

Osimertinib for treating EGFR T790M mutation- positive advanced 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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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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This guidance replaces TA416.

1 Recommendations

- 1.1 Osimertinib is recommended as an option for treating epidermal growth factor receptor (EGFR) T790M mutation-positive locally advanced or metastatic non-small-cell lung cancer (NSCLC) in adults, only if:
- their disease has progressed after first-line treatment with an EGFR tyrosine kinase inhibitor and
 - the company provides osimertinib according to the [commercial arrangement](#).
- 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

This appraisal reviews the additional evidence collected as part of the Cancer Drugs Fund managed access agreement for osimertinib for treating EGFR T790M mutation-positive locally advanced or metastatic NSCLC for adults whose disease has progressed after treatment with an EGFR tyrosine kinase inhibitor (NICE technology appraisal guidance 416).

EGFR T790M mutation-positive locally advanced or metastatic NSCLC that has progressed after treatment with an EGFR tyrosine kinase inhibitor is usually treated with platinum doublet chemotherapy (PDC).

Evidence from clinical trials suggests that people who take osimertinib live longer than those who have PDC, although there is some uncertainty about the results.

Osimertinib meets NICE's criteria to be considered a life-extending treatment at the end of life. Although the cost-effectiveness estimates for osimertinib are uncertain, they are likely

to be within what NICE considers to be an acceptable use of NHS resources. So, osimertinib is recommended.

2 Information about osimertinib

Marketing authorisation indication

- 2.1 Osimertinib (Tagrisso, AstraZeneca) has a 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)'.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The price for 30 tablets (either 40 mg or 80 mg) is £5,770 (BNF online, accessed February 2020). The company has a [commercial arrangement](#) that 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](#) considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the [committee papers](#) for full details of the evidence, including details about the original appraisal (TA416).

As a condition of the positive recommendation and the managed access arrangement in the previous appraisal, the company was required to collect updated efficacy data from the AURA2 and AURA3 studies. Also, data were collected on the use of osimertinib in the NHS through the Cancer Drugs Fund using the Systemic Anti-Cancer Therapy (SACT) dataset.

The committee recognised that there were remaining areas of uncertainty in the analyses presented (see technical report, table 2, page 27) and took these into account in its decision making. The committee discussed the following issues (issues 1 to 6), which were outstanding after the technical engagement stage:

- differences in overall survival estimates between trials and real-world evidence
- treatment switching in AURA3
- choice of model
- choice of extrapolation to predict overall survival
- choice of utility values
- end-of-life criteria.

Clinical need

People with EGFR T790M mutation-positive locally advanced or metastatic NSCLC value having osimertinib as a treatment option

- 3.1 The patient and clinical experts explained that overall survival for lung cancer in the UK is poor. The patient expert noted that people with

epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC) are younger and have usually never smoked. They often get a diagnosis at an advanced disease stage (that is, stage 3b or 4). The committee recalled from the original appraisal that only about 1% of the EGFR mutation-positive population would have the T790M mutation present at diagnosis and that osimertinib would very rarely be used in this setting. The patient expert explained that the adverse events, increased hospital visits, potential admissions, and additional medication associated with platinum doublet chemotherapy (PDC) can affect quality of life. Longer and more frequent hospital trips can mean less time with family and time off work, and can affect a person's social life. The patient expert explained that osimertinib and other tyrosine kinase inhibitors (TKIs) were better tolerated than PDC. But the committee noted that diarrhoea and rashes are more common with TKIs. The clinical expert explained that patients on PDC had worse clinical outcomes and more rapid disease progression than those taking osimertinib. The committee concluded that managing EGFR T790M mutation-positive NSCLC places a burden on people and their families, and that patients value having osimertinib as a treatment option.

Clinical effectiveness

There is uncertainty about whether overall survival estimates from trial data are generalisable to the NHS

- 3.2 As well as new data from the AURA3 trial, there were new SACT data. These data were collected from 357 people who had osimertinib in the Cancer Drugs Fund between October 2016 and September 2018. AURA3 is an open-label trial that included 419 patients with EGFR T790M mutation-positive NSCLC, whose disease had progressed during first-line EGFR TKI treatment. Patients were randomised to have either osimertinib or PDC. The committee noted that overall survival estimates from the SACT dataset were considerably lower for patients on osimertinib compared with AURA3 trial data. The SACT median overall survival was 13.9 months (95% confidence interval [CI] 12.1 to 17.6) compared with 26.8 months for AURA3 (95% CI 23.49 to 31.54). The committee noted that the hazard ratio in AURA3 was not statistically

significant (hazard ratio 0.87; 95% CI 0.67 to 1.13) but it was aware that this estimate did not account for treatment switching (see [section 3.6](#)). The committee concluded that the difference in estimates meant there was uncertainty about the generalisability of the trial data to NHS practice.

There are differences between the populations in the NHS and in AURA3

- 3.3 The Cancer Drugs Fund clinical lead highlighted that there were more patients in the SACT dataset than in the clinical trials and that SACT data were considered to be representative of UK clinical practice. The clinical expert and the Cancer Drugs Fund clinical lead explained that there were several possible reasons for the differences between the estimates from the trial data and the SACT dataset:
- Patients in the SACT dataset were slightly older and possibly less well than patients in the trials. The clinical expert explained that it was possible that patients with comorbidities would have been screened out of the trials, and patients in the SACT dataset may have had significant comorbidities, but this information was not available.
 - The frequency of cerebral metastases in the SACT population was unknown.
 - Patients were included in AURA3 only if they had a performance status of 0 to 1. In the SACT dataset, 6% of patients had a performance status of 2, and in 9% of patients performance status was not known.
 - There was a high proportion (about 65%) of people of East Asian family origin in AURA3. The Cancer Drugs Fund clinical lead explained that the subgroup analyses in AURA3 suggested that osimertinib may have a greater relative benefit in people of East Asian family origin. The company noted that the committee had previously said that the effect of ethnicity alone in influencing outcomes is uncertain.
 - Most patients in the clinical trials had a first-generation TKI (erlotinib or gefitinib) but in the SACT dataset, most patients had a second-generation TKI (afatinib). However, the clinical expert, Cancer Drugs Fund clinical lead and the company explained that there was no evidence to suggest that the difference

in survival could be explained by the difference in first-line treatments.

- The patient expert and clinical expert noted that there may also be variation in time to receiving biopsy results, monitoring of disease progression and access to prospective scanning for brain metastases.

The committee considered that the above factors could have contributed to the differences in survival results between the trials and the SACT dataset, but concluded that this could not be determined.

Modelling of overall survival

The hybrid economic model is appropriate for decision making

- 3.4 After technical engagement, the company submitted a hybrid model based on the one used in the original appraisal, with data imported from AURA3. The committee agreed that AURA3 data should be used and accepted the hybrid model.

Overall survival data from AURA3 should be extrapolated using exponential functions

- 3.5 After technical engagement, the company submitted a new base case that included the ERG's preferred extrapolation, which used exponential functions for both treatment arms from the point that the available Kaplan–Meier data became heavily censored and unreliable. The committee agreed that overall survival data from AURA3 should be used and extrapolated using exponential functions.

Overall survival estimates from AURA3 should be adjusted to account for treatment switching

- 3.6 The company submission outlined that in AURA3 the rate of treatment switching from PDC to osimertinib after disease progression was 71%. The committee thought that this was likely to bias overall survival results because using osimertinib in a third-line setting did not reflect NHS practice. The company used a rank-preserving structural failure time

model to adjust for treatment switching (see the technical report, page 14). The company also provided scenario analyses for duration of treatment effect and methods of censoring. The committee understood that, depending on which scenario was chosen, there was a risk of over or underestimating overall survival for osimertinib compared with PDC. The company base case assumed that a treatment effect only happened while on treatment and re-censoring was only applied in the estimation of the acceleration factor (the estimation of the treatment effect of osimertinib). The ERG highlighted that the company's PDC base-case median crossover-adjusted overall survival result was more optimistic than results from the company's adjusted indirect comparison or from the SACT data. The ERG explained that, although several methods of adjusting for treatment switching were considered by the company, no method was better than any other. The committee agreed that all methods of adjustment, including the rank-preserving structural failure time model, had their weaknesses but that some method of adjustment was needed because of the high level of crossover. The committee concluded that, although it was not possible to determine which scenarios gave the most accurate estimate, the company's preferred adjustment was a reasonable estimate of survival.

Health-related quality of life

Modelling utility values as treatment specific could be reasonable

- 3.7 In its initial submission, the company modelled utility values based on health state. After technical engagement, the company submitted a new base case in which it used treatment-specific utility values rather than health-state utility values. In the company's updated analysis submitted before the committee meeting, the treatment-specific utility values for osimertinib were from AURA2, and for PDC were from LUME-Lung 1. LUME-Lung 1 evaluated docetaxel with or without nintedanib as second-line therapy for patients with stage 3b or 4 recurrent NSCLC which had progressed after first-line chemotherapy. For the osimertinib arm, the company modelled utility values of 0.831, 0.751 and 0.715 for the response, stable disease and progressed disease health states. For the PDC arm, the company used utility values of 0.670, 0.670 and 0.640 for

these states. The committee discussed the appropriateness of modelling utility values to vary between treatment arms. The patient and clinical experts stated that the differences in toxicity profiles between osimertinib and PDC may mean that people in the osimertinib arm report better health-related quality of life. The committee considered that the difference in side effect profiles between osimertinib and PDC meant that it could be reasonable to model treatment-specific utility values.

It is preferable for treatment-specific utility values to use the same source of evidence for both treatment arms

- 3.8 The company used different sources of evidence (the AURA2 and LUME-Lung 1 studies) to inform the utility values used in each treatment arm (see [section 3.7](#)). The committee questioned the likelihood that the utility values for treatment response with PDC (0.67) would be so much lower than for disease progression with osimertinib (0.715). The committee discussed whether the difference in utility values between treatment arms could partly be because of differences between how the AURA2 and LUME-Lung 1 studies were designed and done. The committee concluded that it was preferable for any treatment-specific utility values to be taken from the same source of evidence for each treatment arm.

There is uncertainty about which source of utility values is the best to use

- 3.9 The committee noted that health-related quality-of-life data were collected for both osimertinib and PDC in AURA3. The company explained that it had not used treatment-specific utility values from AURA3 because of the differences between trial arms at baseline. However, the committee questioned whether baseline differences could be accounted for during statistical analysis. The new evidence from AURA3 (response 0.836, stable disease 0.797 and progressed disease 0.717) produced slightly higher utility values than AURA2 (response 0.831, stable disease 0.751 and progressed disease 0.715). The company considered that this similarity showed that the most plausible values were those seen in these trials. The ERG noted that the AURA2 and AURA3 utility values seemed implausibly high when compared with age-related population values. In its base case, the ERG used utility values

from AURA2, but presented another scenario using utility values from LUME-Lung 1 (response and stable disease 0.67, progressed disease 0.64). The company did not believe that it was appropriate to use the LUME-Lung 1 utility values because they were from a different patient population whose disease was treated with cytotoxic chemotherapy, not with an EGFR TKI, and with unknown T790M mutation status. The committee was concerned about the absolute values and relative differences between utility values when comparing the different sources. It also considered how the trial utility values would relate to NHS practice, given the significant difference between the survival outcomes in the AURA trials and those from the SACT dataset. The committee concluded that there was uncertainty about the best source of utility values to use.

The modelled scenarios of health-state utility values from AURA2 and LUME-Lung 1 are the most plausible analyses

- 3.10 The committee considered that there may be a reason for using treatment-specific utility values (see [section 3.7](#)), but it had not seen a plausible analysis using them. The committee noted that the AURA2 and AURA3 utility values were consistent but was concerned that they were implausibly high. The committee was uncertain how the utility values would relate to NHS practice because of the large difference between the survival outcomes with osimertinib in the AURA trials and the SACT dataset. It recalled that the LUME-Lung 1 utility values were much lower than those of the AURA trials, but acknowledged there were differences in patient populations between the trials (see [section 3.9](#)). The committee concluded that, based on the evidence and using a health-state utility approach, the most likely values would fall somewhere between the AURA2 utility values and the LUME-Lung 1 utility values. So, the ERG's 2 modelled scenarios of health-state utility values were considered the most plausible of the available analyses.

Cost-effectiveness results

The company's base-case ICER is higher than what NICE usually

considers a cost-effective use of NHS resources

3.11 In analyses incorporating the commercial arrangement submitted after the committee meeting, the company base case included the following assumptions:

- Rank-preserving structural failure time model to adjust AURA3 survival results (with 'on treatment' effect and re-censoring to inform the acceleration factor).
- Hybrid model A/B (see [section 3.4](#)).
- Overall survival, progression-free survival and time to treatment discontinuation taken from AURA3.
- Exponential extrapolation of overall survival, progression-free survival and time to treatment discontinuation from the point at which Kaplan–Meier data become heavily censored.
- Treatment-specific utility values from AURA3 (osimertinib) and LUME-Lung 1 (PDC).

The company base-case incremental cost-effectiveness ratio (ICER) was £36,034 per quality-adjusted life year (QALY) gained. This estimate included the company's confidential commercial arrangement. The committee concluded that the company's preferred assumptions led to an ICER that is higher than NICE usually considers to be a cost-effective use of NHS resources.

The most plausible ICER is below £50,000 per QALY gained

3.12 The ERG's preferred assumptions were similar to the company's preferred assumptions but were based on utility values modelled according to health state. The key difference between the company and ERG's base case was the source of utility values. In analyses incorporating the updated commercial arrangement, the company preferred treatment-specific utility values using data from AURA3 for osimertinib and LUME-Lung 1 for PDC, giving a base case of £36,034 per QALY gained. The ERG preferred health-state utility values, and used health-state utility values derived from AURA2 data that resulted in a base-case ICER of £41,799 per QALY gained. The ERG also presented a

scenario based on the LUME-Lung 1 utility values which increased the ICER to £49,649 per QALY gained. The committee was aware that NHS England considered that the commercial arrangement delivered additional value, but the analyses relating to this are commercial in confidence. The committee concluded that the most plausible ICER was between £41,799 and £49,649 per QALY gained based on analyses using the company's commercial arrangement. It was lower when the additional commercial information from NHS England was incorporated. Considering the uncertainty about the best source of utility values, the committee agreed that the ICER would likely be closer to the top end of the range.

End of life

Life expectancy for people with EGFR T790M mutation-positive NSCLC is less than 24 months

- 3.13 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](#). In the original appraisal, the committee concluded that people who take osimertinib have a short life expectancy. The clinical experts explained that they would expect people with EGFR T790M mutation-positive NSCLC to live for less than 24 months. The committee concluded that the short life expectancy criterion was met.

Osimertinib extends life by at least 3 months

- 3.14 The point estimates of AURA3 showed a survival difference of more than 3 months for patients having osimertinib compared with PDC. The patient and clinical experts explained that the survival benefit and improved quality of life offered by osimertinib could not be underestimated. The patient expert said that overall survival improved with osimertinib and that because most patients are diagnosed with stage 4 disease, access to osimertinib can be life changing. The committee concluded that osimertinib met the extension-to-life criterion.

Other factors

- 3.15 At the meeting, the patient and clinical experts outlined that there was some regional variation in access to osimertinib during the Cancer Drugs Fund data collection period. Equality of access to treatment is not an equality issue that can be addressed by the committee.
- 3.16 The company did not highlight any additional benefits that had not been captured in the QALY calculations.

Conclusion

Osimertinib is recommended

- 3.17 Overall, considering new evidence from the AURA3 trial, the Cancer Drugs Fund SACT dataset, the commercial arrangement, and the committee's preferred assumptions, the estimates of cost effectiveness were within the range that is considered to be a cost-effective use of NHS resources when the end-of-life criteria were applied. So osimertinib is recommended for use in the NHS for treating EGFR T790M mutation-positive locally advanced or metastatic NSCLC that has progressed after first-line treatment with an EGFR TKI.

4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer that has progressed after first-line treatment with an EGFR tyrosine kinase inhibitor 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.

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.

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