NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

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

The Department of Health and Social Care 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?

Issue date: April 2019

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 document.
- Subject to any appeal by consultees, the final appraisal document 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: 9 May 2019

Second appraisal committee meeting: 23 May 2019

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Osimertinib is not recommended, within its marketing authorisation, for untreated locally advanced or metastatic epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) in adults.

1.2 This recommendation is not intended to affect treatment with osimertinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Locally advanced or metastatic EGFR mutation-positive NSCLC is usually first treated with afatinib, erlotinib or gefitinib.

Evidence from a randomised controlled trial suggests that people who take osimertinib live longer than people who take erlotinib or gefitinib. They also live longer before their disease gets worse. But there is no direct evidence comparing osimertinib with afatinib, which may be more effective than erlotinib and gefitinib.

Osimertinib does not meet NICE's criteria to be considered a life-extending treatment at the end of life. The most plausible cost-effectiveness estimates are above what NICE normally considers an acceptable use of NHS resources. So osimertinib is not recommended.

Osimertinib does not meet NICE's criteria to be included in the Cancer Drugs Fund because it does not have the potential to be cost effective at the price offered.

2 Information about osimertinib

Marketing authorisation indication	Osimertinib (Tagrisso, AstraZeneca) is indicated 'for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations'.
Dosage in the marketing authorisation	80 mg taken orally once daily until disease progression or unacceptable toxicity. EGFR mutation status in tumour or plasma specimens should be determined using a validated test method. Dosing interruption with or without dose reduction may be needed based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to 40 mg once daily.
Price	£5,770 for 80 mg and 40 mg osimertinib (pack of 30 tablets, excluding VAT; British national formulary online, accessed March 2019). The company has a commercial arrangement (managed access agreement including a commercial access agreement). This makes osimertinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The utility value of 0.678 (from the AURA 2 trial, second-line treatment with osimertinib) was more representative of people in the progressed disease state (table 3, pages 24 to 25 of the technical report).

- A combined approach to determine the appropriate resource costs for people in the progressed disease state was acceptable (table 3, pages 24 to 25 of the technical report).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (table 2, pages 22 to 23 of the technical report), and took these into account in its decision making. It discussed the following issues, which were outstanding after the technical engagement stage.

Clinical need

People would welcome a new treatment option

3.1 The patient experts explained that people with untreated locally advanced or metastatic epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) are often very unwell, with many distressing symptoms. There are no curative treatments. The prognosis is generally poor despite treatments such as targeted therapies and immunotherapy. People would therefore welcome new treatments that improve their symptoms, quality of life, and increase how long they live (even if this increase is only small). Locally advanced or metastatic EGFR mutation-positive NSCLC is first treated with an EGFR tyrosine kinase inhibitor, such as afatinib, gefitinib or erlotinib, in line with NICE guidance. The clinical experts explained that people would usually be offered afatinib based on the evidence (see section 3.4). After afatinib, gefitinib or erlotinib, people may be offered either osimertinib (through the Cancer Drugs Fund) if they have developed the T790M resistance mutation in the EGFR gene, or chemotherapy if not. People who are not well enough to have further treatment would be offered best supportive care. After chemotherapy, people may be offered immunotherapy, docetaxel with or without nintedanib, or best supportive care. The clinical experts stated that osimertinib would be beneficial as an additional treatment option because it is better tolerated than existing treatments, with fewer side effects. Also, if osimertinib was a first-line treatment option it would remove the need for

T790M mutation testing. This involves a biopsy, which is invasive and can be psychologically distressing. The committee agreed that additional options would be beneficial and concluded that osimertinib would be a useful addition to first-line treatment.

Clinical evidence

The FLAURA trial is broadly generalisable to people with untreated locally advanced or metastatic EGFR mutation-positive NSCLC in England

3.2 The clinical evidence for osimertinib came from the ongoing FLAURA randomised controlled trial. FLAURA is comparing the efficacy and safety of osimertinib with standard care (erlotinib or gefitinib) for people with locally advanced or metastatic EGFR mutation-positive NSCLC. The inclusion criteria allow people with stable brain metastases to enter the trial but limit the trial population to people with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. The committee was aware that the clinical trial population may be in better health than people with stage IIIb or IV NSCLC in the NHS and that people with many comorbidities were not included in the trial. Also, it noted that afatinib was not a comparator in the standard care arm in FLAURA (see section 3.4) and that many subsequent treatments used in the trial are not routinely used in the NHS. Despite these concerns, the clinical experts explained that the evidence from FLAURA was broadly generalisable to NHS clinical practice. The committee agreed with the clinical experts.

Osimertinib extends progression-free and overall survival compared with gefitinib and erlotinib but the size of the benefit is unclear

3.3 An interim analysis of FLAURA showed that progression-free survival was statistically significantly longer with osimertinib than with erlotinib or gefitinib. At the latest data cut (12 June 2017) median progression-free survival was 18.9 months for osimertinib (95% confidence interval [CI] 15.2 to 21.4) and 10.2 months for standard care (95% CI 9.6 to 11.1). The hazard ratio was 0.46 (95% CI 0.37 to 0.57; $p<0.001$). Overall survival

data were very immature (25% of events) but the interim results showed that osimertinib extended overall survival compared with standard care. This produced a hazard ratio of 0.63 (95% CI 0.45 to 0.88; p=0.007) which was not statistically significant (a p-value of less than 0.0015 was needed for the result to be significant). The committee acknowledged that the FLAURA data were very immature and that there was substantial uncertainty because of the number of events still to be reported. It concluded that osimertinib lengthened progression-free survival, and possibly overall survival, compared with erlotinib or gefitinib but this overall survival benefit was difficult to interpret because the data were very immature.

EGFR tyrosine kinase inhibitors do not all have equal efficacy

3.4 The relevant comparators for this technology appraisal are erlotinib, gefitinib and afatinib. FLAURA compared osimertinib with either gefitinib or erlotinib, but not with afatinib. The Cancer Drugs Fund clinical lead noted that afatinib is currently the most prescribed EGFR tyrosine kinase inhibitor in England for this population. He also stated that previous trials, such as LUX-Lung 7, showed that afatinib statistically significantly improved progression-free survival compared with gefitinib. The clinical experts agreed that gefitinib and erlotinib are likely to have equal efficacy. They stated that people taking afatinib had an increase in response rate to treatment, duration of response and progression-free survival compared with erlotinib and gefitinib and that they usually remained on treatment for longer. The company stated that LUX-Lung 7 did not show a statistically significant increase in overall survival for afatinib compared with gefitinib. It therefore assumed that afatinib was equivalent in efficacy to erlotinib and gefitinib in its economic model. However, the clinical experts explained that LUX-Lung 7 was not powered (that is, it did not have enough people in the trial) to show a difference in overall survival compared with gefitinib. The ERG did its own exploratory indirect treatment comparison that suggested osimertinib statistically significantly improved progression-free survival compared with afatinib but showed no

statistically significant difference in overall survival. The committee concluded that there was evidence of improved progression-free survival with afatinib compared with gefitinib, and erlotinib and gefitinib cannot be assumed to have equal efficacy with afatinib.

Modelling of overall survival

Assuming a 6-year treatment benefit for osimertinib is optimistic

3.5 The company used a partitioned survival structure with 3 health states (progression-free, progressed disease and death) to model overall survival in FLAURA. It used a time horizon of 20 years to capture all relevant costs and benefits for people having treatment. The company initially assumed a treatment benefit for osimertinib for the full 20-year period. The committee agreed with the ERG and clinical experts that this assumption was optimistic considering the data available and would have to be adjusted to reflect a more realistic benefit from osimertinib treatment. The company therefore revised its base case assuming a 6-year duration of treatment effect after the start of treatment (that is, applying a hazard ratio of 1 to both the osimertinib and standard care arms 6 years after starting treatment). The committee recalled that in previous appraisals for locally advanced or metastatic NSCLC, the preferred treatment-effect duration for immunotherapies was 3 to 5 years. However, it acknowledged that these appraisals involved drugs with a different mechanism of action to osimertinib and a maximum treatment duration. Therefore it was not appropriate to compare them. The clinical experts agreed that because osimertinib is associated with improved progression-free survival and duration of response, this would continue after symptomatic and radiological progression for some people. They stated that this could plausibly give about 3 months of additional benefit after stopping treatment with osimertinib compared with erlotinib and gefitinib. This is because osimertinib penetrates the blood-brain barrier better and helps to control brain metastases. The committee recalled that there was no direct evidence comparing osimertinib with afatinib and that

afatinib has greater efficacy compared with erlotinib and gefitinib (see section 3.4). The ERG's preferred analyses used durations of 3 and 5 years. The ERG explained that the company's 6-year duration of treatment effect would mean that people who stopped taking osimertinib within 1 or 2 years of starting it would still benefit for the full 6 years. The ERG emphasised that there are limitations with a partitioned survival model in modelling the duration of treatment effect. This is because a crude approach is needed to make adjustments around the assumptions (for example, assuming equivalence at a single time point). The ERG noted that this does not fully reflect what happens in a clinical setting. The committee concluded that a 6-year duration of treatment effect for osimertinib was optimistic and that without more evidence, the ERG's analyses using a 3- or 5-year duration of treatment effect were more appropriate.

The economic model does not capture the benefits of subsequent treatments appropriately

3.6 The committee was aware of NICE's position statement on handling comparators and treatment sequences in the Cancer Drugs Fund, specifically that 'products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals'. The committee accepted that it could consider the company's approach of including osimertinib as a subsequent treatment (in line with NICE's technology appraisal of osimertinib for locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer) in the model in this appraisal, because the appraisal had already started before the position statement came into effect. People in the standard care arm in the model could have osimertinib as a second-line treatment (assumed to be 33% of people). The committee noted that, although the costs of osimertinib as a second-line treatment were applied in the standard care arm of the model, efficacy was not fully captured. The committee was aware that the subsequent treatments used in the trial

may not reflect NHS practice. It noted that different subsequent therapies would mean different survival prospects and health states that cannot be captured in the modelling. The ERG explained that to overcome the limitations of the model in capturing the efficacy of subsequent treatments, and to create more flexibility to explore varying the duration of treatment benefits, additional health states would be needed. The ERG described how an individual patient simulation model would better account for these issues but it would need lots of additional data and trial data are usually immature. The committee agreed that the company's model was broadly appropriate for decision making. It acknowledged the limitations of the model and, given the immaturity of the data, concluded that the model did not capture the benefits of subsequent treatments appropriately.

The company's modelling of overall survival is acceptable

3.7 At the latest data cut, median overall survival was not achieved in either the osimertinib or standard care arm. To estimate the overall survival of people in FLAURA the company used a piecewise Weibull extrapolation of the Kaplan–Meier curve. This estimated that mean overall survival was 66.96 months with osimertinib and 44.39 months with standard care, assuming a 20-year time horizon in the model. The committee was aware that this extrapolation resulted in the most conservative survival estimates and fitted the data well. It understood that the FLAURA data were immature, which introduced uncertainty into the survival estimates, and that further data collection is planned. It concluded that, although the FLAURA data were immature, the company's and ERG's preferred choice of distribution for modelling overall survival was appropriate.

Cost-effectiveness estimate

The most plausible ICER for osimertinib is higher than what NICE normally considers a cost-effective use of NHS resources

3.8 The committee recalled its preferred modelling assumptions:

- A treatment-effect duration (that is, from the start of treatment) of 3 to 5 years (see section 3.5).
- Weibull extrapolation of overall survival in both the osimertinib and standard care arms (see section 3.5).
- A utility value of 0.678 (see table 3, pages 24 to 25 of the technical report).

Using the Weibull extrapolation of overall survival, all of the pairwise incremental cost-effectiveness ratios (ICERs; including the confidential commercial arrangement) for osimertinib, compared with erlotinib, gefitinib and afatinib were greater than £30,000 per quality-adjusted life year (QALY) gained. Also, the committee noted that the ICER for osimertinib compared with afatinib was based on the assumption that afatinib has equal efficacy to gefitinib and erlotinib. The committee acknowledged that given the available evidence from LUX-Lung 7 and clinical expert opinion, it is possible that afatinib has greater efficacy than gefitinib and erlotinib and if so, the ICER for osimertinib compared with afatinib would increase. Therefore, it concluded that the most plausible ICER for osimertinib is higher than what NICE considers an acceptable use of NHS resources.

End of life

Osimertinib does not meet the short life expectancy criterion, and therefore does not meet the end-of-life criteria

3.9 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. Based on evidence from FLAURA and predictions from the economic model (using the committee's preferred assumptions), the committee concluded that osimertinib was likely to extend life by over 3 months and therefore met the extension-to-life criterion. The company presented registry evidence from a real-world data source, showing that median overall survival for the population in England was less than 24 months. The Cancer Drugs Fund clinical lead and the ERG stated that

it was inconsistent to use the FLAURA data to determine the overall survival benefit of osimertinib, but real-world evidence to determine life expectancy for people having standard care. Also, after consultation on the technical report, the clinical experts stated that about 60% of people in clinical practice were alive 2 years after starting treatment with an EGFR tyrosine kinase inhibitor. The committee noted that the FLAURA data did not show that life expectancy was less than 24 months. In the standard care arm, the economic model (using the committee's preferred assumptions) predicted a mean overall survival of 44.39 months and a median overall survival of 31.54 months. The committee was also aware that evidence from studies in similar populations, such as LUX-Lung 7 and Archer 1050, showed that median overall survival was more than 24 months. The clinical expert stated that although people whose tumours express the T790M resistance mutation would be offered osimertinib as a second-line treatment, the registry's overall survival values could be because people did not have second and third-line treatments quickly after their disease progressed. Although the committee recognised that there could be potential value in real-world evidence from the NHS in England, it noted that the registry data were difficult to compare directly with the FLAURA data because possible confounders in the real-world population (such as comorbidities) were not taken into account. Also, the committee stated that a small number of patients (n=48) in the standard care arm in FLAURA had osimertinib for second-line treatment as part of the study crossover. The company submission notes that the reason for the low rate of crossover was because some patients either stopped treatment and started another therapy or died before their disease progressed. The company stated that it would therefore not expect osimertinib, for eligible patients whose disease progressed on standard care, to significantly compromise overall survival. The committee had accepted the FLAURA trial data as the only source of evidence to populate the model and to inform its decisions throughout the appraisal. So it considered that it was appropriate to base its decision on life

expectancy on the trial data. The committee concluded that osimertinib did not meet the short life expectancy criterion, and therefore did not meet the end-of-life criteria.

Innovation

Osimertinib may be innovative

3.10 The clinical lead for the Cancer Drugs Fund highlighted that follow up in FLAURA is short so the economic model was unlikely to fully capture osimertinib's beneficial effect in the brain. He also stated that osimertinib is better tolerated than other EGFR tyrosine kinase inhibitors with respect to chronic grade 1 and grade 2 skin-related toxicities and this benefit was not captured in the economic model. The committee also understood that osimertinib will reduce the need for repeat bronchoscopic biopsies in people having the currently available EGFR tyrosine kinase inhibitors. However, the committee was unable to determine the potential effect of these factors on the ICER. It concluded that osimertinib may be innovative.

Routine NHS use

Osimertinib is not recommended for routine use in the NHS

3.11 The committee considered all of the available evidence for osimertinib in this appraisal. It concluded that the most plausible ICER is above £30,000 per QALY gained. Also, osimertinib does not meet NICE's end-of-life criteria. Because of this, the committee concluded that osimertinib could not be recommended for routine use based on what NICE normally considers an acceptable use of NHS resources.

Cancer Drugs Fund

Osimertinib is not recommended for use in the Cancer Drugs Fund

3.12 Having concluded that osimertinib could not be recommended for routine use, the committee then considered if it could be recommended for

untreated locally advanced or metastatic EGFR mutation-positive NSCLC within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The company had expressed an interest in the technology being considered for funding through the Cancer Drugs Fund. The committee acknowledged that some of the clinical uncertainty could be addressed through collecting data from patients having osimertinib through the Cancer Drugs Fund and that final data from FLAURA will be available soon. But at the current price, osimertinib does not have plausible potential for cost effectiveness. The ICER is above £30,000 per QALY gained when the commercial arrangement is taken into account. The committee concluded that osimertinib did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund, so did not recommend it for use within the Cancer Drugs Fund.

Other factors

3.13 No relevant equality issues were identified.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. 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.

Professor Gary McVeigh
Chair, appraisal committee
April 2019

Issue date: April 2019

5 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.

Stephen Robinson
Technical lead

Christian Griffiths
Technical adviser

Kate Moore
Project manager

ISBN: [to be added at publication]

Issue date: April 2019