NICE National Institute for Health and Care Excellence

NICE guidance

Osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced non-small-cell lung cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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

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

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendation

1.1 Osimertinib with pemetrexed and platinum-based chemotherapy is recommended, within its marketing authorisation, as an option for untreated advanced non-small-cell lung cancer (NSCLC) in adults whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. Osimertinib with pemetrexed and platinum-based chemotherapy is only recommended if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

Usual treatment for untreated advanced NSCLC with EGFR mutations is osimertinib alone.

Evidence from a clinical trial shows that, compared with osimertinib alone, osimertinib with pemetrexed and platinum-based chemotherapy increases how long it takes before a person's cancer gets worse and how long they live. The effect on how long people live is uncertain because there is limited evidence from clinical trials in the long term. There is also uncertainty in how long people have the treatment.

Despite this uncertainty, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, osimertinib with pemetrexed and platinum-based chemotherapy is recommended.

2 Information about osimertinib with pemetrexed and platinum-based chemotherapy

Marketing authorisation indication

2.1 Osimertinib (Tagrisso, AstraZeneca) with pemetrexed and platinum-based chemotherapy is indicated for 'the first-line treatment of adult patients with advanced NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations'.

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 is £5,770 per pack of 30 tablets in either 40-mg or 80-mg doses (excluding VAT; BNF online accessed January 2025).

2.4 The list price of pemetrexed (25 mg/ml) varies between £128 and £160 per 4-ml vial, between £640 and £800 per 20-ml vial, between £1,280 and £1,600 per 40-ml vial, and is £1,360 per 34-ml vial (excluding VAT; BNF online accessed January 2025).

2.5 The company has a commercial arrangement. This makes osimertinib available to the NHS with a discount. 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.

Clinical management

Current management

3.1 The scope for this evaluation included several treatment options for previously untreated epidermal growth factor receptor (EGFR)-positive non-small-cell lung cancer (NCSLC) as possible comparators, including osimertinib monotherapy. The company suggested that standard care is osimertinib monotherapy, and the clinical expert and EAG agreed. This evaluation assesses the clinical and cost effectiveness of adding pemetrexed and platinum-based chemotherapy to osimertinib (from here the combination is referred to as 'osimertinib with chemotherapy').

Patient expert perspectives

3.2 Clinical and patient experts explained that, although introducing osimertinib improved outcomes for people with previously untreated EGFR-positive NSCLC, progression is likely to happen eventually. A patient organisation highlighted the significant psychological impact of living with EGFR-positive lung cancer, including anxiety and depression. Other significant impacts are fear of progression, social impact (including on family relationships), and financial. A patient expert's statement and patient organisation submission highlighted that treatment options that extend life are needed because there are few effective treatment options. But they also explained that the adverse effects of osimertinib, which in their experience included diarrhoea, appetite loss and skin rashes, can be difficult to manage. They explained that the risk of additional adverse effects caused by adding chemotherapy to osimertinib monotherapy

was concerning. The patient expert added that osimertinib is an oral tablet that can be taken at home. This is less of a physical and emotional burden than travelling to hospital, which would be needed for treatment with chemotherapy. The committee concluded that people with untreated EGFR-positive NSCLC would welcome another treatment option, but the additional adverse effects and burden from adding chemotherapy to osimertinib monotherapy should be considered.

Clinical effectiveness

FLAURA2

3.3 FLAURA2 is an ongoing phase 3, multicentre, international, open-label, superiority, randomised trial comparing osimertinib plus pemetrexed and platinum-based chemotherapy (osimertinib with chemotherapy) with osimertinib alone. The primary outcome of the trial was investigator-assessed progression-free survival (PFS) by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Secondary outcomes included overall survival, time to treatment discontinuation (TTD) and health-related quality of life. The trial enrolled 557 people with previously untreated EGFR-positive locally advanced or metastatic NSCLC. A total of 279 people were randomised to osimertinib with chemotherapy and 278 were randomised to osimertinib alone. PFS was reported when events had occurred in approximately half of participants (April 2023). The results indicated that osimertinib with chemotherapy was more effective at preventing or delaying progression or death than osimertinib alone (hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.49 to 0.79, $p<0.001$). Overall survival was reported from an ad-hoc interim analysis (January 2024). The results indicated that osimertinib with chemotherapy was more effective at delaying death than osimertinib alone (HR 0.75, 95% CI 0.57 to 0.97). FLAURA2 will report on overall survival again when overall survival reaches 60% maturity. The committee concluded that osimertinib with chemotherapy was an effective treatment for previously untreated EGFR-positive locally advanced or metastatic NSCLC.

Central nervous system metastases subgroup

3.4 FLAURA2 included several prespecified subgroups, including people with central nervous system (CNS) metastases at baseline; this was discussed at the first committee meeting. In its analysis of the trial results, the EAG noted that osimertinib with chemotherapy appeared to have comparatively greater effectiveness for people who had CNS metastases at baseline than those who did not. In the subgroup of people who had CNS metastases at baseline, the osimertinib with chemotherapy arm had a PFS hazard ratio of 0.47 (95% CI 0.33 to 0.66). By comparison, in people who did not have CNS metastases at baseline, the hazard ratio was 0.75 (95% CI 0.55 to 1.03). The clinical expert noted that, unless there are clinical signs, people with previously untreated EGFR-positive locally advanced or metastatic NSCLC are not typically scanned for CNS metastases in the NHS. The clinical expert highlighted that everyone in FLAURA2 was scanned for CNS metastases at baseline. This meant that a larger proportion of people in FLAURA2 were identified as having CNS metastases than would be expected to be identified in NHS practice. The clinical expert also noted that scanning for CNS metastases in everyone with previously untreated EGFR-positive locally advanced or metastatic NSCLC would be difficult to implement in the NHS. The NHS England clinical lead for the Cancer Drugs Fund (from here, the Cancer Drugs Fund lead) noted that there may be a risk of overdiagnosis if everyone with EGFR-positive locally advanced or metastatic NSCLC was scanned. This is because scanning may identify CNS metastases that are not clinically relevant and do not cause symptoms, and this could affect the everyday lives of people with EGFR-positive NSCLC. The Cancer Drugs Fund lead also noted that additional scans could delay treatment starting. The committee recognised that the clinical trial results indicated that people with CNS metastases at baseline may have different outcomes from those without. But it did not believe that people with CNS metastases before treatment would be identified in NHS practice without significant changes to the way this disease is managed. The committee was also unclear why the addition of chemotherapy to osimertinib appeared to produce different results between people with and without CNS metastases. It also noted that the company had not taken into account the costs associated with an increase in testing in the NHS for CNS metastases. The committee concluded that it would not consider people with CNS metastases at baseline separately because:

- this population is not routinely identified in clinical practice

- there are risks associated with overdiagnosis and delaying treatment if scans for CNS metastases were routinely used
- the company's model did not include costs associated with scanning for CNS metastases.

Generalisability

3.5 The EAG noted several issues that could affect the generalisability of the results of FLAURA2 to NHS practice, and these were discussed at the first committee meeting. First, it noted that FLAURA2 participants were, on average, younger than the NHS population of people with EGFR-positive locally advanced or metastatic NSCLC. It also noted that the second- and third-line treatments used during the trial might not match those used in the NHS (see section 3.16). Finally, the EAG highlighted that the proportion of people in FLAURA2 with CNS metastases at baseline may have been larger than in NHS practice (see section 3.4). So, it considered that the average treatment effect may have been overestimated in FLAURA2 compared with the NHS population. The EAG recommended that the starting age in the model be changed from 61.0 years (the average age in FLAURA2) to 65.6 years (the average age from published UK survey data [Molife et al. 2023]). The company highlighted that it consulted a UK advisory board, which advised that the FLAURA2 patient population was representative of the UK EGFR-positive locally advanced or metastatic NSCLC population. The Cancer Drugs Fund lead advised that the mean age of people with EGFR-positive locally advanced or metastatic NSCLC in the NHS was 68.5 years and the median age was 70.0 years. But the Cancer Drugs Fund lead noted that the average age may be lower for people having osimertinib with chemotherapy because of the treatment burden of chemotherapy than for osimertinib alone. The committee concluded that people in FLAURA2 were probably younger than the NHS population, and preferred the EAG's approach of using a starting age of 65.6 years. After public consultation, the company changed the starting age in its base case to reflect the committee's preference. The committee concluded that, overall, FLAURA2 was generalisable to practice in the NHS. But it noted that the proportion of people with diagnosed CNS metastases at baseline (see section 3.4) and the second- and third-line treatments (see section 3.16) differed between FLAURA2 and NHS practice,

which contributed to uncertainty around the treatment effect.

Economic model

Company's modelling approach

3.6 The company used a partitioned survival model with 3 health states: progression free, progressed disease and death. The committee agreed that the partitioned survival model is a standard approach to estimate the cost effectiveness of cancer drugs and was suitable for decision making.

Extrapolation of overall survival

3.7 The company analysed overall-survival data from an ad-hoc interim analysis when maturity of overall survival was 41% (January 2024). It found that the data violated the proportional hazards assumption, so it produced separate extrapolation models for each treatment arm. The EAG agreed that the data violated the proportional hazards assumption and that separate curves for each arm were appropriate. The company selected a 2-knot spline model on a normal scale for both treatments in its base case. For the osimertinib with chemotherapy arm, it justified its choice on the basis that it gave the best statistical fit of the spline models and a potentially conservative estimate of long-term survival. The company noted that the extrapolations produced by its 2-knot spline model on a normal scale for the osimertinib monotherapy arm were in line with feedback from its clinical advisers. The EAG disagreed with the company's model selection for the osimertinib monotherapy arm. It noted that all the 1-knot spline models fit the osimertinib monotherapy arm better than the 2-knot models. The EAG believed this indicated that the most suitable extrapolations for each arm could have different shapes. It considered this clinically plausible because chemotherapy has a different mechanism of action from osimertinib. The EAG thought that the data on overall survival from FLAURA, a phase-3 trial comparing first-line osimertinib with other EGFR-tyrosine kinase inhibitors in people with EGFR mutation-positive advanced NSCLC, data from a Dutch registry study describing overall survival in advanced EGFR mutation-positive NSCLC using

different tyrosine kinase inhibitors (Gijtenbeek et al. 2023), and the company's clinical expert's expectations validated its extrapolations. The EAG selected the models it considered to have best statistical fit and most plausibility. These were:

- a 1-knot spline model on the odds scale for the osimertinib monotherapy arm
- a 2-knot spline model on the odds scale for the osimertinib with chemotherapy arm.

The EAG selected models on the odds scale because the 1-knot spline model did not fit on a normal scale. The committee agreed that either the EAG's or the company's approach would be appropriate, but both were associated with uncertainty. So, at the first committee meeting, the committee requested that the company and EAG justify the choice of overall-survival model, including the use of different numbers of knots for each arm.

At consultation, the company believed that the EAG's 1-knot model to extrapolate overall survival beyond the end of the currently available FLAURA2 trial data for osimertinib monotherapy was not plausible. It noted that using the same type of model for each treatment arm is advised in NICE's Decision Support Unit technical support document 14 on survival analysis; the company considered that using the same number of knots for each arm reflects best practice. It also noted that the hazard function for overall survival from FLAURA2 extended beyond the 95% confidence intervals of the hazard function for the EAG's 1-knot predicted model. The EAG considered that spline models with different numbers of knots are considered to be the same type of model, and the curve's shape and extrapolation are affected by the chosen number of knots. The EAG said that curve shape might be expected to differ between the treatment arms because the combination of osimertinib with chemotherapy differs from osimertinib monotherapy in mechanism of action and in the likely second-line treatments. It also noted that the hazard functions for overall survival from FLAURA2 were based on small numbers of patients at the end of the curves and that the confidence intervals around the hazard rates would probably overlap with both the 1- and 2-knot models. The company and EAG agreed that their selected models predicted similar survival until the tail of the curve (approximately 10 years). The committee maintained its consideration that both the EAG's and the company's approach could be appropriate. It noted

that similar estimates of overall survival were predicted by the EAG's and the company's models, particularly in the short term. But it also noted that uncertainty remained in the longer-term estimates, and this was a driver of the cost-effectiveness results. The committee acknowledged that the EAG's model generated a more conservative estimate of overall-survival benefit for osimertinib with chemotherapy compared with osimertinib monotherapy. On balance, the committee concluded that it preferred the EAG's models for decision making.

Treatment duration in FLAURA2

3.8 In FLAURA2, each of the 3 components of treatment had different criteria for stopping. All treatments stopped if there was unacceptable toxicity or withdrawal of consent. Platinum-based chemotherapy was offered for a maximum of 4 cycles or until disease progression (defined by RECIST). Pemetrexed continued after platinum-based chemotherapy as pemetrexed maintenance until disease progression. Osimertinib, either combined with platinum-based chemotherapy and pemetrexed or as monotherapy, could continue beyond progression 'if, in the judgement of the investigator, they [trial participants] were receiving clinical benefit and did not meet any discontinuation criteria' (company submission). The clinical expert and the Cancer Drugs Fund lead noted that in the NHS, as in the trial, treatment with osimertinib is continued beyond progression if there is a clinical benefit. The committee noted that the marketing authorisation states that osimertinib should be used 'until disease progression or unacceptable toxicity', which it recognised did not reflect the trial. The committee was mindful that it could only make recommendations within the marketing authorisation. But it acknowledged that osimertinib is used beyond progression in FLAURA2 and in clinical practice. It concluded that the evidence from FLAURA2 was acceptable to support its decision making.

The committee noted that in FLAURA2 the duration of osimertinib treatment beyond progression was longer in the osimertinib monotherapy arm than in the osimertinib with chemotherapy arm. The clinical expert suggested in the first committee meeting that, by the time progression has occurred, most people in both arms are likely to be having only osimertinib. So, in practice, the use of osimertinib after disease progression was likely to be similar in both arms. At the

first committee meeting, the committee discussed that the trial observations of different osimertinib treatment durations beyond progression between arms could not be explained. At consultation, the company noted a higher rate of discontinuing osimertinib in the osimertinib with chemotherapy arm, with most discontinuations occurring in the first 9 months of treatment. It explained that the shorter osimertinib treatment beyond progression may be the result of discontinuations that happened before progression because of adverse events related to chemotherapy treatment. The company noted that the proportion of people who progressed and had second-line treatment and the median duration of exposure after progression was similar between arms. The committee considered the company's explanation but said that uncertainty remained in the differences observed in the treatment duration beyond progression in the longer term. The company agreed that the longer-term differences in treatment beyond progression between arms in FLAURA2 remain unexplained. The committee also noted, based on comments from the Cancer Drugs Fund lead, that treatment beyond progression might be expected to be longer in the osimertinib with chemotherapy arm than the osimertinib monotherapy arm because there are fewer subsequent treatment options, because chemotherapy is unlikely to be offered again. The committee considered that the trial results showing a difference in treatment duration after progression may have reflected a chance finding or may be because of the risk of reporting and measurement bias in the TTD outcome, as described in the EAG's report. The committee concluded that it was unable to determine if the difference in osimertinib treatment duration beyond progression in FLAURA2 reflects osimertinib's use beyond progression in clinical practice, including in the long term. It also concluded that it expected minimal differences in osimertinib treatment duration beyond progression between the treatment arms in the longer term in clinical practice, but this was uncertain.

Extrapolating duration of treatment

3.9 The company modelled TTD separately for the osimertinib and the pemetrexed components of the osimertinib with chemotherapy arm. The company selected the Gompertz extrapolation model for the osimertinib component and the exponential model for the pemetrexed component. TTD for the platinum-based chemotherapy component was not modelled because platinum-based

chemotherapy is used for a fixed number of treatment cycles. The EAG agreed with these choices. For the osimertinib monotherapy arm, the company chose the gamma model, which had the second-best statistical fit after the log-logistic model. At the first committee meeting, the EAG noted that, of the choices, the gamma extrapolation predicted the greatest duration of treatment beyond PFS. The EAG also noted that when people in the osimertinib monotherapy arm had osimertinib for longer, with higher total costs for osimertinib monotherapy than for people in the combined therapy arm, the cost effectiveness increased in favour of the osimertinib with chemotherapy arm. The EAG preferred the Gompertz model for extrapolating TTD in the osimertinib monotherapy arm. In this extrapolation model, TTD was estimated to be closer to PFS, and people were modelled to have osimertinib for shorter than in the company's preferred gamma model. The EAG selected the Gompertz model because the model fit statistics were similar to other curves, the visual fit to the observed data was good, and the extrapolation was plausible compared with the curve used for PFS. At the first committee meeting, the committee heard from the clinical expert that the true TTD curve was probably between the company's and the EAG's. The committee had concluded that there was not enough evidence to support either the company's or the EAG's base-case model selection. It requested further analyses that would provide more plausible TTD extrapolations.

At consultation, the company conducted a scenario requested by the committee in which both treatment arms had the same duration of osimertinib beyond progression. The company believed the resulting extrapolated curve reflecting time to discontinuing osimertinib in the osimertinib with chemotherapy arm was implausible, because it differed from the data from Kaplan–Meier curves from FLAURA2. The EAG agreed with the company. The company conducted an additional scenario using a Weibull curve for time to discontinuing osimertinib in the monotherapy arm because it predicted values between the company's base-case gamma curve and the EAG's base-case Gompertz curve, aligning with the clinical expert's expectation. But the company chose to maintain the gamma curve of osimertinib monotherapy in its base case. The EAG noted that the Weibull curve for osimertinib monotherapy was closer to the company-preferred gamma curve than the EAG-preferred Gompertz curve. To obtain a curve that was midway between the company's and the EAG's, the EAG created an average of the Gompertz and gamma curves (the 'Gompertz–gamma' curve) for its updated base case. The committee recalled that minimal differences in

osimertinib treatment duration beyond progression were expected between the treatment arms in the longer term in clinical practice, but this was uncertain (see section 3.8). The committee agreed there was uncertainty in the most appropriate TTD curve for osimertinib monotherapy, and this was a key driver of the cost-effectiveness results. It noted that it had requested further analyses with cross-validation of TTD extrapolations with other osimertinib monotherapy TTD data, for example from FLAURA, a trial with an osimertinib monotherapy arm. But the company did not provide these analyses. The committee noted that using a Gompertz or Gompertz–gamma model to estimate time to discontinuing treatment for osimertinib monotherapy also aligned with time to discontinuing osimertinib in the combined osimertinib with chemotherapy arm. Recalling that the clinical expert considered that the true time to discontinuing treatment with osimertinib was probably between the Gompertz and gamma models, the committee concluded that it preferred the EAG's 'Gompertz–gamma' curve.

Modelling of chemotherapy

3.10 At the first committee meeting, the EAG noted concerns with how the company modelled different options for platinum-based chemotherapy. First, the company had assumed that, for those having platinum-based chemotherapy, 50% of people would have cisplatin and 50% would have carboplatin. Clinical advice to the EAG suggested that carboplatin is preferred to cisplatin in NHS practice. So, in the EAG's base case, everyone having platinum-based chemotherapy had carboplatin. The EAG also noted that the company assumed that cisplatin and carboplatin would have 100% relative dose intensity (RDI; the percentage of planned dose a person has), because RDI data for cisplatin and carboplatin was not captured in FLAURA2. The EAG preferred using an RDI of 96.4% for cisplatin and carboplatin, which was accepted in NICE's technology appraisal guidance on pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer. The committee noted that the impact of these assumptions on the incremental cost-effectiveness ratio (ICER) was negligible, but it preferred 100% carboplatin use because it better reflected clinical practice and 96.4% RDI of carboplatin because it was accepted in previous appraisals and was considered appropriate for this treatment. After public consultation, the company changed the proportion having carboplatin or cisplatin and the RDI in its base case to reflect the committee's preference.

Utility values

Progression-free health-state utility

3.11 The company used EQ-5D-5L responses from FLAURA2, mapped to the EQ-5D-3L using the Hernández-Alava algorithm, to estimate a utility value for the progression-free health state for both arms (the exact utility value is considered confidential by the company so cannot be reported here). It used a mixed model for repeated measures (MMRM) and explained that this accounted for missing data. The EAG noted that the company's choice of progression-free utility was higher than the average utility for the general population (0.799 for people aged 55 to 64 years). It noted that the MMRM was unlikely to be suitable for adjusting the FLAURA2 responses for missing data because it needs data to be missing at random. But, because there was a higher proportion of missing utility data during the first 16 weeks of the trial when people were having chemotherapy, the data did not appear to be missing at random, and utility values would be expected to be lower. The EAG also suggested that the Hernández-Alava EQ-5D mapping algorithm appears to overestimate utility in people with NSCLC. The EAG preferred using the progression-free utility value of 0.794 from NICE's technology appraisal guidance on osimertinib for untreated EGFR mutation-positive non-small-cell lung cancer. The committee agreed that the company's value for progression-free utility lacked face validity, so it preferred the EAG's approach. At consultation, the company noted that form completion for EQ-5D-5L was high and consistent between arms. But, to address the committee's concerns, the company conducted a scenario using predictive mean matching (multiple imputation by chained equations) to account for missing utility data. The resulting progression-free utility value was similar to the value it had used in its base case. The EAG thought the company's new approach was more comprehensive, but noted that the company adjusted only for baseline covariables and said that it should have included other outcomes at follow-up time points. The EAG noted that, given the amount of missing data to be imputed, it advised a much larger imputation set. The EAG recommended alternative ways of mapping EQ-5D-5L health states to the EQ-5D-3L utility values using disease-specific scores instead of the Hernández-Alava algorithm, which resulted in utility values for people with NSCLC higher than for the general population. The company noted that NICE specifies that the Hernández-Alava algorithm should be used for reference-case analyses. The committee noted that the value for progression-free utility from the

company's scenario also lacked face validity and was still higher than the average utility for the general population. The committee maintained its preference from the first committee meeting for the EAG's base-case progression-free utility of 0.794.

Utility decrement for adverse events in progression-free health state

3.12 The company calculated and applied a utility decrement in the progression-free health state to account for adverse events (the exact figure is considered confidential by the company so cannot be reported here). It applied the decrement while the adverse event occurred. This was the same approach the company had used in NICE's technology appraisal guidance on osimertinib monotherapy. The EAG highlighted concerns with the disutility applied to account for chemotherapy-related adverse events. It believed that the disutility applied was too small because it did not account for interactions between adverse events. It also believed that the disutility would last longer than the duration of the chemotherapy. The EAG preferred to calculate a decrement using the change in utility from baseline to the progression-free period between arms in FLAURA2. Because the improvement was greater in the osimertinib monotherapy arm, the EAG believed the difference represented the negative effect of chemotherapy on quality of life (the exact figure is considered confidential by the company so cannot be reported here). The company was concerned that people did not have chemotherapy for the full progression-free period, so it was not appropriate for the EAG to apply the decrement to this entire period to account for the impact of chemotherapy on quality of life. The EAG explained that it calculated the decrement using mean utility values estimated for the whole progression-free period (the only data available to the EAG), so it was appropriate to apply it for its entire duration. The committee recalled from the first committee meeting the patient expert's view that adverse effects from osimertinib were difficult to manage and the clinical expert's view that adding chemotherapy is likely to worsen the adverse effects of treatment, so quality of life would be lower when people were having chemotherapy. It also noted that adverse effects from chemotherapy would continue for 1 to 2 months after treatment with chemotherapy had stopped. At the first committee meeting, the committee requested additional analyses to better capture health-related quality of life in

the progression-free state, and to determine the impact of chemotherapy. It suggested this could include using the treatment arm as a covariate to produce treatment-specific utility values or using utility data from the first 16 weeks to inform the appropriate utility decrement.

At consultation, the company did a scenario using treatment-specific disutilities for the duration of chemotherapy. It derived the values using MMRM applied to data from all randomised participants from FLAURA2 using a cut-off at 16 weeks, when platinum-based chemotherapy would finish. The company modelled treatment and progression status as covariates. The resulting utility decrement was even smaller than the value the company used in its base case. The EAG thought this scenario probably underestimated the utility decrement. It was also concerned that the data was probably not missing at random. The EAG would have preferred a multiple-imputation method, adjusting for baseline characteristics, follow-up outcomes and the 'large' imbalance it observed in baseline utility. The committee thought the company's utility decrement for the osimertinib plus chemotherapy arm was too small to account for the adverse effects of chemotherapy. It noted that it would have preferred if the company had adjusted for baseline differences in utility between arms in its analysis. But the committee was also concerned that the EAG's utility decrement may be too small to account for the adverse effects of chemotherapy and that modelling a utility decrement for a chemotherapy used for a limited number of cycles throughout the progression-free period was probably not appropriate. But the committee acknowledged that the EAG had applied the decrement based on the available data for the progression-free period. The committee thought that the EAG's approach to estimating the utility decrement using mean utility values from FLAURA2 was based on the best available evidence. The committee appreciated the many-fold difference in utility estimates by the company (lower) and the EAG (higher). The committee concluded that the EAG's utility decrement more plausibly reflected the health-related quality-of-life detriment expected from the adverse effects of chemotherapy.

Progressed-disease health-state utility

3.13 The company sourced the utility value for the progressed-disease health state of 0.64 from Labbé et al. (2017), a Canadian cohort study of NSCLC that included

183 people whose cancer had EGFR mutations. The company noted this utility value was similar to those accepted in previous NSCLC appraisals. The EAG noted that the high utility value of the progression-free health state (see section 3.12) meant that the difference between the 2 health states was larger than is typically seen in appraisals of NSCLC. The EAG preferred to use the progressed-disease utility value of 0.678 from NICE's technology appraisal guidance on osimertinib for untreated EGFR mutation-positive NSCLC. The committee agreed with the EAG and concluded that a utility value of 0.678 for the progressed-disease health state was suitable. After public consultation, the company changed the utility value for the progressed-disease health state in its base case to reflect the committee's preference.

Costs

Resource use

3.14 In its original base case, the company had used Brown et al. (2013) and advice from its clinical experts to estimate resource use in the model. In general, resource-use costs were lower in the progression-free state and higher in the progressed-disease state. The company explained that by delaying progression, the model estimated lower resource-use costs for osimertinib with chemotherapy than for osimertinib monotherapy alone. It produced separate estimates of resource use for the progression-free and progressed-disease health states. The company considered resource use per person per year for:

- outpatient visits
- MRI scans
- chest CT scans
- other CT scans
- ECGs
- clinical nurse contact time
- accident and emergency visits.

Based on advice from its clinical experts, the EAG amended its estimates of resource use. The Cancer Drugs Fund lead thought the EAG's proposed resource use was valid. But the Cancer Drugs Fund lead believed that the company's estimate of outpatient visits was more accurate than the EAG's. The committee concluded that it was appropriate to model resource use based on the company's estimation of outpatient visits and the EAG's estimations for other resources. After public consultation, the company changed resource use in its base case to reflect the committee's preference.

Resource costs

3.15 In its original base case, the company combined sources to estimate the costs for the resources used in the model, including NHS payment scheme 2023 to 2025 tariffs and Personal Social Services Research Unit costs (PSSRU, 2022). The EAG believed that NHS reference costs 2021 to 2022 better represented the true opportunity cost to the NHS of the resource use in the model. The NICE technical team noted that NHS reference costs are typically used in technology appraisals, but that both represented costs relevant to the UK healthcare system, so are in accordance with NICE's guide to the methods of technology appraisal 2013. The committee concluded that the EAG's approach to using NHS reference costs better represented costs in the NHS. After public consultation, the company changed the resource costs in its base case to reflect the committee's preference.

Distribution of second-line treatments

3.16 The company modelled the second-line treatments people might have after completing treatment with the osimertinib regimens. It used data from FLAURA2 to estimate the distribution of these treatments, then validated the results with its clinical experts. The company's clinical experts noted that in NHS practice some people would have a combination of atezolizumab, bevacizumab, carboplatin and paclitaxel (ABCP). In its original model, the company included a proportion of second-line ABCP use (the exact figure is considered confidential by the

company so cannot be reported here). The EAG believed the company's figure for ABCP use was too high, based on advice from its clinical experts. The EAG noted that this was relevant because a larger proportion of people in the osimertinib monotherapy arm had second-line treatment than in the osimertinib with chemotherapy arm (the exact figures are considered confidential by the company so cannot be reported here). The Cancer Drugs Fund lead estimated that 6% to 7% of people with EGFR-positive locally advanced or metastatic NSCLC would have second-line ABCP, which is lower than the company's estimate. At the first committee meeting, the committee requested a scenario that included 7% of people having ABCP as second-line treatment for both arms. At consultation, the company highlighted the difficulty estimating use of ABCP in the trial because it could not be identified as a standalone regimen within the data. It revised the proportion of use of second-line ABCP in its model to 8.2% based on its systemic anti-cancer treatment (SACT) data request from NHS England and internal company data. The EAG noted that it was unable to verify the company's calculations without access to the internal company data. The EAG used a 7% proportion of ABCP use second line, as requested by the committee, in its updated base case. The committee noted that, although it is possible to update costs to reflect ABCP use in the UK, adjusting overall-survival data from the FLAURA2 trial to account for ABCP use in the UK is not feasible. The committee concluded that it preferred the 7% proportion of ABCP use second line in the EAG's updated base case because it was closest to the estimate from the Cancer Drugs Fund lead. But it noted there was outstanding uncertainty because the clinical outcomes in the trial did not reflect ABCP use in the NHS.

Other factors

Equality

3.17 The committee noted that people with an Asian ethnicity were more likely to have EGFR-positive advanced NSCLC than people not of an Asian ethnicity. Race is a protected characteristic under the Equality Act 2010. A stakeholder submission also noted that the disease is more common in women. The committee agreed these are not equality issues for this appraisal.

Uncaptured benefits

3.18 The committee discussed whether there were any uncaptured benefits of osimertinib with chemotherapy not accounted for in the company's or EAG's modelling. It concluded that all benefits of osimertinib with chemotherapy had been taken into account.

Cost-effectiveness estimates

Acceptable ICER

3.19 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 uncertainty in this appraisal, specifically around the:

- extrapolation of overall survival (see section 3.7)
- extrapolation of TTD of osimertinib in both arms (see sections 3.8 and 3.9)
- proportion of people with CNS metastases (see section 3.4)
- second-line treatments used (see section 3.16).

The committee also recalled that its preferred assumptions on the extrapolation of overall survival and TTD may be considered conservative and favour the osimertinib monotherapy arm (see sections 3.8 and 3.9). It noted that the clinical evidence was informed by a randomised trial that included the population and treatment comparison of interest, indicating less uncertainty than if the appraisal had been based on indirect evidence (see section 3.3). So, the committee 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

3.20 The ICERs cannot be reported here because they incorporate confidential discounts for drugs included within the intervention, comparator and second-line treatments in the model. The company's and the EAG's base cases differed across several key issues. The biggest drivers of the difference in cost-effectiveness estimates were the choices of overall survival and the choice of statistical models with which to extrapolate time to discontinuing osimertinib treatment (see sections 3.6 to 3.9).

Committee's preferred assumptions

3.21 The committee discussed the analyses from the company and the EAG. Its preferred assumptions for the model to estimate cost effectiveness were as follows:

- a starting age of 65.6 years (see section 3.5)
- 100% carboplatin use for platinum-based chemotherapy (see section 3.10)
- an RDI of 96.4% for carboplatin (see section 3.13)
- extrapolating overall survival for osimertinib with chemotherapy using the 2-knot odds model and for osimertinib monotherapy using the 1-knot odds model, as in the EAG's base case (see sections 3.6 and 3.7)
- TTD of osimertinib beyond progressed disease being similar in both arms (see section 3.8)
- extrapolating TTD in the osimertinib monotherapy arm using the EAG's Gompertz–gamma curve (see sections 3.9 and 3.10)
- a progressed-disease utility of 0.678 (see section 3.13)
- a progression-free utility of 0.794 (see section 3.11)
- the EAG's utility decrement to reflect treatment-associated adverse events during the progression-free health state (see section 3.12)
- resource-use figures using the company's estimation of outpatient visits and

the EAG's estimations for the other resources (see section 3.14)

- resource-use costs using NHS reference costs (see section 3.15)
- 7% ACBP use at second line (see section 3.16).

The probabilistic cost-effectiveness estimate generated by the committee's preferred assumptions, and based on the final commercial arrangement, was within the range considered a cost-effective use of NHS resources. The committee acknowledged that the duration of osimertinib treatment in the trial and NHS practice does not precisely reflect the marketing authorisation (see section 3.8). The committee concluded that osimertinib with chemotherapy is recommended for untreated EGFR mutation-positive advanced NSCLC in adults.

Conclusion

Recommendation

3.22 The committee noted that, when its preferred assumptions were applied, the cost-effectiveness estimates based on the final commercial arrangement were within what the committee considered a cost-effective use of NHS resources (see section 3.21). So, osimertinib with chemotherapy is recommended, within its marketing authorisation, for untreated EGFR mutation-positive advanced NSCLC in adults.

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, 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 untreated advanced non-small-cell lung cancer and the tumours have epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations, and the healthcare professional responsible for their care thinks that osimertinib with pemetrexed and platinum-based chemotherapy is the right treatment, it should be available for use in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology 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

Megan John and Amanda Adler
Chair and interim vice-chair, technology appraisal committee D

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.

George Millington and Heather Stegenga
Technical leads

Albany Chandler and Rachel Williams
Technical advisers

Leena Issa and Greg O'Toole

Project managers

Ian Watson
Associate director

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