NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Osimertinib for maintenance treatment of EGFR mutation-positive locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiotherapy

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 evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: August 2025

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using osimertinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 18 September 2025
- Second evaluation committee meeting: To be confirmed

Details of the evaluation committee are given in section 5

1 Recommendations

1.1 Osimertinib should not be used for the maintenance treatment of locally advanced (stage 3) unresectable non-small cell lung cancer (NSCLC) in adults when the tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, and the cancer has not progressed during or after platinum-based chemoradiotherapy.

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 healthcare professional consider it appropriate to stop.

What this means in practice

Osimertinib is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that osimertinib provides value for money in this population.

Why the committee made these recommendations

Usual maintenance treatment for locally advanced unresectable NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations that has not progressed (not got worse) after platinum-based chemoradiotherapy is best supportive care including surveillance (regular outpatient appointments and scans).

Clinical trial evidence shows that osimertinib increases how long people have before their condition gets worse compared with best supportive care. It may also increase how long they live but this is uncertain.

There are also uncertainties in the economic model, including:

- how long people live after their condition has got worse when having best supportive care or osimertinib
- how long people having osimertinib have before their condition gets worse
- the length of time people take osimertinib.

Regardless of the uncertainties, the cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources. So, osimertinib should not be used.

2 Information about osimertinib

Marketing authorisation indication

2.1 Osimertinib (Tagrisso, AstraZeneca) is indicated for 'the treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for osimertinib.

Price

2.3 The list price of osimertinib (40 mg or 80 mg) is £5,770 per 30-tablet pack (excluding VAT; BNF online accessed June 2025).

2.4 The company has a commercial arrangement. This makes osimertinib available to the NHS with a discount and it would have also applied to this indication if osimertinib had been recommended. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by AstraZeneca, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition and clinical management

3.1 Non-small-cell lung cancer (NSCLC) is the third most common cancer in the UK and the leading cause of cancer-related death. In around 10% of people with the condition, NSCLC is epidermal growth factor receptor mutation-positive (EGFRm-positive). This subtype is more common in women, people who do not smoke, and East or South Asian ethnic groups. Locally advanced (stage 3) cancer means the cancer has spread into tissues around the lungs and might have spread into nearby lymph nodes. Unresectable means that the cancer cannot be removed by surgery.

People with EGFRm-positive locally advanced unresectable NSCLC typically have definitive chemoradiotherapy (CRT). After this, there are no targeted maintenance treatment options. After CRT, the condition is managed with best supportive care (BSC). This includes active surveillance imaging (for example, CT scans every 3 months), symptom management and biopsies to confirm recurrence. Osimertinib is proposed as a maintenance treatment after CRT. Once disease progression occurs, people are considered for subsequent systemic treatments. This may include EGFR tyrosine kinase inhibitors (TKIs) such as osimertinib (in line with NICE's technology appraisal guidance on osimertinib for treating EGFR T790M mutation-positive advanced NSCLC) or chemotherapy, depending on prior exposure. But the clinical experts noted that people who have osimertinib as maintenance treatment are unlikely to have retreatment with a TKI after progression. The clinical experts advised that durvalumab may still be used in some centres after CRT. But its

effectiveness in people with EGFRm-positive locally advanced unresectable NSCLC is limited and its use is expected to decline for this population. The committee concluded that treatment options after CRT for EGFRm-positive unresectable NSCLC are limited, and that there is no targeted maintenance treatments available for this population.

Effects on quality of life

3.2 The patient experts described the active surveillance approach after CRT as distressing, with the '3-month scan cycles' creating psychological distress. They said that the sense of 'doing nothing' is functionally and emotionally debilitating. They also highlighted the fear of brain metastases as a specific concern. This is because they can result in loss of independence and driving restrictions, and have a significant impact on quality of life. The patient experts also reported that osimertinib provides a sense of control and reduces uncertainty. While some people on osimertinib have side effects such as diarrhoea (described as unpredictable and socially limiting), the patient experts said that osimertinib is generally well tolerated. They also outlined that a key benefit of osimertinib is that it helps with daily functioning and allows people to avoid hospital-based treatment. The clinical experts supported these views and noted that early treatment with osimertinib can:

- improve outcomes including progression-free survival (PFS)
- reduce the burden of central nervous system (CNS) disease.

But they said that more evidence is needed to determine the impact on long-term outcomes such as overall survival (OS). They also emphasised that early systemic treatment may reduce neurological symptoms. The clinical experts specifically highlighted the risk of brain metastases as a key concern in this population, emphasising the serious functional and psychological impact associated with CNS progression. They said that CNS protection is a significant advantage of osimertinib. They also emphasised the broader psychological impact

of disease control, particularly in younger people with dependent families. The committee concluded that people with EGFRm-positive locally advanced unresectable NSCLC would value effective treatments that:

- reduce the risk of disease progression, particularly CNS progression
- relieve the psychological burden of surveillance.

Clinical effectiveness

LAURA

3.3 Evidence for osimertinib came from LAURA. This is an ongoing randomised, double-blind, placebo-controlled, phase 3 trial in people with EGFRm-positive locally advanced unresectable NSCLC whose cancer had not progressed after platinum-based CRT. A total of 216 people have been randomised to have osimertinib 80 mg once daily (n=143) or placebo (n=73). Treatment is continuing until disease progression or unacceptable toxicity (as per the protocol). The primary outcome measure is PFS. The results from the interim analysis, with a data cut off of January 2024, showed that median PFS was statistically significantly longer in the osimertinib arm than in the placebo arm (39.1 months compared with 5.6 months; hazard ratio [HR] 0.16, 95% confidence interval [CI] 0.10 to 0.24). The committee concluded that osimertinib provided a significant clinical benefit in terms of PFS compared with placebo.

OS

3.4 OS is not a primary outcome measure data in LAURA and the OS data is immature (31% maturity). The current results suggest a potential OS benefit with osimertinib compared with placebo but they are not statistically significant (median OS 58.8 months compared 54.0 months; HR 0.67, 95% CI 0.40 to 1.14). But the clinical experts advised that a survival benefit is plausible, and likely based on longer PFS and earlier treatment. The committee acknowledged that over 78% of people in the

placebo arm have had subsequent osimertinib. It thought that this treatment sequence is reflective of the treatment pathway in the NHS for people having BSC. The clinical experts advised that some people in the placebo arm did not have effective second-line treatment. This was because it was unavailable in their country or because their condition deteriorated before treatment could be started. But they highlighted that maintenance treatment with osimertinib ensures timely access to effective treatment. It may also help more people access subsequent treatment by intervening earlier. The committee noted that 44.4% of people in the osimertinib arm who have stopped treatment have had a subsequent EGFR TKI, and 23.8% have had retreatment with osimertinib. The clinical experts advised that this treatment sequence would not occur in NHS practice. The committee thought that this could have affected the robustness of the results. The EAG suggested that a crossover adjustment could have been applied to mitigate this issue, but the company did not include one in its submission. The committee requested an analysis that included a crossover adjustment because this could reduce bias and more accurately estimate the true survival benefit of osimertinib. It thought that, in the absence of a crossover adjustment, the long-term survival benefit of osimertinib remains uncertain.

The committee acknowledged that OS data did not directly inform the model. OS in the model was estimated based on other outcomes, including time to progression (TTP), PFS and post-progression survival (PPS). The clinical experts advised that modelled estimates of long-term survival used in the company's base case may have been optimistic relative to clinical experience. The committee noted that real-world data and data from LAURA may reduce uncertainty in modelling assumptions. It could do this by allowing observed OS data to be directly incorporated into the model, rather than relying on indirectly modelled survival estimates. The committee thought that a scenario in which OS is directly modelled using observed OS data (including crossover adjustment) would

be informative, so requested this. The committee thought that the OS data was immature. It concluded that a survival benefit for osimertinib may be plausible given the observed PFS benefit. But it thought that this was uncertain because:

- of the immaturity of the OS data
- the OS results were not statistically significant
- subsequent treatments that would not be used in NHS clinical practice had not been adjusted for.

It also concluded that modelling OS directly from the observed data with crossover adjusted analysis would be informative.

BSC as a comparator

3.5 The comparator in LAURA is placebo, which serves as a proxy for BSC in NHS clinical practice. BSC typically includes active surveillance, such as regular CT scans (for example, every 3 months), PET scans or biopsies to confirm suspected recurrence, and symptom management. The company used placebo as the comparator in the economic model. The clinical experts agreed that this was appropriate for people with EGFRm-positive locally advanced unresectable NSCLC after CRT. Also, NICE's technology appraisal guidance on durvalumab for maintenance treatment of unresectable NSCLC after platinum-based chemoradiation recommends it after CRT in locally advanced NSCLC. So, durvalumab was included in the NICE scope as a potential comparator. But the clinical experts advised that durvalumab is not thought to be effective in people with EGFRm-positive NSCLC. It is only used in a very small number of centres and its use in this population is declining in NHS practice. The committee concluded that BSC was the relevant comparator.

Placebo arm results

3.6 The EAG noted that the median PFS results for the placebo arm from LAURA seem to be poor when compared with median PFS in other

published studies. Some stakeholders also questioned whether the current PFS seen in the placebo arm of LAURA underestimate outcomes seen in NHS practice. The clinical experts and the Cancer Drugs Fund clinical lead noted that there were several limitations in some of the studies used in the comparison with LAURA. They highlighted that most were retrospective, based on small sample sizes or selected centres, and not generalisable to NHS care. For example, the PACIFIC trial (Naidoo et al, 2023) included only 11 people with EGFRm-positive NSCLC. But the placebo arm in LAURA is much larger, with 73 people having EGFRm-positive NSCLC. The clinical experts advised that relapse after CRT is often rapid in this population, and described some people in whom progression occurred even before radiotherapy planning. They also emphasised that CNS involvement is common. They thought that LAURA provided a more robust and generalisable dataset than other available sources. The clinical experts and the Cancer Drugs Fund clinical lead advised that the current PFS in the placebo arm in LAURA was slightly lower than expected but was unlikely to differ substantially from real-world NHS outcomes. The committee considered the cross-trial comparisons with other datasets and studies, including PACIFIC, and acknowledged differences in populations and study design. It concluded that the LAURA placebo arm PFS data was plausible, supported by expert clinical experience and appropriate for use in this evaluation.

Generalisability of LAURA

3.7 The EAG noted that LAURA is being carried out across multiple countries. It also includes a younger population than seen in the NHS and a higher proportion of people from an Asian ethnic background. The trial has not included any people from a Black ethnic background. The clinical experts explained that EGFR mutations are more common in people from an Asian ethnic background. Also, variation in ethnic composition is unlikely to affect treatment effect. One clinical expert noted that the stage distribution and baseline characteristics in LAURA are broadly consistent

with those seen in the NHS. The committee agreed that the LAURA population is generalisable to the population in the NHS.

Economic model

Company's modelling approach

3.8 The company used a semi-Markov state transition model with 3 mutually exclusive health states: progression-free, progressed disease and death. Everyone entered the model in the progression-free state, having either osimertinib or placebo as a proxy for BSC. OS was not directly modelled but derived from TTP, PFS and PPS curves. Transition probabilities between health states were based on LAURA data and varied by treatment arm and over time. Health-state-specific utility values were derived from EQ-5D-5L data, with additional quality-of-life decrements applied for adverse events. The committee thought that this modelling approach was reasonable and consistent with models used in other oncology NICE technology appraisals guidance at this line of treatment.

PPS for placebo arm

3.9 LAURA PPS data is immature (around 21% maturity as of January 2024). The company extrapolated PPS using a Gompertz distribution. This was thought to be plausible by 3 of the 5 clinicians it consulted. The EAG preferred to apply a Weibull distribution. This was because it thought that it estimated more clinically plausible outcomes that were in line with OS seen in previous relevant NICE's technology appraisals guidance such as on osimertinib for untreated EGFRm-positive NSCLC (from here TA654). That appraisal was informed by FLAURA, a trial that included people with metastatic NSCLC. The company said that PPS in LAURA should not be compared directly with PPS in FLAURA because the trial populations are not comparable. It argued that people in FLAURA had more advanced NSCLC and a worse performance status, and that all had osimertinib after progression compared with 80.6% in LAURA. The company also cited clinical advice that suggested people in LAURA who have not had

osimertinib may have a worse prognoses.

The EAG disagreed with the company's clinical experts. It noted that, while direct comparisons must be made cautiously, FLAURA could serve as a conservative lower bound for BSC PPS when adjusted appropriately. The EAG highlighted that people in FLAURA had more advanced NSCLC (metastatic), with a mean PPS of around 56 to 60 months in TA654. In contrast, the company's PPS estimates for LAURA's placebo arm are markedly lower, despite assuming a longer duration of osimertinib use after progression in the placebo arm in its economic model. The EAG emphasised that the company's argument was not consistent. If survival is poor, treatment duration should also be shorter. It argued that it was not appropriate to assume both short survival and prolonged treatment duration. The clinical experts explained that, while people in LAURA have had CRT, which may temporarily reduce performance status, many still have still recovered to have systemic treatment. They thought it unlikely that this population would have significantly worse outcomes than the people with metastatic NSCLC in FLAURA. Also, the clinical experts noted that more brain metastases have been picked up after progression in LAURA than in FLAURA. Brain metastases are typically associated with worse outcomes and shorter PPS. But their higher detection in LAURA may reflect differences in detection methods rather than underlying disease severity. The implications of this for treatment duration assumptions remain uncertain. Also, the link between brain metastases and the modelled duration of osimertinib treatment remains unclear.

The committee acknowledged that the company's justification for using Gompertz was based on goodness of fit and visual inspection. But it noted that the statistical fit was very similar between distributions. The committee agreed that the company's PPS modelling for the BSC arm likely underestimated survival. It also thought that it was inconsistent with the long osimertinib treatment duration assumed elsewhere in the model.

The committee also acknowledged that 3 of the 5 healthcare professionals consulted by the company had thought that the Weibull approach was plausible. The committee noted the immaturity of the LAURA data and the central role of PPS in cost-effectiveness modelling. The company said that no further data cuts would include PPS data, and that PPS would also not be collected during any period of managed access. The committee concluded that the EAG's Weibull distribution was more appropriate for decision making.

PPS with osimertinib

3.10 The company used a Gompertz distribution for extrapolating PPS for people initially having osimertinib in its base case. This was because of the increasing hazard of death over time and alignment with the smoothed hazard profile. The EAG also used Gompertz in its base case but did scenario analyses using the exponential distribution to explore uncertainty. The committee acknowledged that the statistical goodness of fit was very similar across Gompertz and exponential distributions. There was high uncertainty in long-term PPS estimates because of the limited maturity of the LAURA data. Median follow up after progression in the osimertinib arm has been short (about 7.5 months), and a substantial proportion of people in which the cancer has progressed have died (24 of 53 people).

The committee considered whether the Gompertz model underestimated the potential for longer-term survival and whether the exponential distribution may be more appropriate. The clinical experts advised that, while 10-year survival after progression was possible, it would be very uncommon. The company's Gompertz-based model estimated a very low survival at 10 years, and the exponential model projected higher survival. The committee thought that the exponential estimates were overly optimistic based on clinical testimony. The clinical experts noted that toxicity and comorbidities would likely prevent extended survival in most people after progression. The committee thought that both Gompertz and

exponential distributions had limitations in extrapolating PPS for people initially having osimertinib. The committee preferred using the Gompertz distribution. This was because it better reflected the rarity of long-term survival and was consistent with the expectations of the clinical experts. But, because some long-term survival may occur, the committee acknowledged that the exponential distribution was informative. The committee concluded that Gompertz was the most appropriate for decision making.

TTP and PFS for osimertinib

3.11 The company used a Weibull distribution for modelling TTP and PFS for people having osimertinib. It highlighted a relatively good statistical fit and support from its clinical experts. The EAG also used the Weibull distribution for its base case. But the EAG raised concerns about the plausibility of long-term PFS estimates produced by the Weibull model. The EAG advised that the Weibull distribution may have overestimated long-term PFS because of its flattening hazard function. Visual inspection of LAURA data suggested that risk of progression may have increased after about 28 months. This was inconsistent with the decreasing hazard predicted by the Weibull distribution.

The EAG noted that only 28 people were still at risk of progression beyond 36 months in LAURA, and that this contributed to extrapolation uncertainty. It proposed the exponential distribution as a sensitivity analysis. It explained that, although this distribution lacked a decreasing hazard, it may be a more conservative and clinically plausible alternative. Using Weibull, the estimated 10-year PFS was 18.5%, which was thought to be high and outside the range of 10.0% to 15.0% expected by the company's clinical experts. In contrast, the exponential model produced a 10-year PFS estimate of 11.6%. One clinical expert described the 10-year PFS estimate from Weibull as too optimistic, and even said that the 5-year estimates were too high.

The committee agreed that the exponential model may have provided a more appropriate approach. It noted that the only scenario provided in which the exponential distribution for TTP and PFS was used also applied the exponential distribution to PPS for people treated with osimertinib. This combination did not reflect the committee's preferred approach to modelling PPS for osimertinib, which was to use a Gompertz distribution (see section 3.10). It understood that a scenario using the exponential distribution for TTP and PFS, and Gompertz distribution to PPS for people having osimertinib was not presented. This was because it resulted in the crossing of the OS curves for osimertinib and BSC, which the company and EAG thought would be implausible. The committee was aware that the crossing was slight. It also noted that it might have reflected the treatment sequences in the LAURA trial, so would not necessarily be implausible. The committee thought that further analyses were needed to explore the appropriate combinations of extrapolations (for TTP, PFS and PPS) and to determine the plausibility of the resulting OS predictions. It thought that, based on the evidence available, the exponential distribution was preferred for TTP and PFS. This was because of its concerns that the Weibull distribution may have overestimated long-term PFS. But it also thought that the Weibull distribution might still be considered a plausible alternative, particularly if:

- the exponential distribution could not be used without generating implausible survival outcomes, or
- further justification is provided for excluding such scenarios.

The committee concluded that further analyses of PFS and TTP extrapolations, taking into account PPS extrapolations and resulting OS predictions, were needed.

Osimertinib time to treatment discontinuation

3.12 The company used a piecewise approach to estimate time to treatment discontinuation (TTD). It used Kaplan–Meier data from LAURA up to

36 months, then an extrapolated exponential curve. The company justified the choice of an exponential curve because:

- of the small number of people at risk beyond 36 months, and
- its clinical experts thought that the distribution was the most plausible for NHS clinical practice.

The company's piecewise approach resulted in a sustained separation of the PFS and TTD curves after 36 months. The EAG noted that this was not supported by LAURA trial PFS and TTD Kaplan–Meier data, and was inconsistent with a treat-to-progression regimen. The EAG preferred using a Weibull distribution for the full TTD curve. This was to maintain consistency with the PFS extrapolation and to avoid introducing an artificial separation between TTD and PFS (see section 3.11). When the Weibull distribution was used to generate TTD estimates, the osimertinib TTD curve lay slightly above the PFS curve after 10 years. In the EAG's base case, osimertinib drug acquisition costs were calculated using the minimum of PFS and TTD. This effectively capped TTD by the PFS curve, meaning that modelled TTD was about the same as PFS.

The committee noted that osimertinib treatment is usually taken until disease progression or unacceptable toxicity. The Cancer Drugs Fund clinical lead noted that, for some people in the NHS, treatment may continue for a short time after disease progression, and this could be for around 3 months. This reflects real-world scenarios in which radiological confirmation of progression may be delayed, and treatment is continued until progression is confirmed. Also, logistical delays such as arranging access to second-line treatments can result in short extensions of osimertinib treatment beyond progression.

The committee acknowledged that the EAG's approach was methodologically preferable. This was because it used a consistent

statistical model from the start of the model, rather than adding an extrapolated function onto a separate observed dataset. The committee also noted that Kaplan–Meier data showed close alignment of PFS and TTD up to 36 months. The committee thought that the company's piecewise method may also be plausible, particularly in the context of sparse long-term data and the clinical justification provided. But it thought that this was uncertain. It acknowledged that it might be possible to collect further data on TTD in clinical practice to reduce uncertainty in treatment duration assumptions. The committee concluded that the same distribution for PFS and TTD was preferable for decision making because it maintained alignment between PFS and TTD over time.

Osimertinib treatment stopping rule

3.13 The company model included a 10-year stopping rule for osimertinib treatment in the intervention arm. This rule was not based on the trial protocol or marketing authorisation. It was introduced based on clinical advice that indefinite treatment is unlikely. The clinical experts noted that some people may continue treatment long term, but that toxicity often accumulates. So, many people would stop treatment earlier because of side effects or comorbidities. But they also cautioned against assuming a uniform stopping point because treatment duration varies depending on individual tolerability and NSCLC trajectory. The EAG preferred removing the stopping rule from the model to reflect real-world treat-to-progression clinical practice and to avoid introducing arbitrary constraints. Importantly, the EAG noted that including the stopping rule in the model only affected treatments costs, not outcomes. The committee noted that removing the stopping rule led to a longer treatment duration and a higher incremental cost-effectiveness ratio (ICER). The committee also noted that long-term PFS was thought to be rare, and that the Weibull distribution used to model PFS may have overestimated this benefit (see section 3.11). So, it thought that estimating extended treatment durations was uncertain because of this. The committee concluded that a fixed 10-year stopping

rule was not appropriate. But it recognised that future real-world data collection, such as in the Cancer Drugs Fund, may help to clarify typical treatment duration and improve confidence in long-term cost-effectiveness estimates.

Subsequent treatments

3.14 The company based subsequent treatment uptake in the model on input from 5 clinical experts. The EAG preferred using data directly from LAURA. The committee noted that, in LAURA, 80.6% of people in the BSC arm have had osimertinib as the first subsequent treatment after progression. This figure was higher than the company's base-case assumption. The EAG revisions resulted in increased costs after progression for the BSC arm and a lower ICER. The committee acknowledged the uncertainty in predicting real-world treatment patterns and recognised the limitations of expert elicitation. The committee concluded that trial-based estimates for subsequent treatments provided better consistency with the model inputs.

Health-state utility values

3.15 The company's progression-free health-state utility value was derived from EQ-5D-5L data collected in LAURA and mapped to EQ-5D-3L. This value exceeded the average health-utility value for the general population (age- and sex-adjusted), which the EAG thought was implausible. The EAG advised that it was unlikely that people with cancer would have better health-related quality of life (HR-QoL) than the general population. So, it revised the progression-free utility value to 0.831 to match the average general population norm. The committee heard that the trial population likely excluded people with significant comorbidities. But it still found it implausible that average HR-QoL exceeded that of the general population. The clinical and patient experts agreed that some reduction in HR-QoL would be expected because of the impact of prior treatment and ongoing symptoms. The committee also considered the progressed-disease utility value, which was informed by FLAURA. To represent

people with metastatic disease, the company used a progression-free value from FLAURA (0.794), which was used in TA654. But the EAG thought that this overestimated HR-QoL after progression. This was because it was based on a small sample of people in FLAURA and did not distinguish between early and late stages of progressive disease. The EAG explained that quality of life often declines further as progression continues. So, using a single utility value that may be higher than the average for the health state over time may have overestimated HR-QoL across the full progression phase. To address this, the EAG revised the utility value to 0.725. This revision was based on an average of progression-free and progressed-disease values from TA654, which included both early and late progressed-disease health states.

Scenario analyses done by the NICE technical team used values from NICE's technology appraisal guidance on osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFRm-positive advanced NSCLC. The scenario analyses confirmed that further reducing the progressed-disease utility value to 0.674 reduced the ICER and that reducing the progression-free utility values to 0.804 increased it. This highlighted the sensitivity of the model to utility values. The committee concluded that the EAG's revised utility values more appropriately reflected HR-QoL in both the progression-free and progressed-disease states than the values used by the company.

Cost-effectiveness estimates

Acceptable ICER

3.16 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also

take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically for:

- the extrapolation of PPS for BSC (see section 3.9) and osimertinib (see section 3.10)
- the extrapolation of TTP and PFS for osimertinib (see section 3.11)
- the plausibility of the combined scenario using the exponential extrapolation for PFS and TTP and Gompertz for PPS for osimertinib, given concerns about crossing OS curves (see section 3.10 and section 3.11)
- the extrapolated treatment duration with osimertinib (see section 3.12).

The committee considered the remaining uncertainty and possible uncaptured benefits (see section 3.21). It concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Company and EAG cost-effectiveness estimates

3.17 The cost-effectiveness results cannot be reported here because they incorporate confidential discounts for drugs included within the model. The company's base case was below £20,000 per QALY. The EAG's base case was above £30,000 per QALY gained. The company's and the EAG's base cases differed across several key issues. The cost-effectiveness results were sensitive to extrapolation methods for survival and duration of treatment.

Committee's preferred assumptions

3.18 The committee thought that the EAG's base case was more aligned with clinical expectations than the company's base case. But it noted uncertainty around the plausibility of certain extrapolation scenarios, including the combination of exponential extrapolation for osimertinib PFS and TTP and Gompertz for PPS (see section 3.10 and section 3.11). The committee also highlighted that a crossover adjustment had not been

applied, despite a high rate of treatment switching in the trial. It thought that such an adjustment was necessary to reduce bias and better estimate the true treatment effect of osimertinib on OS. The committee's preferred assumptions included the following key assumptions:

- PPS for the BSC group modelled using the Weibull distribution (see section 3.9)
- PFS and TTP for osimertinib modelled using exponential distribution (see section 3.10)
- PPS for people treated with osimertinib modelled using the Gompertz distribution (see section 3.11)
- TTD for osimertinib using the same extrapolation as used for PFS to align with PFS modelling (see section 3.12)
- the 10-year stopping rule for osimertinib removed (see section 3.13)
- the proportion of people having subsequent treatment taken from the LAURA trial (see section 3.14)
- a progression-free health-state utility value of 0.831 and a progressed-disease utility value of 0.725 (see section 3.15).

The committee recognised concerns that this combination of assumptions led to potentially implausible survival estimates, particularly the crossing of OS curves. But it added that, given that the treatment sequences and OS curves only slightly crossed, this result may be plausible. Although, it did think that this was uncertain. The resulting ICER, based on these assumptions, exceeded the committee's preferred acceptable ICER for routine commissioning.

Managed access

Feasibility of managed access

3.19 Having established that osimertinib was not cost effective for routine commissioning, the committee discussed whether a managed access recommendation could be appropriate to address the uncertainties

identified in the modelling of osimertinib. The company did not submit a formal managed access proposal, and said:

- OS data from LAURA (expected in 2027) would become available
- a main area of uncertainty, PPS, would not be addressed by either LAURA or routinely available real-world data such as Systemic Anti-Cancer Therapy (SACT) datasets.

The committee acknowledged the lack of future PFS or PPS data. But it noted that the availability of future OS data may be informative and could be used to incorporate OS data directly, for example, when using a partitioned survival model suggested by the EAG. But the company advised that this would not be standard practice for this indication. The committee reviewed key issues in relation to any potential managed access data collection. These included the immaturity of the OS and PPS data, the modelling of TTD and using expert opinion for subsequent treatment rates. The Cancer Drugs Fund clinical lead explained that survival and progression outcomes may remain uncertain. But TTD data would be available from SACT and would offer important real-world insight into treatment patterns and NHS resource use. The committee agreed that, if the conditions for a managed access arrangement could be met, there was potential that evidence collection could address some of the uncertainties. But the committee concluded that, because the company did not submit a managed access proposal, it could not make a recommendation for managed access.

Other factors

Equality

3.20 The committee thought that people with EGFRm-positive NSCLC are more likely to be women and from East Asian or other ethnic minority groups, including people from Bangladeshi, Indian, or Pakistani ethnic

groups. Race and gender are protected characteristics under the Equality Act 2010. The committee concluded that the issue of different disease prevalence cannot be addressed in a technology appraisal.

Uncaptured benefits

3.21 The committee considered whether there were any uncaptured benefits of osimertinib. The clinical and patient experts discussed that osimertinib may offer psychological and functional benefits that are not typically captured in cost-effectiveness models. People whose condition is managed with surveillance after CRT may experience anxiety and reduced sense of control while waiting for potential cancer recurrence. The committee also heard that being able to take active treatment, rather than just having surveillance, is perceived as a meaningful benefit by people with EGFRm-positive locally advanced unresectable NSCLC. Although this is difficult to quantify, the sense of actively doing something is thought to be psychologically important and helps people feel more actively engaged in their care. The clinical experts also noted that osimertinib may reduce the risk of brain metastases, which can have a considerable impact on cognitive function and quality of life. While these potential benefits were acknowledged, the committee concluded that all treatment benefits with osimertinib were captured in the model and the acceptable ICER threshold. So, the committee concluded that all additional benefits of osimertinib had been considered.

Conclusion

Recommendation

3.22 The committee noted that, when its preferred assumptions were applied, the cost-effectiveness estimates were above what it thought was a cost-effective use of NHS resources. So, osimertinib for the maintenance treatment of EGFRm-positive locally advanced unresectable NSCLC after platinum-based CRT should not be used.

4 Evaluation committee members

This topic was evaluated as a single technology evaluation by the highly specialised technologies evaluation committee. The highly specialised technologies evaluation committee and the 4 technology evaluation committees are standing advisory committees of NICE.

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

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Chair, highly specialised technologies evaluation committee

NICE project team

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

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Technical lead

Alan Moore

Technical adviser

Greg O'Toole

Project manager

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Associate director

ISBN: [to be added at publication]