

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

Technology appraisal guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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## 1 Recommendations

- 1.1 Osimertinib is recommended as an option for use within the Cancer Drugs Fund for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer in adults whose disease has progressed only:
- after first-line treatment with an EGFR tyrosine kinase inhibitor and
  - if the conditions in the [managed access agreement](#) for osimertinib are followed.
- 1.2 This guidance is not intended to affect the position of patients whose treatment with osimertinib was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

## 2 The technology

<b>Description of the technology</b>	Osimertinib (Tagrisso, AstraZeneca) is a small-molecule inhibitor that targets the sensitising and T790M mutant forms of the epidermal growth factor receptor (EGFR)-tyrosine kinase receptor.
<b>Marketing authorisation</b>	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 on the company submitting the clinical study report of the phase III AURA3 study comparing osimertinib with platinum-based doublet chemotherapy (expected June 2017).
<b>Adverse reactions</b>	The most common adverse reactions associated with osimertinib include diarrhoea, rash, dry skin, and a reduction in platelet count and some white blood cells. For full details of adverse reactions and contraindications, see the summary of product characteristics.
<b>Recommended dose and schedule</b>	80 mg taken orally once a day until disease progression or unacceptable toxicity.
<b>Price</b>	<p>£5,770.00 per pack (30 tablets) of 80 mg tablets and £5,770.00 per pack (30 tablets) of 40 mg tablets (excluding VAT; MIMS online and company correspondence). Treatment is continued until disease progression.</p> <p>The pricing arrangement considered during guidance development was that the company (AstraZeneca) had agreed a patient access scheme with the Department of Health. This scheme would provide a simple discount to the list price of osimertinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS. The managed access agreement agreed in September 2016 replaced the patient access scheme.</p>

### 3 Evidence

The appraisal committee ([section 7](#)) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group. In response to consultation, the company submitted additional clinical evidence and cost-effectiveness analyses that focused on the population whose condition had been treated with first-line tyrosine kinase inhibitor therapy. See the [committee papers](#) for full details of the evidence.

## 4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of osimertinib, having considered evidence on the nature of locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC) and the value placed on the benefits of osimertinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The committee heard from the patient experts that EGFR mutation-positive NSCLC causes many distressing and debilitating symptoms, and typically has a poor prognosis. It heard that even slight symptomatic improvements are very important for people with this condition, and that even a small extension to life would be significant. The clinical and patient experts stated that people with the T790M mutation represent the minority of those with non-squamous NSCLC (between 0.5% and 6% at diagnosis). The committee heard from the experts that the availability of osimertinib could be a step change in the management of the condition, similar to the arrival of the original tyrosine kinase inhibitors (TKIs). It noted that in about 60% of people with EGFR mutation-positive NSCLC, their disease will become resistant to treatment with other TKIs because of T790M mutations. The clinical experts agreed that there will be fewer visits to hospital associated with osimertinib because it is better tolerated than other treatments, such as platinum-doublet chemotherapy, so an oral targeted therapy for this population is welcomed. The committee concluded that the availability of a new targeted treatment option with improved tolerability would be valuable for people with EGFR T790M mutation-positive NSCLC.

### *Current clinical management of EGFR T790M mutation-positive NSCLC*

4.2 The committee noted that the marketing authorisation for osimertinib is for treating locally advanced or metastatic EGFR T790M mutation-positive NSCLC in adults. It understood that EGFR mutation-positive NSCLC is first treated with EGFR TKIs, such as [afatinib](#), [gefitinib](#) or [erlotinib](#), according to existing NICE guidance. It heard from the clinical experts that people with the T790M mutation that is identified at diagnosis, represent about 1% of the EGFR mutation-positive population and that osimertinib would very rarely be used in this setting. The committee noted the comments from the company and the clinical experts that osimertinib would only be used for people with EGFR mutation-positive NSCLC whose disease had progressed after first-line

EGFR TKIs. It heard from the clinical experts that a repeat biopsy would be needed to confirm whether an EGFR T790M mutation had developed, although testing for this mutation is not currently routine and varies depending on where people are treated in England and Wales. The committee understood from the clinical experts that the most widely used treatment for people whose disease had progressed after treatment with a first-line TKI would be platinum-doublet chemotherapy (including pemetrexed plus carboplatin or cisplatin). The committee concluded that platinum-doublet chemotherapy was the most relevant comparator for osimertinib in this appraisal.

## *Clinical effectiveness*

- 4.3 The committee noted that the key clinical-effectiveness evidence for osimertinib was taken from the non-randomised, non-controlled, single-arm AURA extension and AURA2 studies that included people with EGFR T790M mutation-positive NSCLC whose disease had progressed while having a TKI. It noted that the company's evidence for efficacy of platinum-doublet chemotherapy in the equivalent population came from the IMPRESS study, which was used to do a naive indirect comparison of the results from the AURA extension, AURA2 and IMPRESS studies. The committee noted the evidence review group's (ERG) comments that the trials were designed and carried out to a good standard. The committee understood that people included in the AURA extension, AURA2 and IMPRESS studies were younger and fitter than those seen in clinical practice. It heard from the clinical experts that there will always be concerns that patients recruited to clinical trials could be younger, fitter and so more responsive to treatment than those seen in clinical practice. But, the experts highlighted that these trials were more generalisable than most other lung cancer trials because people with EGFR mutation-positive NSCLC tended to be diagnosed at a younger age, were fitter and not necessarily smokers compared with other types of lung cancer. The committee concluded that the trials used as the basis for evaluating the efficacy of osimertinib in people with EGFR T790M mutation-positive NSCLC that has progressed on a previous TKI were broadly generalisable to clinical practice.
- 4.4 The committee noted that the company had pooled the data from the AURA extension and AURA2 studies. It understood that the ERG had agreed that pooling the results for the 2 AURA trials was reasonable given that the studies were very similar regarding baseline characteristics. It heard from the clinical



and patient experts that an overall-response rate of 66% for osimertinib, as a primary outcome, was not usually seen in patients who had had platinum-doublet chemotherapy and is similar to the response rates seen for TKI agents used for people with untreated EGFR mutation-positive NSCLC. The committee heard that this response rate was important for improvements in the quality of life for people with this condition. The committee noted the additional evidence submitted by the company in response to consultation, which included updated clinical results from the full analysis of the pooled AURA dataset (AURA extension and AURA2; for people having osimertinib as second and later lines of treatment) based on a November 2015 data cut-off. It noted that the estimate of median progression-free survival from this analysis was 11.0 months (95% confidence interval 9.6 to 12.4). The committee was aware that overall-survival data were still immature (23.8% of people had died in the pooled AURA dataset) and that a median overall-survival estimate was not calculable based on the available results. It also noted that the company's response to consultation stated that the more recent data from November 2015 showed a difference in overall survival for osimertinib between the second-line population (after treatment with a first-line EGFR TKI) and the third-line or later populations (the results are academic in confidence and cannot be presented here). The committee concluded that interpreting these results remained challenging in the absence of a direct comparator in the trial, and that this was compounded by the small patient numbers in the trial and the very immature survival data.

## Indirect comparisons

- 4.5 The committee discussed the company's original unadjusted and adjusted indirect comparisons of the pooled AURA data and the single arm from the IMPRESS control group (platinum-doublet therapy) in people whose disease had progressed after a TKI therapy (that is, as a second or later line of treatment). The committee noted that for the adjusted indirect comparison, 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). It noted that for the primary outcome, overall-response rates were 64.6% for the osimertinib arm (based on the adjusted pooled AURA dataset) and 34.8% for the platinum-doublet chemotherapy arm (based on the adjusted IMPRESS trial T790 mutation-positive population). The committee understood that, in the adjusted indirect comparison, osimertinib improved progression-free survival

by 4.4 months compared with platinum-doublet chemotherapy (9.7 months compared with 5.2 months), but that median overall survival was not calculable for osimertinib. The committee heard from the clinical experts that evaluating overall survival in a population such as this is always difficult because people have access to alternative treatments in other trials when the disease progresses, meaning that overall survival is often not estimable or it is not possible to show an improvement. The committee heard from the ERG that the company deserves credit for attempting the indirect comparisons despite the lack of available data and with its associated limitations. The committee acknowledged the company's attempts in the circumstances and understood that showing an overall-survival advantage for osimertinib compared with platinum-doublet chemotherapy would be challenging. The committee concluded that osimertinib offered an advantage for overall-response rates and progression-free survival compared with platinum-doublet chemotherapy for people whose disease has progressed after TKI therapy (that is, as a second or later line of treatment) but improvements in overall survival could not be shown based on the currently available immature evidence.

- 4.6 The committee noted that the company had provided a revised adjusted indirect comparison for osimertinib compared with platinum-doublet chemotherapy, based on the additional November 2015 data analysis for the AURA extension, AURA2 and IMPRESS trials and restricting the population to people whose disease had progressed after a first-line TKI (that is, a second-line only population). This showed that there was a reduction in the median overall survival associated with platinum-doublet chemotherapy compared with the original data analysis submitted by the company (the results are academic in confidence and cannot be presented here). The committee was concerned that because small numbers of people remained in the IMPRESS trial, small changes could have a large effect on the overall-survival results for the comparator arm. The committee heard from the ERG that although the more recent data suggested an improvement in overall survival for osimertinib compared with platinum-doublet chemotherapy, the results should be interpreted with caution because the data were still immature. The committee heard from the company that the more recent data presented from AURA extension and AURA2 were restricted to people with EGFR T790M mutation-positive NSCLC that had progressed after treatment with a first-line TKI because it was more in line with how osimertinib is likely to be used and was more relevant for the comparison with the IMPRESS study. The committee noted that median overall survival for

osimertinib had still not been reached, although the company maintained that osimertinib showed a clinically meaningful and statistically significant overall-survival benefit compared with platinum-doublet therapy in people who have had a first-line TKI. The committee was aware that the AURA3 trial (which directly compared osimertinib with platinum-doublet therapy in people with locally advanced or metastatic EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy) met its primary end point, and showed superior progression-free survival with osimertinib. It noted that analysis of overall survival in AURA3 was still ongoing. The committee concluded that the available data were too immature to robustly estimate the overall-survival advantage of osimertinib compared with platinum-doublet chemotherapy.

## Adverse effects of osimertinib

- 4.7 The committee heard from the clinical and patient experts that osimertinib treatment is associated with excellent tolerability and symptom alleviation. It noted that there was a substantial difference in some adverse events caused by osimertinib compared with platinum-doublet chemotherapy, such as diarrhoea, and that these can be difficult to manage in clinical practice particularly in older people. But, the committee concluded that osimertinib was a well-tolerated treatment in this group compared with cytotoxic chemotherapies such as platinum-doublet chemotherapy.

## Cost effectiveness

### The company's economic model

- 4.8 The committee considered the company's economic model, which used a cohort-based partitioned survival model including 3 health states: progression-free disease, progressed disease and death. The model used a lifetime time horizon (maximum length of 15 years), and costs and benefits were discounted at an annual rate of 3.5%. The cost-effectiveness results reported included the patient access scheme discount agreed between the company and the Department of Health. The committee noted that the ERG considered that the model was well constructed and easy to use. The committee concluded that the company's approach was acceptable and that the economic model was suitable for decision-making.

- 4.9 The committee noted that the company used pooled data from the AURA extension and AURA2 studies to estimate progression-free survival and overall survival for osimertinib, whereas data from the IMPRESS study were used for platinum-doublet chemotherapy. The committee was aware that the company had provided a revised economic model in response to consultation that focused on a comparison of osimertinib with platinum-doublet therapy in people whose disease had progressed after first-line TKI therapy. The committee agreed with the company that this most likely reflected how osimertinib will be used in UK clinical practice and provided the most robust comparison between the AURA extension and AURA2 studies and the IMPRESS study. It noted that the company's revised base-case incremental cost-effectiveness ratio (ICER) was £41,705 per quality-adjusted life year (QALY) gained (incremental costs £64,283; incremental QALYs 1.541) for osimertinib compared with platinum-doublet therapy for people whose disease had progressed after first-line TKI therapy. The committee was aware that, although a more recent data cut (November 2015) was used to update the model, the available data were still immature and the company still had to extrapolate the overall-survival results from the AURA extension, AURA2 and IMPRESS studies to the lifetime time horizon of the model. The committee heard from the ERG that the company should be commended for exploring a range of survival extrapolations. It noted that the extrapolations used for the company's base case (Weibull distributions for both osimertinib and platinum-doublet therapy) resulted in an incremental progression-free survival gain of 6.5 months and an incremental overall-survival gain of 21.0 months for osimertinib compared with platinum-doublet chemotherapy. The committee noted that the overall-survival gain for osimertinib was double that of the company's original base case. However, it heard from the company that this was because of the availability of 6 months of additional data, and that the model was now restricted to a second-line population who have better survival outcomes compared with later-line populations. The committee remained concerned that the number of events in the trial was very small and that restricting the population further reduced the sample size even more. The committee concluded that this increased the uncertainty in estimating differences between the 2 treatments.
- 4.10 The committee noted the ERG's comments that the distributions used to extrapolate overall survival in the company's base case were broadly acceptable given the paucity of relevant survival data available, especially for osimertinib. But, the ERG also commented that because of the immaturity of the available

data, there was no statistical basis for an overall-survival gain for osimertinib compared with platinum-doublet chemotherapy and so no extrapolation was more valid than any other; the ERG highlighted that there was large uncertainty about the robustness of overall-survival estimates. The committee was concerned that depending on the choice of extrapolation to predict overall survival, the company's ICER estimates could vary greatly. It noted that the company's updated economic model, which was restricted to a second-line only population and used the November 2015 data provided fewer extrapolations than were presented in the company's original submission. It heard from the ERG that the Gompertz distribution was a better fit for osimertinib than the Weibull distribution (the distribution used in the base case) but a worse fit for platinum-doublet therapy. The committee heard from the ERG that assuming both intervention and comparator overall-survival projections have to be modelled with the same distribution, and using the Akaike information criterion (a measure of the relative quality of statistical models for a given set of data), a generalised gamma distribution in the company model suggested an ICER of £89,296 per QALY gained (incremental costs £55,097; incremental QALYs 0.617). However, the ERG said that this was not necessarily a more plausible ICER than any other estimate. Although this scenario was not considered likely by the committee, it showed the sensitivity of the ICER to less optimistic assumptions about the survival gains attributable to osimertinib. The committee noted that some of the distributions suggested by the company produced exceptionally high and potentially clinically implausible long-term overall survival. It noted that a less extreme sensitivity analysis, using a generalised gamma distribution to extrapolate survival for osimertinib and a Weibull distribution to extrapolate survival for platinum-doublet therapy, increased the ICER from £41,705 to £60,663 per QALY gained (incremental costs £58,472; incremental QALYs 0.964) and, in its judgement, it considered this a potentially more reasonable analysis than the others presented. The committee concluded that, because of the immaturity of the data, any estimate of an overall-survival gain for osimertinib compared with platinum-doublet chemotherapy was very uncertain and could have a very large effect on the ICER depending on the extrapolation chosen.

## Utility values in the model

- 4.11 The committee noted that the utility values used in the company's base-case analysis were derived from EQ-5D-5L data collected in the AURA2 study and

the modelled values were not treatment specific (that is, utility was 0.815 for progression-free disease and 0.678 for post-progression disease, regardless of the treatment arm in the model). The committee understood from the ERG that the utility value of 0.815 for people in the progression-free health state was higher than in the general population for people of a similar age (although the figure for the general population was estimated using EQ-5D-3L). The committee noted that the utility value for progression-free disease used in the base-case analysis was higher than that seen in the IMPRESS study (0.779), which included a younger second-line only population, but the committee acknowledged that IMPRESS used EQ-5D-3L to derive utility values. The committee heard from the clinical experts that people with EGFR mutation-positive NSCLC are generally younger and fitter than people with other types of lung cancer. The committee heard from the ERG that the company had used a method called 'crosswalking' to calculate the utility values because there was no validated dataset for the UK at the time of submission. The committee questioned whether the high utility values resulted from using the EQ-5D-5L rather than the EQ-5D-3L instrument. The committee agreed that, because a validated EQ-5D-5L dataset for the UK was not available, it was difficult to compare results with values derived from sources using the EQ-5D-3L instrument. It noted that, in response to consultation, the company had provided a revised model for second-line only treatment and had used utility values for progression-free disease based on the IMPRESS study (0.831 for treatment response, 0.751 for stable disease; same values used for both treatments in the model) and a value of 0.715 for progressed disease (based on a midpoint between the AURA EQ-5D-5L crosswalk value and the IMPRESS EQ-5D-3L value). The committee noted that the ERG considered the utility values from the LUME-lung 1 study could be more reasonable (that is, 0.67 utility value for both the response and stable states and 0.64 for the progressed disease state) because the company's values were implausibly high for people with metastatic NSCLC whose disease has progressed after first-line TKI therapy. The committee noted that analyses incorporating the ERG's suggested utility values increased the company's base-case ICER from £41,705 to £47,863 per QALY gained (using the Weibull distribution to extrapolate survival for both treatment arms). Using the alternative extrapolation, in which the survival curve for osimertinib followed a generalised gamma function (see section 4.10), combined with the ERG's suggested utility values increased the ICER from £60,663 to £70,776 per QALY gained. However, the committee heard from the ERG that these values did not take account of the improved response rates for

osimertinib and so a pre-progression utility value of about 0.7 could be more reasonable. The committee concluded that there was uncertainty in the utility values used by the company because they were based on non-UK validated EQ-5D-5L data from a small number of people. It also agreed that, although there were concerns about the face validity of the values from AURA2 compared with the general population, the values suggested by the ERG were not necessarily more appropriate for this population. The committee concluded that the most plausible utility values would fall somewhere between those used by the company in its updated analysis and those suggested by the ERG.

- 4.12 The committee considered the importance of incorporating response rates in the company model. It noted the comments from the clinical and patient experts that response rates for osimertinib were very high and resulted in symptomatic improvements in people having it. The committee considered that an improved response rate with osimertinib compared with platinum-based chemotherapy could result in improvements in quality of life and therefore, in utility, and that this should have been included in the company's model. The committee discussed the company's additional evidence, which included scenario analyses exploring a range of utility values that incorporated a treatment-specific response. It noted that including a treatment response had a minor effect in reducing the ICERs. The committee concluded that the benefits of improving overall-response rates had a minor effect on the company's cost-effectiveness results.

## Costs of osimertinib treatment

- 4.13 The committee noted that in the company's original base-case analysis, acquisition costs of osimertinib were based on progression-free survival. The committee was aware that in the AURA studies, people could continue treatment with osimertinib even after disease progression (59.7% of people continued treatment for at least 7 days and the median duration of treatment was 1.6 months after progression). It noted the ERG's comments that acquisition costs of osimertinib should therefore be based on time-to-treatment discontinuation rather than progression-free survival and this would result in higher costs for osimertinib. The clinical experts agreed that costs of osimertinib based on time-to-treatment discontinuation were the most appropriate to use. The committee noted that the company had submitted a revised model that included costs calculated based on time-to-treatment discontinuation and these

were now incorporated as part of its revised base-case analysis. The committee concluded that time-to-treatment discontinuation had been included appropriately in the company's revised analysis.

- 4.14 The committee noted the ERG's comments that the company model did not include a cost for giving osimertinib and that clinical advice the ERG received suggested that osimertinib is provided, on a monthly basis, in a nurse-led clinic. The committee heard from the company that the costs are partly included in the model as outpatient visits. The clinical experts at the committee meeting agreed with the company but highlighted that the company had not accounted for pharmacy dispensing costs. The committee noted that the company had subsequently addressed this in its revised analysis by including additional monthly costs involved in dispensing osimertinib. The company also updated the model to address some of the ERG's concerns that costs of platinum-doublet therapy were not calculated correctly. The committee concluded that the administration costs of osimertinib were included in the revised base case and concerns around the costs of platinum-doublet therapy had been addressed by the company.

### Most plausible cost-effectiveness estimate

- 4.15 The committee considered the company's revised base-case analysis, which addressed several issues raised by the ERG and the committee (see sections 4.13 and 4.14). It noted that the company's revised base-case ICER was £41,705 per QALY gained (incremental costs £64,283; incremental QALYs 1.541) for osimertinib compared with platinum-doublet therapy in people whose disease had progressed after first-line EGFR TKI treatment. It acknowledged that there were still uncertainties with the utility estimates used in the model, which could affect the ICER and should be taken into account (see section 4.11). However, the committee considered that the largest uncertainty was related to robustly estimating overall survival with very immature data. The committee agreed that, although the choice of overall-survival extrapolation could have a very large effect on the cost-effectiveness estimates, the data were so immature that any estimate of overall survival was extremely uncertain. The committee noted that, for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy, the ICER for osimertinib compared with platinum-doublet chemotherapy could be anywhere between £41,705 and £89,296 per QALY gained (see section 4.10). The



committee agreed that there was such uncertainty in the estimated overall survival it was difficult to determine a robust cost-effectiveness estimate, and was aware of the risk to the NHS of paying for a treatment that was not cost effective. It concluded that a reasonable cost-effectiveness estimate for osimertinib compared with platinum-doublet chemotherapy at this point in time was based on the analysis using an extrapolation of survival for osimertinib that followed a generalised gamma function, which gave an ICER between £60,663 (using the company's utility estimates) and £70,776 per QALY gained (using the ERG's alternative utility estimates).

## *Innovation*

4.16 The committee considered the innovative nature of osimertinib. It heard from the patient and clinical experts that there have been no treatments specifically for people with EGFR T790M mutation-positive NSCLC whose disease is resistant to treatment with TKI agents, and that there is an important unmet need for people with this condition. The committee noted comments from the clinical experts that osimertinib represented a step change in managing NSCLC similar to that seen when TKIs were first introduced for first-line treatment of EGFR-positive NSCLC. But it was aware that the survival benefit associated with osimertinib was very uncertain. The committee understood that osimertinib was associated with very high response rates and that this could feasibly result in improvements in quality of life that could be captured as an additional benefit compared with platinum-doublet chemotherapy. The committee considered the company's response to consultation in which the company had attempted to incorporate the effect of a treatment-specific response on utility values in a scenario analysis. It noted that including a treatment response had a minor effect in reducing the ICERs. The committee concluded that osimertinib is innovative, but there were no additional benefits associated with this treatment that could not be captured in the economic analysis.

## *End-of-life considerations*

4.17 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [final Cancer Drugs Fund technology appraisal process and methods](#). The committee noted the evidence presented by the company, which showed that people with locally advanced or

metastatic EGFR T790M mutation-positive NSCLC cancer have a life expectancy of less than 24 months. The committee was aware that the company had made this case for all populations included in the scope of the appraisal. For example, the company presented evidence to suggest that median overall survival was in the range of 20 months for people who had not had treatment before: about 15 months for people who have been previously treated with an EGFR TKI and have the T790M mutation. The committee concluded that people for whom osimertinib is indicated have a short life expectancy, so this criterion was met. The committee considered that because of the immaturity of the data for osimertinib, any estimate of an overall-survival gain compared with platinum-doublet chemotherapy was very uncertain. However, based on the evidence presented, the committee considered it reasonable to conclude that there was likely to be an overall-survival gain for osimertinib in the previously treated population of over 3 months. The committee concluded that osimertinib could plausibly meet the criteria to be considered a life-extending, end-of-life treatment as more data become available from the AURA studies.

- 4.18 The committee concluded that because the estimates of overall survival were so immature and not sufficiently robust, and the uncertainty in the clinical- and cost-effectiveness data too great, it could not recommend osimertinib for routine use in the NHS for treating EGFR T790M mutation-positive NSCLC.

### *Cancer Drugs Fund considerations*

- 4.19 Having concluded that osimertinib could not be recommended for routine use, the committee then considered if osimertinib could be recommended for treating EGFR T790M mutation-positive NSCLC within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund recently agreed by NICE and NHS England, noting the [addendum to the NICE process and methods guides](#). The committee noted that the company expressed an interest in osimertinib being considered for funding through the Cancer Drugs Fund. The committee considered that the ICER for osimertinib (see section 4.15) was very uncertain and could be between £41,705 and £89,296 per QALY gained, depending on the choice of overall-survival extrapolation. However, the committee acknowledged that osimertinib had the plausible potential to satisfy the criteria for routine use, taking into account its conclusion on the end-of-life criteria (see section 4.17). The committee was aware that although there were uncertainties in the clinical-effectiveness evidence

regarding the overall-survival data from the AURA extension and AURA2 studies (see section 4.4), there will be further updates from the AURA and IMPRESS studies as the data become more mature. Also, the marketing authorisation for osimertinib is conditional on the company providing results to the European Medicines Agency for the ongoing AURA3 study. This study is evaluating osimertinib compared with platinum-doublet chemotherapy in people with EGFR T790M mutation-positive, locally advanced or metastatic NSCLC, whose disease had progressed after first-line EGFR TKI. The clinical study report is expected to be submitted to the European Medicines Agency in June 2017. The committee recognised that additional long-term survival data for osimertinib from the AURA3 study would reduce the clinical uncertainty and allow for a more certain cost-effectiveness estimate. The committee also acknowledged that data collected from use in the NHS through the Cancer Drugs Fund would offer further supportive evidence on the clinical effectiveness of osimertinib. The committee was aware that NICE, NHS England and the company will discuss the data collection as part of the managed access agreement. The committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund, and recommended osimertinib as an option for use within the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy if the conditions in the managed access agreement for osimertinib are followed.

### *Summary of appraisal committee's key conclusions*

TA416	Appraisal title: Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer	Section
<b>Key conclusion</b>		
<p>Osimertinib is recommended as an option for use within the Cancer Drugs Fund for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC) in adults whose disease has progressed only:</p> <ul style="list-style-type: none"> <li>• after first-line treatment with an EGFR tyrosine kinase inhibitor and</li> <li>• if the conditions in the managed access agreement for osimertinib are followed.</li> </ul>		1.1

<b>Current practice</b>		
Clinical need of patients, including the availability of alternative treatments	The committee heard from the patient experts that EGFR mutation-positive NSCLC causes many distressing and debilitating symptoms, and typically has a poor prognosis. The committee concluded that the availability of a new targeted treatment option with improved tolerability would be valuable for people with EGFR T790M mutation-positive NSCLC.	4.1
<b>The technology</b>		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee understood that osimertinib was associated with very high response rates and that this could feasibly result in improvements in quality of life that could be captured as an additional benefit compared with platinum-doublet chemotherapy. The committee considered the company's response to consultation in which the company had attempted to incorporate the effect of a treatment-specific response on utility values in a scenario analysis. It noted that including a treatment response had a minor effect on the incremental cost-effectiveness ratios (ICERs). The committee concluded that osimertinib is innovative, but there were no additional benefits associated with this treatment that could not be captured in the economic analysis.	4.16
What is the position of the treatment in the pathway of care for the condition?	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 committee noted the comments from the company and the clinical experts that osimertinib would only be used for people with EGFR mutation-positive NSCLC whose disease had progressed after a first-line EGFR tyrosine kinase inhibitor (TKI). The committee concluded that platinum-doublet chemotherapy was the most relevant comparator for osimertinib in this appraisal.	2, 4.2

<p>Adverse reactions</p>	<p>The most common adverse reactions associated with osimertinib include diarrhoea, rash, dry skin, and a reduction in platelet count and some white blood cells. The committee concluded that osimertinib was a well-tolerated treatment in this group compared with cytotoxic chemotherapies such as platinum-doublet chemotherapy.</p>	<p>2, 4.7</p>
<p><b>Evidence for clinical effectiveness</b></p>		
<p>Availability, nature and quality of evidence</p>	<p>The committee noted that the key clinical-effectiveness evidence for osimertinib was taken from the non-randomised, non-controlled single-arm AURA extension and AURA2 studies. The committee noted the evidence review group's (ERG) comments that the trials were designed and carried out to a good standard. The committee concluded that the trials used as the basis for evaluating the efficacy of osimertinib in people with EGFR T790M mutation-positive NSCLC that has progressed on a previous TKI were broadly generalisable to clinical practice. It also concluded that interpreting these results remained challenging in the absence of a direct comparator in the trial and that this was compounded by the small patient numbers in the trial and the very immature survival data.</p>	<p>4.3, 4.4</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The committee concluded that the trials used as the basis for evaluating the efficacy of osimertinib in people with EGFR T790M mutation-positive NSCLC that has progressed on a previous TKI were broadly generalisable to clinical practice.</p>	<p>4.3</p>

<p>Uncertainties generated by the evidence</p>	<p>The committee noted that the key clinical-effectiveness evidence was taken from the non-randomised, non-controlled single-arm AURA extension and AURA2 studies. The committee concluded that osimertinib offered an advantage for overall-response rates and progression-free survival compared with platinum-doublet chemotherapy for people whose disease has progressed after TKI therapy (that is, as a second or later line of treatment), but improvements in overall survival could not be shown based on the currently available immature evidence.</p> <p>The committee was concerned that because small numbers of people remained in the IMPRESS trial, small changes could have a large effect on the overall-survival results for the comparator arm. The committee concluded that the available data were too immature to robustly estimate the overall-survival advantage of osimertinib compared with platinum-doublet chemotherapy.</p>	<p>4.3, 4.5, 4.6</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The committee considered the company's subgroup analysis that explored using osimertinib in a second-line only setting compared with platinum-doublet chemotherapy.</p>	<p>4.6</p>
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The committee understood that osimertinib improved progression-free survival by 4.4 months compared with platinum-doublet chemotherapy (9.7 months compared with 5.2 months) for the second- and later-line population. The committee was aware that overall-survival data were still immature (23.8% of people had died in the pooled AURA dataset) and that a median overall-survival estimate was not calculable based on the available results.</p>	<p>4.4, 4.5</p>
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>The company used a cohort-based partitioned survival model that used a lifetime time horizon (maximum length of 15 years). The committee concluded that the company's approach was acceptable and that the economic model was suitable for decision-making.</p>	<p>4.8</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The committee noted that the extrapolations used for the company's base case resulted in an incremental progression-free survival gain of 6.5 months and an incremental overall-survival gain of 21.0 months for osimertinib compared with platinum-doublet chemotherapy. The committee remained concerned that the number of events in the trial was very small, and that restricting the population further reduced the sample size even more.</p> <p>The committee was concerned that depending on the choice of extrapolation to predict overall survival, the company's ICER estimates could vary greatly. The committee concluded that, because of the immaturity of the data, any estimate of an overall-survival gain for osimertinib compared with platinum-doublet chemotherapy was very uncertain and could have a very large effect on the ICER depending on the extrapolation chosen.</p> <p>The committee concluded that there was uncertainty in the utility values used by the company because they were based on non-UK validated EQ-5D-5L data from a small number of people, and there were concerns about the face validity of the values compared with the general population.</p> <p>The committee concluded that time-to-treatment discontinuation had been included appropriately in the company's revised analysis.</p>	<p>4.9, 4.10, 4.11, 4.13</p>
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<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The committee noted that the utility values used in the company's base-case analysis were derived from EQ-5D-5L data collected in the AURA2 study. It heard from the ERG that the company had used a method called 'crosswalking' to calculate the utility values because there was no validated dataset for the UK at the time of submission. The committee concluded that there was uncertainty in the utility values used by the company because they were based on non-UK validated EQ-5D-5L data from a small number of people. It also concluded that, although there were concerns about the face validity of the values compared with the general population, the most plausible utility values would fall somewhere between those used by the company in its updated analysis and those suggested by the ERG.</p> <p>The committee considered the importance of incorporating response rates in the company model. The committee concluded that the benefits of improving overall-response rates had a minor effect on the company's cost-effectiveness results.</p>	<p>4.11, 4.12</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The committee was aware that the company had provided a revised economic model in response to consultation that focused on a comparison of osimertinib with platinum-doublet therapy in people whose disease had progressed after first-line TKI therapy. The committee heard from the company that this most likely reflected how osimertinib will be used in UK clinical practice and provided the most robust comparison between the AURA extension and AURA2 studies and the IMPRESS study.</p>	<p>4.9</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The committee was concerned that, depending on the choice of extrapolation to predict overall survival, the company's ICER estimates could vary greatly. The committee concluded that, because of the immaturity of the data, any estimate of an overall-survival gain for osimertinib compared with platinum-doublet chemotherapy was very uncertain and could have a very large effect on the ICER depending on the extrapolation chosen.</p>	<p>4.10</p>



<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The company's revised base-case ICER was £41,705 per quality-adjusted life year (QALY) gained (incremental costs £64,283; incremental QALYs 1.541) for osimertinib compared with platinum-doublet therapy for people whose disease had progressed after first-line TKI therapy.</p> <p>The committee concluded that a reasonable cost-effectiveness estimate for osimertinib compared with platinum-doublet chemotherapy at this point in time was based on the analysis using an extrapolation of survival for osimertinib that followed a generalised gamma function, which gave an ICER between £60,663 (using the company's utility estimates) and £70,776 per QALY gained (using the ERG's alternative utility estimates).</p>	<p>4.9, 4.15</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>The pricing arrangement considered during guidance development was that the company had agreed a patient access scheme with the Department of Health. This scheme would provide a simple discount to the list price of osimertinib with the discount applied at the point of purchase or invoice. The managed access agreement agreed in September 2016 replaced the patient access scheme.</p>	<p>2</p>
<p>End-of-life considerations</p>	<p>The committee concluded that there was likely to be an overall-survival gain for osimertinib in the previously treated population of over 3 months. The committee concluded that osimertinib could plausibly meet the criteria to be considered a life-extending, end-of-life treatment as more data become available from the AURA studies. However, because the estimates of the overall survival were so immature and not sufficiently robust, and the uncertainty in the clinical- and cost-effectiveness data too great, it could not recommend osimertinib for routine use in the NHS for treating EGFR T790M mutation-positive NSCLC.</p>	<p>4.17, 4.18</p>

<p>Cancer Drugs Fund</p>	<p>The committee was aware that, although there were uncertainties in the clinical-effectiveness evidence regarding the overall-survival data from the AURA extension and AURA2 studies, there will be further updates from the AURA and IMPRESS studies as the data become more mature. The committee recognised that additional long-term survival data for osimertinib would reduce the clinical uncertainty and allow for a more certain cost-effectiveness estimate. Given the uncertainties around extrapolating survival, and the importance of this to the cost-effectiveness analyses, the committee concluded that osimertinib met the criteria to be considered for inclusion in the Cancer Drugs Fund for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after first-line EGFR TKI therapy, if the conditions in the managed access agreement for osimertinib are followed.</p>	<p>4.4, 4.19</p>
<p>Equalities considerations and social value judgements</p>	<p>No equality issues were identified.</p>	<p>–</p>

## 5 Implementation

- 5.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available within the conditions of the managed access agreement. This means that, if a patient has locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer and the doctor responsible for their care thinks that osimertinib is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's [Appraisal and Funding of Cancer Drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#).
- 5.2 Osimertinib has been recommended according to the conditions in the [managed access agreement](#). As part of this, NHS England and AstraZeneca have agreed a commercial access agreement that makes osimertinib available to the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence.

## **6 Recommendations for data collection**

- 6.1 As a condition of the positive recommendation and the managed access arrangement, the company is required to collect updated efficacy data from the AURA2 and AURA3 studies.

## 7 Appraisal committee members and NICE project team

### *Appraisal committee members*

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee D](#).

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### *NICE project team*

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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## Accreditation

