

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

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](#).

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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.

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1 Recommendation

- 1.1 Tarlatamab should not be used to treat extensive-stage small-cell lung cancer in adults whose cancer has progressed after 2 or more lines of treatment, including platinum-based chemotherapy.
- 1.2 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.

What this means in practice

Tarlatamab is not required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendation.

This is because the available evidence does not suggest that tarlatamab is value for money in this population.

Why the committee made this recommendation

There are no approved treatments for extensive-stage small-cell lung cancer that has progressed after 2 or more lines of treatment that included 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 should not be used.

2 Information about tarlatamab

Marketing authorisation indication

- 2.1 Tarlatamab (IMDYLLTRA, Amgen) 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

- 2.2 The dosage schedule is available in the [summary of product characteristics for tarlatamab](#).

Price

- 2.3 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.

Carbon Reduction Plan

- 2.4 For information, the Carbon Reduction Plan for UK carbon emissions is published on [Amgen's Carbon Reduction Plan template \(PDF\)](#).

3 Committee discussion

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

The condition

Details of the condition

- 3.1 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 provides 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

- 3.2 The company positioned tarlatamab for treating 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 cure 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](#). Or, 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 here, 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 platinum-combination chemotherapy again (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) status of 2 or more. These people have best supportive care to manage their symptoms. 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 retreatment 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 status of 0 or 1. The NHS England Cancer Drugs Fund clinical lead (from here, CDF lead) confirmed that NHS England would only commission tarlatamab in this group. The clinical expert also confirmed that healthcare professionals would only consider tarlatamab as a treatment option in people with an ECOG 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 lines of treatment

- tarlatamab would only be a treatment option for people with an ECOG status 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

- 3.3 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, after a dose titration period. The primary outcome was the objective response rate (ORR). In its original evidence submission, the company presented data from the June 2023 data cut of the trial. 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) and the median overall survival (OS) was 14.3 months (95% CI 10.8, upper limit not estimable). At the first committee meeting, the committee noted that the follow-up times in the June 2023 data cut for PFS (confidential and cannot be reported here) and OS (10.6 months) were relatively short. During consultation on the draft guidance, the company presented further data from the October 2023, January 2024 and May 2024 data cuts of the DeLLphi-301 trial. Some outcomes were not reported in the January 2024 and May 2024 data cuts. So, the company used data from the October 2023 data cut in its revised base case to ensure consistency across presented outcomes. The company said that efficacy results from these later data cuts were consistent with those presented in the original evidence submission and the EAG agreed. The EAG noted that some people continued

tarlatamab beyond progression in DeLLphi-301, 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 ECOG status 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. While the PFS and OS results in the later data cuts were consistent with the data cut used in the original submission, the committee noted these provided only a few extra months of follow up. The committee concluded that the DeLLphi-301 trial suggested tarlatamab could be clinically effective, but that the data was uncertain.

Indirect treatment comparison

Company's matching-adjusted indirect treatment comparison

3.4 DeLLphi-301 did not compare tarlatamab with other treatments for ES-SCLC. So, the company in its original evidence submission did an indirect treatment comparison (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 here referred to as standard care). Clinical-effectiveness data for standard care came from the UK Cancer Analysis Service (CAS) study. This was a retrospective, 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 ITC 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-adjusted 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, the company 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 status (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 original MAIC using the June 2023 data cut of the DeLLphi-301 trial 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). After consultation, the company updated its MAIC with data from the October 2023 data cut from DeLLphi-301, which gave similar results (the results are confidential so the exact data cannot be reported here).

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 this reduced confidence in the MAIC results. The EAG also noted that fewer people in the UK CAS study had had treatment with PDL1 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 PDL1 inhibitor) at first line (see [section 3.2](#)). But, the clinical expert at the first committee meeting explained that tarlatamab has a different mechanism of action to a PDL1 inhibitor. So, there was no biological or clinical reason for cancer treated with a PDL1 inhibitor to respond

differently to tarlatamab than cancer not treated with a PDL1 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 at the first committee meeting that the company had only matched the covariates using means, and not variances. It felt that this approach did not fully capture the uncertainty in the analysis. The committee concluded that there was a high degree of uncertainty surrounding the MAIC results given the small overlap in baseline characteristics between the studies and because the analysis was unanchored. At the first committee meeting, the committee agreed that the company should present a MAIC adjusting for variance and alternative methods to population adjustment should be explored. This may include either a simulated treatment comparison with G-computation, or multilevel network meta-regression.

Further ITC analyses provided at consultation

- 3.5 During consultation on the draft guidance, the company provided an updated MAIC with data from the October 2023 data cut of DeLLphi-301, which it used in its updated base case. The company also provided a scenario analysis requested by the committee that adjusts continuous covariates for means and variances (rather than just means). The results of this analysis were similar to the analysis adjusting for means only. The committee was satisfied that adjusting for variances had a minimal impact on the cost-effectiveness results.

The company also provided an alternative ITC using individual patient-level data from the US Flatiron database as the data source for standard care. The company provided this analysis to support its preferred MAIC analysis. The external control arm included data for people at around 280 US oncology practices and academic centres who had first-line platinum-based chemotherapy and at least 2 additional lines of treatment. The Flatiron ITC used standardised mortality ratio (SMR)

weighting to balance the baseline characteristics between both arms. The company suggested that the Flatiron ITC addressed key limitations with the UK CAS MAIC. These include the small effective sample size and the use of TTD as a proxy for PFS, because the Flatiron database collected data on PFS. The EAG considered that the Flatiron ITC led to more uncertainty about the relative treatment effect of tarlatamab compared with standard care. This was because

- it was unclear which DeLLphi-301 data cut was used
- no information was provided on the previous treatments people had in the external control arm
- there were differences in the prognostic factors used in the Flatiron ITC compared with the company base-case MAIC
- the company did not provide information about the distribution of weights for the SMR weighting
- the different censoring rules in DeLLphi-301 and the Flatiron study could bias the results in favour of tarlatamab.

The committee acknowledged the potential strengths of the Flatiron ITC, including the use of individual patient-level data, the sample size and the availability of PFS data for standard care. But, it noted that the company had not provided enough information about the patient characteristics and the treatments people had in this study. Specifically, it was not clear if the US Flatiron dataset reflected the population likely to have tarlatamab in the NHS. Without this clarity, the committee preferred the UK CAS data source for standard care. It noted that the company had provided cost-effectiveness results using the Flatiron ITC. But, it had not presented enough information for the EAG or the committee to assess the validity of the extrapolation of the clinical data within the model. The committee felt that the Flatiron ITC did not address its concerns about the company's ITC approach that used MAIC methodology. It also felt that it introduced more uncertainty about the relative treatment effect of tarlatamab compared with standard care. It concluded that the Flatiron ITC was not informative for decision making. The committee preferred instead to use the MAIC with data from the October 2023 data cut of DeLLphi-301 for decision making.

Adverse events and need for monitoring

3.6 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 CDF 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, but it was provided by the company during consultation on the draft guidance. 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 multidisciplinary team would need further training to monitor and treat side effects. They expected that as healthcare professionals 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 healthcare professionals may stop tarlatamab. Tocilizumab is available in the NHS, although its use varies nationally. The CDF lead confirmed that, if tarlatamab were recommended, it would be a prescribing requirement that tocilizumab should be available. During consultation on the draft guidance, the company provided safety data collected at later data cuts of the DeLLphi-301 trial. The company also provided information on its Risk Management Plan and stated that it will offer training to healthcare staff. The EAG noted that there were no new safety concerns from the October 2023 data cut but that there was a slight increase in the rate of CRS in 1 of the 2024 data cuts. The committee felt reassured that CRS events resolved relatively quickly. But, it noted that resources would be needed to manage CRS and ICANS in hospitals. Resources would also be needed to plan for and train staff on managing adverse effects specific to this new type of treatment. The CDF lead stated that this would be implementable in clinical practice. The committee concluded that tarlatamab can have serious side

effects and these would need healthcare staff training and capacity planning to monitor and manage.

Economic model

Company's modelling approach

- 3.7 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

- 3.8 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, the extrapolated survival data for tarlatamab in the economic model had additional uncertainties. The data informing the modelling was from the MAIC, and at the first committee meeting 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 EAG felt 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. The committee stated 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. During consultation on the draft guidance, the company found that the proportional hazards assumption still did not hold for OS and PFS using the updated October 2023 DeLLphi-301 data cut in its MAIC analysis. So, it fitted the parametric curves for OS, PFS and TTD separately to each treatment arm, as follows:

- For OS, the company chose the exponential distribution for tarlatamab and gamma for standard care. The EAG agreed with the company's choice of distribution for standard care but preferred to use the same distribution for both treatment arms. So, it chose the gamma distribution for tarlatamab OS.
- For PFS, the company chose the log-normal distribution for tarlatamab. For standard care, it used the TTD as a proxy for PFS and chose the generalised gamma. The EAG agreed with this approach.
- For TTD, the company chose the exponential distribution for tarlatamab and the generalised gamma distribution for standard care. The EAG agreed with the company's choice of distribution for standard care TTD but preferred to use the generalised gamma distribution for the tarlatamab TTD. It stated that the exponential distribution did not give a good visual fit and was the worst fit according to the Akaike Information Criterion goodness of fit statistic.

The committee considered the differences in the company and EAG's approaches. It noted that the incremental cost-effectiveness ratio (ICER) was not sensitive to the choice of distribution for tarlatamab OS and that the gamma distribution provided a good visual fit. So the committee preferred to use the gamma distribution for tarlatamab OS. Using the generalised gamma distribution for tarlatamab TTD implies a decreasing risk of stopping treatment over time. Because the rate of adverse events is expected to decrease over time, the committee considered that the risk of stopping treatment is also likely to decrease. So, it preferred to use the generalised gamma distribution for tarlatamab TTD. The committee concluded that the OS and PFS extrapolations were uncertain, but choosing different distributions did not have a large impact on the cost-effectiveness results. Overall, it concluded that the EAG exploratory base-case assumptions for extrapolation of OS, PFS and TTD were its preferred assumptions.

TTD as a proxy for PFS in the standard care arm

- 3.9 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 a small proportion of 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. These could include, but are not limited to, analyses adjusting TTD for the standard care arm by the TTD-to-PFS ratio reported in DeLLphi-301. During consultation on the draft guidance, the company provided a scenario analysis where the TTD-to-PFS ratio for the tarlatamab extrapolations was calculated for each model cycle. This was then applied to the standard care TTD curve to estimate PFS. But, the company maintained TTD as a proxy for PFS for standard care in its base case. It considered that applying the TTD-to-PFS ratio for tarlatamab to standard care was an unsuitable approach for estimating standard care PFS. The company said that any differences between TTD and PFS were likely to be small because survival outcomes for standard care are poor. It also noted that tarlatamab has a novel mechanism of action. So, it may not be clinically valid to assume that the difference observed between TTD and PFS in DeLLphi-301 was applicable to standard care. The company also highlighted that the adverse event profiles between tarlatamab and chemotherapy are different, which may result in different relationships between TTD and PFS. The EAG was satisfied that the scenario requested by the committee had a minimal impact on the cost-effectiveness results. It also agreed with the company's approach of assuming PFS to be equal to TTD for standard care. The committee noted that, while using TTD as an estimate for PFS in the standard care arm remained uncertain, the cost-effectiveness results were not sensitive to adjusting PFS. So, it concluded that it was acceptable to assume PFS was equal to TTD for standard care.

Utility values

Health-state utility values

3.10 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 the EQ-5D-5L descriptive system data to the EQ-5D-3L value set in line with the NICE reference case. The EAG was concerned that the company's health-state utility values were higher than expected when compared with 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 UK standard care. At the first 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 original evidence submission. The EAG noted that it had not identified any alternative well done SCLC studies in the literature to inform the health-state utility values in the model. The EAG's clinical experts stated that people with non-small-cell lung cancer (NSCLC) and people with SCLC after 2 lines of treatment were likely to have a similar quality of life. So the EAG used utility values for people with NSCLC having third- and fourth-line treatments, derived from [Chouaid et al. \(2013\)](#) in its base case. At the first 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 and that there were differences in trial eligibility criteria between Chouaid et al. and 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 it 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

it felt that it likely lay between the company and EAG estimates. The committee recalled that the company's utility values reflected a more 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 might 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.

During consultation on the draft guidance, the company provided the utility values adjusted for the population in the UK CAS study (MAIC-adjusted). Compared with the utility values for the full trial population, in the MAIC-adjusted population the pre-progression utility was unchanged, but the post-progression utility was slightly higher. The company retained the utility values for the full DeLLphi-301 population in its base case because it considered the MAIC-adjusted utilities to be less robust than the unadjusted utilities. The EAG stated that it preferred to use the utility values for the MAIC-adjusted population rather than the full DeLLphi-301 population. The committee noted that the MAIC-adjusted and full DeLLphi-301 population utility values were similar and that the impact on the ICER was minimal. It concluded that it preferred to use the utility values derived for the MAIC-adjusted population because they may better reflect people having standard care.

Costs

Adverse event costs

- 3.11 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 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 healthcare resource group codes applied for febrile neutropenia and leukopenia. But, the company chose 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 CDF 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

- 3.12 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.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

- 3.13 Using the company base-case assumptions, the ICERs for tarlatamab compared with standard care were £28,449 (deterministic) or £29,134 (probabilistic) per

QALY gained. The ICERs were £31,437 (deterministic) or £35,393 (probabilistic) per QALY gained when using the EAG's exploratory base-case assumptions. The committee preferred the EAG's assumptions where these differed from those in the company's post consultation base case. Overall, the committee preferred the following modelling assumptions:

- a basket of standard care chemotherapy treatments included as the only relevant comparator (see [section 3.2](#))
- the updated MAIC with the DeLLphi-301 October 2023 data cut used as the preferred source for the ITC (see [section 3.4](#) and [section 3.5](#))
- the health-state utility values used from the DeLLphi-301 trial, adjusted for the characteristics of the UK CAS study population (see [section 3.10](#))
- the gamma distribution for extrapolation of OS used for both treatment arms (see [section 3.8](#))
- the generalised gamma distribution used for extrapolation of TTD for both treatment arms (see [section 3.8](#))
- the log-normal distribution used for extrapolation of tarlatamab PFS (see [section 3.8](#))
- PFS assumed to be equivalent to TTD for standard care (see [section 3.9](#))
- the EAG's approach used for modelling costs for adverse events (see [section 3.11](#))
- a severity weight of 1.7 applied to the QALYs (see [section 3.12](#))
- probabilistic results used for decision making.

The committee concluded that the ICER using these preferred assumptions was £35,393 per QALY gained.

[NICE's manual on health technology evaluations](#) notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about

the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted that there remained a high level of uncertainty, particularly about the relative clinical effectiveness for tarlatamab estimated from the unanchored MAIC. There also remained a high level of uncertainty around:

- the extrapolation of PFS and OS beyond the period in which data was available
- whether the utility values based on data from DeLLphi-301 would overestimate the quality of life of people having third and later lines of treatment 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 line of treatment is very small. So it may be hard to generate data for this group of people to resolve uncertainty. It noted that the severity of the condition had been accounted for by applying the 1.7 severity weight in the cost-effectiveness calculations. Taking into consideration the degree of uncertainty and difficulty generating evidence in this population, the committee determined that its preferred ICER threshold for decision making was around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Other factors

Equality

3.14 The committee did not identify any equality issues.

Uncaptured benefits

3.15 The committee considered whether there were any uncaptured benefits of tarlatamab. It recalled that the population with ES-SCLC who progress on or after 2 or more lines of treatment was small, with an unmet need for new treatments

(see [section 3.2](#)). The committee noted that unmet need was captured by applying the 1.7 severity weight. It also noted that tarlatamab was a first-in-class treatment. 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.

Conclusion

Recommendation

- 3.16 The committee noted the important uncertainties in the clinical-effectiveness evidence and survival estimates. The cost-effectiveness estimates using its preferred modelling assumptions were over what it considered a cost-effective use of NHS resources. So, tarlatamab should not be used for treating ES-SCLC in adults whose cancer has progressed after 2 or more lines of treatment, including platinum-based chemotherapy.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

Chris Shah and Emma Douch

Technical leads

Mary Hughes

Technical adviser

Kate Moore and Jeremy Powell

Project managers

Emily Crowe

Associate director

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