NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Tarlatamab for extensive-stage small-cell lung cancer after 2 or more treatments

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

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

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

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

Issue date: Jan 2025

Note that this document is not NICE's final guidance on tarlatamab. The recommendations in section 1 may change after consultation.

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using tarlatamab in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 18 February 2025
- Second evaluation committee meeting: 3 June 2025
- Details of the evaluation committee are given in section 4

2 Recommendations

2.1 Tarlatamab is not recommended, within its marketing authorisation, for treating extensive-stage small-cell lung cancer in adults whose cancer has progressed after 2 or more lines of treatment, including platinum-based chemotherapy.

2.1 This recommendation is not intended to affect treatment with tarlatamab 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.

Why the committee made these recommendations

There are no approved treatments for extensive-stage small-cell lung cancer that has progressed after 2 or more lines of treatment, including platinum-based chemotherapy. So, people usually have chemotherapy again or best supportive care.

Clinical trial evidence suggests that tarlatamab increases how long people have before their cancer gets worse and how long they live. But, the extent of this benefit is uncertain because the trial did not compare tarlatamab with chemotherapy. It has been indirectly compared with chemotherapy but the results are uncertain.

Because of the uncertainties in the clinical evidence, the cost-effectiveness estimates are also uncertain. All the cost-effectiveness estimates are above the range that NICE considers an acceptable use of NHS resources. So, tarlatamab is not recommended.

3 Information about tarlatamab

Marketing authorisation indication

3.1 Tarlatamab is indicated for ‘the treatment of adult patients with extensive-stage small-cell lung cancer (ES-SCLC) with disease progression on or

after at least two prior lines of therapy including platinum-based chemotherapy'.

Dosage in the marketing authorisation

3.2 The dosage schedule is available in the summary of product characteristics for tarlatamab.

Price

3.3 The list price of tarlatamab is £955 per 1 mg vial or £9,550 per 10 mg vial (excluding VAT; company submission). The company has a commercial arrangement, which would have applied if tarlatamab had been recommended.

4 Committee discussion

The evaluation committee considered evidence submitted by Amgen, a review of this submission by the evidence assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

4.1 Small-cell lung cancer (SCLC) is an aggressive cancer that spreads rapidly. Extensive-stage (ES)-SCLC is cancer that has spread beyond a single radiotherapy field. This may be widely through the initial lung to the other lung or to nearby lymph nodes or other parts of the body. ES-SCLC accounts for up to 80% of all SCLC diagnoses. The clinical experts explained that the prognosis for people with ES-SCLC is poor, with a projected survival rate of around 9 months after starting treatment. There is a high relapse rate after the first treatment and people with SCLC have a lot of symptoms. A patient organisation submission highlighted that a diagnosis of SCLC is devastating. There is a large impact on quality of life for people with the condition and their family and carers, who would highly value a new treatment that provided even modest extensions to life. The

committee concluded that SCLC is a highly aggressive condition with a large quality-of-life impact.

Clinical management

Treatment pathway and comparators

4.2 The company positioned tarlatamab for treatment of ES-SCLC after progression on 2 or more lines of treatment. This was a narrower population than outlined in the NICE final scope, but was aligned with the marketing authorisation for tarlatamab. The clinical expert explained that there is no curative treatment for ES-SCLC. The main aim of treatment is to shrink the tumour, delay progression and improve quality of life. Most people with untreated SCLC have immunotherapy as recommended in NICE's technology appraisal guidance on atezolizumab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer. Alternatively, some people may have cisplatin-based combination treatment. People whose cancer progresses within 3 to 6 months of finishing first-line treatment may have cyclophosphamide with doxorubicin and vincristine (from now on, CAV) or topotecan (see NICE's technology appraisal guidance on topotecan for the treatment of relapsed small-cell lung cancer). People with a chemotherapy-free interval of over 6 months after finishing first-line treatment who then have disease progression may have their cancer re-challenged with platinum-combination chemotherapy (carboplatin or cisplatin with etoposide) or carboplatin alone. Radiotherapy may also be offered alongside systemic treatments. Clinical experts explained that there are no treatments approved for ES-SCLC that has progressed on 2 or more lines of treatment. They highlighted that, at this point, most people are extremely unwell and have an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or more. These people have best supportive care for symptom management. A small proportion of people with ES-SCLC after 2 or more lines of treatment are well enough for further systemic treatment. These people have the same chemotherapy treatments offered at second line. But this offers little

survival benefit over best supportive care because SCLC tumours are increasingly resistant to chemotherapy as the condition progresses. There were no patient experts able to attend the committee meeting. The clinical expert explained that, in their experience, people were aware that re-treatment with chemotherapy would only offer a few additional months of life but would be accompanied by toxicities and treatment burden. So, some people well enough for chemotherapy may choose best supportive care. The committee noted that tarlatamab can have serious side effects and that additional hospital visits are needed for monitoring (see section 3.6). This may affect whether people choose tarlatamab as a treatment option. The committee was aware that the clinical effectiveness and safety of tarlatamab had only been assessed in people with an ECOG performance status score of 0 or 1. The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) confirmed that NHS England would only commission tarlatamab in this group. The clinical expert also confirmed that clinicians would only consider tarlatamab as a treatment option in people with an ECOG performance status of 0 or 1. The committee concluded that:

- there is an unmet need for new treatments for ES--SCLC after progression on or after 2 or more previous lines of treatment
- tarlatamab would only be a treatment option for people with an ECOG performance status score of 0 or 1
- people who would choose best supportive care rather than chemotherapy would also be likely to choose best supportive care rather than tarlatamab.

So, the committee concluded that best supportive care is not a relevant comparator for tarlatamab and the only relevant comparator is chemotherapy.

Clinical effectiveness

DeLLphi-301 trial

4.3 The clinical evidence for tarlatamab came from the DeLLphi-301 trial, which is an ongoing, open-label, uncontrolled study. It included people with relapsed or refractory SCLC that had progressed or recurred after 1 platinum-based regimen and at least 1 other treatment. The clinical-effectiveness data for tarlatamab came from 99 people in the subgroup who had 10 mg of tarlatamab,. People had tarlatamab every 2 weeks, following a dose titration period. The primary outcome was the objective response rate (ORR). At the June 2023 data cut, the ORR was 40.4% (97.5% confidence interval [CI] 29.4 to 52.2). The median progression-free survival (PFS) was 4.9 months (95% CI 2.9 to 6.7 months) and the median overall survival (OS) was 14.3 months (95% CI 10.8 months, upper limit not estimable). The EAG noted that some people continued tarlatamab beyond progression, which is not permitted by the summary of product characteristics. Also, it was concerned about potential unblinding of the PFS assessment by blinded independent central review, for assessments done outside of the scheduled assessments. The committee noted that everyone in the DeLLphi-301 trial had an a ECOG performance status score of 0 or 1, which aligned with the expected population who would have tarlatamab in clinical practice (see section 3.2). There was no evidence directly comparing tarlatamab with chemotherapy and the follow-up times for PFS (confidential and cannot be reported here) and OS (10.6 months) were relatively short. The committee concluded that the DeLLphi-301 trial suggested tarlatamab could be clinically effective, but that the data was uncertain.

Indirect treatment comparison (ITC)

Company's ITC methodology

4.4 DeLLphi-301 did not compare tarlatamab with other treatments for ES-SCLC. So, the company did an ITC to establish the effectiveness of

tarlatamab compared with a range of chemotherapy treatments (38% CAV, 20% platinum chemotherapy with etoposide and 42% topotecan, from now on, standard care). Clinical-effectiveness data for standard care came from the UK Cancer Analysis Service (CAS) study. This was a retrospective, UK real-world evidence study that combined registry data from adults who had treatment for SCLC in the NHS in England. The company chose this study for the indirect treatment comparison because it was current and representative of people with ES-SCLC having treatment in the NHS and the treatments used. Because the company did not have individual patient data for the UK CAS study, it did a matching indirect treatment comparison (MAIC). The MAIC was unanchored because there was no comparator arm in DeLLphi-301 or in the UK CAS study. In the MAIC, it applied a weight to the baseline characteristics from DeLLphi-301 to balance covariates (variables that could affect the results) with those in the UK CAS study. The MAIC adjusted for sex, ECOG performance status score (0 or 1), presence of brain and liver metastases, chemotherapy-free interval, age and stage at diagnosis and time from diagnosis to line of treatment. The outcomes compared were OS and PFS. The committee noted that the UK CAS study did not collect data on PFS, so the company used time to treatment discontinuation (TTD) as a proxy for PFS for the standard care arm. Data from people who had tarlatamab after progression was censored from the OS and TTD analyses, at the point their cancer progressed. Compared with a range of standard care treatments, the results of the MAIC suggested that tarlatamab increased PFS (hazard ratio [HR] 0.184, 95% CI [0.100 to 0.340]) and OS (HR 0.367 [95% CI 0.202 to 0.667]). The committee concluded that the company's ITC suggested there are OS and PFS benefits for tarlatamab.

Uncertainty around the indirect comparison

4.5 The committee noted the inherent uncertainty in an unanchored MAIC. This is because MAICs are susceptible to large amounts of systematic error unless all prognostic variables and effect modifiers are accounted for

(as described in NICE Decision Support Unit's technical support document 18). The EAG was concerned that the company's effective sample size after matching was small. This suggested there was little overlap in population characteristics between the DeLLphi-301 and UK CAS studies and reduced confidence in the MAIC results. The EAG further noted that fewer people in the UK CAS study had had treatment with PD-L1 inhibitors than in the DeLLphi-301 study. This had not been adjusted for by the company and means that the UK CAS study may not be aligned with current UK practice, in which most people have atezolizumab (a PD-L1 inhibitor) at first line (see section 3.2). But, the clinical expert at the committee meeting explained that tarlatamab has a different mechanism of action to a PD-L1 inhibitor. So, there was no biological or clinical reason for cancer previously treated with a PD-L1 inhibitor to respond differently to tarlatamab than cancer not treated with a PD-L1 inhibitor. The EAG also highlighted a lack of consensus among the company's clinical experts as to whether age and sex were prognostic variables. But, the company had included these covariates in its base case because they were included in other published population adjustments for SCLC. The committee noted subgroup analyses from the DeLLphi-301 study that showed a difference in overall response rate by age. So, it agreed that the prognostic factors included in the company's base case were likely appropriate. But, the committee was concerned that the company had only matched the covariates using means, and not variances. It considered that that this approach did not fully capture the uncertainty in the analysis. It acknowledged that including variances in the adjustment would further decrease the effective sample size, but agreed that it would be helpful to see this analysis after consultation on the draft guidance. Given the small overlap in baseline characteristics between the studies, it also agreed that alternative methods to population adjustment should be explored, which may include either a simulated treatment comparison (STC) with G-computation, or multi-level network meta-regression (ML-NMR). It agreed that, although uncertainty would remain,

similar results from covariate adjustment methods for population adjustment may increase confidence in the company's base case MAIC. The committee concluded that the prognostic factors in the company's base-case MAIC were acceptable but the results were highly uncertain. The committee acknowledged that its suggested further analyses may not fully resolve the uncertainties. But, they would be informative and potentially support the company's estimated relative effectiveness of tarlatamab compared with standard care.

Adverse events and need for monitoring

4.6 Tarlatamab is associated with potentially serious side effects such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). In the DeLLphi-301 study, CRS was reported for 50% of people, and ICANS and associated neurological events were reported for 7% of people. The committee noted comments from the Cancer Drugs Fund lead, that a later data cut from DeLLphi-301 suggested that CRS occurs in the first few weeks of treatment and resolves reasonably quickly. It is generally low grade, but this can still need hospital admission. The committee was aware that this data cut was not available at the time of the company submission. So, it would welcome seeing all further available information on adverse events in response to consultation. The committee noted that strict monitoring requirements were included in the summary of product characteristics for tarlatamab. These include a hospital admission for starting treatment and the need to remain near to a treatment centre for a short period after having the first dose. The committee considered how this would be implemented in clinical practice. The clinical expert at the committee meeting explained that tarlatamab is a new type of medicine (a bispecific T-cell engager), so oncologists, haematologists and the wider multidisciplinary team would need further training to monitor and treat side effects. Also the clinical expert expected that as clinicians gained experience, tarlatamab would only be used in a very specific group of people who can tolerate the potential side effects and treatment burden

(see section 3.2). The committee noted that there is a treatment available to manage CRS (tocilizumab) or clinicians may stop tarlatamab. Tocilizumab is available in the NHS, although its use varies nationally. The Cancer Drugs Fund lead confirmed that, if tarlatamab were recommended, it would be a prescribing requirement that tocilizumab should be available and used if needed. The committee concluded that tarlatamab has serious side effects, which will need healthcare staff training and capacity planning to monitor and manage.

Economic model

Company's modelling approach

4.7 The company used a partitioned survival model that included 3 health states: progression-free, progressed and death. The comparator was a range of standard care treatments, split according to use in the UK CAS study (see section 3.4). The committee considered that the partitioned survival model is a standard approach for estimating the cost effectiveness of cancer medicines and is suitable for decision making.

Survival extrapolations

Choice of survival curves

4.8 Survival data for tarlatamab and for standard care needed to be extrapolated over the longer term, beyond the available clinical data. Because the data from the DeLLphi-301 trial was immature (median follow-up time of 10.6 months for OS), the extrapolated survival data for tarlatamab in the economic model had additional uncertainties. The committee was aware that a further data cut from the DeLLphi-301 trial was available since the company submission. The data informing the modelling was from the MAIC, and the company and EAG agreed that the proportional hazard assumption did not hold for both PFS and OS. So, the company fitted standard parametric curves to the trial data for tarlatamab and standard care separately. For tarlatamab, it used the DeLLphi-301 data after weighting in the MAIC and censoring data for people who

continued tarlatamab after progression. The following parametric curves were chosen by the company:

- For OS: an exponential curve for both arms because this was the best fit for the DeLLphi-301 data.
- For PFS: a log normal parametric curve for tarlatamab and an exponential curve for standard care. TTD was used as a proxy for PFS in the standard care arm (see section 3.4). Parametric curves were chosen based on the best fit to each arm.

The EAG considered it was more appropriate to use the best fitting curve to the UK CAS study data to determine the appropriate parametric curve for both OS and PFS. This was because the UK CAS study included more people and had a longer follow-up time than the DeLLphi-301 trial. Both the company and EAG fitted the same type of parametric curve to each arm to extrapolate overall survival, based on the advice in NICE Decision Support Unit's technical support document 14. Whereas the company used an exponential curve for OS for both arms, , the EAG preferred to use the gamma curve for OS for both arms, which best fitted the UK CAS data. The EAG considered that the same type of distribution should also be fitted to each arm to extrapolate PFS. So, it fitted the exponential curve to PFS data for tarlatamab and TTD data for standard care in its base case. The committee stated that analyses that used the exponential distribution to extrapolate outcomes for both tarlatamab and standard care assumed proportional hazards between arms. This was because the exponential model assumed a constant hazard function. So, because the proportional hazards assumption did not hold, it was inappropriate to use the exponential curve for both arms. It acknowledged that there was a case for fitting different parametric curves to each arm rather than fitting an exponential curve to each treatment arm. The committee noted there is a further data cut from DeLLphi-301, which would provide more mature PFS and OS data for tarlatamab. It agreed that

the company should explore the best fitting parametric curve for each arm at consultation. It considered that, if justified, different extrapolation curves may be applied to each arm. But, if fitting the same curve to each arm, the choice of curve should be informed by the treatment arm that has the most mature data. The committee concluded that because of the immature data, the OS and PFS extrapolations were uncertain. It agreed that a full exploration of the best-fitting parametric curve should be done for any new data submitted at consultation.

TTD as a proxy for PFS in the standard care arm

4.9 The committee recalled that the company had used TTD as a proxy for PFS in the standard care arm (see section 3.4). It was concerned that TTD may not be a suitable surrogate for PFS. The clinical experts explained that the risk of haematological toxicity is higher after several rounds of chemotherapy, so people might stop standard care treatments before progression. But, this is likely to be few people because third-line treatments have a short period of effectiveness. There was also a notable difference between PFS and TTD in the DeLLphi-301 trial when censoring the PFS data for people who continued tarlatamab after progression. The committee considered that using TTD data to estimate PFS for the standard care arm was uncertain. It was aware that the company had submitted a scenario using TTD for both tarlatamab and standard care. But, it agreed that additional analyses should explore different approaches to modelling PFS in the standard care arm, including but not limited to analyses adjusting TTD for the standard care arm by the ratio between PFS and TTD that was reported in DeLLphi-301. Scenario analyses could include using the ratio between PFS and TTD obtained from a systematic review of the literature. The committee agreed that these analyses should be provided at consultation. It also considered that further data cuts from DeLLphi-301 may reduce the uncertainty in the long-term OS and PFS estimates.

Utility values

Health state utility values

4.10 The company derived health-state utility values for the progression-free and post-progression health states from EQ-5D-5L data collected in the DeLLphi-301 trial. It mapped this data to EQ-5D-3L utility scores using the algorithm by Hernandez-Alava, and adjusted for age and sex. The EAG was concerned that the company's health-state utility values were higher than expected when compared to the general public. It was also concerned that they were based on the full DeLLphi-301 population, not the population after matching to the UK CAS study, which would better represent standard care in the UK. At the committee meeting, the company stated that it had also derived utility values using the MAIC matched population. But it had not provided these estimates in its submission. This was because, although the utility value for baseline and progression free SCLC were similar to estimates using data from the full DeLLphi 301 population, the utility value for progressed SCLC was higher when using the MAIC population. The committee agreed that this data should be provided by the company at consultation. The EAG noted that it had identified no alternative well done SCLC studies in the literature to inform the health-state utility values in the model. It highlighted that the company's estimates were higher than those reported by Chouaid et al. (2013), which included people with non-small-cell lung cancer (NSCLC). The EAG used the subgroup of people with NSCLC having their third and fourth lines of treatment to derive the health-state utilities. The EAG's clinical experts stated that people with NSCLC and SCLC after 2 lines of treatment were likely to have a similar quality of life. So, the EAG used the NSCLC utility estimates from Chouaid et al. in its base case. At the committee meeting, the clinical expert explained that SCLC is considerably more aggressive than NSCLC. So, the quality of life for someone with NSCLC is likely to be better than for someone with SCLC. The committee noted this contrasted with the utility values reported in

Chouaid et al., which were lower than those derived from the DeLLphi-301 trial. The committee was concerned that:

- the Chouaid et al. estimates were based on data from people with a different type of lung cancer
- there may also have been differences in the performance status scores and number of previous treatments between this study and DeLLphi-301, which may have affected quality of life.

The clinical expert agreed that the lower utility values reported by Chouaid et al. compared with DeLLphi-301 were likely because of differences in trial eligibility criteria, specifically differences in:

- performance status: Chouaid et al. included people with an ECOG score of 2 who were excluded from DeLLphi-301
- number of previous lines of treatment: Chouaid et al. grouped together people having third and fourth-line treatments. So, it was possible that Chouaid et al included a higher proportion of people who had fourth-line treatments than were included in DeLLphi-301.

The committee was aware that the population in DeLLphi-301 may have had a higher quality of life than people with ES-SCLC in clinical practice. This is because people are specifically selected for clinical trials and the utility value for progressed ES-SCLC was calculated from data including people who had tarlatamab after progression. But, the company stated that they did not expect ongoing tarlatamab use to improve outcomes for people whose cancer had already progressed. The committee agreed that the quality of life for people with ES-SCLC after 2 or more lines of treatment in clinical practice was unknown, but likely lay between the company and EAG estimates. It recalled that the company's utility values reflected the relevant population and that the use of trial data to inform utilities aligns with the recommendations in NICE's manual on health technology evaluations. It concluded that the

company's utility values may be higher than what may be expected in the population with ES-SCLC, but it is unclear by how much the company's utilities are overestimates. Given the options available, the committee preferred to use utility estimates from DeLLphi-301 for decision making.

Costs

Adverse event costs

4.11 The company modelled costs for adverse events of grade 3 and above occurring in more than 3% of people in either treatment arm. It also included costs for grade 1 or 2 CRS and ICANS. A one-off cost for tocilizumab was included in the management costs for CRS. The cost per cycle was calculated based on the trial duration and the proportion of people with adverse events. Unit costs per adverse event were taken from the NHS England Payment Scheme 2023 to 2024, and costs for CRS and ICANS were taken from the DeLLphi-301 trial, the BNF and the NHS Reference Costs 2021 to 2022. The EAG noted that for most cases in which multiple potential healthcare resource group (HRG) codes could apply for a single adverse event, the company used the most expensive code. It was concerned that this might have overestimated the costs for adverse events. So, the EAG used a weighted average across all available severities of adverse event levels in its base case. It also noted that the same set of HRG codes applied for febrile neutropenia and leukopenia, but the company had chosen to use the most expensive cost for febrile neutropenia and the least expensive for leukopenia. The EAG considered this unsuitable and matched the cost for febrile neutropenia to non-sepsis infection in its base case. The committee acknowledged that the EAG's approach was consistent with approaches taken in previous technology appraisals. The Cancer Drugs Fund lead advised that the EAG's approach more closely reflected the costs incurred by the NHS. The committee concluded that the EAG's approach to including the costs associated with treating adverse events was appropriate.

Severity

4.12 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 quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity (a severity modifier). The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. In both the company and EAG base cases, the proportional QALY shortfall was greater than 0.95. So, based on the estimates that were presented to it, the committee concluded that the severity weight of 1.7 applied to the QALYs was appropriate. But, the committee acknowledged that the calculations informing the severity modifier should be assessed after consultation if estimates of total QALYs for standard care change.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

4.13 The incremental cost-effectiveness ratios (ICERs) for the comparison of tarlatamab with standard care were £34,507 using the company base-case assumptions and £56,825 per QALY gained when using the EAG's base-case assumptions. The committee noted that the difference in the company's and EAG's preferred base cases was primarily driven by the choice of utility values. The EAG's preferred parametric curve for PFS and OS increased the ICER further. For the model assumptions, the committee preferred to:

- Include a basket of standard care chemotherapy treatments as the only relevant comparator.
- Use the health-state utility values from the DeLLphi-301 trial.
- Not use the exponential distribution fitted to both treatment arms to extrapolate either PFS or OS if the proportional hazards assumption does not hold. The committee noted that it would take into account

updated survival curves fitted to the most recent DeLLphi-301 data cut that the company should provide in response to consultation.

- Use the EAGs approach to modelling costs for adverse events.
- Apply a severity weight of 1.7 to the QALYs. The calculations informing the severity modifier should be assessed after consultation if estimates of total QALYs on standard care change.

The committee concluded that the ICERs from using either the company's or the EAG's preferred assumptions were higher than the range normally considered an acceptable use of NHS resources. The committee noted that there was a high degree of uncertainty about:

- the relative clinical effectiveness estimated from the unanchored MAIC
- how well TTD reflected PFS on standard care
- the extrapolation of PFS and OS
- whether the utility values based on data from DeLLphi301 would overestimate the quality of life of people having third and later lines of treatments for SCLC in clinical practice.

The committee was aware that the proportion of people who survive and are well enough to have third or later lines of treatments is very small, meaning that it may be hard to generate data for this group of people to resolve uncertainty. But, it noted that having data from a later data cut from DeLLphi-301 may resolve some uncertainty. Also, it was aware that there were analyses (see section 3.9) that the company could provide to help the committee understand the extent of the uncertainty and determine its preferred ICER threshold for decision making.

Uncertainties to explore further in the modelling

4.14 The committee recalled the high level of uncertainty surrounding some of the modelling assumptions. It noted that the company should explore using the following in the model:

- additional scenarios around the methodology for the ITC:
  - a MAIC adjusting for variance
  - an STC or ML-NMR
- alternative approaches for estimating the relative treatment effect of tarlatamab compared with standard care on PFS in the indirect comparison and in the modelling of PFS, including:
  - adjusting TTD for the standard care arm by the ratio between PFS and TTD reported in DeLLphi-301
  - conducting scenario analyses using the ratio between PFS and TTD obtained from a systematic review of the literature
- updated OS and PFS results from the most recent DeLLphi-301 data cut, including:
  - a full review of the best-fitting parametric curves to the updated data, modelling curves separately when needed to reflect the underlying hazards
  - an updated proportional and absolute QALY shortfall analysis to assess whether the severity modifier still applies to the updated base case
- utility values derived from the subgroup of the DeLLphi 301 trial included in the MAIC.

Other factors

Equality

4.15 The committee did not identify any equality issues.

Uncaptured benefits

4.16 The committee considered whether there were any uncaptured benefits of tarlatamab. It recalled that the population with ES-SCLC with progression on or after 2 or more lines of treatment was small with an unmet need for new treatments (see section 3.2). But, it did not identify additional benefits of tarlatamab not captured in the economic modelling. So the committee

concluded that all additional benefits of tarlatamab had already been taken into account.

Innovation

4.17 The clinical experts considered tarlatamab to be a step change in the treatment of SCLC. There are no approved treatments after second line, and current options have limited survival benefit (see section 3.2). The committee recalled that few people are fit enough to have systemic treatments after 2 lines of treatment and that there is a high unmet need in this population (see section 3.2). It acknowledged that indirect treatment comparisons suggested a survival benefit for tarlatamab compared with standard care. But it agreed that the extent of this benefit was unclear because of uncertainty in the company's MAIC (see section 3.5). It also noted that tarlatamab was a first-in-class treatment that could be used for people whose cancer no longer responded to chemotherapy or PD-L1 inhibitor immunotherapy (see sections 3.5 and 3.6). It concluded that tarlatamab may be innovative.

Conclusion

Recommendation

4.18 The committee noted the important uncertainties in the clinical-effectiveness evidence and survival estimates. Both the company's and EAG's cost-effective estimates are above what is considered a cost-effective use of NHS resources. So, tarlatamab is not recommended. The committee concluded that the company should provide additional information for consideration at the next evaluation committee meeting (see section 3.9).

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 A.

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

Radha Todd

Chair, technology appraisal committee A

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 Douch

Technical lead

Mary Hughes

Technical adviser

Kate Moore

Project manager

Emily Crowe

Associate director

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