NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer

1 Recommendations

1.1 Amivantamab plus lazertinib can be used, 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.

What this means in practice

Amivantamab plus lazertinib 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. Amivantamab plus lazertinib must be funded in England within 90 days of final publication of this guidance

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

Why the committee made these recommendations

Usual treatment for NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations is osimertinib alone, or osimertinib plus pemetrexed and platinum-based chemotherapy (from now, osimertinib plus chemotherapy).

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Clinical trial evidence shows that amivantamab plus lazertinib increases how long people have before their condition gets worse and how long people live compared with osimertinib alone. But how well amivantamab plus lazertinib works compared with osimertinib plus chemotherapy is uncertain because of the unsuitability of the methods used to compare them.

There are uncertainties with some of the assumptions used for long-term extrapolations in the economic model. But the most likely cost-effectiveness estimates for amivantamab plus lazertinib are within the range that NICE considers an acceptable use of NHS resources. So, it can be used.

2 Information about amivantamab plus lazertinib

Marketing authorisation indication

2.1 Amivantamab (Rybrevant, Johnson & Johnson) plus lazertinib (Lazcluze, Johnson & Johnson) is indicated 'for the first-line treatment of adult patients with advanced non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations'.

Dosage in the marketing authorisation

2.2 The dosage schedules are available in the summary of product characteristics for amivantamab and the summary of product characteristics for lazertinib.

Price

2.3 The price of amivantamab is £1,079 for a 350 mg per 7-ml vial (excluding VAT; BNF online accessed June 2025). The price of lazertinib is £4,128.50 for 56 x 80-mg tablets, and £6,192.75 for 28 x 240-mg tablets (company submission).

2.4 The company has commercial arrangements for amivantamab and lazertinib (both simple discount patient access schemes). These make

amivantamab and lazertinib available to the NHS with discounts. The sizes of the discounts are commercial in confidence.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Johnson & Johnson will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Johnson & Johnson, 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 condition

3.1 Non-small-cell lung cancer (NSCLC) is staged from 1A to 4B according to the size of the tumour, location of involved lymph nodes and the presence of distant metastases. NSCLC diagnosed as stage 3 (locally advanced) or stage 4 (metastatic) is advanced. People with locally advanced NSCLC commonly present with a cough. Other symptoms include shortness of breath, coughing up blood and pain. People with metastatic NSCLC may also have headaches, an enlarged liver, changes in mental health, weakness and seizures. Epidermal growth factor receptor (EGFR) mutation-positive NSCLC is more common in women and people who do not smoke. The patient expert noted that a diagnosis of EGFR mutation-positive NSCLC can cause high levels of psychological distress. The committee concluded that advanced EGFR mutation-positive NSCLC can substantially affect health-related quality of life.

Clinical management

3.2 There are several NICE recommended options for treating EGFR mutation-positive NSCLC:

- First-line treatments include:

  - tyrosine kinase inhibitors (TKIs), which are no longer widely used
  - osimertinib alone (recommended in NICE's technology appraisal guidance on osimertinib for untreated EGFR mutation-positive NSCLC)
  - osimertinib plus pemetrexed and platinum-based chemotherapy (from now, osimertinib plus chemotherapy; recommended in May 2025 in NICE's technology appraisal guidance on osimertinib with pemetrexed and platinum-based chemotherapy for untreated EGFR mutation-positive advanced NSCLC, from now TA1060).
- Second-line treatments include:
  - atezolizumab plus bevacizumab, carboplatin and pemetrexed (recommended in NICE's technology appraisal guidance on atezolizumab in combination for treating metastatic non-squamous NSCLC)
  - platinum-doublet chemotherapy
  - best supportive care.

The patient expert explained that there was uncertainty about whether people might have osimertinib after progression on amivantamab plus lazertinib. This is because NICE has recommended second-line osimertinib after an EGFR TKI in NICE technology appraisal guidance on osimertinib for treating EGFR T790M mutation-positive advanced NSCLC. The clinical expert explained that, because osimertinib and lazertinib are very similar drugs, there would be no biological rationale to use osimertinib alone after progression on amivantamab plus lazertinib. The NHS Cancer Drugs Fund clinical lead agreed. The clinical expert further explained that someone experiencing high toxicity with amivantamab plus lazertinib would likely stop amivantamab but continue with lazertinib. This is because amivantamab is associated with a worse adverse events profile. The committee concluded that there would be no

reason to switch to osimertinib alone at second line, given the similarities between lazertinib and osimertinib.

Comparators

3.3 The NICE final scope included osimertinib plus chemotherapy 'subject to NICE appraisal' as a comparator. The company did not submit any modelling for osimertinib plus chemotherapy. The company said that:

- it did not consider osimertinib plus chemotherapy to be established in clinical practice
- it was not recommended at the time it made the evidence submission
- its clinical experts did not consider it to be established clinical practice when questioned
- despite being recommended by NICE, it is still not in routine commissioning.

The clinical expert explained that there is no single standard care for EGFR mutation-positive advanced NSCLC. Osimertinib alone is preferable for some people but osimertinib plus chemotherapy is better for others. They said that there is no clear clinical consensus on which groups might benefit more from either osimertinib plus chemotherapy or amivantamab plus lazertinib. But they noted that both treatments show similar improvements over osimertinib alone. The clinical expert said that osimertinib alone will be used less over time because healthcare professionals prefer to use an escalated (combination) therapy when possible. But they noted that people over 80 years might prefer osimertinib alone, rather than amivantamab plus lazertinib or osimertinib plus chemotherapy because of concerns about adverse events.

The patient expert explained that there is a clear split among members of EGFR Positive UK who have EGFR mutation-positive NSCLC, with many people preferring not to add chemotherapy to osimertinib alone.

They noted that, generally, younger people would prefer the combination treatment. The patient expert also noted that some people may choose osimertinib alone because they want an oral-only treatment. This is to avoid clinical environments and intravenous infusions, and because they preferred a feeling of normality. But some people want the best possible outcomes and are willing to tolerate a worse adverse event profile and higher treatment burden. The committee noted this and thought that it was plausible that osimertinib plus chemotherapy was the more important comparator. This was because people who are willing or able to tolerate a combination treatment would likely choose between amivantamab plus lazertinib or osimertinib plus chemotherapy. It also noted that seeing an indirect comparison of these 2 treatments might help people with the condition choose between them if amivantamab plus lazertinib were to be recommended.

At the first committee meeting, the Cancer Drugs Fund clinical lead explained that cancer treatments generally take about 3 months after recommendation to reach ‘steady state’ usage. They explained that, in the first month after osimertinib plus chemotherapy was recommended, 23% of osimertinib usage for this indication was with chemotherapy, adding that they expected this to rise further. The committee noted that osimertinib plus chemotherapy was included as a potential comparator in the NICE scope but acknowledged that it was not recommended at the time of the company submission. But it agreed that osimertinib plus chemotherapy is established in NHS clinical practice. The committee concluded that both osimertinib alone and osimertinib plus chemotherapy were relevant comparators. It noted that it would need to see clinical and cost-effectiveness estimates comparing amivantamab plus lazertinib with osimertinib plus chemotherapy before it could make a decision.

In response to the draft guidance, the company updated its model to allow for a comparison between amivantamab plus lazertinib and osimertinib plus chemotherapy. The company still thought that osimertinib plus chemotherapy was not a relevant comparator and thought that it was unfair to request this comparison. The Cancer Drugs Fund clinical lead confirmed that, because osimertinib plus chemotherapy is recommended, it now makes up about 30% of treatments in this population. The committee noted the company's argument but it also noted that usage of osimertinib plus chemotherapy had risen since the first meeting and might plausibly rise further. It recalled that younger fitter people and people prepared to accept a greater risk of side effects might plausibly choose between osimertinib plus chemotherapy and amivantamab plus lazertinib. So, at the second committee meeting, the committee concluded that osimertinib plus chemotherapy was the more important comparator than osimertinib alone. At the third committee meeting, the Cancer Drugs Fund clinical lead explained that osimertinib plus chemotherapy's use has increased to 34% and further increases are anticipated.

Clinical effectiveness

The MARIPOSA trial

3.4 The clinical-effectiveness evidence came from MARIPOSA, which was a phase 3 open-label randomised controlled trial comparing amivantamab plus lazertinib with osimertinib alone. The trial recruited 429 people to the amivantamab plus lazertinib arm and 429 people to the osimertinib arm. Key outcomes of the trial that informed the cost-effectiveness model (see section 3.11) were:

- progression-free survival (PFS; informed by an August 2023 data cut off)
- overall survival (OS; informed by a December 2024 data cut off)

- time to treatment discontinuation (TTD; informed by a December 2024 data cut off).

MARIPOSA showed a statistically significant improvement for amivantamab plus lazertinib over osimertinib alone for:

- PFS (hazard ratio [HR] 0.70, 95% confidence intervals [CI] 0.58 to 0.85) and
- OS (HR 0.75, 95% CI 0.61 to 0.92).

The committee noted that the amivantamab plus lazertinib arm had a greater incidence of adverse events than the osimertinib arm, including pulmonary embolism, infusion-related reactions, rashes and nail toxicity. The clinical experts explained that this was largely because of amivantamab. The committee thought that MARIPOSA showed that amivantamab plus lazertinib was superior to osimertinib, although it noted that there was some uncertainty about this benefit in certain subgroups. It concluded that it would like to see the PFS modelled using the latest available data. In response to consultation, the company provided PFS data from the latest data cut of MARIPOSA, explaining that only investigator assessed PFS was available from this data cut. The company did an indirect treatment comparison (ITC; see section 3.6) and updated its model (see sections 3.11 to 3.15) to incorporate this data. The committee concluded that the company updates were suitable for decision making.

Generalisability of MARIPOSA

3.5 The mean age in MARIPOSA is considered confidential by the company and cannot be reported here. The median age was 64 years in the amivantamab plus lazertinib arm and 63 years in the osimertinib arm, and 55% of people in the trial were under 65 years. The Cancer Drugs Fund clinical lead explained that the Systemic Anti-Cancer Therapy (SACT) Dataset data showed that, for the last 4,000 people to use osimertinib

alone for advanced NSCLC, the median age was 70 years and the mean age was 68.5 years. The committee noted that, in MARIPOSA, there appeared to be some important differences in PFS between age subgroups, including

- people under 65 years (n=472; HR 0.50, 95% CI 0.39 to 0.65)
- people over 65 years (n=386; HR 1.06, 95% CI 0.80 to 1.41)
- people under 75 years (n=754; HR 0.70, 95% CI 0.57 to 0.85)
- people over 75 years (n=104; HR 0.77, 95% CI 0.46 to 1.30).

The committee thought that the clinical trial data suggested that amivantamab plus lazertinib is less effective in older people. The clinical expert said that there was no biological reason that amivantamab plus lazertinib would work differently according to age. But the committee noted that this could be linked to older people stopping treatment faster because of a worse adverse event profile, and so getting less treatment benefit. The company explained that the trial was not powered to detect subgroup differences. Both the company and the clinical expert thought that the effect size in the over 75 years group appearing similar to the whole population meant that assumptions around effectiveness and age should be treated with caution. The committee noted that the over 75 years subgroup was much smaller than the under 75 years subgroup and its confidence intervals overlapped with those of the over 65 years subgroup. The committee understood that, because the median age in NHS practice was 70 years, most people in the target population would be over 65 years, while in the MARIPOSA study most people were under 65 years. People over 65 years may plausibly get less benefit from amivantamab plus lazertinib, which may be a generalisability issue. The committee acknowledged the patient and clinical expert statements that older people might be more likely to choose osimertinib alone (see section 3.2 and section 3.3), but it still thought that this was a generalisability issue. To ensure that differences in age between the

trial and NHS populations were not an important generalisability concern, the committee concluded that it would like to see:

- subgroup analyses for the over 65 years subgroup
- Kaplan–Meier curves for the over 65 years subgroup for all relevant time-to-event outcomes
- cost-effectiveness modelling of the over 65 years subgroup.

In its response to the draft guidance, the company noted that it did not agree with providing cost-effectiveness analysis for the over 65 years subgroup. This was because it thought that the trial was not powered to detect subgroup differences. Also, it did not think that age was a treatment-effect modifier. The company provided a clinical-effectiveness subgroup analysis for different age groups (the company considers these age groups confidential, so they cannot be reported here). The company noted that the results of the subgroup analysis showed that the effects of age were not consistent as the cut-off age increased. It suggested that the differences in relative efficacy seen in the over 65 years subgroup in MARIPOSA were a result of overperformance of the osimertinib arm in that subgroup because of statistical chance. The company also advised that the correlation between age and efficacy was not seen in other trials of amivantamab. It thought that age was a poor marker of frailty and would not be expected to be an effect modifier as much as, for example, Eastern Cooperative Oncology Group status. It maintained its preference for using the mean age of people in MARIPOSA as its starting age in the model. The EAG thought that the evidence may have been insufficient to show meaningful differences in benefit for amivantamab plus lazertinib compared with osimertinib for the over 65 years subgroup. But it still maintained its preference for using the average age from the SACT Dataset.

The committee noted that the risk of stopping amivantamab appeared

to increase as age increased, which also appeared in the comparison against lazertinib alone. The Cancer Drugs Fund clinical lead explained that the average age for people accessing osimertinib alone was 72 years and for people accessing osimertinib plus chemotherapy was 62 years. The committee noted that the impact of generalisability may be different depending on the specific comparator. It noted that people having osimertinib plus chemotherapy were likely fitter than people having osimertinib alone (see section 3.3) and that this might limit the impact of the generalisability concerns. But it also thought that it was plausible that people having amivantamab plus lazertinib might be older than people having osimertinib plus chemotherapy. It thought that, were amivantamab plus lazertinib to be recommended, there might be 3 distinct populations based around age, fitness and tolerance to side effects. But it also noted that the starting age in the model had a small impact on cost effectiveness. The committee concluded that it would have liked to see more evidence that the results from MARIPOSA were generalisable to the NHS population. It thought that the absence of this evidence was associated with uncertainty. The committee concluded that there were still some generalisability concerns, which it would consider in its decision making.

ITCs by the company and EAG

3.6 The company considered evidence from FLAURA2, a phase 3 multicentre randomised open-label trial, for the efficacy of osimertinib plus chemotherapy. FLAURA2 compared osimertinib plus chemotherapy with osimertinib alone. It found that the proportional hazard assumption did not apply between amivantamab plus lazertinib and osimertinib plus chemotherapy for either PFS or OS. This is important for some methods of ITC. The company also considered using a parametric ITC to compare drugs based on differences in distribution parameters such as shape and scale. This approach can implicitly allow for a time-varying relative treatment effect. But, because different distributions have different numbers of parameters, this approach needs each arm in the comparison

to have the same distribution. The company did not think that this was appropriate. This was because the curves selected by the committee in TA1060 did not match the best fitting curves identified for amivantamab plus lazertinib and osimertinib alone (see section 3.16). So, to account for differences in the populations of the trials, the company used the comparative efficacy of the osimertinib-alone arm from each trial. It used them to adjust the results of the PFS and OS curves of the osimertinib plus chemotherapy arm (the specific hazard ratios the curves were adjusted by are considered confidential by the company, so cannot be reported here).

The EAG noted that there was nothing to suggest that an ITC between MARIPOSA and FLAURA2 was unsuitable. It said that the company's chosen method of ITC did not appear suitable. The EAG noted that the adjustments for PFS and OS were in opposite directions (that is, PFS was better in 1 trial but OS was better in the other trial). The EAG thought this meant that the differences were more likely caused by statistical noise rather than any actual differences in the trial populations making the method unsuitable as an adjustment of differences in the trial populations. The EAG used an unadjusted comparison of amivantamab plus lazertinib and osimertinib plus chemotherapy in its base case. It thought that this was acceptable because the baseline characteristics between MARIPOSA and FLAURA2 were similar and there were only small differences in the hazard ratios for both PFS and OS. But it noted that an ITC accounting for time-varying treatment effects and population heterogeneity would be more appropriate. The committee noted the uncertainties around the ITC and asked the company to explore alternative methods (see section 3.7).

Committee's ITC preferences

3.7 The committee thought that neither approach was sufficient to compare amivantamab plus lazertinib with osimertinib plus chemotherapy. It also thought that the results from both approaches were highly uncertain. It

agreed with the EAG that it was unclear whether, or how much, the company's approach using hazard ratios from the common osimertinib-alone arm actually adjusted for population differences or was a result of random variation. It noted the company's explanation for not doing a parametric network meta-analysis. But it also thought that it would have been reasonable to explore long-term extrapolations using different curve fits to TA1060 to provide a parametric network meta-analysis scenario. The committee thought that, even if the company did not consider this appropriate, there were other ITC approaches that allowed for time-varying hazards or population adjustment and, in some instances, both. These approaches had not been explored and included:

- fractional polynomial network meta-analysis
- multilevel network meta-regression (ML-NMR)
- matching adjusted indirect comparison (MAIC) with curves fitted separately to each arm.

The committee noted that the company had aggregate data for both trials, individual patient data for MARIPOSA and reconstructed individual patient data for FLAURA2 (see section 3.6). It thought that these options could have and should be explored using an updated FLAURA2 data cut. At the second committee meeting, the committee concluded that it would like to see a more formal ITC method employed to compare amivantamab plus lazertinib with osimertinib plus chemotherapy for efficacy and safety outcomes to inform various aspects of the modelling (see section 3.16 and section 3.17).

Updated ITC analyses

3.8 At the third committee meeting, to address the committee's concerns, the company explored approaches, including:

- An unanchored MAIC: It chose an unanchored MAIC for its base case because it thought that this approach would not introduce additional uncertainty and bias.

- An anchored MAIC: It explained that it did an anchored MAIC in a scenario but did not use it for the base case because of:
  - the similarity between the populations in MARIPOSA and FLAURA2 and matching had limited impact on the hazard ratio
  - the lack of treatment effect modification by differences in measured baseline characteristics
  - the proportional hazards assumption was not appropriate.
- A piecewise Cox model: It explained that the hazard ratios fluctuated substantially across intervals, and the results differed substantially depending on the time periods chosen. It thought this highlighted sensitivity to cut-points with intervals sometimes based on a few events. So, it thought the estimates using this approach were unstable and had wide confidence intervals.
- A fractional polynomial model: It clarified that fractional polynomial models do not capture the complexity of observed data so lack clinical plausibility and visual fit.
- Parametric ITCs: It thought that the parametric ITCs were unstable. This was because the long-term OS in FLAURA2 suggested a very complex hazard over time, which could only be captured with flexible distributions.

The company chose an unanchored MAIC for its base case because of the limitations and implausible long-term projections of survival with osimertinib–chemotherapy from the other methods. The EAG explained that an anchored MAICs adjusted for population differences between MARIPOSA and FLAURA2. But it thought that they needed the proportional hazard assumption, which was violated (see section 3.6). The EAG also said that parametric ITCs, fractional polynomial ITCs using parametric models, piecewise Cox regression models and fractional polynomial ITC using Cox regression did not adjust for population differences between MARIPOSA and FLAURA2. So, it thought that an unanchored MAIC was appropriate because they:

- allowed for population adjustment
- accommodated time-varying hazard ratios
- allowed for extrapolation of all arms in a FLAURA2-like population.

So, the EAG agreed with the company that an unanchored MAIC was most suitable for its base case. The committee was aware that the company did not explore ML-NMR. The committee questioned the company and the EAG about the choice of an unanchored MAIC for their base cases and population adjustment. This was because of the minimal difference in the populations from MARIPOSA and FLAURA2. The EAG clarified that population adjustment did not make a big difference overall. But it explained that there were some differences in the long-term outcomes when extrapolating from the adjusted results, which affected the cost-effectiveness results. So, it preferred a population adjustment, even though:

- the mean values at each covariate level were slightly different
- the covariates were correlated and showed some variation
- the adjustment did not reduce the effective sample size.

The committee noted that the small change in effective sample size, and the similarity of the adjusted and unadjusted Kaplan–Meier curves indicated that not much adjustment was done. So, there might be limited value to the MAIC approach. The committee was aware that the NICE Decision and Technical Support Unit's technical support document on population-adjusted indirect comparisons (MAIC and STC) TSD18 suggested that, when anchored MAICs can be applied, they are preferred over unanchored MAICs. Unanchored MAICs may be only considered in the absence of a connected network of randomised studies. Also, unanchored methods for population adjustment are problematic and should not be used when anchored methods can be applied. The committee thought that all the methods explored by the company and the EAG were uncertain, and that there

was not enough justification provided for each method. The committee noted that the EAG had provided scenarios using different ITCs. The committee thought that both the company's and EAG's ITCs were uncertain because they used the results of unanchored MAICs. It concluded that because of the similarity of the trial populations, the unanchored MAIC was acceptable for use in the base case. But it noted that it would take the associated uncertainty into account in its decision making.

Subcutaneous amivantamab and clinical effectiveness

3.9 After the first committee meeting, a subcutaneous formulation of amivantamab was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) in this indication. In its response to the draft guidance, the company advised that it thought that there would be no reason for people to use intravenous amivantamab instead of the subcutaneous formulation. It presented the results of PALOMA-3, which showed that subcutaneous amivantamab was pharmacokinetically non-inferior to intravenous amivantamab. It also suggested that PFS, OS and TTD were longer for subcutaneous amivantamab than for intravenous amivantamab. The company maintained that, apart from the rate of infusion-related reactions, and acquisition and administration costs, the modelling assumptions from intravenous amivantamab applied to the subcutaneous formulation. The EAG noted that PFS, OS and TTD could reasonably be different for subcutaneous and intravenous amivantamab. It also thought that this could lead to either better or worse estimates of cost effectiveness for amivantamab plus lazertinib, and added uncertainty to the cost-effectiveness evidence. The clinical expert and the Cancer Drugs Fund clinical lead advised that it was likely that subcutaneous amivantamab would be used exclusively over intravenous amivantamab. The patient expert advised that the subcutaneous formulation would be strongly preferred by people with EGFR mutation-positive advanced NSCLC. At the second committee meeting, the committee thought the company's assumption that only subcutaneous amivantamab would be

used was suitable. But it also noted the EAG's concerns. It concluded that there was some residual uncertainty in the cost-effectiveness evidence, which could either benefit or disadvantage amivantamab.

Safety ITC

3.10 At the second committee meeting, the committee noted that amivantamab plus lazertinib may produce some unexpected adverse events compared with those seen in previous trials of amivantamab alone and lazertinib alone. This is why a protocol amendment was implemented for prophylactic anticoagulation in MARIPOSA. To address the committee's concerns, the company did an adjusted comparison of the adverse events of amivantamab plus lazertinib compared with osimertinib plus chemotherapy and osimertinib alone. It analysed comparative safety using a Bayesian network meta-analysis and applied an anchored MAIC. The company said that differences in mechanism of action of each regimen result in distinct safety profiles and adverse event patterns. It thought that the results suggested that osimertinib plus chemotherapy has a worse safety profile. The results are considered confidential by the company, so cannot be reported here. The EAG agreed that the company's ITC methodology was appropriate. But it explained that the results numerically favoured amivantamab plus lazertinib over osimertinib plus chemotherapy, even though the credible intervals for the reported odds ratio crossed 1. This meant that it was possible that there was no difference between the adverse event profiles.

The committee noted that the proportion of grade 3 or higher adverse events and serious adverse events was higher in the osimertinib-alone arm of MARIPOSA than of FLAURA2. It thought that this was unexpected and associated with uncertainty given both the trial and trial populations were similar. It was aware that the osimertinib-alone arm served as an anchor in the company's safety ITC. The clinical experts explained that this finding may have been because of the frequency of the follow up in MARIPOSA and FLAURA2. Both trials followed different protocols even

though the participants had the same treatment. The committee noted that people are likely to report more adverse events if they are seen more often in clinical practice. At the third committee meeting, the company also presented data from COCOON. This was a phase 2 study that compared intravenous amivantamab plus lazertinib alongside enhanced dermatological care (emollients and antimicrobials) with standard care. It showed that the incidence of grade 2 or higher dermatological adverse events was lower with enhanced dermatological care than with standard care (42% compared with 75%; odds ratio 0.24, 95% CI 0.13 to 0.45). The company said that this meant that the actual adverse event profile of amivantamab plus lazertinib would be lower in clinical practice than in MARIPOSA. The committee thought that the enhanced care trialled in the COCOON study would be relatively easy to implement for NHS dermatology. The committee acknowledged that the results of COCOON suggested that amivantamab plus lazertinib might have a better adverse events profile than was used in the safety ITC. The committee identified several limitations with the company's safety ITC and its use of COCOON. It also noted limitations with using the subcutaneous formulation to support the case for amivantamab plus lazertinib having a better adverse events profile than osimertinib plus chemotherapy. These limitations included that:

- the results of the ITC had confidence intervals that crossed the line of null effect
- the ITC did not include people who stopped the treatment and so was selective and not a comprehensive ITC
- the analysis did not account for or comment on differences in study design and adverse event reporting or follow up
- COCOON suggested a significant reduction in lower grade dermatological adverse events but less of a reduction in more severe adverse events
- the subcutaneous formulation might reduce infusion related reactions (which was captured separately in the modelling) but other adverse

events were more important.

The committee acknowledged that the ITC results, COCOON evidence and the subcutaneous formulation suggested it was plausible that amivantamab plus lazertinib had a better adverse event profile than osimertinib plus chemotherapy. But it noted that this remained uncertain. The committee concluded that the ITC was constrained by important differences between the trials. It added that a fuller analysis would have included an assessment of study design, baseline characteristics, follow-up and how adverse events were captured in the model. Because these factors varied in the studies, it felt that the adverse events from the studies were not fully comparable. So it was uncertain if one regimen would have a better overall adverse event profile than another.

Economic model

Company's modelling approach

3.11 To model the cost effectiveness of amivantamab plus lazertinib and osimertinib alone, the company used a partitioned survival model with 3 health states: 'progression free', 'progressed disease' and 'death'. The efficacy of amivantamab plus lazertinib was informed directly from extrapolations of PFS, OS and TTD data (considering amivantamab and lazertinib separately; see section 3.12 and section 3.13) from MARIPOSA (see section 3.4). The company chose a cycle length of 1 week with a half-cycle correction and a lifetime time horizon of 30 years. The committee concluded that the overall structure of the model was generally acceptable for decision making, but recalled the generalisability issue (see section 3.5). So, it noted that it would like to see model baseline characteristics match NHS practice when possible (for example, age set to mean ages provided by Cancer Drugs Fund clinical lead, see section 3.5). The company responded at the third committee meeting by updating the model starting age to 68.5 years in line with the SACT data.

Modelling PFS and OS for osimertinib plus chemotherapy

PFS and OS for osimertinib plus chemotherapy: second meeting

3.12 The company modelled osimertinib plus chemotherapy by fitting curves to the reconstructed Kaplan–Meier data from FLAURA2. The company used data from FLAURA2 published in TA1060 to generate pseudo individual patient data. It used this data to produce PFS and OS extrapolations, which were then adjusted using the company's hazard-ratio approach. The company selected the same curves as were used in TA1060 for consistency with that appraisal. This was the:

- Weibull distribution for PFS
- 2-knot odds spline distribution for OS.

The EAG agreed with this choice and used the same distributions in its base case. The committee recalled it had requested updated ITCs (see section 3.8). It concluded the selected distributions were appropriate but that it would want to see additional modelling of longer-term outcomes for osimertinib plus chemotherapy once exploration of alternative ITCs had been completed.

PFS and OS for osimertinib plus chemotherapy: third meeting

3.13 In response to the committee's request for additional analyses, the company used the unanchored MAIC to adjust the MARIPOSA trial to better match the FLAURA2 trial in its base case (see section 3.8). The company explained that there was no updated data for PFS. As a result, the selected base case for PFS (Weibull) remains unchanged (see section 3.12). For OS it fitted standard parametric and spline models to extrapolate the unadjusted osimertinib plus chemotherapy arm from FLAURA2. It explained that it had selected a 2-knot hazard spline model based on Akaike Information Criterion, Bayesian Information Criterion, clinical opinion and expert clinical validation. This implied that other spline models suggested clinically implausible long-term survival estimates. The

EAG explained that, after reviewing the Akaike and Bayesian Information Criteria, visual fit, hazard plots and clinical plausibility, it thought that 2-knot odds and 2-knot normal spline models were also appropriate for OS extrapolations. It explained that the Akaike and Bayesian Information Criteria were almost identical across the 3 models, but long-term estimates slightly differed. The hazard plots for 2-knot odds and 2-knot normal spline model suggested a decreasing tail of the smoothed hazard plot. Conversely, the hazard plot from the 2-knot hazard model had an increasing tail. The EAG thought that there were 3 plausible distributions that could be used to extrapolate OS for osimertinib plus chemotherapy:

- 2-knot hazard spline (company and EAG base case)
- 2-knot normal spline (EAG scenario)
- 2-knot odd spline.

The committee noted that the company's base case modelled a survival benefit for amivantamab plus lazertinib compared with osimeritinib plus chemotherapy. The committee questioned the validity of the company's approach. This was because the observed Kaplan–Meier data from FLAURA2 suggested a small advantage for osimertinib plus chemotherapy when compared visually with the amivantamab plus lazertinib data from MARIPOSA. The company said that Kaplan–Meier curves showed the survival benefit of osimertinib plus chemotherapy over amivantamab plus lazertinib peaked around month 36. It thought that amivantamab plus lazertinib and osimertinib plus chemotherapy have different mechanisms of action. It further explained that amivantamab's better resistance mechanisms, response quality and immunomodulatory effects might offer a basis for its sustained survival benefit. The committee noted the different maturity of the data-cuts from MARIPOSA and FLAURA2, with longer follow up for FLAURA2. The committee noted heavy censoring in MARIPOSA around month 30, which did not happen until around month 42 in FLAURA2. It thought that the plateau seen towards the end of the MARIPOSA data might be

an artefact of the low numbers at risk. It also did not think that the observed data showed a survival benefit for amivantamab plus lazertinib compared with osimertinib plus chemotherapy. The committee thought that it was possible that the 2 regimens were equally effective. The committee was aware that the EAG's 2-knot normal spline scenario predicted long-term OS for osimertinib plus chemotherapy that was similar to the long-term Weibull distribution of amivantamab plus lazertinib. The committee thought that this scenario was as plausible as the 2-knot hazard spline model used in the company's base case. The committee noted that there was uncertainty around the choice of distribution. It selected the 2-knot hazard spline for its base case but thought that this might overestimate the relative effectiveness of amivantamab plus lazertinib compared with osimertinib plus chemotherapy. It felt that this choice was associated with substantial uncertainty.

Modelling TTD for osimertinib plus chemotherapy

TTD for osimertinib plus chemotherapy: second meeting

3.14 When modelling osimertinib plus chemotherapy at the second meeting, the company advised that published data was less complete for TTD. So, it used the parametric curves presented in TA1060 to produce its extrapolations. For TTD, the osimertinib and pemetrexed components of osimertinib plus chemotherapy were modelled separately. For the osimertinib component, the company used the average of the Gompertz and gamma curves (from here, the Gompertz-gamma approach), which it said was the committee's preference in TA1060. It noted that using just the Gompertz curve meant that the TTD curve for the osimertinib component of osimertinib plus chemotherapy crossed the curve for osimertinib alone, which lacked face validity.

The EAG thought that the company had misinterpreted the committee's preference in TA1060 for the TTD curve of the osimertinib component of

osimertinib plus chemotherapy. The EAG highlighted that the committee's preference in TA1060 was to use the Gompertz curve for the osimertinib component of TTD, which the EAG applied in its base case. It also noted the company's concerns about the curves crossing over. It provided a scenario in which the TTD curve of the osimertinib component of osimertinib plus chemotherapy was capped to the osimertinib-alone curve (from here the capped-Gompertz approach). This approach meant that TTD for the osimertinib component of osimertinib plus chemotherapy could never be lower than that for the osimertinib-alone arm.

The company acknowledged that it had misinterpreted the committee's preference in TA1060https://www.nice.org.uk/guidance/ta1060. But, it thought that the Gompertz-gamma approach was still more appropriate than the Gompertz alone because of the crossing of the curves. The company also did not agree with using the EAG's scenario because it implied a change in the hazard of stopping treatment, which it thought was unreasonable. The committee thought that there was not enough evidence to determine the most appropriate TTD curve for the osimertinib component of osimertinib plus chemotherapy. It said that it would like to see exploration of modelling TTD in line with any updated ITC analyses provided (see section 3.13).

TTD for osimertinib plus chemotherapy: third meeting

3.15 After the second committee meeting, for TTD of the osimertinib component of osimertinib plus chemotherapy, the company retained the Gompertz-gamma average approach (see section 3.14). This was based on clinical validation, visual fits and curve comparison with data on:

- the osimertinib-alone TTD
- osimertinib plus chemotherapy PFS
- osimertinib plus chemotherapy OS.

The EAG noted that the company's base case remained unchanged

from the second meeting. The EAG changed its base case to use the company's Gompertz-gamma average approach of osimertinib component of osimertinib plus chemotherapy. But it explained that using this curve for TTD for osimertinib plus chemotherapy had long-term predictions that were further from the PFS extrapolation for osimertinib plus chemotherapy than when using capped-Gompertz approach (see section 3.17). The EAG retained the capped-Gompertz approach as a scenario analysis. The committee noted that there might be some use of osimertinib beyond progression. But it thought that the TTD curves for the osimertinib component of osimertinib plus chemotherapy should be broadly in line with the PFS curves. It accepted the company's Gompertz-gamma approach for decision making. But it thought that the gap between the PFS and TTD curves meant that this assumption was associated with high uncertainty.

Modelling of PFS and OS for amivantamab plus lazertinib and osimertinib alone

3.16 The company extrapolated PFS for the amivantamab plus lazertinib and osimertinib alone arms using the gamma distribution. The company modelled OS using extrapolations from the Kaplan–Meier data from MARIPOSA (see section 3.4) when modelling both amivantamab plus lazertinib and osimertinib alone. It chose a Weibull distribution to extrapolate the OS data for both amivantamab plus lazertinib and osimertinib alone. It said that the Weibull distribution had strong statistical and visual fit, and closely aligned with its clinical experts' predictions (these are considered confidential by the company and so cannot be reported here). The EAG thought that the Weibull distribution was the most suitable parametric distribution to model amivantamab plus lazertinib. It also noted that 1- and 2-knot hazard splines were also appropriate. But it added that neither the Weibull nor the spline models provided a great representation of the observed hazard function from the trial.

The EAG used the Weibull distribution in its base case to model OS for amivantamab plus lazertinib. But it also explored the impact of the 1-knot hazard spline as a plausible alternative scenario. For osimertinib alone, the EAG thought that parametric models were suitable for modelling OS. It also thought that the Weibull and the gamma distributions were appropriate. It noted that both distributions had good statistical fit, a reasonable hazard shape and were close to the company's clinical experts' estimates. The EAG used the Weibull distribution in its base case for osimertinib alone but explored the impact of the gamma model as a plausible alternative scenario. Both the company and EAG retained the Weibull distribution for amivantamab plus lazertinib when using the new unanchored MAIC adjusted Kaplan–Meier curves (see section 3.13) The committee thought that, in both arms, the Weibull distribution appeared plausible and broadly in line with clinical expert estimates. It noted that the EAG's scenarios were also plausible. The committee concluded that for both amivantamab plus lazertinib and osimertinib alone arms:

- Gamma distributions were suitable for decision making for PFS
- Weibull distributions were suitable for decision making for OS.

Modelling of TTD for amivantamab plus lazertinib, and osimertinib alone

3.17 The company modelled longer-term TTD by fitting parametric curves to the TTD Kaplan–Meier data from MARIPOSA for osimertinib alone and separately for both amivantamab and lazertinib. It selected the exponential distribution to extrapolate the TTD curves for all 3 components. It said that it had a strong statistical and visual fit, and close alignment with its clinical expert estimates. Both the clinical expert and landmark estimates predicted by the model are considered confidential by the company and cannot be reported here. The EAG explained that the exponential distribution could only model a constant hazard. It did not think that the risk of stopping treatment would be

constant across the entire model time horizon, which is implied by using the exponential distribution. It preferred to fit a:

- 2-knot normal spline model for TTD for amivantamab
- 1-knot hazard spline model for TTD for lazertinib
- 1-knot normal spline for TTD for osimertinib.

The EAG thought that these distributions had a good statistical and visual fit. It also thought that they provided estimates that were in line with the company's clinical experts' 8-year predictions, and in some cases closer to it than the exponential distribution. The committee thought that the risk of stopping treatment was unlikely to be the same across the lifetime of the model. It noted that it was likely that stopping treatment might be in the early stages of the model, while people who have adverse events stop treatment, before possibly evening out. It concluded that it preferred the EAG's distributions for modelling TTD. In its response to the draft guidance, the company updated its base-case TTD extrapolations to the EAG's distributions.

Modelling of subsequent treatments in the osimertinib plus chemotherapy arm

3.18 In response to the draft consultation, the company updated its model to allow for comparison between amivantamab plus lazertinib and osimertinib plus chemotherapy (see section 3.11). To model subsequent treatments in the osimertinib plus chemotherapy arm, the company made several assumptions. These were to:

- use the same treatments as in the osimertinib-alone arm (100% of second-line treatment and 25% of third-line treatment platinum-based chemotherapy)
- align the start of subsequent treatment with the pemetrexed component TTD curve
- use a one-off cost for the administration of subsequent oral treatments

- use the costs from its original base case for the administration of subsequent chemotherapy treatments.

The EAG disagreed with the company's assumptions for subsequent treatments in the osimertinib plus chemotherapy arm. It was given clinical advice that people who had osimertinib plus chemotherapy at first line would be unlikely to have retreatment with platinum-based chemotherapy in later lines. The EAG's clinical adviser said that these people would have docetaxel (with nintedanib if fit enough) at second line and best supportive care at third line. The EAG noted that, in TA1060, the committee accepted that the platinum-based chemotherapy will stop first (4 cycles). Then the pemetrexed component of the osimertinib plus chemotherapy treatment regimen tended to be stopped second, followed by osimertinib. So, it preferred that the start of subsequent treatment was aligned with the osimertinib component's TTD curve. The EAG also aligned the administration costs for subsequent treatments with first-line costs in the company's updated base case. For this, it used a monthly cost for the administration of oral treatments and administration costs for chemotherapy from TA1060.

The clinical experts advised that the choice of subsequent treatments for people who had had osimertinib plus chemotherapy at first line was not consistent between healthcare professionals. They estimated that the use of platinum-based chemotherapy and docetaxel at second line would be roughly equal. The committee noted that it was unclear what proportion of docetaxel use would be with nintedanib, as recommended in NICE's technology appraisal guidance on nintedanib for previously treated locally advanced, metastatic, or locally recurrent NSCLC. So, it said that it would like this to be explored. It also said that it would like the use of atezolizumab with bevacizumab, carboplatin and paclitaxel

as a third-line treatment to be explored, which the EAG included as a scenario. The committee concluded that it would like to see:

- 50% of treatment at second line should be platinum-based chemotherapy and 50% should be docetaxel
- treatment at third line should be 100% best supportive care
- subsequent treatments should be aligned with the osimertinib component's TTD curve
- the EAG's assumption for the administration costs for subsequent treatments were most suitable.

In response, both the company and the EAG aligned their base cases with the committee's preferred approach of modelling subsequent treatments.

Utility values

Source of utility values in the progression-free health state

3.19 The company modelled treatment-independent utilities (the same value for both arms of the model) in the progression-free health state in its base case. It also modelled disutility for treatment-emergent grade 3 or 4 adverse events and grade 2 or lower venous thromboembolisms. The EAG explained that, even when accounting for modelling these adverse events separately, there still seemed to be a difference in utility between the model arms. The EAG preferred to model treatment-dependent utilities (different values for amivantamab plus lazertinib and osimertinib alone) in the progression-free health state. The utility values used are considered confidential by the company and cannot be reported here. The committee questioned why the progression-free value for amivantamab plus lazertinib appeared to be close to the progressed-disease value used in the model and whether this was plausible. The clinical expert replied that amivantamab infusion was associated with a range of adverse events (see section 3.2). They also said that people in clinical trials are under

very close observation, so any progression would be detected quickly. They also said it would potentially be small-volume progression that was not associated with an immediate change in symptom burden. Because of this, they thought the progressed-disease utility might have been an overestimate. They thought that it was plausible that the progression-free utility for amivantamab plus lazertinib would be close to the progressed-disease utility. The patient and clinical experts both reported that management of adverse events had improved since MARIPOSA was done (see section 3.9). They suggested that this meant that the utility values derived from the trial may be lower than in NHS clinical practice. So, they suggested that using the same utility values for amivantamab plus lazertinib and osimertinib alone may be suitable.

The committee acknowledged that management of adverse events had improved. The committee also noted that some of the difference in utility was accounted for in modelling of adverse events. But it noted that only the most severe adverse events were modelled and that there were many others not modelled that would have a cumulative effect. The committee also recalled the input from the patient expert that some people may prefer to avoid a clinical environment needed for infusions. So, there would be a trade-off between better outcomes and a worse adverse event profile (see section 3.3). So, it thought that it was not plausible that people having amivantamab plus lazertinib would have the same utility as people having osimertinib alone. The committee concluded that the utility values for the progression-free health state should be modelled separately for the amivantamab plus lazertinib and the osimertinib-alone arms.

After the first committee meeting, a subcutaneous formulation of amivantamab was approved by the MHRA (see section 3.9). In its response to the draft guidance, the company said that the relative impact on quality of life between amivantamab plus lazertinib and osimertinib alone would be significantly less relevant because of the subcutaneous

administration of amivantamab. It noted that subcutaneous amivantamab showed a reduction in certain adverse events and improved patient satisfaction compared with intravenous amivantamab in the PALOMA trials. So, it thought that treatment- dependent utility values for the progression-free health state were not suitable. The company noted that progression-free utility values in TA1060 were similar between treatment arms. It updated its base case to use utility values from TA1060 for all treatments. The EAG disagreed with the company's preference of using treatment-independent utilities. It noted that, while the duration of hospital time may be lower for the subcutaneous formulation of amivantamab, there would still be an impact on quality of life from:

- attending hospital every 2 weeks
- lower than grade 3 adverse events, which were still common with the subcutaneous formulation.

The EAG also noted that a utility decrement was applied to the full progression-free health state for the osimertinib plus chemotherapy arm in TA1060. This was to account for the effect on quality of life from adding chemotherapy. But it was unable to confirm whether this decrement was similar to the difference between amivantamab plus lazertinib and osimertinib alone that it applied. The patient expert said that the subcutaneous formulation of amivantamab would have a positive impact on people's quality of life. They also highlighted that chemotherapy has a strong negative impact on people's quality of life.

The committee noted that the utility values for the progression-free and progressed-disease health states for amivantamab plus lazertinib in the EAG's base case were fairly similar (the company considers the exact utilities to be confidential and so cannot be reported here). It thought that this could be because amivantamab plus lazertinib may have a bigger negative impact on quality of life than osimertinib alone. The committee noted that PALOMA-3 reported increases in some adverse

events between the subcutaneous and intravenous formulations of amivantamab but decreases in others. It noted that some of these events (grade 3 and above events experienced by 5% or more of the trial population) were accounted for in the model by applying decrements and the others were assumed to be covered by the utility values used. So, the committee thought that it was implausible that 3 different treatment regimens all with different methods of administration would have the same utility value. It noted that it was plausible that the subcutaneous formulation of amivantamab would improve quality of life compared with the intravenous formulation. So, it thought that using the MARIPOSA utility values for the subcutaneous formulation might be a conservative choice. But it noted that the size of this benefit was uncertain. At the second committee meeting, it thought that the company should explore having different progression-free utilities in the 3 treatment arms in the model. It also concluded that the ITC that compared adverse events between the 3 treatments might help to inform such modelling.

Updated progression-free utilities

3.20 To address the committee's request, the company applied treatment-specific utility values for the progression-free health state from MARIPOSA for amivantamab plus lazertinib and osimertinib plus chemotherapy. The company explained that the safety ITC suggested improved utilities for people having amivantamab plus lazertinib in clinical practice than for people having it in MARIPOSA because:

- of a better safety profile for amivantamab plus lazertinib than for osimertinib plus chemotherapy (see section 3.10)
- grade 3 or higher adverse events and serious adverse events may have been underestimated in FLAURA2
- of the advantages of subcutaneous amivantamab
- of better dermatological management (see section 3.10).

The EAG noted that osimertinib plus chemotherapy may lower utility because of the above reasons. But the company's safety ITC did not identify a statistically significant difference in adverse events between treatment arms. The EAG agreed that people having subcutaneous amivantamab plus lazertinib and with better dermatological management could have higher utilities in clinical practice. It explained that the size of any utility gain is uncertain. So, the EAG, preferred to use treatment-dependent progression-free utility estimates from MARIPOSA in its base case, and the same utility values for amivantamab plus lazertinib and osimertinib plus chemotherapy. It thought that this might be a conservative modelling choice but that the size of any difference was uncertain. The committee noted that the company did not explore the potential for utilities to improve in people having osimertinib plus chemotherapy when the chemotherapy element of the combination treatment is stopped. The company provided a scenario in which amivantamab plus lazertinib had higher progression-free utility than osimertinib plus chemotherapy. The committee concluded that people having subcutaneous amivantamab plus lazertinib with enhanced dermatological and adverse event management could have a higher utility than MARIPOSA. But it thought that the size of any improvement was uncertain without supporting evidence. It concluded that it would prefer to see the same progression-free utility modelled for amivantamab plus lazertinib and osimertinib plus chemotherapy. It added that it would take into account that this was likely to be a conservative modelling choice.

Utility in the progressed-disease health state

3.21 The committee noted the differences in subsequent treatments between arms. For example, the inclusion of docetaxel and or nintedanib at second line or a repeat course of chemotherapy in the osimertinib plus chemotherapy arm. It thought that this meant that treatment dependant utilities for the progressed-disease health state for osimertinib plus chemotherapy might be appropriate. The committee concluded that it

would like to see exploration of separate utility values for amivantamab plus lazertinib and osimertinib plus chemotherapy in the progressed-disease health state. It also thought that the progressed-disease utility value from TA1060 was more appropriate than the value from MARIPOSA. At the third committee meeting, the company updated its modelling to include the progressed-disease utility value from TA1060. The committee acknowledged this and concluded that it should be used in the base case. But it noted that there was uncertainty around whether the osimertinib plus chemotherapy arm might have a different progressed-disease utility to reflect the differing subsequent treatments. It concluded that the direction of this uncertainty was unclear.

Costs

Administration costs for amivantamab

3.22 At the first committee meeting, the committee concluded that the intravenous administration costs should be modelled in line with the Cancer Drugs Fund clinical lead's input (see the first NICE draft technology appraisal guidance on amivantamab with lazertinib for untreated EGFR mutation-positive advanced non-small-cell lung cancer). In response to the draft guidance, the company changed the administration costs for amivantamab because of the introduction of the subcutaneous version (see section 3.9). It noted that Baldwin et al. (2025) stated that the subcutaneous formulation of amivantamab can be given in a 30-minute appointment. The company also highlighted that the average chair time in PALOMA-3 was 36 minutes. It chose the N10AF Healthcare Resource Group (HRG) code for administration costs for subcutaneous amivantamab. This is associated with a 45-minute face-to-face, cancer related, specialist nursing appointment. The EAG noted that the N10AF HRG code is used for community nursing so was unsuitable to use for an outpatient procedure. It also noted that Baldwin et al. stated that, when the subcutaneous formulation is used in a combination, it will be delivered in a hospital day unit. The EAG thought that it would be reasonable that

subcutaneous amivantamab would be given as an outpatient procedure once clinicians had experience with using it. So, it used the SB12Z HRG code in its base-case costs for subcutaneous amivantamab. The Cancer Drugs Fund clinical lead agreed that the SB12Z code was most suitable for subcutaneous amivantamab. The committee concluded that the SB12Z code should be used for the cost for administering subcutaneous amivantamab. At the third committee meeting, the committee noted that the company had updated the cost for administering subcutaneous amivantamab in line with SB12Z.

Cost-effectiveness estimates

Committee's preferred assumptions

3.23 The committee concluded that the company's overall model structure was acceptable for decision making (see section 3.6). It recalled that its preferred assumptions were:

- to use the age from the SACT Dataset cohort to inform the baseline model characteristics (see section 3.5)
- that all the amivantamab administered would be using the subcutaneous formulation (see section 3.9)
- for the osimertinib plus chemotherapy arm, that 50% of people would have platinum-based chemotherapy and 50% would have docetaxel at second line, and that 50% of people having docetaxel would have it with nintedanib (see section 3.18)
- for the osimertinib plus chemotherapy arm, that everyone would have best supportive care at third line (see section 3.18)
- that subsequent treatment start aligned with the osimertinib component for the osimertinib plus chemotherapy arm (see section 3.18)
- to use the EAG's assumptions for administration costs for subsequent treatments in the osimertinib plus chemotherapy arm and to use HRG code SB12Z for subcutaneous amivantamab administration costs (see section 3.22)

- to use the Weibull distribution to model PFS in the osimertinib plus chemotherapy arm (see section 3.12) and the gamma distributions to extrapolate PFS in the amivantamab plus lazertinib and osimertinib alone arms (see section 3.16)
- to use the 2-knot normal for amivantamab, the 1-knot hazard for lazertinib and the 1-knot normal for osimertinib alone for TTD (see section 3.17)
- to use the Weibull distribution to model OS in the amivantamab plus lazertinib and osimertinib-alone arms (see section 3.16)
- to use the 2-knot normal and 2-knot hazard spline for osimertinib plus chemotherapy OS (see section 3.17)
- to use the treatment-specific utilities for the progression-free health state and the utility value from TA1060 for the progressed-disease health state (see sections 3.19 to 3.21).

Uncertainties

3.24 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjust 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 key uncertainties around:

- the methods used for the ITCs and a lack of justification as to why (see section 3.8)
- choice of TTD curve for osimertinib plus chemotherapy (see sections 3.14 to 3.15)
- long-term extrapolations of OS for amivantamab plus lazertinib, osimertinib-alone and osimertinib plus chemotherapy (see sections 3.12 to 3.13).

The committee acknowledged that the management of the adverse events has improved in clinical practice, which may not have been fully captured in the model (see section 3.25). The committee noted the uncertainty in the ITCs and long-term extrapolations. This includes a plausible scenario that suggested that amivantamab plus lazertinib might have no long-term benefit over osimertinib plus chemotherapy. The committee concluded it would take this into account in its decision making.

Other factors

Equality

3.25 The committee noted that EGFR mutation-positive NSCLC is more common in women and people from Asian ethnic groups. The committee also noted that amivantamab plus lazertinib may also have different efficacy in people over 65 years. Race, age and sex are protected characteristics under the Equality Act 2010. But, because its recommendation does not restrict access to treatment for some people over others, the committee agreed these were not potential equalities issues.

Uncaptured benefits

3.26 The committee considered whether there were any uncaptured benefits of amivantamab plus lazertinib. It noted that there were some improvements in adverse events from using subcutaneous amivantamab rather than intravenous amivantamab, which the model was based on. The committee concluded it would take this into account during decision making.

Conclusion

Recommendation

3.27 The committee took into account its preferred assumptions, key uncertainties in the evidence and other factors in its decision making.

Taking these into account, the ICERs based on the committee preferred assumptions were within the range that NICE normally considers an acceptable use of NHS resources. So, amivantamab plus lazertinib can be used.

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 untreated EGFR mutation-positive advanced non-small-cell lung cancer and the healthcare professional responsible for their care thinks that amivantamab plus lazertinib 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 technologies 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

Raju Reddy

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.

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