Single Technology Appraisal

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance 2 from Accord:**
   a. Draft guidance 2 Comments
   b. Draft guidance 2 Appendix A
   c. Draft guidance 2 Appendix B

   There were no comments from other stakeholders, invited experts or submitted through the NICE website.

2. **External Assessment Group documents**
   a. Critique of company comments on the Draft Guidance 2
   b. Pre-ACM 3 addendum

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Draft guidance comments form

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. • The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have

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	regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Accord Healthcare
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	NA
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Company commitment to providing access to patients** The Company is committed to the NICE process in bringing serplulimab to eligible patients with extensive-stage small-cell lung cancer (ES-SCLC). The Company welcomes the opportunity to comment on NICE's draft guidance and provide additional information for the EAG's and Committee's consideration ahead of the Committee Meeting: • Summary of Structured Expert Elicitation providing insights into time on treatment at and beyond progression with immunotherapy in the NHS in the UK (Appendix A). • Summary of an advisory board including 4 leading clinicians in the NHS, emphasising the robustness and generalisability of the ASTRUM-005 outcomes to clinical practice in the UK and the validity of the time on treatment (TToT) curves and assumptions. The panel of experts invited at the advisory board agreed with the NICE committee's preferred base-case for OS and PFS, but did not agree with the Committee preferred base-case for TToT (Appendix B).

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	• Summary of the updated base-case results from the model, including treatment discontinuation at progression based on UK clinical practice and aligned with the Summary of Product Characteristics (SmPC), clinical advice, and the Committee's request. Appendices are provided for the Committee and EAG's consideration, including a report of the SEE methodology (Appendix A), a report of the advisory board (Appendix B) and a summary of the model results. The Company would like to confirm their agreement to the following Committee's assumptions, as outlined in the draft guidance: • Use of the Bucher ITC hazard ratios to extrapolate PFS and OS in the atezolizumab and durvalumab arms (see section 3.5 and section 3.9) • Use of the independent log-logistic models for the PFS and OS of the serplulimab and platinum-based chemotherapy-only arms (see section 3.8 and section 3.11) • Use of the height and weight based on the reweighted non-Asian population in ASTRUM-005 (see section 3.13) • Use of progression-based health state utilities, based on the whole-population ASTRUM-005 data and estimated using a mixed-effects approach (see section 3.14) • Use of a severity weight of 1.2 (see section 3.15) The Company considers that several key items of evidence—namely the structured expert elicitation (SEE), the updated TToT modelling aligned with UK practice, and the advisory board consensus—have not yet been fully reflected in the current draft guidance. These data directly address areas of perceived uncertainty highlighted by the Committee, and therefore should be incorporated into the next stage of the assessment to ensure all relevant evidence is taken into account.
2	**Unmet need in ES-SCLC** NICE's draft guidance states that serplulimab "does not address an unmet need" and that existing options adequately treat ES-SCLC, but also states that "ES-SCLC has poor prognosis and limited treatment options". This suggests that there is a remaining unmet need in ES-SCLC, which was explored and confirmed in the Company's Advisory Board. Clinicians disagreed with NICE's conclusion that current treatment options adequately address the unmet need in ES-SCLC (a full report is provided in Appendix A). Clinicians also agreed that serplulimab offers a clinically meaningful alternative which targets this unmet need, providing a durable first-line benefit in a highly severe condition, and represents the first meaningful improvement in ES-SCLC since the introduction of atezolizumab. The median overall survival benefit for serplulimab in ASTRUM-005 was greater than the benefit observed for atezolizumab in IMpower133 (15.8 months vs 12.3 months). This benefit was confirmed in the matching-adjusted indirect comparison (MAIC) provided in the Company submission ([redacted]. In addition to this, serplulimab can be seamlessly integrated in NHS clinical practice given the similarity in administration compared with other recommended immunotherapies such as atezolizumab and durvalumab. During the advisory board, three major unmet-need domains were highlighted.

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	Low access to first line therapy in practice: Clinicians noted that up to 50% of ES-SCLC patients never receive any systemic therapy, due to poor performance status, rapid clinical decline, late presentation, or logistical/systemic barriers. This means: • Any therapy capable of improving first-line survival disproportionately benefits patients. • The magnitude of incremental benefit in a trial underestimates the real-world value of improved first-line efficacy. High attrition to second-line therapy: Experts emphasised that <30% of patients reach second-line treatment in UK real-world practice. Thus: • The majority of patients rely entirely on the efficacy of their first-line regimen. • A therapy demonstrating improved durable benefit in first-line therefore directly targets a core unmet need. Lack of maintenance strategies Clinicians noted that ES-SCLC has no effective maintenance paradigm, and that extending durability of immunotherapy benefit is a major area of unmet clinical need. **Clinicians unanimously agreed that there is currently an unmet need for a first-line treatment providing improved survival and a broader range of options for patients and clinicians in the NHS in the UK**. Clinicians specifically highlighted the potential survival benefit serplulimab may offer given the robust benefit demonstrated in ASTRUM-005 and associated indirect treatment comparisons presented in the submission over current immunotherapies such as atezolizumab and durvalumab. Given the unanimous clinician feedback and the substantial body of evidence submitted, the Company believes the draft guidance does not fully reflect the continuing unmet need in ES-SCLC. The conclusion that existing options adequately treat ES-SCLC is inconsistent with both clinical experience and published survival outcomes. Accordingly, the current interpretation presented in the draft guidance is not a reasonable reflection of the totality of clinical evidence or real-world practice.
3	**Time on treatment and plausibility of current assumptions** The Committee expressed concern about uncertainty in post-progression treatment and its generalisability to the UK. Clinician opinion was elicited to understand the plausibility of treatment post-progression in the UK. The advisory board and SEE results were used to better understand the plausibility of treatment beyond progression in the NHS: • In the advisory board, clinicians stated that the current TToT curve was not reflective of current outcomes, overly optimistic, and biologically implausible in ES-SCLC (Appendix B). Clinicians were shown the range of TToT curves explored by the Company and EAG during the submission process (see Figure 1). There was significant scepticism around the plausibility of the long tail of the time on treatment curve in the current base case TToT curve. Clinicians unanimously felt it was clinically implausible for patients to remain on treatment 10+ years, even for a small subset of patients. The group estimated that realistically, only around 4-8% of patients would likely still be on treatment at the 4-year mark and less than 5% at 5 years and stated that non-zero continuation beyond 10 years was biologically and

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	clinically implausible. Clinicians stated that treatment with immunotherapy in ES-SCLC is usually discontinued upon progression in the UK. A very small number of patients are considered "super-responders", but clinicians shared currently having up to two or three patients alive each after 4 years of treatment, and an even smaller proportion of patients on treatment. Overall, clinicians felt the time on treatment curve needed to be revised to better reflect real-world clinical practice and experience, where patients tend to discontinue treatment at progression. The clinicians also unanimously agreed that the EAG's proposed TToT curves were implausible. *Figure 1: TToT scenarios* [redacted] **Abbreviations**: KM, Kaplan-Meier; TToT, time to off treatment. • In the advisory board, clinicians also shared that their criteria for stopping treatment would not differ across atezolizumab, durvalumab and serplulimab (Appendix B). Clinicians shared that although patterns of progression can differ, treatment is generally stopped at progression in clinical practice in the NHS. ES-SCLC is an aggressive disease, and clinicians agreed that on average, patients progress or relapse rapidly. Any differences in post-progression management are unlikely to invalidate the core survival benefit of serplulimab demonstrated in ASTRUM-005. Clinicians universally stated that continuing immunotherapy beyond 3-5 years in ES-SCLC was not standard, due to toxicity, cumulative risk, diminishing returns and lack of biological rationale. It is exceptionally rare for patients to survive beyond 4-5 years, further reducing the number of patients likely to be on treatment post-progression. • In the SEE, clinicians were asked whether they agreed with the limited benefit of treatment ES-SCLC with immunotherapy beyond progression (see Appendix A). In summary, 4 out of 5 clinicians agreed or strongly agreed that there is no benefit of treating patients beyond progression. One clinician disagreed, quoting that treatment post-progression is only considered for a highly selected and limited subgroup of patients presenting with oligo-progressive disease, where locally ablative strategies such as radiotherapy or stereotactic ablative radiotherapy (SABR) are clinically indicated. However, patients with oligo-progressive disease are not considered progressed patients in ASTRUM-005 under the RECIST criteria. As such, this response does not represent a true divergence in clinical opinion, and when interpreted within the context of RECIST progression used in the trial and the model, all clinicians were aligned that immunotherapy should not continue beyond progression. • In the SEE, clinicians provided values on the maximum treatment duration of treatment with serplulimab (see Appendix A). The pooled median of clinicians' judgments for the maximum number of years on treatment was 5.2 years. • In addition to the above, the funding mandate for atezolizumab and durvalumab in England is only up to the point of disease progression and enforced using the Blueteq form system. The Summary of Product Characteristics for serplulimab includes similar recommendation ("The recommended dose is 4.5 mg/kg bodyweight serplulimab every 3 weeks until disease progression or unacceptable toxicity"). Based on the feedback collected in the SEE and advisory board, clinicians agreed that the proportion of patients on treatment post-progression would likely be lower in clinical practice than what is modelled, without impacting the overall estimated benefit of serplulimab on OS and PFS. The Company has therefore incorporated a stopping rule in the model to reflect

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this feedback, which prevents patients who have progressed to continue treatment in the model. This is applied both in the model, and also in the parametric survival analysis for TToT where patients who remained on treatment post-progression were instead assumed to have discontinued. This refinement has been applied to both the serplulimab and atezolizumab arms within the model. In the base-case, the modelled curves are still expected to be an overestimation compared with anticipated clinical practice, given the model predicts a small proportion of patients to be on treatment beyond year 6.

To maintain cost-effectiveness, the patient access scheme (PAS) price per vial for serplulimab has been adjusted to [redacted] (equivalent to a [redacted] discount) per vial. This adjustment elicits an ICER of [redacted]. The summary results of this are provided below in Table 1.

Table 1: Updated Summary Results

	Serplulimab – ASTRUM-005 (independent model)	Atezolizumab – HR vs serplulimab	Incremental
Total discounted costs	[redacted]	[redacted]	[redacted]
Total discounted QALYs (1.2x QALY weight)	1.98	1.52	0.46
ICER (cost/QALY gained)			[redacted]

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

The Company considers that the TToT assumptions applied in the draft guidance are not reasonable interpretations of either the trial data or routine NHS practice. Clinician consensus strongly refutes the plausibility of extended post-progression therapy durations, and the updated modelling directly resolves this uncertainty. As such, retaining implausible assumptions in the provisional recommendations would underestimate cost-effectiveness and misinterpret the clinical evidence. On this basis, the provisional recommendations are not yet suitable for NHS guidance as they rely on assumptions that clinicians deem biologically and clinically implausible.

4

Robustness of ASTRUM-005 and clinical plausibility of trial results

The Company believes that the current draft guidance underestimates the robustness and generalisability of the ASTRUM-005 results. The evidence provided—including consistency across subgroups, alignment with UK real-world outcomes, and expert validation—should mitigate the uncertainty cited by the Committee. The current interpretation therefore does not fully reflect a reasonable or balanced reading of the totality of evidence.

The Company would like to re-emphasise the robustness and results of the ASTRUM-005 trial as presented in the evidence submission and response to the first draft guidance. ASTRUM-005 is a large, global, double-blind, randomised Phase 3 study with balanced baseline characteristics across arms and a well-conducted methodology aligned with NICE standards. The OS benefit is statistically significant, clinically meaningful, and durable, with separation of the survival curves maintained out to 42 months (median OS of 15.8 months vs 11.1 months) and a hazard ratio of 0.60 (95% CI 0.49–0.73)[1]. During the advisory board, clinicians repeatedly emphasised that the profile and magnitude of benefit seen with serplulimab is fully in keeping with, and potentially more than what they observe in practice when a genuinely active agent is introduced in ES-SCLC, particularly the more sustained OS tail compared with some PD-L1 inhibitors. Additionally, the control arm in ASTRUM-005 is consistent with what clinicians expect in clinical practice in the NHS in the UK.

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	Furthermore, subgroup analyses demonstrate consistent benefit across all clinical categories, including age, sex, smoking status, and race, with no evidence of effect modification. This consistency directly addresses NICE's concern regarding the geographic makeup of the study population and strongly supports the generalisability of results to the NHS population. During the advisory board, clinicians commented further on the results from ASTRUM-005 (Appendix B). They described the efficacy and safety profile as credible and transformational for patients, emphasising that most patients don't live beyond a year on current standard of care. They also highlighted that serplulimab showed separation of survival curve and sustained long-term benefit compared with IMpower133, which displayed "banana-shaped" curves merging in the tails. ES-SCLC is an aggressive cancer with poor survival outcomes and very small patient numbers surviving to second-line treatment. Clinicians viewed the survival benefit demonstrated in ASTRUM-005 to represent the first durable improvement in outcomes in this setting since the introduction of chemo-immunotherapy and a more impressive benefit that any of the other studies in ES-SCLC to date. They concluded that the data are robust and internally consistent.
5	**Pharmacological affinity of serplulimab** This mechanistic evidence has not been acknowledged in the current draft guidance but provides additional biological plausibility supporting the observed OS benefit. In the Company's view, the exclusion of this evidence from the draft recommendations suggests that not all relevant data have yet been incorporated. In response to the first draft guidance, the Company provided additional literature on the improved affinity profile of serplulimab compared with atezolizumab and durvalumab. The evidence and mechanistic considerations were discussed in the advisory board, and clinicians agreed there is a credible biological rationale that not all PD-1/PD-L1 inhibitors behave equivalently. The clinical advisors at the advisory board heard from a Clinical Pharmacologist consultant that although the structure of PD-L2 is similar to PD-L1, the binding affinity between PD-L2 and PD-1 is two- to sixfold higher than that with PD-L1, suggesting PD-L2 is an important molecule in immune escape (Appendix B). The advisors agreed this could pharmacologically explain the impact of serplulimab inhibiting the interaction of PD-1 with both PD-L1 and PD-L2. In addition, the clinicians also heard about a recent publication that showed that high (≥75th) PD-L2 RNA expression is about 30% in lung cancer [2]. Clinicians noted that while mechanistic details are complex, serplulimab binds very tightly to PD-1 and blocks both PD-L1 and PD-L2, which may underpin the more durable OS tail observed in ASTRUM-005.
6	**Conclusion** Given the evidence presented for serplulimab, the Committee has already recognised the severity of ES-SCLC and applied a 1.2 severity modifier. Furthermore, much of the perceived uncertainty stems from assumptions (e.g., time on treatment) that additional analyses, clarifications, and expert input directly resolve. As a result, the residual uncertainty is modest and consistent with other appraisals in similarly severe conditions. The Company therefore believe that this appraisal should be considered for a willingness to pay threshold greater than £25,000 per QALY in reference to the announced change to the NICE willingness-to-pay threshold to £25,000-£35,000.

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	In light of the totality of clinical, mechanistic and economic evidence—together with expert consensus and updated modelling—the Company believes that the draft recommendations are not a suitable basis for NHS guidance in their current form. The analyses submitted directly address the areas identified as uncertain by the Committee, and the residual uncertainty is modest and consistent with numerous appraisals in similarly severe conditions. Therefore, the Company considers that the clinical and cost-effectiveness evidence has not yet been reasonably interpreted in the draft guidance, and that the updated results support a recommendation of serplulimab within the NHS. Ultimately, the Company remains committed to working collaboratively with NICE to secure access for NHS patients. The Company believed that, with the clarifications and updated analyses submitted, alongside the willingness to explore commercial flexibility, the Committee will be able to reach a recommendation that recognises both the strength of the clinical evidence and the urgent unmet need in this devastating condition.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The

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References:

1. Cheng, Y., et al., *Serplulimab versus placebo plus chemotherapy as first-line treatment for extensive-stage small-cell lung cancer: Efficacy and safety from the end-of-study analysis of the international phase 3 ASTRUM-005 study.* Journal of Clinical Oncology, 2025. **43**(16_suppl): p. 8093-8093.
2. Patwari, A., et al., *PD-L2 Landscape and Correlation with Outcome: An Immunomic Analysis.* JCO Oncol Adv, 2026. **3**(1).

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Prepared for Accord

Appendix A: Structured expert elicitation to support health technology assessment of serplulimab in the UK

Report

February 2026

Prepared by Jane Moorhouse and Adelaide Shaw-Maguire

Abbreviations

ES-SCLC	Extensive-stage small-cell lung cancer
FIM	Fixed intervals method
HTA	Health technology assessment
KOL	Key opinion leader
MRC	Medical Research Council
NICE	National Institute of Health and Care Excellence
RECIST	Response Evaluation Criteria in Solid Tumours
SABR	Stereotactic ablative radiotherapy
SCLC	Small-cell lung cancer
SEE	Structured expert elicitation
TSD	Technical Support Document
VIM	Variable intervals method

Contents

Introduction

Small-cell lung cancer (SCLC) is the most aggressive form of lung cancer and is associated with the loss of tumour suppressor genes and abnormal PD-L1 expression on tumour cells [1-3]. Extensive-stage SCLC (ES-SCLC) is a subtype of SCLC that is deemed incurable with current treatment palliative in nature [4]. Patients with SCLC experience symptoms including cough, wheezing, shortness of breath (dyspnoea), and coughing up blood (haemoptysis), with the disease associated with a high burden to HRQoL. Patients with metastases can experience additional symptoms [4, 5]. Paraneoplastic syndromes are also common in SCLC [6].

Serplulimab is a humanised monoclonal antibody indicated for the treatment of adult patients with ES-SCLC. It binds to the programmed cell death-1 (PD-1) receptor, blocking its interaction with ligands PD-L1 and PD-L2 leading to broader immune suppression than therapies that only inhibit PD-L1. The clinical efficacy and safety of serplulimab have been demonstrated in a Phase 3, randomised, double-blind, placebo-controlled trial in which serplulimab plus chemotherapy showed significant benefits in OS, PFS, objective response rate, and duration of response compared to placebo plus chemotherapy.

As part of the ongoing UK health technology assessment (HTA) submission process, a health economic model has been developed to demonstrate the value of serplulimab. As there are no clinical trial data for treatment with serplulimab beyond 60 months, there is uncertainty around the discontinuation rates after the fourth year of treatment, which is a key component of this health economic model.

As such, the main objective of this research was to use HTA body-recommended approaches to elicit clinical estimates for the yearly discontinuation rates of people with ES-SCLC after the fourth year of treatment with serplulimab. This research will then be used to inform the health economic modelling and as part of the ongoing HTA submissions in the UK for serplulimab for the treatment of ES-SCLC, and capture uncertainty.

Objectives

The main objectives of this study were:

- To elicit clinical consensus on the benefit of treating ES-SCLC patients with immunotherapy post-progression.
- To elicit clinical estimates for the maximum number of years for which patients with ES-SCLC would remain on treatment with serplulimab.

Discontinuation was defined as a drop-off from treatment for clinical or personal reasons which are not pre-determined. Such reasons included death, intolerance, acute toxicity, a perceived lack of meaningful effect, changes in personal circumstances, negative patient psychology, cost, new treatment options, or any combination thereof. Discontinuation could also be due to disease progression, as judged by a patient's clinician, which may be aligned with Response Evaluation Criteria in Solid Tumours (RECIST) guidelines (version 1.1) [7]. RECIST 1.1 defines progression as:

- At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).
- In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm.
- The appearance of one or more new lesions is also considered progression.

An additional objective of this study was to elicit clinical estimates for discontinuation rates after the fourth year of treatment.

These clinical judgements can inform the cost-effectiveness modelling and ongoing HTA submissions in the UK for serplulimab in ES-SCLC.

Methodology

Overview

A structured expert elicitation (SEE) study was conducted based on methodology developed by the University of York and others, and previously funded by the Medical Research Council (MRC) [8]. This methodology was developed following a systematic review of elicitation approaches and targeted searches for specific methodological aspects, such as expert selection, fitting, and aggregation. Its findings were used to define a set of principles that underpin the use of SEE in healthcare decision-making and subsequently a reference protocol, which has previously been cited by NICE in its manual for HTA submissions [9]. This study was conducted in alignment with the York protocol [10] and the principles in the Decision Support Unit Technical Support Document (TSD) on expert elicitation for long-term survival outcomes (TSD 26) [11]. The specific methodology used in this study is shown in Table 1.

Table 1: Overview of SEE methodology

Element	Reference methods suggested	Methodology used in this study
Experts	• Recruitment will be driven by the context; however, the SEE should pursue diversity, representing the full range of valid experts' beliefs. Experts should be willing to participate. • Focus on gathering substantive expertise or experience. Normative skills can be developed during the training session as part of the SEE. • Minimise and record conflicts of interest among the experts. Include experts external to the SEE task, i.e. not those involved in developing the task. • At least five experts should be included in the SEE.	• Consultant medical oncologists working with ES-SCLC patients in day-to-day practice (n=7). • Based in the UK. • Substantial experience in treating patients with ES-SCLC (4+ years).
Quantities elicited	• Simple observable quantities should be elicited where possible; ratios or complex parameters, such as regression coefficients, should not be elicited directly. • Dependence between variables should be captured in SEE. Expressing dependent variables in terms of independent variables is preferable when experts do not have strong normative skills. • Wording should be clear and quantities should be decomposed where this means a better fit with experts' mental models.	• Quantities of interest were simple and observable. • There was no dependence between variables.
Approach to elicitation	• Beliefs should be elicited from experts individually, even if a group interaction follows. • Although interaction between experts can be structured through face-to-face sessions, constraints in healthcare decision-making, such as a lack of experienced facilitators, will mean this	• A training activity was provided for offline review. • An online survey link was then shared with the clinical experts, who were asked to complete it within 4 days of receipt.

Element	Reference methods suggested	Methodology used in this study
	takes place via a Delphi-style remote process. • Between-expert variation should be explored explicitly.	• An evidence brief was provided as part of the online survey. • All experts were offered the opportunity to discuss the training activity and survey in a call with the research team as required.
Method	• Both VIM and FIM work well; however, decision-makers should aim for consistency across applications.	• FIM.
Aggregation	• Statistical distributions should be fitted to experts' individually elicited judgements. • Following fitting, a summary of the individual distributions should be obtained using linear pooling with equal weighting of experts. • Any adjustments applied should be to improve coherence and consistency – not to reduce variability. Internal and external review can be used to assess validity.	• Statistical distributions were fitted to experts' individually elicited judgements. • Responses were aggregated into a single probability distribution, using linear opinion pooling with equal weighting of experts. • No adjustments were made to individual responses.
Delivery	• Face-to-face where possible to allow a facilitator to deliver training to the expert. • Feedback to experts should be given during the SEE. Following feedback, experts should be given an opportunity to revise their distributions, either during or after a SEE session.	• The training activity was provided as a 1-hour offline review task. • All experts had the opportunity to discuss the training activity and survey in a call with the research team as required. • During the SEE, experts were asked to test their initial judgements and refine if they felt it was necessary.
Training and piloting	• Training is crucial and should focus on avoiding bias and expressing uncertainty. • Piloting should be undertaken.	• An offline training activity was provided to avoid bias and uncertainty. • Piloting was undertaken.
Rationale and documentation	• The rationale for how the experts made their judgements should be collected after the SEE. • All methodological choices for the SEE must be documented and justified.	• The rationale for how the experts made their judgements was collected. • All methodological choices were documented and justified.

Source: Horscroft et al. 2022 [10]

Abbreviations: ES-SCLC, extensive-stage small-cell lung cancer; FIM, fixed intervals method; KOL, key opinion leader; SEE, structured expert elicitation; VIM, variable intervals method.

Quantities of interest

The following quantities of interest were explored in this SEE.

Quantity of interest 1: Treatment benefit post-progression

To what extent would you agree with the following statement: “There is limited benefit in treating ES-SCLC patients with immunotherapy post-progression.”

Quantity of interest 2: Maximum duration of treatment with serplulimab

Consider a population of patients with ES-SCLC. These patients initiated treatment with serplulimab in combination with carboplatin and etoposide as a first-line treatment at Year 0. Chemotherapy was administered for the first 4 cycles in combination with serplulimab, after which serplulimab maintenance was continued.

You will now be asked to make probabilistic judgements on the number of years since treatment initiation at which no patients in this population would still be receiving treatment. In other words, after a total of how many years of treatment with serplulimab will all ES-SCLC patients have discontinued their treatment?

Quantity of interest 3: Discontinuation of serplulimab after 4 years of treatment

Consider the same population of patients with ES-SCLC who had initiated treatment with serplulimab in combination with carboplatin and etoposide as a first-line treatment at Year 0. Chemotherapy was administered for the first 4 cycles in combination with serplulimab, after which serplulimab maintenance was continued. 100 patients are still receiving this treatment at the end of year 4.

a) You will now be asked to make probabilistic judgements on the number of patients with ES-SCLC who remain on treatment with serplulimab at the end of the fifth year of treatment. Or in other terms, how many of the 100 patients who remain on treatment by the end of the fourth year of treatment with serplulimab will not discontinue by the end of year 5?

b) You will now be asked to make probabilistic judgements on the number of patients with ES-SCLC who remain on treatment with serplulimab after a further two years of treatment. Or in other terms, how many of the patients that remain on treatment at the end of the fifth year of treatment with serplulimab (as you answered previously) will not discontinue by the end of year 7?

Experts

Experts were identified by Accord, based on the following pre-determined eligibility criteria:

- Consultant medical oncologists working with ES-SCLC patients in day-to-day practice.
- Based in the UK.
- Substantial experience in treating patients with ES-SCLC (4+ years).

A total of 7 experts participated in the study. Accord was responsible for identifying experts and passing on their contact details to Initiate to conduct contracting and manage any queries. Communications with the healthcare professionals were conducted in accordance with the Association of the British Pharmaceutical Industry Code of Conduct. All participants were provided with honoraria, reflecting the fair market value for the services provided as determined by Accord.

Training

Before completing the survey, the experts were required to undertake a 1-hour offline review activity, involving a review of training slides comprising the following topics:

- The objectives of the study and how the outputs may be used.
- The methodology, including the concepts of subjective probability and probabilistic judgements.
- Common forms of bias.

As part of the online survey, participants were provided with an evidence brief to review, which summarised the key evidence relevant to the quantities of interest. This aimed to contextualise the quantities of interest and minimise availability bias, when judgements are based on evidence, experiences, or events that are easy to recall and ignore evidence that is less memorable.

All experts had the opportunity to have a call with the Initiate team to discuss any queries regarding the training activity or survey.

Approach to elicitation

The York MRC protocol (Table 1) was considered appropriate for this SEE study because it allows for a greater number of quantities of interest to be explored; the quantities of interest were not sufficiently complex to require behavioural aggregation; and time constraints.

Survey development and piloting

The survey was piloted with an Initiate researcher to ensure that the associated study materials were sufficient; the language appropriate for a clinical audience; and the online survey functionality was appropriate.

Administration

The SEE was conducted using an online SEE survey platform (Dark Peak Analytics SEE Platform [12]) and was designed to minimise the risk of bias. After each judgement was elicited, experts were asked to critically reflect on their initial answers and make any changes to their initial answers, if necessary. The survey took approximately 1 hour for the clinical experts to complete. The evidence brief was shared with the experts as part of the online survey.

The training slides for the offline training activity were shared with the experts alongside a link to the online survey, with experts being asked to spend 1-hour on the training activity before proceeding to the survey itself.

All experts had the opportunity to have a call with the Initiate team to discuss any queries regarding the training activity or survey.

When the survey was completed, Initiate conducted an initial review to assess clinician responses for any ambiguous or unexpected responses. Following administration of the survey, it was noted that there was ambiguity around the duration of administration of chemotherapy. This was clarified with the experts via email. Each expert was given the opportunity to revise their judgements if they did not reflect their beliefs. Follow up calls were held where needed.

Individual judgements

For quantity of interest 1, the experts were asked to state their level of agreement using a Likert scale: strongly agree/agree/neutral/disagree/strongly disagree.

For quantities of interest 2 and 3, the experts were asked to provide probabilistic judgements using the Roulette method (or ‘chips and bins’). This was selected as SEE guidance states that experts may prefer this method as it more intuitive than the other methods [10]. A probability distribution was fitted

to each expert's individually elicited judgements using the Dark Peak Analytic SEE Platform [12], which uses the SHELF R Shiny app [13].

Aggregation and reporting

Responses were combined into a single probability distribution for each probabilistic quantity of interest (2 and 3). The SEE used mathematical aggregation to fully capture the clinicians' subjective uncertainty and variability across clinicians, as recommended in the York MRC reference protocol (Table 1) [8, 10].

Linear opinion pooling – an arithmetic average of the distributions from each expert with equal weights – was used to generate the aggregated distribution for each quantity of interest. Mathematical aggregation does not require experts to converge to a group distribution, allowing variability between experts to be reflected within an overall distribution.

NICE recommends that the reporting of the methods used for expert elicitation follow existing reporting guidelines when possible. The results from this study have been reported in line with guidance from the York MRC reference protocol and Iglesias et al [8, 14].

Results

Quantity of interest 1: Treatment benefit post-progression

Of the 5 experts who answered this question, 4 either agreed or strongly agreed that there is limited benefit in treating ES-SCLC patients with immunotherapy post-progression. One expert disagreed and provided the following rationale:

"I only consider the continuation of immunotherapy post-progression for a highly selected and limited subgroup of patients presenting with oligo-progressive disease, where local ablative strategies such as radiotherapy or stereotactic ablative radiotherapy (SABR) are clinically indicated."

Quantity of interest 2: Maximum duration of treatment with serplulimab

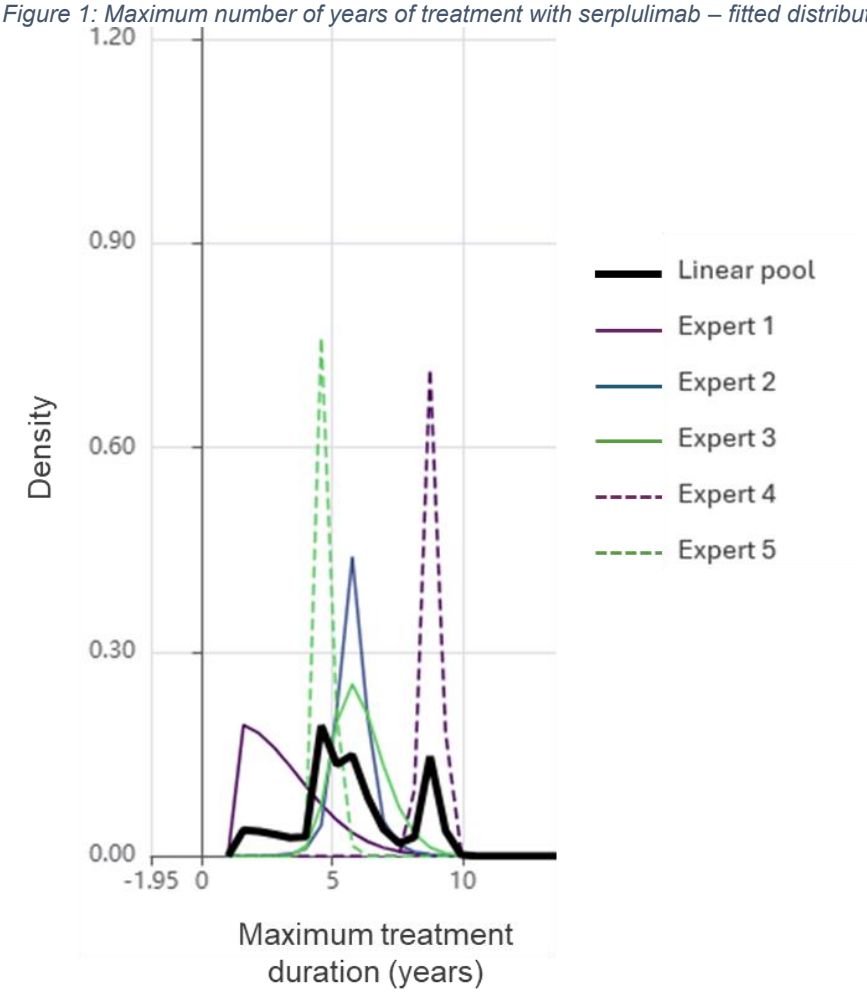
The pooled results for the maximum number of years of treatment with serplulimab is shown in Table 2. The fitted distributions are shown in Figure 1.

The judgements for one expert were excluded as they were not logical or plausible (50+ years). Each expert was confident in their judgement and judgements were fairly consistent between experts. Overall, the experts felt that total duration of treatment would be fairly short with contributing factors being disease progression, toxicity, patient choice, the age and frailty of the patient population, presence of comorbidities, and non-cancer-related mortality.

Table 2: Maximum number of years of treatment with serplulimab – pooled results

Quantity of interest	Median (50th percentile)	Interquartile range (25th – 75th percentile)	95% credible interval (5th – 95th percentile)
Treatment duration	5.20	4.21, 6.66	1.71, 8.69
1 expert was excluded as their responses were not logical.			

Figure 1: Maximum number of years of treatment with serplulimab – fitted distributions



Quantity of interest 3: Discontinuation of serplulimab after 4 years of treatment

Experts were asked to consider the number of patients remaining on treatment at years 5 and 7. While they agreed that the number was likely to be very low, there was a lack of consensus. The chips and bins methodology caused conceptual confusion given such small numbers of patients were considered likely to remain on treatment at these timepoints. More than 50% of the experts noted that this question was challenging to answer with some stating that their responses were somewhat arbitrary given lack of data and likely low patient numbers. It was therefore not considered appropriate to aggregate these data.

Discussion

Strengths and limitations of the study

SEE is recommended by NICE to minimise bias when eliciting judgements from clinical experts and provide a measure of their uncertainty. This study used a robust methodology in line with the reference protocol developed by the University of York and others [8], which has previously been cited in the NICE manual [9].

A further strength of the study was that it included clinicians who have in-depth knowledge of patients with ES-SCLC. An evidence brief was provided to them to read before the study to ensure that they were familiar with the relevant clinical data. Clinicians may not be familiar with probabilistic elicitation. Therefore, training was provided before the survey, including a practice example, clarification of the quantities of interest, and time for questions.

Participants were offered the opportunity to ask members of the research team questions about the training activity and survey in a call as needed. Several experts asked such questions, which likely improved the accuracy of their judgements.

Expert elicitation studies are subject to bias, including cognitive bias (anchoring or availability bias) and motivation bias (confirmation or (un)desirability bias). This study attempted to minimise these biases by providing an evidence brief and training and asking for plausible limits before asking the experts to allocate their chips. However, it is impossible to negate all bias in a study such as this.

Conclusion

This study provides a compelling clinical consensus that immunotherapy should not continue beyond progression. Moreover, probabilistic judgements showed that the maximum number of years on treatment was short, with a pooled median of 5.20 years (interquartile range: 4.21 – 6.66; 95% credible interval: 1.71 – 8.69).

In the absence of empirical evidence, expert judgement is required but is subject to bias. This study used a structured methodology to minimise bias and capture the level of uncertainty around experts' judgements. However, further research is needed to reduce remaining uncertainty around the quantities explored in this study.

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Prepared for: **Accord Healthcare**

Serplulimab in ES-SCLC

Prepared for NICE Draft Guidance Consultation for serplulimab in ES-SCLC (ID6346)

Date: 13th February 2026

Executive Summary

A panel of UK thoracic oncologists reviewed key issues raised in NICE's draft guidance for serplulimab, particularly concerns around:

- Plausibility of the time-to-off-treatment (TToT) extrapolations
- Alignment of ASTRUM-005 control-arm behaviour with clinical practice
- Biological and clinical plausibility of long-term treatment continuation
- Unmet need in extensive-stage small cell lung cancer (ES-SCLC)
- Generalisability of Astrum-005 to NHS population including comparability of Asian vs non-Asian populations

Clinicians were consistent and clear on several points:

- The control arm in ASTRUM-005 behaves as expected, lending credence to the trial quality and magnitude of benefit.
- The current long term TToT curve is clinically implausible, especially beyond year 4–6.
- Real-world TToT is substantially lower than the current curve suggests.
- Long-term continuation of immunotherapy (IO) beyond progression is not clinically practiced.
- Generalisation from ASTRUM-005 to the NHS is appropriate, and ethnicity is unlikely to result in differences in clinical response rates.
- There is clear unmet need as survival rates are still low in ES-SCLC making gains in first-line particularly meaningful.

Purpose of the meeting

- Gather real-world clinician insight on:
    - Expected duration of IO use in ES-SCLC
    - Plausible long-term survival and treatment patterns
    - Continuity of IO beyond progression
    - How ASTRUM-005 results compare with UK practice
- Clarify how clinicians interpret specific NICE concerns in the draft guidance.
- Understand the unmet need of ES-SCLC in the UK.

Attendees

This research was conducted with the following experts.

Medical oncologist specialising in Lung, Bladder and Prostate cancer
Medical oncologist and consultant specialising in the treatment of non-small cell lung cancer, small cell lung cancer, mesothelioma, thymic malignancies
Consultant Medical Oncologist specialising in Lung and Urology tumours
Consultant Medical Oncologist specialising thoracic and gastrointestinal cancers as well as immunotherapy and clinical trials
Associate Professor and Clinical Pharmacologist

Clinical Discussion on Time to off Treatment (TToT)

Strong consensus: the current TToT curve is not clinically plausible

Clinicians repeatedly emphasised that the current TToT extrapolation is unrealistic, particularly:

- At 2 years: Clinicians universally stated that the curve (see Figure 1) overestimates the proportion of patients on treatment, with several noting they rarely have any ES-SCLC patients still on IO at 2 years.
- At 4 years: Clinicians indicated the curve is optimistic even under trial conditions, and real-world- rates would be lower.
- Beyond 6–10 years: the curve shows some patients continued treatment > 10-years. Clinicians unanimously described this as biologically and clinically implausible, given disease behaviour and historical UK survival experience.
- Clinicians experience round the table was that a minority of patients (termed “super responders”) would be in immunotherapy at 5-years.

When questioned about Figure 1: TToT scenarios

[redacted]

Abbreviations: KM, Kaplan-Meier; TToT, time to off treatment.

- Table 1, the clinical experts agreed that this is a possibility but could not envisage treatment beyond 6-10 years

Figure 1: TToT scenarios

[redacted]

Abbreviations: KM, Kaplan-Meier; TToT, time to off treatment.

Table 1: Trial participants still on treatment at year 4 (42-months treatment), ASTRUM-005

[redacted]

In line with ASTRUM-005, clinicians stated that treatment is usually discontinued upon progression in the UK. A small number of patients are considered “super-responders”, but this represents a small proportion of patients. Clinicians shared currently having up to two or three patients alive each after 4 years of treatment, and an even smaller proportion of patients on treatment. The proportion of patients on treatment at 5 years is therefore likely to be less than 5%. Clinicians also shared that their criteria for stopping treatment would not differ across atezolizumab, durvalumab and serplulimab.

TToT should not persist significantly in the long-term

While the exact timepoint varied by expert:

- Most said the TToT curve should not persist significantly beyond 5-6 years, given only a small subset of patients survive beyond this timepoint.
- They noted trials might show slightly longer-term treatment than UK practice, but that the current model predictions were not clinically plausible.

Post-Progression Treatment & Carryover Effect

There was nuanced debate regarding post-progression treatment, including:

- Possible carryover effects from IO that enhance later chemotherapy responses.
- Whether IO continuation beyond progression offers additional benefit (clinicians agreed: no strong evidence; unlikely in SCLC).

Clinicians shared that although patterns of progression can differ, treatment is stopped at progression in clinical practice in the NHS and indeed there is no funding mandate for treatment beyond progression in England. ES-SCLC is an aggressive disease, and clinicians agreed that on average, patients progress or relapse rapidly. Any differences in post-progression management are unlikely to invalidate the core survival benefit of serplulimab.
Clinicians universally stated:

- Continuing IO beyond 3–5 years in ES-SCLC is not routine clinical practice.
- Toxicity, quality of life. cumulative risk, diminishing returns, and lack of biological rationale make long-term continuation implausible.

Interpretation of ASTRUM-005 Efficacy and Curves

Agreement that ASTRUM-005 control arm is clinically plausible

Clinicians felt the ASTRUM-005 control arm aligns with would be seen in clinical practice and other trials, thus strengthening confidence that serplulimab's observed OS benefit reflects genuine effect.

Magnitude of OS benefit is clinically meaningful

Clinicians repeatedly emphasised that:

- A ~2-month incremental OS benefit on top of chemo-IO (vs historical 1-year survival ceiling) feels clinically meaningful.

Generalisability: Asian vs Non-Asian Populations

No pharmacological basis for ethnic differences in IO response

Experts stated explicitly that there is no evidence suggesting that patients treated with immune checkpoint inhibitors would respond differently in SCLC based on their ethnicity.

UK clinicians' real-world experience supports generalisability

Clinicians agreed that the outcomes of ASTRUM-005 were generalised to their practice in the UK, supported by the forest plot of pre-specified subgroup analyses showing no difference by race or smoking status.

Unmet Need in ES-SCLC

Clinicians strongly disagreed that there is no unmet need in the UK

Clinicians reframed unmet need across clear areas:

1. **Access to first-line treatment**
2. **Attrition to second-line:** Only ~30% reach second-line therapy in practice. Therefore, first-line benefit is crucial and has disproportionate value.

3. **Absence of therapies that provide a clinically meaningful improvement in OS over existing treatment**
4. **Maintenance phase optimisation:** SCLC lacks effective maintenance strategies and improving durability of response is an area of major unmet need.

All clinicians unequivocally agreed that there is an unmet need to improve patient care in ES-SCLC the UK, which would be addressed by providing access to serplulimab. Clinicians also drew a parallel with ALK-inhibitor options in NSCLC, of which there are multiple recommended for use in the NHS, as clinicians value access to multiple options. As a result, access to serplulimab would improve clinician and patient choice and a potential additional survival benefit. Several clinicians serplulimab as having:

- A clinically meaningful differentiator (notably, a longer OS tail).
- The potential to become a preferred option if recommend.

Comparative Positioning vs Atezolizumab & Durvalumab

Clinicians noted:

- Atezolizumab dominates UK practice largely not because of superior efficacy. But because it was the first immunotherapy to be reimbursed for treating ES-SCLC and durvalumab has only been available for treating ES-SCLC over the past 12 months.
- The ability to administer atezolizumab subcutaneously was cited as a benefit but primarily from a chair-time/logistics perspective and not because of clinical outcomes.

Pharmacological affinity of serplulimab

The clinical advisors at the advisory board heard from a Clinical Pharmacologist consultant that although the structure of PD-L2 is similar to PD-L1, the binding affinity between PD-L2 and PD-1 is two- to sixfold higher than that with PD-L1, suggesting PD-L2 is an important molecule in immune escape [1]. The advisors agreed this could pharmacologically explain the impact of serplulimab inhibiting the interaction of PD-1 with both PD-L1 and PD-L2. In addition, the clinicians also heard about a recent publication that showed that high (≥75th) PD-L2 RNA expression is about 30% in lung cancer [2]. Clinicians noted that while mechanistic details are complex, serplulimab binds very tightly to PD-1 and blocks both PD-L1 and PD-L2, which may underpin the more durable OS tail observed in ASTRUM-005.

Conclusion

The clinical expert panel provided robust, practice-based input to inform the response to the NICE draft guidance. Their insights strongly support the plausibility, generalisability, clinical relevance, and appropriateness of serplulimab for use in the NHS.

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Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

EAG response to consultation on draft guidance

Produced by Newcastle University

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1 Company commitment to providing access to patients

Thank you for the Company comments on the draft guidance, and for providing additional materials, including the structured expert elicitation, advisory board report, and the updated model results. We acknowledge the Company's agreement with the NICE Committee's preferred base-case for overall survival (OS), and progression-free survival (PFS), and disagreement with the preferred based-case for time to off treatment (TToT). We address these additional evidence/analyses in subsequent sections.

2 Unmet need in ES-SCLC

The EAG agrees with the draft NICE guidance statement noting that 'the committee recognised the severe impact that ES-SCLC has on people's quality of life and survival' and there is an 'unmet need for more effective treatment options for ES-SCLC' (p. 5).[1] The advisory board report[2] provided by the Company does highlight the unmet need for the indication, including access to first-line treatment, attrition to second-line, absence of therapies that provide a clinically meaningful improvement in overall survival over existing treatments and maintenance phase optimisation. They considered that access to serplulimab could offer a clinically meaningful differentiator (most notably, a longer overall survival tail) and expand treatment options for both clinicians and patients. The EAG acknowledges that there is unmet clinical need for people with ES-SCLC and serplulimab would provide another effective treatment option. However, the existence of this unmet need does not in itself demonstrate that the intervention under consideration addresses this need relative to the relevant comparators (atezolizumab and durvalumab).

The draft guidance stated that the clinical expert attending committee didn't consider serplulimab to address the unmet need but would offer an alternative immunotherapy plus chemotherapy treatment option in the first-line setting (p. 6).[1] Nowhere does the draft guidance state that existing options adequately treat ES-SCLC (as stated in the draft guidance comments form by the Company).[3] Nor have the EAG seen further compelling new evidence from the Company detailing how serplulimab addresses this unmet need. Clinicians at the advisory board noted that current immunotherapies dominate in clinical practice largely due to availability rather than superior efficacy,[1] and they discussed mechanistic evidence (introduced by a Clinical Pharmacologist) suggesting serplulimab's dual PDL1/PDL2 blockade may contribute to its observed durable survival effect. The EAG acknowledge that treatment choice would increase if serplulimab was to be recommended and agree that atezolizumab dominates practice not necessarily because of superior efficacy, but rather treatment familiarity (as confirmed by the EAG's clinical expert). As noted in the EAG report,[4] we agree that the trial evidence is indicative of superiority of serplulimab compared to standard of care and possibly atezolizumab, however the Company's trial and indirect treatment comparison have methodological limitations which raise considerable uncertainty. As suggested in the Points for Clarification,[5] and in the EAG report,[4] a multi-level network meta regression would in part alleviate this, however this was not undertaken by the company.

Whilst treatment options would be broadened should serplulimab be recommended, the EAG is not satisfied that new evidence is presented that clearly demonstrates that serplulimab addresses this unmet need significantly. The EAG notes that the advisory board report provided by the Company does not include conflicts of interest statements, and no information is presented on how the experts were identified or recruited. Given the Company's reliance on this expert input, the lack of transparency limits the ability to assess potential bias. As advisory board findings represent expert opinion, which sits low in the hierarchy of evidence, the evidential weight placed on the report is limited.

3 Time on treatment and plausibility of current assumptions

There have been a few changes to modelling TToT from the original company submission to now. A summary of the evidence for ACM1 and ACM2 are presented to provide context for the evidence for ACM3.

Evidence for ACM1

In the original company submission, the time to TToT for serplulimab was modelled using parametric model (log-logistic model) fitted to the Kaplan-Meier curve from ASTRUM-005. For atezolizumab, the TToT was derived by multiplying the reciprocal of OS HR (MAIC) with the hazard rates of stopping treatment in serplulimab arm.[6] In the company model, the percentage of patients in the PFS state was multiplied by the percentage of patients on treatment from the TTOT curve to derive the percentage of patients in PFS and on treatment.[7] The same was done for the PD state. This assumes that the percentage of patients on treatment is the same in the PFS and PD states.[4] But disease progression is an important factor for treatment discontinuation. So, the percentage of patients in PD receiving treatment was capped at 20% in the EAG base case and other scenarios were also explored.[4]

The EAG suggested that a flexible model could have been fitted to the TToT KM curve, with an exponential decline for extrapolation resulting in a low percentage on treatment by 10 years. In the EAG base-case, a 3-knot spline model was used until an appropriate time point.[4]

DG 1

For serplulimab, the committee expressed a preference for the log-logistic model for TToT. For atezolizumab and durvalumab, the committee requested a comparison of TToT data (such as median TToT values) for serplulimab, atezolizumab and durvalumab, and alternative TToT modelling assumptions.[8]

Evidence for ACM2

In the company submission as part of the evidence for ACM2, several scenarios were explored for modelling TToT.[9] The EAG reviewed these scenarios and explored additional scenarios to inform the committee.[10] Based on these scenarios, the EAG base case adopted the method of using the ratio of median progression-free survival to median time to off-treatment, but multiplying it with the time-to-progression hazard rate rather than the probability of being in the progression-free survival state (company method of applying the ratio). However, which approach produces the most plausible TToT curve is a clinical question.

DG 2

For atezolizumab, the committee stated it would consider both the company's approach and the EAG approach to applying the ratio of median progression-free survival to median time to

off-treatment. The committee expressed doubts about the likelihood of continuing on treatment after disease progression.[1]

Evidence for ACM3

After ACM 2, the EAG raised a concern that the method used for deriving TTOT, by multiplying the loglogistic TTOT curve by the % in PFS and the % in PD, respectively, double counts death as an event. In effect, the percentage of the entire cohort on treatment was multiplied by the percentage alive at each time point. The consequence of the approach taken is the cost of treatment is underestimated. Therefore, an alternative method of multiplying the loglogistic TTOT curve by $\frac{\%\ in\ PFS}{\%\ in\ PFS+\%\ in\ PD}$ (for calculating PFS on treatment) and $\frac{\%\ in\ PD}{\%\ in\ PFS+\%\ in\ PD}$ (for calculating PD on treatment) for each model cycle was suggested.

Consequently, the company submitted a revised model with the TTOT curve for serplulimab applied to all the patients rather than multiplying the proportion on treatment by the proportion alive.

In addition, the Kaplan-Meier dataset was revised as patients still in the study post-progression were incorrectly classified as being on treatment even if they were not on treatment. The newly fitted log-logistic curve is presented in Figure 1 alongside the original KM curve and the old log-logistic curve. The company did not present the new KM curve.

Furthermore, in response to the committee's concerns around treatment after progression, the company produced additional evidence by conducting a structured expert elicitation (SEE). The findings were as follows.

- The clinicians reached a strong consensus that the TTOT curve was unrealistic and clinically not plausible. They noted that at 2 years, they rarely have any ES-SCLC patients still on IO, and the current curve overestimates the proportion of patients. Even under trial conditions, the TTOT curve is optimistic, and the real-world rates would be much lower at 4 years. The patients do not continue IO treatment beyond 3 – 5 years in routine clinical practise due to toxicity, quality of life, cumulative risk, diminishing returns, and lack of biological rationale. Also, it was biologically and clinically implausible to have patients on treatment beyond 10 years unlike the predictions in the model.[2]
- The TTOT curve should not persist significantly beyond 5 – 6 years, because only is a small subset of patients survive at this timepoint.[2]
- The criteria for stopping treatment would not differ across atezolizumab, durvalumab and serplulimab. Clinicians shared that although patterns of progression can differ, treatment is generally stopped at progression in clinical practice in the NHS. For atezolizumab and durvalumab, the funding in England is only up to the point of disease progression and enforced using the Blueteq form system.[3]
- The pooled median of clinicians' judgments for the maximum number of years on treatment was 5.2 years.[11]

The company revised the cost-effectiveness model. The revised model includes the following TToT features:

- The new log-logistic model for TToT for serplulimab based on the revised KM dataset.
- The EAG method of applying the ratio of PFS and TToT medians for the comparators.
- The proportion of the cohort who are in the PFS state and receiving treatment equals the proportion of the cohort who are on treatment.
- The model includes a treatment stopping rule at disease progression. No patients in the disease progression state receive serplulimab or a comparator treatment. The proportion of the cohort receiving treatment is capped at the proportion of patients in the PFS state.

EAG comment:

The TToT curve for both serplulimab and atezolizumab are always lower than the respective PFS curves, so the stopping rule has no effect. The ratio of medians approach will produce a TToT curve that is greater than the PFS curve for durvalumab. A stopping rule would set the TToT curve to be the PFS curve for durvalumab. However, the committee considers atezolizumab to be the relevant comparator. As mentioned by the company, the proportion of patients on treatment are likely to be greater than the clinical expert expectations from the company SEE.

There is an error in the company model in calculating the TToT curve for atezolizumab. The company multiplied the PFS cycle progression probabilities by the ratio of median PFS to median TToT (correct), but then found the probability of being on treatment by multiplying the probability of being in the PFS state at each cycle by the derived treatment cessation probability for that cycle. This does not account for the cumulative effect of the adjusted probabilities in the previous cycles and results in a TToT curve very similar to the PFS curve. The EAG has accounted for the cumulative effect of the treatment cessation probabilities in an edited model. The TToT curve for atezolizumab in Figure 5 is the adjusted TToT produced by the EAG. The EAG adjusted cost-effectiveness results are presented in Table 3.2.

The company reported TToT curves for serplulimab and atezolizumab in Figure 2 and Figure 3. The EAG has produced TToT curves and compared them to the PFS curve for serplulimab and atezolizumab in Figure 4 and Figure 5.

Figure 1: Serplulimab KM-curve, original committee preferred TToT and revised TToT

Source: DG2 Comment form[3]
Abbreviations: KM = Kaplan-Meier

Figure 2: Serplulimab PFS and TToT plot

Source: obtained from DG2 revised company model[12]
Abbreviation: TToT = time to treatment discontinuation, PFS = progression free survival

Figure 3: Atezolizumab PFS and TToT plot

Source: obtained from DG2 revised company model[12]
Abbreviation: TToT = time to treatment discontinuation, PFS = progression free survival

Figure 4: PFS and TToT curves for serplulimab

Source: Modified revised company model[13]
Abbreviation: TToT = time to treatment discontinuation, PFS = progression free survival

Figure 5: PFS and TToT curves for atezolizumab

Source: Modified revised company model[13]
Abbreviation: TToT = time to treatment discontinuation, PFS = progression free survival

Company revised model deterministic result

The company implemented a PAS discount of [redacted] on serplulimab and the updated cost-effectiveness results are given in Table 3.1**Error! Reference source not found.**. A QALY weight of x1.2 was applied in the model. Serplulimab + carboplatin + etoposide was more effective by 0.46 QALY and costlier by [redacted] than atezolizumab + carboplatin + etoposide, resulting in an ICER of [redacted]. The EAG identified an error in the model (See Table 3.2).

Table 3.1: Revised company model deterministic incremental results

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICER
Serplulimab + carboplatin + etoposide	[redacted]	1.98	[redacted]	0.46	[redacted]
Atezolizumab carboplatin + etoposide	[redacted]	1.52			

Source: DG2 Comment form[12]
Abbreviations: QALY = quality adjusted life-years, SoC = standard of care

EAG-corrected company model deterministic result

In the EAG-corrected company model, the total cost for atezolizumab changed to [redacted]. Consequently, the incremental cost increased to [redacted] while the incremental QALY was 0.45. The resulting ICER was [redacted] (see Table 3.2). Considering the new NICE threshold range £25,000-£35,000 proposed, the ICER was more than the lower limit but less than the upper limit of the threshold.

Table 3.2: EAG-corrected company revised model result

Treatment	Total Cost	Total QALY	Incremental Cost	Incremental QALY	ICER
Serplulimab + carboplatin + etoposide	[redacted]	1.98	[redacted]	0.45	[redacted]
Atezolizumab carboplatin + etoposide	[redacted]	1.54			

Source: EAG-corrected company revised model
Abbreviations: QALY = quality adjusted life-years, SoC = standard of care

4 Robustness of ASTRUM-005 and clinical plausibility of trial results

The EAG agree that ASTRUM-005 is helpful for decision making, and its design and conduct is robust. However, there are remaining issues around the generalisability of trial participants (being predominantly Asian), and trial settings (e.g., differences in standard of care). Furthermore, additional uncertainty is introduced with indirect treatment comparisons employed to assess the relative efficacy of serplulimab versus atezolizumab and serplulimab versus durvalumab. The EAG agrees that sub-group analyses appear to demonstrate consistent benefit across all clinical categories, however we note that there is remaining uncertainty for some analyses owing to small patient numbers (e.g., females, non-Asian, ECOG performance status=0, never smokers). The EAG also acknowledges that insights derived from the advisory board suggest trial data as robust and 'serplulimab's observed OS benefit reflects genuine effect' (p. 5) [compared to placebo plus carboplatin etoposide]. The EAG has no reason to doubt this effect.

However, no compelling new evidence is presented by the Company and as such our conclusions detailed in the EAG report[4] still stand.

5 Pharmacological affinity of serplulimab

The EAG acknowledges the company's additional information, which includes a summary of an advisory board[2]) that collected insights from four clinical thoracic oncologists, and one clinical pharmacologist, in response to NICE's draft guidance. The summary also includes a section on the pharmacological affinity of serplulimab, which describes the clinical pharmacologist stating the binding affinity of proteins PD-1 to PD-L1 vs PD-L2, the latter presenting a higher binding affinity. This relationship between PD-1 and PD-L2, provides supportive evidence for an involvement of PD-L2 in the escape of tumour cells from the immune system and therefore a role in cancer cell survival.[14] The clinical experts were reported to agree this might help explain serplulimab's mechanism of action, including its effects on targeting PD-1 and thereby inhibiting PD-1's interaction with PD-L1 and PD-L2. This corroborates with previous comments from the EAG, agreeing that through targeting PD-1, serplulimab may disrupt both PD-L1 and PD-L2 and lead to greater suppression of T-cell inhibition, and thus enhance the anti-tumour response. However, the EAG stipulate that direct evidence for this causation in a clinical context is lacking.

Additionally, in the advisory board the clinical experts were stated to have heard about a recent publication regarding gene expression levels of PD-L2 in lung cancer, however, whether prompted or if further discussion on this publication occurred was not explicitly stated. The recent publication cited provides evidence from a pan-cancer cohort (N=514; 489 patients) that out of 20 lung cancer samples included, 6 (30%) showed high RNA expression levels for PD-L2 (indicated by ≥75th percentile rank).[15] Furthermore, while the included lung cancer samples in the pan-cancer cohort were from patients with advanced/metastatic disease, the lung cancer type was not specified so it is unclear whether samples were small-cell or non-small cell lung cancer, nor were PD-L2 levels assessed at the protein (or functional) level.

Overall, the EAG agree it is biologically plausible that the pharmacological profile of serplulimab may enable a superior response in patients with ES-SCLC. They further agree that serplulimab and has been indirectly shown to be superior to atezolizumab and durvalumab within evidence generated and highlighted by the company.[5, 6, 9] However, differences in patient characteristics and settings across trials warrants caution in the interpretation of the differences in treatment effect estimates. Furthermore, as stated above, while the EAG note that while the four clinicians were stated to be leading clinicians in the NHS, the methods and processes used to select participants for the advisory board meeting, as well as their declaration of any conflicts of interest, were not provided.

6 References

1 National Institute for Health and Care Excellence. Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer. *GID-TA11405* 2026.

2 Accord Healthcare. Serplulimab in ES-SCLS. Prepared for NICE draft guidance consultation for serplulimab in ES-SCLC (ID6346); 2026.

3 Accord. Serplulimab Accord DG2 comments form 26022026CS [CON].docx [ID6436]: Accord; 2025.

4 Whitehall J, Jayachandaran L, Thomson K, Al-Assaf A, Sotire T, Still M, et al. Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]. EAG Report. Newcastle upon Tyne; 2025.

5 Accord. Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]: clarification questions. Barnstaple,: Accord; 2025.

6 Accord. Serplulimab with carboplatin and etoposide for untreated extensive-stage small cell lung cancer [ID6346]. Single technology appraisal. Company evidence submission: Document B. Barnstaple: Accord; 2025.

7 Accord. Serplulimab cost effectiveness model 11022025KM [ID6346]. Company evidence submission. Barnstaple: Accord; 2025.

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9 Accord. Serplulimab with carboplatin and etoposide for untreated extensive-stage small cell lung cancer [ID6346]. Single technology appraisal. Company DG comments form 17092025 IC [CON]. Barnstaple: Accord; 2025.

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11 Accord. Serplulimab Accord DG2 Appendix A 26022026CS [noCON].docx [ID6436]: Accord; 2025.

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14 Wang Y, Du J, Gao Z, Sun H, Mei M, Wang Y, et al. Evolving landscape of PD-L2: bring new light to checkpoint immunotherapy. British Journal of Cancer. 2023 2023/03/01;128(7):1196-207.

15 Patwari A, Nishizaki D, Jensen T, DePietro P, Pabla S, Kato S, et al. PD-L2 Landscape and Correlation with Outcome: An Immunomic Analysis. JCO Oncol Adv. 2026 Jan;3(1).

7 Appendix

The proportion of patients in the progression-free (PF) and disease progression (PD) states for atezolizumab and durvalumab are presented in Figures 13-16.

Figure 6: Atezolizumab PFS, proportion on treatment

Figure 7: Atezolizumab PD, proportion on treatment

Figure 8: Durvalumab PFS, proportion on treatment

Figure 9: Durvalumab PD, proportion on treatment

Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer [ID6346]

Pre ACM3 EAG Report Addendum

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[redacted]

Outstanding issues

NICE had a few follow-up questions regarding the evidence and the company submitted a model with the error identified by the EAG corrected.

1. ***Do you believe there are any remaining differences between your base case and the company's base case, especially concerning the TToT extrapolations?***

For effectiveness, for atezolizumab, the company used the Bucher ITC estimates, which is the same as the revised EAG base case.

For TTOT, the company essentially took the same approach as the EAG. There is only a very minor difference in that the company applied the ratio to the transition probability whereas the EAG applied it to the rate, but in this case this is extremely similar. Using the rate instead of the probability, the ICER reduces by only [redacted].

There is no longer any serplulimab or atezolizumab treatment in the PD state, which is different from the previous company base case and the EAG base case. This is consistent with the clinical expert opinion the company referred to in DG2 and in the company post-ACM2 evidence submission. The only significance of this is a relatively small impact on subsequent treatment cost. In the deterministic analysis, the percentage on treatment is smaller than the percentage in the PFS state for both serplulimab and atezolizumab at all time points. TToT is capped at PFS for probabilistic sensitivity analysis.

The height and weight are the same.

2. ***Are you happy that the company have implemented the changes from their previous model correctly, excepting the error highlighted in the critique? Thinking mainly about the updated Kaplan-Meier (KM) data. Would you like to see the company present this? Or are you happy with what was available in the model?***

The model the company submitted correcting for the error the EAG identified regarding the implementation of the TToT/PFS ratio to the PFS curve was correct.

Initially, the company did not present the KM data, or information regarding model fit. When the company submitted the corrected model, the new KM data and plots of the

fitted parametric models presented. The visual fit for the loglogistic model looked as good as it did previously. The company did not present AIC/BIC statistics, but stated that the loglogistic model was the best fit using these criteria.

3. ***Do you believe that the OS benefit (if any) from treatment after progression in the serplulimab trials will have a non-significant impact on cost-effectiveness estimates? Are benefits of treatment after progression being included without costs? (noting the company stated in their consultation response "based on the feedback collected in the SEE and advisory board, clinicians agreed that the proportion of patients on treatment post-progression would likely be lower in clinical practice than what is modelled, without impacting the overall estimated benefit of serplulimab on overall survival (OS) and progression-free survival (PFS).")***

The evidence for overall survival (OS), by definition, is based on the entire cohort in each arm of the trial where the proportion of patients in the disease progression and disease-free states changes over time. The effectiveness estimates are likely to be valid over a period of time when there are sufficient numbers still at risk over the Kaplan-Meier follow-up period, using a model with adequate fit to the data. For serplulimab, there was no evidence to reject the proportional hazard assumption compared to carboplatin+etoposide alone. It was not completely certain that the proportional hazards assumption held for atezolizumab versus carboplatin + etoposide alone. However, on balance the committee agreed that the Bucher ITC effect evidence is appropriate.

In the EAG base case in the original EAG report, treatment waning was implemented from year 3.5 to year 6.5, where 3.5 years was selected according to a minimum of 53 patients still at risk in the Kaplan-Meier curve for serplulimab (7 at risk for placebo). By recommendation of the committee, the company implemented immediate loss of effectiveness at 5 years to be consistent with a previous appraisal. This was implemented by setting serplulimab probabilities of dying at those for atezolizumab after 5 years. Consequently, after 5 years, both the serplulimab and atezolizumab probabilities of dying may be smaller than that for carboplatin+etoposide alone. An alternative approach would have been to set the probabilities of dying for both serplulimab and atezolizumab to the probabilities associated with carboplatin+etoposide alone.

The company has not provided a Markov model to explore no treatment effect at progression. If they had a Markov model they would have to assume that the hazard ratio estimate from the overall survival curves applies to the progression-free survival state; there is no treatment benefit after progression. Using only the company's Partitioned Survival Model, the EAG can only attempt to assess the potential impact of no treatment effect post progression by varying the time at which the treatment effect is assumed to be zero (hazard ratio = 1), using the company method of applying no treatment effect. It can be argued that the loglogistic model up to 3 years (85 serplulimab and 16 placebo at risk) or 3.5 years (53 serplulimab and 7 placebo patients still at risk) is a reasonable fit to the Kaplan-Meier curve. Using the company model corrected by the EAG with the loglogistic model, the deterministic ICER is [redacted] with loss of treatment effect at 5 years, [redacted] with loss of treatment effect at 3.5 years, [redacted] with loss of treatment effect at 3 years.