NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

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

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

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

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

Contents

1 Recommendations

1.1 Amivantamab with carboplatin and pemetrexed can be used during the managed access period as an option for untreated advanced non-small-cell lung cancer (NSCLC) with activating EGFR exon 20 insertion (ex20ins) mutations in adults. It can only be used if the conditions in the managed access agreement for amivantamab with carboplatin and pemetrexed are followed.

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

NICE, NHS England and Johnson & Johnson have a managed access agreement for amivantamab with carboplatin and pemetrexed. This means it can be used as an option in the NHS in England during the managed access period. During this time, more evidence will be collected to address any uncertainties. After this, NICE will review and update this guidance.

Amivantamab with carboplatin and pemetrexed can only be used if the conditions in the managed access agreement are followed.

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

Why the committee made these recommendations

Usual treatment for untreated advanced NSCLC with ex20ins mutations is 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 carboplatin with pemetrexed. But because the trial is ongoing, it is uncertain whether people who have amivantamab with carboplatin and pemetrexed live longer.

Because of the uncertainty in the clinical evidence, the most likely cost-effectiveness estimates are uncertain, and some are above the range that NICE considers an acceptable use of NHS resources. So amivantamab with pemetrexed and carboplatin cannot be recommended for routine use. But amivantamab with carboplatin and pemetrexed has the potential to be cost effective if some of the uncertainties in the evidence are resolved. This could be done by collecting more long-term evidence during a managed access period. So, amivantamab with carboplatin and pemetrexed is recommended for use with managed access.

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. This makes amivantamab with carboplatin and pemetrexed available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on Johnson & Johnson's webpage on their responsibility to the planet.

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

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

3.1 Epidermal growth factor receptor (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, trans men and non-binary people registered female at birth, as well as people from Asian ethnicities and people with no history of smoking. They 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. They explained that even a few months of additional survival benefit from a treatment would be extremely meaningful for people with this condition and their carers. 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, amivantamab–chemotherapy) in squamous cell NSCLC. It explained that this is because ex20ins mutations are rare in squamous cell NSCLC and the key clinical trial did not include people with ex20ins mutation-positive squamous cell NSCLC. The clinical experts explained that people with ex20ins mutation-positive squamous cell NSCLC cannot have amivantamab–chemotherapy because the combination includes pemetrexed, and pemetrexed is only licensed 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 cell NSCLC because this is outside the marketing authorisation for pemetrexed. 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 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 ex20ins mutation-positive NSCLC. But the clinical experts explained that these offer limited benefit for 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 for 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 for ex20ins mutation-positive NSCLC. At the first committee meeting, the NHS England Cancer Drugs Fund lead (from here, CDF lead) confirmed that using 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 who 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 (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 Response Evaluation Criteria in Solid Tumours (RECIST) criteria. Amivantamab–chemotherapy was offered until unacceptable toxicity or disease progression. But people could continue amivantamab–chemotherapy beyond disease progression if the investigator believed they were 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 arm. Pemetrexed 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 was 0.76 (95% CI 0.50 to 1.14). The committee concluded that amivantamab–chemotherapy improved PFS compared with chemotherapy and that the relative effectiveness on OS was uncertain. But it acknowledged that the OS data was still relatively immature and that further data cuts from the trial would be useful to resolve some uncertainty.

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 used until progression. The CDF lead stated that practice in the NHS would follow the evidence base. They added that there may be times when 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 have liked 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 using amivantamab–chemotherapy in NHS practice would likely 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 the start of the model, the cohort starts in the progression-free health state and people either stay in that health state or transition to the other health states in each cycle. 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. It was also 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's approach was reasonable. The committee questioned whether a partitioned-survival model was best for the decision problem. The committee noted 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). Given this, it thought the partitioned-survival model approach was associated with uncertainty and a state-transition model might have been more appropriate. But it 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 used 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 and lacks face validity. It concluded that the company should take this into account when extrapolating longer-term health benefits (see section 3.8 and section 3.9).

In its response to the draft guidance consultation, the company said that the effect of chemotherapy in PAPILLON was greater for overall survival than for progression-free survival. It thought that this supported the notion that most of the efficacy benefit for chemotherapy occurred after disease progression. It thought that this would also be the case for amivantamab–chemotherapy, or that even more of the health benefits would occur in the post-progression state than for chemotherapy. The EAG still had concerns about whether this was plausible in practice for a treatment that was used until disease progression or unacceptable toxicity. It also noted that 90% of life-year gains occurred after the observed data period and no explicit modelling scenario had been provided to explore what treatment-effect waning might look like. So, the EAG felt it was very uncertain to model a post-progression benefit continually. During the second committee meeting, the clinical experts agreed that there was some rationale for a post-progression benefit. They thought that chemotherapy alone has a modest benefit in treating this condition and would not usually be associated with reductions in tumour size. They also explained that amivantamab was effective in reducing tumour size. This means that progression seen with amivantamab might be associated with smaller tumour volumes after an initial reduction in size after treatment. The experts explained that this could provide the mechanism for a post-progression benefit because people on amivantamab–chemotherapy could be relatively fitter after disease progression compared with people on chemotherapy. They might tolerate subsequent treatments better and for longer. They might also be more able or willing to have diagnostic testing to identify any resistance mechanisms in their cancer and to have an optimum treatment approach. The experts also expected better quality of life post progression because of the lower disease burden associated with lower tumour volumes. They also noted that better mental health could also impact outcomes. The company explained that the proportions predicted by the extrapolations in its base case reflected the relative difference between OS and PFS seen in PAPILLON. The committee acknowledged the clinical expert testimony regarding the rationale for a post-progression benefit. It noted that while 73% of the amivantamab–chemotherapy arm in PAPILLON had a complete or partial

response, 47% of the chemotherapy arm did too. So, the committee thought that chemotherapy alone did cause some reduction in tumour size. It acknowledged that PAPILLON reported a larger mean percentage reduction for amivantamab–chemotherapy (53%) than for chemotherapy (34%). But it thought it was uncertain what effect this would have on post-progression survival. It noted that without longer-term evidence on the post-progression benefit of amivantamab–chemotherapy (see section 3.4), the magnitude of the benefit was unclear, which caused uncertainty in the modelling. The committee did note that some of this uncertainty might be reduced by additional follow up from the PAPILLON trial.

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 was selected alongside the gamma curve as the most appropriate by clinical expert consensus at its advisory board. The EAG's clinical expert gave a lower estimate for longer-term survival (10% to 15% at 5 years). The EAG noted that the estimate of survival given by the company's clinical experts at their pre-meeting questionnaire was 27.5%. The EAG explained that it assigned more value to the pre-meeting questionnaire than the consensus at the advisory board. This was because experts had only been presented with a limited selection of curves at the advisory board. The EAG also thought 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 at second line, which may have helped to inform estimates of OS at the company's pre-meeting questionnaire. They also explained that they had more experience with amivantamab–chemotherapy from earlier trials, which helped to inform their estimates. 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 because it gave the closest match to the Weibull curve

fitted to the 2-stage estimate-adjusted OS data for chemotherapy, which was the company's preferred approach at the time of the advisory board. The clinical expert opinion from its advisory board pre-meeting questionnaire was 10% survival at 5 years. The clinical experts present at the meeting agreed that a chemotherapy 5-year survival estimate of 10% from the company's pre-meeting questionnaire was reasonable. They also explained that there was longstanding experience with this chemotherapy regimen in NHS practice. The EAG had concerns that the company's choice of curve underestimated the OS for chemotherapy based on the company's pre-meeting questionnaire 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 the 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 felt that there may be merit in exploring curves in between the 2 distributions. It also noted that the company and EAG base cases fitted 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 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 alone extends into the long term, even when most people had stopped treatment. This implies a post-progression benefit, which is uncertain (see section 3.7).

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. This was 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 ex20ins 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 (in which amivantamab was not recommended for treating ex20ins mutation-positive NSCLC) 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 any effect waning was already captured was 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 the 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. The committee asked to see exploration of treatment-effect waning included in the company modelling, either implicitly within the OS curve selection or using an explicit modelling

mechanism. In its response to the draft guidance consultation, the company reiterated that it did not consider it appropriate to model treatment-effect waning. This was because the smoothed hazard ratio from PAPILLON did not indicate any treatment waning within the 28-month period. It also noted that the median OS from the key trial in TA850 was 23 months, so it considered it reasonable to expect a greater OS in this setting. So the company did not provide the requested treatment waning scenarios.

Conclusions on modelling of OS

3.11 At the first committee meeting, 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 in which 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 of 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 PAPILLON (for example, through a period of managed access, if the criteria for managed access were fulfilled).

  During the draft guidance consultation, the company provided scenarios exploring:

- fitting the same parametric curves to both arms of the model (gamma,

Weibull, log-logistic)

- the implied hazard ratios for long-term OS and alternate methods for modelling the longer-term relative treatment effect (fixing the hazard ratio at the last observation and applying the ratio of PFS to OS from chemotherapy to amivantamab PFS from the end of the observed data).

  But the company did not provide the requested curve exploring a fit between Weibull and Gompertz for amivantamab–chemotherapy OS. The NICE technical team generated curves which explored a 50:50 split between Weibull and Gompertz and a 75:25 split between Weibull and Gompertz for the second committee meeting. At this meeting, clinical experts noted that the EAG's clinical expert's 10-year survival estimates for amivantamab–chemotherapy seemed pessimistic. They thought that around 50% survival at 3 years and 30% survival at 5 years would be appropriate. For chemotherapy, the clinical experts agreed with the EAG's clinical expert's opinion, noting that they would expect very low 10-year survival. This is because exon20ins mutation-positive disease has a high propensity to spread to the brain and chemotherapy has very limited benefit in this population. The committee acknowledged the various clinical expert estimates. But, it recalled that the Decision Support Unit's Technical Support Document 14 required strong evidence to fit different curves to both arms of a model (see section 3.9). It noted that the differing mechanisms of action could provide some justification but still thought that it had not seen any strong evidence to support using different distributions. So, the committee concluded that the same distribution should be used to extrapolate both arms of the model. It noted that the Weibull curve was deemed most appropriate by the company's advisory board and was broadly in line with, if slightly above, the clinical expert estimates from the second meeting. The committee thought that the immaturity of the OS data was a key uncertainty. It concluded that the Weibull curve should be used to extrapolate OS for chemotherapy. But it considered that the preferred extrapolation for amivantamab–chemotherapy was highly uncertain. The committee recalled it had seen scenarios exploring extrapolations between the Weibull and Gompertz curves. It noted that of all the distributions it had seen, the Weibull, and Weibull-Gompertz 75:25 and 50:50 could all be plausible. It noted there were big differences between the survival estimates obtained between these extrapolations and between the cost-effectiveness estimates produced. The

committee concluded that further data from the PAPILLON trial during a period of managed access might allow some of the uncertainty to be resolved and allow it to identify the most plausible distribution.

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 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 amivantamab's treatment duration. 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 PAPILLON 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 3.7). At the first committee meeting the committee 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. At draft guidance consultation, the company provided a scenario with progression-free-disease health-state utility values that matched those used in TA850. It considered that using utility values from other appraisals in NSCLC was not appropriate. It explained that this was because they are not specific to people with ex20ins mutations and involve different interventions and prior lines of therapy. But it added that TA850 may be relevant. The committee thought that the results from this scenario did not show a large effect on the overall cost-effectiveness results. The committee concluded that the utility values from

PAPILLON were appropriate for decision making.

Costs

Administration costs for amivantamab

3.14 Amivantamab incurs costs to cover its administration by intravenous infusion. Various administration costs are available to represent different complexities of intravenous infusion. There are also costs for the different lengths of time spent in the chemotherapy day centre when starting treatment with amivantamab–chemotherapy and administration in the maintenance phase. These costs are represented by Healthcare Resource Group (HRG) codes. The committee recalled that in the NICE technology appraisal guidance on amivantamab with lazertinib for untreated EGFR mutation-positive advanced NSCLC (from here, TA1122), the company had modelled inappropriate HRG codes in its base case for the administration of amivantamab. In its base case the company applied the HRG code SB12Z, which accounts for 30 to 60 minutes chair time for amivantamab with pemetrexed (post carboplatin). The summary of product characteristics for amivantamab suggests an infusion time of 2 hours or more. In TA1122, the CDF lead gave HRG codes verified by NHS England clinical pharmacists. The committee in that appraisal (also committee D) concluded that:

- day-case costs should be used for decision making instead of outpatient costs
- the NHS reference costs should be used
- the following HRG codes should be used:
  - SB14Z, for day 1 doses in the induction period
  - SB15Z, for day 2 and day 8 doses in the induction period
  - SB13Z, for amivantamab after the induction period.

At the second committee meeting the company explained that its draft guidance response had been submitted before the conclusions of TA1122

had been published. Because of this, it had not been able to update the modelling but agreed that the administration costs concluded on in TA1122 were appropriate for decision making. The company also stated that the approach to modelling pemetrexed in the chemotherapy arm should reflect that used in the NICE technology appraisal guidance on osimertinib with pemetrexed for untreated EGFR mutation-positive NSCLC (from here, TA1060). That is, to use an average of the SB13Z and SB15Z codes. The CDF lead noted that the pemetrexed infusion time was only 10 minutes but also acknowledged that in daily practice people might be in the day centre for longer. As such, the SB13Z or SB15Z codes could realistically reflect the cost to the NHS. The committee concluded that:

- the administration costs for amivantamab–chemotherapy should be modelled in line with TA1122
- the administration costs for pemetrexed maintenance should be modelled in line with TA1060 (an average of SB13Z and SB15Z).

Adverse events

3.15 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 PAPILLON 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. After the draft guidance consultation the company updated its base-case modelling to include the costs for only the most severe adverse events, in line with the committee's preferred assumptions.

Dosing in the model

3.16 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's base case. In its updated base case the company incorporated the committee's preferred assumptions regarding dosing frequency, which resulted in similar cost-effectiveness results.

Vial sharing

3.17 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 composed 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 them. 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. At draft guidance consultation the company confirmed there was no vial sharing allowed in its base-case model. It explained that any fractions present in the model were a result of the different numbers of vials offered to a cohort of people of different weights who would have different doses. It explained that the model represents a cohort with only full vials modelled across the cohort. The committee acknowledged this explanation and was satisfied that the model did not include vial sharing.

Dose skipping

3.18 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 reduce 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 3.19). The committee concluded that it wanted 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 also wanted to see a scenario that explores modelling no dose skipping across all treatments in both arms and a scenario that models dose skipping to be equal across all treatments and arms. At draft guidance consultation the company provided 2 of the requested scenarios exploring dose skipping, but it did not feel that modelling no dose skipping was appropriate. The committee noted that these scenarios had very limited effect on the cost-effectiveness estimates and concluded that the

company's modelling of dose skipping was appropriate for decision making.

Severity

3.19 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 the mental health of 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.

Cost-effectiveness estimates

Committee's preferred assumptions

3.20 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 3.3)
- use Weibull extrapolations of TTDD for both components of amivantamab–chemotherapy (see section 3.12)

- use Weibull extrapolations for OS for chemotherapy alone (see section 3.11)
- 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 3.15)
- use administration costs based on assumptions and HRG codes accepted in TA1122 and TA1060 (see section 3.14).

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

- the immaturity of the OS data from the PAPILLON trial (see section 3.4)
- the extrapolations of OS in the amivantamab–chemotherapy arm (see section 3.8).

Acceptable ICER and most plausible ICER

3.21 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £25,000 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 took into account the lack of targeted treatment options for this mutation and the poor survival with chemotherapy alone. 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 3.9). It concluded that an acceptable ICER threshold for a recommendation for routine commissioning would be towards the lower end of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained). But it concluded that with the available data there was too much uncertainty around OS with amivantamab–chemotherapy (see section 3.11) to determine the committee's preferred ICER. So, it could not establish whether it was within the range usually considered a cost-effective use of resources even when the severity modifier was applied. So, amivantamab–chemotherapy could not be recommended for routine commissioning.

Managed access

3.22 The committee concluded that amivantamab–chemotherapy could not be recommended for routine use in the NHS. So, it then considered if it could be recommended for use during a managed access period for treating ex20ins mutation-positive advanced NSCLC. The committee considered whether a recommendation with managed access could be made and discussed:

- If there is plausible potential to satisfy the criteria for routine use. The committee concluded that amivantamab–chemotherapy did have the plausible potential to be cost effective in routine use.
- If the remaining key uncertainties, including the immaturity of OS data (see section 3.4) and the OS extrapolations in both arms (see section 3.8), could be addressed by evidence from managed access. The committee concluded that new evidence from the ongoing PAPILLON trial and real-world evidence from the Systemic Anti-Cancer Therapy (SACT) database collected from people having treatment with amivantamab–chemotherapy in the NHS as detailed in the company's managed access proposal could address some of this uncertainty.

  So, the committee concluded that amivantamab–chemotherapy met the criteria for a recommendation with managed access. It recommended amivantamab–chemotherapy as an option for ex20ins mutation-positive advanced NSCLC if the conditions in the managed access agreement are followed. When the guidance is next reviewed the company should use the committee's preferred assumptions (unless new evidence indicates otherwise) as set out in section 3.20.

Other factors

Equality

3.23 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, trans men and non-binary people registered female at birth. 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

3.24 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

3.25 The committee recalled the uncertainties in the evidence for amivantamab–chemotherapy and the other factors involved in its decision making. It noted that it could not establish a most plausible ICER but had seen a range of plausible ICERs. Taking the uncertainties into account, the range of ICERs based on preferred assumptions was higher than what NICE normally considers a cost-effective use of NHS resources. So, it concluded that amivantamab–chemotherapy could not be recommended for routine use. But the committee acknowledged that, despite substantial uncertainty, amivantamab–chemotherapy is likely to offer improved clinical outcomes for some people in clinical practice. The committee thought that amivantamab–chemotherapy does have plausible potential to be cost effective, and that some of the uncertainties may be resolved with further data collection (see section 3.22). So, amivantamab with carboplatin and pemetrexed can be used with managed access for treating advanced NSCLC with activating epidermal growth factor receptor ex20ins mutations.

4 Implementation

4.1 When NICE recommends a treatment as an option for use during the managed access period, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has untreated advanced non-small-cell lung cancer with activating EGFR exon 20 insertion mutations and the healthcare professional responsible for their care thinks that amivantamab with carboplatin and pemetrexed is the right treatment, it should be available for use, in line with NICE's recommendations and the criteria in the managed access agreement.

4.2 Drugs with a draft recommendation for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. See 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. 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 the drug or treatment, or other technology, is approved for use during the managed access period. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, for use during the managed access period, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

Megan John
Chair, technology appraisal committee D

Vice chair

Raju Reddy
Vice chair, technology appraisal committee D

NICE project team

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

Emma Bajela
Technical lead

Samuel Slayen
Technical adviser

Greg O'Toole and Jennifer Upton
Project managers

Ian Watson
Associate director

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