NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Amivantamab with carboplatin and pemetrexed for untreated EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using amivantamab with carboplatin and pemetrexed in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: February 2025

Note that this document is not NICE's final guidance on amivantamab with carboplatin and pemetrexed. The recommendations in section 1 may change after consultation.

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using amivantamab with carboplatin and pemetrexed in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 28th March 2025
- Second evaluation committee meeting: TBC
- Details of the evaluation committee are given in section 4

1. Recommendations

1.1 Amivantamab with carboplatin and pemetrexed should not be used for untreated advanced non-small cell lung cancer (NSCLC) with activating EGFR exon 20 insertion (ex20ins) mutations in adults.

1.2 This recommendation is not intended to affect treatment with amivantamab with carboplatin and pemetrexed that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Amivantamab with carboplatin and pemetrexed is not required to be funded in the NHS in England for untreated advanced ex20ins mutation-positive NSCLC in adults. It should not be used routinely in the NHS in England.

This is because there is not enough evidence available to determine if amivantamab with carboplatin and pemetrexed offers value for money.

Why the committee made these recommendations

Usual treatment for untreated advanced NSCLC with ex20ins mutations includes carboplatin with pemetrexed or best supportive care.

Clinical trial evidence shows that amivantamab with carboplatin and pemetrexed increases how long people have before their condition gets worse compared with just carboplatin and pemetrexed. But the effect of amivantamab with carboplatin and pemetrexed on how long people live is uncertain because there is limited clinical trial evidence.

There are uncertainties in the economic evidence, including the method used to estimate how long people live. Because of this, it was not possible to determine the most likely cost-effectiveness estimates. So, amivantamab with carboplatin and pemetrexed should not be used.

2. Information about amivantamab

Marketing authorisation indication

2.1 Amivantamab (Rybrevant, Johnson & Johnson) in combination with carboplatin and pemetrexed is indicated for 'the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor (EGFR) Exon 20 insertion mutations'.

Dosage in the marketing authorisation

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

Price

2.3 The list price for amivantamab is £1,079 per 350-mg vial (excluding VAT; BNF online, accessed February 2025).

2.4 The company has a commercial arrangement, which would have applied if amivantamab had been recommended.

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.

The condition

EGFR exon 20 insertion-positive non-small-cell lung cancer

3.1 EGFR exon 20 insertion (ex20ins) mutations are rare in non-small-cell lung cancer (NSCLC), with around a few hundred cases diagnosed in England and Wales each year. They are more common in women, people from Asian ethnicities and people with no history of smoking, and are also associated with poorer outcomes than other EGFR mutations. These cancers are also resistant to tyrosine kinase inhibitors, which are commonly used to treat other types of EGFR mutation-positive NSCLC. The patient experts explained that for many people with ex20ins mutation-positive NSCLC diagnosis is unexpected. It can also be particularly devastating when people are diagnosed at an advanced stage, when the cancer has already spread to other parts of the body. They explained that in people with ex20ins mutation-positive NSCLC, the condition has a significant effect on their quality of life, causing high levels of anxiety and psychological distress. The lack of treatment options can lead to feelings of isolation when with friends and even within groups of people with other types of lung cancer. Clinical experts highlighted that there is an unmet need for people with ex20ins mutation-positive NSCLC. They also highlighted that there are currently no specific clinical guidelines or targeted treatment options for the condition available in the NHS.

Squamous histology

3.2 The company did not provide any evidence for amivantamab with carboplatin and pemetrexed (from here on amivantamab–chemotherapy) in squamous cell NSCLC. It explained that this is because ex20ins mutations are rare in squamous NSCLC and the key clinical trial did not include people with ex20ins mutation-positive squamous NSCLC. The clinical experts explained that people with ex20ins mutation-positive squamous NSCLC cannot have amivantamab–chemotherapy because the combination includes pemetrexed, and pemetrexed is only licenced for non-squamous disease (see the summary of product characteristics for

pemetrexed). The committee noted this. It concluded that any recommendations from this appraisal would not apply to ex20ins mutation-positive squamous NSCLC. This is because it can only make recommendations within the current marketing authorisations of all medicines in the intervention.

Clinical management

Treatment options and comparators

3.3 There is no specific treatment pathway for people with untreated ex20ins mutation-positive advanced NSCLC and no NICE-recommended targeted treatment options for this disease subtype. Various tyrosine kinase inhibitors are recommended for EGFR mutation-positive NSCLC and these recommendations could technically apply to people with ex20ins mutation-positive NSCLC. But the clinical experts explained that these offer limited benefit in treating ex20ins mutation-positive NSCLC (see section 3.1) and should not be used. The patient organisation submission included results of a survey of people with ex20ins mutation-positive NSCLC. It stated that 70% of people had platinum-based chemotherapy (such as carboplatin with pemetrexed) and 30% had a tyrosine kinase inhibitor (mainly osimertinib). But, the patient expert noted that this was from a small survey of fewer than 30 people and some of the people may have accessed their treatment privately. The clinical expert explained that there might be some inappropriate prescribing of tyrosine kinase inhibitors in ex20ins mutation-positive NSCLC by inexperienced healthcare professionals. But they added that this is likely to decrease as awareness increases. The company thought that the breakdown of treatment in practice was 70% carboplatin with pemetrexed and 30% pembrolizumab with chemotherapy. The EAG's clinical expert made a similar estimate. The clinical experts reported that treatment options other than chemotherapy alone, such as pembrolizumab with chemotherapy, are sometimes used off-label but that this was inappropriate. They explained that there was no evidence of efficacy of immunotherapies like

pembrolizumab in ex20ins mutation-positive NSCLC. The NHS England cancer drugs fund lead (from here, CDF lead) confirmed that any use of immunotherapies for EGFR mutation-positive disease was off-label, outside the NICE recommendations, and therefore not commissioned. They added that much of this off-label use would likely be in people who started treatment before getting a genomic test result and are not within the population for this appraisal. The CDF lead agreed that using immunotherapies to treat ex20ins mutation-positive NSCLC could not be considered standard practice. The clinical experts explained that the mainstay of treatment was carboplatin with pemetrexed. The committee concluded that the only relevant comparator for this appraisal was carboplatin with pemetrexed (from here, chemotherapy).

Clinical effectiveness

The PAPILLON Clinical trial

3.4 The PAPILLON trial is an ongoing randomised, open-label, multicentre phase 3 superiority trial. It is comparing amivantamab–chemotherapy; n=153) with chemotherapy alone (n=155) in people with untreated, locally advanced or metastatic NSCLC with activating ex20ins mutations. The primary endpoint was progression-free survival (PFS) under blinded review using RECIST criteria. Amivantamab–chemotherapy was offered until unacceptable toxicity or disease progression. But people could continue on amivantamab–chemotherapy beyond disease progression if the investigator believed they was benefitting from the treatment. The median duration of treatment was 9.72 months in the amivantamab–chemotherapy arm and 6.74 months in the chemotherapy only arm. Pemetrexed treatment was offered until disease progression and carboplatin was administered for 4 cycles. The company submitted a May 2023 final data-cut for PFS. It showed a median PFS of 11.37 months (95% confidence interval [CI] 9.79 to 13.70) in the amivantamab–chemotherapy arm and 6.70 months (95% CI 5.59 to 7.33) in the chemotherapy arm. The PFS hazard ratio was 0.40 (95% CI 0.30 to 0.53).

The company used an October 2023 second data-cut for overall survival (OS), which had a data maturity of 22%. Median OS was not reached for the amivantamab–chemotherapy arm. The OS hazard ratio for amivantamab–chemotherapy compared with chemotherapy alone was 0.76 (95% CI 0.50 to 1.14). The committee concluded that amivantamab–chemotherapy improved PFS compared with chemotherapy alone and that the relative effectiveness on OS was uncertain. But it acknowledged that the OS data was still relatively immature.

Treatment beyond progression

3.5 The committee noted that the trial allowed for amivantamab–chemotherapy treatment beyond progression if the investigator felt that the person was still benefitting. The marketing authorisation specifies that amivantamab should only be given until progression. The CDF lead stated that practice in the NHS would follow the evidence base. They added that there may be times where healthcare professionals would continue treatment with amivantamab–chemotherapy beyond progression if they felt people would benefit from it. The committee agreed that there was a mismatch between the trial and the marketing authorisation and noted that NICE can only recommend within the marketing authorisation. The committee would like to see PFS and time to treatment discontinuation for amivantamab–chemotherapy plotted on the same graph to assess the size of this mismatch. But the committee concluded that use of amivantamab–chemotherapy in NHS practice would be likely to reflect the key trial.

Economic model

Company's modelling approach

3.6 The company presented a 3-state partitioned-survival model. The model consisted of health states for progression-free disease, progressed-disease and death. At each cycle, the cohort starts in the progression-free health state and either stays in that health state or transitions to the other

health states. The company chose a 1-week cycle length to capture the varied dosing schedules of the comparators. The company stated that a partitioned-survival model is the most common structure used in oncology models and was deemed suitable for decision making by previous NICE committees in other advanced NSCLC evaluations. The EAG noted that the NICE Decision Support Unit recommends state-transition modelling is done alongside partitioned-survival modelling to confirm the plausibility of the model extrapolations and explore key uncertainties. But the EAG agreed that the company approach was reasonable. The committee questioned whether a partitioned-survival model was best for the decision problem. The committee thought that, given the relative immaturity of the OS data (see section 3.9) and the concerns about plausibility of extrapolated quality-adjusted life years (QALYs; see section 3.7), the partitioned-survival model approach was associated with uncertainty. It thought a state-transition model might have been more appropriate but concluded that the company's model structure was acceptable for decision making.

Plausibility of extrapolated benefits

3.7 The company and EAG modelling of amivantamab–chemotherapy accrued the majority of life-year and QALY gains in the progressed-disease health state. The EAG thought this was implausible given that treatment is only given until disease progression or unacceptable toxicity. The committee thought that it is logical to expect a greater proportion of the incremental QALYs to accrue in the progression-free health state when people are on treatment. It did acknowledge that a post-progression benefit might be plausible based on the mechanism of action of amivantamab but it had seen no strong evidence to support this. It felt that modelling in which the majority of QALY gains accrue in the progressed-disease health state was associated with uncertainty. It concluded that the company should take this into account when extrapolating longer-term health benefits (see sections 3.8 and 3.9).

Base-case OS extrapolations

3.8 The company fitted a Weibull distribution to the OS data for amivantamab–chemotherapy to extrapolate it to the 40-year time horizon of the model. The company felt that this was the most appropriate curve because it fit with the clinical expert opinion from its advisory board (27.5% survival at 5 years) and provided a good visual fit. The EAG clinical expert gave a lower estimate for longer-term survival (10% to 15% at 5 years). But the EAG explained that any clinical expert opinion should be taken with caution, because there is limited experience with amivantamab–chemotherapy in NHS practice. A clinical expert responded that there was longer-term clinical trial experience with amivantamab in the second-line setting, which may have helped to inform estimates of OS at the company's advisory board. The EAG felt that long-term estimates of OS with amivantamab–chemotherapy were very uncertain. It used the Weibull distribution in its base case but used a scenario with the Gompertz distribution to explore more pessimistic survival in keeping with its expert's estimates. For chemotherapy, the company fitted a gamma distribution to the OS data for chemotherapy. This was based on the clinical expert opinion from its advisory board (10% survival at 5 years) and fit to the observed data. The clinical experts present at the meeting agreed that the 5-year survival estimate of 10% from the company's advisory board was reasonable. They also explained that there was longstanding experience with this chemotherapy regimen in NHS practice. The committee heard from the clinical expert at the meeting that they had provided advice to the company for this appraisal. They were therefore concerned that there may be 'double counting' of clinical expert opinion. The company stated that the clinical expert at the meeting was not present at the advisory board where the estimates for OS for both arms of the model had been made. The committee noted this. The EAG had concerns that the company's choice of curve underestimated the OS for chemotherapy based on the company's advisory board and the EAG's

own clinical expert input (5% at 5 years). The EAG preferred to use a log-logistic curve to extrapolate OS for chemotherapy alone.

Uncertainties in extrapolating OS beyond the trial

3.9 The committee agreed that clinical experts' opinions for OS with amivantamab–chemotherapy beyond the end of the trial should be interpreted with caution. This was because of the limited use of amivantamab–chemotherapy in NHS clinical practice, and the range of different opinions. The committee was aware that the Weibull and Gompertz distributions gave substantially different predictions, and considered that there may be merit in exploring curves in between the 2 distributions. It also noted that the company and EAG base cases fit different parametric models to the 2 treatment arms (see section 3.8). It recalled that the Decision Support Unit's Technical Support Document 14 states that fitting different models allows for very differently shaped distributions, and strong evidence is required to justify this approach. The EAG and company agreed that the different mechanisms of action of amivantamab–chemotherapy compared with chemotherapy alone could justify this. The committee noted that this was plausible but did not consider it to be strong evidence. The committee also felt that the extrapolations of OS suggested that the benefit of amivantamab–chemotherapy over chemotherapy extends into the long term, even when the majority of people had stopped treatment. This implies a post-progression benefit, which is uncertain (see section 3.6)

Treatment-effect waning

3.10 The company base case did not model any explicit waning of the treatment effect of amivantamab, either on or off treatment. It did not do this because:

- the median PFS in the amivantamab–chemotherapy arm of PAPILLON was 11.4 months, so there was unlikely to be any treatment-effect waning over such a short time

- the committee in NICE's technology appraisal of amivantamab for previously treated EGFR exon 20 insertion mutation-positive NSCLC (from here referred to as TA850) agreed that treatment-effect waning was usually applied for immunotherapies with stopping rules
- any treatment-effect waning would be implicitly captured in the selected distributions for extrapolating PFS and OS

The committee noted that TA850 looked at a later line of treatment (previously treated rather than untreated) in which there were very poor outcomes. Some of the justification for concluding that effect waning was unlikely was then linked to the poor survival outcomes and short life expectancy. These factors may not apply in this appraisal. The committee also noted that the modelling suggests a hazard ratio reflecting a big treatment effect between amivantamab–chemotherapy and chemotherapy beyond 2 years, even when few people remain on amivantamab–chemotherapy. This may imply a post-progression benefit and the absence of treatment-effect waning even after stopping treatment. The committee agreed that it would like to see the hazard rates and implied hazard ratio over the lifetime of the model plotted and explained with reference to numbers of people remaining on treatment. It also agreed that any assumptions on treatment-effect waning are reliant on having credible extrapolations of OS, which were uncertain in this appraisal (see section 3.9). It concluded that treatment-effect waning could not be ruled out and should be explored through selecting appropriate OS curves or explicit modelling of treatment-effect waning.

Conclusions on modelling of OS

3.11 The committee felt that there was substantial uncertainty associated with extrapolating OS, because:

- it is difficult to validate long-term extrapolations of OS because of differing expert opinions and the limited experience with amivantamab–chemotherapy in NHS practice

- both company and EAG base cases fitted different distributions to the different model arms and it is unclear whether this is justified
- the benefits of both amivantamab–chemotherapy and chemotherapy accrued mainly in the progressed-disease health state (see section 3.6) and this implies a post-progression benefit, which is uncertain
- the modelling of OS implies a maintained treatment effect even when people have stopped treatment, which is uncertain (see section 3.10)
- the OS data was immature (see section 3.4)

The committee concluded that it was unable to establish a plausible approach for extrapolating OS. It needed additional evidence including:

- exploring OS curves for amivantamab–chemotherapy that might give estimates of OS for amivantamab between those of the Gompertz and Weibull distributions
- justifying, in detail, the decision to fit different models to the 2 arms of the model and scenarios exploring fitting the same parametric model to both arms
- modelling where hazards were equalised in both arms, at the point of progression or at the point where the observed trial data from PAPILLON ends, to explore the possibility that there is no post-progression benefit to amivantamab treatment
- plotting the OS implied hazard ratio over the lifetime of the model and justifying this with reference to the number of people still on treatment
- exploring the value of more mature OS data from the PAPILLON trial (for example, through a period of managed access, if the criteria for managed access were fulfilled).

Time to treatment discontinuation or death

3.12 The company modelled time to treatment discontinuation or death (TTDD) by fitting separate Weibull curves to the trial TTDD data for both the amivantamab and chemotherapy components of amivantamab–chemotherapy. The company explained that the Weibull curve had a good

visual and statistical fit to the observed data for TTDD with amivantamab and also matched clinical expert opinion. The company also suggested that its choice was conservative. This was because it would accumulate greater acquisition costs for amivantamab over the model time horizon compared with the Gompertz distribution, which was statistically a better fit. The EAG felt that a log-logistic curve was more appropriate because it had concerns that, based on its own expert opinion, a Weibull curve would underestimate the treatment duration for amivantamab. For the TTDD for the chemotherapy component of the amivantamab–chemotherapy arm, the EAG preferred to use an exponential curve. The committee noted that the TTDD data from the PAPILLON trial for both arms was relatively mature and that the Weibull distribution provided a relatively good fit to this data for both arms. The committee felt that the log-logistic and exponential distributions appeared to overestimate TTDD for both components of the amivantamab–chemotherapy arm. The committee was aware that plausible modelling of TTDD would need to be considered alongside any updated modelling of OS, particularly in relation to treatment effects after progression or discontinuation. It concluded that, based on the currently available evidence, a Weibull curve is likely to be appropriate for extrapolating the TTDD data for both components of amivantamab–chemotherapy.

Utility values

Most appropriate utility values to use

3.13 The company modelled utility in the progression-free and progressed-disease health states based on the quality-of-life data collected in PAPILLON, which used the EQ-5D-5L questionnaire. The utility values are considered confidential by the company and cannot be reported here. The patient expert felt that the severe anxiety and depression (see section 3.1) experienced by people with ex20ins mutation-positive NSCLC would not be fully captured by the EQ-5D-5L questionnaire. The committee acknowledged this but noted that the EQ-5D questionnaires

are widely used in health technology assessment and contain questions to assess anxiety and depression. For consistency, they are also the preferred method of measuring health-related quality of life in NICE appraisals. The EAG noted that there was missing data from both health states, with a substantial amount missing from the progressed-disease health state. The EAG was concerned that if the data was not missing at random then the utility values might not be accurate. The amount of missing data is considered confidential by the company and cannot be reported here. The committee noted that the utility values in this appraisal were higher in both health states than in several other appraisals in NSCLC. It thought this was somewhat counterintuitive given the poorer prognosis of ex20ins mutation-positive NSCLC (see section 3.1) and the patient expert's testimony on its psychological effects. The committee noted that scenario analyses submitted by the EAG exploring different utility values did not have a large effect on the incremental cost-effectiveness ratios (ICERs). The committee noted the uncertainty around the health benefits accrued in the progressed-disease health state (see section 3.14). Because of this, it concluded that it would like to see utility values used in previous appraisals in NSCLC explored for this health state as part of future analyses.

Costs

Adverse events

3.14 The unit costs chosen by the company for adverse events in the base-case model were lower than in some other NICE technology appraisals in NSCLC. The company explained that its approach followed a standard costing approach. It calculated total costs of all codes of non-elective short-stay adverse events from the national schedule of NHS costs (2022/2023). It then weighted them by the total number of those events. The company justified this approach, noting that the codes it used were in line with those used in previous technology appraisals and were validated with clinical opinion. The EAG was concerned that the company's

approach underestimated costs for adverse events. This was because it used a weighted average cost of all grades of events applied to only the grade 3 and 4 adverse events in the model. The EAG also stated it was unclear why the company had used only the cost of non-elective short-stay adverse events. The EAG's base case included only unit costs for the most severe adverse events for non-elective short stays to match those used in the model. It also included a scenario to explore the impact of including costs for all severe adverse events (not just non-elective short stays). A clinical expert explained that handling of common adverse events had improved since the trial and healthcare professionals were experienced in using high-dose corticosteroids to treat skin reactions. A patient expert confirmed that they had experienced skin irritations but that healthcare professionals had treated and resolved them quickly. The company argued that this justified its approach to the costing of adverse events. The committee acknowledged this point, noting that the incidence of infusion-site reactions was lower in the PAPILLON trial than previous studies of amivantamab monotherapy. But it felt that the cost codes used should match the adverse events modelled and concluded that the EAG's approach was more appropriate for decision making.

Dosing in the model

3.15 The company modelled dosing of amivantamab–chemotherapy by assuming that a fraction of the required dose is given each cycle, instead of the full dose each relevant cycle followed by a break. The EAG was concerned that this could underestimate the costs of amivantamab–chemotherapy and preferred to model dosing as it would happen in the NHS. The committee agreed that this averaging out of dosing would underestimate costs. It concluded that it would prefer to model doses of amivantamab in the cycles in which they were due, in line with the EAG base case.

Vial sharing

3.16 The EAG thought that the company approach implicitly allowed vial sharing for amivantamab because the company modelled fractions of vials. The clinical experts explained that ex20ins mutation-positive NSCLC was so rare that vial sharing would not be possible in clinical practice. But they also noted that it would not be necessary because everyone would have a dose comprised of full vials. The company confirmed that the summary of product characteristics for amivantamab only allowed dose reductions by full vials so there would be no need to share vials. The company did not think that its model allowed vial sharing. The EAG explained that there were fractions of vials present in the model because the company multiplied the required number of vials at any given weight or cycle by the relative dose intensity from the PAPILLON trial. The relative dose intensity is considered confidential by the company and cannot be reported here. The EAG thought that this implied vial sharing and in its base case applied a scenario to round these fractions up to whole numbers. The committee considered the expert testimony that vial sharing would not be possible in clinical practice and concluded that vial sharing should not be permitted in the model.

Dose skipping

3.17 The company reported the percentages of doses skipped in the PAPILLON trial by people in each body weight category (less than or more than 80 kg). These values are considered confidential by the company and cannot be reported here. The dose-skipping percentages were used to reduce the per-cycle costs for amivantamab in every cycle of the model. The committee thought that this could potentially underestimate the costs of amivantamab if people skip fewer doses in clinical practice. It recalled that the clinical experts had explained that adverse events such as infusion reactions on the skin were most severe in the first cycle (see section 3.15). The committee thought that it was plausible that dose-skipping rates might fall over time if adverse events

improved with time or as people who experienced toxicity stopped treatment. It also recalled that the clinical experts had stated that management of adverse events such as skin rashes had improved since the PAPILLON trial (see section 3.11). The committee concluded that it would like the company to report dose-skipping estimates from the first and subsequent cycles of the PAPILLON trial and for the modelling to reflect any differences in these values. It would also like to see a scenario that explores modelling no dose skipping across all treatments in both arms and one where dose skipping was modelled to be equal across all treatments and arms.

Severity

3.18 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The committee heard that there is a substantial unmet need for targeted treatment options for people with ex20ins mutation-positive NSCLC. There are very few treatment options, and the condition is associated with a poor prognosis and a substantially decreased quality of life. Patient experts highlighted the substantial impact ex20ins mutation-positive advanced NSCLC can have on mental health for people affected in terms of depression and anxiety. The committee considered that the mental health effects of the condition are likely to be captured in EQ-5D. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. Taking into account these estimates, the committee concluded that based on the currently available evidence the severity weight of 1.2 applied to the QALYs was appropriate. But it noted that utility values and modelling of overall survival in the chemotherapy arm may affect the severity calculation, which may need to be revisited once uncertainties have been resolved.

Cost-effectiveness estimates

Committee's preferred assumptions

3.19 The committee recalled its preferences for the cost-effectiveness modelling, which were to:

- apply the decision only to non-squamous histology (see section 3.2)
- model chemotherapy as the only comparator (see section 3.4)
- use Weibull extrapolations of TTDD for both components of amivantamab–chemotherapy (see section 3.6)
- ensure the model does not allow vial sharing (see section 3.9)
- use cost codes for only the most severe non-elective short-stay adverse events because these were the only ones modelled to occur (see section 3.13)
- use utility values from previous appraisals in NSCLC (see section 3.13).

The committee noted that even when its preferred assumptions were incorporated into the modelling, substantial uncertainty remained, including in:

- the extrapolations of OS in both arms and which parametric models are used for each arm (see section 3.8)
- the immaturity of the OS data from the PAPILLON trial (see section 3.8)
- the appropriateness of the rates of dose skipping and how this should be modelled across the time horizon of the model (see section 3.18)
- the estimates of health state utility linked to missing data (see section 3.12).

The committee concluded that because of these uncertainties it was unable to establish a most plausible ICER for amivantamab–chemotherapy compared with chemotherapy alone. It outlined additional analyses that need to be explored to address some of the uncertainties. These included:

- fuller justification of the decision to fit different parametric models to the different model arms and exploration of fitting the same models to both arms (see section 3.9)
- exploration of OS curves for amivantamab–chemotherapy that would give survival estimates between the Gompertz and Weibull distributions (see section 3.9)
- exploration of the implied hazard ratio for OS with reference to people on treatment and a discussion of post-progression benefit and treatment-effect waning (see section 3.10)
- exploration of treatment-effect waning, either modelled implicitly within OS curve selection or using an explicit modelling mechanism (see section 3.10)
- reporting of dose skipping by cycle in PAPILLON trial and amending the model to reflect this as well as exploration of the impact of assuming:
  - no dose skipping for all treatments
  - equal dose skipping occurring across both treatment arms.

Acceptable ICER

3.20 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per 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. The committee also took into account the lack of targeted treatment options available for this specific mutation and the emotional burden on people with ex20ins mutation-positive NSCLC and their carers. It noted the rarity of ex20ins mutation-positive NSCLC and the difficulties this can create in generating evidence. But, the committee noted the high level of uncertainty (see section 3.20). The committee was unable to identify a threshold because this would need to

account for both the resolvable uncertainties in the analyses requested and the currently unresolvable uncertainties.

Other factors

Equality

3.21 The committee considered issues that had been raised during the appraisal process. Stakeholders explained that ex20ins mutation-positive NSCLC is associated with people who have never smoked. It also has a higher prevalence in people from Asian ethnicities and among women. The committee agreed that differences in prevalence cannot usually be resolved in a technology appraisal, but it can consider whether a specific equality issue has a significant impact on access to treatment. It concluded that there were no equalities issues that could be addressed in this appraisal.

Uncaptured benefits

3.22 The committee considered whether there were any uncaptured benefits of amivantamab–chemotherapy compared with chemotherapy alone. It did not identify additional benefits of amivantamab–chemotherapy not captured in the economic modelling. So the committee concluded that the model had captured all additional benefits of amivantamab–chemotherapy.

Conclusion

Recommendation

The committee concluded that amivantamab–chemotherapy should not be used for untreated ex20ins mutation-positive advanced NSCLC. Given the uncertainty, the committee was not able to establish a plausible cost-effectiveness estimate, and could not conclude that amivantamab–chemotherapy would be a cost-effective option. The committee concluded

that additional evidence is needed. So amivantamab with carboplatin and pemetrexed should not be used.

4. 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

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.

Emma Bajela

Technical lead

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