NICE National Institute for Health and Care Excellence

NICE guidance

Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy

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 is not recommended, within its marketing authorisation, for treating locally advanced or metastatic non-small-cell lung cancer (NSCLC) after platinum-based chemotherapy in adults whose tumours have epidermal growth factor receptor (EGFR) exon 20 insertion mutations.

1.2 This recommendation is not intended to affect treatment with amivantamab 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 clinician consider it appropriate to stop.

Why the committee made these recommendations

Current treatment for locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations after platinum-based chemotherapy can include platinum-based chemotherapy again, immunotherapies, and docetaxel with or without nintedanib.

Indirect comparisons using real-world evidence on immunotherapies, platinum-based chemotherapy, and docetaxel with or without nintedanib, suggest that amivantamab increases how long people live, and how long they have before their cancer gets worse. But this is uncertain because there is no direct comparison, and because of the way the real-world evidence was chosen and presented. So, the cost-effectiveness estimates are also uncertain.

Amivantamab meets NICE's criteria to be considered a life-extending treatment at the end of life. But, even taking this into account, the most plausible cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources. So, amivantamab is not recommended for routine use. Collecting more data would not resolve the uncertainties, so it is not recommended for use in the Cancer Drugs Fund.

2 Information about amivantamab

Marketing authorisation indication

2.1 Amivantamab (Rybrevant, Janssen) is indicated for the 'treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, whose disease has progressed on or after platinum-based chemotherapy'.

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 50 mg vial (excluding VAT; BNF online, accessed October 2022).

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

3 Committee discussion

The appraisal committee considered evidence submitted by Janssen, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical management

People with EGFR exon 20 insertion mutation-positive advanced NSCLC will welcome a new treatment option that is targeted and well tolerated

3.1 The clinical experts explained that epidermal growth factor receptor (EGFR) exon 20 insertion mutations are rare and only seen in a few people with non-small-cell lung cancer (NSCLC). Compared with other EGFR mutations, they are more common in women, people from an East Asian family background and people who do not smoke. Exon 20 insertion mutations are also associated with poorer outcomes than other EGFR mutations. The patient experts explained that, in people with exon 20 insertion mutation-positive NSCLC, the condition has a significant effect on their quality of life, and that of their families and carers. The patient experts highlighted the need for targeted treatments that have a lower toxicity and improved survival outcomes than current treatments. The clinical experts explained that there is no standard treatment for exon 20 insertion mutation-positive NSCLC (see section 3.2) and no treatment options that specifically target the mutations. The committee concluded that there is an unmet need for more effective treatment options that specifically target the exon 20 insertion mutations.

Comparators

EGFR tyrosine kinase inhibitors are not appropriate comparators

3.2 The clinical experts explained that there is no standard treatment pathway for people with exon 20 insertion mutation-positive NSCLC. Treatment choice depends on stage of disease, PD-L1 status, and patient and clinician preference. Treatment options can include docetaxel with or without nintedanib, immunotherapy (such as atezolizumab, nivolumab or pembrolizumab) or best supportive care. Because there is no established standard treatment pathway, the company included a blended comparator arm in its submission. The company's original base case included immunotherapy treatments, EGFR tyrosine kinase inhibitors (TKIs), platinum-based chemotherapy and non-platinum-based chemotherapy. The company explained that its choice of blended comparators reflected the treatments used in 2 real-world evidence sources:

- a US cohort that included pooled data from Flatiron Health Spotlight, ConcertAI and COTA data sources

- routinely collected population-level data from the National Cancer Registration and Analysis Service (NCRAS) in England.

The clinical experts explained that EGFR TKIs have limited efficacy when there are exon 20 insertion mutations. Because of this, they are rarely used in this population and are unlikely to represent standard care in the NHS. The ERG noted that including an ineffective treatment option (that is, EGFR TKIs) in the blended comparator arm may have led to overestimating the comparative efficacy of amivantamab. But scenario analyses excluding EGFR TKIs from the blended comparator arm had a limited effect on overall survival, progression-free survival and time to next treatment estimates. The committee noted that the NCRAS data included use of EGFR TKIs. But this was from a very small population and so may not have reflected the broader NHS population (the population size is considered confidential by the company and cannot be reported here). The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) stated that EGFR-TKI use is not considered routine practice in the NHS. Considering the limitations of the available real-world evidence from England and the input from the clinical experts, the committee concluded that EGFR TKIs were not an appropriate comparator. After consultation, the company's updated base case removed EGFR TKIs as a comparator.

Using a blended comparator arm increases uncertainty

3.3 The company's approach compared amivantamab with the average clinical effectiveness across all treatments in a blended comparator arm. The company explained that there was no robust way to define standard care (see section 3.2), making it unfeasible to identify a single treatment that would be displaced by amivantamab. So, the most relevant comparator can only be accurately reflected by a blended comparator group, meaning that a fully incremental analysis is not possible. The committee noted that the company's approach meant that amivantamab was compared with the average clinical effectiveness across all treatments in the blended comparator group. It concluded that this substantially increased the uncertainty of the comparator-arm evidence.

Clinical evidence

Amivantamab is clinically effective, but the size of this benefit compared with current treatments is difficult to establish

3.4 The main evidence for amivantamab came from CHRYSALIS, a single-arm, open-label, phase 1b trial. Results from March 2021 showed a median progression-free survival of 6.74 months (95% confidence interval [CI] 5.45 to 9.66) and a median overall survival of 22.77 months (95% CI 17.48 to not estimated). Overall survival results from March 2022 were also available but are considered confidential by the company and cannot be reported here. The clinical experts considered these results to be clinically meaningful. The ERG highlighted that a smaller population (n=114) was used for the CHRYSALIS efficacy analyses than for the safety population (n=153) analyses. It noted that this may have exaggerated the treatment benefits of amivantamab. During technical engagement, the company explained that a larger safety population was used to gather safety data from as large a group as possible. The company also submitted safety analyses for the smaller (n=114) population to show that similar adverse events were reported in both populations. The company said that it did not provide updated efficacy analyses from the larger (n=153) population. This was because not all people in the safety population had had at least 3 disease assessments, so were not eligible to be included in the efficacy analysis set. Overall, the committee concluded that CHRYSALIS showed clinically meaningful results for amivantamab. But it thought that the lack of direct comparative evidence meant the size of this benefit compared with current treatments was difficult to establish.

The approach used to identify real-world evidence for the blended comparator arm may not be robust and is associated with uncertainty

3.5 There was no comparator in CHRYSALIS (see section 3.4), and no relevant trials were identified in a systematic literature review comparing amivantamab with the relevant comparators. So, the company did an adjusted treatment comparison comparing amivantamab with a blended

comparator (see section 3.2) using real-world evidence. Because exon 20 insertion mutations affect the outcomes of people with NSCLC, the real-world evidence included was limited to people with NSCLC with these mutations. Two sources were identified: pooled US real-world evidence (used in the company's base case) and evidence from the NCRAS in England (used in scenario analyses). The company explained that the US real-world evidence was chosen for the base case because:

- of its substantially larger sample size
- clinical experts considered the evidence to be generalisable to clinical practice in England (sample sizes are considered confidential by the company and so cannot be reported here).

In addition, the US real-world evidence included data on progression-free survival, time to next treatment, overall survival and overall response rate outcomes. In contrast, the NCRAS evidence only provided data on time to next treatment and overall survival. The ERG agreed that, because of the larger sample size and because it included data on more outcomes, it was appropriate to use the US real-world evidence in the base case. But the ERG noted that the company did not provide a full, justified rationale for its choice of real-world evidence sources. Also, it was concerned that the real-world evidence sources had not been reviewed systematically. So, the company may have missed relevant sources. The committee concluded that, of the 2 data sources included, the pooled US real-world evidence may have been the best source of evidence. But it was concerned that the company had not provided enough information on how the sources were chosen from the pool of all potential data sources. It concluded that the approach to identifying real-world evidence to use in the blended comparator arm may not have been robust and was associated with uncertainty.

The way the company has used real-world evidence is associated with some areas of uncertainty and may bias the results

3.6 The committee noted that, in general, there are several key differences between real-world evidence and clinical trials. Specific to this appraisal, efficacy and safety endpoints were followed up regularly in CHRYSALIS, but there were no scheduled visits in routine care in the real-world

evidence. Also, treatment monitoring and follow up on treatment adherence may have differed between CHRYSALIS and routine care. This would have affected the efficacy and safety results. Progressed disease is less accurately captured in retrospective studies (such as from the US real-world evidence) than in prospective studies in which people generally have closer monitoring and specific criteria are applied. The committee considered that, despite these known limitations with real-world evidence, it can be valuable for resolving gaps in knowledge when best-practice methods are applied, such as those described in the NICE real-world evidence framework. It also acknowledged the rarity of exon 20 insertion mutation-positive NSCLC and the lack of direct comparative efficacy data. This meant that the real-world evidence may have been the best available source of evidence for the comparator arm. At the first committee meeting, the committee was concerned that the company had not provided enough information on data provenance, accuracy and suitability, and had not explored the effect of missing data. To address these concerns, the company provided additional information on the real-world evidence sources used in the model. It provided a completed DataSAT real-world evidence checklist and did sensitivity analyses to assess the effect of missing data. Outcomes for each of the 3 US real-world evidence sources were provided individually, including the hazard ratios for overall survival, progression-free survival and time to next treatment. The ERG noted that the pooled-analysis results were conservative when compared with the individual results of the sensitivity analyses and were generally consistent across the 3 datasets. The company also provided further information on the eligibility criteria and baseline characteristics across the 3 US real-world evidence sources. The ERG noted some differences in the care settings and baseline characteristics between data sources. It also noted some potential selection bias in the eligibility criteria. The committee acknowledged the additional information provided by the company and agreed that it had reduced some areas of uncertainty, such as the effect of missing data. But there were some remaining gaps in the information and analyses provided by the company. Overall, the committee concluded that some areas of uncertainty remained and some of this uncertainty was currently unresolvable. It noted that the level of uncertainty could have been reduced if the company had shown that a systematic approach had been taken to selecting real-world evidence sources. The committee

concluded that this uncertainty may have biased the results in the modelling.

Indirect treatment comparison

The company's indirect comparison is suitable for decision making, but using this is associated with uncertainty

3.7 To account for differences in populations between CHRYSALIS and the real-world evidence sources, the company adjusted for key prognostic variables and baseline characteristics. These were identified before the analysis by a systematic literature review and validated by clinical experts. For the US real-world evidence, data was adjusted using inverse probability weighting (IPW). The company explained that IPW was not suitable for the NCRAS evidence because of its small sample size, so it used covariate adjustment instead. Because of data availability, 8 covariates could be adjusted for in the US real-world evidence, and 7 could be adjusted for in the NCRAS evidence. The covariates adjusted for are considered confidential by the company and so cannot be described here. The ERG explained that the company's methods of adjustment appeared robust, but were limited by the covariates chosen for adjustment. Because of this, there may have been residual confounding. Also, although using IPW appeared acceptable, alternative forms of adjustment such as propensity score matching could have been applied to the US real-world evidence. The ERG noted that propensity score matching did not improve the balance between covariates compared with the IPW method. The committee concluded that the indirect comparison using IPW for adjustment was suitable for decision making. But it also noted that the indirect treatment comparison was associated with uncertainty. This was because of the potential residual confounding noted by the ERG, and the potential evidence issues associated with the blended comparator data (see section 3.5).

Results from the indirect treatment comparison show statistically significant improvements with amivantamab, but are uncertain

3.8 The indirect comparisons showed statistically significant improvements in overall survival and progression-free survival with amivantamab compared with the blended comparator arm when the US real-world evidence was used. The committee noted that scenario analyses using the NCRAS evidence for the comparator arm increased the treatment effect of amivantamab. The exact results of the indirect treatment comparison are considered confidential by the company and so cannot be reported here. The ERG explained that the results of the analyses were associated with uncertainties. These included that they were limited by the number of covariates included for adjustment and that there were issues with the company's approach to comparing clinical trial and real-world data (see section 3.7). Overall, the committee concluded that the indirect treatment comparison showed statistically significant improvements with amivantamab compared with standard care, but that the exact level of improvement was uncertain.

Utility values in the economic model

It is acceptable to use utility values from past appraisals

3.9 In its base case, the company took utility values for the progression-free survival state (0.713) and the post-progression state (0.569) from NICE's technology appraisal guidance on nivolumab for advanced NSCLC after chemotherapy. The company explained that it had some data on quality of life from CHRYSALIS. But it did not use this in the model because the number of EQ-5D-5L responses from CHRYSALIS was low at time of data cut-off. It also explained that the clinical experts it consulted considered the population in NICE's technology appraisal guidance on nivolumab was appropriate to use in place of the amivantamab population. The company explained that EQ-5D-5L data from CHRYSALIS was only collected for a limited number of people, and only for the progression-free survival state. The committee noted that there may have been differences between the CHRYSALIS population and the population in

NICE's technology appraisal guidance on nivolumab. It also noted that using robust quality-of-life data from CHRYSALIS would have been preferrable, but that it would accept the company's preferred utility values instead. Overall, the committee concluded that, because of the limitations of the available CHRYSALIS EQ-5D-5L data, the company's base-case approach to utilities was acceptable.

Assumptions in the economic model

The company's model structure is suitable for decision making

3.10 The company used a partitioned survival model with 3 mutually exclusive health states: progression-free survival, progressed disease and death. This approach allowed the company to use outcome data from the adjusted treatment comparison. It also enabled the clinical benefits of amivantamab to be captured by reflecting the increased proportion of people expected to be alive or progression free over time. The committee agreed that the model structure was suitable for decision making.

It is appropriate to use parametric modelling for survival in the blended comparator arm

3.11 The company used Kaplan–Meier curves directly to represent survival outcomes for the blended comparator arm, and argued that this was appropriate because of the maturity of the data. The ERG explained that because follow up occurs at specific intervals, Kaplan–Meier curves have a 'stepped' nature. This means that at each measurement, all people who have died or whose condition has progressed will leave the health state at once. The ERG explained that this may introduce bias into the modelling of survival outcomes for the blended comparator arm, and considered it more appropriate to use parametric modelling. The ERG's base case used a Weibull curve to represent overall survival and a log-logistic curve to represent progression-free survival in the blended comparator arm. At technical engagement, the company did scenario analyses using parametric modelling to represent the blended comparator arm. The company explained that these scenarios had a

minimal effect on the model results. NICE Decision Support Unit Technical Support Document 14 states 'parametric models are likely to represent the preferred method for incorporating survival data into health economic models in the majority of cases'. Based on this, the committee concluded that it was more appropriate to use parametric modelling to represent survival in the blended comparator arm.

It is appropriate to base time on treatment on time to treatment discontinuation data from CHRYSALIS

3.12 The company's base case modelled time to treatment discontinuation (TTD) based on the duration of progression-free survival. The company explained that this was because people having amivantamab would be expected to stop treatment at progression, as per the marketing authorisation. It also explained that, because of closer monitoring, progression during CHRYSALIS was likely to have been detected earlier than it would be in clinical practice. This could mean that the base-case approach underestimated the benefits of amivantamab. The committee noted that the costs may also have been underestimated compared with clinical practice. The company noted that TTD data was not available from the real-world evidence that was used for the comparator arm. Because of this, it considered that using TTD for amivantamab, but progression-free survival for the comparator arm, would be a conservative approach. The ERG noted that treatment duration with amivantamab in CHRYSALIS was longer than progression-free survival. So, it considered that the company's approach removed the costs of amivantamab used after progression from the modelling without removing any benefits from continuing to use it. One of the clinical experts suggested that people may continue having amivantamab after radiological disease progression if the clinician thinks they are still benefitting from it. This would be for about 2 to 3 months, although this will vary widely. The committee noted this was consistent with the difference between median TTD and median progression-free survival from the modelling. The Cancer Drugs Fund lead said that there was justification for using a different approach between the amivantamab and comparator arms. This is because chemotherapy has a different risk-benefit profile to amivantamab, so clinicians may apply a different threshold for when to stop treatment and may stop closer to disease

progression. The committee considered NICE's recent technology appraisals in NSCLC (such as NICE's technology appraisal guidance on tepotinib for treating advanced NSCLC). It noted that most had used TTD data, rather than progression-free survival. Overall, the committee considered that:

- the duration of modelled costs and benefits of amivantamab should have been aligned
- amivantamab's use in the trial reflected its likely use in clinical practice
- it may be more likely that, in clinical practice, the comparator treatments are stopped on disease progression.

So, the committee concluded that using TTD data from CHRYSALIS was appropriate for estimating the time on treatment.

It is appropriate to extrapolate the TTD data using the Gompertz curve

3.13 The ERG explained that its approach was to use the CHRYSALIS TTD data, with an exponential curve applied to model time on treatment. This was because the exponential curve had the best statistical fit. During consultation, the company said that statistical fit was not the only consideration when selecting the most appropriate curve. It noted that the Gompertz curve also had a good fit to the data, especially at the start of the Kaplan–Meier curve where there is more patient data available. It added that the Gompertz curve was more aligned with the hazard curve for TTD, where hazards decreased initially before increasing from around month 5. The company provided a scenario analysis using the CHRYSALIS TTD data, with the Gompertz curve applied. The committee recalled its discussion from the first committee meeting, when it thought that the exponential curve was the more appropriate curve to select. Taking into consideration the additional information provided by the company, the committee acknowledged that both Gompertz and exponential curves had good visual fits to the CHRYSALIS data. It also noted the importance of considering how the hazard function aligned with the trial data. It concluded that selecting the Gompertz curve for modelling the time to TTD was appropriate for

estimating the time on treatment in the base case. But it noted that scenario analyses using the exponential curve should also be considered in its decision making.

It is appropriate to exclude treatment-effect waning from the modelling

3.14 The company's base case assumed that the amivantamab treatment effect is continued throughout the time horizon. The company said that people with exon 20 insertion mutation-positive NSCLC have poor prognosis with a short life expectancy. So, treatment-effect waning is unlikely to be seen. Also, if there is treatment waning, it would be highly unlikely to have a clinically meaningful effect because of the short time periods over which it could occur. The company highlighted that overall survival data showed that treatment benefit was maintained at follow up. Also, clinician input confirmed that outcomes at 2 years and 5 years were aligned with their expectations. The ERG considered that there was limited evidence to support a lifelong treatment effect of amivantamab. At technical engagement, the company provided a scenario in which it applied linear treatment waning from 3 years after amivantamab treatment was stopped until efficacy was equal to that of the blended comparator arm. The company explained that this was consistent with the approach taken in NICE's technology appraisal guidance on nivolumab. One of the clinical experts considered amivantamab's treatment effect is likely to be somewhere between that of existing oral EGFR TKIs (which provide little benefit after progression) and immunotherapies (which may provide long-term benefit). The committee noted that waning has typically been applied in previous appraisals for immunotherapies when stopping rules have been applied. It also noted the limited impact of the treatment-effect waning scenario done by the company. Based on this, the committee concluded that it was appropriate to exclude treatment-effect waning from the modelling.

Costs in the economic model

Exon 20 insertion mutation testing costs should be included in

the economic model

3.15 In line with section 5.9.1 of NICE's guide to the methods of technology appraisal, the NICE scope for amivantamab states that the 'costs associated with diagnostic testing in people with NSCLC who would not otherwise have been tested should be included' in modelling. The company did not include exon 20 insertion mutation testing in its base case. It explained that these costs were expected to be included in routine NHS testing. The Cancer Drugs Fund lead explained that the gold standard for detecting exon 20 insertion mutations is next generation sequencing. But the availability of this varies across the NHS. Many treatment centres use polymerase chain reaction (PCR) instead, which is expected to identify about 50% of people with exon 20 insertion mutation-positive NSCLC. Because of this, using amivantamab (or other exon 20 insertion mutation targeted treatments) in the NHS would mean switching from current local PCR testing to next generation sequencing at Genomic Laboratory Hubs. This could result in a 50% increase in detecting exon 20 insertion mutation-positive NSCLC. But the Cancer Drugs Fund lead suggested that this increase may only be 33% because there is already some next generation sequencing testing being done. They explained that it would be appropriate to add a testing cost of £550 per person with exon 20 insertion mutation-positive NSCLC. This cost would account for a 2% incidence of exon 20 insertion mutations and the standard cost of adding a mutation test onto a next generation sequencing panel of £34. At the request of the committee, the company provided a scenario that included the mutation testing costs. The committee concluded that exon 20 insertion costs should be included in the amivantamab arm of the economic model.

End of life

Amivantamab meets the criteria to be considered a life-extending treatment at the end of life

3.16 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company proposed that amivantamab met the

criteria for being a life-extending treatment for people with short life expectancy (normally less than 24 months). Both the company's base case and the model using the committee's preferred assumptions predicted a mean and median overall survival with current standard care of substantially less than 24 months (the exact values are considered confidential by the company and cannot be reported here). Having considered the survival data from the US real-world evidence, the committee concluded that amivantamab met the end of life criterion for short life expectancy. The company's and ERG's modelling suggested that amivantamab was associated with a gain in overall survival of substantially more than 3 months (the exact values are considered confidential by the company and cannot be reported here). The committee noted the uncertainty in the real-world evidence and model estimates previously discussed (see section 3.6, section 3.7 and section 3.8). It concluded that, despite the uncertainty, amivantamab met both of NICE's criteria to be considered a life-extending treatment at the end of life.

Cost-effectiveness results

Because of the uncertainty, an acceptable ICER would be below £50,000 per QALY gained

3.17 NICE's guide to the methods of technology appraisal notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. It recalled its conclusion from the first meeting that an acceptable ICER would be around £20,000 per QALY gained. But the committee also agreed that the end of life criteria applied to amivantamab. When the end of life weighting was applied, the committee said that the maximum acceptable ICER would be substantially less than £50,000 per QALY gained. The committee acknowledged that, since the first committee meeting, the company had attempted to reduce the uncertainty around the use and selection of

real-world evidence. But it noted the high level of outstanding uncertainty in the company's model, specifically:

- the lack of direct comparative evidence
- the effect of evidence selection issues because of the lack of systematic identification of real-world evidence sources
- the potential for residual confounding in the indirect treatment comparison
- the potential effect of selection bias because of differences in the eligibility criteria for the real-world evidence sources
- the lack of a fully incremental analysis because of using a blended comparator.

The committee also took into account the lack of targeted treatment options available for this specific mutation and the emotional burden on people with EGFR exon 20 insertion mutation-positive NSCLC and their caregivers. It also heard that people with lung cancer may experience stigma, which could delay them seeking treatment. It noted the rarity of EGFR exon 20 insertion mutation-positive NSCLC and the difficulties this can create in generating evidence. The fact that amivantamab met the end of life criteria in this indication was also considered. Taking these factors into account and the uncertainty that remained, the committee concluded that an acceptable ICER would need to be below the maximum acceptable ICER for end of life treatments (£50,000 per QALY gained).

The most plausible ICER is above £50,000 per QALY gained

3.18 The company's updated base-case deterministic and probabilistic ICERs for amivantamab compared with the blended comparator arm were around £50,000 per QALY gained. This was when confidential commercial arrangements for amivantamab and all the comparators were included, so the exact ICERs cannot be reported here. The company's base case included the following assumptions, which were preferred by the committee:

- excluding EGFR TKIs from the blended comparator arm (see section 3.2)
- using the IPW method for the indirect treatment comparison (see section 3.7)

- using utility values from NICE's technology appraisal guidance on nivolumab (see section 3.9)
- using parametric modelling to represent survival in the blended comparator arm (see section 3.11)
- excluding treatment waning (see section 3.14).

But, for modelling time on treatment, the company's updated base case used the progression-free survival data from CHRYSALIS (see section 3.12). This differed from the committee's preferred approach, which was to use TTD data with the Gompertz curve applied (see section 3.13). The committee began by considering scenarios that included the additional costs for EGFR exon 20 insertion mutation testing (see section 3.15). It noted that these ICERs were all above £50,000 per QALY gained. So, both the company's and the ERG's preferred methods for modelling time on treatment gave ICERs that were above the maximum possible ICER once testing costs were included. But the committee's preferred approach increased the ICER substantially. The committee also noted the remaining uncertainty in the cost-effectiveness estimates and concluded that it could not recommend amivantamab for routine use.

Cancer Drugs Fund

Amivantamab does not meet the criteria to be included in the Cancer Drugs Fund

3.19 Having concluded that amivantamab could not be recommended for routine use, the committee then considered whether it could be recommended for treating exon 20 insertion mutation-positive NSCLC in the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The company thought that the Cancer Drugs Fund would allow observational data collection on baseline characteristics, overall survival, TTD and subsequent therapies through the Systemic Anti-Cancer Therapy dataset. It also suggested that the Cancer Drugs Fund would allow data from NCRAS to be linked to other datasets, to increase the sample size

of the real-world evidence available from NHS clinical practice. The company suggested that this may resolve the uncertainties with the US real-world evidence. The committee recalled that the main uncertainties in this appraisal related to the limitations of the company's approach to existing real-world evidence (including the real-world evidence selection issues to identifying real-world evidence sources; see section 3.5). The Cancer Drugs Fund lead said that, because CHRYSALIS was mature, making amivantamab available in the Cancer Drugs Fund would not generate data that would resolve the main uncertainties. They suggested that it may be difficult to get relevant additional data from the NCRAS that would increase the sample size of the retrospective real-world evidence available from NHS clinical practice. The committee recalled that the most plausible ICER was above £50,000 per QALY gained and noted the remaining uncertainty around this ICER. The committee concluded that it is unlikely that Cancer Drugs Fund data collection would reduce the uncertainties and improve the cost-effectiveness estimate for amivantamab. So, amivantamab could not be recommended for use in the Cancer Drugs Fund.

Other factors

Amivantamab is innovative but all benefits are captured in the analysis

3.20 The committee considered amivantamab to be innovative because it represents a step-change in the treatment of exon 20 insertion mutation-positive NSCLC. The company considered that there were additional benefits of amivantamab that were not captured within the model. It suggested that improvements in the aspects of daily life most valued by people with lung cancer and their caregivers were not intrinsically captured in the QALY framework. These aspects include being able to maintain independence, 'feeling normal' and having hope for the future. The company also noted that EGFR-positive NSCLC is associated with significant stigma because of being associated with smoking behaviours. This is despite this population having a larger proportion of people who are never-smokers, relative to other lung cancers. This stigma can result in a delay in diagnosis, which places a higher value on treatments for

cancer at an advanced stage. The committee recognised that there is stigma associated with a lung cancer diagnosis and that the prognosis for people with EGFR-positive NSCLC is poor. It considered principle 9 of the principles that guide the development of NICE guidance and standards. This states that the committee should take into account that 'stigma may affect people's behaviour in a way that changes the effectiveness of an intervention and routine quality-of-life assessments may not capture the benefits of treatment'. No evidence of this was provided in this appraisal, nor of how treatment with amivantamab would relieve the stigma of a lung cancer diagnosis. It acknowledged the significant unmet need for these people because of a lack of targeted treatment options being available for this specific mutation. The committee also recognised the significant emotional burden that a diagnosis of EGFR-positive NSCLC has on both people with lung cancer and their caregivers. It thought that many of the benefits highlighted by the company, such as maintaining usual activities, would typically be captured with the EQ-5D tool that underpins the QALY calculations. It noted that the poor prognosis and lack of treatment options were reflected by the end of life weighting being applied (see section 3.16). The committee accepted that amivantamab provides important benefits for people with exon 20 insertion mutation-positive NSCLC. It considered the unmet need and the burden of stigma in its deliberations. But the committee did not consider that there were any additional benefits that had not been captured in the QALY calculations.

There are no equality issues relevant to the recommendations

3.21 The company explained that exon 20 insertion mutation NSCLC is associated with people who have never smoked and has a higher prevalence in people from an East Asian family background. It also noted that lung cancer is often associated with stigma, which may result in a delay in seeking diagnosis and treatments. This may mean initial treatment options are not effective. The company considered that this stigma may be greater in people who have never smoked and people with an East Asian family background. The committee appreciated that differences in prevalence cannot usually be resolved in a technology appraisal, although it can consider whether a specific equality issue has a significant impact on access to treatment. The committee noted that

there was no evidence suggesting an increase in stigma in people protected by equality legislation. Also, the recommendation for amivantamab is for the full population in the marketing authorisation. So, the committee agreed that its recommendation would not have a different effect on people protected by the equality legislation than on the wider population. The committee concluded that there were no equality issues relevant to the recommendations.

Conclusion

Amivantamab is not recommended

3.22 The committee concluded that amivantamab is not recommended for treating EGFR exon 20 insertion mutation-positive NSCLC after platinum-based chemotherapy. The committee considered the uncertainty and the range in the cost-effectiveness estimates. It noted that the most plausible ICER was above the range considered to be a cost-effective use of NHS resources when the end of life modifier was applied.

4 Appraisal committee members and NICE project team

Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

NICE project team

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

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Technical advisers

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Accreditation