NICE National Institute for Health and Care Excellence

NICE guidance

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

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.

Contents

1 Recommendations

1.1 Osimertinib can be used, within its marketing authorisation, as an option to treat unresectable locally advanced (stage 3) non-small-cell lung cancer (NSCLC) in adults. It is an option 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.

Osimertinib can only be used if the company provides it according to the commercial arrangement.

What this means in practice

Osimertinib must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Osimertinib must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that osimertinib provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

Usual treatment for unresectable locally advanced 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 receiving osimertinib have before their condition gets worse
- the length of time people take osimertinib.

The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, osimertinib can 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 April 2026).

2.4 The company has a commercial arrangement (commercial access agreement). This makes osimertinib available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 For information, AstraZeneca's Carbon Reduction Plan for UK carbon emissions is published on AstraZeneca's webpage on sustainability.

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. It is epidermal growth factor receptor mutation-positive (EGFRm-positive) in around 10% of cases. 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 the cancer progresses, 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 are 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 delay 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 EGFRm-positive locally advanced unresectable NSCLC that had not progressed after platinum-based CRT. A total of 216 people were randomised to have osimertinib 80 mg once daily (n=143) or placebo (n=73). Treatment is continued 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 compared with placebo in terms of PFS. The company provided a more recent November 2024 data cut for OS only. The OS data was immature (31% maturity). It suggested a potential OS benefit with osimertinib compared with placebo but was not statistically significant (median OS 58.8 months compared with 54.0 months; HR 0.67, 95% CI 0.40 to 1.14). The clinical experts advised that a survival benefit is plausible because of longer PFS and earlier treatment. The committee agreed 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.

BSC as a comparator

3.4 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. NICE's technology appraisal guidance on durvalumab for maintenance treatment of unresectable NSCLC after platinum-based chemoradiation recommends durvalumab 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 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.

Trial crossover

3.5 People who initially had placebo in LAURA were allowed osimertinib upon disease progression. Over 78% had subsequent osimertinib. The committee thought this treatment sequence reflected the treatment pathway in the NHS for people having BSC. The clinical experts advised that not all people in the placebo arm had an effective second-line treatment. This was because it was unavailable in their country or because their condition deteriorated before treatment could be started. The experts emphasised that maintenance treatment with osimertinib ensures timely access to effective treatment.

Retreatment with osimertinib

3.6 The committee noted that 28 out of 63 people (44.4%) in the osimertinib arm in LAURA who stopped treatment had a subsequent EGFR TKI, and 15 out of 63 people (23.8%) in the osimertinib arm 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. In its response to draft guidance consultation, the company did a crossover adjustment to account for retreatment with osimertinib in LAURA. It considered the rank-preserving structural failure time method to be the most appropriate for this analysis. The EAG was satisfied with the company analysis and thought it a conservative approach. So, the committee agreed that the impact of retreatment with osimertinib on OS results was unlikely to need separate consideration.

Generalisability of LAURA

3.7 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 PFS seen in the placebo arm of LAURA underestimated outcomes seen in NHS practice. The clinical experts and the NHS England Cancer Drugs Fund clinical lead (from here, the Cancer Drugs Fund 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 (see figure 1 in Naidoo et al. 2023) included only 11 people with EGFRm-positive NSCLC. But the placebo arm in LAURA is much larger, with 73 people with 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 lead advised that the 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 to use in this evaluation.

The EAG noted that LAURA is being carried out across multiple countries. It also includes a younger population than that 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.

Other relevant clinical trials: FLAURA and FLAURA2

3.8 FLAURA and FLAURA2 are both clinical trials that included people with metastatic NSCLC. FLAURA compared osimertinib monotherapy with standard care. The trial informed NICE's technology appraisal guidance on osimertinib for untreated EGFRm-positive NSCLC (from here, TA654). FLAURA2 compared osimertinib plus platinum-based chemotherapy with osimertinib monotherapy. The trial informed NICE's technology appraisal guidance on osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFRm-positive advanced NSCLC. The company used data from FLAURA2 to inform one of its modelling assumptions. The EAG used comparisons with data from FLAURA to inform its modelling assumptions. The committee was aware that metastatic NSCLC is the sequential step after disease progression for people in the LAURA trial. It acknowledged that comparisons between progressed disease in LAURA and progression-free disease in FLAURA and FLAURA2 could be informative. But it noted that comparisons should be made cautiously because people in these trials had more advanced NSCLC than people with progressed disease in LAURA.

Economic model

Company's modelling approach

3.9 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 was derived from time-to-progression (TTP), PFS and post-progression-survival (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. During the first meeting, the committee noted that real-world data and directly modelling OS data from LAURA may reduce uncertainty in the modelling assumptions. In its response to draft guidance consultation, the company noted that the model structure would need to be changed to allow OS data to be directly incorporated. It thought that doing

this to use relatively immature OS data would not considerably reduce overall uncertainty, and that the current semi-Markov structure was appropriate. The EAG agreed that using currently available OS data in a partitioned survival model would not materially reduce the uncertainty of the OS results. The committee acknowledged these points and thought that a partitioned survival model would be appropriate if more mature data was available. The committee considered the current relatively immature OS data and concluded that the company's modelling approach was reasonable and consistent with models used in other oncology NICE technology appraisals guidance at this line of treatment. So, it concluded that the model was appropriate for decision making.

Placebo arm post-progression osimertinib treatment duration

3.10 People in the placebo arm of LAURA were able to have osimertinib upon progression. Median post-progression osimertinib treatment duration in LAURA was based on 50 people and 16 events. The company explained that this data was immature (23% maturity). So, in its model, post-progression osimertinib treatment duration was informed by the modelled mean treatment duration of the osimertinib monotherapy arm in FLAURA2. Clinical advice to the company suggested that people with progressed disease in the LAURA placebo arm would have osimertinib for longer than people who were progression-free in FLAURA2. This was based on longer median PPS in LAURA (41.8 months) compared with median OS in FLAURA2 (36.7 months). So, the osimertinib treatment duration estimate used in the company model was increased by a specific number of months. The company considers both the FLAURA2 modelled mean treatment duration for the osimertinib monotherapy arm, and the number of months it was increased by, to be confidential, so they cannot be reported here.

The EAG noted that the latest November 2024 data cut of the LAURA trial showed a sharp decline in the placebo arm OS Kaplan–Meier estimate. The EAG said this indicated that the post-progression osimertinib treatment duration may be shorter than was assumed in the company model. The EAG explored a scenario using the post-progression mean osimertinib treatment duration for the placebo arm of LAURA at the January 2024 data cut. This was shorter than the company's preferred value. The company considers both durations to be confidential, so they cannot be reported here. The EAG thought TA654 was a

useful comparison for this outcome. In TA654, the committee-preferred osimertinib treatment duration for the progression-free setting was 21.96 months. After adjusting its mean post-progression osimertinib treatment duration to account for the proportion of people who did not have osimertinib after progression, the EAG felt its scenario was similar to the progression-free state in TA654. The committee agreed that the company model likely overestimated post-progression osimertinib treatment duration and noted that the treatment duration estimate in the EAG scenario was similar to that in TA654. But the committee was aware that people with progressed disease in LAURA would likely have less advanced NSCLC than people without progression in FLAURA (see section 3.8). So, it expected osimertinib treatment duration to be longer than in TA654. The committee decided on a value for post-progression osimertinib treatment duration that was between the estimates in the company model and EAG's scenario. The company considers the committee's exact preferred duration to be confidential, so it cannot be reported here.

Placebo arm post-progression survival

3.11 The company extrapolated PPS in the placebo arm using a Gompertz distribution. It consulted 5 healthcare professionals, and 3 thought it plausible. The EAG preferred a generalised gamma distribution in combination with its shorter post-progression osimertinib treatment duration (see section 3.10). This was because it thought that it estimated more clinically plausible outcomes that were in line with OS seen in TA654. The generalised gamma distribution had a similar statistical fit to the Gompertz, and produced a 10-year OS estimate within the range suggested by healthcare professionals consulted by the company. The company said that PPS in LAURA should not be compared directly with PPS in FLAURA because the trial populations were not comparable. It argued that people in FLAURA had more advanced NSCLC and a worse performance status, and that all had osimertinib after progression in the comparator arm compared with 80.6% in LAURA. The company also cited clinical advice suggesting that people in the LAURA placebo arm who did not get osimertinib upon progression may have a worse prognosis. The EAG noted that the company used a comparison with FLAURA2 to calculate the post-progression osimertinib treatment duration for the placebo arm in its model (see section 3.10). The EAG highlighted that it was not consistent for the company to argue that the trial populations of LAURA and

FLAURA were not comparable, while simultaneously making a comparison between LAURA and FLAURA2 elsewhere in its model.

As part of its scenario analysis, the EAG attempted to calculate the total PPS, osimertinib treatment duration and survival duration after people stopped osimertinib treatment in the LAURA placebo arm. It adjusted osimertinib treatment duration to account for the proportion of people who did not have osimertinib after progression. Then it deducted this from the total PPS to produce the mean survival after stopping osimertinib (and the mean survival for people who did not have osimertinib). The EAG disagreed with the company's clinical experts' opinion that LAURA and FLAURA should not be compared. It noted that, although direct comparisons must be made cautiously, FLAURA could serve as a conservative lower bound for BSC PPS when adjusted appropriately. The EAG noted that in its scenario analysis, total PPS was similar to expected survival from FLAURA in TA654 (56.15 months to 60.22 months). The EAG highlighted that the company's estimated placebo PPS was markedly lower than the survival estimates from FLAURA in TA654. This was despite:

- the population in FLAURA having more advanced disease, and
- the company assuming a longer duration of osimertinib use after progression in the placebo arm in its economic model than the committee's preferred assumption using FLAURA in TA654.

The EAG also highlighted that the mean survival after stopping osimertinib was much lower than the osimertinib treatment duration in the company's estimate. 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 EAG noted the clinical advice that led to the company's post-progression osimertinib treatment duration (see section 3.10). It suggested that the duration of osimertinib treatment was prognostic for survival and that the 2 were linked. But the clinical experts emphasised that they would expect people in the LAURA placebo arm to have poor survival after stopping osimertinib regardless of how long they had been having it.

The company disagreed with the EAG's approach to estimating the

osimertinib treatment duration in the placebo arm, and the mean survival after stopping treatment. Because the model was a cohort model, the company said it was not plausible to disaggregate the PPS into people who had and did not have osimertinib. It was also not possible to calculate the length of post-progression osimertinib treatment for people who had it. The company also reiterated concerns with comparing these survival outcomes with data from TA654. For the survival estimates from FLAURA in TA654, all people had osimertinib. So, the company argued this comparison lacked validity.

The company's justification for using the Gompertz distribution was based on goodness of fit and visual inspection. But the committee noted that the statistical fit was very similar across the distributions. It 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 concluded that the EAG's generalised gamma distribution was more appropriate for decision making. It thought that the mean survival after stopping osimertinib was likely shorter than the estimate in the EAG's scenario. This was based on the clinical expert opinion that people had very poor survival after stopping osimertinib. The committee assumed a higher post-progression osimertinib treatment duration than that used in the EAG's scenario analysis (see section 3.10). But the simultaneous assumption of a shorter mean survival after stopping osimertinib meant the committee's preferred total PPS in the LAURA placebo arm aligned with the estimate in the EAG's scenario. The committee acknowledged that the EAG's predicted PPS fell below the committee's preferred PPS from TA654, and the EAG felt this was perhaps pessimistic. But the committee noted that the EAG's preferred PPS modelling generated a longer PPS than the company's preferred modelling. Overall, it concluded that the EAG's PPS survival modelling was appropriate based on the advice from the clinical experts at the meeting.

Osimertinib post-progression survival

3.12 The company extrapolated PPS in the osimertinib arm using a Gompertz distribution. This was because of the increasing hazard of death over time and

alignment with the smoothed hazard profile. The EAG also used the Gompertz distribution 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 the Gompertz and exponential distributions. The long-term PPS estimates were very uncertain 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 10-year survival after progression was possible but 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 given the clinical experts' opinion. The clinical experts noted that toxicity and comorbidities would likely prevent extended survival for most people after progression. The committee thought that both the 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 clinical experts' expectations. But, because some long-term survival may occur, the committee acknowledged that the exponential distribution was informative. The committee concluded that the Gompertz distribution was the most appropriate for decision making.

Osimertinib time to progression and progression-free survival

3.13 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. But the EAG raised concerns about the plausibility of long-term PFS estimates produced by the Weibull model. It 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 increase after about 28 months. This was inconsistent with the decreasing hazard predicted by the Weibull distribution. In its response to draft

guidance consultation, the company provided additional combinations of curve distributions.

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 the Weibull distribution, 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%. In its response to draft guidance consultation, the company noted that the expected 10-year PFS range of 10.0% to 15.0% was taken from a global advisory board. This advisory board did not formally validate modelled extrapolation curves. The company stated that it did a UK clinical validation exercise specifically to inform the validity of its modelled curves. It noted that 4 out of 5 healthcare professionals thought the Weibull curve was the most clinically plausible extrapolation of TTP. The company argued that the UK validation exercise should take precedent when considering clinical validation of the modelled survival curves. The clinical experts at the committee meetings described the 10-year PFS estimate from the Weibull distribution as too optimistic and said that even the 5-year estimates were too high. They noted that people with the condition usually only survive for a short time after progression and that very few people have TKI treatment for more than 10 years. The EAG noted that advice from the global advisory board and the clinical experts was consistent in that the PFS estimates produced by the Weibull curve 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 the osimertinib group. This combination did not reflect the committee's preferred approach to modelling PPS for osimertinib, which was to use a Gompertz distribution (see section 3.12). It understood that a scenario using the exponential distribution for TTP and PFS, and the Gompertz distribution for 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 noted that the

crossing was slight, and thought the curves appeared to be coinciding. It noted that it was hard to draw a conclusion about this without having confidence intervals around the curves. It also noted that osimertinib rechallenge was allowed and this may have affected the extrapolations. The committee highlighted that this distribution combination resulted in early separation of the osimertinib and placebo OS curves. This captured the benefit of osimertinib treatment before the curves crossed. It concluded 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.

Osimertinib time to treatment discontinuation

3.14 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, because there was no separation between the LAURA trial PFS and TTD Kaplan–Meier curves. It highlighted that in the company's piecewise approach, separation occurred when the exponential distribution was used to extrapolate TTD, not at the timepoint informed by clinical evidence. The EAG also noted that the company's approach was inconsistent with a treat-to-progression regimen. The EAG preferred to use the same distribution as PFS 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 3.13). 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 is usually taken until disease progression or unacceptable toxicity. The Cancer Drugs Fund lead noted that, for some people in the NHS, treatment may continue for around 3 months after disease progression. This is because 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. It 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. The committee concluded that using the same distribution for PFS and TTD was preferable for decision making because it maintained alignment between PFS and TTD over time. It preferred the exponential distribution applied to the time horizon of the model, rather than the company's piecewise approach.

Osimertinib treatment stopping rule

3.15 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 3.13). 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

3.16 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

3.17 The company's progression-free health-state utility value was derived from EQ-5D-5L data collected in LAURA and mapped to the EQ-5D-3L. This value exceeded the average health-utility value for the general population (adjusted for age and sex), 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 (HRQoL) 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 HRQoL exceeded that

of the general population. The clinical and patient experts agreed that some reduction in HRQoL 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 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 HRQoL 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 HRQoL 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 HRQoL in both the progression-free and progressed-disease states than the values used by the company.

Cost-effectiveness estimates

Acceptable ICER

3.18 NICE's manual on technology appraisal and highly specialised technologies guidance notes that, above a most plausible ICER of £25,000 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 duration of osimertinib treatment for people in the placebo arm whose cancer progressed (see section 3.10)
- the extrapolation of PPS for BSC (see section 3.11)
- the extrapolation of TTP and PFS for osimertinib (see section 3.13)
- the extrapolated curves when using the exponential curve for PFS and TTP, and the Gompertz curve for PPS, for osimertinib (see section 3.12 and section 3.13)
- the extrapolated treatment duration with osimertinib (see section 3.14).

The committee considered the remaining uncertainty and possible uncaptured benefits (see section 3.22). It concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained).

Company and EAG cost-effectiveness estimates

3.19 The cost-effectiveness results cannot be reported here because they incorporate confidential discounts for drugs included in the model. The company's base-case ICER was below the £25,000 to £35,000 per QALY gained range. The EAG's base-case ICER was above £35,000 per QALY gained. The cost-effectiveness results were sensitive to the extrapolation methods for survival and duration of treatment. The EAG presented a scenario at the second committee meeting that provided alternative assumptions for these parameters which generated a cost-effectiveness estimate that was between £25,000 and £35,000 per QALY gained.

Committee's preferred assumptions

3.20 The committee preferred the combination of most of the assumptions in the EAG's scenario analysis. It noted uncertainty around the combination of

exponential extrapolation for osimertinib PFS and TTP, and Gompertz for PPS (see section 3.12 and section 3.13), but thought this scenario was more aligned with clinical expectations than the company's base case. The only assumption the committee differed on compared with the EAG's scenario analysis was the post-progression osimertinib treatment duration for the BSC group. The committee's preferred assumptions included the following:

- using a post-progression osimertinib treatment duration for the BSC group that was in between the company base case and EAG scenario analysis durations (see section 3.10)
- modelling PPS for BSC using the generalised gamma distribution (see section 3.11)
- modelling PPS for osimertinib using the Gompertz distribution (see section 3.12)
- modelling PFS and TTP for osimertinib using the exponential distribution (see section 3.13)
- using the same extrapolation method for TTD and PFS for osimertinib to align with PFS modelling, applying the exponential distribution from the model start, rather than using a piecewise approach (see section 3.14)
- removing the 10-year stopping rule for osimertinib (see section 3.15)
- taking the proportion of people having subsequent treatment from the LAURA trial (see section 3.16)
- using a progression-free health-state utility value of 0.831 and a progressed-disease utility value of 0.725 (see section 3.17).

The committee acknowledged that this combination of assumptions led to potentially implausible survival estimates, particularly the meeting of the OS curves. But it added that the OS curves only slightly crossed, and that the degree of uncertainty around this was unknown. The resulting ICER, based on these assumptions, was below the committee's preferred acceptable ICER for routine commissioning.

Other factors

Equality

3.21 EGFRm-positive NSCLC is more likely to affect women, trans men and non-binary people registered female at birth and people 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 issue of different disease prevalence cannot be addressed in a technology appraisal.

Uncaptured benefits

3.22 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. Being able to have 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 committee's acceptable ICER. So, the committee concluded that all additional benefits of osimertinib had been considered.

Conclusion

Recommendation

3.23 The committee noted that, when its preferred assumptions were applied, the cost-effectiveness estimates were below what it considers a cost-effective use of NHS resources. So, osimertinib can be used, within its marketing authorisation, as an option for the maintenance treatment of EGFRm-positive locally advanced unresectable NSCLC after platinum-based CRT.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days 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 cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England 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 guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

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 unresectable, locally advanced non-small-cell lung cancer and the healthcare professional responsible for their care thinks that osimertinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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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