PDC.

Results from the adjusted comparison are consistent with those from the unadjusted comparison. The ORR results indicate a statistically significant improvement in favour of osimertinib compared to PDC (64.6% and 34.8% respectively; OR=4.76; 95% CI: 2.21 to 10.26; p<0.001). The disease control rate (DCR) results also indicate a statistically significant improvement in favour of osimertinib compared to PDC (92.1% and 76.1% respectively; OR=4.39; 95% CI: 1.71 to 11.28; p=0.002). The PFS results indicate a statistically significant difference in favour of osimertinib compared to PDC (HR=0.280; 95% CI: 0.185 to 0.422; p<0.0001). Median PFS is 9.7 months for the osimertinib cohort compared to 5.2 months for the PDC cohort. Analysis of OS indicated an overall hazard ratio of 1.022 (95% CI 0.387 to 2.696) for osimertinib versus PDC. The data indicated that treatment with osimertinib is better tolerated than treatment with PDC.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The ERG is satisfied with the company's search strategy and stated inclusion and exclusion criteria. The ERG is confident that searching was carried out to an acceptable standard and is not aware of any additional studies that should have been included in the company's systematic review.

1.3.1 Direct evidence

The ERG considers that the AURAext and AURA2 studies were designed and conducted to a good standard. In particular, the use of blinded independent central review (BICR) in the assessment of the radiological results lends robustness to the PFS outcomes. Furthermore, the use of a single treatment arm design means that the OS data from the AURAext study

and AURA2 study cannot be contaminated by treatment crossover. However, 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. The interpretation of the results of the AURAext and AURA2 studies is also hampered by the very immature survival data.

The extent to which the submitted evidence reflects outcomes that would be seen in NHS clinical practice is limited by lack of confidence in the magnitude of the outcomes from the AURAext and AURA2 studies. Patients included in these studies are younger and fitter than EGFRm+ patients who would be eligible for treatment with osimertinib in the NHS. Very few EGFRm+ patients in the NHS receive more than one or two treatments after an EGFR-TKI; this is in contrast to patients in the AURAext and AURA2 studies who received up to 14 treatments.

The AURAext study was open to recruitment at two centres in the UK; however, it is not clear how many patients were recruited from the UK. The AURA2 study was not open to recruitment from UK centres.

1.3.2 Unadjusted and adjusted comparisons

The ERG commends the company's efforts to carry out an adjusted comparison. However, the robustness of the outcomes is limited by the small number of patients represented in the PDC cohort. In addition, the company was unable to consider some of the important demographic and disease characteristics (e.g., number of previous EGFR-TKI treatments) required by the matching process.

In particular, the OS results from the adjusted comparison should be interpreted with caution as only 11.5% of the osimertinib data and 29.4% of the PDC data were mature at the time that the analysis was carried out. The ERG and the company agree that the OS data are too immature to allow any meaningful interpretation of results.

1.4 Summary of submitted cost effectiveness evidence

The company developed a de novo cohort-based partitioned survival model in Microsoft Excel to compare the cost effectiveness of osimertinib with PDC in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy (i.e. ≥second-line therapy). The model comprised three health states: progression-free (PF), progressed-disease (PD) and death. All patients entered the model in the PF state. Variants of this model structure have been used in previous NICE STAs. The model time horizon was set to 15 years with a 1-week cycle length. As

recommended by NICE, a discount rate of 3.5% was used for both costs and outcomes; outcomes were measured in quality adjusted life years (QALYs). The model perspective was that of the UK NHS. Survival estimates were based on data collected from the AURAext and AURA2 studies (for osimertinib) and from patients in the control arm of the IMPRESS trial with EGFR T970M positive mutations (for PDC) and other published sources. Utility values were calculated from data collected during the AURA2 study and the IMPRESS trial. Resource use and costs were estimated based on information from the AURAext and AURA2 studies and the IMPRESS trial, published sources and advice from clinical and economic experts. The company also compared osimertinib versus PDC in a second-line population only, versus docetaxel in a second-line population only and versus docetaxel in a ≥third-line population only.

The base case comparison of osimertinib versus PDC resulted in an incremental cost effectiveness ratio (ICER) per QALY gained of [redacted] with osimertinib being more expensive [redacted] and more effective [redacted] life years and [redacted] QALYs). The company carried out a range of deterministic sensitivity analyses. The most influential parameters were utility values, particularly for the PD state, and choice of discount rate. The probabilistic sensitivity analysis (PSA) results showed that the probabilistic ICER of [redacted] per QALY gained had a ≤5% chance of being cost effective at a threshold of £30,000 per QALY gained and a 35% probability of being cost effective at a threshold of £50,000 per QALY gained. The ICER per QALY gained for osimertinib versus PDC in a second-line only population was [redacted]; versus docetaxel in a second-line only population was [redacted] and versus docetaxel in a ≥third-line only population was [redacted]. The company performed scenario analyses using different survival modelling approaches, health state utility values and resource use and costs. Only the choice of survival modelling approach had a significant influence on the size of the ICER per QALY gained; using a Gompertz distribution for PFS and OS yielded an ICER of [redacted] per QALY gained.

1.5 Summary of the ERG's critique of cost effectiveness evidence

The ERG considers that there are several fundamental issues that cast doubt on the cost effectiveness results produced by the company model.

Over 90% of the QALY benefit from osimertinib estimated from the model arises when OS trial data are no longer available. The available OS data for osimertinib and PDC are not statistically significantly different and are very immature, especially so for osimertinib. The only statistically significant evidence on effectiveness incorporated in the model is an improvement in PFS with osimertinib, the extent of which is uncertain due to the single-arm nature of the AURA studies.

The ERG considers that lack of statistical significance in OS between osimertinib and PDC during the period for which data are available means that there is no basis to project differential OS. Even if there were a statistically significant difference between osimertinib and PDC for the period that data were available, as the OS data are so immature, any projection could only be speculative with the degree of uncertainty in the projection being impossible to quantify.

The populations within the AURA studies and the IMPRESS trial appear to be fitter than the EGFRm+ patients who would be expected to be seen in routine NHS practice. This casts doubt on the appropriateness of using the AURA and IMPRESS OS datasets to represent the UK EGFRm+ population even if it was fully mature.

The ERG therefore considers the OS projections employed by the company to be based on opinion rather than to be supported by evidence. To support this view, the ERG cites the wide variation in ICERs that the company shows (CS, p234) could be produced depending on the selection of different statistically plausible, if not necessarily clinically plausible, projections of OS.

The ERG considers that all of the ICERs estimated using the company OS projections – including the ERG model amendments - should therefore be treated as 'what if?' scenarios as they are not underpinned by statistically significant clinical effectiveness evidence.

Even if the company's OS projection was accurate, the company has underestimated the acquisition costs of osimertinib and failed to take into account any administration cost of osimertinib as an oral chemotherapy. Using time to treatment discontinuation data (TTD) from the AURA studies and the IMPRESS trial and a cautious estimate of the NHS Reference Cost for oral chemotherapy administration results in substantial increases in the size of the ICER per QALY gained from the company base case.

The ERG also considers that the utilities applied in the company model appear to be implausible as they are higher in the PF state (0.815) than the general population norm for patients of the same age at the start of the model (0.80). Whilst no utility values are available specifically for the population described in the CS, the ERG considers that there are alternative utility values that, whilst they are by no means perfect, may be closer to the actual values of the target population compared to the utility values used in the model.

The ERG did not identify any statistically significant difference in PFS and OS by line of treatment for osimertinib and did not consider the evidence on single-agent chemotherapy to

be convincing. As such, the ERG does not consider the results of the company's subgroup analyses to be informative.

1.6 Summary of company's case for End of Life criteria being met

The company has put forward a case that osimertinib meets NICE's End of Life criteria based on the following points:

- the available clinical effectiveness data from the IMPRESS trial suggest that patients previously treated with an EGFR-TKI have a median OS of less than 24 months
- the results of the company's economic modelling suggest a mean OS gain of over 12 months with osimertinib compared with PDC
- the number of patients eligible for treatment with osimertinib is 300 per year.

1.7 ERG commentary on End of Life criteria

The ERG agrees with the company that, in England, approximately 300 patients each year will be eligible for treatment with osimertinib. The ERG considers that patient life expectancy in the second-line setting life is less than 24 months. The ERG's view is that the OS benefit from treatment with osimertinib cannot be established with any confidence until more mature OS data are available.

1.8 ERG commentary on the robustness of evidence submitted by the company

1.8.1 Strengths

Clinical evidence

- The company provided a detailed submission that fulfilled as many requirements of the final scope issued by NICE as is currently possible given the available clinical effectiveness data
- The AURAext and AURA2 studies were of good methodological quality and included a BICR of radiological outcomes
- The company made use of the IPD available from the IMPRESS trial
- The ERG's requests for further clinical information were fulfilled promptly and to a good standard

Cost effectiveness evidence

- The economic model was well constructed, easy to navigate and there were no flaws in the algorithms
- The company has undertaken a large number of subgroup and scenario analyses to explore the impact of the uncertainty in the OS data
- The company went to great lengths to compare the cost effectiveness of osimertinib to chemotherapy even when no head-to-head trial data were available.

1.8.2 Weaknesses and areas of uncertainty

Clinical evidence

- There is no RCT evidence available to support the use of osimertinib for locally advanced or metastatic EGFR T790M mutation-positive NSCLC for any line of treatment
- The clinical evidence supporting treatment with osimertinib in the CS is derived from two single-arm studies
- The pooled OS data derived from the AURAext and AURA2 studies are very immature (12.7% mature)
- The company was unable to compare osimertinib with 11 of the comparators listed in the final scope issued by NICE due to a lack of relevant clinical effectiveness evidence
- The results of the company's unadjusted and adjusted analyses should be treated with caution due to the limited and immature survival data available
- The company's use of references in the CS was confusing and often inaccurate.

Cost effectiveness evidence

- There is no clinical or statistically significant basis to support any difference in OS between osimertinib and PDC. As such, there is no basis to project a difference in OS in the company model
- The use of PFS data, rather than TTD data, underestimates the cost of osimertinib treatment and overestimates the cost of PDC treatment
- The utility values used in the company model are high. There are alternative utility values that the ERG considers to be more plausible than those used by the company
- Treatment with osimertinib statistically significantly improves PFS compared to treatment with PDC. The ERG considers that the company base case should comprise a PFS gain for osimertinib and no OS gain. The ERG considers that hypothetical OS gains should be employed only in the company's scenario analyses.

1.9 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG suggested five amendments that could be made to the company model. Two amendments suggested changes to the costs in the company model, two offered alternative utility values and a final amendment removed the OS gain for osimertinib over PDC with only a gain in PFS for osimertinib compared to PDC remaining.

The ERG also noted minor errors related to AE costs, discounting and the PDC costs per dose. However, as the impact of correcting these minor errors would only have a small impact on the size of the ICERs, the ERG did not include these minor errors when compiling the list of suggested model amendments. Similarly, the testing costs for the EGFR T790M mutation were estimated to have only a small impact on the size of the ICERs whether they were included or not in the model.

Application of the ERG changes to costs and the ERG's alternative utility values resulted in ICERs for osimertinib compared to PDC of [redacted] per QALY gained or [redacted] per QALY gained depending on the source of the alternative utility values used in the model. In addition, when only the improvement in PFS with osimertinib is included (i.e.., there is no OS gain as only PFS is statistically significantly improved for osimertinib versus PDC) then the ERG estimates the ICER for osimertinib compared to PDC to be [redacted] per QALY gained or [redacted]x per QALY gained, again depending on the source of the alternative utility values used in the model.

All of the ERG's revised ICERs are based on list prices.

2 BACKGROUND

2.1 Critique of the company description of underlying health problem

Section 3.1 of the company submission[1] (CS) includes an overview of locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC). Section 3.2 of the CS includes a description of the effects of the disease on patients, carers and society. Information about the life expectancy of this population in England is presented in Section 3.4 of the CS. Key points from these sections are included as bulleted items in Box 1 and Box 2. The Evidence Review Group (ERG) considers that these points appropriately summarise the underlying health problems.

Box 1 Company overview of locally advanced or metastatic EGFR T790M mutation-positive NSCLC

Lung cancer types, subtypes and incidence rates

- Lung cancer is the most common cancer worldwide and the leading cause of cancer death worldwide with an estimated annual death toll of 1.59 million people. The majority of lung cancer cases are diagnosed when patients have either locally advanced or distant metastatic disease that is not amenable to curative surgery

- Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Within the UK, approximately 38,000[2] people are diagnosed with lung cancer every year of which NSCLC accounts for 88%[2]

- Advanced NSCLC (aNSCLC) is further divided into subtypes depending on the molecular profile and predominant oncogenic driver of the tumour. One of these is aNSCLC with an epidermal growth factor receptor sensitising mutation (EGFRm+). The prevalence of EGFR mutations in NSCLC varies according to the different histological subtypes and patient ethnicity. In a Caucasian aNSCLC population, EGFR mutations account for approximately 10%[3] of all cases. Clinical guidelines recommend routine testing for EGFR mutations before selecting a first-line therapy for aNSCLC

- Most advanced EGFRm+ tumours initially respond to tyrosine kinase inhibitors (EGFR-TKIs), but subsequently develop resistance to therapy on average 10–14 months after commencing treatment. This can be either due to secondary mutations or via activation of bypass signalling pathways (c-Met amplification). EGFR T790M mutations account for 50% to 60%[4-6]of all cases of acquired resistance. The EGFR T790M mutation is rarely detected (approximately 1%[3] of patients) in EGFR-TKI naive tumours (also known as de novo or primary mutations).

Source: CS, Section 3.1

Box 2 Company's overview of effects of the disease on patients, carers and society

Prognosis

- The 5-year survival rate for patients in the UK who are diagnosed with locally advanced (stage IIIB) NSCLC is very low at 7% to 9% and an even worse prognosis (5 year survival equal to 1%) is associated with the presence of distant metastases (stage IV)
- Treatment with EGFR-TKIs has resulted in an improved life expectancy for patients with EGFRm+ disease of approximately 20 to 24 months[7-12] from the point of initial diagnosis
- At disease progression and for patients who develop EGFR-TKI resistance and who are treated with platinum doublet chemotherapy, median overall survival (OS) is approximately 17 months according to the results of the IMPRESS[13] trial
- The prognostic role of the EGFR T790M mutation is not fully understood. In the dataset from the IMPRESS[13] trial, median progression-free survival (PFS) was consistent (5.3 months and 5.4 months) for EGFR T790M mutation-positive and EGFR T790M mutation-negative patients respectively. The OS Kaplan-Meier (K-M) plots between the EGFR T790M mutation-positive and negative control group (treated with platinum-doublet chemotherapy) showed a degree of separation from 12 months onwards.

Effects of disease on carers and society

- Lung cancer is the most common cause of death in the UK, accounting for more than one in five cancer deaths. In 2012, 35,751 deaths from lung cancer across the UK were recorded
- In the UK, costs associated with lung cancer exceed the cost of all other cancer types
- For the year 2013 to 2014, hospital admissions in England associated with lung cancer (ICD10 C34) reached 88,350 and accounted for 108,216 completed consultant episodes and 282,717 bed days
- Most NSCLC patients experience multiple symptoms; the majority of metastatic patients endure three or more, with cough, pain and dyspnoea being the most common
- NSCLC symptoms directly affect physical functioning and well-being. This has a direct impact on patients' health related quality of life, which is significantly reduced amongst patients with early stage disease
- Chemotherapy is associated with acute, potentially life-threatening side-effects and serious longer-term toxicities**.** Chemotherapy-treated patients require frequent clinic visits
- NSCLC can cause a burden for people who provide informal care due to its direct psychological impact
- As the disease progresses, informal care givers may also experience an economic burden due to taking time off work whilst caring.

Source: CS, Section 3.2 and Section 3.4

Clinical advice to the ERG is that patients with EGFR mutation-positive (EGFRm+) NSCLC have a better prognosis than patients in an unselected advanced NSCLC population as they are younger and have fewer co-morbidities.

The ERG agrees with the company (CS, p51) that the advent of treatment with EGFR-TKIs has led to increased life expectancy for patients with EGFRm+ disease. The ERG notes that in the pivotal trials[7-12,14-16] exploring the efficacy of EGFR-TKIs, overall survival (OS) results of up to 34 months[17] have been reported.

The ERG notes that the OS outcomes from the IMPRESS[13] trial (reported in

Box 2) are preliminary outcomes as the data are immature. In addition, the data are derived from patients in the control arm of the IMPRESS trial who were retrospectively identified as having EGFR T790M mutation-positive NSCLC.

The ERG understands that the prevalence of EGFRm+ disease in the NSCLC population varies according to histological subtype and ethnicity. The prevalence in a Caucasian population is approximately 10%[3] but may be greater in other ethnicities.[17] A small proportion of patients (approximately 1%[3]) have EGFR T790M mutation-positive disease at first diagnosis. Of the EGFRm+ patients whose first-line treatment is an EGFR-TKI, between 50% and 60% are found to have developed the EGFR T790M mutation at disease progression.[4-6]

2.2 Critique of the company overview of current service provision

An overview of current service provision is presented in Section 3.3 of the CS. The company discusses the appropriate published NICE guidance[18-20] and international treatment guidelines in Section 3.5 of the CS.

It is correctly reported in Section 3.5 of the CS that there is no published NICE guidance or international guidelines that are tailored specifically to the treatment of patients with EGFR T790M mutation-positive advanced or metastatic NSCLC.

In the UK NHS, patients who have EGFRm+ disease at diagnosis are treated with an EGFR-TKI, either gefitinib, erlotinib or afatinib (TA192,[18] TA258[19] and TA310[20] respectively). Clinical advice to the ERG is that, for the (very few) patients who are identified as having primary EGFR T790M mutation-positive disease at diagnosis (approximately 1%[3]), treatment starts with an EGFR-TKI followed by an early switch to platinum doublet chemotherapy (PDC), usually pemetrexed+cisplatin, at the clinician's discretion. Not all centres routinely test for the EGFR T790M mutation.

The company presents a treatment algorithm outlining the existing treatment pathway for patients with EGFRm+ NSCLC and the anticipated NHS treatment pathway for patients with EGFR T790M mutation-positive disease (see Figure 1). The ERG considers that the algorithm presented by the company reflects current clinical practice and would capture the treatment pathway in the event that osimertinib were recommended by NICE for use in the NHS. The ERG agrees with the company that pemetrexed with cisplatin or carboplatin is usually offered following disease progression on an EGFR-TKI. The ERG notes that nintedanib+docetaxel is now recommended by NICE for use after failure of first-line chemotherapy.

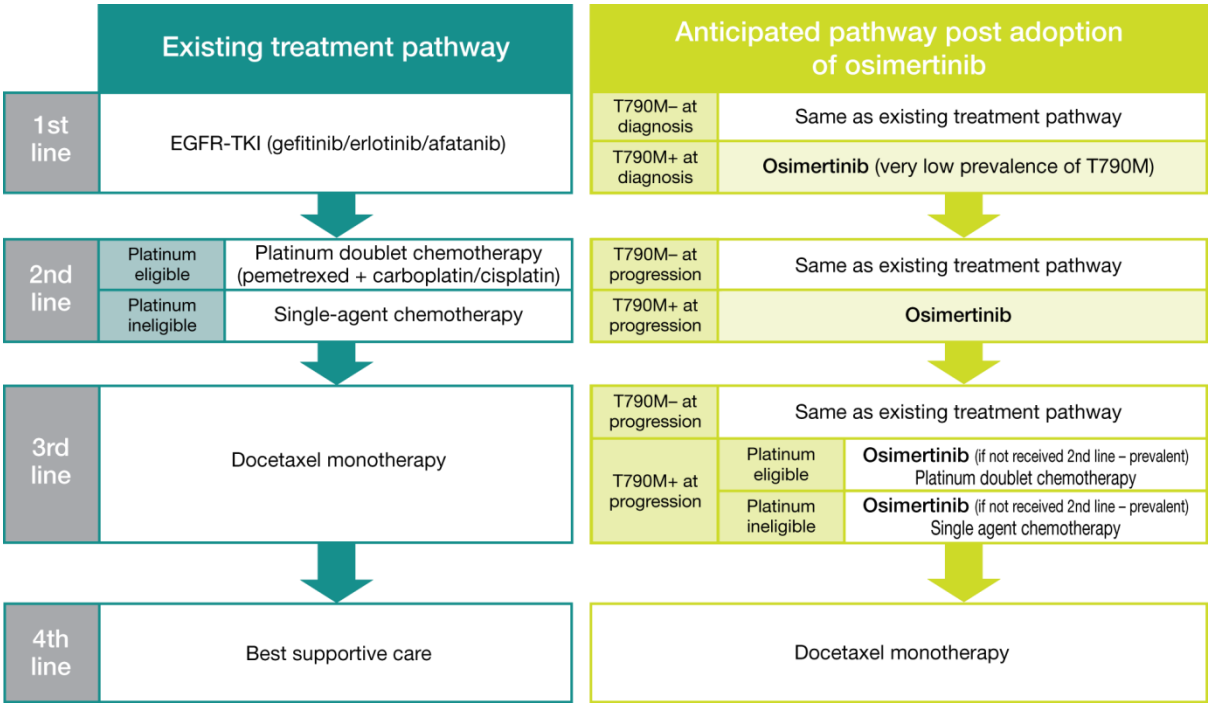


Figure 1 NHS treatment algorithm presented by the company

Source: CS, Figure 3.2

The ERG notes that the European Medicines Agency (EMA) marketing authorisation[21] is for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC. The marketing authorisation does not specify a particular line of treatment; however, the company expects osimertinib will mainly be used as a second-line treatment, after failure of an EGFR-TKI (CS, p53). The company discusses the use of osimertinib as first- and third-line and further treatments in the NHS and states that:

- the number of patients treated at first-line is likely to be small given the low prevalence of the EGFR T790M mutation at diagnosis
- an existing third-line patient population is a 'one-off' group.

2.2.1 Testing for the EGFR T790M mutation in the NHS

The ERG is aware that, in the NHS, mutation testing is currently carried out via tissue biopsy. Patients are routinely tested for the presence of the EGFR mutation at diagnosis; very few tissue biopsies are carried out after treatment has commenced. Testing for the EGFR T790M mutation is not routinely carried out in the NHS either at diagnosis or after treatment failure with a first-line EGFR-TKI. The company acknowledges (CS, p44) that tissue biopsy at disease progression after treatment with an EGFR-TKI is not routinely carried out in the NHS and its introduction will therefore necessitate a change in service provision.

Company's anticipated testing protocol in the NHS

The company observes (CS, p44) that blood plasma testing (ctDNA) is becoming available to cancer patients in the NHS; however, ctDNA testing carries a high false negative rate. In line with the Summary of Patient Characteristics (SmPC),[21] the company states that all patients with a negative result for the EGFR T790M mutation following a ctDNA test should be retested using a tissue biopsy.

The company points out (CS, p44) that ctDNA testing mitigates the complications associated with the acquisition of lung tissue samples (for example, pneumothorax, infection and bleeds) and may be a preferred option for patients with later stage disease and poor performance status (PS).

The company states (CS, p45) that although the tissue testing pathway is well established within the NHS (particularly in the first-line setting), ctDNA testing is a less expensive alternative and offers more rapid results. The company reports that feasibility studies into the pathway for ctDNA processing within the NHS are expected to begin in the second quarter of 2016.

The CS (p45) includes an algorithm to illustrate the optimal testing pathway for EGFR T790M mutation status in the NHS (Figure 2) as perceived by the company. Clinical advice to the ERG is that tissue biopsy testing is available at approximately 85% of NHS treatment centres and is conducted mainly at diagnosis. Not all centres test for the presence of the EGFR T790M mutation at diagnosis and very few centres currently re-biopsy patients after treatment is initiated. This means that the use of osimertinib in the NHS will require a change in practice to facilitate EGFR T790M mutation testing following disease progression on a first-line EGFR-TKI. Given the low estimated incidence and prevalence rate of primary EGFR T790M mutation-positive disease, it is unlikely that patients will ever be routinely tested for the EGFR T790M mutation at diagnosis. Ideally, until a ctDNA test is available to the NHS, all patients would be offered a tissue biopsy at relapse after a first-line EGFR-TKI to determine their EGFR T790M mutation status and inform second-line treatment decisions; however, clinical advice to the ERG is that there are concerns about patients' willingness to tolerate the biopsy procedure.

The ERG notes that the SmPC[21] for osimertinib recommends that patients with a negative ctDNA test result should have the result confirmed by a tissue biopsy test. This means that in the absence of a ctDNA test that is 100% sensitive, the 40% to 50% of patients who do not have the EGFR T790M mutation will be offered a tissue biopsy test to confirm the negative ctDNA test result.

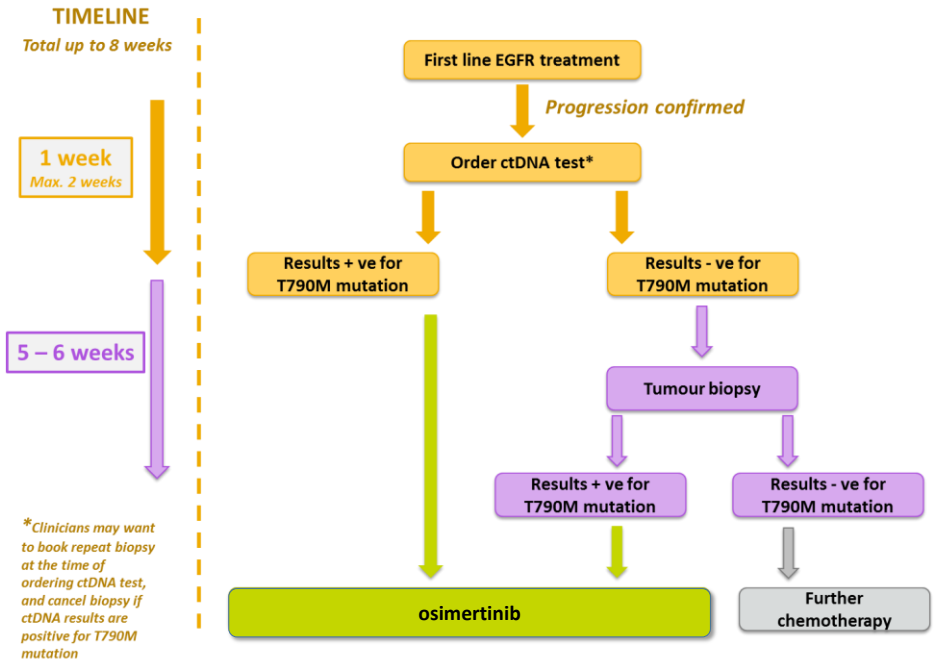


Figure 2 Company's anticipated optimal NHS testing pathway for EGFR T790M mutation status

Source: CS, Figure 2.1

2.3 Innovation

The company states (CS, p46) that osimertinib was included in the Medicine and Healthcare Regulatory Agency (MHRA) Early Access to Medicines Scheme (EAMS).[22] The purpose of the EAMS is to give patients with life-threatening or debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet clinical need.

The company provides text from the MHRA assessment report[22] (CS, p46) to support the claim that osimertinib is an innovative treatment:

> *'EGFR T790M mutation-positive lung cancer is a life threatening disease. Patients with this condition have very limited treatment options, reduced life expectancy and there is an urgent need for more therapies. In clinical studies, osimertinib was able to slow or shrink the cancer in these patients. Other currently available treatments have limited activity. The MHRA has considered the benefits of osimertinib in this difficult to treat condition and concluded that the benefits are greater than the risks'.*

The ERG agrees with the MHRA that treatment with osimertinib appears promising but cautions that the available data are derived from two single-arm studies (AURAext[23] and AURA2[24]) and the survival and safety data are currently very immature. The final outcome

data from the ongoing AURA3[1] phase III randomised controlled trial (RCT) will be more robust.

The ERG agrees with the company (CS, p58) and the MHRA that patients with EGFR T790M mutation NSCLC are a group of patients with no specific treatments available to them. The ERG considers that osimertinib appears to be better tolerated than treatment with pemetrexed+cisplatin and that, in terms of drug administration, patients generally prefer the oral method of administration (osimertinib) to intravenous infusion (PDC).

The company reports (CS, p29) that osimertinib is the first drug to be approved under the EMA's EU PRIME scheme.[25] The purpose of the EU PRIME scheme is to provide support for the development of medicines that target an unmet medical need. When the application for marketing authorisation is submitted to the EMA, medicines awarded EU PRIME status are eligible for accelerated assessment.

2.4 Number of patients eligible for treatment with osimertinib

The company estimates (CS, p245) that approximately 300 patients every year are likely to be eligible for treatment with osimertinib (Table 1). The ERG considers the company's estimate to be reasonable but notes that the figure of 10% used to estimate the proportion of patients with EGFRm+ tumours relates to Caucasian patients and that this figure is higher in other ethnic groups.[17]

Table 1 Company estimate of the number of patients in England eligible for treatment with osimertinib

Parameter	Estimated proportion of patients	Number of patients (incident)	Number of patients (prevalent)
Lung cancer diagnosis[2]		31,393	25,276
Confirmed NSCLC [2]	59%	18,447	14,853
Patients with stage III/IV disease[2]	77%	14,204	11,437
Patients tested for EGFR mutation status[2]	87%	12,372	9,961
Patients with EGFR mutation*	10%	1,237	996
EGFRm+ patients receiving 1st-line anti-cancer treatment [2]	58%	713	574
EGFRm+ patients who progress on 1st-line anti-cancer treatment and receive active treatment*	Incident 65% Prevalent 50%	463	287
Patients with T790M mutation – eligible population[6,26]	60%	278	172

Source: CS, Table 6.1
*AstraZeneca internal research

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the decision problem described by the company in the CS in relation to the final scope issued by NICE[27] is presented in Table 2. Each parameter is discussed in more detail in the text following the table.

Table 2 Summary of parameter details included in the final scope issued by NICE and the company's decision problem

NICE scope **Parameter and specification**	**Decision problem addressed in the company's submission**
Population People with locally advanced or metastatic EGFR T790M mutation-positive NSCLC	As per final scope, except that no cost effectiveness results are presented for the treatment-naïve population
Intervention Osimertinib	As per final scope
Comparator(s) For people who have not received previous treatment: afatanib, erlotinib and gefitinib	Very limited evidence describing the clinical effectiveness of erlotinib and afatanib is presented in the CS (p166-171) for previously untreated patients
For people who have received previous treatment with an EGFR-TKI: PDC (including pemetrexed+carboplatin or pemetrexed+cisplatin)	As per final scope The base case cost effectiveness analysis compares osimertinib with PDC in ≥second-line patients A subgroup analysis is provided to compare the cost effectiveness of osimertinib with PDC in second-line patients
For people who have received previous treatment with an EGFR-TKI and in whom PDC is not appropriate: single-agent chemotherapy including gemcitabine, paclitaxel, vinorelbine and docetaxel	As per final scope Clinical effectiveness data are limited. A subgroup analysis is provided to compare the cost effectiveness of osimertinib with docetaxel in second-line patients
For people who have received previous treatment with an EGFR-TKI and chemotherapy: docetaxel (+/- nintedanib), nivolumab (subject to ongoing NICE appraisal), ramucirumab (subject to ongoing NICE appraisal), single agent chemotherapy including gemcitabine, paclitaxel, vinorelbine (for those for whom treatment with docetaxel is not appropriate) and BSC	Clinical effectiveness data are limited and only relate to treatment with single-agent chemotherapy A subgroup analysis is provided to compare the cost effectiveness of osimertinib with single-agent chemotherapy at ≥third-line
Outcomes The outcome measures to be considered include: PFS, OS, ORR, AEs and HRQoL	As per final scope
Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective	As per final scope

NICE scope Parameter and specification	Decision problem addressed in the company's submission
The availability of any patient access schemes for the comparator technologies should be taken into account The use of osimertinib is conditional on the presence of the T790M mutation in the EGFR gene. The economic modelling should include the costs associated with testing for EGFR T790M mutations in people with NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of additional testing	
Subgroups to be considered None (other than the subgroup populations mentioned in population)	As per final scope
Other considerations None	As per final scope

AE=adverse event; EGFR=epidermal growth factor receptor; HRQoL=health related quality of life; NICE=National Institute for Health and Care Excellence; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PDC=platinum doublet chemotherapy; PFS=progression-free survival; QALY=quality adjusted life year; TKI=tyrosine kinase inhibitor; BSC=best supportive care.
Source: CS, adapted from Table 1.1

3.1 Osimertinib clinical evidence

There is no direct clinical evidence comparing osimertinib with any of the comparators listed in the final scope issued by NICE. To compare osimertinib versus PDC (base case comparator) the company had to (i) pool very immature clinical data from two single-arm studies (ii) retrospectively identify patients in the control arm of the IMPRESS trial who tested positive for the EGFR T790M mutation and (iii) carry out an unadjusted and an adjusted treatment comparison. Consequently, the ERG is concerned that the clinical evidence presented by the company to support the use of osimertinib in patients who have received previous treatment with an EGFR-TKI is not robust. Furthermore, as the OS data from the pooled AURA[1] dataset were only 12.7% mature at the time of writing the CS, there are no reliable long-term safety outcome data available.

3.2 Population

The population described in the final scope issued by NICE is people with locally advanced or metastatic EGFR T790M mutation-positive NSCLC. This is the same as the population described in the conditional licence for osimertinib issued by the EMA.[3]

Treatment line is not specified in either the final scope issued by NICE or in the conditional EMA licence.[28] The company expects osimertinib to be used as a second-line treatment following relapse whilst receiving first-line treatment with an EGFR-TKI. The clinical evidence submitted by the company is derived from two single-arm studies (AURAext and AURA2) that 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.

The company explains (CS, p166 to p167) that clinical effectiveness data to support the use of osimertinib as a first-line treatment are limited to the experience of five patients who were treated with osimertinib as part of the AURA phase I extension study. The company states that the EMA's decision to grant a licence for the use of osimertinib in all treatment lines was based on a biological assumption of its effectiveness as a first-line treatment as no clinical studies have been conducted in treatment-naïve patients. The ERG accepts the company's explanation and notes that the European Public Assessment Report (EPAR[28]) issued by the EMA confirms the company's explanation.

For the specified patient population, clinical advice to the ERG is that patients with EGFRm+ disease who are treated in the NHS are typically aged between 65 years and 70 years and the majority are of ECOG PS 1 or 2. The ERG notes that patients in the studies discussed in the CS, AURAext and AURA2, are younger (median 62.2 years) and fitter (ECOG PS 0 or 1) than EGFRm+ patients treated in the NHS. Similarly, patients 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.

The ERG notes that 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.

3.3 Intervention

The intervention specified in the final scope issued by NICE is osimertinib. Osimertinib is a small molecule irreversible inhibitor that targets the sensitising and EGFR T790M mutant forms of the EGFR-TKI.[27] It has a conditional licence in Europe for the treatment of adults with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.[3] The licence is conditional on the company providing the EMA with the results of a phase III RCT (AURA3) by July 2017 (CS, p40). The company expects that, in NHS clinical practice, osimertinib will mainly be used as a second-line treatment, after failure with an EGFR-TKI.

Osimertinib is available as a film coated tablet (40mg or 80mg). The daily dose is 80mg until disease progression or unacceptable toxicity.

3.3.1 Testing for the EGFR T790M mutation

In the SmPC[21] for osimertinib it is stipulated that treatment should only be initiated after the patient's EGFR T790M mutation status is positively confirmed by a clinical laboratory test using a validated test method. It is further cautioned in Section 4.4 of the SmPC[21] that

patients' whose plasma-based ctDNA test results in a negative outcome should receive a follow-up tissue biopsy test as approximately 20% of plasma tests are believed to give false negative results (CS, p210). The company discusses the issues relevant to testing for the EGFR T790M mutation within the NHS in the CS (p43 to p45).

The company states that the pathway for acquiring, handling and testing tissue samples and reporting results is already well established in the NHS as up to 90% of treatment-naïve patients with NSCLC are routinely tested for the EGFR mutation. The company has confirmed with the UK National Quality Assessment Services (NEQAS) that the majority of laboratories (88%) currently validated for testing for EGFR mutations are able to test for the EGFR T790M mutation using existing test platforms. The company is confident that EGFR T790M mutations are already being identified and states that there are, therefore, no additional cost implications in terms of equipment, reagent or manpower. The company recognises, however, that, if osimertinib is recommended for use in the NHS, the volume of tests required to identify the presence of the EGFR T790M mutation is likely to increase, based on the increasing use of biopsy at relapse.

3.4 Comparators

There are a number of comparators listed in the final scope issued by NICE and these vary by line of treatment.

The company has provided clinical effectiveness evidence for the comparison of osimertinib with PDC for EGFR T790M patients who have been previously treated with an EGFR-TKI. The evidence for the effectiveness of PDC was obtained following a retrospective analysis of tumour samples from patients recruited to the control/PDC arm of the IMPRESS trial. Although 132 patients were recruited to this arm of the IMPRESS trial, a retrospective analysis showed that only 61 patients had tumours expressing the EGFR T790M mutation. The company used data from this subgroup of patients from the IMPRESS trial and from the pooled AURA dataset in an adjusted treatment comparison to allow the clinical efficacy of treatment with osimertinib to be compared with PDC.

The ERG agrees with the company that:

- there are no clinical effectiveness data that directly compare osimertinib with any of the other 11 comparators specified in the final scope issued by NICE
- there are no clinical effectiveness data available, either for an EGFR T790M mutation-positive population, or for an EGFRm+ population, that would allow a treatment comparison to be carried out to inform a robust comparison of osimertinib with any of the other comparators specified in the final scope issued by NICE. The only clinical evidence available allows comparison of osimertinib with PDC.

However, the ERG notes that the company uses subgroup analyses to consider additional comparators in the cost effectiveness section of the CS. Based on the information presented in the CS, the ERG assumes that relevant survival data are used directly in these analyses. For second-line patients only, osimertinib is compared with PDC and also with docetaxel. For ≥third-line patients, osimertinib is compared with single-agent chemotherapy (docetaxel). The ERG considers that all of the economic subgroup analyses rely on limited clinical evidence.

The company makes strong assumptions regarding the choice of comparators used in the economic analyses. First, the company assumes that the clinical evidence describing 'placebo+pemetrexed+cisplatin' from the IMPRESS trial can be used to represent PDC. The ERG notes that, in clinical practice, PDC may also comprise other treatments e.g. vinorelbine, gemcitabine, docetaxel or paclitaxel in combination with cisplatin or carboplatin. However, the ERG also acknowledges that, for the specified patient population, pemetrexed+cisplatin is the most commonly used PDC in the UK NHS. The company also assumes that docetaxel monotherapy efficacy data from patients (untested for EGFR T790M mutation) that are described in the studies by Park[29] and by Schuler[30] can be used to represent the efficacy data associated with any single-agent chemotherapy for the treatment of second-line and third-line or further patients, respectively, with EGFR T790M mutations.

3.5 Outcomes

Clinical evidence is reported in the CS for all of the outcomes specified in the final scope issued by NICE, overall survival (OS), progression-free survival (PFS), response rate (reported as objective response rate [ORR], disease control rate [DCR] and duration of response [DoR]), adverse events (AEs) of treatment and health related quality of life (HRQoL). The ERG notes that the OS data that are currently available from the pooled AURA dataset and the IMPRESS trial are still very immature (12.7% and approximately 33% respectively).

3.6 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 15-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS perspective. The company's economic model includes the costs associated with four possible testing strategies to identify patients with EGFR T790M mutation-positive tumours.

3.7 Subgroups

No subgroups were specified in the final scope issued by NICE in addition to the distinct patient populations specified in the comparator section.

3.8 Other considerations

The company did not identify any equality issues. The ERG is aware that the company has submitted a Patient Access Scheme (PAS) proposal to the Department of Health. The list prices of osimertinib, cisplatin, pemetrexed and docetaxel are used in all of the cost effectiveness analyses presented in the CS.

4 CLINICAL EFFECTIVENESS

This section provides a structured summary and critique of the clinical effectiveness evidence submitted by the company in support of the use of osimertinib for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

4.1.1 Systematic review methods

The company conducted a systematic review to identify studies of relevance to the appraisal under discussion. A summary of the systematic review methods employed by the company, with accompanying ERG comments, is presented in Table 3. Full details can be found in the CS (p60 to p72).

Overall, the ERG is satisfied that the company's systematic review methods were of an adequate standard, and were relevant to the final scope issued by NICE and to the company's decision problem. The ERG notes that, in the systematic review, the company has restricted the patient population to those who have failed treatment with an EGFR-TKI (i.e. the previously treated population). The ERG agrees with company that this is appropriate as evidence suggests that only 1% of patients are likely to have tumours with the EGFR T790M mutation at diagnosis.[3]

Table 3 Summary and ERG comment on the systematic review methods used by the company

Review method	ERG comment
Searching	
• RCT and non-RCT data searches • Databases searched included Medline, Medline in Process, Embase and CENTRAL (search strategies are described in Appendix CS, 1.1) from inception to 4th January 2016 • Grey literature was searched for clinical studies and conference abstracts	• The company states that, due to lack of data specific to the EGFR T790M mutation-positive population, a broad search was carried out to include advanced or metastatic NSCLC and EGFRm+ patients regardless of EGFR T790M status. The ERG considers it appropriate to widen the search criteria • As expected, due to the recent drug name change, the drug terms used by the company do not include the term 'osimertinib' but do include 'AZD9291' • The company limited the patient population to those who were pre-treated with at least one EGFR-TKI. The final scope issued by NICE and the licensed indication do not specify a particular line of treatment. The company states (CS, p59) that there are very limited data on the use of osimertinib in a treatment-naïve NSCLC population. The ERG agrees with the company • The ERG was able to replicate the searches • The company searched the appropriate conference abstracts • The ERG verified the data in the PRISMA flowchart presented in the CS via the clarification process • The ERG is confident that no relevant studies were missed
Eligibility criteria	
• Two independent assessors assessed study eligibility	• Use of two independent assessor improves the quality of reviews • Only articles published with full-text in the English language were considered • The patient population is defined in the inclusion criteria as those with advanced or metastatic NSCLC with acquired EGFR/or T790M mutation and at least one prior EGFR-TKI therapy. The patient population in the final scope issued by NICE and in the licence is not restricted to a particular line of therapy. The ERG accepts that there is no clinical evidence relevant to treatment in treatment-naïve patients
Data extraction	
• Two independent assessors extracted data • A pre-defined extraction form was used	• The company has not reported the method used to extract study data. Quality assurance regarding data extraction is therefore uncertain
Quality assessment and risk of bias	
• Descriptive critical appraisal of all included RCTs and non-RCTs was undertaken using the NICE recommended method[31]	• Unclear if two independent assessors were employed • The Downs and Black[32] appraisal tool was applied to the non-RCTs. The included RCT was appraised using a hybrid of criteria derived from the Jadad[33] scale and the recommendations of Centre for Reviews and Dissemination at the University of York.[34] The ERG considers the company quality assessment strategy is appropriate.

EGFR=epidermal growth factor receptor; ERG=Evidence Review Group; NSCLC=non-small cell lung cancer; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT=randomised controlled trial; TKI=tyrosine kinase inhibitor;
Source: CS Table 4.21

4.1.2 Evidence synthesis

No RCTs comparing osimertinib with any treatment in patients with EGFR T790M mutation-positive NSCLC were identified.

The company presents direct evidence for the clinical efficacy of osimertinib from two single-arm studies, the AURAext study and the AURA2 study. The CS includes a narrative description of the AURAext and AURA2 studies and results from the analysis of data pooled from these two studies (i.e., pooled AURA dataset).

4.2 Critique, analysis and interpretation of trials of the technology

4.2.1 Identified studies

Key studies

The company presents evidence for the clinical effectiveness of the intervention from the AURAext (phase I/II) and the AURA2 (phase II) studies. Both are single-arm studies involving patients with EGFR T790M mutation-positive NSCLC treated with osimertinib. The company identified an ongoing phase III RCT (AURA3) comparing osimertinib with PDC; this study is not due to report until 2017. A dosing study, AURA1, has also been undertaken. However, the company considers that results from this study are not relevant to the current appraisal.

In the absence of any trial evidence comparing the clinical effectiveness of osimertinib with any of the comparators specified in the final scope issued by NICE, the company has employed evidence from the subgroup of patients in the control arm of the IMPRESS trial whose tumours were (retrospectively) identified as having the EGFR T790M mutation. The IMPRESS trial is a phase III RCT in which patients with EGFRm+ NSCLC who had progressed on treatment with an EGFR-TKI were randomised to receive either gefitinib+cisplatin+pemetrexed (intervention) or placebo+cisplatin+pemetrexed (control).

Other studies

In total, the company's search identified ten studies, the AURAext[23] and AURA2[24] study (combined as AURA pooled dataset[1]), the IMPRESS trial,[13] and eight other studies[29,35-41] that could potentially be used to inform an indirect comparison of the clinical effectiveness of osimertinib with a comparator specified in the final scope issued by NICE. The eight studies[29,35-41] assessed the use of PDC (n=3) or single-agent chemotherapy (n=5) in patients who had previously received first-line EGFR-TKI treatment. The majority of recruited patients had confirmed EGFRm+ NSCLC; however, none of the studies included testing for the presence of the EGFR T790M mutation.

Six[29,37-41] of the eight studies were retrospective observational studies rejected by the company for the following reasons: i) small patient numbers ii) the patients observed in the studies differed from the patients included in the pooled dataset of the AURAext and AURA2 studies iii) the definitions of key endpoints in the studies were considered to be inconsistent with the definitions used in the prospective studies[23,24,35,42] (CS, p67). The two other studies, both RCTs,[29,30] were considered by the company to be inappropriate due to the small number of patients recruited to the comparator arm in each trial. The ERG agrees with the company's assessment.

The company presents a summary of details about the included and excluded studies in Table 4.4 of the CS (p68). The ERG is not aware of any other studies relevant to the decision problem.

4.2.2 Methodological approach for the synthesis and analysis of data from key studies

The company employed two approaches to compare the effectiveness of osimertinib (using pooled data from the AURAext and AURA2 studies) with PDC (using data from the IMPRESS trial): an unadjusted comparison and a comparison that included adjustments for differences in patient baseline characteristics. The company explains that data from the AURAext and AURA2 studies were pooled to increase the precision of the estimate of the primary endpoint.

4.2.3 Statistical approach adopted for the conduct and analysis of data from included studies

A full description and critique of the AURAext and AURA2 studies and the IMPRESS trial is presented in this section of the ERG report. Information relevant to the statistical approach taken by the company to analyse data from these sources has been taken directly from the clinical study reports (CSR),[23,24,42] the statistical analysis plans (TSAP),[43-45] the protocols and from the CS.

Trial populations

For the AURAext and AURA2 studies, all efficacy outcomes other than PFS, the sensitivity analysis of ORR and best objective response (BOR) by blinded independent central review (BICR), and investigator RECIST outcomes were analysed using the 'evaluable for response' analysis population. This specific population comprises patients who received at least one dose of osimertinib and had measureable disease at baseline according to an independent review of imaging data. PFS, the sensitivity analyses of ORR and BOR by BICR, and investigator RECIST outcomes were analysed using the full analysis set (FAS) population; this population comprises all patients who received at least one dose of osimertinib.

For the analysis of all efficacy outcomes in the IMPRESS trial, the FAS population was used. The FAS population follows the intention-to-treat (ITT) principle so all patients were analysed according to the treatment arm to which they were initially randomised, regardless of which treatment they actually received. Safety outcomes were analysed using the safety analysis set, consisting of all patients who received at least one dose of study medication.

Outline of analyses

Patient recruitment to the AURAext study started in May 2014 and finished in October 2014. The data cut-off for the data presented in the CS was 1st May 2015.

The AURA2 study started recruiting patients in June 2014 and the last patient was recruited in October 2014. The data cut-off for the data presented in the CS was also 1st May 2015. For the AURA2 study no formal interim analyses were planned. However, the investigators analysed the data at approximately 3 months and 8 months after the last patient was recruited. The results presented in the CS are from the 8-month data cut-off. The final database lock will be at the end of the study, at 12-24 months after the last patient was recruited.

Patient recruitment to the IMPRESS trial started in March 2012 and the last patient was recruited in December 2013. The primary data cut-off for this trial was 5th May 2014. Two data cut-offs were planned, the primary data cut-off for the primary PFS analysis and the final data cut-off for the final OS analysis. The primary PFS analysis was conducted on a total of 205 progressions (77.4% maturity). At the time of the primary PFS analysis, the OS data were also analysed (87 patient deaths had occurred, 33% maturity). [redacted]

Study outcomes

The definitions and methods of analysis for the primary and secondary efficacy outcomes from the AURAext and AURA2 studies and the IMPRESS trial are listed in

Table 4. The ERG is satisfied that all of the outcomes were pre-specified in the TSAP and that all of the outcomes were fully reported in the CSR.

Table 4 Analysis strategy for key efficacy endpoints

Endpoint	Definition	Statistical method
AURAext and AURA2: primary outcome		
ORR	The percentage of patients with at least one visit response of CR or PR that was confirmed at least 4 weeks later according to RECIST 1.1 by BICR	The analysis of ORR was presented together with 95% exact (Clopper-Pearson) CI by study and overall for the pooled AURA dataset. Overall ORR based on the pooled data was calculated as the number (%) of patients with BOR of confirmed CR or PR from both studies. A similar analysis of ORR was also presented by treatment cohort (2nd- versus ≥3rd-line) and overall. The ORR in each treatment cohort based on the pooled data was calculated as the number (%) of patients with BOR of confirmed CR or PR from each treatment cohort across two studies
AURAext and AURA2: secondary outcomes		
DoR	The time from the date of first documented response, (that is	DoR (months) in responding patients based on the BICR was summarised using the median and 95% CI. The median was

	subsequently confirmed) until the date of documented progression or death in the absence of disease progression	calculated using the K-M method. The number and percentage of responding patients remaining in response at >3; >6; >9; >12 months was summarised. Analyses were presented by study and for the pooled AURA dataset. A K-M plot was presented for the overall pooled population
DCR	The percentage of patients who had a BOR of CR or PR or SD for at least 6 weeks (allowing for a 1-week visit window)	DCR presented together with 95% exact (Clopper-Pearson) CIs
Tumour shrinkage	Tumour size is the sum of the longest diameters of the TLs. The best percentage change in tumour size from baseline was determined for each patient, ie, maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction from baseline based on all post-baseline assessments prior to progression or the start of subsequent therapy	To assess the depth of tumour shrinkage, the proportion of patients who achieved >30%, >50% and >75% reduction in TL tumour size was summarised descriptively. The percentage change in TL tumour size from baseline was summarised using descriptive statistics and presented for each visit
PFS	The time from date of first dose until the date of objective disease progression as defined by RECIST or death (by any cause in the absence of progression) regardless of whether the patient withdrew from osimertinib therapy or received another anticancer therapy prior to progression	PFS was displayed in a K-M plot for the pooled population. The total number of events, median PFS (calculated from the K-M plot, with 95% CIs), and the percentage PFS at 3, 6, 12 and 18 months was summarised by study and overall for the pooled AURA dataset. Similar analyses of PFS were presented by treatment cohort and overall. A K-M plot was presented for each treatment cohort
OS	The time from the date of first dose until death due to any cause	Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive
IMPRESS: primary outcome		
PFS	The time from randomisation until objective disease progression as detailed in RECIST or death (by any cause in the absence of progression) regardless of subsequent treatment	The primary analysis compared PFS between treatment groups using a Cox PH model that included terms for treatment and age (<65, ≥65 years), and prior response to gefitinib (SD versus PR and CR combined). The HR (gefitinib: placebo) was estimated together with its 95% CI and p-value
IMPRESS: secondary outcomes		
OS	The time from the date of randomisation until death due to any cause. Any patient not known to be dead at the time of analysis was censored based on the last recorded date on which the patient was known to be alive	The analysis of OS compared the OS between treatment groups using a PH model adjusted for adjusted for age (<65 years, ≥65 years) and prior response to gefitinib. The HR (gefitinib: placebo) was estimated together with its 95% CI and p-value. A K-M plot of OS was presented and the median survival time from the K-M curve was presented. The median OS, 9, 12, and 18-month rates were also presented
ORR	The number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression or last evaluable assessment, in the absence of progression were included in the assessment of ORR. This was irrespective of whether or not patients discontinued treatment or received a subsequent therapy prior to progression	The response rate was calculated for each randomised treatment based on the percentage of patients who had a BOR (based on RECIST) of CR or PR. Objective tumour response was compared between the randomised treatment groups using a logistic regression model. The model allowed for the effect of randomised treatment and the same covariates as used in the analysis of PFS. The odds ratio for treatment (gefitinib: placebo) was estimated from the model as was the 95% CI and p-value. The p-value was based on twice the change in log-likelihood resulting from the addition of a treatment factor to a model containing the covariates detailed above
DCR	The percentage of patients who achieved disease control at 6 weeks following randomisation. Disease control was defined as a best objective response of CR, PR or SD	The DCR was analysed using the same methodology as ORR

	≥6 weeks. If a patient experienced a CR/PR very shortly after starting treatment but then progressed or became NE by 6 weeks, then they were not included as having disease control at 6 weeks	
Symptoms and HRQoL	Data on symptoms and HRQoL were assessed using the FACT-L questionnaire. FACT-L has been validated with respect to its psychometric properties and sensitivity to clinical changes	The change from baseline was summarised for each of the FACT-L total score, TOI and LCS by randomized treatment, for each week that HRQoL was assessed and where there were 20 or more patients with available data across treatment groups. The mean change from baseline and 95% CI at each of these weeks were also plotted for each treatment group separately. The number and percentage of patients with each of the best overall responses were presented for each treatment group. The HRQoL improvement rates (for FACT-L total score, TOI and LCS) were summarised descriptively by treatment groups and analysed using the same methodology as ORR. The improvement rate was calculated for each randomised treatment group. The time to worsening data were analysed using a PH model including terms for treatment received and the covariates as defined for PFS. The HR and 95% CI and p-value were presented. The KM curves for time to worsening were also plotted. The median was presented, in addition to the number of patients who worsened by 3 and 6 weeks
AURA2 study only: EQ-5D-5L and EQ-VAS	To assess utilities to support health technology assessment and health economic modelling in patients	Simple summaries of the data were provided and included the frequency of response to each of the 5 questions by protocol-led visit. A summary at each protocolled visit of the expected number of questionnaires and the actual number of questionnaires received was also presented. This included the number of questionnaires received as a percentage of the expected number at each protocol-led visit. In addition, EQ-5D-5L scores and individual questions from the EQ-5D-5L questionnaire were summarised at each scheduled time point and by treatment group using descriptive statistics

BICR=blinded independent central review; BOR=best objective response; CI=confidence interval; CR=complete response; DCR=disease control rate; DoR= duration of response; EQ-5D=euro quality of life – 5 dimensions; HR=hazard ratio; KM=Kaplan-Meier; NE=not evaluable; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards PR=partial response; RECIST= Response Evaluation Criteria in Solid Tumours; SD=stable disease; TL=target lesion
Source: CS (adapted from sections 4.11.1.2 and 4.11.2.2) and protocol (Section 5.7.4.2)

Censoring methods

The censoring methods employed in the AURAext study, the AURA2 study and the IMPRESS trial are shown in Table 5.

Table 5 Censoring methods

	OS	PFS
AURAext and AURA2 studies	Any patient without documentation of death at the time of analysis was censored based on the last recorded date on which the patient was known to be alive	Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST assessment. However, if the patient had progressed or died after three or more missed RECIST assessments visits, the patient was censored at the time of the latest evaluable RECIST assessment prior to the missed visits. If the patient had no evaluable visits or did not have baseline data they were censored at zero days unless they died within two visits of baseline
IMPRESS trial	Any patient without documentation of death at the time of analysis was censored based on the last recorded date on which the patient was known to be alive	Patients, who had not progressed or died at the time of the statistical analysis, were censored on the date of their last target lesion/non-target lesion (TL/NTL) assessment from their last evaluable RECIST assessment. If a patient had progressed or died after ≥2 missed visits, the patient was censored at the time of the latest evaluable RECIST assessment. If the patient had no evaluable visits or did not have baseline data, the patient was censored at zero days.

OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria In Solid Tumours
Source: CS, p99 and p132

Subgroup analyses

Subgroup analyses were conducted, using the pooled AURA dataset to explore ORR and duration of response (DoR) by BICR across the key subgroups listed in Table 6. The analysis of ORR together with 95% exact (Clopper-Pearson) confidence intervals (CIs) was presented by treatment cohort and overall for each category of subgroup. Forest plots of ORR by BICR were constructed for each treatment cohort and for the overall study population. DoR by BICR was summarised using the median and 95% CI by both treatment cohort and the overall population for each of the subgroup categories.

The IMPRESS trial subgroup analyses were conducted to explore the consistency of treatment effect of PFS across the key subgroups listed in Table 6. A Cox Proportional Hazards (PH) model was used to investigate the treatment effect in each of the subgroups. The hazard ratios (HRs) and 95% CIs were summarised and presented in a forest plot, along with the overall primary analysis results.

Health related quality of life

Three patient reported outcome questionnaires were used in the AURAext and AURA2 studies to collect data on the impact of osimertinib on patients' disease-related symptoms and HRQoL:

- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30[46])
- The Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13[47])
- The EuroQoL–5 dimensions–5 levels (EQ-5D-5L[48]) questionnaire (AURA2 study only).

These HRQoL outcomes were exploratory endpoints, so only summary data were collected and no statistical testing was carried out.

In the IMPRESS trial, data on symptoms and HRQoL were collected using the Functional Assessment of Cancer Therapy–Lung (FACT-L[49]) questionnaire, the EQ-5D-3L questionnaire and the EQ visual analogue scale (EQ-VAS[48]). The company presents the results from the FACT-L questionnaire in various different forms, including the results from change from baseline, the improvement rates for the FACT-L questionnaire data, the frequency of responses received for each question and the number of EQ-5D VAS completed.

The ERG considers that the approaches taken by the company to explore the available HRQoL data are acceptable.

Proportional hazards

The analyses carried out by the company to generate PFS and OS HRs to demonstrate the relative effectiveness of the two treatments assessed by the IMPRESS trial were conducted using Cox PH modelling. The validity of this method relies on the hazards of the two comparative drugs being proportional.

To investigate the assumption of PH, the company inspected Log-log plots (log cumulative hazard versus log time); if the curves for each treatment arm were approximately parallel, the assumption of PH was valid. If inspection of the Log-log plot raised any concerns, a time dependent covariate was fitted to the model to assess the extent to which any deviance from being parallel represents random variation.

As part of the clarification process, the ERG asked the company to provide details of the analyses that had been undertaken to determine whether the assumption of PHs holds for

the PFS data. The company explained that the assumption of PH was tested by examining plots of the log(event) versus log(time) time data from both arms of the IMPRESS trial. Visual examination of the graph suggested that the resultant lines were not parallel, which raised concerns about the validity of the PH assumption. To assess the extent to which the deviance from being parallel was due to random variation, a time dependent covariate was fitted to the Cox PH model. The p-value for the test of non-proportional hazards was [redacted] (provided in the company clarification response to question A6), suggesting that there is insignificant evidence of non-proportionality.

No details are provided in the CS to suggest that any testing has been carried out to test whether the assumption of PHs holds for the OS data. However, examination of the Kaplan-Meier (K-M) data presented in the CS (Figure 4.19, p154) suggests that the PH assumption may hold when considering the OS data from all patients without EGFR T790M mutation-positive disease (irrespective of treatment) and the patients in the control arm with EGFR T790M mutation-positive disease.

Pooling data from the AURAext and AURA2 studies

The company pooled the data from the AURAext and AURA2 studies to produce a single dataset that was subsequently used to calculate summary efficacy and safety end-points. The company states that using pooled data increases the precision of outcome estimates.

Pooling the data from the two AURA studies was carried out by merging the individual patient data (IPD). Study identifiers were anonymised and variables which were calculated/computed were derived identically across the studies. The company considers that the two AURA studies are largely comparable, having similar inclusion/exclusion criteria as well as similar baseline demographic and disease characteristics.

During the clarification process, the ERG asked the company to undertake analyses to show whether the efficacy results from the pooled AURA dataset differ from those generated using the AURAext and AURA2 study data independently. The company repeated the analyses for the two primary efficacy endpoints (PFS and ORR) comparing the data for the AURAext and AURA2 studies separately with PDC. The PFS and ORR analyses for the individual AURAext and AURA2 studies were conducted versus PDC using the same methodology as for the pooled analysis and the results indicate that the pooled results are consistent with the results achieved when the AURAext and AURA2 studies are compared separately versus PDC.

The ERG considers that it is reasonable to pool data from the AURAext and AURA2 studies, and the approach taken to do so was appropriate.

ERG assessment of statistical approach

A summary of the checks made by the ERG regarding the statistical approach adopted by the company to analyse data from the AURAext study, the AURA2 study and the IMPRESS trial is provided in Table 6.

Table 6 ERG assessment of statistical approaches used to analyse data from the AURAext and AURA2 studies and the IMPRESS trial

Component	AURAext and AURA2 studies		IMPRESS trial	
	Statistical approach	**ERG comments**	**Statistical approach**	**ERG comments**
Sample size calculation	Provided in the CS (p96-97)	The ERG considers that the methods used to calculate the sample size are correct	Provided in the CS (p135)	The ERG considers that the methods used to calculate the sample size are correct
Protocol amendments	Provided in the CSR (Section 5.8.1)	The ERG notes that the changes detailed in the protocol amendments are unlikely to have been driven by the results of the trial and are, therefore, not a cause for concern. All protocol amendments were carried out prior to the analyses being conducted	Provided in the CSR (Section 5.8.1)	The ERG notes that the changes detailed in the protocol amendments are unlikely to have been driven by the results of the trial and are therefore not a cause for concern. All protocol amendments were carried out prior to any analyses being conducted
Missing data approach	No details provided	It is not possible for the ERG to review these results as they have not been provided	No details provided	It is not possible for the ERG to review these results as they have not been provided
Subgroup analyses	For ORR and DoR • Patients who received EGFR-TKI or those whose treatment prior to study start was not an EGFR-TKI • Ethnicity (Asian or Non-Asian) • Gender (Male or Female) • Age at screening (<65 or ≥65) • Mutation status prior to start of study (Exon 19 deletion or L858R or Other) • Duration of most recent prior EGFR-TKI (<6 months or ≥6 months) • Smoking history (never or ever) • Brain metastases at entry (yes or no) • Patients with EGFR T790M	It is not possible for the ERG to review these results as the pooled results used to perform the subgroup analyses are not provided in the CSR	For PFS: • Region (Asia or European Union) • Time from progression to randomisation (≤2 weeks or >2 weeks) • Smoking history (never or current/former) • Prior response to gefitinib (SD or PR and CR combined) • Exon 19 deletion (present or absent/unknown) • L858R mutation (present or absent/unknown) • Age (<65 years or ≥65 years) • Gender (male or female) • Disease stage at diagnosis	The ERG is satisfied that the results of all subgroup analyses are provided in the CSR

	mutation positive or patients that are EGFR T790M negative • Region (North America or Asia or Europe or rest of world)		(1=locally advanced or 0=metastatic, 'other') • Time to progression for initial gefitinib (≤10 months or >10 months) • Site of disease at baseline (brain/CNS or non-brain/CNS) • WHO performance status (0=normal activity or 1=restricted activity)	
Adverse events	Safety was assessed through summaries of most common AEs, SAEs and patients who had at least one adverse event	It is not possible for the ERG to review these results as results generated from the pooled dataset are not provided in the CSRs	Safety was assessed through summaries of most common AEs, SAEs, AEs leading to treatment discontinuation, AEs of CTCAE grade 3 or higher, dose interruptions and dose reductions	It is not possible for the ERG to review these results as they are not provided in the CSR
Health-related quality of life	• EORTC-QLQ-C30 • EORTC QLQ-LC13 • EQ-5D-5L questionnaire	The ERG is satisfied that the methodology used to analyse HRQoL data is appropriate	• FACT-L • EQ-5D questionnaire	The ERG is satisfied that the methodology used to analyse HRQoL data is appropriate

AE=Adverse Event; CR=complete response; CS=company submission; CSR=clinical study report; DoR=duration of response; EGFR-TKI=epidermal growth factor receptor tyrosine kinase inhibitor; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 3; EQ-5D=EuroQol-5 Dimensions; ERG=Evidence Review Group; FACT-L=Functional Assessment of Cancer Therapy—Lung; HRQoL=health- related quality of life; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PR=partial response; SAE=Serious Adverse Event; SD=stable disease; WHO=World Health Organisation
Source: CS, CSRs and ERG comment

4.2.4 Key study characteristics of the included studies

The company reports (CS, p87) that the AURAext study is a phase II extension study and is part of an overarching phase I/II, open label, dose-escalation, expansion and extension cohort study programme, known as AURA. The company describes the AURA2 study as a phase II, open-label study.

There are no published papers that describe the AURAext and AURA2 studies. However, as well as information presented in the CS, the company has provided the CSRs for both studies.

The key characteristics of the AURAext and AURA2 studies are listed in Table 7. The studies are being conducted internationally and include a combined total of 411 patients with EGFR T790M mutation-positive NSCLC who have progressed following previous treatment. All patients are treated with 80mg of osimertinib once daily. Previous treatments include, but are not limited to, an EGFR-TKI. The ERG notes that the AURAext study inclusion criteria stipulate previous treatment with an EGFR-TKI and other anti-cancer treatments, whilst the AURA2 study criteria stipulate previous treatment with an EGFR-TKI and PDC (other previous lines of treatment are also permitted). The ERG notes that the AURAext study was open to recruitment at two centres in the UK; however, it is not clear how many patients have been recruited from the UK. The AURA2 study was not open to recruitment from UK centres.

Table 7 Key characteristics of the AURAext and AURA2 studies

	AURAext (osimertinib 80mg)	AURA2 (osimertinib 80mg)
Location	International (including 2 UK centres)	International (no UK centres)
Design	Phase II extension, open label, single arm	Phase II, open label, single arm
Population	N=201 patients with T790M mutation-positive EGFR NSCLC Two patient cohorts: 1. Patients with disease progression following first-line therapy with an EGFR-TKI 2. Patients with disease progression following treatment with an EGFR-TKI and other anti-cancer treatments	N=210 patients with T790M mutation-positive EGFR NSCLC Two patient cohorts: 1. Patients with disease progression following first-line therapy with an EGFR-TKI 2. Patients with disease progression following treatment with an EGFR-TKI and a platinum-based doublet (possibly other lines of treatment also)
Intervention	Osimertinib (80mg) until disease progression or cessation of clinical benefit	Osimertinib (80mg) until disease progression or cessation of clinical benefit
Primary outcome	ORR	ORR
Secondary outcomes	Duration of response, disease control rate, tumour shrinkage, PFS, OS, safety, HRQoL	Duration of response, disease control rate, tumour shrinkage, PFS,OS, safety, HRQoL
Duration of study	The first patient started treatment on 14th May 2014 and the last patient started treatment on 21st October 2014. The data cut-off for the present appraisal was 1st May 2015	The first patient started treatment on 13th June 2014 and the last patient started treatment on 27th October 2014. The data cut-off for the present appraisal was 1st May 2015

EGFR=epidermal growth factor receptor; HRQoL=health related quality of life; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; TKI-tyrosine kinase inhibitor
Source: CS, p87 to p98

The key baseline characteristics of patients included in the AURAext and AURA2 studies are listed in Table 8. The ERG notes that the baseline characteristics of the patients in the two studies are similar.

Table 8 Key characteristics of patients in the AURAext and AURA2 studies

	AURAext (osimertinib 80mg) N=201	AURA2 (osimertinib 80mg) N=210	Total N=411
Mean age (sd)	61.4 (10.58)	62.9 (10.91)	62.2 (10.76)
Age group n (%)			
<50 years	30 (14.9)	20 (9.5)	50 (12.2)
≥50 to <65 years	86 (42.8)	88 (41.9)	174 (42.3)
≥65 to <75 years	64 (31.8)	69 (32.9)	133 (32.4)
≥75 years	21 (10.4)	33 (15.7)	54 (13.1)
WHO PS n (%)			
0	68 (33.8)	84 (40)	152 (37)
1	132 (65.7)	126 (60)	258 (62.8)
2	1 (0.5)	0	1 (0.2)
Female n (%)	133 (66.2)	146 (69.5)	279 (67.9)
Race n (%)			
White	76 (38.2)	72 (34.3)	148 (36.2)
Asian	114 (57.3)	132 (62.9)	246 (60.1)
Other/not reported	9 (4.5)	6 (2.9)	15 (3.7)
Number of prior anti-cancer treatments n (%)			
1	61 (30.3)	69 (32.9)	130 (31.6)
2	49 (24.4)	45 (21.4)	94 (22.9)
3	33 (16.4)	38 (18.1)	71 (17.3)
4	22 (10.9)	22 (10.5)	44 (10.7)
5	14 (7.0)	7 (3.3)	21 (5.1)
>5	22 (10.9)	29 (13.8)	51 (12.4)
Mean (sd)	2.8 (1.92)	3.0 (2.43)	2.9 (2.20)
Min and max	1 and 11	1 and 14	1 and 14
Number of prior EGFR-TKI treatments n (%)			
1	111 (55.2)	131 (62.4)	242 (58.9)
2	47 (23.4)	42 (20)	89 (21.7)
3	33 (16.4)	18 (8.6)	51 (12.4)
4	7 (3.5)	9 (4.3)	16 (3.9)
5	2 (1.0)	4 (1.9)	6 (1.5)
>5	1 (0.5)	6 (2.9)	7 (1.7)
Mean (sd)	1.7 (0.98)	1.8 (1.34)	1.7 (1.18)
Min and max	1 and 6	1 and 9	1 and 9

	AURAext (osimertinib 80mg) N=201	AURA2 (osimertinib 80mg) N=210	Total N=411
Histology type n (%)			
Adenocarcinoma: NOS	171 (85.1)	170 (81)	341 (83)
Adenocarcinoma: acinar	11 (5.5)	10 (4.8)	21 (5.1)
Adenocarcinoma: papillary	10 (5.0)	17 (8.1)	27 (6.6)
Adenocarcinoma: bronchiolo-alveolar	3 (1.5)	1 (0.5)	4 (1.0)
Adenocarcinoma: solid with mucous formation	0	2 (1.0)	2 (0.5)
Adenosquamous carcinoma	1 (0.5)	1 (0.5)	2 (0.5)
Squamous cell carcinoma	0	2 (1.0)	2 (0.5)
Other	5 (2.5)	7 (3.3)	12 (2.9)
EGFR mutation type n (%)			
T790M	197 (98)	208 (99)	405 (98.5)
Exon 19 deletion	142 (70.6)	137 (65.2)	279 (67.9)
L858R	51 (25.4)	67 (31.9)	118 (28.7)
G719X	4 (2.0)	4 (1.9)	8 (1.9)
S768I	3 (1.5)	3 (1.4)	6 (1.5)
Exon 20 insertion	2 (1.0)	1 (0.5)	3 (0.7)
EGFR T790M only	5 (2.5)	1 (0.5)	6 (1.5)
Overall disease classification n (%)			
Metastatic	197 (98)	198 (94.3)	395 (96.1)
Locally advanced	4 (2.0)	12 (5.7)	16 (3.9)
Brain metastases n (%)	74 (36.8)	87 (41.4)	161 (39.2)
Visceral metastases n (%)	173 (86.1)	168 (80)	341 (83)
Baseline sum of target lesions mean (sd)	60.7 (37.08)	59.7 (40.57)	60.2 (38.82)
Baseline sum of target lesions tumour size			
<40mm	65 (32.3)	68 (32.4)	133 (32.4)
40 to 79mm	86 (42.8)	90 (42.9)	176 (42.8)
80 to 119mm	31 (15.4)	26 (12.4)	57 (13.9)
≥120mm	17 (8.5)	15 (7.1)	32 (7.8)

EGFR=epidermal growth factor receptor; PS=performance status; sd=standard deviation; TKI=tyrosine kinase inhibitor; WHO=World Health Organisation
Source: CS, Table 4.17 to Table 4.20

Figures in Table 8 show that 32% of patients in the AURAext and AURA2 studies received osimertinib as a second-line treatment after an EGFR-TKI. This means that the majority of patients (68%) received osimertinib as a third-line (or greater) treatment.

The ERG notes that, in comparison to patients recruited to the AURAext and AURA2 studies, patients with EGFRm+ NSCLC currently treated in the NHS are older and are less fit. Clinical advice to the ERG is that, typically, patients in this population treated in the NHS are aged between 65 and 70 years and the majority have an ECOG PS of 1 or 2. Patients recruited to the two AURA studies have a mean age of 62 years and an ECOG PS of 0 or 1.

Clinical advice to the ERG is that the ethnic case-mix of patients treated in the NHS is the reverse of that in the AURAext and AURA2 studies. In these two studies, 36.2% of patients were described as white and 60% were described as Asian.

In addition, figures in Table 8 show that, despite patients in the AURAext and AURA2 studies having experienced a substantial number of anti-cancer treatments prior to study entry, they were considered fit enough for treatment with osimertinib (ECOG PS 0 or 1).

The ERG further notes that there are patients included in the AURAext and AURA2 studies who have received multiple EGFR-TKI treatments (up to six in the AURAext study and up to nine in the AURA2 study). Clinical advice to the ERG is that in NHS clinical practice, patients are typically treated with only one EGFR-TKI (although a second may be offered in the case of toxicity, or if the patient is not considered to be fit enough to receive chemotherapy).

The vast majority (96%) of patients included in the AURAext and AURA2 studies have tumours that are of adenocarcinoma histology and have metastatic disease (96%). This disease profile is consistent with EGFRm+ patients treated in the NHS.

4.2.5 Assessment of risk of bias for the AURA studies

The company conducted a risk of bias assessment for the AURAext and AURA2 studies using the Downs and Black checklist[32] (Table 9). The Downs and Black checklist[32] is listed in the NICE methods guide[50] as being appropriate for use when assessing cohort studies. The results of the company assessment of the AURA studies, with accompanying ERG comments, are shown in Table 9.

In general, the ERG agrees with the company assessment, but differs in responses to Q24 and Q25 (allocation concealment and adjustment for confounders). The company omitted to include Q27 of the checklist and the ERG has added it to Table 9. The ERG considers that the AURAext and AURA2 studies were designed, conducted and reported to a good standard. The ERG notes that the blinded independent review of the radiological outcomes in the AURAext and AURA2 studies lends weight to the efficacy results. However, the ERG highlights that the AURAext and AURA2 studies are non-randomised, single-arm studies without a control group. As a consequence, the results of the studies cannot be considered as reliable or robust as the results of a RCT (outcomes could, for example, be the result of chance, patient characteristics or the Hawthorne effect). In addition, the OS data available from the AURAext and AURA2 studies are very immature (pooled OS dataset is 12.7% mature).

Table 9 Results of company quality assessment of the AURAext and AURA2 studies with ERG comments

Downs and Black checklist item	AURAext	AURA2	ERG comment
Reporting			
Q1: Aim clearly described	Yes	Yes	Agree
Q2: Outcomes clearly described	Yes	Yes	Agree
Q3: Patients characteristics clearly described	Yes	Yes	Agree
Q4: Interventions clearly described	Yes	Yes	Agree
Q5: Principal confounders clearly described	Yes	Yes	Agree
Q6: Main findings clearly described	Yes	Yes	Agree
Q7: Random variability for the main outcome provided	Yes	Yes	Agree
Q8: Adverse events reported	Yes	Yes	Agree
Q9: Lost to follow up reported	Yes	Yes	Agree
Q10: Actual p-value reported	No	No	Agree
External validity and bias			
Q11: Sample asked to participate representative of the population	Yes	Yes	Partially agree
Q12: Sample agreed to participate representative of the population	Yes	Yes	Agree
Q13: Staff participating representative of the patient's environment	Yes	Yes	Agree
Q14: Attempt to blind participants	No	No	Agree
Q15: Attempt to blind assessors	Yes	Yes	Agree
Q16: Data dredging results stated clearly	Yes	Yes	Agree
Q17: Analysis adjusted for length of follow up	Yes	Yes	Agree
Q18: Appropriate statistics	Yes	Yes	Agree
Q19: Reliable compliance	Yes	Yes	Agree
Q20: Accurate outcome measures	Yes	Yes	Agree
Statistical bias and power			
Q21: Same population	Yes	Yes	Agree
Q22: Participants recruited at the same time	Yes	Yes	Agree
Q23: Randomised?	No	No	Agree
Q24: Adequate allocation concealment?	UTD	UTD	No. The studies were not randomised
Q25: Adequate adjustment for confounders?	UTD	UTD	Disagree. Subgroup analyses were conducted to assess key factors that may impact on outcomes
Q26: Loss of follow up reported?	Yes	Yes	Agree
Q27: Did the study have sufficient power to detect a clinically important event? (score between 1 and 5)	Not addressed in CS	Not addressed in CS	5. Sample sizes were calculated and presented in the CS

UTD=unable to determine; ERG=Evidence Review Group
Source: CS, Table 4.21

4.3 Results from the AURAext and AURA2 studies

Results reported in the CS for both the AURAext and AURA2 studies use data from the 1st May 2015 data-cut. The company states (CS, p118) that median follow-up for PFS by BICR is 6.9 months in the AURAext study and 6.7 months in the AURA2 study. Median follow-up for OS is 8.3 months in the AURAext study and 7 months in the AURA2 study (CS, p119). The ERG notes that 83 patients continued osimertinib treatment for at least 7 days after progression, the median duration of treatment with osimertinib treatment after progression was 1.6 months (range 0.4 to 8.4).

The company presents individual study data from the AURAext and AURA2 studies and also the results from the analyses of pooled AURAext and AURA2 study data. The focus of the CS is on results from the pooled AURA dataset. The company claims (CS, p112) that the AURAext and AURA2 studies are comparable in terms of patient populations, design and outcome measures. The ERG agrees with the company that the AURA studies are comparable and that it is reasonable to combine the data from the two studies.

4.3.1 Objective response rate (primary outcome)

The BICR assessment of the pooled 'evaluable for response' dataset (Table 10) yielded an ORR of 66.1% (95% CI: 61.2 to 70.7). The results of two sensitivity analyses (64.2% and 70.6 %) were similar to the BICR result.

Table 10 Summary of overall response rate

Analysis set Study	N	Number of patients with confirmed response	ORR (%)	95% CI
BICR assessment of 'evaluable for response' analysis set				
AURAext	199	122	61.3	54.2 to 68.1
AURA2	199	141	70.9	64.0 to 77.1
Total	398	263	66.1	61.2 to 70.7
BICR assessment of FAS (sensitivity analysis)				
AURAext	201	122	60.7	53.6 to 67.5
AURA2	210	142	67.6	60.8 to 73.9
Total	411	264	64.2	59.4 to 68.9
Investigator assessment of FAS (sensitivity analysis)				
AURAext	201	142	70.6	63.8 to 76.8
AURA2	210	148	70.5	63.8 to 76.6
Total	411	290	70.6	65.9 to 74.9

BICR=blinded independent central review; CI=confidence interval; FAS=full analysis set: ORR=overall response rate
Source: CS, Table 4.22

Subgroup analyses

The ORR data were analysed across patient subgroups. The subgroups included line of treatment, Asian or non-Asian, male or female, <65 years or ≥65 years, EGFR mutation

status (M+ or M-), duration of prior EGFR-TKI treatment (<6 months or ≥6 months), brain metastases (yes or no), smoking status (ever or never), last treatment prior to enrolment (<30 days or ≥30 days or not EGFR), EGFR T790M detected in plasma sample (positive or negative), and region of origin (North America or Asia or Europe and Rest of World).

Figure 4.8 in the CS (p114) illustrates that ORRs by BICR range from 58.9% (patients with L858R mutations, n=112) to 72.2% (patients for whom the EGFR T790M mutation was not detected via a plasma sample, n=162). The company highlights (CS, p113) that the ORR for second-line patients (66.9%) is very similar to the ORR for ≥third-line patients (65.7%).

During the clarification process, the ERG requested the p-values for the tests for interaction for the performed subgroup analyses. Statistically significant subgroup differences were observed for ethnicity [redacted]), mutation status prior to start of study [redacted]), and EGFR T790M status in baseline plasma sample [redacted]). These results (from company clarification response to question A8) suggest that the treatment effect is statistically significantly greater for Asian patients than for non-Asian patients, for patients with Exon 19 deletion mutation present than for patients with L858R mutation present, and for patients with an EGFR T790M mutation that is detected in blood plasma than for patients in whom the mutation is not detected in blood plasma.

The company reports other measures of patient response to treatment:

- **Best objective response by BICR in the 'evaluable for response' population'**: In the pooled population, two patients (0.5%) had a complete response (CR) to treatment whilst 261 patients (65.6%) had a partial response (PR). The findings were similar for PR in the AURAext and AURA2 studies (61.3% and 69.8% respectively)
- **Duration of response by BICR**: Median DoR had not been reached (maturity of 22.8%). A K-M analysis using pooled data from patients who had responded to treatment estimated that 94.9% of patients would achieve a response lasting at least 3 months and that 55.3% of patients would achieve a response lasting at least 9 months. Duration of response by investigator assessment (maturity of 27.6%) was 8.5 months (95% CI: 8.5 to not calculable)
- **Disease control rate by BICR in the FAS:** In the pooled population, the DCR was 91%. Similar DCRs were recorded for patients in the AURAext and AURA2 studies (90.5% and 91.5% respectively)
- **Tumour shrinkage by BICR in the 'evaluable for response' population**: Mean percentage change from baseline in target lesion size in the pooled dataset was 45.01% (standard deviation [SD] 28.01). Similar tumour shrinkage rates were reported in both the AURAext and AURA2 studies (-41.09% [SD 24.71] and -48.94% [SD 30.54] respectively). The company reports that evidence of tumour shrinkage was generally noted at the first follow up scan at 6 weeks.

4.3.2 Progression-free survival and overall survival

The company reports that at the time of the data-cut, all patients had been followed up for at least 6 months. Median PFS, calculated using the pooled AURA dataset, was 9.7 months (95% CI: 8.3 to not calculable) (Table 11). Median PFS was not calculable from the AURAext study data and, using AURA2 study data, was 8.6 months (95% CI: 8.3 to 9.7).

The company reports that the OS data are immature (12.7% for the pooled AURA dataset) and median OS has not yet been reached in either the AURAext study or in the AURA2 study.

Table 11 Summary of progression-free survival and overall survival (FAS)

	AURAext (osimertinib 80mg) (n=201)	AURA2 (osimertinib 80mg) (n=210)	Total (osimertinib 80mg) (n=411)
Progression-free survival by BICR			
Total number of events	80	79	159
Median PFS months (95% CI)	NC (8.1 to NC)	8.6 (8.3 to 9.7)	9.7 (8.3 to NC)
Median follow-up (months)	6.9	6.7	6.8
% Progression-free at 3 months (95% CI)	81.5 (75.3 to 86.2)	84.9 (79.2 to 89.1)	83.2 (79.2 to 86.5)
% Progression-free at 6 months (95% CI)	72.0 (65.1 to 77.8)	69.7 (62.8 to 75.7)	70.9 (66.1 to 75.1)
% Progression-free at 9 months (95% CI)	54.6 (46.4 to 62.1)	47.7 (36.2 to 58.4)	51.9 (45.3 to 58.1)
Overall survival			
Total number of deaths	28	24	52
Median OS	NC	NC	NC
Survival at 3 months % (95% CI)	96.5 (92.80 to 98.32)	97.1 (93.72 to 98.70)	96.8 (94.59 to 98.14)
Survival at 6 months % (95% CI)	93.0 (88.41 to 95.77)	91.7.0 (86.97 to 94.76)	92.3 (89.27 to 94.54)
Survival at 9 months % (95% CI)	84.0 (77.49 to 88.74)	87.1 (80.83 to 91.49)	85.3 (80.85 to 88.71)
Patients in survival follow-up n (%)	168 (83.6)	181 (86.2)	349 (84.9)
Median follow-up (months)	8.3	7.0	7.4

CI=confidence interval; NC=not calculable; OS=overall survival; PFS=progression-free survival; BICR=blinded independent committee review; FAS=full analysis set
Source: CS, Table 4.27 and Table 4.28

4.4 Health related quality of life

The HRQoL data presented in the CS (p120 to p124) were collected using the European Organisation for Research and Treatment of Cancer Quality of Life questionnaires, the EORTC-QLQ-30[46] and the lung cancer specific questionnaire EORTC-QLQ-L13.[47]

Assessment points were at baseline and at each clinic visit up to week 42. During the first 6 months, the company reports a >90% completion rate in the AURAext study and a >70% completion rate in the AURA2 study.

The methods of collecting data to complete the two EORTC questionnaires differed between the AURAext and AURA2 studies in that paper-based and electronic hand-held devices were used respectively, and the company provides this as the reason why they did not pool the collected HRQoL data (CS, p120).

The EORTC-QLQ-C30[46] questionnaire comprises a measure of global health status, five functional dimensions (physical, social, role, emotional, and cognitive functioning) and nine symptom domains (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). The EORTC-QLQ-LC13[47] questionnaire is a measure of symptoms that are specific to lung cancer and includes 13 items. The company highlights (CS, p120) that no major differences were noted in patient reported outcomes between second-line patients and ≥third-line patients.

As part of the AURA2 study, data were also collected using the EQ-5D-5L questionnaire and the EQ-VAS.[50] The ERG notes that the AURA2 population baseline index score (a population with advanced or metastatic NSCLC) is higher than the UK population norm for the 55-64 years of age group. However, this difference in index score is difficult to interpret as a) there is no UK value set for the EQ-5D-5L tool and b) the UK population norms were estimated using the EQ-5D-3L tool.

AURAext

Responses to the EORTC-QLQ-C30 indicated:

- a consistent positive responses on symptomatic domains and quality of life domains up to week 42
- a clinically significant improvement in overall global health status from week 12 to week 30 (44% and 48% of patients)
- a clinically meaningful increase in diarrhoea reported at week 6 (37% of patients) and week 30 (26% of patients)
- that, at 6 months, 62% of patients had not reported any deterioration in dyspnoea, cough or pain.

Responses to the EORTC-QLQ-LC13 indicated:

- a clinically meaningful improvement from baseline, starting at week 6 and at each time point, was reported for dyspnoea (35% to 45% of patients), cough (31% to 39% of patients), chest pain (28% to 33% of patients), pain in arm or shoulder (17% to 28% of patients) and pain in other parts of the body (36% to 39% of patients)

- a clinically meaningful worsening in sore mouth was reported, starting at week 12 and for the follow-up time points, by 19% to 27% of patients. The remaining patients reported stability or improvement in sore mouth.

AURA2

Responses to the EORTC-QLQ-C30 indicated there is a:

- consistent positive response on symptomatic domains and quality of life domains up to week 30
- clinically meaningful improvement in social functioning for the first 24 weeks (38% to 44% of patients)
- clinically meaningful improvement in appetite loss at weeks 6, 18 and 24 (29% to 34% of patients)
- clinically meaningful improvement in insomnia at weeks 12 and 18 (34% to 35% of patients)
- clinically meaningful improvement in fatigue at week 18 (49.6% of patients)
- clinically meaningful worsening in diarrhoea reported at weeks 6 (30% of patients).

Responses to the EORTC-QLQ-LC13 indicated that there is a:

- clinically meaningful improvement from baseline, starting from week 2/4 to week 36, was reported for dyspnoea (25% to 39% of patients), cough (31% to 40% of patients) and chest pain (20% to 31% of patients). From week 6 to week 36, 23% to 29% of patients reported improvements in arm or shoulder pain, but this improvement was not clinically meaningful.

Responses to the EQ-5D-5L and VAS indicated that:

- from week 12 onwards, patients treated with osimertinib experienced a clinically significant improvement from baseline. The minimal important difference (MID) for cancer was ≥7.5 on VAS and 0.1 on the Health Utilities Index[51] [HUI] score).

The ERG cautions that as the HRQoL data are reported separately for each study, the results are based on relatively small numbers of respondents. At baseline, the number of respondents who completed the EQ-5D-5L questionnaire and the EQ-VAS was 175; by week 36, only 30 patients completed the questionnaires. Further details relating to HRQoL measures are reported in the CS (Tables 4.29 and 4.30).

4.4.1 Key study characteristics of the IMPRESS trial

The IMPRESS trial is a double-blind, placebo-controlled, multi-centre RCT. Patients (n=265) with EGFRm+ NSCLC who had progressed on treatment with gefitinib were randomised in a 1:1 ratio to receive either gefitinib+pemetrexed+cisplatin or placebo+pemetrexed+cisplatin (PDC).

As noted previously in this report, the efficacy of osimertinib was compared with efficacy data from the subset of patients in the control arm (PDC) of the IMPRESS trial who were

identified (retrospectively) as having EGFR T790M mutation-positive disease. The company had access to tumour samples from 98% of patients in the IMPRESS trial and was, therefore, able to undertake this retrospective identification. The company reports (CS, p147) that 54% of patients from the IMPRESS trial tested positive for the EGFR T790M mutation and that this prevalence rate is consistent with reported prevalence rates in other studies. The ERG agrees that the estimated prevalence of EGFR T790M mutation-positive NSCLC is likely to be approximately 50% to 60% in patients who have progressed on or after treatment with a first-line EGFR-TKI.[4,5,52] In the control (PDC) arm of the IMPRESS trial, 61 patients (46.2%) were identified as having EGFR T790M mutation-positive disease.

The early overall population results from the IMPRESS trial are available in a published peer-reviewed paper[13] and, in addition to information presented in the CS, the company has provided the CSR for the IMPRESS trial. The company expects that the final OS results from the IMPRESS trial will be published in [redacted] (company clarification response). The key characteristics of the IMPRESS trial are provided in Table 12.

Table 12 Key characteristics of the IMPRESS trial

Characteristic	IMPRESS trial
Location	Europe and Asia-Pacific region (no UK centres)
Design	Phase III, double- blind, placebo-controlled RCT, 61 centres in 11 countries
Population	265 patients with locally advanced or metastatic EGFRm+ NSCLC. Patients had progressed after first-line treatment with gefitinib 4 months minimum duration of treatment with gefitinib with a response lasting at least 4 months or stable disease for at least 6 months
Intervention	Gefitinib (250mg daily), cisplatin (75mg per m^2) and pemetrexed (500mg per m^2) for up to six cycles. After six cycles, patients continued on gefitinib until progression
Comparator	Placebo (once daily), cisplatin+pemetrexed (as per intervention). After six cycles patients continued on placebo until progression
Primary outcome	PFS (investigator-assessed)
Secondary outcomes	OS, ORR, disease control rate, HRQoL, safety
Duration of study	The first patient was randomised on 29th March 2012 and the last patient was randomised on 20th December 2013. The data cut-off for the present appraisal was 5th May 2014.

EGFRm+=epidermal growth factor receptor mutation-positive; HRQoL=health related quality of life; ORR=overall response rate; OS=overall survival; PFS=progression-free survival
Source: CS, p128 to p130

The key baseline characteristics of patients recruited to the IMPRESS trial, including the subgroup of patients with EGFR T790M mutation-positive disease who were randomised to the control (PDC) arm of the trial, are shown in Table 13.

Overall, the patient characteristics are well balanced between the two treatment arms. However, the ERG notes that the patients in the intervention arm are older than patients in the control arm (59.3 years versus 57 years). The subgroup of patients (n=61) in the

IMPRESS trial who were randomised to the control arm and (later) identified as having EGFR T790M mutation-positive disease are younger than the overall trial population (55.8 years versus 58.1 years). In all other respects, however, the patients with EGFR T790M mutation-positive disease appear to have similar characteristics to the whole IMPRESS trial population.

Clinical advice to the ERG is that patients in the population of interest treated in clinical practice in the NHS are older and less fit than the patients recruited to the IMPRESS trial. As noted earlier in Section 4.2.4 of this report, clinical advice to the ERG is that patients in the population of interest who are treated in the NHS are typically aged between 65 years and 70 years and the majority have an ECOG PS of 1 or 2. The overall patient population in the IMPRESS trial has a mean age of 58.1 years and an ECOG PS of 0 or 1. Clinical advice to the ERG is that the case-mix of Asian and white patients treated in the NHS is the reverse of the case-mix reported in the IMPRESS trial. In the IMPRESS trial 21% of patients are described as white and 77.7% are described as Asian.

Table 13 Key baseline characteristics of patients participating in the IMPRESS trial

	Gefitinib+cisplatin +pemetrexed	PDC	PDC EGFR T790M mutation-positive patients
Number of patients	133	132	61
Mean age (sd)	59.3 (10.63)	57 (11.25)	55.8 (10.20)
Age group n (%)			
<65 years	90 (67.7)	98 (74.2)	51 (83.6)
>65 years	43 (32.3)	34 (25.8)	10 (16.4)
WHO PS n (%)			
0	55 (41.4)	53 (40.2)	22 (36.1)
1	78 (58.6)	79 (59.8)	36 (63.9)
Disease stage at baseline n (%)			
Metastatic disease	124 (93.2)	119 (90.2)	58 (95.1)
Locally advanced disease	7 (5.7)	7 (9.3)	3 (4.9)
Female n (%)	87 (65.4)	84 (63.6)	38 (62.3)
Race n (%)			
White	29 (21.8)	29 (22)	12 (19.7)
Asian	104 (78.2)	102 (77.3)	48 (78.7)
Black or African American	0	1 (0.8)	1 (1.6)
Time to progression for initial gefitinib treatment n (%)			
≤10 months	52 (39.1)	58 (43.9)	NR
>10 months	81 (60.9)	74 (56.1)	NR
Never smoked n (%)	88 (66.2)	91 (68.9)	NR
Adenocarcinoma histology n (%)	126 (94.8)	131 (99.2)	59 (96.7)
Brain metastases at baseline n (%)	44 (31)	31 (23.5)	NR
Exon 19 deletion n (%)	85 (63.9)	86 (65.2)	NR
L858R n (%)	40 (30.1)	42 (31.8)	NR

PDC=platinum doublet chemotherapy, specifically placebo+pemetrexed+cisplatin; NR=not reported; PS=performance status; sd=standard deviation; TKI=tyrosine kinase inhibitor; WHO=World Health Organisation; NOS=not otherwise stated
Source: CS, Table 4.34 and Table 4.35

4.4.2 Assessment of risk of bias for the IMPRESS trial

The company conducted a risk of bias assessment for the IMPRESS trial using the minimum criteria recommended in the NICE methods guide.[50] The company has rated the overall quality of the trial using the Jadad[33] score (maximum score of 5) and has rated the allocation concealment aspect of the IMPRESS trial using a grading system where A means adequate and D means no allocation concealment was attempted.

Overall, the ERG agrees with the company assessment of risk of bias (Table 14) and considers the IMPRESS trial to be of good quality.

Table 14 Company assessment of risk of bias for the IMPRESS trial with ERG comments

Assessment criteria	Company assessment	ERG comment
JADAD score	4	The ERG considers that the IMPRESS trial warrants the maximum score of 5
Allocation concealment	A	Agree. Central block randomisation using interactive voice response system would prevent knowledge of treatment allocation
Was randomisation carried out appropriately?	Low risk. Patients were assigned to treatment arms via central block randomisation in a 1:1 ratio using interactive web response system or interactive voice response system during the first visit (initial screening)	Agree
Were the groups similar at the outset of the study in terms of prognostic factors?	Low risk. The baseline characteristics between the two treatment arms were well balanced	Agree. However, patients randomised to the control arm were slightly younger than those randomised to the intervention arm
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low risk. This was a double-blind study. All study investigators and participants were masked to treatment allocation. To ensure masking of study investigators and participants, all gefitinib and placebo packaging was identical. Apart from safety reasons, nobody was allowed access to the randomisation scheme or study results until completion of the randomised treatment period to minimise any potential bias in data handling and to safeguard the integrity of the masking of study investigators	Agree
Were there any unexpected imbalances in dropouts between groups?	Low risk. Study withdrawals were adequately reported and incorporated in the patient flow diagram	Agree
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low risk. The authors measured all outcomes as reported in the protocol (NCT01544179)	Agree
Did the analysis include an ITT analysis? Was this appropriate and were appropriate methods used to account for missing data?	Low risk. The safety and efficacy analysis was performed using mITT and ITT populations respectively	Agree

ITT=intention to treat; mITT=modified intention to treat;
Source: CS, Table 4.36

4.4.3 Results from the IMPRESS trial

The company presents the results from the IMPRESS trial based on the data that were collected up until 5th May 2015 (CS, p148 to p156). Median follow-up for PFS was 11.2 months. Both results for the overall trial population and those for the subgroup of patients in the control arm with EGFR T790M mutation-positive disease are presented in this section.

4.4.4 Progression-free survival (investigator-assessed) and overall survival

Progression-free survival (primary outcome)

At the time of the analysis, the PFS data in the FAS population were 77.4% mature. Figures in Table 15 show no statistically significant differences between the PFS results for the intervention and control arms of the trial (PFS=5.4 months in both arms). The PFS result for the control arm EGFR T790M mutation-positive patient subgroup (PFS=5.3 months) was similar to the PFS results for the overall trial population.

The company presents a K-M plot of the PFS data (CS, Figure 4.16) for the overall trial population and states: i) that the curves for the treatment arms do not cross and ii) the treatment effects of the intervention and the control therapies were consistent over time. The ERG agrees with the company that the PH assumption appears valid.

The results of the company subgroup analyses for the overall population of the IMPRESS trial are presented in Figure 4.17 of the CS. Subgroup analyses were conducted for: age (<65 years or ≥65 years), male or female, region of origin (Asia or Europe), previous response to gefitinib (CR+PR or stable disease), EGFR mutation subtype (Exon 19 deletion or L838R deletion), smoking status (present or former or never), disease state at diagnosis (metastatic or non-metastatic), time from progression to randomisation (>2 weeks or ≤2 weeks), time to progression for initial gefitinib therapy ≤10 months or >10 months), brain metastases at baseline (yes or no) and WHO PS (0 or 1). Significant interactions were noted for:

- Asia (HR=0.80) versus Europe (HR=0.95)
- Never smokers (HR=0.70) versus current or former smokers (HR=1.16)
- Exon 19 deletion present (HR=0.76) versus Exon 19 absent/unknown Exon 19 (HR=0.97)
- WHO PS 0 (HR=0.68) versus WHO PS 1 (HR=0.95).

During the clarification process, the ERG requested the corresponding p-values for the tests for interaction for these analyses. However, the company only sent results for the tests of interaction for the control arm of the IMPRESS trial. This means that the ERG is unable to

assess which of the subgroup analyses are significant and therefore cannot comment on the company's conclusions.

The company also presents a PFS K-M data plot by treatment arm and biomarker status (CS, Figure 4.18). The company states that a (non-significant) treatment effect of gefitinib was recorded in patients without EGFR T790M mutation-positive disease (HR=0.67; 95% CI: 0.43 to 1.03, p=0.0745). In contrast, no treatment effect of gefitinib was recorded for patients with EGFR T790M mutation-positive disease (HR=0.97; 95% CI: 0.67 to 1.42, p=0.8829). The company interprets this finding as providing support to the biological hypothesis that, in the absence of the EGFR T790M mutation, the tumour may still respond to treatment with an EGFR-TKI.

Overall survival

At the time of the analysis, FAS population OS data from the IMPRESS trial were immature. The company reports that follow-up for survival is ongoing and that more mature data will be available (following a [redacted]

The analysis of OS data (Table 15) from the overall IMPRESS trial population demonstrates a statistically significant treatment effect for patients in the control arm (HR=1.62; 95% CI: 1.05 to 2.52, p=0.029). Median OS is 17.2 months (95% CI 15.6 to NR) in the control arm compared with 14.8 months (95% CI: 10.4 to 19.0) in the intervention arm. OS for the subgroup of patients in the control arm with EGFR T790M mutation-positive disease was 15.7 months, which is lower than the OS for the whole control arm population (17.2 months) but higher than that for the intervention arm population (14.8 months). The ERG cautions that the OS results are based on immature data.

The company reports that 45.9% of patients in the intervention arm and 54.5% of patients in the control arm had received further anti-cancer treatment after discontinuation of their study treatment (CS, p153).

Table 15 Progression-free survival and overall survival from the IMPRESS trial

	Gefitinib+cisplatin +pemetrexed	PDC	PDC EGFR T790M mutation-positive patients
Number of patients	133	132	61
Progression-free survival (investigator-assessed)			
Total number of events	98	107	51
Median PFS months (95% CI)	5.4 (4.5 to 5.7)	5.4 (4.5 to 5.5)	5.3
Median follow-up (months)	11.2	11.2	NR
% Progression-free at 4 months (95% CI)	73.5 (64.8 to 80.4)	67.8 (59 to 75.2)	NR
% Progression-free at 6 months (95% CI)	40.8 (31.5 to 49.8)	36 (27.4 to 44.6)	NR
% Progression-free at 8 months (95% CI)	28.2 (19.8 to 37.1)	17.3 (10.9 to 25.1)	NR
Overall survival			
Total number of deaths	50	37	20
Median OS months (95% CI)	14.8 (10.4 to 19.0)	17.2 (15.6 to NR)	15.7
Hazard ratio (95% CI)	1.62 (1.05 to 2.52), p-value=0.029		NR

CI=confidence interval; NR=not reached; OS=overall survival; PFS=progression-free survival: PDC=platinum doublet chemotherapy, specifically placebo+pemetrexed+cisplatin
Source: CS: Table 4.37, Table 4.38 and p153

Objective response rate

The ORR reported in the CS is based on the percentage of patients with a BOR of CR or PR (according to RECIST criteria) using investigator-assessed data. The proportion of patients with a response is similar in the intervention (31.6%) and control (34.1%) arms of the trial for the overall populations (OR=0.92; 95% CI: 0.55 to 1.55, p-value=0.760). Similarly, just over a third (39.3%) of patients in the control arm with EGFR T790M mutation-positive disease were assessed as responding.

Health related quality of life

HRQol in the IMPRESS trial was measured using the Functional Assessment of Cancer Therapy – Lung (FACT-L[49]) questionnaire and the EQ-VAS. The company states (CS, p155) that the results from the FACT-L questionnaire: i) are not relevant to the decision problem and ii) are not used in the comparison with the pooled AURA dataset. The company has, therefore, not included a detailed discussion of the FACT-L data collected during the IMPRESS trial. The ERG agrees with the company's decision.

The EQ-VAS scores for a subset of the FAS population are summarised in Table 4.40 of the CS (p156). The company states that the patient response rate for completion and evaluability rate of the questionnaires was similar in the intervention and control arms of the

trial. The ERG highlights that the EQ-VAS scores are higher than those collected as part of the AURA2 study.

4.5 Adverse events from the AURAext study, the AURA2 study and the IMPRESS trial

Adverse event data from the AURAext study, the AURA2 study, the pooled AURA dataset and the IMPRESS trial are reported in the CS (p157 to p161). A comparison of the pooled AURA dataset and in the IMPRESS trial AE data is presented and discussed as part of the adjusted comparison (CS, p78 and p79).

4.5.1 Pooled AURA dataset

The company reports (CS, p157) that median treatment duration in the AURAext study was 8.2 months and 7.4 months in the AURA2 study.

The ERG notes (Table 16) that, in the pooled AURA dataset, the majority (97.6%) of patients treated with osimertinib experienced an AE and almost one third (29.4%) of patients experienced an AE of grade 3 or higher. One fifth (20.2%) of patients had a serious adverse event (SAE) and one fifth of patients (19.7%) had their dose of osimertinib reduced due to AEs. Seventeen patients (4.1%) discontinued their treatment due to AEs and nine patients (2.2%) died as a result of an AE. It is reported in the CSRs for the AURAext and AURA2 studies that grade 3 or above AEs included respiratory disorders (13%), infections (6%), investigations (5.8%) and blood disorders (5% in AURA2). It is also reported that more SAEs were experienced by patients receiving osimertinib as a third-line (or greater) treatment than were experienced by patients receiving osimertinib as a second-line treatment.

The company reports that the most commonly reported AEs were consistent across the studies and are consistent with the AEs known to be associated with EGFR-TKI treatment.

Table 16 Categories of AEs from the pooled AURA dataset, FAS

Category of adverse event	AURAext N=201, n (%)	AURA2 N=210, n (%)	Total N=411, n (%)
Patients with any AE	198 (98.5)	203 (96.7)	401 (97.6)
AE ≥grade 3	60 (29.9)	61 (29.0)	121 (29.4)
SAEs	41 (20.4)	42 (20.0)	83 (20.2)
Fatal SAEs	4 (2)	5 (2.4)	9 (2.2)
AEs leading to discontinuation	9 (4.5)	8 (3.8)	17 (4.1)
AEs leading to dose modification	40 (20.4)	41 (19.5)	81 (19.7)

AE=adverse event; SAE=serious adverse event, FAS=full analysis dataset
Source: CS, Table 4.41

The information in Table 17 shows that, in the pooled AURA dataset, diarrhoea and rashes and acne were the most frequently reported AEs at any grade (42.3% and 41.4%

respectively). The company states (CS, p158) that the incidences of decreased appetite, fatigue and nausea were 'mostly mild in nature and non-serious.' Clinical advice to the ERG is that, in NHS clinical practice, incidences of diarrhoea and fatigue can be difficult to manage, particularly in an elderly population.

Table 17 AEs from the pooled AURA dataset (≥10% of patients), FAS

	AURAext N=201, n (%)		AURA2 N=210, n (%)		Total N=411, n (%)	
Adverse event	Any grade	≥grade 3	Any grade	≥grade 3	Any grade	≥grade 3
Diarrhoea	93 (46.3)	2 (1.0)	81 (38.6)	2 (1.0)	174 (42.3)	4 (1.0)
Rashes+acnes	81 (40.3)	1 (0.5)	87 (41.4)	1 (0.5)	170 (41.4)	2 (0.5)
Dry skin	43 (21.4)	0	52 (24.8)	0	95 (23.1)	0
Paronychia	40 (19.9)	0	32 (15.2)	0	72 (17.5)	0
Nausea	35 (17.4)	2 (1.0)	34 (16.2)	0	69 (16.8)	2 (0.5)
Decreased appetite	36 (17.9)	2 (1.0)	29 (13.8)	1 (0.5)	65 (15.8)	3 (0.7)
Constipation	30 (14.9)	1 (0.5)	32 (15.2)	1 (0.5)	62 (15.1)	1 (0.2)
Cough	32 (15.9)	0	25 (11.9)	1 (0.5)	57 (13.9)	1 (0.2)
Fatigue	25 (12.4)	2 (1.0)	32 (15.2)	0	57 (13.9)	2 (0.5)
Pruritus	25 (12.4)	0	32 (15.2)	0	57 (13.9)	0
Back pain	27 (13.4)	1 (0.5)	25 (11.9)	2 (1.0)	52 (12.7)	3 (0.7)
Stomatitis	27 (13.4)	0	22 (10.5)	0	49 (11.9)	0
Platelet count decreased	27 (13.4)	1 (0.5)	20 (9.5)	1 (0.5)	47 (11.4)	2 (0.5)
Headache	22 (10.9)	0	20 (9.5)	1 (0.5)	42 (10.2)	1 (0.2)

FAS=full analysis dataset
Source: CS, Table 4.42

4.5.2 IMPRESS trial

The company reports (CSR, p108) that the mean total treatment duration in the intervention and control arms of the IMPRESS trial was 165 days and 155 days respectively. The data in Table 18 show that, across all categories of AEs, patients in each of the trial arms experienced similar rates of AEs.

Table 18 Categories of common AEs (≥10%) from the IMPRESS trial, safety analysis set

Category of AE	Gefitinib+cisplatin +pemetrexed (N=133)	PDC (N=132)
Patients with any AE	126 (95.5)	130 (98.5)
AE ≥grade 3	59 (44.7)	55 (41.7)
Fatal AEs	5 (3.8)	8 (6.1)
AEs leading to discontinuation	10 (7.6)	13 (9.8)
AEs leading to dose modification	6 (4.5)	7 (5.3)
SAEs	NR (28)	NR (21.2)
SAE leading to discontinuation	(3)	(8)

AE=adverse event; PDC=platinum doublet chemotherapy, specifically placebo+cisplatin+pemetrexed; SAE=serious adverse event
Source: CS, p159 and published paper (Soria 2015)

The data in Table 19 list the most commonly reported AEs experienced by patients in the IMPRESS trial. The three most frequent AEs in the intervention and control arms of the trial were nausea (64.4% and 61.4%), decreased appetite (49.2% and 34.1%) and vomiting (41.7% and 33.3%).

The company reports (CS, p161) that decreased neutrophil count, anaemia, neutropenia and decreased white blood cell count were the most commonly experienced (≥5%) AEs of grade 3 or higher.

Table 19 AEs from the IMPRESS trial (≥10% of patients), safety analysis set

Adverse event	Gefitinib+cisplatin +pemetrexed (N=132), n (%)	PDC (N=132), n (%)
Any AE	126 (95.5)	130 (98.5)
Nausea	85 (64.4)	81 (61.4)
Decreased appetite	65 (49.2)	45 (34.1)
Vomiting	55 (41.7)	44 (33.3)
Anaemia	42 (31.8)	33 (25.0)
Constipation	34 (25.8)	35 (26.5)
Diarrhoea	44 (33.3)	19 (14.4)
Neutropenia	29 (22.0)	28 (21.2)
Fatigue	28 (21.2)	23 (17.4)
Leucopenia	27 (20.5)	22 (16.7)
Asthenia	15 (11.4)	30 (22.7)
Neutrophil count decreased	16 (12.1)	22 (16.7)
Pyrexia	22 (16.7)	14 (10.6)
Cough	18 (13.6)	15 (11.4)
White blood cell count decreased	17 (12.9)	13 (9.8)
Headache	10 (7.6)	19 (14.4)
Dyspnoea	16 (12.1)	10 (7.6)
Back pain	11 (8.3)	14 (10.6)
Rash	14 (10.6)	11 (8.3)
Stomatitis	14 (10.6)	5 (3.8)

AE=adverse event; PDC=platinum doublet chemotherapy, specifically placebo+cisplatin+pemetrexed
Source: CS, Table 4.43

4.6 Critique of trials included in the unadjusted and adjusted comparisons

4.6.1 Methodological approach to the unadjusted and adjusted comparisons

The company employed two methods to compare the clinical effectiveness results from the pooled AURA dataset with those from the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease. The two methods were a simple unadjusted comparison and an adjusted comparison. The adjusted comparison involved adjustments to control for differences in baseline characteristics between the populations in the two datasets.

Unadjusted comparison

The unadjusted comparison simply involved comparing key efficacy outcomes (ORR, PFS and OS) from the two datasets.

Adjusted comparison

The methods employed by the company to carry out the adjustments and estimate outcomes are summarised in Box 3.

Box 3 Summary of adjustment approach and outcome calculation methods

Patients from the AURAext and AURA2 studies were matched with patients from the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease. Matching was based on baseline demographic and disease characteristics. Patients for whom there was no match were dropped from the analysis at this point.

Prior to estimating efficacy outcomes, differences between baseline demographic and disease characteristics were accounted for using a three-step process:

a. selection of baseline variables that were statistically significantly different between groups (based on a p-value of <0.2)
b. generation of a propensity score to represent aggregated differences in variables selected and trimming of the data set by removal of patients for which there was no similar propensity score in the alternative group and
c. incorporation of propensity score as covariate in analysis of treatment effect of osimertinib for each endpoint to adjust for remaining differences between the two groups.

The estimated propensity score was defined as the conditional probability that the distribution of observed baseline covariates will be similar between treated and untreated patients, i.e. patients are equally likely to be treated with osimertinib or PDC in the absence of baseline differences. It acts as a proxy for randomisation.

The baseline demographic and disease characteristics that were used in the regression

model to estimate the propensity scores and the final trimmed dataset were age, ethnicity, baseline target lesion size and smoking history. The final datasets included in the adjusted analysis comprised 287 patients from the AURA studies and 51 patients from the control arm of the IMPRESS trial. The trimmed dataset is referred to as the T790M+ adjusted dataset.

For the matched populations, the treatment effect of osimertinib versus PDC was assessed for key efficacy and safety endpoints as follows:

- PFS: Cox PH model with treatment as a factor and propensity score as a covariate
- OS: based on independent assessment review and performed at the time of the PFS analysis using a Cox PH model
- ORR and DCR: carried out using logistic regression with treatment as a factor and propensity score as a covariate.

PH=proportional hazards; ORR=objective response rate; PDC=platinum doublet chemotherapy; PFS=progression-free survival; OS=overall survival; DCR=disease control rate
Source: CS, Section 4.10.3

ERG critique of the company's adjusted comparison

The ERG appreciates the lengths taken by the company to facilitate a comparison of the effectiveness of osimertinib with PDC, but considers that only a well-controlled, head-to-head RCT can avoid unobserved confounding.

The ERG notes that the adjustments that have been made only relate to age, ethnicity, baseline target lesion size and smoking history, all of which (except for age) are well balanced between the two datasets. No adjustments have been made to account for differences in either line of treatment (including number of previous EGFR-TKIs) or brain metastases; clinical advice to the ERG suggests that these may be important prognostic factors.

In addition, when testing for statistically significant differences in baseline variables, the company used a p-value of <0.2 instead of a conventional significance level of 0.05; the rationale behind this choice is not explained. Furthermore, the company has not provided details of all of the baseline summary variables that were tested for possible inclusion; the ERG has, therefore, been unable to check whether there are any further uncontrolled differences between the trials.

2. Over and above concerns about the immaturity of the OS data, the ERG notes that of the datasets was substantially reduced following adjustments (

Table 21). The pooled AURA dataset was reduced from n=411 to n=287 for the PFS and OS analyses, and to n=277 for the ORR and DCR analyses. The T790M+ adjusted dataset was reduced from n=61 to n=51 for the PFS and OS analyses, and to n=46 for the ORR and DCR analyses.

Characteristics of studies included in the clinical efficacy comparisons

The company provides baseline characteristics related to patients in the pooled AURA dataset (n=411) and to the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease (n=61). The baseline characteristics of the patients in the individual datasets used in the adjusted comparisons are unknown.

The baseline characteristics of the patients included in the pooled AURA dataset and in the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease are shown in Table 4.7 of the CS. The eligibility criteria used to recruit patients to the two AURA studies and to the IMPRESS trial differ slightly. The pooled AURA dataset includes both patients receiving second-line and patients receiving subsequent lines of treatment, whilst the IMPRESS trial only recruited patients who had received one prior EGFR-TKI therapy. Furthermore, whilst patients in the AURAext and AURA2 studies were not required to have had a prior treatment response to an EGFR-TKI, patients in the IMPRESS trial had to have had a prior objective clinical benefit (as measured by CR or PR) and a minimum duration on first-line gefitinib treatment of 4 months. Another key difference in eligibility criteria is that the two populations used different methods to identify EGFR T790M mutation status. The Roche Cobas method was used in the AURAext and AURA2 studies and the BEAMing digital PCR method was used (retrospectively) to identify patients with T790M mutation-positive disease recruited to the IMPRESS trial.

Despite the differences in inclusion criteria, overall, the baseline patient demographic characteristics of patients included in the pooled AURA dataset and the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease are well balanced. The key differences between datasets are in terms of age and presence of brain metastases. The subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease is slightly younger than patients in the pooled AURA dataset, with a mean age of 55.8 years compared to 62.2 years. Only 16.4% of patients in the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation positive disease were ≥65 years, whereas in the pooled AURA dataset population 45.5% of patients were ≥65 years old. Furthermore, compared with patients in the pooled AURA dataset, fewer patients in the control arm of the IMPRESS trial who had EGFR T790M mutation-positive disease had brain metastases at baseline (40.4% versus 34.4%

respectively). The company considers that both the age and the brain metastases imbalances may have a prognostic effect favouring the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease.

Key differences between the pooled AURA dataset population and the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease are summarised in Table 20.

Table 20 Key baseline differences between the AURA studies and the IMPRESS subgroup

Demographic characteristics		Pooled AURA dataset	EGFR T790M mutation-positive population
Number		411	61
Indication		≥Second-line	Second-line
Treatment		Osimertinib 80mg	Placebo+PDC
Age (years)	Mean (SD)	62.2 (10.76)	55.8 (10.20)
	Median (min-max)	63 (35-89)	55 (38-79)
	% ≥65 years	187 (45.5%)	10 (16.4%)
Brain metastatic at baseline		166 (40.4%)	21 (34.4%)

EGFR=epidermal growth factor receptor; SD=standard deviation; PDC=platinum doublet chemotherapy
Source: CS, Table 4.7

4.6.2 Assessment of risk of bias of the trials included in the unadjusted and adjusted comparisons

The company conducted an assessment of the risk of bias for the AURAext and AURA2 studies, which is discussed in Section 4.2.5, and for the IMPRESS trial, which is discussed in Section 4.4.2, of this report. The ERG considers that the assessments of risk of bias conducted by the company were appropriate. The ERG considers that the AURA studies were designed and conducted to a good standard (with the caveat that both were single-arm studies) and that the IMPRESS trial was of very good quality.

4.6.3 Results from the unadjusted and adjusted comparisons

Unadjusted comparison of study results

The results of the unadjusted comparison are provided in

Table 21.

The ORR observed within the pooled AURA dataset (ORR=66.1%) was significantly higher than the ORR observed in the IMPRESS EGFR T790M mutation-positive control group (ORR=39.3%). Furthermore, patients in the pooled AURA dataset had a median PFS of 9.7 months compared to 5.3 months for the IMPRESS EGFR T790M mutation-positive control group, indicating a statistically significant difference of 4.4 months. However, the results need to be interpreted with caution as, at the time of analysis, the 95% CIs for PFS were either not calculable or not reached as the data were very immature with only 12.7% of patients having had OS events in the pooled AURA dataset and only 32.8% of patients in the EGFR T790M mutation-positive control group of the IMPRESS trial having had OS events. The median OS was not reached for patients in the pooled AURA dataset. In the control arm of the IMPRESS trial, median OS was 15.7 months for patients with EGFR T790M mutation-positive disease; the company did not report 95% CIs.

Adjusted comparison of study results

The results from the adjusted comparison for ORR, PFS and OS are provided in

Table 21.

The ORR results indicate a statistically significant improvement in favour of osimertinib compared to PDC (64.6% and 34.8% respectively, OR=4.76; 95% CI: 2.21 to 10.26; p<0.001). Similarly, the DCR results indicate a statistically significant improvement in favour of osimertinib compared to PDC (92.1% and 76.1% respectively, OR=4.39; 95% CI: 1.71 to 11.28; p=0.002). The PFS results indicate a statistically significant difference in favour of osimertinib compared to PDC (HR=0.280; 95% CI: 0.185 to 0.422; p<0.0001). Median PFS is 9.7 months for the osimertinib cohort compared to 5.2 months in the matched PDC cohort. Due to the very small number of patients experiencing events (osimertinib, n=33; PDC, n=15) median OS could not be calculated (HR=1.022; 95% CI 0.387 to 2.696; p=0.9654).

The ERG investigated whether the PH assumption employed by the company to calculate PFS and OS HRs hold by digitising the data presented in Figure 4.2 (PFS) and Figure 4.3 (OS) of the CS and then plotting the cumulative hazard associated with osimertinib treatment versus the cumulative hazard associated with PDC treatment (H-H plot). The PFS H-H plot suggests that the PH assumption does not hold for PFS and, therefore, the PFS HR result must be interpreted with caution. Interpretation of the OS H-H plot is less clear and the issue is complicated by the lack of data. However, based on the data available, it would not be unreasonable to assume that hazards are broadly proportional.

The ERG notes that key efficacy results from the adjusted and unadjusted analyses are very similar (

Table 21).

Table 21 Comparison of key efficacy outcomes (unadjusted and adjusted)

Study / Outcome		Unadjusted data sets			Adjusted data sets	
		Pooled AURA dataset	PDC (IMPRESS trial)		Pooled AURA dataset	IMPRESS trial T790M+adjusted dataset
			Whole population	EGFR T790M+ subgroup		
Number		411	132	61	PFS/OS: 287 ORR: 277	PFS/OS: 51 ORR: 46
ORR	Total responses, n (%)	264 (66.1)	45 (34.1)	24 (39.3)	179 (64.6)	16 (34.8)
PFS	Total events, n (%)	159 (38.9)	107 (81.1)	51 (83.6)	106 (36.9)	42 (82.4)
	Median, months (95% CI)	9.7 (8.9 to NC)	5.4 (4.6 to 5.5)	5.3 (NR)	9.7 (8.3 to NC)	5.3 (4.0 to 6.1)
OS	Total events, n (%)	52 (12.7)	37 (28)	20 (32.8)	33 (11.5)	15 (29.4)
	Median, months (95% CI)	NR	17.2 (15.6 to NC)	15.7 (NR)	NC (NC to NC)	21.7 (12.55 to NC)

CI=confidence interval; NC=not calculable; NR=not reported; ORR=overall response rate; OS=overall survival; PDC=platinum doublet chemotherapy, specifically placebo+pemetrexed+cisplatin; PFS=progression-free survival
Source: CS, Table 4.8, Table 4.11, Table 4.12 and Table 4.14

Conclusions of the clinical effectiveness section

The phase I/II study evidence presented in the CS in support of the clinical effectiveness of osimertinib for treating EGFR T790M mutation-positive NSCLC suggests that osimertinib may be a promising treatment for this population.

Direct evidence - key issues and uncertainties

The AURAext and AURA2 studies were designed as single-arm studies. This raises challenges in interpreting study results. The lack of results from a comparator arm means that how much of the reported effects of osimertinib are the result of treatment, the natural course of the disease or a placebo effect is unclear. The lack of a comparator arm also means that no direct comparison of the clinical effectiveness of osimertinib with any of the comparators listed in the final scope issued by NICE is available.

A particular difficulty in this appraisal is the lack of mature survival data. The OS in the pooled AURA dataset has reached only 12.7% maturity; this clearly precludes any reliable assessment of the OS benefit of treatment with osimertinib.

The ERG questions the generalisability of the results from the AURAext and AURA2 studies to the population of interest treated in the NHS. The patients recruited to the studies were younger and fitter (ECOG PS 0 or 1) than similar patients seen in NHS clinical practice. The

majority (two-thirds) of recruited patients received osimertinib as a third- fourth- or fifth-line treatment following a first-line EGFR-TKI and a first-line chemotherapy. The ERG is aware that very few patients seen in clinical practice in the NHS are well enough to tolerate more than one or two chemotherapy treatments. Patients from only two UK centres contributed to the data in the pooled AURA dataset.

The company has pooled IPD data from the AURAext and AURA2 datasets and generated efficacy results from this dataset. The company explains that the rationale behind this approach was to improve the precision of outcomes. The ERG considers that, as these two studies are very similar in terms of recruitment criteria and patient baseline characteristics, it was reasonable to pool the data. Furthermore, results generated independently using data from the two studies are similar to results generated from the pooled dataset.

Unadjusted and adjusted comparisons

The company should be commended for the effort that they have taken to formulate a comparator dataset. The comparator dataset comprises patients recruited to the control (PDC) arm of the IMPRESS trial who were (retrospectively) identified as having EGFR T790M mutation-positive disease. The ERG, however, has concerns that data from single-arm, non-controlled studies (AURAext and AURA2) are compared with data from a retrospectively identified subgroup participating in a good quality placebo-controlled, double-blind RCT (IMPRESS). Furthermore, this IMPRESS subgroup only includes 61 patients and OS data are only 32.8% mature.

The ERG commends the company for attempting to control for differences in baseline dataset differences by carrying out an adjusted comparison. However, [redacted]

The results from the unadjusted comparison indicate that osimertinib is more clinically effective, as measured by PFS and ORR than treatment with PDC (median OS has not yet been reached). The safety data suggest that treatment with osimertinib is more tolerable than treatment with PDC.

Other key issues and uncertainties

The evidence presented in the CS compares the clinical effectiveness of osimertinib with PDC. No evidence is available to compare osimertinib with any of the other 11 comparators specified in the final scope issued by NICE.

The mutation testing protocol required for the use of osimertinib is not in place in the NHS. T790M mutation testing after first-line treatment to establish the presence or absence of the EGFR T790M mutation is feasible as the infrastructure is in place; however, EGFR T790M mutation testing after first-line treatment is not standard practice in the NHS.

5 COST EFFECTIVENESS

This section provides a structured critique of the economic evidence submitted by the company to support the cost effectiveness of osimertinib. The company model focuses on patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy.

The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company also provided an electronic version of their economic model that was developed in Microsoft Excel.

5.1 Objective of the company systematic review

The company's search was conducted to identify evidence to support the development of the company's cost effectiveness model. The company carried out a single review to identify studies that included descriptions of economic evaluations as well as information on resource use and costs. Initially, the review focussed on identifying evidence relating to patients with EGFR-TKI mutation-positive disease and/or T790M mutations with acquired resistance to an EGFR-TKI. However, due to a lack of available evidence, the remit of the review was broadened to include patients:

a) harbouring EGFR and/or T790M mutations following any prior therapy
b) with unknown EGFR and T790M mutation status following treatment failure with an EGFR-TKI.

Details of the search strategies employed by the company are provided in Appendix A2.1 of the CS. The data sources for the economic systematic review are outlined in Table 22. The searches were conducted in January 2016.

5.1.1 Eligibility criteria used in study selection

Table 22 Data sources for the economic systematic review

Search strategy component	Sources	Date limits
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies	MEDLINE® MEDLINE® In-process Excerpta Medical Database (Embase®) Cochrane® Central Register of Controlled Trials (CENTRAL) Cochrane National Health Service Economic Evaluation Database (NHS EED) EconLit®	01 Jan 2004 to 21 Jan 2016
Conference proceedings	HTA International	2012–2016
	International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	
	European Society for Medical Oncology (ESMO)	
	American Society of Clinical Oncology (ASCO)	

Source: CS, Table 5.1

5.1.2 Inclusion criteria

The inclusion/exclusion criteria used by the company to facilitate study selection are presented in Table 23. The company used different study designs to identify economic evaluations (S1) and quality of life studies (S2).

Table 23 Inclusion/exclusion criteria for the economic review

	Economic evaluations	Rationale
Patient population (P)	Age: adults aged ≥18 years Gender: any Race: any Disease: patients with advanced/metastatic NSCLC who are EGFR and/or T790M mutant and who have failed at least one EGFR-TKI ±other anticancer regimens	The patient population of interest to the review comprised adult patients with advanced/metastatic NSCLC of any race and gender because NSCLC can occur at any age but is most common in adults aged between 40 years and 70 years. Therefore, studies focusing solely on children and adolescents were not included in this review
Intervention (I)	Osimertinib	This is the intervention of interest within the decision problem
Comparator (C)	Any pharmacological intervention Placebo Best supportive care	The searches for economic review were not restricted to any interventions in order to collate all available published economic evidence in patients with advanced/metastatic NSCLC harbouring EGFR/T790M mutations following prior therapy
Outcome (O)	Studies were not be excluded based on the reported outcomes	The aim of the review was to identify relevant economic evaluations that also reported costs

	Economic evaluations	Rationale
Study design 1 (S1)	All economic evaluation studies based on models Cost-effectiveness analysis Cost-utility analysis Cost-minimisation analysis Cost-benefit analyses Budget impact models Resource use studies Cost/economic burden of illness	The aim of the review was to identify relevant economic evaluations that also reported costs
Study design 2 (S2)	Randomised controlled trials Database studies Prospective observational studies Retrospective observational studies	The aim of the review was to identify relevant studies that reported quality of life data
Line of therapy	Second- or further-line of therapy	This is the relevant line of treatment
Search timeframe	2004 to 2016	This period was deemed relevant to reflect models that are representative of the current NSCLC landscape
Language	Only studies with the full-text published in English language were included	It is expected that the majority of evidence in this disease area will be available in the English language
Exclusion criteria	Reviews, letter to the editors, and editorials Case studies/case series Case reports Cross-sectional studies	The design of such studies was not relevant to the decision problem These are generally smaller studies with higher risk of bias, hence excluded
	Studies investigating the role of radiotherapy, chemo-radiotherapy, hormonal therapy, or surgery only were excluded Studies investigating the role of maintenance/consolidation therapy after surgery were also excluded Adjuvant or neo-adjuvant therapy were excluded No subgroup analysis	Only pharmacological interventions (chemotherapies and targeted therapies) were considered as relevant comparators for osimertinib Studies that included children and adults and did not provide subgroup analysis for the adult populations Studies which enrol a mixed population of stage I, II, IIIa, and stage IIIb/IV NSCLC and did not provide subgroup analysis for the disease stage IIIb/IV

Source: CS, Table 5.2

5.1.3 Included and excluded studies

The company identified five studies[51-55] for inclusion in a qualitative synthesis. None of the studies included osimertinib as an intervention or as a comparator. None of the studies included patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who had progressed on or after EGFR-TKI therapy.

The company reported that it did find one conference abstract describing a study that included the primary population. However, no reference to this conference proceeding was listed in the CS.

5.1.4 Findings from cost effectiveness review

The company provided a summary of the five included studies.[51-55] However, the company did not comment on the results from any of these studies.

5.2 ERG critique of the company's literature review

The ERG is satisfied with the company's search strategies and is confident that there are no studies that fully meet the company's inclusion criteria. The databases searched and search terms used appear to be reasonable. The ERG considers the wider search for published economic literature (e.g. inclusion of a broad population of patients) to be appropriate when taking into account the shortage of relevant clinical and economic data for the specific patient population of interest to this appraisal.

5.3 Summary and critique of company's submitted economic evaluation by the ERG

5.4 ERG's summary of company's submitted economic evaluation

The company base case cost effectiveness analysis compares osimertinib with platinum doublet chemotherapy (PDC – specifically, cisplatin+pemetrexed), and adopts a lifetime horizon of 15 years. In the CS (p181), the company states that the economic evaluation is carried out from the perspective of the NHS and Personal Social Services (PSS) and includes the resource use and costs associated with treatment acquisition, treatment administration, disease management, AEs and EGFR T790M mutation testing. In the model, the cycle length is 1-week to facilitate comparison with most chemotherapy regimens and a half-cycle correction is employed. In line with the current NICE Reference Case,[50] costs and quality adjusted life years (QALYs) are discounted at an annual rate of 3.5%.

The company also carried out scenario analyses and subgroup analyses to explore the cost effectiveness of osimertinib versus PDC, and versus single-agent chemotherapy, in different patient populations.

5.4.1 Model structure

The company developed a de novo cohort based survival model that comprised three health states: progression-free (PF), progressed disease (PD) and death. The partitioned survival model is similar to that of other treatments for advanced cancers that have been submitted to NICE as part of the STA process. In the model, OS = PF + PD. The structure of the company model is shown in Figure 3.

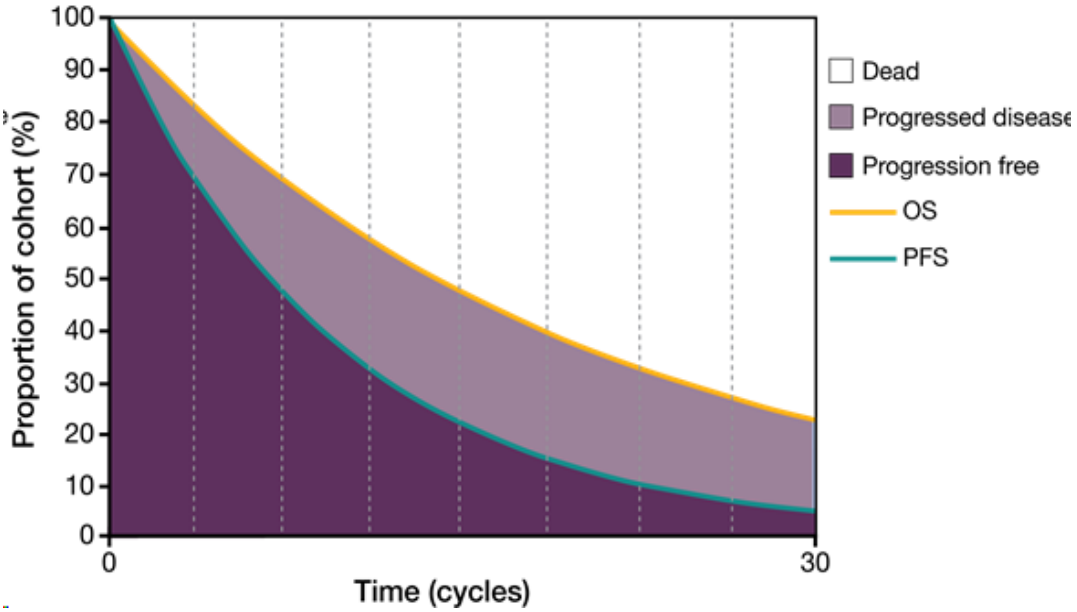


Figure 3 Partitioned survival analysis model structure

OS=overall survival; PFS= progression-free survival
Source: CS, Figure 5.2

As described in Section 5.5.2 of the CS, the company assumes that the three health states represent the key sequence of events that patients may experience over the course of their treatment, with the additional assumption that these events are progressive, mutually exclusive and irreversible.

5.4.2 Population

The economic evaluation considers 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. The age of patients starting treatment in the model is 62.17 years; this is based on the average age of patients in the AURAext and AURA 2 studies. The body surface area (BSA) of patients in the model is assumed to be 1.68m^2.

5.4.3 Interventions and comparators

Osimertinib is implemented in the model in line with the anticipated licensed dose, i.e. one 80mg tablet to be taken once per day. The base case comparator is PDC (i.e., pemetrexed+cisplatin); this treatment is administered every 3 weeks by intravenous infusion at a dose of 500mg/m^2 over 10 minutes for pemetrexed, and at a dose of 75mg/m^2 over 2 hours for cisplatin. Pemetrexed+cisplatin is the current standard of care in the NHS for patients with EGFR mutation-positive disease who have failed first-line treatment with an EGFR-TKI.

In a scenario analysis, osimertinib is compared with up to six cycles of docetaxel monotherapy; this treatment is administered every 3 weeks by intravenous infusion at a dose of 75mg/m^2 over 60 minutes. Up to four cycles of docetaxel is the current standard of care in the NHS for patients with non-squamous lung cancer who do not have EGFR mutation-positive disease and who have failed first-line treatment with pemetrexed+cisplatin.

5.4.4 Perspective, time horizon and discounting

The company states that the economic evaluation is undertaken from the perspective of the NHS/PSS. In the model the maximum lifetime is set at 15 years, this is slightly shorter than other similar models[56] that have been recently submitted to the NICE STA process. Both costs and benefits are discounted at a rate of 3.5% per annum.

5.4.5 Treatment effectiveness and extrapolation in the base case

Disease progression and overall survival model inputs (osimertinib versus PDC)

Data from the AURAext (n=201) and AURA2 (n=210) studies were pooled and used to demonstrate the PFS and OS associated with treatment with osimertinib. At the time of data cut-off, the PFS data were 39% mature and the OS data were 12.7% mature. PDC clinical data were derived from patients (n=60) with T970M mutation-positive disease in the control arm of the IMPRESS trial. The company recognised that, due to the immaturity of the data, it was difficult to test proportional hazards assumptions. Therefore, the analysis used independent survival models for osimertinib and comparator treatments.

The company followed standard guidance for fitting and selecting survival functions. A full step-wise description of the statistical analysis undertaken by the company, which was based on NICE DSU guidance[57] is presented in the CS (Section 5.3.5 to Section 5.3.9, Figure 5.3). The company investigated the use of a range of parametric models: Gompertz, Generalised Gamma, Log-normal, Log-logistic, Exponential and Weibull. In accordance with the DSU guidance[57], the company selected the same parametric models for both treatment arms.

Based on visual inspection only, the Gompertz, Weibull and Generalised Gamma distributions appeared to provide the most adequate estimates of PFS for PDC. For osimertinib, the Weibull model appeared to provide the best fit to the pooled AURA dataset.

Based on statistical goodness-of-fit tests (Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]), the Weibull distribution had the best fit for osimertinib and the second best fit for PDC, whilst the Gompertz distribution had the best fit for PDC and the

second best fit for osimertinib. The company concluded that the goodness-of-fit for OS was not conclusive and differed between studies.

In summary, the Gompertz distribution was selected for PFS as it had the best visual fit for both osimertinib and PDC. The Weibull distribution was selected for OS as it appeared to produce the most reasonable fit to the non-parametric OS data that are currently available from the AURAext and AURA2 studies and from the IMPRESS trial. OS and PFS survival curves used in the base case are shown in Figure 4.

The median PFS and OS for osimertinib and PDC are shown in Figure 5. The data show that, compared with PDC, treatment with osimertinib results in an incremental PFS gain of 4.8 months and an incremental OS gain of 10.6 months.

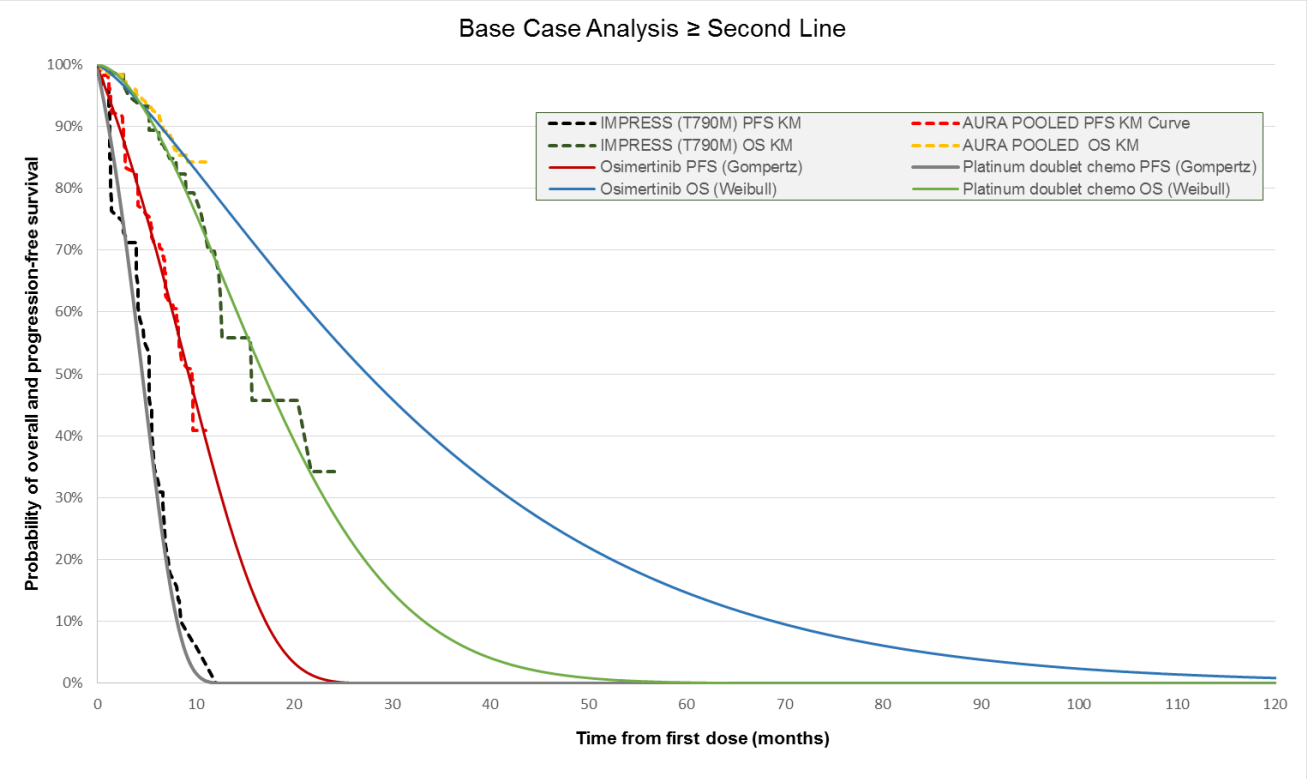


Figure 4 Overall survival and progression-free survival curves used in the base case analysis

OS=overall survival; PFS=progression-free survival; KM=Kaplan-Meier
Source: CS, Figure 5.7

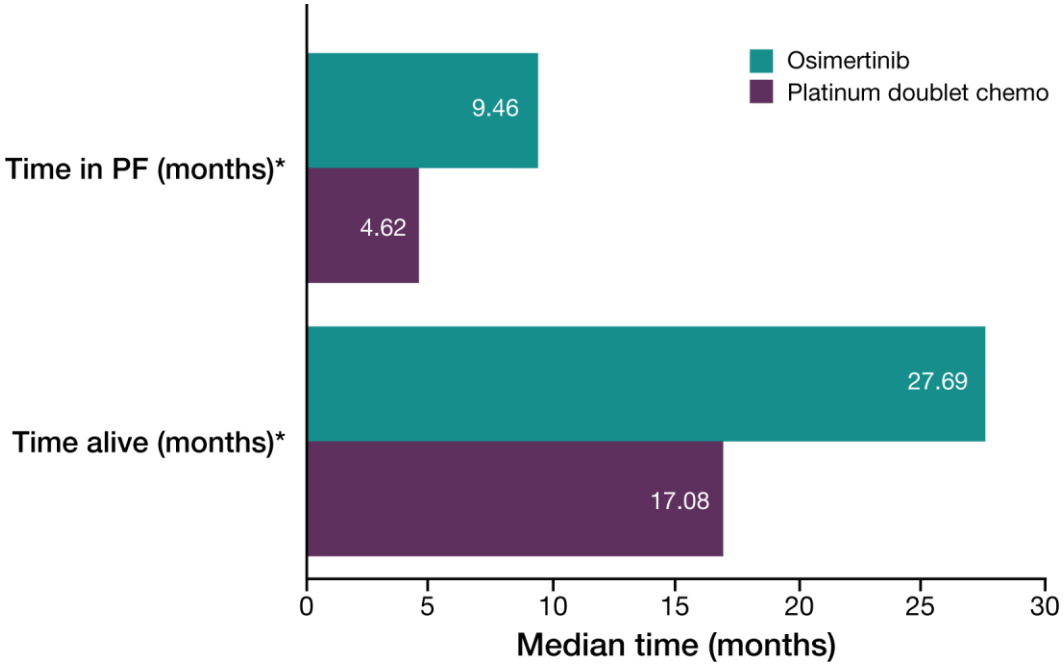


Figure 5 Median duration of the parametric distributions used in the base case analysis

PF=progression-free; *undiscounted results
Source: CS, Figure 5.8

Data from single-agent chemotherapy studies – second-line only subgroup

There are no published survival data available to demonstrate the effect of docetaxel monotherapy on patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR-TKI therapy. The company, therefore, has assumed that docetaxel has the same efficacy as pemetrexed in the second-line only setting. Data from the study by Park[29] were used in the company model; this study included 37 patients in the pemetrexed arm whose EGFR T790M mutation status is unknown.

Data from single-agent chemotherapy studies – ≥third-line only subgroup

The company used data from the Schuler[30] study in their model; in this study there were 68 patients included in the analysis. The company assumed that all single-agent chemotherapies had the same efficacy in the ≥third-line setting. The study by Shuler[30] was not specific to patients with EGFR T790M mutation-positive disease and documentation of EGFR mutation status was not mandatory prior to study entry, instead a clinically enriched EGFR inclusion criterion was used.

For simplicity, the parametric distributions selected to model PFS and OS for these subgroup analyses were the same as the distributions used in the base case analysis.

5.4.6 Health related quality of life

The original systematic review carried out by the company did not identify any HRQoL or utility studies that were relevant to the decision problem described in the final scope issued by NICE.

HRQoL data were collected using the EQ-5D-5L during the AURA2 study. As an EQ-5D-5L tariff has not been formally published or recommended by NICE, the EQ-5D-5L crosswalk index values[58] for the UK were applied. The utility values collected during the AURA2 study are shown in Table 24.

Table 24 Average EQ-5D-5L utility values for progression-free and progressed disease states from AURA2 study

Health state	N	Mean utility	Standard deviation
Base case analysis (≥second-line population)			
Progression-free	158	0.815	0.183
Post-progression	39	0.678	0.314
Second-line only population			
Progression-free	50	0.853	0.139
Post-progression	11	0.726	0.319
≥Third-line population			
Progression-free	108	0.798	0.198
Post-progression	28	0.659	0.316

Source: CS, Table 5.15

HRQoL data were collected using the EQ-5D-3L during the IMPRESS trial. The utility values collected from patients in the control arm of the IMPRESS trial are shown in Table 25.

Table 25 Average EQ-5D-3L index value from IMPRESS (control arm)

Health state	N	Mean utility	Standard deviation
Progression-free	117	0.779	0.210
Post-progression	88	0.679	0.271

Source: CS, Table 5.16

Treatment specific utility values were not used in the company base case analysis for the PF and PD health states. Instead, the company used values from the AURA2 study only. The company is confident that this is the most appropriate approach to adopt for the base case analysis. However, to test this assumption, the company applied treatment specific utility values in scenario analyses.

5.4.7 Adverse events

Utility decrements, due to grade 3 or grade 4 AEs were included in the company base case analysis. The company assumed that the disutility associated with AEs lasted for period of 4 weeks. To estimate utility decrements, the company mainly used previously published values from a study by Nafees.[59] The AE disutilities used in the company model are shown in Table 26.

Table 26 Disutilities associated with adverse events

Adverse event	Disutility	Source
Diarrhoea	0.047	Nafees 2008[59]
Rash (grouped term)	0.032	Nafees 2008[59]
Nausea	0.048	Nafees 2008[59]
Fatigue/asthenia	0.073	Nafees 2008[59]
Vomiting	0.048	Nafees 2008[59]
Febrile neutropenia	0.090	Nafees 2008[59]
Neutropenia/Leucopenia/ neutrophil count decreased	0.090	Nafees 2008[59]
Febrile neutropenia	0.090	Nafees 2008[59]
Anaemia	0.073	Assumed to be same as fatigue/asthenia
Platelet count decreased	0.05	Assumption based on previous STA[56]
Oedema peripheral	0.05	Assumption
Constipation	0.05	Assumption
Cough	0.05	Assumption
Stomatitis	0.05	Assumption
Headache	0.05	Assumption
Back pain	0.05	Assumption

Source: CS, Table 5.18

In the model, AEs were entered as one-off events. The costs of the AEs used in the model are listed, with sources, in Table 27.

Table 27 Cost of adverse events

Adverse event	Cost	Source/comment
Diarrhoea	£431.54	NHS Reference Costs 2014–15[60] FZ36G-FZ36Q Gastrointestinal Infections with Multiple Interventions – Non-elective short stay (Weighted Average) [NHS 2015]
Rash (grouped term)	£435.92	NHS Reference Costs 2014–15[60] JD07A-JD07K Skin Disorders with Interventions – Non-elective short stay (Weighted Average) [NHS 2015]
Nausea/vomiting	£449.94	NHS Reference Costs 2014–15[60] FZ91A-FZ91M Non-Malignant Gastrointestinal Tract Disorders with Multiple Interventions – Non-elective short stay (Weighted Average) [NHS 2015]
Decreased appetite	£83.00	NHS Reference Costs 2014–15[60] Assumed one outpatient dietician visit [NHS 2015]
Platelet count decreased	£502.63	NHS Reference Costs 2014–15 [60] SA12G-SA12K Thrombocytopenia – Non-elective short stay (Weighted Average) [NHS 2015]
Neutropenia/ leucopenia/ neutrophil count decreased	£478.31	NHS Reference Costs 2014–15[60] SA35A-SA35E Agranulocytosis – Non-elective short stay (Weighted Average) [NHS 2015]
Fatigue/asthenia/anaemia	£610.63	NHS Reference Costs 2014–15[60] SA01G-SA01K Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia – non-elective short stay (Weighted Average) [NHS 2015]
Oedema peripheral	£365.66	NHS Reference Costs 2014–15[60] WH10A-WH10B Unspecified Oedema – Non-elective short stay (Weighted Average) [NHS 2015]
Constipation	£0.00	Assumed to be zero cost
Cough	£0.00	Assumed to be zero cost
Stomatitis	£0.00	Assumed to be zero cost – as per ipilimumab TA319[61] NICE submission [NICE 2014]
Headache	£0.00	Assumed to be zero cost – as per ipilimumab TA319[61] NICE submission [NICE 2014]
Febrile neutropenia	£2,426.86	NHS Reference Costs 2014–15[60] SA35A-SA35E Agranulocytosis – Non-elective long stay (Weighted Average) [NHS 2015]
Back pain	£421.67	NHS Reference Costs 2014–-15[60] HC32H-HC32K: Low Back Pain Without Interventions – Non-elective short stay (Weighted Average) [NHS 2015]

Source: CS, Table 5.30

5.4.8 Resources and costs

EGFR T790M mutation testing

It is assumed in the model that only identified EGFR T790M mutation-positive patients are treated with osimertinib. In the CS, the company describes four possible testing strategies:

1. tissue biopsy
2. ctDNA (plasma) test followed by tissue biopsy in patients identified as being EGFR T790M negative by ctDNA (plasma) test
3. ctDNA (plasma) test alone
4. tissue biopsy followed by ctDNA (plasma) test.

EGFR T970M incidence and test sensitivity and specificity of all four tests are presented in the CS (Table 5.19). In addition, the EGFR T790M diagnostic strategy outputs are also reported in the CS (Table 5.20). However, only testing strategies 1 and 2 are considered in the base case analysis where the company assumes that 20% of patients undergo tissue biopsy alone and 80% undergo ctDNA (plasma) test followed by tissue biopsy. The same diagnostic strategies, incidence and test performance estimates apply in all scenario analyses.

The cost of EGFR T790M mutation testing includes the acquisition cost of the test plus other costs that are incurred during the visit to undertake the test (Table 28).

Table 28 EGFR T790M test costs

Resource	Tissue biopsy	ctDNA	Source/Comment
Test cost	£147	£147	Tissue biopsy: based on cost of cobas EGFR Test[62] ctDNA: assumed to be same as tissue biopsy
Sample procedure	£578	£325	Tissue biopsy: £578 NHS Ref Costs: DZ70Z Endobronchial Ultrasound Examination of Mediastinum[60] ctDNA: assumption
Total cost	**£725**	**£472**	**Total costs applied in the model**

Source: CS, Table 5.21

Drug acquisition costs of initial treatment

The treatment dosing, administration and drug acquisition costs used in the model are shown in Table 29. At the discretion of the investigators, patients could continue to receive osimertinib beyond disease progression. The dosages for pemetrexed+cisplatin and docetaxel monotherapy are based on average patient characteristics, in terms of body weight, BSA and glomerular filtration rate, of patients included in the AURAext and AURA2

studies. The base case analysis uses patient characteristics from all of the patients in the AURAext and AURA2 studies, whilst data from the second-line only and ≥third-line subgroups are used in the subgroup analyses. The patient characteristics used to inform drug acquisition costs are presented in the CS (Table 5.22). Treatment dosing, administration and acquisition costs are presented in Table 29.

Table 29 Treatment dosing, administration and drug acquisition costs used in the model

		Osimertinib	PDC		Docetaxel monotherapy
			Pemetrexed	Cisplatin	
Label information	Admin method	Oral	IV	IV	IV
	Dose per admin	78.9mg	500mg/m^2	75mg/m^2	75mg/m^2
	Frequency	Once daily	Once every third week		
	Duration	TDP	TDP or maximum 6 doses		
Package information	Formulation	80mg	100mg	1mg	20mg/ml
	Pack size	30	1	10	7
	Price	£4722	£160.00	£3.24	£20.95
Dosing used in model	Required dose	80mg	840mg/m^2	126mg/m^2	126mg/m^2
	Vials/caps per admin (with waste)	1.00	9.00	13.00	1.00
	Vials/caps per admin (without waste)	1.00	8.40	12.59	0.90

PDC=platinum doublet chemotherapy; TDP=treatment until disease progression; admin=administration
Source: CS, Table 5.23 and BNF 2015; eMIT (accessed January 2016)

Drug administration costs

For osimertinib (oral medication), administration costs were assumed to be £0. The drug administration costs for all intravenous therapies comprise the costs of chemotherapy infusion and premedication with dexamethasone. In the model, administration costs are applied to all patients on treatment and are shown in Table 30.

Table 30 Unit costs, resource use and total administration costs used in the model

Treatment	Cost item	Unit cost	Sum	Source
Platinum doublet chemotherapy	Chemotherapy IV infusion – First attendance	£239.12	£245.16	NHS Ref Costs 2015; DH 2011[60,63]
	Dexamethasone (8mg/day for 3 days)	£6.04		
	Chemotherapy IV infusion – Subsequent attendances	£326.46	£332.50	
	Dexamethasone (8mg/day for 3 days)	£6.04		
Docetaxel monotherapy	Chemotherapy IV infusion – First attendance	£239.12	£251.19	
	Dexamethasone (16mg/day for 3 days)	£12.07		
	Chemotherapy IV infusion – Subsequent attendances	£326.46	£338.53	
	Dexamethasone (16mg/day for 3 days)	£12.07		

Source: CS, Table 5.24

Drug costs

A summary of the drug monitoring costs used in the company model is shown in Table 31. Costs were taken from NHS Reference Costs (2014-15).[60] Frequencies were based on data submitted to NICE as part of the nintedanib STA submission[56] and were applied to all treatments.

Table 31 Unit costs, resource use and total weekly monitoring costs used in the model

Treatment	Cost item	Numbers per week	Unit cost	Sum
Osimertinib	–	–	–	£0.00
Platinum doublet chemotherapy	Liver function test	0.153	£7.00	£4.61
	Renal function test	0.153	£10.00	
	Complete blood count	0.667	£3.00	
Docetaxel	Complete blood count	0.667	£3.00	£2.00

Source: CS, Table 5.25

Subsequent treatment costs

The company assumes that patients who progress whilst on treatment with second-line osimertinib will subsequently be treated with PDC and then with single-agent pemetrexed or docetaxel. The company assumes that patients who progress on second-line PDC will subsequently be treated with single-agent chemotherapy and then with best supportive care. In the model the distribution of patients across subsequent treatments for each second-line treatment is based on UK clinical expert opinion. The duration of all subsequent treatments is assumed to be the same as the modelled duration of the second-line treatment. The cost of subsequent treatment is applied as a one-off cost for all patients entering the PD state (Table 32).

Table 32 Distribution and costs of subsequent treatment

To ↓ / From →	Osimertinib	PDC	Docetaxel
Base case analysis (≥2nd-line) and 2nd-line only subgroup			
Platinum doublet chemotherapy	80%	0%	0%
Docetaxel monotherapy	50%	50%	15%
Best supportive care	70%	50%	85%
Total	200%*	100%	100%
≥3rd-line subgroup			
Platinum doublet chemotherapy	0%	N/A	0%
Docetaxel monotherapy	50%	N/A	15%
Best supportive care	50%	N/A	85%
Total	100%	N/A	100%
Total cost per patient on subsequent treatment (≥second-line)	£7,304	£609	£183

PDC=platinum doublet chemotherapy
*Note that total proportion for osimertinib is 200% in 2L or ≥2L setting to reflect that patients will have two subsequent treatments following progression on osimertinib treatment
Source: CS, Table 5.26

Health state unit costs and resource use

In the CS (Tables 5.27 and 5.28), the company gives a detailed summary of the costs and resource use associated with disease management in the PF and PD health states. In addition, the company provides a breakdown of a one-off 'end of life/terminal care' cost that is applied in the model (CS, Table 5.29). In summary, the total weekly cost of disease management in the PF and PD health states is £77.42 and £139.52 respectively. The overall weighted 'end of life/terminal care' cost is £3,905.26.

5.4.9 Cost effectiveness results

Total costs, life years gained (LYG), QALYs and incremental costs per QALY gained for the cost effectiveness comparison of treatment with osimertinib versus PDC are shown in Table 33. In the base case, osimertinib generates more benefits than PDC [redacted]LYG and +[redacted] QALYs) at an increased cost of [redacted]. The company base case incremental cost effectiveness ratio (ICER) for osimertinib versus PDC is [redacted] per QALY gained.

Table 33 Base case results

Technologies	Total costs	Total LYG	Total QALYs	Δ Costs	Δ LYG	Δ QALYs	ICER per QALY gained
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]	[redacted]				

PDC=platinum doublet chemotherapy; Δ=change; LYG=life years gained; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio
Source: CS, Table 5.32

5.4.10 Sensitivity analyses

Deterministic sensitivity analyses

The company undertook one-way sensitivity analyses by varying key model parameters by +/- 20% around the mean values applied in the base case. The results of these analyses are shown in Table 34 and Figure 6.

The results show that the ICER per QALY gained is most sensitive to the utility values used in the model, particularly for the PD state. In addition, the model is sensitive to the choice of discount rate.

Table 34 Results of deterministic sensitivity analysis – osimertinib vs PDC

Parameter		Parameter values			Lower value (ICER)	Upper value (ICER)
		Lower value	Base case	Upper value		
Body surface area (m²)		1.34	1.68	2.02	[redacted]	[redacted]
Discount rate	Costs	0.0%	3.5%	[redacted]	[redacted]	[redacted]
	Outcomes	0.0%	3.5%	[redacted]	[redacted]	[redacted]
Disease management	PF	£62	£77	[redacted]	[redacted]	[redacted]
	PD	£112	£140	[redacted]	[redacted]	[redacted]
	TC	£3,124	£3,905	[redacted]	[redacted]	[redacted]
Drug acquisition cost: PDC		£369	£461	£554	[redacted]	[redacted]
Drug acquisition cost: Docetaxel		£5	£6	£8	[redacted]	[redacted]
Testing cost	ctDNA	£378	£472	[redacted]	[redacted]	[redacted]
	Biopsy	£752	£940	[redacted]	[redacted]	[redacted]
Health state utility	Osimertinib: PF	0.652	0.815	[redacted]	[redacted]	[redacted]
	Osimertinib: PD	0.542	0.678	[redacted]	[redacted]	[redacted]
	PDC: PF	0.652	0.815	[redacted]	[redacted]	[redacted]
	PDC: PD	0.542	0.678	[redacted]	[redacted]	[redacted]

PF=progression-free; PD=progressed disease; TC=terminal care; PDC=platinum doublet chemotherapy; ICER=incremental cost effectiveness ratio
Source: CS, Table 5.39

Figure 6 Tornado diagram – osimertinib versus PDC

Source: CS, Figure 5.11

Probabilistic sensitivity analysis

The company undertook a probabilistic sensitivity analysis (PSA) to derive the mean ICER per QALY gained for the comparison of osimertinib versus PDC. The PSA was run for 10,000 iterations. Results from the PSA are shown in Table 35. The probabilistic ICER per

QALY gained for osimertinib versus PDC is [redacted], which is comparable to the deterministic ICER per QALY gained of [redacted].

Table 35 Average results based on the probabilistic sensitivity analysis (10,000 iterations)

Treatment	Total costs	QALYs	Δ costs	Δ QALYs	ICER per QALY gained
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]			

Δ= change; PDC=platinum doublet chemotherapy; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio
Source: CS, Table 5.37

The cost effectiveness plane and cost effectiveness acceptability curve for the comparison of osimertinib versus PDC are shown in Figure 7 and Figure 8.

At a cost effectiveness threshold of £50,000 per QALY gained osimertinib has a 35% probability of being cost effective compared with PDC. At a cost effectiveness threshold of £30,000 per QALY gained osimertinib has a <2% probability of being cost effective compared with PDC.

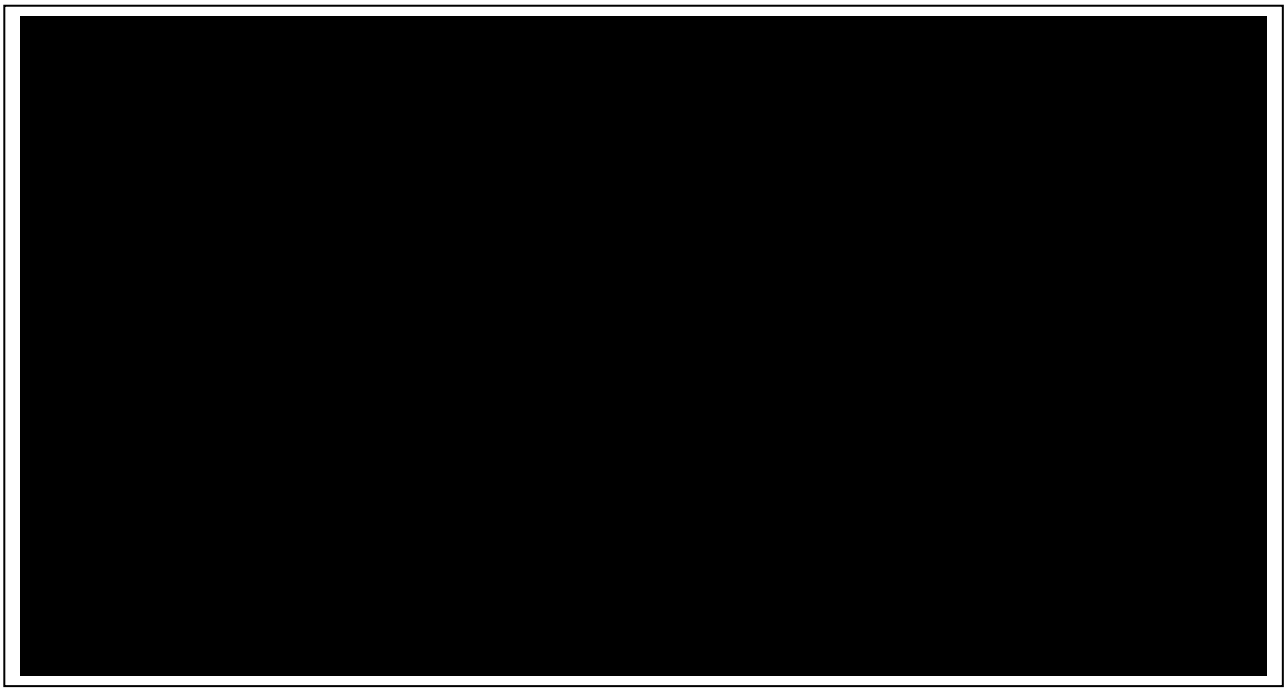


Figure 7 Cost effectiveness plane for osimertinib versus PDC

Source: CS, Figure 5.9

Figure 8 Cost effectiveness acceptability curve for osimertinib versus PDC

Source: CS, Figure 5.10

5.4.11 Scenario analyses

The company undertook several scenario analyses to explore alternative approaches to: survival modelling, as well as different values for health state utilities, resource use and costs. Full descriptions of the scenario analyses undertaken by the company are described in Section 5.8.3 of the CS. The results of the scenario analyses for osimertinib versus PDC are shown in Table 36.

Table 36 Results of scenario analyses for osimertinib versus PDC

Scenario	Total costs (£)		Total QALYs		Incremental		ICER per QALY gained
	Osimertinib	PDC	Osimertinib	PDC	Costs	QALYs	
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival modeling							
IMPRESS ITT population PFS/OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS & OS distribution – Log logistic (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS & OS distribution – Log normal (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS & OS distribution – Weibull (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS & OS distribution – Generalised Gamma (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS & OS distribution – Gompertz (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS & OS distribution – exponential (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state utility values							
Treatment-specific utilities (osimertinib/AURA; PDC/IMPRESS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD utility decrement (Nafees[59]): -0.1798 (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Resource use and costs							
Exclude T790M test costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment after RECIST progression - osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Assume pemetrexed generic costs (75% discount)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PD=progressed disease; PFS=progression-free survival; OS=overall survival; PDC=platinum doublet chemotherapy; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year gained; ITT=intention to treat
Source: CS, Table 5.40

5.4.12 Subgroup analyses

To explore the cost effectiveness of osimertinib compared with other the comparators listed in the final scope issued by NICE, the company performed three main separate subgroup analyses:

- osimertinib versus PDC in a second-line population only
- osimertinib versus docetaxel monotherapy in a second-line population only
- osimertinib versus single agent chemotherapy in a ≥third-line population only.

In each of the subgroup analyses, the following parameters were dependent on line of treatment: patient demographics (CS, Table 5.22), survival data (CS, Section 5.3), safety (CS, Table 5.14) and subsequent treatments (CS, Table 5.26).

Osimertinib versus PDC in a second-line population only

Using data specific to the second-line only population of the AURAext and AURA2 studies (for osimertinib) and data from the IMPRESS trial (for PDC), the ICER per QALY gained for osimertinib versus PDC is [redacted] as shown in Table 37. When health state utility values from the AURA2 study were applied to both treatment arms for the second-line only population, the ICER per QALY gain decreased slightly to [redacted].

Table 37 Subgroup analysis – osimertinib versus PDC (second-line only population)

Treatment	Total cost	Total QALYs	Δ costs	Δ QALYs	ICER per QALY gained
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PDC	[redacted]	[redacted]			

Δ=change; PDC=platinum doublet chemotherapy; QALY=quality adjusted life years; ICER=incremental cost effectiveness ratio
Source: CS, Table 5.42

Osimertinib versus docetaxel monotherapy in a second-line population only

Using data specific to the second-line only population of the AURAext and AURA2 studies (for osimertinib) and data from the study by Park[29] (for single-agent docetaxel), the ICER per QALY gained for osimertinib versus docetaxel is [redacted] as shown in Table 38. When health state utility values from the AURA2 study were applied to both treatment arms for the second-line only population, the ICER per QALY gain decreased slightly to [redacted].

Table 38 Subgroup analysis – osimertinib versus docetaxel monotherapy (second-line only population)

Treatment	Total cost	Total QALYs	Δ costs	Δ QALYs	ICER per QALY gained
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]			

Δ=change; QALYS=quality adjusted life years; ICER=incremental cost effectiveness ratio
Source: CS, Table 5.43

Osimertinib versus single agent chemotherapy in a ≥third-line population only

Using data specific to the ≥third-line only population of the AURAext and AURA2 studies (for osimertinib) and data from the study by Shuler[30] (for single-agent docetaxel), the ICER per QALY gained for osimertinib versus single agent chemotherapy is [redacted] as shown in Table 39. When health state utility values from the AURA2 study for the ≥third-line population were applied to both treatment arms, the ICER per QALY gain increased slightly to [redacted]

Table 39 Subgroup analysis – osimertinib versus single agent chemotherapy (≥third-line population)

Treatment	Total cost	Total QALYs	Δ costs	Δ QALYs	ICER per QALY gained
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Single agent chemotherapy	[redacted]	[redacted]			

Δ=change; QALYS=quality adjusted life years; ICER=incremental cost effectiveness ratio
Source: CS, Table 5.4

5.4.13 Model validation and face validity check

In order to validate the de novo cost effectiveness analysis, the company carried out the following checks:

1. the predicted model outcomes for the base case analysis were compared to the observed pooled AURA dataset to confirm that the model behaved as expected and produced PFS and OS curves similar to the observed data

2. as it was not possible to verify predicted long-term outcomes due to the absence of external long-term data, the company analysed the relationship between PFS and OS data from other trials in advanced NSCLC to check if the company model estimated a ratio of OS to PFS that could be considered to be clinically plausible. The results from these analyses are available in the CS (Table 5.47).

In summary, the company is confident that the base case cost effectiveness estimates generated by the model are valid and are unlikely to be biased in favour of osimertinib.

5.5 ERG critique of company's submitted economic evaluation

5.5.1 NICE reference case checklist

Table 40 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Defining the decision problem	The scope developed by NICE	Yes – although first-line patients were included in the scope, the ERG agrees with the company that these comprise a very small number of patients. The ERG considers that there is insufficient evidence of the clinical effectiveness of osimertinib in a first-line setting to include these patients in this economic evaluation
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Partial. The model only includes NHS costs. Personal Social Service costs have not been considered
Perspective on costs	NHS and PSS	Patient related direct health effects are considered. No impact on carers has been considered in the model
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes – 15 year time horizon
Synthesis of evidence on health effects	Based on systematic review	Yes
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Partially – crosswalk values used for EQ-5D-5L
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and effects (currently 3.5%)	Yes

EQ-5D-5L=EuroQol-5 dimension, 5 levels; QALY=quality adjusted life year

5.5.2 Drummond checklist

Table 41 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partial	The immaturity of the OS data means that currently no statistically significant evidence exists that the treatment extends OS. However, a PFS benefit is statistically significant.
Were all the important and relevant costs and consequences for each alternative identified?	Partial	The ERG considers that the company should have included more detail relating to adverse events in their model
Were costs and consequences measured accurately in appropriate physical units?	Partial	The ERG revised the following parameter estimates in the company's model: utility values, treatment costs and administration costs
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	However, discounting was applied weekly rather than annually
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Partial	Deterministic and probabilistic sensitivity analyses were undertaken. Further scenario analyses were required to test the key assumptions in the model
Did the presentation and discussion of study results include all issues of concern to users?	No	Key scenario analyses were not undertaken – notably around time on treatment and the efficacy of treatment being limited to a change in PFS - and therefore the results were not presented

OS=overall survival; PFS=progression-free survival; ERG=Evidence Review Group

5.6 Detailed critique of company's economic model

Sections 5.6.1 to 5.6.5 of the ERG report provide details of five issues that have a major impact on the cost effectiveness results generated by the company model (i.e., estimation of OS, estimation of PFS, cost of osimertinib therapy, QoL and cost of administering osimertinib). Issues that only have a minor impact on the cost effectiveness results are described in Section 5.6.6.

The company provided the model in Microsoft Excel. The ERG considers that it was well constructed with no flaws in the algorithms and was straightforward to use.

5.6.1 Overall survival estimation

Company model results for the comparison of osimertinib versus PDC suggest that over 90% of the QALY gains associated with treatment with osimertinib are generated after 10 months, i.e. during the period when no trial data on osimertinib are available. This means that confidence in the results generated by the company model is highly dependent on the degree to which the projection of osimertinib OS employed in the company model, past the point trial data for osimertinib is available, reflects reality.

The company considered a range of distributions to model OS for both osimertinib and PDC with each distribution used to represent OS over the whole model time horizon (15 years). The company first used statistical tests (AIC and BIC) to help choose a distribution to represent OS. The ERG notes that AIC and BIC do not provide an indication that a particular distribution has an acceptable goodness of fit or, indeed, they do not identify the extent to which one distribution may fit the data better than another. However, the company's choice of distribution was also influenced by visual inspection, as well as a discussion around clinical plausibility. The ERG, therefore, considers that the company's approach to selecting a distribution to represent OS for both osimertinib and PDC was broadly acceptable given the paucity of relevant survival data available – especially for osimertinib. The ERG also notes that it would have been preferable to use all of the available clinical trial data before employing the statistical distribution, rather than using the company's choice of distribution over the whole time horizon. However, in this case, given that the trial data are only available for 10 months for osimertinib, the ERG considers that using actual OS data before employing a distribution would have made an insignificant impact on the cost effectiveness results.

Whilst the approach employed by the company to select a parametric model to represent OS is satisfactory for both osimertinib and PDC, the ERG considers there are a number of

issues that cast substantial doubt on the plausibility of the OS projections for osimertinib and, to a lesser extent but still significantly, for PDC in the company model.

Lack of statistical evidence of differential OS

Any extrapolation beyond the period for which trial data are available is implicitly based on the assumption that the OS associated with osimertinib treatment is different from the OS associated with PDC treatment, and that such a difference is shown to exist within the period during which trial data are available.

Table 4.14 in the CS reported an OS hazard rate for the adjusted analysis of [redacted]

To further explore the potential statistical difference in OS between osimertinib and PDC, the ERG requested K-M OS data from the IMPRESS trial and the two AURA studies as part of the clarification process. ERG analyses of these data show that there is no statistically significant difference between the (pooled) K-M OS data for patients with EGFR T790M mutations participating in the two AURA studies and the K-M OS data for patients with EGFR T790M mutations included in the control arm of the IMPRESS trial (Log-rank test, p=0.33). This indicates that there is no statistical evidence that the two K-M data sets were derived from patients with different OS.

With no statistically significant evidence of difference in OS between osimertinib and PDC during the period that trial data are available, the ERG considers that there is no statistical justification to support the use of different OS projections for osimertinib and PDC.

Proportion of benefit arising from extrapolation

The ERG considers that any ICER that relies on a QALY benefit that is over 90% generated by a projection is highly uncertain and that this level of uncertainty renders its use in decision-making questionable. The ERG considers that statistical and modelling techniques can only be employed to help describe this uncertainty and cannot be used to overcome it. Whilst OS data for PDC from the IMPRESS trial are more mature than the OS data for osimertinib (approximately 33% for PDC compared to 12.7% for osimertinib), the ERG considers the projections of OS for PDC to be only slightly less uncertain than for osimertinib.

The ERG applauds the company for investigating this uncertainty and for demonstrating how this uncertainty affects the size of the estimated ICERs. For example, in the CS (p234), the company provides the results of a scenario analysis where the use of different projection

methods is investigated. The cost effectiveness results vary depending on the method used. For example, using a Log normal distribution for PFS and OS generates an ICER per QALY gained of [redacted] whereas using a Gompertz distribution for PFS and OS generates an ICER per QALY gained of [redacted].

The ERG considers that all of the distributions that were used in the scenario analysis can, visually, be considered to provide a good fit to the available osimertinib OS K-M data. However, the ERG is not confident that any of the ICERs generated by the company model are sufficiently robust to inform decision-making.

Company acknowledgement of weakness of OS data

As part of the clarification process the ERG requested post-progression survival (PPS) and post-treatment discontinuation survival data (PTDS). The company did not supply these data, in part because the data were too immature. The exact response from the company was:

> *We believe that there are likely to be significant issues with the interpretation of these time-to-event outcomes due to the immaturity of currently available data and the high level of censoring of patients in the post-progression period from AURAext/2.* (Source: Company clarification response. QB1)

Patients who die before progression, or who die before treatment discontinuation, are considered to be in the PPS state and treatment is discontinued at the point of death. The ERG considers that the maturity of the PPS and PTDS data, and the level of censoring are, therefore, identical to the maturity and censoring of the OS data sets for the two AURA studies and the IMPRESS trial. This point is also highlighted in the CS where the following statement is made about the limitations of the current evidence base:

> *While confidence regarding the analyses of the primary endpoints of ORR, secondary endpoints of PFS and safety/tolerability assessments can be considered high, caution should be exercised when interpreting the results of the OS analyses. The OS data are very immature at the time of analysis (Osimertinib 11.5% maturity [adjusted analysis, n=287] and platinum doublet chemotherapy 29.4% maturity [adjusted analysis, n=51]). Consequently in the matched adjusted comparison in both groups the KM risk set beyond 12 months is very limited (n <15 patients) leading to unstable estimates beyond this time point, especially for the estimation of medians.* (Source: CS, p164)

In summary, the ERG agrees with the company that the OS, PPS and PTDS data from the pooled AURA dataset and the IMPRESS trial are immature and should be interpreted with caution.

Weak link between PFS and OS

The company presents data on time spent in the PFS and OS states, as predicted by the company model, as a means of justifying the distribution chosen to represent OS (CS, Table 5.47). The ERG acknowledges that the ratio of time in OS to PFS predicted by the company model is similar for patients treated with osimertinib (2.85) and for patients treated with PDC (2.96), and is within the range of ratios observed in other trials for patients receiving other second-line treatments. However, the reported range across studies is large (between 2.18 and 5.38 for active treatment arms and 2.24 and 7.60 in control arms), which suggests that the relationship between OS and PFS is complex and that there is no basis to assume that the same, or similar, OS/PFS ratios exist. This view is supported by the authors of a DSU[57] report that contains details of a literature review that was undertaken to examine the relationship between PFS and OS in people with advanced or metastatic cancers. The authors found that the evidence supporting a relationship between PFS and OS varies considerably by cancer type and, furthermore, is not always even consistent within one cancer type. In addition, they advise that:

> *…any cost-effectiveness analysis which makes a strong assumption regarding the relationship between PFS and OS should be treated with caution.* (Source: DSU report,[57] p39)

Generalisability of trial data to the UK population

Aside from concerns about the reliability of the OS representation of both osimertinib and PDC within the company model, the ERG considers that, even if the OS data were fully mature, they would not reflect the experience of the population described in the final scope issued by NICE. This is because the populations included in the two AURA studies and the IMPRESS trial have a baseline ECOG PS of 0 or 1 and, in the two AURA studies, have received at least one (and up to 14) previous lines of treatment. Clinical advice to the ERG is that only about 40% of NHS patients with advanced NSCLC are likely to have an ECOG PS of 0 to 1. Furthermore, very few NHS patients with metastatic NSCLC receive even three lines of treatment and, at the most, 30% of patients whose cancer progresses on or following treatment with an EGFR-TKI are well enough to receive chemotherapy.

The absence of trial data on patients with ECOG PS ≥2 and on patients who are too unwell to receive chemotherapy means that the impact of osimertinib or PDC in a UK population

who would be eligible for treatment under the final scope issued by NICE is not fully known. However, the ERG considers that the OS of a population that is less well than the populations included in the two AURA studies and in the IMPRESS trial is likely to be shorter than the OS demonstrated by the aforementioned trials.

5.6.2 Progression-free survival estimation

The PFS K-M data from the two AURA studies and the EGFR T790M mutation-positive population included in the control arm of the IMPRESS trial are statistically significantly different (Log-rank test, $p<0.001$). There is, therefore, statistical justification to assume differential PFS for osimertinib and PDC over the period for which IPD are available, and then to extrapolate the difference past that time point. This approach should only be carried out if acknowledging that the PFS data from a single arm phase II study (such as the AURA2 study) have greater potential for bias than the PFS data from a phase III RCT (such as the IMPRESS trial). The ERG considers that the projections employed by the company should be considered with a degree of caution.

As was the case when considering the projection of OS, PFS data were incorporated into the company model through the use of parametric curves estimated from the available PFS data from the two AURA studies and from the subgroup of patients with EGFR T790M mutations in the control arm of the IMPRESS trial. The ERG considers that whilst the company's approach to parametric model selection is broadly acceptable, it is preferable if IPD can be incorporated directly into a model where it is available and that a parametric curve should only be employed when those data become unavailable or unreliable. However, in this case, the trial data so closely match the curves chosen by the company that implementation of the available K-M data prior to introducing a parametric survival curve, rather than using the parametric model from time zero, does not result in a significant change to the size of the ICERs generated by the company model. In fact, using K-M data in the model followed by the extrapolations suggested by the company leads to a change in the incremental QALYs of just [redacted] and an increase in the ICER per QALY gained for the comparison of osimertinib with PDC of [redacted] (an increase of approximately [redacted]. The ERG, therefore, considers that the method employed within the company model to represent PFS is, in this instance, satisfactory.

In summary, the results of analyses carried out by the ERG demonstrate that, when comparing the survival of patients receiving osimertinib with the survival of patients receiving PDC, there is no statistically significant difference between available K-M OS data but there is a statistically significant difference between available K-M PFS data. The ERG has carried out a scenario analysis that reflects this, i.e. differential PFS between osimertinib and PDC

but OS equal to that modelled by the company for PDC (due to the slightly greater maturity of the data from EGFR T790M mutation-positive patients in the control arm of the IMPRESS trial compared to the AURA studies). This analysis generates incremental QALYs of [redacted] and an ICER of [redacted] per QALY gained.

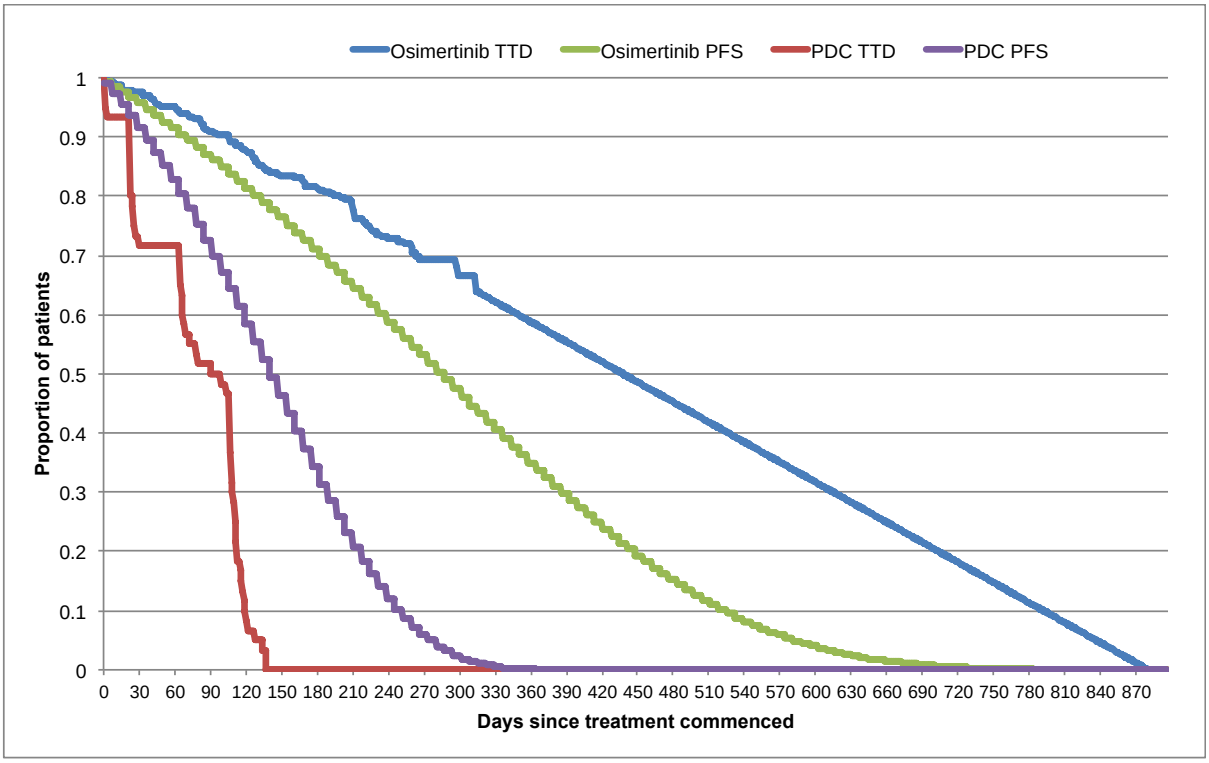
5.6.3 Cost of osimertinib treatment

In the two AURA studies, patients were permitted to continue receiving osimertinib after disease progression. As such, PFS is not a good basis for estimating treatment cost. As part of the clarification process, the ERG requested TTD data from the two AURA studies and for the EGFR T790M mutation-positive patients in the control arm of the IMPRESS trial. The pooled TTD data from the two AURA studies were 36% mature, with the last event recorded on day 313. The TTD data from EGFR T790M mutation-positive patients in the control arm the IMPRESS trial were 100% mature.

ERG analysis of the TTD data from the two AURA studies showed that they followed a simple linear decline. The ERG estimated the linear trend between days 0 and 313 and then continued the trend after day 313 to estimate TTD beyond the point that data were available. This resulted in an estimate of all patients stopping treatment with osimertinib by day 880, or around 2.5 years. If the hazard rate were to become constant at any point past day 313 then the TTD data would follow an exponential curve. If an exponential curve were used, it is likely that there would be a longer tail of patients remaining on treatment than is suggested by the linear projection of TTD with resultant higher costs for osimertinib.

The cost of PDC treatment is primarily driven by PFS status but is limited to a maximum number of four cycles of treatment in the model to match the protocol for pemetrexed-cisplatin therapy. The TTD data from the EGFR T790M mutation-positive patients in the control arm of the IMPRESS trial are complete and have been used, by the ERG, directly in the company model to generate an alternative estimate of the cost of treatment with PDC instead of using PFS as in the company base case.

A comparison of TTD and PFS data using pooled data from the two AURA studies (osimertinib) and data from the EGFR T790M mutation-positive patients included in the control arm (PDC) of the IMPRESS trial is displayed in Figure 9.



TTD=time to treatment discontinuation; PFS=progression-free survival; PDC=platinum doublet chemotherapy
Source: ERG analyses using TTD data requested via clarification process

Figure 9 TTD as estimated by the ERG and PFS as in the company model

5.6.4 Health related quality of life

The utility values used in the company's base case are taken directly from the AURA2 study. The figures used in the company model are 0.815 for the PF state and 0.678 for the post-progression state. These figures are the same, irrespective of whether patients are treated with osimertinib or PDC. The ERG considers that these values may not represent the HRQoL of the population with EGFR T790M disease treated in the NHS in a second-line setting as:

- the health states were taken from patients who were not from the UK
- the ECOG PS of patients was 0 or 1. According to clinical advice to the ERG, this would not be the case for a UK population where a number of patients with ECOG PS ≥2 would be treated.

In addition, there are several other factors that cast doubt on the validity of the utility values used in the company model:

- the HRQoL tool used in AURA2 was the EQ-5D-5L questionnaire and, as acknowledged within the CS (p205), this tool does not yet have a validated health state valuation set for the UK
- the mean utility value of people aged 55-64 in the UK is 0.80.[64] Whilst this mean utility value includes some people who are very ill, it seems implausible that a patient with advanced NSCLC will have a higher utility value (0.815) than the average person in the UK who is of a similar age.

There are no published alternative utility values that relate explicitly to the population of interest. On balance, the ERG considers that there are two studies that provide utility values that could be closer to the real utility of the target population than those in used in the company model: utility values collected during the LUME-Lung 1[65] trial and utility values reported in the Nafees study.[59]

The LUME-Lung 1[65] trial compares treatment with nintedanib+docetaxel with placebo+docetaxel in a population of previously treated patients with locally advanced or metastatic NSCLC (adenocarcinoma tumour histology). The utility values collected during the trial (and used in the STA[56]) range from 0.66 to 0.71 for patients in the PF state, whilst 0.64 is used to represent the utility of patients in the post-progression state. The population in the LUME-Lung 1[65] trial was slightly younger than the population in the AURA2 study (58 vs 62 years) and included fewer patients with brain metastases (10% vs 40%).

In the CS for the appraisal of nintedanib,[56] a range of utility values, adjusted for ECOG PS and brain metastases, are reported over a period of 30 weeks for patients in the PF state. The ERG considers that the midpoint value at 15 weeks (0.687) is a fair value to use to represent utility whilst in the PF state and has, therefore, used this value, along with the value of 0.64 to represent utility in the post-progression state.

The ERG considers that figures collected during the LUME-Lung 1[65] trial are likely to provide inaccurate utility estimates, especially for patients in the post-progression state where utility for (potentially) several years is derived at, or shortly after, the point of disease progression. In addition, the population included in the LUME-Lung 1[65] trial is, on average, likely to be healthier than patients with advanced or metastatic NSCLC being treated on or after failure of a TKI (e.g., LUME-Lung 1[65] trial patients had fewer brain metastases than patients in the AURA studies).

The ERG has also explored the impact on QALYs and ICERs of using lower utility values as provided in the Nafees[59] study. Nafees[59] estimated a utility value from a general population

assessment of NSCLC health states using the standard gamble method. The resultant figures are 0.653 for stable disease and 0.47 for progressed disease. Whilst valuations of health states from Nafees[59] are taken from the general population, the health states themselves were not taken from patients but are simple descriptors based upon breast cancer health states. A single 'stable' and 'progressed' state was also described rather than the range of health states that would be experienced by patients in PF and post-progression states. As such, the Nafees[59] values are also flawed but they do provide an alternative estimation of ICERs and it is possible that they may provide a better reflection of the experience of those with advanced or metastatic NSCLC than currently available from trial data, even if the way they were derived was not robust.

The impact on QALYs and resultant ICERs from the use of the different utility values considered by the company and by the ERG is summarised in Table 42.

Table 42 Utility values applied in company model and considered by ERG with resultant ICERs

Source	Patient population	Utility elicitation tool	PFS	PPS	QALYs		ICER per QALY gained
					Osimertinib	PDC	
AURA2 (company base case)	Second-line NSCLC after EGFR-TKI; ECOG status 0-1; T790M patients only	EQ-5D-5L	0.815	0.678	[redacted]	[redacted]	[redacted]
LUME-Lung 1[65] (ERG preferred value)	Second-line NSCLC with PDC as first-line (96% of patients); T790M status unconfirmed; ECOG status 0-1	EQ-5D-3L	0.687	0.64	[redacted]	[redacted]	[redacted]
Nafees[59]	General UK population	Bespoke standard gamble	0.653	0.47	[redacted]	[redacted]	[redacted]

PFS=progression-free survival; PPS=post-progression survival; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
Source: CS, Table 5.17, published studies

5.6.5 Osimertinib administration cost

The company model does not include a cost for the administration of osimertinib. Clinical advice to the ERG is that osimertinib is provided, on a monthly basis, in a nurse led clinic. The 2014-15 NHS Reference Cost[60] to deliver exclusively oral chemotherapy (SB11Z, setting: "Other") is £128. This is the lowest reference cost in the Reference Cost Schedule[60] for the delivery of oral chemotherapy. There is no simple way to apply this cost to the company model so the estimated cost of administering osimertinib has been calculated using the TTD data (provided in response to an ERG request during the clarification process). The effect of introducing a cost for administering osimertinib is to increase the total

cost per patient by [redacted] and to increase the ICER for osimertinib versus PDC to [redacted] per QALY gained.

5.6.6 Minor amendments

The ERG has identified issues relating to several of the parameter values used in the company model. However, exchanging the company values for the ERG's preferred values only has a minor impact on the size of the ICERs generated by the model.

Calculation of PDC costs per dose

The PDC treatment costs used in the company base case are based upon the age, weight and gender distribution of patients in the AURA studies.

Sacco[66] identified the characteristics of UK patients receiving palliative chemotherapy. The ERG considers that the characteristics of this patient group are more likely to reflect the characteristics of NHS patients undergoing second-line therapy than the characteristics used in the company base case. The estimated values for UK lung cancer patients in this group from the study by Sacco[66] have a body weight of 63.4kg for females and 74.7kg for males, with mean body surface area (BSA) of 1.66m^2 for females and 1.89m^2 for males. Application of these values in the company model results in an ICER for the comparison of osimertinib versus PDC of [redacted] per QALY gained, [redacted] per QALY gained.

Model structure

The company has developed a partitioned survival model and this structure has been used in previous NICE appraisals[56,67] of drugs for the treatment of advanced or metastatic cancer. This structure suffers from the limitation that it produces a counterintuitive finding i.e., the less time that patients stay in the PFS state, the more cost effective the intervention becomes. This model limitation has been discussed in previous ERG reports[68,69] as being challenging as it makes exploring the impact of assumptions around PFS on the cost effectiveness results problematic. Whilst this is not a major issue in this model, as the concerns around OS dominate the uncertainty in the ICER, the impact of choice of model structure on the ability to properly explore uncertainty in model parameters and assumptions should be fully considered in the CS.

Model time horizon

The time horizon used in the company model is 15 years. The ERG considers that this is optimistic given the population described in the final scope issued by NICE and the case, put forward by the company, that the Appraisal Committee should consider osimertinib as a life-extending, End of Life treatment.[50] However, as only [redacted] of the QALY gain for patients treated with osimertinib rather than PDC is accrued between years 10 and 15, i.e. 0.7% of the total (from baseline) QALY gain, the ERG considers that whilst a 15-year time horizon is probably optimistic, its use makes an insignificant difference to the size of the ICERs generated by the company model.

Discounting method

Discounting was applied continuously after year one to each weekly cycle. This is an incorrect application of the discount rate as costs and benefits should be summed over 12 months and then the annual discount rate should be applied. The company model cannot be easily modified to apply discounting correctly; however, the ERG does not consider that correcting this error will make any noticeable difference to the size of the ICERs generated by the company model.

Adverse events

In selecting AEs, the company has focussed only on events that are classified as being ≥grade 3. According to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE),[70] a grade 3 AE is described as '*Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL. Where self-care ADL (activities of daily living) refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bed-ridden'*. Given this definition, some of the values chosen by the company appear to be arbitrary and implausible, both in terms of cost and disutility.

For example, there are zero costs associated with constipation, cough, stomatis and headache, and a low cost is associated with 'decreased appetite'. In addition, the disutility values associated with fatigue in particular and for AEs in general that would require hospitalisation appear to be low.

As osimertinib appears to be more tolerable than PDC, application of zero costs and implausibly low utility values for AEs, therefore, produces conservatively high ICERs when comparing the cost effectiveness of osimertinib and PDC. In addition, the AEs included in the company model result in £103 of additional cost, and 0.016 QALY loss, for PDC

compared to osimertinib. If all AEs were excluded from the model, then the ICER for osimertinib compared to PDC would rise by [redacted] to [redacted] per QALY gained.

In summary, the ERG considers that some of the costs and disutilities associated with AEs that are used in the company model may be unrealistic. However, as the magnitude of these parameter values only has a minor impact on the size of the ICER per QALY gained for the comparison of osimertinib versus PDC, and the approach taken by the company is conservative, the ERG has not reanalysed the ICERs using different AE costs and disutilities.

Testing costs

The ERG undertook a scenario analysis excluding testing costs for the EGFR T790M mutation. This reduced costs per patient by £1,351 thus lowering the ICER by [redacted] to [redacted] per QALY gained.

5.7 Subgroup analysis

The company undertook a number of subgroup analyses. These included considering different lines of treatment and use of docetaxel monotherapy rather than PDC.

As part of the clarification process the ERG requested OS, PFS and TTD data, by line of treatment, provided separately for the AURAext and AURA2 studies. Analyses carried out by the ERG found no statistical difference (using the Log rank test) for OS, PFS or TDD by line of treatment, irrespective of whether the data were considered by study (AURAext or AURA2) or if the pooled AURA dataset was used. As such, the ERG considers that the subgroup analyses by line of treatment, whilst correctly undertaken by the company, are not informative.

The ERG considers that the analysis of the cost effectiveness of osimertinib versus docetaxel, whilst worthy of pursuit by the company, is severely limited by the available clinical effectiveness data. In the analysis, the company has assumed that all single-agent chemotherapy drugs share equivalent efficacy that this is independent of EGFR T790M mutation status, to the point that the analysis against single agent chemotherapy (docetaxel in the company model) would be insufficiently robust even if AURA study OS data were mature.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

A summary of the impact of the ERG's amendments to the company model 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 or further line setting, after failure of an EGFR-TKI, is included in ERG=Evidence Review GroupTable 43. The ERG has only implemented changes that have a major impact on the size of the ICERs and has not included changes relating to the minor issues described in Section 5.5.6. Details of all of the Microsoft Excel revisions made by the ERG to the company model are presented in Appendix 1 (and in the associated spreadsheet).

If the company's projection of OS were replicated in the NHS, then the biggest impact on the size of the ICERs from the ERG amendments would arise from the use of more accurate costs for the acquisition and administration of osimertinib and PDC. Use of TTD data to calculate the acquisition costs of osimertinib and PDC, in combination with an administration cost for osimertinib, increases the incremental cost of osimertinib compared to PDC from [redacted] in the company base case to [redacted]. This results in an increase in the ICER from [redacted] per QALY gained (Scenario A) to [redacted] per QALY gained (Scenario B).

Changes in utility values result in smaller changes to the size of the ICERs compared to changing costs. However, these utility value changes increase the size of the ICER substantially from the company base case ICER. Applying the ERG utility amendments increases the ICER for osimertinib compared to PDC from the company base case ICER to [redacted] per QALY gained using the LUME-lung 1[65] values (R3) and [redacted] per QALY gained using the values from Nafees[59] (R4).

Applying both cost and utility changes to the company base case ICER results in ICERs of [redacted] per QALY gained using the LUME-lung 1[65] utility values (Scenario C) and [redacted] per QALY gained using the Nafees[59] values (Scenario D).

If only the improvement in PFS is modelled, with equal OS for osimertinib and PDC due to the lack of statistically significant evidence to suggest otherwise, then application of the ERG cost amendments results in an ICER of [redacted] per QALY gained (Scenario E). Application of the ERG cost and utility amendments results in an ICER of [redacted] per QALY gained using the LUME-lung 1[65] utility values (Scenario F) and [redacted] per QALY gained using the Nafees[59] values (Scenario G).

ERG=Evidence Review GroupTable 43 ERG adjustments to company base case

Model scenario and revisions	**Osimertinib**			**PDC**			**Incremental**			**ICER**	
	Cost	**QALYs**	**Life years**	**Cost**	QALYs	Life years	Cost	QALYs	Life years	**£/QALY**	**Change from base case**
A. Company's base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1) Use of TTD data to cost drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Application of administration cost for osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. Base case + (R1:R2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) LUME-Lung 1[65] utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C. Base case + (R1:R3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Nafees[59] utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
D. Base case + (R1:R2 and R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R5) Osimertinib generates a gain in PFS but not OS compared to PDC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
E. Base case + (R1:R2 and R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
F. Base case + (R1:R3 and R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
G. Base case + (R1:R2, R4:R5)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER=incremental cost effectiveness ratio; OS=overall survival; PFS=progression-free survival; PDC=platinum doublet chemotherapy; QALY=quality adjusted life year; TTD=time to treatment discontinuation

6.1 Conclusions of the cost effectiveness section

The ERG considers that there are several fundamental issues that cast doubt on the cost effectiveness results produced by the company model.

First, over 90% of the QALY benefit from osimertinib estimated from the model arises when OS trial data are no longer available. The available OS data for osimertinib and PDC are not statistically significantly different and are very immature, especially so for osimertinib. The only statistically significant evidence on effectiveness incorporated in the model is an improvement in PFS with osimertinib, the extent of which is uncertain due to the single-arm nature of the AURA studies.

The ERG considers that lack of statistical significance in OS between osimertinib and PDC during the period for which data are available means that there is no basis to project differential OS.

With such immature OS data, even if there were a statistically significant difference between osimertinib and PDC during the period that data were available, any projection could only be speculative with the degree of uncertainty in the projection impossible to quantify. For example, whether the OS curve has a multi-phase distribution, or if the phases shift post the point of data that are available, is unknown.

Even if the OS data were sufficiently mature, the populations within the AURA studies and the IMPRESS trial appear to be fitter than the patients who would be expected to be seen in routine NHS practice. This casts doubt on the appropriateness of using the AURA and IMPRESS OS datasets to represent the UK population. Even if the OS projections were accurate for the patients in the trials, they would probably overestimate survival for the average target UK patient eligible for treatment with osimertinib.

The ERG therefore considers that the OS projections employed by the company are based on opinion rather than on robust clinical effectiveness evidence. To support this view, the ERG cites the wide variation in ICERs that the company shows (CS, p234) could be produced depending on the selection of different statistically plausible, if not necessarily clinically plausible, projections of OS.

The ERG considers that all of the ICERs estimated using the company OS projections – including the ERG model amendments - should therefore be treated as ‘what if?’ scenarios as they are not underpinned by statistically significant clinical effectiveness evidence.

Second, even if the company's OS projection was accurate, the company has underestimated the acquisition costs of osimertinib and failed to take into account any administration cost of osimertinib as an oral chemotherapy – for the latter costs there are established NHS Reference Cost Schedules.[60] Using TTD data from the AURA studies and the IMPRESS trial and a cautious estimate of the NHS Reference Cost[60] for oral chemotherapy administration results in substantial increases in the size of the ICER per QALY gained from the company base case.

Third, utilities applied in the model appear to be implausibly high. Although drawn from AURA2 data, the EQ-5D-5L rather than EQ-5D-3L was used. Whilst no utility values are available specifically for the population described in the model, the ERG considered that there are alternative utility values that, whilst they are by no means perfect, could be used instead of the utility values used by the company.

The ERG did not identify a statistically significant difference in PFS and/or OS by line of treatment for osimertinib and did not consider the clinical effectiveness evidence on single-agent chemotherapy to be convincing. As such, the ERG does not consider the results of the company's subgroup analyses, by line of treatment or when osimertinib is compared to docetaxel, to be informative.

Application of the ERG changes to costs and the ERG's alternative utility values results in ICERs for osimertinib compared to PDC of [redacted] per QALY or [redacted] per QALY gained depending on the alternative utility values used in the model. If only the improvement in PFS with osimertinib is then included (PFS data being the only statistically significant effectiveness evidence included in the model) then the ERG estimates the ICER for osimertinib compared to PDC to be [redacted] per QALY gained or [redacted] per QALY gained, again depending on the alternative utility values used in the model.

7 END OF LIFE CRITERIA

The company puts forward the case (CS, Section 4.13) that osimertinib meets the NICE End of Life criteria.[50] These 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 and
- treatment is licensed, or otherwise indicated, for small patient populations.

The company claims that osimertinib meets these criteria because:

- the available data from the IMPRESS trial (second-line treatment) suggest that patients previously treated with an EGFR-TKI have a median OS of less than 24 months
- the results from the company's economic model suggests that the mean OS associated with treatment with osimertinib is 13.5 months longer than OS associated with PDC treatment
- the number of patients eligible is 300 per year.

The ERG agrees with the company that available median OS data from the PDC arm of the IMPRESS trial indicate that patients with advanced NSCLC with T790M mutation and previously treated with an EGFR-TKI have a life expectancy of less than 24 months. The ERG also agrees that the eligible population is small. However, the ERG considers that, at this stage, there is no clinical effectiveness evidence to suggest that, when compared with PDC, treatment with osimertinib results in an OS gain of at least 3 months. Results of analyses carried out by the ERG show that when treatment with osimertinib is compared with PDC there is currently no clinical or statistically significant difference in OS. This may be, as stated by the company, due to the immaturity of the OS data, but at this stage any claim that treatment with osimertinib results in better OS than treatment with PDC is speculation.

8 OVERALL CONCLUSIONS

Clinical effectiveness data

The clinical effectiveness evidence presented by the company in support of the use of osimertinib for patients with EGFR T790M mutations who have previously failed EGFR-TKI treatment cannot be considered to be robust. There are no results available from RCTs that include osimertinib as an intervention or as a comparator, and the only on-going RCT of osimertinib (versus PDC) is not due to report until 2017. The company has submitted evidence for the clinical effectiveness of osimertinib from two ongoing phase I/II single-arm studies. Of the 411 patients recruited to these studies 31.4% had received osimertinib as second-line therapy and 68.6% as ≥third-line therapy. Data from AURAext and AURA2 are immature; the OS and PFS data from the pooled dataset are 12.7% and 38.9% mature, respectively. The immaturity of the PFS data also means that the safety profile of osimertinib should be viewed with caution. The EMA also noted the limitations of the company's data when they issued a conditional licence for osimertinib.

There are doubts about whether the clinical data used to demonstrate the relative effectiveness of osimertinib compared to treatment with PDC are robust. To create this dataset the company used data from the control (PDC) arm of the IMPRESS trial (a phase III RCT). Tumour samples from patients in this arm were tested (retrospectively) for the EGFR T790M mutation. The resultant dataset was small (n=61) and although the PFS data for this group are relatively mature (83.6%), the OS data are only 32.8% mature. The company should be commended for the effort taken to create a comparator dataset. They should also be commended for applying a methodology to adjust for different patient characteristics between trials. [redacted]

Lack of mature survival data has hindered the company's claims that treatment with osimertinib is more clinically effective, or more cost effective, than PDC in patients with T790M mutations who have failed EGFR-TKI treatment. Using the limited survival data available it is impossible for the company to put forward a robust argument in support of osimertinib using traditional methods of analysis (e.g. RCT results, indirect treatment comparisons or life-time economic evaluations). The ERG acknowledges the company's efforts to showcase the strengths of osimertinib. However, until more mature data are available the strengths and weaknesses associated with treatment with osimertinib will remain unclear.

Model OS gain

The ERG considers that the company's base case ICER for the comparison of osimertinib with PDC is implausible due to treatment with osimertinib being associated with an unsubstantiated OS gain. The immaturity of the data means that there is no clinical evidence on which to base this gain. Furthermore, analyses undertaken by the ERG demonstrate that there is no statistical evidence to support this OS gain. Therefore, any ICER that relies on this assumption is inherently flawed. When the only adjustment made to the company base case is to remove the OS gain, the ICER for the comparison of treatment with osimertinib versus PDC rises to [redacted] per QALY gained.

Utility values

The utility values used in the company's model were collected during the AURA2 study. However, the EQ-5D-5L index score at baseline is higher than that for the UK population of the same age (albeit that the latter were collected using the EQ-5D-3L tool). Furthermore, during the AURA2 study, utility was measured every 6 weeks whilst patients were receiving treatment (up to a maximum of 42 weeks) and, at all of these time points (except for week 42 when the questionnaire was only completed by four people), the index score was higher than at baseline. In addition, very little information is available from the AURA2 study about patient utility after treatment progression. Values are only available at the point of treatment discontinuation and at 28 days follow up. Values are also provided 'Post IP follow-up' but the timing of this event is not clear. The ERG, therefore, considers the utility values used in the company base case are problematic and offers two alternative sources. The ERG recognises that both alternatives also have limitations. However, they do provide alternative and less optimistic perspectives. As both sets of ERG preferred utility values are lower than those used in the company base case, their use leads to an increase in the size of the base case ICER.

EGFR T790M mutations

Currently, there is no routine EGFR T790M testing of tumours in NHS clinical practice. The organisational infrastructure may already be in place but, as for all new testing protocols, EGFR T790M testing of tumours requires careful NHS planning as well as the cooperation of NHS staff and patients.

There is a possibility of a tertiary acquired mutation identified after treatment with osimertinib for EGFR T790M mutation-positive NSCLC.[71] Osimertinib is one of a number of EGFR T790M targeted drugs (e.g., rociletinib by Clovis Oncology; BI 1482694 by Boehringer Ingelheim) and, as new clinical trial data are published and T790M testing becomes established in clinical practice, current gaps in efficacy data and safety profiles will be filled.

8.1 Implications for research

The protocols for AURAext and AURA2 studies permitted continuation of treatment after confirmed disease progression. Continuation of post-progression treatments appears to be becoming commonplace in oncology trials and the ERG suggests that it would be useful to record, and report, both PFS and TTD outcomes from RCTs and routine clinical practice.

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10 APPENDICES

Appendix 1: ERG changes to submitted company model

ERG Section 6 results table revision	Associated detail	Implementation instructions
R1. TTD data for on treatment costs	OSI_TTD.xlsx. These changes generate alternative costs in the model. QALY changes resulting from these changes should be ignored.	For osimertinib ***In Workbook OSI_TTD.xls*** In Sheet 'Values' Copy range **O4:O783** ***In company model*** In Sheet 'PatFlow_B' Paste values to cells **G13:G792** For PDC ***In Workbook OSI_TTD.xls*** In Sheet 'Values' Copy range **P4:P783** ***In company model*** In Sheet 'PatFlow_B' Paste values to cells **O13:O792**
R2. Calculation of osimertinib administration cost	OSI_TTD.xlsx	Calculated by ERG. Workings can be found in OSI_TTD.xlsx in Sheet 'Values' **Column E**
R3. LUME-Lung 1 utility		In Sheet 'CountryData' Set value in cell I679 = 0.687 Set value in cell I680 = 0.640
R4. Nafees utility		In Sheet 'CountryData' Set value in cell I679 = 0.653 Set value in cell I680 = 0.470
R5. Osimertinib generates a gain in PFS but not OS		In Sheet 'PatFlow_B' Copy cells **Q13:Q792**

ERG Section 6 results table revision	Associated detail	Implementation instructions
compared to PDC		Paste values in range **I13:I792** Enter formula in cell **H13 '=1-G13-I13'** Copy formula in cell **H13** to **H14:H792**

Factual Inaccuracies in response to ERG Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Osimertinib for locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer [ID874]

Single technology appraisal (STA)

File name	Version	Contains confidential information	Date
ID874_Osimertinib_FactualErrorCheck[CIC_AIC]	1.0	Yes	9 May 2016

AstraZeneca UK Ltd
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FACTUAL INACCURACIES

CLINICAL EFFECTIVENESS

Issue 1 Lack of statistically significant difference in OS between osimertinib and PDC

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.3.1, page 14 "The ERG considers that lack of statistical significance in OS between osimertinib and PDC during the period for which data are available means that there is no basis to project differential OS. Even if there were a statistically significant difference between osimertinib and PDC for the period that data were available, as the OS data are so immature, any projection could only be speculative with the degree of uncertainty in the projection being impossible to quantify." Section 8, page 117 "The ERG considers that the company's base case ICER for the comparison of osimertinib with PDC is implausible due to treatment with osimertinib being associated with an unsubstantiated OS gain. The immaturity of the data means that there is no clinical evidence on which to base this gain." The ERG's assertion that there is no basis on which to project differential OS between osimertinib and platinum doublet chemotherapy is inaccurate in light of the additional evidence that has become available following the original submission in February 2016. AstraZeneca would be willing to share further details of the updated data that have become available as well as the updated adjusted indirect comparison	Please remove the following text of the ERG report: Section 1.3.1, page 14 "The ERG considers that lack of statistical significance in OS between osimertinib and PDC during the period for which data are available means that there is no basis to project differential OS. Even if there were a statistically significant difference between osimertinib and PDC for the period that data were available, as the OS data are so immature, any projection could only be speculative with the degree of uncertainty in the projection being impossible to quantify." Section 8, page 117 "The ERG considers that the company's base case ICER for the comparison of osimertinib with PDC is implausible due to treatment with osimertinib being associated with an unsubstantiated OS gain. The immaturity of the data	In light of important additional data that have become available following the original submission made in February 2016, the ERG's assertion that there is no basis on which to project differential OS between osimertinib and platinum doublet chemotherapy is inaccurate and no longer valid.	The ERG's preliminary view of the additional data presented in the company's FAC is that whilst it is of interest it does not fundamentally influence the decision faced by the AC in that: • The clinical evidence presented by the company to support treatment with osimertinib is derived from two single arm Phase I/II trials • 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 • Patients included in the AURAext and AURA2 studies are younger and fitter than EGFRm+ patients who would be eligible for treatment with osimertinib in the NHS • The data used to inform the PDC comparison were obtained from the subgroup of patients (n=61) included in the control arm of the IMPRESS

with NICE and the ERG and which we believe provide further confidence and support for the projected outcomes obtained in our economic model. However, as these data have only just been presented, AstraZeneca has not yet had the opportunity to update the relevant cost-effectiveness analyses although we are in the process of doing so. We request that these analyses could be shared with the ERG as soon as possible so they could be taken into consideration moving forward.	means that there is no clinical evidence on which to base this gain."		trial whose tumours were identified retrospectively as having the EGFR T790M mutation. In addition: • Whilst updated PFS data have been presented, no updated TTD data have been made available • The updated OS data are still very immature (osimertinib: [redacted] and PDC: 29.4%) • When considering the updated OS associated with treatment with osimertinib and PDC (ID874_FAC,_[redacted]) it is unclear whether the assumption of proportional hazards holds. If it does not, then the company's hazard ratio estimates are unreliable.

Issue 2 Relevance to UK clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 1.3.1, page 12 "The AURAext study was open to recruitment at two centres in the UK; however, it is not clear how many patients were recruited from the UK." Although not strictly a factual error, we wish to clarify to the ERG that four patients in the	"The AURAext study was open to recruitment at two centres in the UK; *following clarification from the company, it is known that four patients were recruited in the UK*."	Factually inaccurate statement.	The ERG notes the clarification from the company. No change required.

AURAext study were recruited in the UK.			

Issue 3 Outline of Analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.3, page 35: "For the AURA2 study no formal interim analyses were planned. However, the investigators analysed the data at approximately 3 months and 8 months after the last patient was recruited." This is incorrect. Interim analyses at 3 and 8 months were pre-specified as stated in the relevant study protocol for AURA2.	"For the AURA2 study interim analyses at 3 and 8 months were pre-specified in the study protocol for AURA2".	Factually inaccurate statement.	The text in the ERG report is changed to the following: *There were no formal analyses planned for this study, but 2 data cut off points were planned at approximately 3 months and 8 months after the last patient had been enrolled.*

Issue 4 ERG Assessment of statistical approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.2.3, Table 6, page 42: "Missing data approach [AURAext and AURA2 studies]: No details provided." This is incorrect. The Statistical Analysis Plans [provided to the ERG in response to clarification questions] for both AURAext and AURA2 prospectively provided plans for handling the following missing data: • Missing Target Lesion Data • Imputation methods if a best % change cannot	"Missing data approach [AURAext and AURA2 studies]: *provided in the relevant SAPs*"	Factually inaccurate statement.	The ERG agrees that some details on the company's approach to dealing with missing data are stated in the Statistical Analysis Plans. Table 6 has been amended accordingly.

be calculated • Censoring methods for PFS and OS • Time-matched analysis and missing QT/QTC information • Missing EORTC QLQ-C30 data • Missing/partial dates • How to handle missing subgroup information			

Issue 5 Results from the IMPRESS trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.4.4, page 59: "During the clarification process, the ERG requested the corresponding p-values for the tests for interaction for these analyses. However, the company only sent results for the tests of interaction for the control arm of the IMPRESS trial". This is incorrect. AstraZeneca provided the p-values for the test of differences between the levels of a subgroup in AURAext/2 and IMPRESS to answer the clarification question (A8) specifically about prognostic differences between the levels of a subgroup.	Remove the following paragraph from pp.59-60: "During the clarification process, the ERG requested the corresponding p-values for the tests for interaction for these analyses. However, the company only sent results for the tests of interaction for the control arm of the IMPRESS trial. This means that the ERG is unable to assess which of the subgroup analyses are significant and therefore cannot comment on the company's conclusions. "	Factually inaccurate statement.	This is a misunderstanding of the ERG's clarification request (question A8) by the company. The ERG requested the p-values relevant to Figure 4.17 of the CS (p151), a forest plot of PFS subgroup analyses in the overall IMPRESS trial population. In response, the company provided p-values relevant to the placebo arm only of the IMPRESS trial. We have removed the statement from the report.

Issue 6 ERG critique of the company's adjusted comparison

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 4.6.1, page 66 and Section 4.6.3, page 73: "The ERG notes that the adjustments that have been made only relate to age, ethnicity, baseline target lesion size and smoking history, all of which (except for age) are well balanced between the two datasets. No adjustments have been made to account for differences in either line of treatment (including number of previous EGFR-TKIs) or brain metastases" [p.66] ""The ERG notes that the company was unable to control for differences that may be important, including line of treatment and presence of brain metastases." [p.73] [redacted] These statements are incorrect. The first step of the adjustment approach was to select baseline variables for which there was a statistically significant difference between the two treatment groups at baseline. This involved statistical significance testing for a large number of baseline factors (full list provided in the technical report – Adjusted Indirect Comparison of osimertinib vs Standard of Care [D5160C0000a]). Those variables that were statistically significant were used in a model to generate an aggregated score which adjusted for differences. The variables finally selected included the list as stated by the ERG but additionally there was adjustment for other	Please remove the following text from the ERG report: "The ERG notes that the adjustments that have been made only relate to age, ethnicity, baseline target lesion size and smoking history, all of which (except for age) are well balanced between the two datasets. No adjustments have been made to account for differences in either line of treatment (including number of previous EGFR-TKIs) or brain metastases" [p.66] ""The ERG notes that the company was unable to control for differences that may be important, including line of treatment and presence of brain metastases." [p.73] [redacted]	Factually inaccurate statements.	The ERG agrees that these are factual inaccuracies and has amended the report as suggested.

statistically significant variables; sites of metastases (Respiratory, Hepatic, pericardial effusion, prior radiotherapy, TNM classification – distant metastases & regional lymph nodes. A full list of the variables used in the final propensity score model is provided in the technical report. The first step of the adjustment approach was to select baseline variables for which there was a statistically significant difference between the two treatment groups at baseline (based on a p value of <0.2). The baseline characteristic "Patients with a medical history of brain metastases" was tested and was not statistically significant different between treatment groups (AURA Phase II 36.8% vs PDC 35.0%, p value=0.7882). Therefore it was not selected as a factor to be included in the propensity score model which would then represent aggregated differences between the two treatment groups. Line of treatment was not included in the adjustment approach and the estimation of the propensity score, as this would have likely been the same as restricting the analysis to second-line only patients in AURAext/2. To address the potential impact of line of treatment beyond the variables that were already included in the PS model, one subgroup analysis included second-line only patients. Results were consistent with the primary analyses – see the accompanying technical report for further details.			
Section 4.6.1, page 66: "In addition, when testing for statistically significant differences in baseline variables, the company used a p-value of <0.2 instead of a conventional significance level of 0.05; the rationale behind this choice is not explained."	"In addition, when testing for statistically significant differences in baseline variables, the company used a p-value of <0.2 *rather than a conventional significance level of 0.05 to allow a wider selection of baseline variables to be included in*	Factually inaccurate statement.	The ERG is unable to locate the explanation in the technical document cited by the company (D5160C0000a Adjusted Indirect Comparison of Osimertinib vs Standard of Care).

As explained in the relevant technical report accompanying the main submission, a p-value of <0.2 was chosen as a higher than a conventional significance level of 0.05 to allow a wider selection of baseline variables to be included in the final model to explain as much as possible the differences in baseline characteristics between the two treatment groups.	*the final model to explain as much as possible the differences in baseline characteristics between the two treatment groups."*		
Section 4.6.1, page 67: "The baseline characteristics of the patients in the individual datasets used in the adjusted comparisons are unknown." We provided a summary of the baseline demographic and disease characteristics of the patients in the individual datasets used in the adjusted indirect comparison are presented in the technical report submitted in addition to the main submission (see Table 9, page 38). These are consistent with the baseline characteristics presented in the relevant CSRs and the main submission.	"The baseline characteristics of the patients in the individual datasets used in the adjusted indirect comparison *were provided* in an accompanying technical report and were consistent with the baseline characteristics presented in the company's submission."	Factually inaccurate statement.	This is an error. The statement has been removed from the ERG report.
Section 4.6.1, page 67: "Despite the differences in inclusion criteria, overall, the baseline patient demographic characteristics of patients included in the pooled AURA dataset and the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease are well balanced. The key differences between datasets are in terms of age and presence of brain metastases". Although not factually incorrect, the ERG should acknowledge the following: (i) For the adjusted comparison, the baseline characteristic "Patients with a medical history of brain metastases" was tested and was not	"Despite the differences in inclusion criteria, overall, the baseline patient demographic characteristics of patients included in the pooled AURA dataset and the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease are well balanced. The key differences between datasets are in terms of age and presence of brain metastases. *However, in the company's adjusted comparison, age was included as a factor in the*	The text as currently written is possibly misleading by suggesting there are differences in terms of age and presence of brain metastases between AURAext/2 and the PDC cohort from IMPRESS.	The ERG acknowledges the company's concerns and has amended the report to reflect these.

statistically significant (AURAext/2 36.8% vs PDC 35.0%; p value=0.7882). Therefore it was not selected as a factor in the generation of a propensity score which would then represent aggregated differences between the two treatment groups. (ii) Age was identified as a key variable for which there were differences between the two treatment groups at baseline and was therefore included in the model used to generate a propensity score which would then represent aggregated differences between the two treatment groups.	*model used to generate a propensity score whilst the baseline characteristic "Patients with a medical history of brain metastases" was tested and was not statistically significant (AURAext/2 36.8% vs PDC 35.0%; p value=0.7882).*		

COST EFFECTIVENESS

Issue 7 Discounting method

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 5.6.6, page 109. The ERG stated, in-line with NICE recommendations, that costs and benefits should be discounted annually. This should be done by accumulating costs and benefits annually and then applying the annual discount rate. The ERG indicated that the discount rate in the model is applied continuously every week (after year 1).	The ERG should remove this statement from the report.	The company agrees that intra-year discounting should not be applied (i.e. 1/52 discount rate continuously every week). The company economic model used a technique where weekly costs and benefits are discounted using the annual discount rate and then accumulated over the time horizon. The main reason for using this technique is that it saves space, calculation time, and provides flexibility. But in essence, and effectively, this is the same calculation as proposed by the ERG and gives the exact same results.	The method employed by the company only works if the model run finishes on a complete year, otherwise the last year will be too heavily discounted. It might not make any significant difference in this submission, but it could make a difference for treatments where, for example, every patient is dead at 18 months. The ERG, therefore, considers that their comment should remain in the ERG report, particularly as its presence will help ensure that future models submitted to NICE do not include the same flawed methodology.

Issue 8 Administration costs of osimertinib

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 5.6.5, p.107 "The company model does not include a cost for the administration of osimertinib. Clinical advice to the ERG is that osimertinib is provided, on a monthly basis, in a nurse led clinic."	"It is expected that administering osimertinib will already be included in PFS monitoring costs. No additional administration is required in a hospital setting."	The PF state costs include what would realistically be expected to be involved with administering osimertinib treatment as patients are routinely monitored in an outpatient setting during the progression free phase of the	Clinical advice to the ERG is that oral chemotherapy would incur an administration cost. This administration cost would be in addition to the PFS monitoring costs included in the company model.

The PF state costs include what would realistically be expected to be involved with administering osimertinib treatment as patients are routinely monitored in an outpatient setting during the progression free phase of the model		model	

Issue 9 Cost of osimertinib treatment

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 5.6.3, page 104. "The pooled TTD data from the two AURA studies were 36% mature, with the last event recorded on day 313." This is incorrect. From the May 2015 data cut-off, pooled TTD data from the AURAext/2 studies were 28% mature (116/411 TTD events).	"The pooled TTD data from the two AURA studies were 28% mature, with the last event recorded on day 313."	Factually incorrect.	The ERG has amended the text in their report.
10 Appendices, page 124 The ERG provided changes made to the submitted company model (Appendix 1; page 122) and gave details on how this was done. The company tried to replicate these scenarios using the data provided by the ERG, but not all scenarios lead to the same results.	The company asks for clarity around **Appendix 1 (page 124): R1. TTD data for on treatment costs.** Potentially this is only an error in the description, and not the approach, taken by the ERG. The formulas for the drug acquisition, administration and monitoring costs should be edited on the sheet 'Cost_calc' (column H:J for OSI, and column V:X for PDC) so they	When trying to replicate the ERG approach, the company arrived at different results than the ERG. Using the proposed amendment, the company obtained different results to those presented in the ERG report (Table 43; page 110). This makes the company believe that it might be an error in the report, and not necessarily in the way the ERG has approached it. In particular, the TTD values cannot	The ERG acknowledges that the wording in the appendix could have been clearer but the calculation was undertaken correctly. Only the administration and acquisition costs changed with the amendment (Cells N:51:P52 on the 'Results Sheet') Using the proposed ERG amendment the costs in Table 43 are correct. The appendix has been reworded to avoid confusion.

	link to the ERG's TTD data for respective weekly cycle.	be copy/pasted into these ranges, as proposed in the ERG, because this replaces the PFS values – and in turn affects the disease management costs, QALYs, etc. The ERG also clearly stated that the intention is not to affect QALYs. Even if the intention was to replace PFS with TTD, the ERG's approach would be incorrect because, without any additional formula edits, the model yields incorrect (>100%) patients in the model each weekly cycle.	

Issue 10 Link between PFS and OS

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Section 5.6.1 p.102– "Weak link between PFS and OS". The ERG use the conclusions of the DSU report published in 2012 which covers a variety of tumour types and generally older studies of non-targeted chemotherapy regimens, to dismiss the findings of our own research, which is specific to advanced NSCLC, and argue that there may be a weak link between PFS and OS in the second-line setting. However, recently published research specifically investigating the correlation between PFS and OS in phase III trials of molecular-targeted agents in advanced NSCLC concluded that, in trials where patients seldom crossover from control to	The ERG should clarify in their report that the findings of the DSU report are relevant only to first-line chemotherapy for advanced NSCLC and may not necessarily be relevant to molecular-targeted agents, such as osimertinib in second-line or later settings.	The ERG's assertion of a weak link between PFS and OS is not supported by the available published evidence specific to advanced NSCLC.	The ERG was not stating that there was never a relationship between improved PFS and OS but that the relationship can vary widely between treatments and so is a poor proxy for OS improvements. This is also the conclusion reached the DSU (who explored data from first line studies and further line studies). The authors of the Hotta et al study found evidence that a PFS/OS relationship does exist where there is no crossover to an active therapy but does not indicate the magnitude of this effect beyond a reported R-squared value. The Hotta et al study results demonstrate a strong association between PFS and OS only in the circumstances where post-study treatments were seldom employed. The ERG considers that:

active therapy post progression, the association between PFS and OS was strong. [REF: K Hotta et al. 2013. Progression-free survival and overall survival in phase III trials of molecular-targeted agents in advanced non-small-cell lung cancer. Lung Cancer 2013 Jan; 79(1):20-6]			1. data relating to the use of osimertinib are so immature that it is currently unclear whether patients who have taken it will go on to receive subsequent lines of treatment 2. determining a relationship between PFS and OS involves retrospective analysis of data from completed clinical trials a. extrapolation of such a relationship to molecular targeted agents with different mechanisms of action and different mechanisms of acquired resistance may not be appropriate b. published relationships are based on measures of median PFS and median OS from completed trials; median survival values may change as datasets mature. In addition, due to the growing range of treatment options available to T790M patients, it is likely that these patients would cross over to another active therapy having failed on osimertinib, such as onto PDC.

Issue 11 Docetaxel monotherapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
5.4.3, p.78. The ERG report incorrectly states that "in a scenario analysis, osimertinib is compared	"In a scenario analysis, osimertinib is compared with up to *four* cycles of docetaxel	The text implies that the model has overestimated the duration and hence the costs of docetaxel	This is a factual error. The ERG has amended their report by replacing the number six with the

with up to six cycles of docetaxel monotherapy…" In the economic model, duration of docetaxel monotherapy is limited to a maximum four cycles for this scenario analysis (as referred to in our submission, page 212). This same error is repeated in Table 29, page 86 of the ERG report.	monotherapy…"	monotherapy in this scenario analysis.	number four on p78 and in Table 29 (p86).

Issue 12 AiC/CiC Marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
ID874 Osimertinib ERG Confidential Appendix PAS, page 3. The title to Table 1 refers to the exact size of the discount offered on the list price of osimertinib. If this document is to be released to consultees and commentators as part of any forthcoming ACD/FAD consultation, this figure will need to be redacted.	Please add the following CiC marking: Table 1 Cost effectiveness results (osimertinib versus PDC) with PAS included for osimertinib ([redacted])	The size of the discount offered on the list price of osimertinib is commercial in confidence.	The whole PAS appendix is confidential and therefore no changes are required.

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for locally advanced or metastatic EGFR and T790M mutation-positive non-small cell lung cancer [ID874]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 15/121/09

Completed 20th April 2016

DOES CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

This document contains erratum in respect of the ERG report following the factual accuracy check by AstraZeneca.

Changes made to the original text in the ERG report are highlighted in grey.

Outline of analyses

Patient recruitment to the AURAext study started in May 2014 and finished in October 2014. The data cut-off for the data presented in the CS was 1st May 2015.

The AURA2 study started recruiting patients in June 2014 and the last patient was recruited in October 2014. The data cut-off for the data presented in the CS was also 1st May 2015. There were no formal interim analyses for this study, but two data cut off points were planned at approximately 3 months and 8 months after the last patient was recruited. The results presented in the CS are from the 8-month data cut-off. The final database lock will be at the end of the study, at 12-24 months after the last patient was recruited.

Patient recruitment to the IMPRESS trial started in March 2012 and the last patient was recruited in December 2013. The primary data cut-off for this trial was 5th May 2014. Two data cut-offs were planned, the primary data cut-off for the primary PFS analysis and the final data cut-off for the final OS analysis. The primary PFS analysis was conducted on a total of 205 progressions (77.4% maturity). At the time of the primary PFS analysis, the OS data were also analysed (87 patient deaths had occurred, 33% maturity). [redacted]

Study outcomes

The definitions and methods of analysis for the primary and secondary efficacy outcomes from the AURAext and AURA2 studies and the IMPRESS trial are listed in

Table 1. The ERG is satisfied that all of the outcomes were pre-specified in the TSAP and that all of the outcomes were fully reported in the CSR.

Table 1 Analysis strategy for key efficacy endpoints

Endpoint	Definition	Statistical method
AURAext and AURA2: primary outcome		
ORR	The percentage of patients with at least one visit response of CR or PR that was confirmed at least 4 weeks later according to RECIST 1.1 by BICR	The analysis of ORR was presented together with 95% exact (Clopper-Pearson) CI by study and overall for the pooled AURA dataset. Overall ORR based on the pooled data was calculated as the number (%) of patients with BOR of confirmed CR or PR from both studies. A similar analysis of ORR was also presented by treatment cohort (2nd- versus ≥3rd-line) and overall. The ORR in each treatment cohort based on the pooled data was calculated as the number (%) of patients with BOR of confirmed CR or PR from each treatment cohort across two studies
AURAext and AURA2: secondary outcomes		
DoR	The time from the date of first documented response, (that is subsequently confirmed) until the date of documented progression or	DoR (months) in responding patients based on the BICR was summarised using the median and 95% CI. The median was calculated using the K-M method. The number and percentage of responding patients remaining in response at >3; >6; >9; >12

	death in the absence of disease	months was summarised. Analyses were presented by study and

Table 2 ERG assessment of statistical approaches used to analyse data from the AURAext and AURA2 studies and the IMPRESS trial

Component	AURAext and AURA2 studies		IMPRESS trial	
	Statistical approach	**ERG comments**	**Statistical approach**	**ERG comments**
Sample size calculation	Provided in the CS (p96-97)	The ERG considers that the methods used to calculate the sample size are correct	Provided in the CS (p135)	The ERG considers that the methods used to calculate the sample size are correct
Protocol amendments	Provided in the CSR (Section 5.8.1)	The ERG notes that the changes detailed in the protocol amendments are unlikely to have been driven by the results of the trial and are, therefore, not a cause for concern. All protocol amendments were carried out prior to the analyses being conducted	Provided in the CSR (Section 5.8.1)	The ERG notes that the changes detailed in the protocol amendments are unlikely to have been driven by the results of the trial and are therefore not a cause for concern. All protocol amendments were carried out prior to any analyses being conducted
Missing data approach	No details provided	It is not possible for the ERG to review these results as they have not been provided	No details provided	It is not possible for the ERG to review these results as they have not been provided
Subgroup analyses	For ORR and DoR • Patients who received EGFR-TKI or those whose treatment prior to study start was not an EGFR-TKI • Ethnicity (Asian or Non-Asian) • Gender (Male or Female) • Age at screening (<65 or ≥65) • Mutation status prior to start of study (Exon 19 deletion or L858R or Other) • Duration of most recent prior EGFR-TKI (<6 months or ≥6 months) • Smoking history (never or ever) • Brain metastases at entry (yes or no) • Patients with EGFR T790M	It is not possible for the ERG to review these results as the pooled results used to perform the subgroup analyses are not provided in the CSR	For PFS: • Region (Asia or European Union) • Time from progression to randomisation (≤2 weeks or >2 weeks) • Smoking history (never or current/former) • Prior response to gefitinib (SD or PR and CR combined) • Exon 19 deletion (present or absent/unknown) • L858R mutation (present or absent/unknown) • Age (<65 years or ≥65 years) • Gender (male or female) • Disease stage at diagnosis	The ERG is satisfied that the results of all subgroup analyses are provided in the CSR

4.4.3 Results from the IMPRESS trial

The company presents the results from the IMPRESS trial based on the data that were collected up until 5th May 2015 (CS, p148 to p156). Median follow-up for PFS was 11.2 months. Both results for the overall trial population and those for the subgroup of patients in the control arm with EGFR T790M mutation-positive disease are presented in this section.

4.4.4 Progression-free survival (investigator-assessed) and overall survival

Progression-free survival (primary outcome)

At the time of the analysis, the PFS data in the FAS population were 77.4% mature. Figures in **Error! Reference source not found.** show no statistically significant differences between the PFS results for the intervention and control arms of the trial (PFS=5.4 months in both arms). The PFS result for the control arm EGFR T790M mutation-positive patient subgroup (PFS=5.3 months) was similar to the PFS results for the overall trial population.

The company presents a K-M plot of the PFS data (CS, Figure 4.16) for the overall trial population and states: i) that the curves for the treatment arms do not cross and ii) the treatment effects of the intervention and the control therapies were consistent over time. The ERG agrees with the company that the PH assumption appears valid.

The results of the company subgroup analyses for the overall population of the IMPRESS trial are presented in Figure 4.17 of the CS. Subgroup analyses were conducted for: age (<65 years or ≥65 years), male or female, region of origin (Asia or Europe), previous response to gefitinib (CR+PR or stable disease), EGFR mutation subtype (Exon 19 deletion or L838R deletion), smoking status (present or former or never), disease state at diagnosis (metastatic or non-metastatic), time from progression to randomisation (>2 weeks or ≤2 weeks), time to progression for initial gefitinib therapy ≤10 months or >10 months), brain metastases at baseline (yes or no) and WHO PS (0 or 1). Significant interactions were noted for:

- *Asia (HR=0.80) versus Europe (HR=0.95)*
- *Never smokers (HR=0.70) versus current or former smokers (HR=1.16)*
- *Exon 19 deletion present (HR=0.76) versus Exon 19 absent/unknown Exon 19 (HR=0.97)*
- *WHO PS 0 (HR=0.68) versus WHO PS 1 (HR=0.95).*

TEXT DELETED

The company also presents a PFS K-M data plot by treatment arm and biomarker status (CS, Figure 4.18). The company states that a (non-significant) treatment effect of gefitinib was recorded in patients without EGFR T790M mutation-positive disease (HR=0.67; 95% CI: 0.43 to 1.03, p=0.0745). In contrast, no treatment effect of gefitinib was recorded for patients with EGFR T790M mutation-positive disease (HR=0.97; 95% CI: 0.67 to 1.42, p=0.8829). The company interprets this finding as providing support to the biological hypothesis that, in the absence of the EGFR T790M mutation, the tumour may still respond to treatment with an EGFR-TKI.

Overall survival

At the time of the analysis, FAS population OS data from the IMPRESS trial were immature. The company reports that follow-up for survival is ongoing and that more mature data will be available (following a [redacted]

The analysis of OS data (**Error! Reference source not found.**) from the overall IMPRESS trial population demonstrates a statistically significant treatment effect for patients in the control arm (HR=1.62; 95% CI: 1.05 to 2.52, p=0.029). Median OS is 17.2 months (95% CI 15.6 to NR) in the control arm compared with 14.8 months (95% CI: 10.4 to 19.0) in the intervention arm. OS for the subgroup of patients in the control arm with EGFR T790M mutation-positive disease was 15.7 months, which is lower than the OS for the whole control arm population (17.2 months) but higher than that for the intervention arm population (14.8 months). The ERG cautions that the OS results are based on immature data.

The company reports that 45.9% of patients in the intervention arm and 54.5% of patients in the control arm had received further anti-cancer treatment after discontinuation of their study treatment (CS,p153)

model to estimate the propensity scores and the final trimmed dataset were age, ethnicity, baseline target lesion size and smoking history. The final datasets included in the adjusted analysis comprised 287 patients from the AURA studies and 51 patients from the control arm of the IMPRESS trial. The trimmed dataset is referred to as the T790M+ adjusted dataset.

For the matched populations, the treatment effect of osimertinib versus PDC was assessed for key efficacy and safety endpoints as follows:

- *PFS: Cox PH model with treatment as a factor and propensity score as a covariate*
- *OS: based on independent assessment review and performed at the time of the PFS analysis using a Cox PH model*
- *ORR and DCR: carried out using logistic regression with treatment as a factor and propensity score as a covariate.*

PH=proportional hazards; ORR=objective response rate; PDC=platinum doublet chemotherapy; PFS=progression-free survival; OS=overall survival; DCR=disease control rate
Source: CS, Section 4.10.3

ERG critique of the company's adjusted comparison

The ERG appreciates the lengths taken by the company to facilitate a comparison of the effectiveness of osimertinib with PDC, but considers that only a well-controlled, head-to-head RCT can avoid unobserved confounding.

TEXT REMOVED

Over and above concerns about the immaturity of the OS data, the ERG notes that the size of the datasets was substantially reduced following adjustments (**Error! Reference source not found.**). The pooled AURA dataset was reduced from n=411 to n=287 for the PFS and OS analyses, and to n=277 for the ORR and DCR analyses. The T790M+ adjusted dataset was reduced from n=61 to n=51 for the PFS and OS analyses, and to n=46 for the ORR and DCR analyses.

Characteristics of studies included in the clinical efficacy comparisons

The company provides baseline characteristics related to patients in the pooled AURA dataset (n=411) and to the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease (n=61). TEXT REMOVED

The baseline characteristics of the patients included in the pooled AURA dataset and in the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease are shown in Table 4.7 of the CS. The eligibility criteria used to recruit patients to the two AURA studies and to the IMPRESS trial differ slightly. The pooled AURA

dataset includes both patients receiving second-line and patients receiving subsequent lines of treatment, whilst the IMPRESS trial only recruited patients who had received one prior

EGFR-TKI therapy. Furthermore, whilst patients in the AURAext and AURA2 studies were not required to have had a prior treatment response to an EGFR-TKI, patients in the IMPRESS trial had to have had a prior objective clinical benefit (as measured by CR or PR) and a minimum duration on first-line gefitinib treatment of 4 months. Another key difference in eligibility criteria is that the two populations used different methods to identify EGFR T790M mutation status. The Roche Cobas method was used in the AURAext and AURA2 studies and the BEAMing digital PCR method was used (retrospectively) to identify patients with T790M mutation-positive disease recruited to the IMPRESS trial.

Despite the differences in inclusion criteria, overall, the baseline patient demographic characteristics of patients included in the pooled AURA dataset and the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease are well balanced. The key differences between datasets are in terms of age and presence of brain metastases. The subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease is slightly younger than patients in the pooled AURA dataset, with a mean age of 55.8 years compared to 62.2 years. Only 16.4% of patients in the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation positive disease were ≥65 years, whereas in the pooled AURA dataset population 45.5% of patients were ≥65 years old. Furthermore, compared with patients in the pooled AURA dataset, fewer patients in the control arm of the IMPRESS trial who had EGFR T790M mutation-positive disease had brain metastases at baseline (40.4% versus 34.4% respectively). The ERG notes that in the company's adjusted comparison, age was included as a factor in the model used to generate a propensity score whilst the baseline characteristic "patients with a history of brain metastases" was tested and was not statistically significant. The company considers that both the age and the brain metastases imbalances may have a prognostic effect favouring the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease.

Key differences between the pooled AURA dataset population and the subgroup of patients in the control arm of the IMPRESS trial with EGFR T790M mutation-positive disease are summarised in Table 3.

Table 3 Key baseline differences between the AURA studies and the IMPRESS subgroup

Demographic characteristics		Pooled AURA dataset	EGFR T790M mutation-positive population
Number		411	61
Indication		≥Second-line	Second-line
Treatment		Osimertinib 80mg	Placebo+PDC
Age (years)	Mean (SD)	62.2 (10.76)	55.8 (10.20)
	Median (min-max)	63 (35-89)	55 (38-79)
	% ≥65 years	187 (45.5%)	10 (16.4%)
Brain metastatic at baseline		166 (40.4%)	21 (34.4%)

EGFR=epidermal growth factor receptor; SD=standard deviation; PDC=platinum doublet chemotherapy Source: CS, Table 4.7

4.6.2 Assessment of risk of bias of the trials included in the unadjusted and adjusted comparisons

The company conducted an assessment of the risk of bias for the AURAext and AURA2 studies, which is discussed in Section **Error! Reference source not found.**, and for the IMPRESS trial, which is discussed in Section **Error! Reference source not found.**, of this report. The ERG considers that the assessments of risk of bias conducted by the company were appropriate. The ERG considers that the AURA studies were designed and conducted to a good standard (with the caveat that both were single-arm studies) and that the IMPRESS trial was of very good quality.

4.6.3 Results from the unadjusted and adjusted comparisons

Unadjusted comparison of study results

The results of the unadjusted comparison are provided in **Error! Reference source not found.**.

The ORR observed within the pooled AURA dataset (ORR=66.1%) was significantly higher than the ORR observed in the IMPRESS EGFR T790M mutation-positive control group (ORR=39.3%). Furthermore, patients in the pooled AURA dataset had a median PFS of 9.7 months compared to 5.3 months for the IMPRESS EGFR T790M mutation-positive control group, indicating a statistically significant difference of 4.4 months. However, the results need to be interpreted with caution as, at the time of analysis, the 95% CIs for PFS were either not calculable or not reached as the data were very immature with only 12.7% of patients having had OS events in the pooled AURA dataset and only 32.8% of patients in the EGFR T790M mutation-positive control group of the IMPRESS trial having had OS events. The median OS was not reached for patients in the pooled AURA dataset. In the control arm of the IMPRESS trial, median OS was 15.7 months for patients with EGFR T790M mutation-positive disease; the company did not report 95% CIs.

Adjusted comparison of study results

The results from the adjusted comparison for ORR, PFS and OS are provided in **Error! Reference source not found.**.

The results from the adjusted comparison for ORR, PFS and OS are provided in **Error! Reference source not found.**.

The ORR results indicate a statistically significant improvement in favour of osimertinib compared to PDC (64.6% and 34.8% respectively, OR=4.76; 95% CI: 2.21 to 10.26; p<0.001). Similarly, the DCR results indicate a statistically significant improvement in favour of osimertinib compared to PDC (92.1% and 76.1% respectively, OR=4.39; 95% CI: 1.71 to 11.28; p=0.002). The PFS results indicate a statistically significant difference in favour of osimertinib compared to PDC (HR=0.280; 95% CI: 0.185 to 0.422; p<0.0001). Median PFS is 9.7 months for the osimertinib cohort compared to 5.2 months in the matched PDC cohort. Due to the very small number of patients experiencing events (osimertinib, n=33; PDC, n=15) median OS could not be calculated (HR=1.022; 95% CI 0.387 to 2.696; p=0.9654).

Results of subgroup analyses for 2nd-line patients only were consistent with the primary analyses.

The ERG investigated whether the PH assumption employed by the company to calculate PFS and OS HRs hold by digitising the data presented in Figure 4.2 (PFS) and Figure 4.3 (OS) of the CS and then plotting the cumulative hazard associated with osimertinib treatment versus the cumulative hazard associated with PDC treatment (H-H plot). The PFS H-H plot suggests that the PH assumption does not hold for PFS and, therefore, the PFS HR result must be interpreted with caution. Interpretation of the OS H-H plot is less clear and the issue is complicated by the lack of data. However, based on the data available, it would not be unreasonable to assume that hazards are broadly proportional.

The ERG notes that key efficacy results from the adjusted and unadjusted analyses are very similar (**Error! Reference source not found.**).

majority (two-thirds) of recruited patients received osimertinib as a third- fourth- or fifth-line treatment following a first-line EGFR-TKI and a first-line chemotherapy. The ERG is aware that very few patients seen in clinical practice in the NHS are well enough to tolerate more than one or two chemotherapy treatments. Patients from only two UK centres contributed to the data in the pooled AURA dataset.

The company has pooled IPD data from the AURAext and AURA2 datasets and generated efficacy results from this dataset. The company explains that the rationale behind this approach was to improve the precision of outcomes. The ERG considers that, as these two studies are very similar in terms of recruitment criteria and patient baseline characteristics, it was reasonable to pool the data. Furthermore, results generated independently using data from the two studies are similar to results generated from the pooled dataset.

Unadjusted and adjusted comparisons

The company should be commended for the effort that they have taken to formulate a comparator dataset. The comparator dataset comprises patients recruited to the control (PDC) arm of the IMPRESS trial who were (retrospectively) identified as having EGFR T790M mutation-positive disease. The ERG, however, has concerns that data from single-arm, non-controlled studies (AURAext and AURA2) are compared with data from a retrospectively identified subgroup participating in a good quality placebo-controlled, double-blind RCT (IMPRESS). Furthermore, this IMPRESS subgroup only includes 61 patients and OS data are only 32.8% mature.

The ERG commends the company for attempting to control for differences in baseline dataset differences by carrying out an adjusted comparison. However, with the exception of age, the adjustments undertaken by the company only controlled for parameters that were already well balanced. As such, results from the adjusted and unadjusted comparisons were similar TEXT REMOVED

The results from the unadjusted comparison indicate that osimertinib is more clinically effective, as measured by PFS and ORR than treatment with PDC (median OS has not yet been reached). The safety data suggest that treatment with osimertinib is more tolerable than treatment with PDC.

Other key issues and uncertainties

The evidence presented in the CS compares the clinical effectiveness of osimertinib with PDC. No evidence is available to compare osimertinib with any of the other 11 comparators specified in the final scope issued by NICE.

The mutation testing protocol required for the use of osimertinib is not in place in the NHS. T790M mutation testing after first-line treatment to establish the presence or absence of the EGFR T790M mutation is feasible as the infrastructure is in place; however, EGFR T790M mutation testing after first-line treatment is not standard practice in the NHS.

but OS equal to that modelled by the company for PDC (due to the slightly greater maturity of the data from EGFR T790M mutation-positive patients in the control arm of the IMPRESS trial compared to the AURA studies). This analysis generates incremental QALYs of [redacted] and an ICER of [redacted] per QALY gained.

5.6.3 Cost of osimertinib treatment

In the two AURA studies, patients were permitted to continue receiving osimertinib after disease progression. As such, PFS is not a good basis for estimating treatment cost. As part of the clarification process, the ERG requested TTD data from the two AURA studies and for the EGFR T790M mutation-positive patients in the control arm of the IMPRESS trial. The pooled TTD data from the two AURA studies were 28% mature, with the last event recorded on day 313. The TTD data from EGFR T790M mutation-positive patients in the control arm the IMPRESS trial were 100% mature.

ERG analysis of the TTD data from the two AURA studies showed that they followed a simple linear decline. The ERG estimated the linear trend between days 0 and 313 and then continued the trend after day 313 to estimate TTD beyond the point that data were available. This resulted in an estimate of all patients stopping treatment with osimertinib by day 880, or around 2.5 years. If the hazard rate were to become constant at any point past day 313 then the TTD data would follow an exponential curve. If an exponential curve were used, it is likely that there would be a longer tail of patients remaining on treatment than is suggested by the linear projection of TTD with resultant higher costs for osimertinib.

The cost of PDC treatment is primarily driven by PFS status but is limited to a maximum number of four cycles of treatment in the model to match the protocol for pemetrexed-cisplatin therapy. The TTD data from the EGFR T790M mutation-positive patients in the control arm of the IMPRESS trial are complete and have been used, by the ERG, directly in the company model to generate an alternative estimate of the cost of treatment with PDC instead of using PFS as in the company base case.

A comparison of TTD and PFS data using pooled data from the two AURA studies (osimertinib) and data from the EGFR T790M mutation-positive patients included in the control arm (PDC) of the IMPRESS trial is displayed in **Error! Reference source not found.**.

8 OVERALL CONCLUSIONS

Clinical effectiveness data

The clinical effectiveness evidence presented by the company in support of the use of osimertinib for patients with EGFR T790M mutations who have previously failed EGFR-TKI treatment cannot be considered to be robust. There are no results available from RCTs that include osimertinib as an intervention or as a comparator, and the only on-going RCT of osimertinib (versus PDC) is not due to report until 2017. The company has submitted evidence for the clinical effectiveness of osimertinib from two ongoing phase I/II single-arm studies. Of the 411 patients recruited to these studies 31.4% had received osimertinib as second-line therapy and 68.6% as ≥third-line therapy. Data from AURAext and AURA2 are immature; the OS and PFS data from the pooled dataset are 12.7% and 38.9% mature, respectively. The immaturity of the PFS data also means that the safety profile of osimertinib should be viewed with caution. The EMA also noted the limitations of the company's data when they issued a conditional licence for osimertinib.

There are doubts about whether the clinical data used to demonstrate the relative effectiveness of osimertinib compared to treatment with PDC are robust. To create this dataset the company used data from the control (PDC) arm of the IMPRESS trial (a phase III RCT). Tumour samples from patients in this arm were tested (retrospectively) for the EGFR T790M mutation. The resultant dataset was small (n=61) and although the PFS data for this group are relatively mature (83.6%), the OS data are only 32.8% mature. The company should be commended for the effort taken to create a comparator dataset. They should also be commended for applying a methodology to adjust for different patient characteristics between trials. TEXT REMOVED

Lack of mature survival data has hindered the company's claims that treatment with osimertinib is more clinically effective, or more cost effective, than PDC in patients with T790M mutations who have failed EGFR-TKI treatment. Using the limited survival data available it is impossible for the company to put forward a robust argument in support of osimertinib using traditional methods of analysis (e.g. RCT results, indirect treatment comparisons or life-time economic evaluations). The ERG acknowledges the company's efforts to showcase the strengths of osimertinib. However, until more mature data are available the strengths and weaknesses associated with treatment with osimertinib will remain unclear.

10 APPENDICES

Appendix 1: ERG changes to submitted company model

ERG Section 6 results table revision	Associated detail	Implementation instructions
R1. TTD data for on treatment costs	OSI_TTD.xlsx. These changes generate alternative acquisition and administration costs in the model ('Results' Sheet Cells N51:P52). QALY changes and all other cost changes resulting from these changes should be ignored.	For osimertinib ***In Workbook OSI_TTD.xls*** In Sheet 'Values' Copy range **O4:O783** ***In company model*** In Sheet 'PatFlow_B' Paste values to cells **G13:G792** For PDC ***In Workbook OSI_TTD.xls*** In Sheet 'Values' Copy range **P4:P783** ***In company model*** In Sheet 'PatFlow_B' Paste values to cells **O13:O792**
R2. Calculation of osimertinib administration cost	OSI_TTD.xlsx	Calculated by ERG. Workings can be found in OSI_TTD.xlsx in Sheet 'Values' **Column E**
R3. LUME-LUNG 1 utility		In Sheet 'CountryData' Set value in cell I679 = 0.687 Set value in cell I680 = 0.640
R4. Nafees utility		In Sheet 'CountryData' Set value in cell I679 = 0.653 Set value in cell I680 = 0.470
R5. Osimertinib generates a gain in PFS but not OS		In Sheet 'PatFlow_B' Copy cells **Q13:Q792**

ERG Section 6 results table revision	Associated detail	Implementation instructions
compared to PDC		Paste values in range **I13:I792** Enter formula in cell **H13 '=1-G13-I13'** Copy formula in cell **H13** to **H14:H792**

Patient access scheme submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Osimertinib for the treatment of locally advanced or metastatic EGFR and T790M mutation positive non-small cell lung cancer

Single technology appraisal (STA)

February 2016

AstraZeneca UK Ltd

600 Capability Green, Luton LU1 3LU

1 Introduction

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

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

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

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and 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 the Department of Health.

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

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

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

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

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

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

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the ‘Guide to the methods of technology appraisal’ (http://publications.nice.org.uk/guide-to-the-methods-of-technology-appraisal-2013-pmg9).

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

3 Details of the patient access scheme

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

The patient access scheme will apply to osimertinib (Tagrisso®), which is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC).

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

The patient access scheme aims to improve patient access and the cost effectiveness of osimertinib within its licensed indication.

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

The patient access scheme 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 patient access scheme will apply to the licensed population, which is adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC).

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 is not dependent upon any criteria and is simply applied as a lower fixed price per pack.

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

The scheme will apply to all NHS patients for whom osimertinib is indicated and where the NHS institutions in England and Wales have entered into an agreement with appropriate confidentiality provisions with AstraZeneca.

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

The discounted price per pack will be applied at the point of invoice.

[redacted]

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

The discounted price per pack will be applied at the point of invoice.

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

The scheme will operate exactly the same as when a product would be ordered at list price, except for the invoice reflecting the discounted price rather than the NHS List price.

3.10 Please provide details of the duration of the scheme.

The proposed patient access scheme will be conditional upon:

(i) NICE issuing positive guidance for osimertinib for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC;

(ii) the relevant NHS Trust entering into a contract with AstraZeneca that contains appropriate confidentiality provisions; and will remain in place so long as NICE positive guidance exists for osimertinib and subject to Department of Health agreement

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

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

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for

pharmacists and physicians and patient information documents. Please include copies in the appendices.

Not applicable.

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

Not applicable.

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 manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

Not applicable.

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.

Not applicable.

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.

The PAS has been applied by reducing the current NHS list price of osimertinib.

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.

The clinical effectiveness data used in the economic model which includes the patient access scheme is identical to that presented in the manufacturer's main submission.

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 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

The PAS is a simple discounted price per pack at the point of invoice and therefore will not be associated with any operational or implementation costs.

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.

Not applicable.

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.

Table 1. Cost-effectiveness results – base case (without PAS)

	Osimertinib	Platinum doublet chemotherapy
Intervention (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	[redacted]

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

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

Table 2. Cost-effectiveness results – base case (with PAS)

	Osimertinib	Platinum doublet chemotherapy
Intervention (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	[redacted]	[redacted]
LYG	[redacted]	[redacted]
LYG difference	[redacted]	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	[redacted]	[redacted]
ICER (£)	[redacted]	£42,959

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

Table 3. Incremental results – base case analysis (without PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum doublet chemotherapy	[redacted]	[redacted]	[redacted]				

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

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

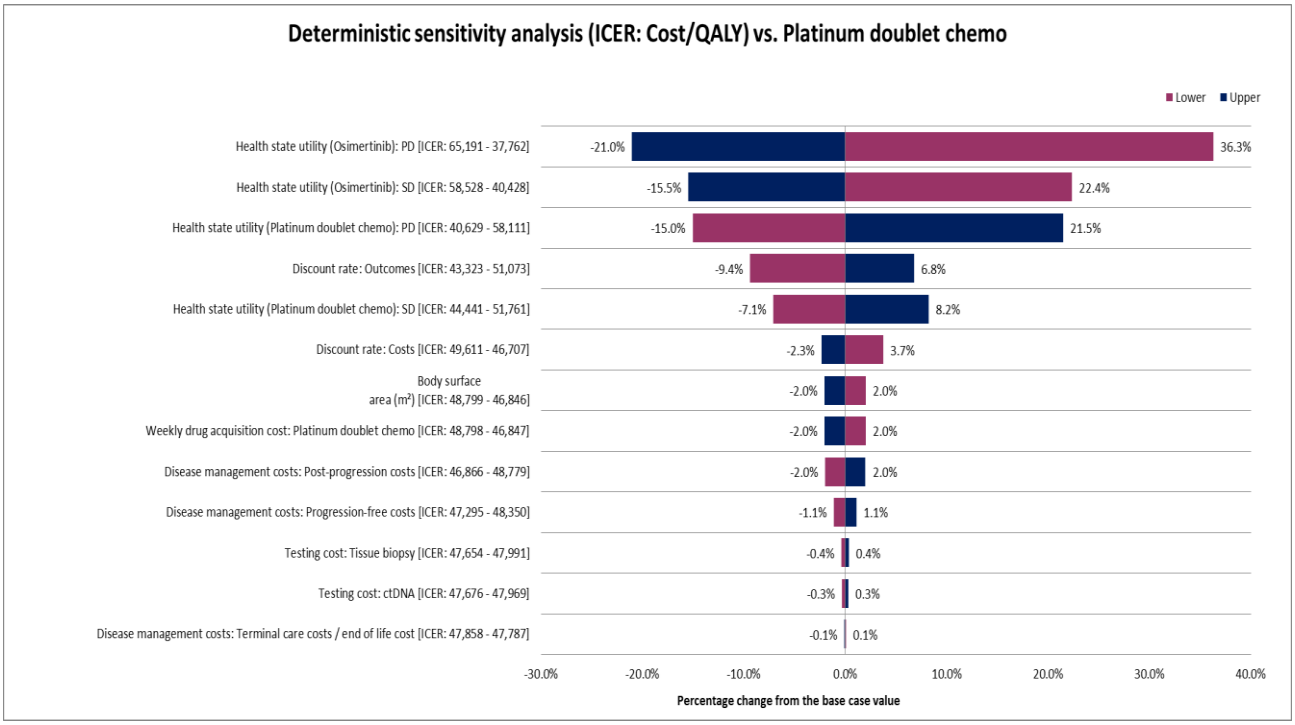
Table 4. Incremental results – base case analysis (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£42,959
Platinum doublet chemotherapy	[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 manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.



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

The results of the probabilistic sensitivity analysis based on 10,000 Monte-Carlo simulations are presented in Figure 1. The mean probabilistic ICER

calculated from the outputs of the 10,000 simulations was £42,148 per QALY gained.

Figure 1. Cost-effectiveness acceptability plane

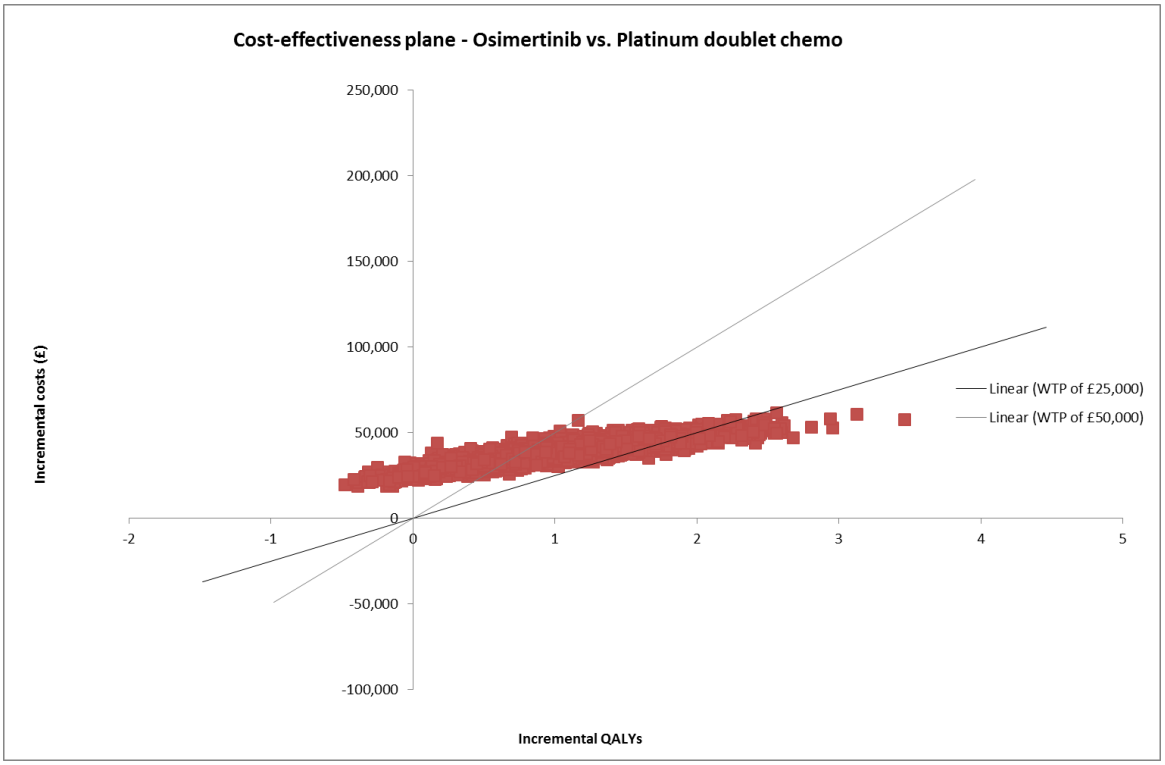
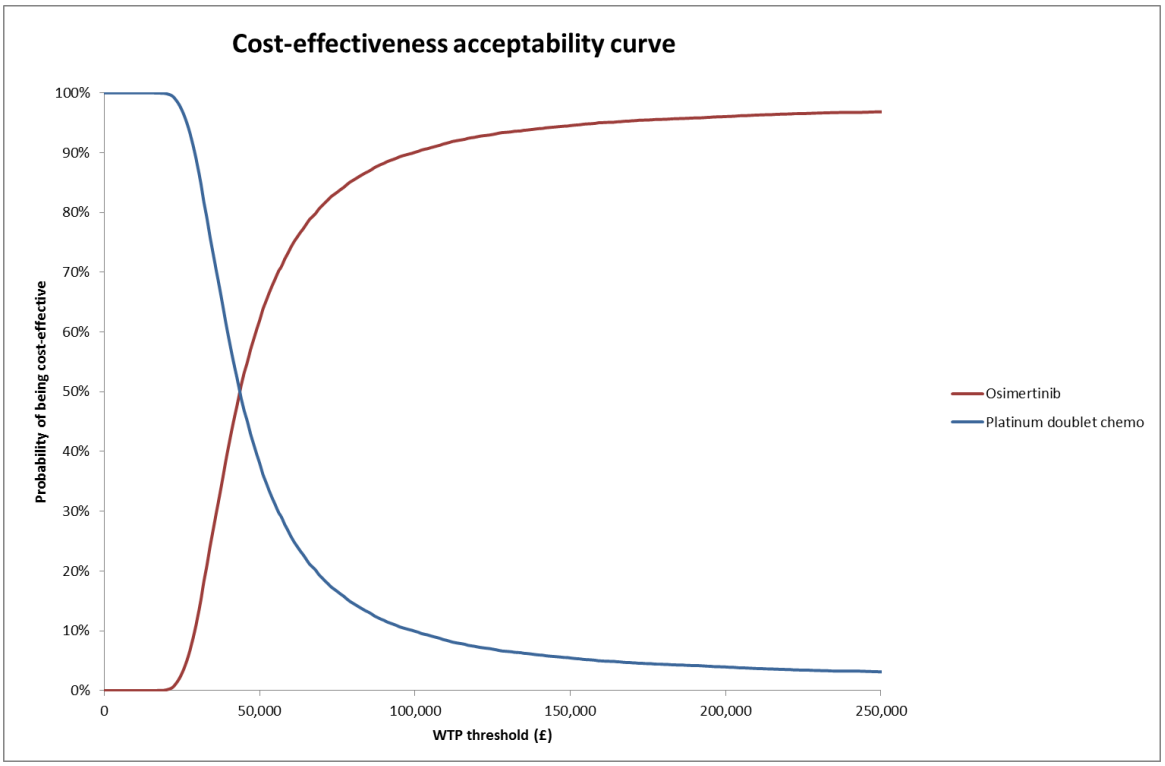


Figure 2 shows the probability that osimertinib is cost effective based on a range of cost-effectiveness thresholds (cost effectiveness acceptability curve). At a cost-effectiveness threshold of £50,000, the probability of osimertinib being considered cost effective versus platinum doublet chemotherapy was 62%.

Figure 2. Cost-effectiveness acceptability curve



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

Table 5. Results of scenario analyses for osimertinib versus platinum doublet chemotherapy (with PAS)

Scenario	Total cost (£) Osimertinib	Total cost (£) PDC	Total QALYs Osimertinib	Total QALYs PDC	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**42,959**
(i) Survival modelling							
IMPRESS ITT population PFS/OS data	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	49,853
PFS and OS Distribution – Log Logistic (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,299
PFS and OS Distribution – Log Normal (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	31,289
PFS and OS Distribution – Weibull (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	47,822
PFS and OS Distribution – G Gamma (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	145,984
PFS and OS Distribution – Gompertz (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,052,785
PFS and OS Distribution – Exponential (both arms)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,430
(ii) Health state utility values							
Treatment-specific utility values (Osimertinib – AURA2; PDC – IMPRESS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43,125
PD Utility decrement (Nafees et al): -0.1798	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,604
(iii) Resource use and costs							
Exclude T790M test costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	41,344
Treatment after RECIST progression - osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44,583
Pemetrexed generic costs (75% discount)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	46,015

Subgroup Analyses (with PAS)

(i) Second-line only population

Table 6: Subgroup Analysis – Osimertinib vs. Platinum-based chemotherapy (AURAext/2 second-line only population)

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	39,610
PDC	[redacted]	[redacted]			

Table 7: Subgroup Analysis – Osimertinib vs. docetaxel monotherapy (AURAext/2 ≥ second-line population)

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	47,358
Docetaxel monotherapy	[redacted]	[redacted]			

(ii) ≥ Third-line Population

Table 8: Subgroup analysis – osimertinib vs. docetaxel monotherapy (AURAext/2 ≥ Third-line population)

Treatment	Total cost (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	40,900
Docetaxel monotherapy	[redacted]	[redacted]			

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.

Not applicable.

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 (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Please see sections 4.9-4.11.

5 Appendices

5.1 Appendix A: Additional documents

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

5.2 Appendix B: Details of outcome-based schemes

5.2.1 If you are submitting a proven value: price increase scheme, as defined in the PPRS, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2.2 If you are submitting an expected value: rebate scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2.3 If you are submitting a risk-sharing scheme, as defined in the PPRS, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the proposed relationship between future price changes and the evidence to be collected.

Not applicable.

5.2.4 For outcome-based schemes, as defined in the PPRS, please provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

5.2.5 If you are submitting a risk-sharing scheme, please specify the period between the time points when the additional evidence will be considered.

Not applicable.

5.2.6 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered.

Not applicable.

5.2.7 Please provide the other data used in the economic modelling of the patient access scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.2.8 Please present the cost-effectiveness results as follows.

- For proven value: price increase schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For expected value: rebate schemes, please summarise in separate tables:
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming).
- For risk-sharing schemes, please summarise in separate tables:
  - the results based on current evidence and current price
  - the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
  - the results based on the current evidence and the lower price (if the new evidence is not forthcoming)
  - the anticipated results based on the expected new evidence and the proposed higher price.

A suggested format is shown in table 3, section 4.7.

Not applicable.

5.2.9 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2.8 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable.

STA Report Confidential Appendix

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Osimertinib for locally advanced or metastatic EGFR and T790M mutation-positive non-small cell lung cancer [ID874]

Confidential appendix including osimertinib patient access scheme discount

This report was commissioned by the NIHR HTA Programme as project number 15/121/09

26th April 2016

CONTAINS COMMERICAL IN CONFIDENCE DATA

ALL TABLES AND FIGURES IN THIS APPENDIX ARE CONFIDENTIAL

1 INTRODUCTION

As part of the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process to consider the clinical and cost effectiveness of osimertinib (Tagrisso®) for locally advanced or metastatic epidermal growth factor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), AstraZeneca (the company) developed an economic model using Microsoft Excel.

In the company submission (CS), base case cost effectiveness results are presented for the comparison of osimertinib versus platinum doublet chemotherapy (PDC). The Evidence Review Group (ERG) report for this appraisal summarises the base case cost effectiveness results presented in the CS. In addition, it includes results generated after applying a number of ERG amendments to the company model. The results presented in the ERG report have been generated using list prices for all drugs.

The amendments made by the ERG to the company model are:

- use of time to treatment discontinuation data (TTD) to calculate the acquisition costs of osimertinib and PDC (R1)
- application of an administration cost for osimertinib (R2)
- use of health state utility values from LUME-Lung 1 study[1] (R3)
- use of use of health state utility values from a study by Nafees[2] (R4)
- PFS gain only (i.e., equal OS for osimertinib and PDC).

This confidential appendix includes the deterministic cost effectiveness results generated by the company model when the confidential Patient Access Scheme (PAS) discount is applied to osimertinib.

2 DETERMINISTIC RESULTS

Cost effectiveness results (using PAS prices for osimertinib) for the comparison of osimertinib versus PDC are displayed in **Error! Reference source not found.**.

The results show that, once the relevant PAS discount is applied to osimertinib, osimertinib remains more expensive than PDC in the company base case and when all of the ERG's suggested amendments have been implemented.

CONFIDENTIAL APPENDIX

The ERG's revised base case ICERs per QALY gained for osimertinib versus PDC, when all of the preferred revisions are combined and using the PAS price for osimertinib, range from £513,286 (Scenario G) to £1,334,543 (Scenario F) per QALY gained.

Table 1 Cost effectiveness results (osimertinib versus PDC) with PAS included for osimertinib [redacted]

Model scenario and revisions	**Osimertinib**			**PDC**			**Incremental**			***ICER***	
	Cost	**QALYs**	**Life years**	**Cost**	QALYs	Life years	Cost	QALYs	Life years	**£/QALY**	**Change from base case**
A. Company's base case	[redacted]									***£42,959***	
R1) Use of TTD data to cost drug acquisition	[redacted]									£64,870	£21,911
R2) Application of administration cost for osimertinib	[redacted]									£45,444	£2,485
B. Base case + (R1:R2)	[redacted]									**£67,249**	**£24,290**
R3) LUME-Lung 1[1] utility	[redacted]									£47,459	£4,500
C. Base case + (R1:R3)	[redacted]									**£74,267**	**£31,308**
R4) Nafees[2] utility	[redacted]									£57,853	£14,894
D. Base case + (R1:R2 and R4)	[redacted]									**£90,531**	**£47,572**
R5) Osimertinib generates a gain in PFS but not OS compared to PDC	[redacted]									£366,596	£323,637
E. Base case + (R1:R2 and R5)	[redacted]									**£648,736**	**£605,777**
F. Base case + (R1:R3 and R5)	[redacted]									**£1,334,543**	**£1,291,584**
D. Base case + (R1:R2, R4:R5)	[redacted]									**£513,286**	**£470,327**

PAS=patient access scheme; PDC=platinum doublet chemotherapy; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; TTD=time to treatment discontinuation; PFS=progression-free survival; OS=overall survival

3 REFERENCES

1. Reck M, Kaiser R, Mellemgaard A, Douillard JY, Orlov S, Krzakowski M, *et al*. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): A phase 3, double-blind, randomised controlled trial. Lancet Oncol. 2014; 15:143-55.
2. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008; 6:84.

Additional Evidence provided in response to ERG Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Osimertinib for locally advanced or metastatic, EGFR and T790M mutation positive non-small cell lung cancer [ID874]

Single technology appraisal (STA)

AstraZeneca UK Ltd
600 Capability Green, Luton LU1 3LU

Summary

Throughout the ERG report, the immaturity of the submitted evidence in the manufacturer submission is highlighted, in particular in relation to the modelled OS benefit for osimertinib in comparison to platinum doublet chemotherapy. In its report, the ERG argues there is *'no basis to project differential OS due to the lack of statistical significance in OS between osimertinib and PDC during the period for which data are available'*.

AstraZeneca is aware that new evidence can normally not be presented at this stage of the process. However, in light of the above, it believes it is important to make the ERG and Appraisal Committee aware that, since the manufacturer submission in February 2016, more mature evidence from the phase I/II AURAext and phase II AURA2 studies has become available, based on a November 2015 DCO. An update of the pooled AURA dataset using this additional evidence has also been conducted.

[redacted]

[redacted]

A summary of the above outlined new evidence is presented within this document as AstraZeneca considers it inaccurate to state that there is no basis on which to project differential OS [redacted]

These data should be considered supportive to the original manufacturer submission and consistent with the projected clinical and economic value proposition, providing further confidence in the assumptions made as part of the base case economic model. As these data have only just been presented, AstraZeneca has not yet had the opportunity to update the relevant cost-effectiveness analyses but is in the process of doing so. We request that these analyses could be shared with the ERG as soon as possible so they could be taken into consideration going forward.

Additional Evidence

More mature evidence in the licensed indication

In April 2016, the data were presented at the European Lung Cancer Conference (ELCC) in Geneva in, Switzerland, and reinforce the efficacy and safety profile for osimertinib previously seen in the AURA clinical trials programme. A key summary on the most relevant endpoints is provided below.

Progression-Free Survival

In the updated analysis, median PFS in the FAS based on assessments by BICR (55.2% maturity) was 11.0 months (95% CI: 9.6, 12.4) compared to 9.7 months (95% CI: 8.3, NC) based on the previous data cut off (38% maturity).

Figure 1: Progression-free survival by central review by study and total, Kaplan-Meier plot (FAS) – November 2015 DCO

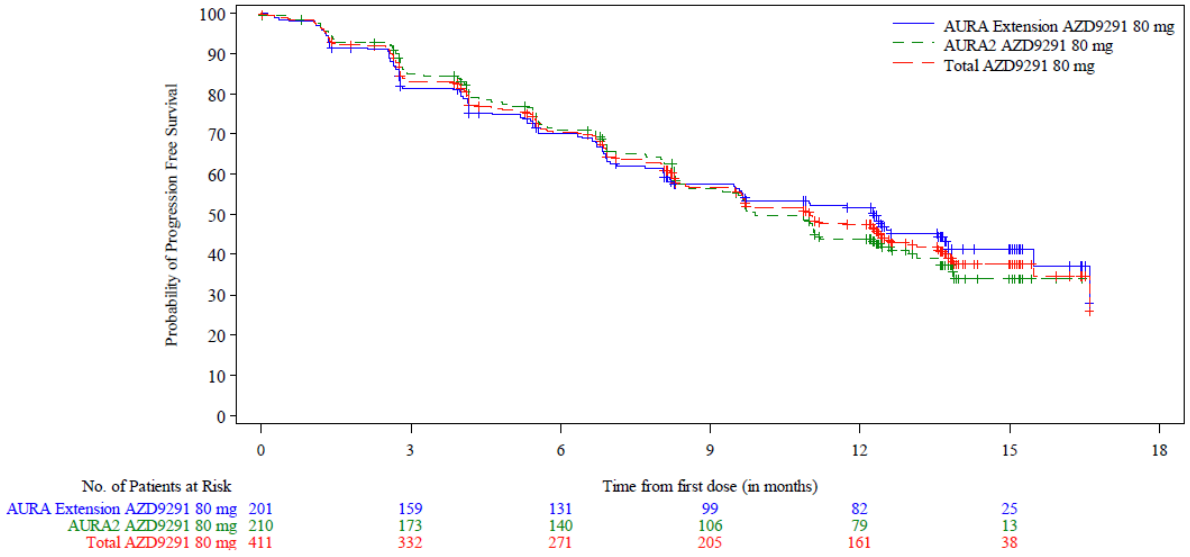


Table 1: Progression-free survival by BICR by study (FAS) – November 2015 DCO

	AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
Total number of events[a]	107	120	227
Median progression free survival (months)[b]	12.3	9.9	11.0
95% CI for median progression free survival	9.5, 13.8	8.5, 12.3	9.6, 12.4
Progression free at 3 months (%)	81.5	85.0	83.3
95% CI for PFS at 3 months	75.3, 86.2	79.3, 89.2	79.3, 86.6
Progression free at 6 months (%)	70.0	70.9	70.4
95% CI for PFS at 6 months	63.0, 75.9	64.1, 76.7	65.7, 74.7
Progression free at 9 months (%)	57.6	56.3	56.9
95% CI for PFS at 9 months	50.3, 64.2	49.1, 62.9	51.8, 61.6
Progression free at 12 months (%)	51.6	43.9	47.5
95% CI for PFS at 12 months	44.2, 58.5	36.8, 50.8	42.4, 52.5
Median follow-up for PFS (Months)	8.3	9.4	8.6
Median follow-up for PFS (Months) (censored patients only)	13.6	12.5	12.6

Based on follow-up at DCO, the Kaplan-Meier estimated probability of being alive and progression-free based on BICR assessment was 83.3% (95% CI: 79.3, 86.6) at 3 months, 70.4% (95% CI: 65.7, 74.7) at 6 months, 56.9% (95% CI: 51.8, 61.6) at 9 months and 47.5% (95% CI: 42.4, 52.5) at 12 months (Table X).

Overall Survival

IMPRESS

[redacted]

AURAext/AURA2

As highlighted in the ERG report, the presented OS data in the company submission were very immature (12.7%). The updated data (November 2015 DCO), whilst still immature (23.8%), support a clear separation between the AURA pooled KM data when compared to the IMPRESS OS KM plot as illustrated in Figure 3 [redacted]. It therefore supports the projected differential OS benefit and previously submitted cost-effectiveness analysis. The KM curve should be interpreted with caution beyond 13-15 months due to the high degree of censoring leading to a small risk set to inform the curve.

Figure 3: Overall survival by central review, Kaplan-Meier plot (FAS) – November 2015 DCO

[Figure Removed]

The Kaplan-Meier estimate of the proportion of patients alive on osimertinib based on BICR assessment of the FAS was [redacted]

Table 2: Survival status at time of data cut-off and median OS by study (FAS) – November 2015 DCO

[Table Removed]

[redacted] In the AURA pooled dataset, survival at 14 months is approximately [redacted]. At 12 months, before the AURA data becomes heavily censored, [redacted] of patients were alive compared to [redacted] This should be considered in the context of more than 60% of patients in the AURA pooled data set being 3rd line or later compared to IMPRESS being a purely second line population, making the comparison a conservative one.

[redacted]

[redacted]

Table 3: Analysis of Overall Survival – Updated adjusted indirect comparison

		Number (%) of patients with events	Median OS (months) 95% CI	Treatment effect (Osimertinib vs PDC)		
Treatment	**N**			**Hazard ratio**	**95% CI**	**2 sided *p*-value**
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum doublet chemotherapy	[redacted]	[redacted]	[redacted]			

Figure 4: Overall survival in updated adjusted indirect comparison by central review, Kaplan-Meier plot (FAS) – November 2015 DCO

[Figure Removed]

In addition, in its report, the ERG argued that very few EGFRm+ patients in the NHS receive more than one or two treatments after an EGFR-TKI in contrast to patients in the AURAext and AURA2 studies, making the AURA pooled population not representative of UK standard of care. As set out in the manufacturer submission, the expected positioning of osimertinib in the treatment pathway is second line. This is supported by the design of the AURA3 confirmatory Phase III clinical trial in a second-line only cohort of patients. In light of the above, the 2nd line cohort analyses are relevant and should be considered by the ERG and Appraisal Committee going forward.

[redacted]

Figure 5: Overall survival by treatment cohort and total, Kaplan-Meier plot (FAS) – November 2015 DCO

[Figure Removed]

Supportive first line evidence

The phase I data presented at the ELCC show that when osimertinib was used as a first-line treatment among 60 patients (pooled 80mg and 160mg dose cohorts) with epidermal growth factor (EGFR) mutation positive advanced NSCLC:

- 77% of patients responded to treatment as measured by tumour shrinkage (objective response rate or ORR; 95% confidence interval (CI): 64%-87%).
- The median length of time that patients' disease was defined as 'progression-free' was 19.3 months, with 55% of patients remaining progression-free at 18 months (95% CI: 41%-67%).
- The median duration of response was non-calculable (NC) (95% CI: 12.5 months to NC) at the time of data cut off, with 53% of patients continuing to respond at 18 months (95% CI: 36%-67%).
- The most common adverse events were rash (78% overall; 2% ≥Grade 3), diarrhoea (73% overall; 3% ≥Grade 3), dry skin (58% overall; 0 ≥Grade 3) and paronychia (50% overall; 3% ≥Grade 3). All of the Grade 3 or above events in these categories occurred at the 160mg dose.

These latest data in a first line setting, as well as the updated analysis in the currently licensed population, support the role of osimertinib in meeting a significant unmet medical need and give confidence in the durability of patient responses.