The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using osimertinib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE’s guidance on using osimertinib in the NHS in England.

For further details, see NICE’s guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 14 July 2016
Second appraisal committee meeting: 27 July 2016
Details of membership of the appraisal committee are given in section 6.
1 Recommendations

1.1 Osimertinib is not recommended within its marketing authorisation for treating locally advanced or metastatic epidermal growth factor receptor T790M mutation-positive non-small-cell lung cancer in adults.

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

| Description of the technology | Osimertinib (Tagresso, AstraZeneca) is a small-molecule inhibitor that targets the sensitising and T790M mutant forms of the epidermal growth factor receptor (EGFR)-tyrosine kinase receptor. |
| Marketing authorisation | 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 AURA3 study comparing osimertinib with platinum-based doublet chemotherapy (expected June 2017). |
| Adverse reactions | 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. |
| Recommended dose and schedule | 80 mg taken orally once a day until disease progression or unacceptable toxicity. |
| Price | £4,722.30 per pack (30 tablets) of 80-mg tablets and £4,722.30 per pack (30 tablets) of 40-mg tablets (excluding VAT; MIMS online and company submission). Treatment is continued until disease progression. The company has agreed a patient access scheme with the Department of Health. If osimertinib had been recommended, 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. |

3 Evidence

The appraisal committee (section 6) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group. 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 and therefore 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, in accordance with 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 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-based 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 that the preliminary estimate of median progression-free survival using the pooled AURA extension and AURA2 dataset was 9.7 months (95% confidence interval [CI] 8.3, upper confidence interval non-calculable). The committee was aware 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) and that a median overall-survival estimate was not calculable based on the available results. The committee concluded that interpreting these results was challenging in the absence of a direct comparator in the trial and that this was compounded by the very immature survival data.

Indirect comparisons

4.5 The committee was aware that the company presented results of an unadjusted comparison and an adjusted indirect comparison of the pooled AURA data and the single arm from the IMPRESS control group (platinum-doublet therapy). 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 this patient group, but improvements in overall survival could not be shown based on the currently available immature evidence.

4.6 The committee was aware that the company had presented additional data based on a data analysis in November 2015 for the AURA extension, AURA2 and IMPRESS trials. The committee noted that the company had provided a revised adjusted indirect comparison for osimertinib compared with platinum-doublet chemotherapy, based on the additional data, and that there was a reduction in the median overall survival associated with platinum-doublet chemotherapy. 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 from AURA extension and AURA2 were conservative because they included people from all treatment lines (that is, those who had had many lines of treatment compared with those in IMPRESS). The committee concluded that the available data was too immature to robustly estimate the overall-survival advantage of osimertinib compared with platinum-doublet chemotherapy.

**Subgroup analyses**

4.7 The committee considered the company’s subgroup analysis, which explored using osimertinib in second-line only and later-line settings...
compared with platinum-doublet chemotherapy and single-agent chemotherapy. It noted that the company’s subgroup analyses was exploratory and based on small numbers. It understood from the ERG that no statistically significant difference could be shown in progression-free survival and overall survival by line of treatment for osimertinib and did not consider the results of the subgroup analyses informative for decision making. The committee concluded that there was insufficient evidence to inform the clinical-effectiveness estimates for the subgroups explored by the company.

**Adverse effects of osimertinib**

The committee heard from 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**

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 include 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 acknowledged that the
company’s model evaluated cost effectiveness of osimertinib only in people with EGFR T790M mutation-positive NSCLC whose disease had progressed after treatment with an EGFR TKI agent and that this was in line with the expected use in clinical practice (see section 4.2). The committee concluded that the company’s approach was acceptable and that the economic model was suitable for decision-making.

4.10 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, while data from the IMPRESS study were used for platinum-doublet chemotherapy. The committee was aware that the available data were still immature and that the company extrapolated 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 extrapolations. The committee noted that the extrapolations used for the company’s base case resulted in an incremental progression-free survival gain of 4.8 months and an incremental overall-survival gain of 10.6 months for osimertinib compared with platinum-doublet chemotherapy. It noted the ERG’s comments that the extrapolations used 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 incremental cost-effectiveness ratio (ICER) estimates could vary between £31,289 and about £1,052,785 per quality-adjusted life year (QALY) gained. It also noted the ERG’s exploratory analyses, which assumed no
overall-survival gain for osimertinib compared with platinum-doublet chemotherapy, increased the company’s base-case ICER from £42,959 to £366,596 per QALY gained. 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.

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 these were not treatment specific (that is, utility was 0.815 for progression-free disease and 0.678 for post-progression disease, regardless of which treatment they had had). 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 survival 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. The committee was aware that the company’s deterministic-sensitivity analyses showed that the ICER
was sensitive to varying the utility values. The committee noted that the ERG suggested alternative values from the LUME-Lung 1 study and from Nafees et al. (2008), and in its exploratory analyses, these alternative values increased the base-case ICER from £42,959 to £47,459 and £57,853 per QALY gained respectively. The committee understood from the clinical experts that the values from the study by Nafees et al. were not appropriate to use because they were not based on EQ-5D instrument (it used visual analogue scale and standard gamble utility methods). 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.

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 could have been included in the company’s model. The committee concluded that the benefits of improving overall-response rates should have been included in the company’s model and could have resulted in a treatment-specific utility gain for osimertinib compared with platinum-doublet chemotherapy.

**Costs of osimertinib treatment**

4.13 The committee noted that in the company’s 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 when time-to-treatment-discontinuation data were used to calculate the cost of osimertinib in the ERG’s exploratory analyses, this increased the company’s base-case ICER for osimertinib compared with platinum-doublet chemotherapy from £42,959 to £64,870 per QALY gained for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after treatment with an EGFR TKI agent. The committee concluded that time-to-treatment discontinuation should have been used to calculate acquisition costs of osimertinib.

4.14 The committee noted the ERG 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 ERG had done an exploratory analysis that included a cost for giving osimertinib, which increased the company’s ICER from £42,959 to £45,444 per QALY gained. The committee concluded that the administration costs of osimertinib were partly included in the base case and were in between the company’s and the ERG’s estimates and had a minor effect on the ICER.

**Most plausible cost-effectiveness estimate**

4.15 The committee considered that the company’s base-case analysis should have used time-to-treatment-discontinuation data to calculate osimertinib acquisition costs, which increased the company’s base-case ICER for
osimertinib compared with platinum-doublet chemotherapy from £42,959 to £64,870 per QALY gained. It acknowledged that there were considerable uncertainties with the utility estimates used in the model, which could plausibly increase the ICER further. The committee noted that assuming no overall-survival gain (only a progression-free-survival gain) for osimertinib compared with platinum-doublet chemotherapy increased the company’s base-case ICER to £366,595 per QALY gained; this increased further if time-to-treatment-discontinuation data were also used. The committee agreed that although the choice of overall-survival extrapolation had 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 concluded that for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after treatment with an EGFR TKI agent, the most plausible ICER for osimertinib compared with platinum-doublet chemotherapy was at least £64,870 per QALY gained.

**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 TK inhibitors 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. However, the
committee had not been presented evidence demonstrating this, and it could not make a judgement about the impact on the ICER. 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 considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with a short life expectancy. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 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.

In addition, when taking these criteria into account, the committee must be persuaded that the estimates of the extension to life are sufficiently robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.18 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. The committee agreed that the life expectancy was likely to be less than 24 months, but that the overall-survival estimates for the previously treated population were not sufficient to robustly determine whether osimertinib offers at least an additional 3 months extension to life. The committee concluded that osimertinib did not meet the criteria to be considered a life-extending, end-of-life treatment because the data were too uncertain and that osimertinib was not recommended as a cost-effective use of NHS resources.

4.19 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 understood that because of the timing of this appraisal, the company had not had an opportunity to present a case for including osimertinib in the Cancer Drugs Fund. However, the committee heard from the company that osimertinib may be considered for funding through the Cancer Drugs Fund. The committee considered that the most plausible ICER for osimertinib (see section 4.16), was substantially higher than the range normally considered a cost-effective use of NHS resources, and so osimertinib did not have the plausible potential for satisfying the criteria for routine use. The committee was aware that although there were uncertainties in the clinical-effectiveness evidence 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 upon the company providing results to the European Medicines Agency for the ongoing AURA3 study,
which is evaluating osimertinib compared with platinum-doublet chemotherapy and is due to be reported to the European Medicines Agency in June 2017. The committee concluded that osimertinib did not meet the criteria to be considered for inclusion in the Cancer Drug Fund

**Pharmaceutical Price Regulation Scheme 2014**

4.20 The committee was aware of NICE’s position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

**Summary of appraisal committee’s key conclusions**

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<tr>
<th>TAXXX</th>
<th>Appraisal title: Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer</th>
<th>Section</th>
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<tr>
<td>Key conclusion</td>
<td>Osimertinib is not recommended within its marketing authorisation for treating locally advanced or metastatic epidermal growth factor receptor T790M mutation-positive non-small-cell lung cancer in adults.</td>
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**Current practice**
Clinical need of patients, including the availability of alternative treatments | The committee heard from the patient experts that EGFR mutation-positive non-small-cell lung cancer (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 epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC. | 4.1

The technology

Proposed benefits of the technology | 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, However, the committee had not been presented evidence demonstrating this, and it could not make a judgement about the impact on the ICER. 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)' | Section 2
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 first-line EGFR tyrosine kinase inhibitors (TKIs). The committee concluded that platinum-doublet chemotherapy was the most relevant comparator for osimertinib in this appraisal

| Adverse reactions | 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. | Section 2 |

### Evidence for clinical effectiveness

<p>| Availability, nature and quality of evidence | 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)’s 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 | 4.3, 4.4 |
| 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 was challenging in the absence of a direct comparator in the trial and that this was compounded by the very immature survival data. |</p>
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<tr>
<td>Relevance to general clinical practice in the NHS</td>
<td>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.</td>
<td>4.3</td>
</tr>
<tr>
<td>Uncertainties generated by the evidence</td>
<td>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 this patient group, but improvements in overall survival could not be shown based on the currently available immature evidence. 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.</td>
<td>4.3</td>
</tr>
<tr>
<td>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</td>
<td>The committee considered the company’s subgroup analysis that explored using osimertinib in second-line only and later-line settings compared with platinum-doublet chemotherapy and single-agent chemotherapy. The committee concluded that there was insufficient evidence to inform the</td>
<td>4.7</td>
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### Clinical-effectiveness estimates for the identified subgroups

| Estimate of the size of the clinical effectiveness including strength of supporting evidence | The committee understood that osimertinib improved progression-free survival by 4.4 months compared with platinum-doublet chemotherapy (9.7 months compared with 5.3 months). The committee was aware 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) and that a median overall-survival estimate was not calculable based on the available results. | 4.4, 4.5 |

### Evidence for cost effectiveness

| Availability and nature of evidence | 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. | 4.9 |

| Uncertainties around and plausibility of assumptions and inputs in the economic model | The committee was concerned that depending on the choice of extrapolation to predict overall survival, the incremental cost-effectiveness ratio (ICER) estimates could vary between £31,289 and about £1,052,785 per quality-adjusted life year (QALY) gained. The committee concluded that because of the immaturity of the data, any estimate of an | 4.10 |
| Incorporation of health-related quality-of-life benefits and utility values | 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. 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... | 4.11 4.13 |

| overall-survival gain for osimertinib compared with platinum-doublet chemotherapy was very uncertain. 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. The committee concluded that time-to-treatment discontinuation should have been used to calculate acquisition costs of osimertinib. | |
sources using the EQ-5D-3L instrument. The committee considered the importance of incorporating response rates in the company model. The committee concluded that the benefits of improving overall-response rates should have been included in the company’s model and could have resulted in a treatment-specific utility gain for osimertinib compared with platinum-doublet chemotherapy.

| Are there specific groups of people for whom the technology is particularly cost effective? | The committee concluded that there was insufficient evidence to inform the clinical-effectiveness estimates for the subgroups explored by the company. | 4.7 |
| What are the key drivers of cost effectiveness? | The committee was concerned that depending on the choice of extrapolation to predict overall survival, the company’s ICER estimates could vary between £31,289 and about £1,052,785 per QALY gained (including the patient access scheme discount). It also noted the ERG’s exploratory analyses, which assumed no overall-survival gain for osimertinib compared with platinum-doublet chemotherapy, increased the company’s base-case ICER from £42,959 to £366,595 per QALY gained (including the patient access scheme discount). The committee noted that when time-to-
| 4.10 | 4.13 |
| Most likely cost-effectiveness estimate (given as an ICER) | The committee concluded that for people with EGFR T790M mutation-positive NSCLC whose disease had progressed after treatment with an EGFR TKI agent, the most plausible ICER for osimertinib compared with platinum-doublet chemotherapy was at least £64,870 per QALY gained (including the patient access scheme discount). |
| Additional factors taken into account |
| Patient access schemes (PPRS) | The company has agreed a patient access scheme with the Department of Health. If osimertinib had been recommended, this scheme would provide a simple discount to the list price of osimertinib with the discount applied at the point of purchase or invoice. |
| End-of-life considerations | The committee concluded that people for whom osimertinib is indicated have a short life expectancy, so this criterion was met. The committee concluded that osimertinib did not meet the criteria to be considered a life-extending, end-of-life treatment because the data were too uncertain and that osimertinib... |
| **Cancer Drugs Fund** | The committee was aware that although there were uncertainties in the clinical-effectiveness evidence from the AURA extension and AURA2 studies, there will be further updates from the AURA and IMPRESS studies as the data become more mature. Also, results from the AURA3 trial (on which the marketing authorisation is conditional) are due to be reported to the European Medicines Agency in June 2017.

The committee considered that the most plausible ICER for osimertinib (see section 4.16), was substantially higher than the range normally considered a cost-effective use of NHS resources, and so osimertinib did not have the plausible potential for satisfying the criteria for routine use. The committee concluded that osimertinib for locally advanced or metastatic EGFR T790M mutation-positive NSCLC cancer did not meet the criteria to be considered for inclusion in the Cancer Drug Fund. |

| **Equalities considerations and social value judgements** | No equality issues were identified. | - |
5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance or on the availability of the results of the AURA3 trial, which is comparing osimertinib and platinum-doublet chemotherapy in people with EGFR T790M mutation-positive non-small-cell lung cancer (results due to be reported to the European Medicines Agency in June 2017). NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Gary McVeigh
Chair, appraisal committee
June 2016

6 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.

Christian Griffiths
Technical Lead

Sally Doss
Technical Adviser

Kate Moore
Project Manager

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