# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final draft guidance

# Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer

## 1 Recommendation

1.1 Serplulimab with carboplatin and etoposide can be used, within its marketing authorisation, as an option for untreated extensive-stage small-cell lung cancer in adults. Serplulimab with carboplatin and etoposide can only be used if the company provides it according to the commercial arrangement (see section 2).

### What this means in practice

Serplulimab with carboplatin and etoposide must be funded in the NHS in England for the condition and population in the recommendation, if it is considered the most suitable treatment option. Serplulimab with carboplatin and etoposide must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that serplulimab with carboplatin and etoposide provides benefits and value for money, so it can be used routinely across the NHS in this population.

### Why the committee made these recommendations

Usual treatment for most people with untreated extensive-stage small-cell lung cancer is atezolizumab plus carboplatin and etoposide.



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Clinical trial evidence shows that serplulimab plus carboplatin and etoposide increases how long people have before their cancer gets worse and how long people live compared with placebo plus carboplatin and etoposide.

Serplulimab plus carboplatin and etoposide has not been directly compared in a clinical trial with atezolizumab plus carboplatin and etoposide. The results of an indirect comparison are uncertain because of the methods used.

There are also some uncertainties in the economic model. But when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are within the threshold that NICE considers an acceptable use of NHS resources. So, serplulimab plus carboplatin and etoposide can be used.

# 2 Information about serplulimab

## Marketing authorisation indication

2.1 Serplulimab (Hetronifly, Accord Healthcare) 'in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small-cell lung cancer (ES-SCLC)'.

## Dosage in the marketing authorisation

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

## Price

2.3 The list price of serplulimab is £1,321.83 per 100-mg vial (excluding VAT; BNF online accessed May 2026).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes serplulimab available to the NHS with a discount. The size of the discount is commercial in confidence.

## Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Accord Healthcare will be included here when guidance is published.

# 3 Committee discussion

The evaluation committee considered evidence submitted by Accord Healthcare, 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

### Small-cell lung cancer

3.1 Small-cell lung cancer (SCLC) is an aggressive type of cancer that grows rapidly and spreads quickly to other parts of the body. Common symptoms include weight loss, malaise, bone pain, breathlessness and coughing up blood. A patient expert submission explained that a diagnosis of SCLC is devastating for the person with the condition, and their families and carers, because of its aggressive, symptomatic and progressive nature. Around 70% of people with SCLC have extensive-stage disease, when the cancer has spread beyond 1 lung and the nearby lymph nodes to other parts of the body. Both the patient and clinical experts at the first committee meeting highlighted that extensive-stage SCLC (ES-SCLC) has a poor prognosis with limited treatment options.

In response to the second draft guidance consultation (from here, second consultation), the company re-emphasised the unmet need for people with ES-SCLC. It presented evidence from a clinical advisory board that highlighted areas of unmet need in this population. This included low access to first-line treatment, high attrition with second-line treatment, and a lack of maintenance treatments that provide a clinically meaningful improvement in overall survival (OS) over current treatment options. At the third committee meeting, the clinical experts said that the serplulimab clinical trial showed a greater OS benefit compared with placebo than

seen in the clinical trials of current treatment options, which will be welcomed by people with ES-SCLC. The committee recognised the clinical experts input but noted that:

- comparisons across trials were uncertain because of differences in the trial populations (see section 3.4)
- the serplulimab clinical trial results still have uncertainty regarding generalisability to the NHS (see section 3.4)
- there was significant uncertainty in the indirect treatment comparison (ITC) used to estimate the relative treatment effect of serplulimab compared with atezolizumab (see section 3.5).

The EAG acknowledged an unmet clinical need in ES-SCLC and that serplulimab could offer another treatment option. But it was not satisfied that the evidence presented clearly shows that serplulimab significantly addresses this unmet need relative to current treatment options. The committee recognised the severe impact that ES-SCLC has on people's quality of life and survival. It acknowledged the unmet need for more options for effective treatments for ES-SCLC, especially when compared to other forms of lung cancer.

## Treatment pathway and comparators

3.2 The company positioned serplulimab with carboplatin and etoposide as a first-line treatment for ES-SCLC, in line with its marketing authorisation. Current first-line treatment options for ES-SCLC are:

- platinum-based chemotherapy, such as carboplatin with etoposide
- atezolizumab plus carboplatin with etoposide (from here, atezolizumab)
- durvalumab plus etoposide and either carboplatin or cisplatin (from here, durvalumab).

Between 10% and 20% of people with ES-SCLC move on to second-line treatment (clinical expert advice in NICE's technology appraisal guidance on atezolizumab [TA638]). At the first committee meeting, the

clinical expert stated that first-line treatment for ES-SCLC, that is an immunotherapy plus chemotherapy, is well established in NHS practice. So, no additional changes would be needed to implement serplulimab. They said that serplulimab was not expected to fully address the unmet need for SCLC (see section 3.1), but it would offer an alternative immunotherapy plus chemotherapy treatment option in the first-line setting. The committee noted that the comparators atezolizumab and durvalumab were recommended in adults only if they have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see section 3.3). The NHS England national specialty adviser for cancer drugs (from here, national specialty adviser) highlighted that more than 96% of people with untreated ES-SCLC have atezolizumab. The clinical expert explained that atezolizumab has become established clinical practice and that evidence suggests that atezolizumab and durvalumab are likely to have similar efficacy. Also, durvalumab is only administered intravenously, whereas atezolizumab could be administered subcutaneously, which is often preferred by people with the condition and healthcare professionals (see section 3.18). The committee agreed that serplulimab with carboplatin and etoposide would be an alternative first-line treatment option. It concluded that atezolizumab is the most relevant comparator in this evaluation.

## Clinical effectiveness

### ASTRUM-005

3.3 Clinical evidence for serplulimab with carboplatin and etoposide came from the ASTRUM-005 trial. ASTRUM-005 was a phase 3, multicentre, randomised controlled trial comparing the effectiveness of serplulimab with carboplatin and etoposide with placebo plus carboplatin and etoposide. The primary outcome was OS, which significantly improved in the serplulimab arm compared with placebo. Progression-free survival (PFS) was a key secondary endpoint and significantly improved in the

serplulimab arm. The ASTRUM-005 population was people with ES-SCLC who had an ECOG performance status of 0 or 1. The committee considered whether applying a restriction to the eligible population to align with the ECOG performance status of ASTRUM-005 was appropriate. The committee noted that a similar population restriction was applied in TA638 and NICE's technology appraisal guidance on durvalumab (TA1041), in which evidence from people with an ECOG performance status of 0 or 1 was not considered generalisable to people with an ECOG performance status of 2 or higher. At the first committee meeting, the clinical expert said it would be unlikely that serplulimab would be used by people with an ECOG performance status of 2 or higher. The committee thought that restricting by ECOG performance status could have implications for equality. It also noted that a restriction would not have an impact on treatment decisions because it was unlikely that serplulimab would be used by people with an ECOG performance status of 2 or higher in clinical practice. So the committee did not feel a need to restrict its recommendation by ECOG performance status.

### Generalisability of trial populations

3.4 There is no direct evidence comparing serplulimab with atezolizumab or durvalumab. Data for atezolizumab was sourced from IMpower133, a phase 3 trial comparing atezolizumab plus carboplatin and etoposide with placebo plus carboplatin and etoposide. Data for durvalumab was sourced from CASPIAN, a phase 3 trial comparing:

- durvalumab with etoposide and either carboplatin or cisplatin
- etoposide with either carboplatin or cisplatin.

All 3 trials (ASTRUM-005, IMpower133, CASPIAN) used to source clinical-effectiveness evidence were similar in design. But the EAG highlighted differences in trial setting and timing, as well as notable differences in patient characteristics between the trials and the NHS population. All the trials had higher proportions of males, particularly

ASTRUM-005 in which more than 80% were male. The EAG explained that, in the UK, lung cancer incidence is similar between males and females. Most people in ASTRUM-005 were Asian and a high proportion (19.8%) did not smoke. Clinical advice to the EAG noted it was rare for people who do not smoke to be diagnosed with SCLC in UK clinical practice. Also, a substantial proportion of people in the trials had second-line treatment, when clinical advice from TA638 suggested that between 10% and 20% of people in the NHS would have second-line treatment. Expert clinical advice to the company agreed that the subgroup analyses from ASTRUM-005 showed no difference in PFS and OS between Asian and non-Asian subgroups. At the first committee meeting, the clinical expert also suggested that, in the NHS, there are people with ES-SCLC who have never smoked and who tend to have a poorer prognosis than people who have smoked. So, real-world outcomes for serplulimab may be more favourable than in ASTRUM-005 in which there is a higher proportion of people who have never smoked. The EAG said ASTRUM-005 was not powered to detect significant differences based on race subgroups and there was no robust evidence to validate treatment effect modifiers in people with ES-SCLC.

In response to the second consultation, the company reiterated that the consistent effect of serplulimab across subgroups supported the generalisability of the results to the NHS population. The company also highlighted that its clinical advisory board thought that the results of ASTRUM-005 were consistent with what they would expect in NHS practice. The EAG noted that the small numbers in key subgroups (such as women, non-Asian ethnic groups and people who do not smoke) meant that uncertainty remained about the generalisability of the results. The EAG also highlighted that the company did not provide sufficient information about its advisory board to assess potential bias, such as conflicts of interest or how healthcare professionals were identified and recruited. The committee concluded there was uncertainty in the

generalisability of the populations of ASTRUM-005, IMpower133 and CASPIAN to the NHS, so the generalisability of the trial outcomes to the NHS was unclear.

## Indirect treatment comparisons

### Methods

3.5 The company's submission presented 2 anchored matching-adjusted indirect comparisons (MAICs): one to compare serplulimab with atezolizumab and another to compare serplulimab with durvalumab. Baseline characteristics of the ASTRUM-005 intention-to-treat population were adjusted to IMpower133 or CASPIAN data, before applying Cox proportional hazards regressions to estimate the relative efficacy between serplulimab and either atezolizumab or durvalumab. Overall, the ITCs suggested that serplulimab improves PFS and OS compared with either atezolizumab or durvalumab, with or without adjustment of baseline variables. The EAG highlighted that a limited number of characteristics was included in each ITC. The EAG noted that some characteristics, such as race and previous cancer treatment, were notably different between the trials but were not adjusted for in the base-case MAICs. The company explained that adjusting for these characteristics would result in excessively low effective sample sizes, leading to unreliable outcomes. Also, previous cancer treatment was not reported in CASPIAN. The EAG acknowledged this but noted that the uncertainty remains. At the clarification stage, the EAG requested that the company provide a multilevel network meta-regression to address the uncertainties around between-study variations because it would allow more flexibility to generate population-adjusted outcomes. But the company asserted that the MAICs were more suitable and addressed between-trial differences through the matching and reweighting of baseline data. The EAG acknowledged that the multilevel network meta-regression would also be uncertain because of the limited population overlap identified by the MAICs, but it maintained that this approach would have been useful to

explore. The committee was concerned that the MAICs did not offer a robust approach for decision making in this evaluation. It said it was not appropriate to compare hazard ratios across 2 different matched populations. It also recalled the uncertainty in the generalisability of the trial populations to the NHS (see section 3.4) and that the MAICs reflected the trial populations of IMpower133 and CASPIAN. The committee noted that the results of unmatched Bucher ITCs and the MAICs were similar, implying that the treatment effect modification of the adjusted variables was not very strong. The company agreed and said it would also expect to see similar results if another adjustment method was used, such as the multilevel network meta-regression. The committee noted a multilevel network meta-regression would not address all the uncertainty around the between-study differences but would allow for comparisons to be made against the comparators in 1 population. The committee agreed that the Bucher ITCs were the best available evidence in the submission for comparing serplulimab with atezolizumab or durvalumab. But because these were highly uncertain, the committee requested to see a network meta-analysis (with time-varying hazard ratios; see section 3.9) that would allow for the relative effectiveness of serplulimab to both atezolizumab and durvalumab to be considered.

In response to the first consultation, the company produced fixed-effects fractional polynomial network meta-analyses (FP NMAs). It noted that FP NMAs offer a flexible, time-varying method that allow hazard rates to change over time, so could address potential violations of the proportional hazards assumption. The company fitted first- and second-order FP NMA models. It noted that the first-order models showed limited fit to the observed survival data and the second-order models had convergence issues and wide credible intervals which limited the reliability of the relative effect estimates. So, the company thought that the MAICs remained the most appropriate ITC approach. The EAG highlighted that if the populations across trials are assumed to be comparable when

considering effect modifiers (see section 3.4), then all the ITCs should produce similar results. It also explained that when there are multiple comparators being evaluated, other ITC methods, for example, Bucher or multi-level network meta-analyses, are preferred to MAICs. This is because they either assume a similar population, or they can adjust to a common population. Considering this, the EAG stated that the Bucher ITC is a suitable method to use. The EAG agreed with the company that there were limitations with the FP NMAs and uncertainties in the assessment of proportional hazards, noting that the assumption did not hold in the CASPIAN PFS data. Accounting for these factors, the EAG selected the Bucher ITCs as the most appropriate approach for the PFS and OS hazard ratio estimates for atezolizumab, and OS hazard ratio estimate for durvalumab. The EAG chose the best-fitting second-order FP NMA model for the relative PFS estimate for durvalumab, because this model did not rely on the proportional hazards assumptions and had a better statistical fit than the first order FP NMA models.

The committee reiterated its concerns with the MAICs and considered the EAG's preferred ITCs. The committee questioned the EAG's use of 2 different models to estimate the relative PFS treatment effect for atezolizumab and durvalumab. It shared concerns about the internal validity of this, noting that each method has different underlying assumptions and that using results from different analyses means that correlations estimated in the FP NMA are not taken into account. The committee also thought that the FP NMA, although a more flexible approach, did not fit the data better than the ITCs provided at the first meeting. It noted the company's and EAG's concerns around the proportional hazards assumption and that it did not hold in the CASPIAN PFS data. So, for the durvalumab arm in particular, the committee noted that none of the ITCs fit the data well. But, the committee recalled that durvalumab is used by less than 4% of people with untreated ES-SCLC in the NHS and that atezolizumab is the most relevant comparator in this

evaluation (see section 3.2). So, the consequences of the decision risk associated with the comparison with durvalumab were less than for the comparison with atezolizumab. The committee stated that there were limitations with all of the ITCs presented and that more complex approaches such as MAICs and FP NMAs did not reduce this uncertainty. It concluded that the Bucher ITCs were highly uncertain, but remained the best available evidence presented for comparing serplulimab with atezolizumab.

### Relative effectiveness

3.6 The company's ITCs suggested that serplulimab improves PFS and OS compared with either atezolizumab or durvalumab, with or without adjustment of baseline variables (see section 3.5). At the first committee meeting, the clinical expert noted that, in practice, they would expect similar clinical effectiveness across the immunotherapies. They suggested that the improvements in PFS and OS with serplulimab compared with the other immunotherapies were because of trial differences. The national specialty adviser also stated that they would not expect better outcomes with serplulimab. The company stated that the improved effectiveness may be because serplulimab binds to the programmed cell death protein 1 receptor (PD-1) and blocks its interaction with the ligands PD-L1 and PD-L2 on cancer cells. It highlighted that both atezolizumab and durvalumab inhibit only PD-L1. The committee noted that the company's submission did not present evidence comparing the efficacy of inhibitors that target PD-1 versus PD-L1 alone, and it was aware of other PD-1 inhibitors that did not show increased efficacy. The committee agreed that, if available, the company should provide evidence supporting serplulimab's stronger efficacy than other PD-1 and PD-L1 inhibitors to support the committee's decision making.

In response to the first consultation, the company stated that serplulimab has 2 key differentiating features compared with atezolizumab and durvalumab. Firstly, its distinct mechanism of action compared with PD-L1

inhibitors, as mentioned in the first committee meeting. Secondly, its unique molecular structure and binding characteristics compared with PD-1 inhibitors such as nivolumab and pembrolizumab. The EAG acknowledged the molecular evidence for serplulimab disrupting both PD-L1 and PD-L2, which may enable a greater anti-tumour response. But it highlighted that the company did not present any direct evidence from ASTRUM-005 showing that PD-L1 or PD-L2 expression was associated with improved outcomes for people with ES-SCLC having serplulimab. The EAG said that evidence is needed to confirm if serplulimab disrupts the action of both PD-L1 and PD-L2 and that this results in clinically meaningful outcomes. It highlighted that signs of superiority of serplulimab compared with currently available treatments should be treated with caution because of generalisability concerns between the trials and to the NHS target population (see section 3.4). The clinical expert at the second committee meeting agreed and said that they were not aware of any translational evidence in ES-SCLC that related to mechanism of action or PD-1.

In response to the second consultation, the company reiterated that serplulimab's distinct mechanism and affinity profile could explain the greater survival benefit compared with atezolizumab and durvalumab. Its advisory board agreed that there is a credible biological rationale that PD-1 and PD-L1 inhibitors do not all work in the same way. They also highlighted a recent study indicating that 30% of people with lung cancer have high PD-L2 expression, so serplulimab's ability to block both pathways may help explain the durable OS benefit observed in ASTRUM-005. The EAG noted that the referenced study included multiple cancer types, and only included 20 people with lung cancer and did not specify how many had SCLC. It also reiterated that there was still no direct evidence showing that PD-L1 or PD-L2 expression was associated with improved outcomes for people with ES-SCLC having serplulimab. At the third meeting, the clinical experts said that there was no robust data to

suggest there is a difference in efficacy between PD-1 and PD-L1 inhibitors. The committee noted that serplulimab had not been directly compared with atezolizumab or durvalumab and that the ITC evidence suggested that serplulimab improved PFS and OS compared with either treatment. But it concluded that the relative treatment effect estimates for serplulimab, atezolizumab and durvalumab were uncertain. This is because of the limitations associated with the ITCs (see section 3.5) and because the results differed to clinical expert opinion.

## Cost effectiveness

### Company's modelling approach

3.7 The company provided a partitioned survival model to estimate the cost effectiveness of serplulimab compared with atezolizumab, durvalumab and platinum-based chemotherapy alone. The model included 3 health states: progression-free, progressed disease and death. The model used a cycle length of 1 week over a 20-year lifetime horizon. The probability of being in each health state was based on extrapolated PFS, OS and time to off-treatment (also known as time-to-treatment discontinuation) curves. The committee concluded that, overall, the company's model structure was acceptable for decision making.

### Extrapolation of PFS and OS

#### Serplulimab and platinum-based chemotherapy-only arms

3.8 For the serplulimab and platinum-based chemotherapy-only arms, PFS and OS were extrapolated from ASTRUM-005 data. The company fitted independent parametric models, and selected the log-logistic model as the most appropriate option for both arms and survival outcomes. In its original base case, the EAG preferred to apply 3-knot spline models, provided by the company in response to clarification, for both arms and survival outcomes, adjusting the longer-term survival to account for the potential overestimation of the longer-term fit (see section 3.10). At the first committee meeting, the EAG acknowledged that it thought the

company's log-logistic models were clinically plausible in the long term because it adjusted its own curves to match the company's long-term survival estimates. The committee concluded that the company's log-logistic models for the serplulimab and platinum-based chemotherapy-only arms were clinically plausible and acceptable for decision making.

### Atezolizumab and durvalumab arms

3.9 For the comparisons with atezolizumab and durvalumab, the company submission estimated PFS and OS extrapolations by applying constant hazard ratios derived from the MAICs (see section 3.5). The EAG reported concerns with the proportional hazards assumptions between serplulimab and atezolizumab and between serplulimab and durvalumab. It suggested that sensitivity analyses using models that relax this assumption could have been done to explore the uncertainty. The committee concluded that the validity of the proportional hazards assumption between serplulimab and atezolizumab and between serplulimab and durvalumab was uncertain.

In response to the first consultation, the company provided scenario analyses using time-varying hazards from the FP NMAs (see section 3.5). It noted that the best-fitting first-order models produced cost-effectiveness results similar to those produced when using MAICs. The company stated that this suggests that after the initial time period, serplulimab had a lower hazard of progression or death compared with atezolizumab, durvalumab, and carboplatin and etoposide, which is consistent with the findings of the MAICs. So, the company maintained its base-case approach, applying hazard ratios estimated from the MAICs to extrapolate PFS and OS for atezolizumab and durvalumab. The committee reiterated its concerns with the MAICs and considered the PFS and OS extrapolations when using the EAG's preferred ITCs. The committee recalled the uncertainty around the proportional hazards assumption, including that it did not hold in the CASPIAN PFS data (see section 3.5). It stated that the flexible time-varying hazards approach did not produce extrapolations that fit the

observed data well, particularly in the durvalumab arm. It thought that using constant hazard ratios was therefore more acceptable for the comparison with atezolizumab than for the comparison with durvalumab. The committee recalled that atezolizumab is the main comparator for this indication (see section 3.2). So, for the comparison of serplulimab with atezolizumab, the committee agreed that none of the curves fit the observed data well, but that the Bucher ITCs were the best available hazard ratios to extrapolate PFS and OS (see section 3.5).

### Treatment effect waning

3.10 The company's base case applied constant hazard ratios from the MAICs to derive the relative effect estimates between serplulimab and atezolizumab and between serplulimab and durvalumab (see section 3.9). The company explained that the shape of the Kaplan–Meier curves from the ASTRUM-005 data suggested that there is no loss of treatment effect within the trial period (median of 42 months at the final analysis). It said that this differed to what was observed in the IMpower133 trial for atezolizumab, because the Kaplan–Meier curves began to converge towards the end of the trial follow-up period. So, the company assumed no loss of relative treatment effect for serplulimab, but provided scenario analyses exploring different treatment effect durations. The EAG's original base case included treatment effect waning for the serplulimab arm. It assumed a 3.5-year treatment effect duration followed by a 3-year waning period in which the OS hazard ratio linearly increased towards 1. The EAG also explored serplulimab treatment effect waning scenarios for its revised base case after the first consultation. The committee acknowledged that ASTRUM-005 showed evidence of serplulimab's efficacy compared with placebo plus carboplatin and etoposide. It recalled that the ITC evidence suggested that serplulimab improved PFS and OS compared with either atezolizumab or durvalumab based on data collected during the trials' follow-up periods, but that clinical experts expected similar efficacy between the immunotherapies. It also recalled that longer-term relative effectiveness remained uncertain (see

section 3.6). So, the committee decided that it was not appropriate to assume a constant relative treatment effect for the 20-year time horizon. In the absence of robust evidence beyond the trial period, the committee considered what would be the most likely long-term survival for people with ES-SCLC after having serplulimab. It was aware that the company had explored a treatment effect duration of 60 months followed by waning of the serplulimab arm to the atezolizumab arm in its scenario analysis. It also recalled that the committee in TA683 had decided to apply a 60-month treatment effect duration. The committee concluded that a 60-month treatment effect duration from starting treatment was plausible and consistent with previous ES-SCLC evaluations. But, it concluded there was remaining uncertainty on the relative long-term treatment effect of serplulimab.

## Extrapolating time to off-treatment

### Serplulimab and platinum-based chemotherapy-only arms

3.11 Similar to PFS and OS, in the company's submission, it applied independent log-logistic curves to the serplulimab and platinum-based chemotherapy-only data from ASTRUM-005. The company said that this approach was used to estimate longer-term time to off-treatment and to accurately capture costs associated with serplulimab. This is because in ASTRUM-005, people were allowed to continue treatment with serplulimab after first progression. Similar approaches were taken in the IMpower133 and CASPIAN trials for atezolizumab and durvalumab, and in TA638. The committee noted that, despite this, time to off-treatment for serplulimab mapped closely to PFS in ASTRUM-005. In response to the first consultation, the EAG updated its base case to use the log-logistic curves to model time to off-treatment for serplulimab and platinum-based chemotherapy only arms. At the second committee meeting, the committee concluded that the company's log-logistic models for the serplulimab and platinum-based chemotherapy-only arms were acceptable for decision making.

### Atezolizumab and durvalumab arms

3.12 For the comparisons with atezolizumab and durvalumab, in the first committee meeting the company and the EAG derived time to off-treatment by multiplying the reciprocals of the hazard ratio estimates from the MAICs for OS with hazard rates for stopping serplulimab. The committee recalled its concerns with the MAICs (see section 3.5). It requested further analyses to compare time to off-treatment for serplulimab with atezolizumab and durvalumab.

In response to the first consultation, the company provided a comparison of the median duration of treatment exposures for serplulimab (22.0 weeks), atezolizumab (20.4 weeks) and durvalumab (28.0 weeks) from their respective trials. The company also provided the scenarios requested by the committee, including:

- a scenario in which time to off-treatment is assumed to be equivalent to PFS for serplulimab, atezolizumab and durvalumab
- a scenario in which the gap between time to off-treatment and PFS for serplulimab in ASTRUM-005 is modelled to capture treatment beyond progression, and the same gap is also assumed to apply for estimating time to off-treatment for atezolizumab and durvalumab from their respective PFS extrapolations
- a scenario using the trial-observed ratios of median PFS to median time to off-treatment, applied to the PFS curves to generate the time-on-treatment curves, per treatment arm.

The company stated that the first scenario assumes that people only stop serplulimab because of progression. So, it is likely to overestimate time on treatment because people will likely stop treatment for other reasons, such as tolerability, before they have progression. The EAG agreed and added that some people also continue to have treatment after progression. For the second scenario, the company said that applying the gap between time to off-treatment and PFS from ASTRUM-005 to the

atezolizumab and durvalumab arms leads to an imbalance in the cost and efficacies for the comparator arms. The EAG agreed. The company believed the third scenario to be too simplistic. For example, the median time on treatment in the CASPIAN trial for durvalumab was greater than the median PFS. The EAG disagreed that this was an issue. The EAG base case adapted the third scenario by multiplying the ratio of median time to off-treatment to median PFS with the comparators' PFS hazard rates, instead of the PFS curves. The company retained its original base-case approach in the second committee meeting, explaining that using the time to off-treatment curves directly from ASTRUM-005 alongside hazard ratios from the MAICs for atezolizumab and durvalumab ensures that treatment costs and efficacy data in the model are balanced appropriately. The committee preferred the third scenario because it reflected the relationship between PFS and time to off-treatment observed in each of the trials and did not rely on hazard ratios calculated from the MAICs. For the third committee meeting, the company applied the third scenario as its base case. The committee noted that applying the median PFS to median time to off-treatment ratio to either the PFS hazard rates (EAG approach) or directly to the PFS survival curves (company approach) had a minimal impact on cost-effectiveness. It concluded that it would consider both approaches in its decision making.

### Stopping treatment on disease progression

3.13 After the second committee meeting, the company informed NICE that, after clinical validation, the modelled time to off-treatment does not reflect clinical practice. Clinical experts advised that people would stop immunotherapy at the point of disease progression, which aligns with current practice for atezolizumab and the summary of product characteristics for serplulimab. The committee chair invited the company to submit additional information on this issue for consideration at a third committee meeting.

In response to the second consultation, the company reiterated that it had

received clinical advice that stated that immunotherapy for ES-SCLC is usually stopped upon disease progression in the UK. This was supported by clinical experts at the third committee meeting, who noted that ES-SCLC progression is often quick and aggressive, and that very few people are treated beyond disease progression. To reflect this, the company revised its time-to-off-treatment modelling by implementing an assumption that people whose cancer had progressed do not continue treatment. Time on treatment was capped so it could not exceed PFS. This was applied to the serplulimab and atezolizumab treatment arms (see sections 3.11 and 3.12). The EAG noted that the serplulimab and atezolizumab time-to-off-treatment curves were always lower than the respective PFS curves, so the assumption had no effect. It stated that the new analysis removed treatment costs in the progressed disease health state, but that it was not possible to explore a scenario that also removed the treatment benefit after progression because the company had not used a Markov model. The company noted that clinical advice suggested that there would be no benefit of treating beyond progression. The EAG considered the company's implementation of the assumption to be suitable and adopted it in its base case. The committee concluded that the updated time-to-off-treatment modelling was suitable for decision making.

## Height and weight

3.14 Dosing of serplulimab and chemotherapy treatments are based on weight and body surface area. In the model, the company used the mean body weight (68.4 kg) and height (167 cm) from ASTRUM-005. The EAG noted that the ASTRUM-005 population (predominantly Asian and male) does not reflect the NHS population (see section 3.4). It highlighted that the weight and height from the trial may not be representative of the NHS population. It highlighted the National Lung Cancer Audit, which reported that in England around 50% of people with SCLC are female and the median age at diagnosis is 70 years. It also stated that the average weight of people aged 65 to 74 is 79.3 kg and the average height is 166.8 cm (Health Survey for England). The national specialty adviser said that the

median age of people having atezolizumab for untreated ES-SCLC was 68 years. The EAG suggested that using a lower weight and height than that of the NHS population could underestimate drug costs for serplulimab and platinum-based chemotherapy, for the same expected effectiveness. This would bias results in favour of serplulimab in the comparisons with atezolizumab and durvalumab because atezolizumab and durvalumab are fixed-dose treatment regimens. In response to the first consultation, the company explained that the EAG's estimates from the Health Survey for England were reflective of the general population and were likely to overestimate the weight of the population in England with ES-SCLC. The company updated its base case to use height (166.9 cm) and weight (76.4 kg) values estimated from reweighting the non-Asian population in ASTRUM-005 to reflect that 50% of the target population in England are female. The EAG agreed that this approach was appropriate. The committee concluded that using the reweighted weight and height data from the non-Asian population in ASTRUM-005 was acceptable for decision making.

### Health-state utility values

3.15 Utility values in the company's base case were informed by EQ-5D-5L data from ASTRUM-005, mapped to EQ-5D-3L. The values were calculated without accounting for repeated measures. The committee lead team highlighted that the company's utility values (PFS: 0.838; progressed disease: 0.805) were notably higher than values derived for non-small-cell lung cancer, yet SCLC is usually considered more aggressive. The company highlighted that the non-small-cell lung cancer utilities presented should not be used for comparison with ES-SCLC because they are historical values and there are differences in the population and methods used to estimate the utilities. The committee said that the health-state utility values were still higher than expected for ES-SCLC. It also noted that the utility values were closer to values expected for the general population. The clinical expert agreed that the health-state utility values were higher than expected for ES-SCLC. The lead team also

noted that least-squares mean estimates are subject to attrition bias. The lead team suggested that a better approach would be to estimate utility values using a mixed-effects model and scenarios that explore utility values from alternative data sources. The EAG provided scenario analyses using utility values from Nafees et al. (2008) (PFS: 0.673; progressed disease: 0.473) and Chouaid et al. (2013) (PFS: 0.71; progressed disease: 0.67), both of which reflect a population with non-small-cell lung cancer and are not based on trial data. The committee noted that the utility values for the ASTRUM-005 non-Asian subgroup were lower than those for the overall population and closer to previously used utility values. But the committee concluded that, although the values were more clinically plausible, the small population numbers of the non-Asian subgroup added uncertainty to the results. So, the committee preferred to use the whole-population data and requested an updated analysis that uses a mixed-effects approach.

After the first consultation, the company provided updated utility values using a mixed linear effects model and applied the progression-based utilities in its base case (PFS: 0.830; progressed disease: 0.796). The EAG highlighted that the values were similar to the least-squares mean estimates presented in the first committee meeting and that they remain higher than some published utility values for SCLC. But it noted the updated values were likely more accurate than the least-squares mean estimates and so applied the updated utilities in its revised base case. The clinical expert explained that the introduction of immunotherapy for ES-SCLC has increased survival for a small number of people, but that they had not seen a notable increase in health-related quality of life. So, they did not expect utilities to be higher for people with ES-SCLC having serplulimab than for people having other treatments. The committee recalled the uncertainties associated with the generalisability of ASTRUM-005 to the NHS population, highlighting that it was primarily done in an

Asian population (see section 3.4). But the committee acknowledged that the utilities were:

- estimated from EQ-5D data collected in the relevant clinical trial (NICE's preferred measure and source of data for health-related quality of life), which had a high response rate
- analysed using the committee-preferred approach
- aligned with the health states used in the company's model.

So, despite the potential limitations in face validity compared with existing utility values in lung cancer and for the general population, the committee concluded that progression-based health state utilities, based on the whole-population ASTRUM-005 data and estimated using a mixed-effects approach, were acceptable for decision-making.

## Severity

3.16 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 (a severity modifier) to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's technology appraisal and highly specialised technologies guidance manual. The company's and EAG's revised base cases after the second consultation met the QALY shortfall criteria for a 1.2 severity modifier weight. Using the committee's preferred assumptions, the severity modifier threshold was met. The committee concluded that a severity weight of 1.2 should be applied.

## Other factors

### Equality

3.17 The committee did not identify any equality issues.

### Uncaptured benefits

3.18 The committee considered whether there were any uncaptured benefits of serplulimab. The NICE technical team highlighted that atezolizumab could be administered subcutaneously, whereas serplulimab and durvalumab are administered only intravenously (see section 3.2). The clinical expert at the first meeting noted that, in their practice, approximately 20% of people had switched to having atezolizumab subcutaneously in the maintenance phase of treatment. They also noted that the availability of subcutaneous administration was a factor when choosing a treatment because it has time and resource savings compared with intravenous administration. The national specialty adviser estimated that at least 50% of people were having atezolizumab subcutaneously in NHS practice. The clinical expert and national specialty adviser highlighted the additional benefits of subcutaneous administration, including convenience for the patient. In the company's and EAG's base cases, 100% of people were assumed to have atezolizumab intravenously. The EAG provided additional scenarios exploring the cost of subcutaneous administration of atezolizumab during the maintenance phase, including modelling 75% of people having atezolizumab subcutaneously and 25% of people having atezolizumab intravenously, as modelled in TA1041. The committee preferred to account for the cost of administration of atezolizumab in the model in line with TA1041 and noted that this had a small impact on the cost-effectiveness results. But the committee acknowledged that the additional benefits of subcutaneous administration had not been captured in the model for atezolizumab. It concluded that it would take into account any potential uncaptured benefits of atezolizumab in its acceptable incremental cost-effectiveness ratio (ICER) threshold (see section 3.20).

## Cost-effectiveness estimates

### Company and EAG cost-effectiveness estimates

3.19 The company's and EAG's base cases differed by the approach to extrapolate time to off-treatment in the atezolizumab and durvalumab

arms. This difference has a minimal impact on cost effectiveness and did not impact decision making (see section 3.12). The company's and EAG's base-case assumptions were between £25,000 and £35,000 per QALY gained when compared with atezolizumab and including a severity weight of 1.2 (the exact ICERs are confidential because of confidential comparator prices).

## Acceptable ICER

3.20 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits (see section 3.18). The committee noted the high level of uncertainty, specifically that:

- the population characteristics of the clinical trial differed from the expected NHS population and the generalisability was unclear (see section 3.4)
- uncertain ITCs were used, including an MAIC approach that lacked robustness, FP NMAs that did not fit the observed data well and an unadjusted Bucher approach (see section 3.5)
- the benefits of serplulimab calculated from the data differed from clinical experts' expectation of similarity with the comparators (see section 3.6)
- there was uncertainty in the relative difference in PFS and OS between serplulimab and atezolizumab and the duration of serplulimab's treatment benefit (see section 3.9 and section 3.10)
- the relative differences in time to off-treatment between serplulimab and atezolizumab were uncertain (see section 3.12)

- the utility values sourced from ASTRUM-005 were notably higher than would be expected for people with ES-SCLC (see section 3.15)
- there were likely to be uncaptured benefits of using atezolizumab subcutaneously that were not captured in the model (see section 3.18).

The committee also recalled that serplulimab was not expected to fully address the unmet need for SCLC in the first-line setting (see section 3.2). At the third meeting, the committee felt that some of the uncertainty in the modelling had been reduced. But, it noted that key uncertainties in the data remained, such as uncertainty in the Bucher ITCs and the generalisability of the trial data. So, the committee concluded that an acceptable ICER would be towards the lower end of the threshold range usually considered a cost-effective use of NHS resources.

### Committee's preferred assumptions

3.21 The committee's preferred assumptions were to model:

- Bucher ITC hazard ratios to extrapolate PFS and OS in the atezolizumab arm (see section 3.5 and section 3.9)
- independent log-logistic models for the PFS, OS and time to off-treatment extrapolation of the serplulimab and platinum-based chemotherapy-only arms (see section 3.8 and section 3.11)
- the time to off-treatment extrapolation for the atezolizumab and durvalumab arms using the ratio of the median time to off-treatment over the median PFS for atezolizumab or durvalumab. The committee considered both the EAG's and company's approach to apply the ratio in its decision making (see section 3.12)
- that treatment is stopped on disease progression (see section 3.13)
- height and weight based on the reweighted non-Asian population in ASTRUM-005 (see section 3.14)

- progression-based health state utilities, based on the whole-population ASTRUM-005 data and estimated using a mixed-effects approach (see section 3.15)
- a severity weight of 1.2 (see section 3.16).

### Conclusion

#### Recommendation

3.22 The committee concluded that its preferred cost-effectiveness estimate was within the cost-effectiveness range considered an acceptable use of NHS resources (see section 3.20). So, it concluded that serplulimab with carboplatin and etoposide can be used as an option for untreated ES-SCLC in adults.

## 4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on

all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has untreated extensive-stage small-cell lung cancer and the healthcare professional responsible for their care thinks that serplulimab with carboplatin and etoposide is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Evaluation committee members and NICE project team

## Evaluation committee members

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

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

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

## Chair

**Raju Reddy**

Interim chair, technology appraisal committee D

## NICE project team

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

**Lauren Elston, Cara Gibbons, and George Millington**

Technical leads

**Rachel Williams and Cara Gibbons**

Technical advisers

**Kate Moore and Louise Jafferally**

Project managers

**Lorna Dunning and Ross Dent**

Associate directors

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