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 **Comments on the Draft Guidance from** Accord
   a. Draft Guidance Comments from Accord
   b. Appendix A
   c. Appendix B

2. **External Assessment Group critique of company comments on the Draft Guidance**

No responses were submitted by consultees, commentators, invited experts or through the NICE website.

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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	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 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 Ltd.

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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.	Not applicable.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable.
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 requested by the Committee. As part of the response, the Company has provided: • Additional literature on the distinct mechanism of action of serplulimab compared with PD-L1 inhibitors, and unique affinity compared with PD-1 inhibitors in ES-SCLC. • Summary of independently published network meta-analyses (NMAs), showing consistency with the results with our NMA within this submission • Revised base-case for the economic model including results from the non-proportional hazards NMA, updated baseline weight and quality of life estimates using a linear mixed effects model.

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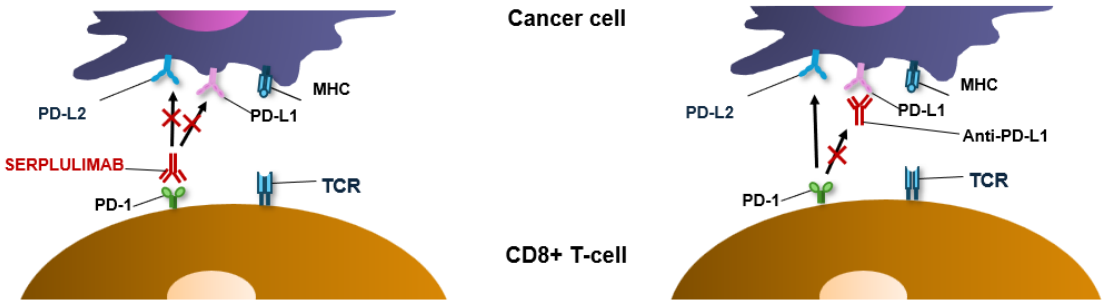
2	**Serplulimab as a clinically meaningful alternative to existing treatments in ES-SCLC** During the committee meeting, the clinical expert stated that "serplulimab was not expected to address the unmet need for small-cell lung cancer (section 3.1 of the draft guidance), but it would offer an alternative immunotherapy plus chemotherapy treatment option in the first-line setting." The Company would like to reiterate that serplulimab is an efficacious treatment option for ES-SCLC, based on its exceptional therapeutic potential, clinical opinion and statistical modelling. The pivotal study (ASTRUM-005) showed a median OS of 15.8 months, which is greater than the median OS within the pivotal studies of atezolizumab (median OS 12.3 months; IMpower133) and durvalumab (median OS 12.9 months; CASPIAN) [1-3]. Clinical experts have stated the goal of treatment for patients with ES-SCLC is to improve OS whilst maintaining quality of life. Based on the results of ASTRUM-005, serplulimab meets the clinical experts' goal of treatment. Serplulimab shows two key differentiating features compared with current immunotherapy agents available: • **Distinct mechanism of action compared with PD-L1** inhibitors such as atezolizumab and durvalumab, as serplulimab directly targets the PD-1 receptor rather than its ligand (PD-L1). [4] • **Unique molecular structure** and binding characteristics compared with PD-1 inhibitors such as pembrolizumab and nivolumab, with differences in binding affinity and epitope recognition [5]. **Distinct mechanism of action:** Cancer cells can "switch off" immune cells by using protein ligands called PD-L1 and PD-L2 that bind to PD-1 receptors on T-cells. This results in suppression of T-cell activation and limiting anti-tumour activity. PD-L1 inhibitors such as atezolizumab and durvalumab work by blocking PD-L1 ligands, which results in disrupting the PD-L1/PD-1 interaction. However, this still leaves PD-L2 free to bind with PD-1 receptors. It should be noted that PD-L2 has approximately three-fold higher affinity than PD-L1, thus emphasising the advantage of dual blockade [6]. Serplulimab is different because it inhibits the PD-1 receptor directly on the T-cells. This means it can disrupt linkage with both PD-L1 and PD-L2, leading to a more complete suppression of T-cell inhibition (Figure 1). *Figure 1: Mechanism of action of serplulimab* **A more complete immune activation resulting from dual PD-L1 + PD-L2 pathway inhibition**  Comparison of mechanism of action of serplulimab with anti-PD-L1 agents • PD-1 blockade on T cells prevents interaction with both PD-L1 and PD-L2 on the surface of tumour cells. • Anti-PD-L1 agents interact with PD-L1, only partially block this pathway. • Additional blockade may elicit a more intense T-cell activation hence a stronger anti-tumour response.

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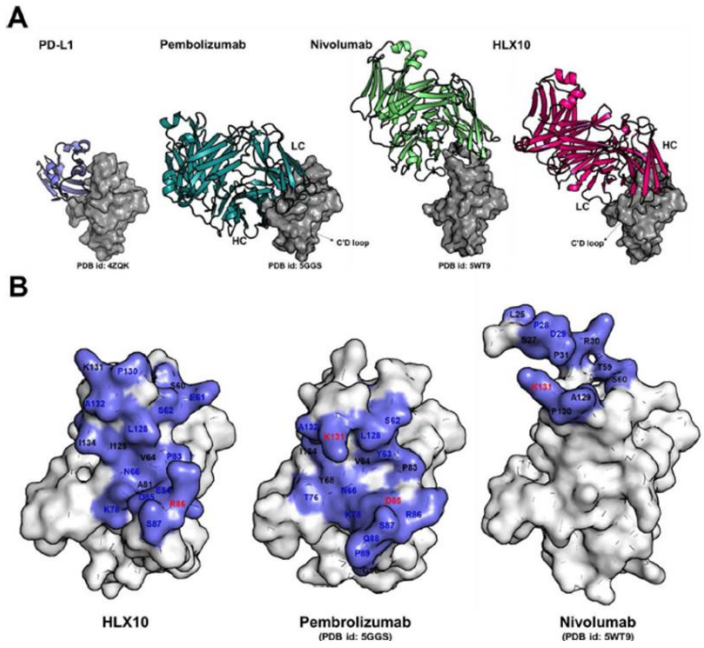
Unique molecular structure and binding characteristics:
Beyond the broader suppression described above, serplulimab (HLX10) also exhibits a unique structural binding characteristic that differentiates it from other PD-1 inhibitors (pembrolizumab and nivolumab). Protein crystallography studies have showed that serplulimab exhibits an opposite heavy and light chain usage compared to pembrolizumab, which indicated a more complete spatial interaction with PD-1. After introducing the S228P mutation, the Fab arm exchange process of IgG4 mAb is prevented, which ensures the structure stability of serplulimab (see Figure 2).

Figure 2: Comparison of binding epitope of serplulimab (HLX10) with pembrolizumab and nivolumab



Furthermore, with high affinity and promising PD-1 blockade effects, serplulimab can reach a saturated PD-1 receptor occupancy at a relatively low dose. Additionally, the high affinity and slow dissociation rate enable serplulimab to maintain a continuous blockade throughout the treatment, robustly induce PD-1 receptor endocytosis, downregulate PD-1 expression on the surface of T-cells, and restore T-cell activity. Serplulimab has demonstrated high potency to disrupt the interaction between PD-1 and its natural ligands, eliciting an immune response through CD4+ T cells proliferation and cytokine (IL-2, interferon γ) secretion. Its anti-tumour activities were demonstrated in *in vivo* xenograft studies. The *in vitro* and *in vivo* efficacy data provide a solid biological plausibility for its known activity and constitute the basis for its applications in the treatment of solid tumours. Antibody-mediated PD-1 internalisation was evaluated at various time points in PD-1 overexpressing Jurkat cells co-incubated with serplulimab, pembrolizumab, or nivolumab. After 6 hours incubation, serplulimab mediated endocytosis of PD-1 reached peak, while pembrolizumab and nivolumab mediated endocytosis of PD-1 was relatively weak, demonstrating that serplulimab, compared to pembrolizumab or nivolumab, induces a robust and sustained endocytosis of PD-1 receptors, resulting in a more effective alleviation of PD-1-mediated T-cell suppression (Figure 3).

Figure 3: Comparison of internalisation rates among PD-1 antibodies [5])

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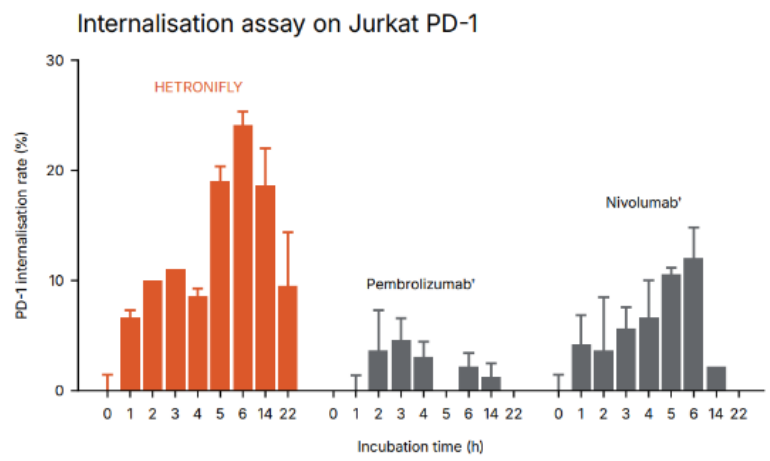
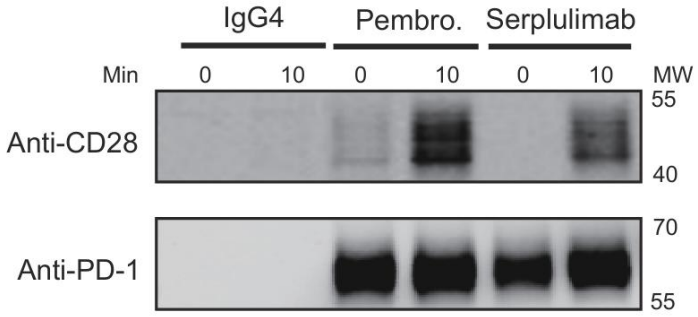


Comparison of internalisation rates among anti-PD-1 antibodies. Membrane retained PD-1 in Jurkat-PD-1 cells following 22h incubation time of HETRONIFLY, nivolumab and pembrolizumab was stained with goat anti-Human IgG Fc secondary antibody. Each detected signal was subdivided to the signal of total membrane PD-1 without treatment. Each datapoint represents mean ± SD of duplicate.

Moreover, serplulimab can also reduce the recruitment of CD28 by PD-1, further retaining the signal transmitted by CD28, thereby rapidly activating the AKT protein of the signalling pathway to promote the sustained activation of T-cells (Figure 4), indicating that serplulimab preserves signalling via CD28 and restores T-cell function to a greater extend comparing to pembrolizumab. These results suggest that serplulimab operates differently from pembrolizumab and nivolumab by modulating PD-1 membrane availability and the association between PD-1 and CD28.

Figure 4: Immunoprecipitations performed with serplulimab showed significantly lower levels of PD-1-CD28 complex after T-cell activation, then pembrolizumab



Serplulimab also has lower anti-drug antibody (ADA) production, improving treatment durability and patient benefit [7]. Additionally, serplulimab consistently demonstrated favourable outcomes in overall survival (OS) and comparable incidence of grade ≥3 adverse events relative to other checkpoint inhibitors used in ES-SCLC [8-11]. Additional literature has been provided to further support the affinity of serplulimab in ES-SCLC [12].

To summarise, the evidence presented strongly supports the numerically widest differences vs placebo of any immune checkpoint inhibitor in first-line ES-SCLC. It is underpinned by (1) serplulimab's unique mechanism of action arising from dual PD-L1 and PD-L2 blockade, as well as (2) from its higher affinity for the PD-1 receptor. This provides a

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strong biological rationale to justify the favourable outcome of ASTRUM-005 in comparison to failures of other trials with anti-PD1 agents in the same setting.

Serplulimab showed a clinically meaningful survival benefit compared with atezolizumab and durvalumab:
The matching-adjusted indirect comparison (MAIC) provided as part of the Company submission showed consistent hazard ratios (HRs) favouring serplulimab:

- vs atezolizumab: in matched analysis, treatment with serplulimab was estimated to result in improved OS and progression-free survival (PFS) in comparison with atezolizumab, with estimated hazard ratios (HRs) of [redacted]) and [redacted]), respectively, and;
- vs durvalumab: in matched analysis, treatment with serplulimab was estimated to result in improved OS and PFS in comparison with durvalumab, with estimated HRs of [redacted] and [redacted] respectively.

The consistency and magnitude of the benefit of serplulimab suggest a clinically meaningful survival advantage compared with atezolizumab and durvalumab.

Additionally, there have been six independently published NMAs using different methodologies that have ranked serplulimab first for OS. This is consistent with the results of the MAICs provided within the submission and model base-case (see Figure 5).

Figure 5: Results of independently published NMAs [8-11, 13, 14]

Study	Methodology	Indirect comparisons (IO + chemo)	Serplulimab ranking
Zhu et al, 2022	Network meta-analysis used frequency and fixed-effect multivariable meta-regression models	**SER**, **ATZ**, **DRV**, DRV + TRE, ADE, NIVO, PEM	1st for OS 1st for PFS
Zhang et al, 2023	Bayesian network meta-analysis	**SER**, **ATZ**, **DRV**, DRV + TRE, ADE, IPI, PEM, NIVO, ATEZ+TIR	1st for OS 1st for PFS
Wang et al, 2023	Bayesian fixed-effect consistency models	**SER**, **ATZ**, **DRV**, DRV + TRE, ADE, IPI, PEM	1st for OS 1st for PFS
Du et al, 2023	Systematic literature review and fixed-effects NMA model	**SER**, **ATZ**, **DRV**, DRV + TRE, ADE, IPI, PEM	1st for OS 1st for PFS
Yang et al, 2024	Bayesian network meta-analysis	**SER**, BEN+ANL, **ATZ**, **DRV**, DRV + TRE, ADE, TIS, TOR, NIVO, PEM	1st for OS in <65 and brain metastases
Liu et al, 2024	Frequentist network meta-analysis	**SER**, BEN+ANL, **ATZ**, **DRV**, DRV + TRE, ADE, TIS, TOR, NIVO, PEM	1st for OS 1st for ORR

Abbreviations: ADE, adebrelimab; ATZ, atezolizumab; BEN+ANL: benralizumab + anlotinib; DURV, durvalumab; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PEM, pembrolizumab; SER, serplulimab; TIS, tislelizumab; TOR, toripalimab; TRE, tremelimumab.

The evidence package for serplulimab is robust:
The pivotal trial for serplulimab (ASTRUM-005) was a well-conducted, multinational, randomised controlled study with overall survival (OS) as the primary endpoint. At the final analysis, the trial had a median follow-up of 42.38 months, providing a mature and sustained view of long-term survival outcomes [15].

Durvalumab was recommended for use in the NHS for ES-SCLC based on the CASPIAN trial, which had a median follow-up of 39.4 months at its final data cut-off [3] which is comparable in duration to ASTRUM-005. The survival benefit for durvalumab was modest compared with serplulimab (HR 0.71). Serplulimab, by comparison, demonstrated a greater survival benefit (HR 0.60) with consistent benefit across subgroups including age, sex, ECOG status, and PD-L1

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	expression. Similarly, in TA638, atezolizumab was recommended despite the uncertainty in long-term survival estimates from the IMpower133 trial. These comparisons highlight that serplulimab's evidence package is robust compared to its comparators, with greater and more sustained survival benefits supported by mature data and consistent subgroup analyses. This positions serplulimab as a compelling first-line treatment option for ES-SCLC. **Serplulimab fits seamlessly into current NHS practice:** As an immunotherapy plus chemotherapy regimen, no changes to existing treatment pathways are required for the introduction of serplulimab. Clinical experts interviewed during the submission process stated that the unmet need for patients with first-line ES-SCLC in the UK is very high, with new products such as serplulimab needed to provide greater survival benefits (as described in Appendix M of the Company submission package). As a result, serplulimab provides a clinically safe and meaningful alternative to existing treatments in ES-SCLC. Given the strength and maturity of the clinical evidence, the consistent survival benefit across subgroups, and the favourable safety profile, the Company urges the Committee to consider serplulimab as a clinically meaningful and robust treatment option for patients with untreated ES-SCLC. The unmet need in this population remains high, with limited therapeutic innovation and poor long-term outcomes. Serplulimab offers the potential to extend survival and improve quality of life for patients facing a rapidly progressing and aggressive disease. For many, the opportunity to live longer with fewer treatment-related complications represents a meaningful shift in their experience of care. In light of these factors, serplulimab is a meaningful addition to the treatment landscape and should be considered for a positive recommendation to enable timely access for patients in need.
3	**Generalisability of clinical trials** The draft guidance states that "the generalisability of the trial outcomes to the NHS is unclear due to differences in patient characteristics between the trials and the NHS population." The Company would like to reiterate that ASTRUM-005 was a large, Phase 3 randomised controlled trial (RCT), with pre-planned subgroup analyses that showed no signal for race, sex or weight (as shown in Figure 6). Differences in subsequent treatment are likely to have a negligible effect on outcomes given that very few patients are fit enough to progress to subsequent lines of treatment in clinical practice. The absence of head-to head trial data between serplulimab and atezolizumab/durvalumab has been addressed by providing MAICs as part of the Company submission, and a subsequent NMA as part of the response to this draft guidance (see Comment 6). *Figure 6: Figure 14: Subgroup analysis for the primary outcome of overall survival (extended follow-up analysis – data cutoff 7th May 2024))*

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	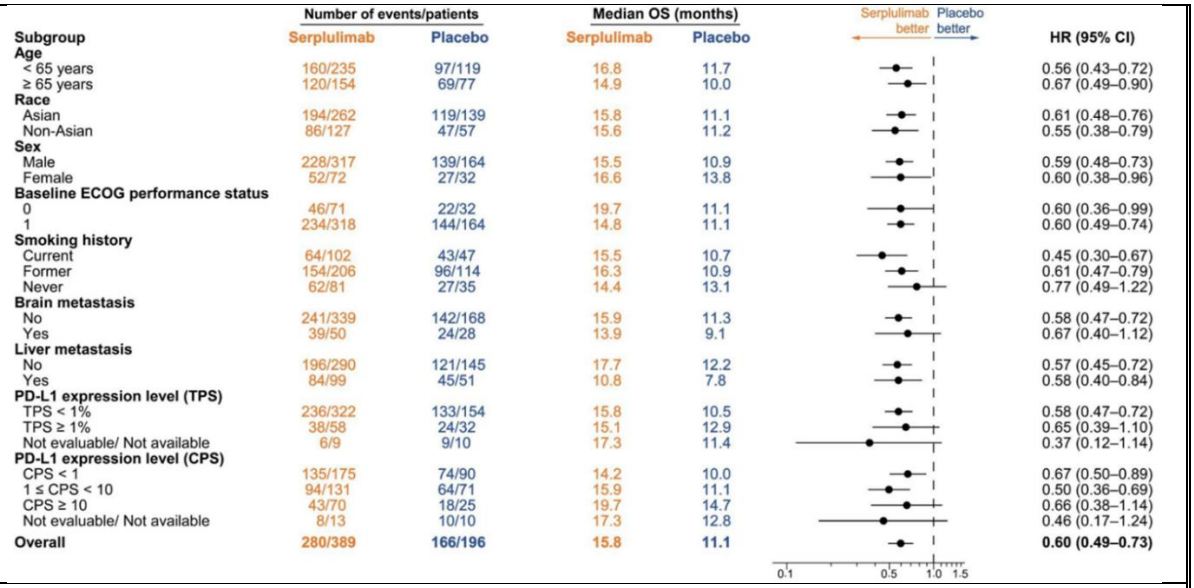

Subgroup	Number of events/patients: Serplulimab	Number of events/patients: Placebo	Median OS (months): Serplulimab	Median OS (months): Placebo	HR (95% CI)
Age					
< 65 years	160/235	97/119	16.8	11.7	0.56 (0.43–0.72)
≥ 65 years	120/154	69/77	14.9	10.0	0.67 (0.49–0.90)
Race					
Asian	194/262	119/139	15.8	11.1	0.61 (0.48–0.76)
Non-Asian	86/127	47/57	15.6	11.2	0.55 (0.38–0.79)
Sex					
Male	228/317	139/164	15.5	10.9	0.59 (0.48–0.73)
Female	52/72	27/32	16.6	13.8	0.60 (0.38–0.96)
Baseline ECOG performance status					
0	46/71	22/32	19.7	11.1	0.60 (0.36–0.99)
1	234/318	144/164	14.8	11.1	0.60 (0.49–0.74)
Smoking history					
Current	64/102	43/47	15.5	10.7	0.45 (0.30–0.67)
Former	154/206	96/114	16.3	10.9	0.61 (0.47–0.79)
Never	62/81	27/35	14.4	13.1	0.77 (0.49–1.22)
Brain metastasis					
No	241/339	142/168	15.9	11.3	0.58 (0.47–0.72)
Yes	39/50	24/28	13.9	9.1	0.67 (0.40–1.12)
Liver metastasis					
No	196/290	121/145	17.7	12.2	0.57 (0.45–0.72)
Yes	84/99	45/51	10.8	7.8	0.58 (0.40–0.84)
PD-L1 expression level (TPS)					
TPS < 1%	236/322	133/154	15.8	10.5	0.58 (0.47–0.72)
TPS ≥ 1%	38/58	24/32	15.1	12.9	0.65 (0.39–1.10)
Not evaluable/ Not available	6/9	9/10	17.3	11.4	0.37 (0.12–1.14)
PD-L1 expression level (CPS)					
CPS < 1	135/175	74/90	14.2	10.0	0.67 (0.50–0.89)
1 ≤ CPS < 10	94/131	64/71	15.9	11.1	0.50 (0.36–0.69)
CPS ≥ 10	43/70	18/25	19.7	14.7	0.66 (0.38–1.14)
Not evaluable/ Not available	8/13	10/10	17.3	12.8	0.46 (0.17–1.24)
Overall	**280/389**	**166/196**	**15.8**	**11.1**	**0.60 (0.49–0.73)**

4	**Section 3.7: Extrapolation of progression-free survival and overall survival**
	
	In section 3.7 of the draft guidance, the Committee requested to see further comparisons of the progression-free survival (PFS) and overall survival (OS) extrapolations for the serplulimab arm with the extrapolations for atezolizumab and durvalumab. The base case PFS and OS extrapolations for serplulimab, atezolizumab, and durvalumab, overlaid on the respective Kaplan-Meier curves, are presented in Figure 7 (OS) and Figure 8 (PFS). For atezolizumab, the extrapolations appear to slightly overestimate OS and PFS compared to the Kaplan-Meier based on pseudo-individual patient data from the atezolizumab arm from IMpower133, resulting in a conservative assessment of the relative efficacy of serplulimab against atezolizumab in the base case. For durvalumab, the extrapolations also appear to slightly overestimate OS and PFS compared to the Kaplan-Meier based on pseudo-individual patient data from the durvalumab arm from CASPIAN, resulting in a conservative assessment of the relative efficacy of serplulimab against durvalumab in the base case. The relative differences between treatment arms in the model predicted estimates of median OS and PFS generally align well with the trial-observed median OS and PFS in ASTRUM-005, IMpower133, and CASPIAN:
	
	• OS (months):
	  ○ Model prediction: serplulimab, 16.90; atezolizumab, 13.45; durvalumab,14.14
	  ○ Trial-observed: serplulimab, 15.77; atezolizumab, 12.30; durvalumab, 12.90
	• PFS (months):
	  ○ Model prediction: serplulimab, 7.70; atezolizumab, 5.86; durvalumab, 5.63
	  ○ Trial-observed: serplulimab, 5.82; atezolizumab 5.2; durvalumab, 5.1
	
	Figure 7: Extrapolations for OS – serplulimab, durvalumab and atezolizumab
	
	[redacted]
	
	Figure 8: Extrapolations for PFS – serplulimab, durvalumab and atezolizumab
	
	[redacted]

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	The Committee also requested justification for the choice of extrapolation approach for atezolizumab and durvalumab with consideration to the expected relative treatment effect between them and serplulimab. In the base case, extrapolations of OS and PFS for the atezolizumab and durvalumab arms were generated by applying HRs from the MAIC to the selected log-logistic distribution in the serplulimab arm. This approach was deemed most appropriate as it does not rely on the assumption that there is no difference between the trials in the distribution of effect-modifying variables when assessing the relative efficacy of serplulimab and atezolizumab/durvalumab, because any differences are adjusted for as part of the MAIC. HRs were assumed to be constant in the model base case; the validity of this approach and the results of sensitivity analyses using time-varying HRs are discussed further in comment #5. Importantly, given the shape of the Kaplan-Meier curves in the data from ASTRUM-005, there is no indication for the loss of treatment effect within the trial period. This contrasts with what was observed in the data from IMpower133 presented in TA638, as the Kaplan-Meier curves began to converge toward the end of the trial, indicating reduction of treatment effect. Furthermore, ASTRUM-005 had a considerably longer follow-up compared to IMpower133, which provides a greater time for any potential loss of treatment effect to be observed. Therefore, in the base-case, no loss of relative treatment effect is assumed; however, the impact of different assumptions regarding the duration of treatment effect is explored in scenario analysis presented in the company submission.
5	**Section 3.8: Constant hazard ratios** In section 3.8 of the draft guidance, the Committee requested further analyses that model serplulimab, atezolizumab, and durvalumab using a network meta-analysis with time-varying HRs. To provide a scenario using a network meta-analysis (NMA) with time-varying HRs, fractional polynomial (FP) NMAs were conducted using time-to-event outcomes OS and PFS from ASTRUM-005, IMPower133, and CASPIAN trials. FP NMAs offer a flexible, time-varying method that allows hazard rates to change over time, with the aim to address potential violations of the proportional hazards (PH) assumption. Further details of the methods and results are provided in 'Draft Guidance Comments Appendix B'. The PH assumption was supported for both OS and PFS in ASTRUM-005. In IMPower133 and CASPIAN, there were some concerns, due to early curve crossings, and for CASPIAN PFS the Schoenfeld residuals test. However, overall patterns and non-significant tests for other endpoints suggest the PH assumption could not be formally rejected. These assessments should be interpreted with caution due to use of reconstructed data for comparator trials. Both first and second order FP NMA models were fitted. First-order models showed limited fit to the observed survival seen in the KM curves. Many second-order models faced convergence issues and wide credible intervals for HR estimates, limiting reliable estimation of relative effects in this small network of three trials. These limitations mean results from the FP NMAs should be interpreted with caution. Nonetheless, the best-fitting FP NMA models have been included as scenarios in the cost-effectiveness model. Findings from FP NMA models are included in the cost effectiveness model as scenarios. First order models produced ICERs broadly aligned with the base case using MAICs. The best-fitting first-order models had minimal impact on overall results, indicating that after the initial time period, serplulimab had a lower hazard of progression or death compared to atezolizumab, durvalumab, and carboplatin-etoposide – consistent with the MAICs. Second-order models showed high uncertainty in relative effect estimates and many had convergence issues.

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	Overall, the company considers the MAICs in the base case to be most appropriate approach, given the considerations around the PH assumption, the minor differences observed with first-order FP NMA results, and the ability of MAICs to adjust for between trial differences in patient characteristics. FP NMA models provide useful context and have been included as scenario analyses within the cost-effectiveness model. However, they are subject to limitations – particularly in terms of model fit and convergence in a small network. It is also important to note that while FP NMAs offer flexibility, overfitting to KM curves can lead to unrealistic extrapolations.
6	**Section 3.9: Extrapolating time to off-treatment** Treatment durations in ASTRUM-005, IMpower133, and CASPIAN In section 3.9 of the draft guidance, the committee requested a comparison of time-to-off-treatment data (such as median time-to-off treatment values) for serplulimab, atezolizumab and durvalumab across the ASTRUM-005, IMpower133 and CASPIAN trials, respectively. The median duration of treatment exposure (weeks, number of treatment doses) across the intervention arms in ASTRUM-005, IMpower133, and CASPIAN were: • Serplulimab (ASTRUM-005): 22 weeks, 8 doses • Atezolizumab (IMpower133; TA638): 4.7 months (20.4 weeks), 7 doses • Durvalumab (CASPIAN; TA1041): 28 weeks, 7 doses In terms of the median number of treatment doses, serplulimab (8 doses) was associated with greater time on treatment compared to atezolizumab and durvalumab (7 doses each). This may be attributed to the improved efficacy and/or tolerability of serplulimab compared to atezolizumab and durvalumab. Durvalumab had the greatest time on treatment in weeks as durvalumab monotherapy was administered once every 4 weeks, compared to administration once every 3 weeks for all other regimens. Additional time to off-treatment scenarios The committee also requested additional scenarios for the extrapolation of time to off-treatment, the results of which are provided in Appendix A. Firstly, a scenario in which time to off-treatment is assumed to be equivalent to PFS for serplulimab, atezolizumab, and durvalumab was explored. In this scenario, it is assumed that patients discontinue treatment only due to disease progression; therefore, it is likely that this scenario overestimates time on treatment, as patients will likely discontinue treatment for other reasons e.g., tolerability, before they progress. A scenario was also explored 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. Applying the same gap observed from ASTRUM-005 to the atezolizumab and durvalumab arms leads to an imbalance in the costs and efficacy for these arms, particularly for durvalumab as a longer time on treatment was observed in CASPIAN; therefore, this approach underestimates time on treatment for durvalumab. The final scenario used 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 considers this to be an overly simplistic approach to modelling time on treatment. This is

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	exemplified in the durvalumab arm, for which the median time on treatment in CASPIAN was greater than median PFS. Overall, the company considers the approach taken to modelling time to off-treatment in the base case most appropriate to balance costs and efficacy in each treatment arm, using the time to off-treatment curves directly from ASTRUM-005, and applying HRs from the MAIC to derive the time to off-treatment curves for atezolizumab and durvalumab. Using the time to off-treatment curves directly from the trials ensures that treatment costs and efficacy data included in the model are balanced appropriately.
7	**Choice of height and weight in the economic model** In Section 3.10 of the draft guidance, the Committee agreed that the weight and height used to inform the model should be based on the expected NHS population. The height and weight estimates from the Health Survey for England, provided by the EAG, are representative of the general population and likely overestimate the weight of the population in England with ES-SCLC. To provide a more accurate reflection of the height and weight of the ES-SCLC population in England, the height and weight from the Non-Asian population in ASTRUM-005 were reweighted to reflect that 50% of the patient population in England are female. In ASTRUM-005, the mean average height/weight of the Non-Asian population was 73.06kg/160.83cm for females, and 79.71kg/172.86cm for males. The reweighted population height/weight was calculated by taking the mean average of the mean average Non-Asian male and female height/weights (i.e., assuming 50% female patients in the patient population): 76.38kg/166.85cm. The impact of using the updated height and weight estimates on the model results are provided as a scenario in Appendix A, and these inputs are also incorporated in the revised model base case in comment #9.
8	**Choice of health-state utility values in the economic model** In Section 3.11 of the draft guidance, the committee requested updated health-state utility values for the whole population in ASTRUM-005 calculated using a linear mixed effects approach. A summary of the fitted models is provided in Appendix A; data from the 7th May 2024 data cut were used in the analysis. In summary, the utility values for patients in the 'progression-free' and 'progressed disease' health states were 0.830 and 0.796, respectively. The impact of using the updated health state utility values on the model results are provided as a scenario in Appendix A. The updated health state utility values are also incorporated in the revised model base case in comment #9.
9	**Revised cost-effectiveness model** The company has revised the cost-effectiveness model, considering feedback from both the committee and the EAG. The following model changes have been implemented: • Additional height/weight inputs to better reflect the NHS population with ES-SCLC, using data from the Non-Asian population in ASTRUM-005 reweighted to be 50% female (see comment #7). These inputs are included in the revised company base case. • Updated utility values calculated using linear mixed-effects approach (see comment #8). These utility values are included in the revised company base case.

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	• Additional time to off-treatment scenarios have been included in the model. As described in comment #6, the company considers the approach taken in the base case, using the time to off-treatment curves, to be most appropriate for modelling time on treatment. • Time-varying hazard ratios from the fractional polynomials network meta-analysis for modelling overall survival and progression-free survival in the atezolizumab and durvalumab arms have been included in the model. As discussed in comment #5, the company considers the MAICs in the base case to be most appropriate approach due to the considerations with regards the PH assumptions, the minor differences seen when using the FP NMAs results and the ability of MAICs to adjust for between trial differences in patient characteristics. A full breakdown of the revised model base case results and sensitivity analyses are provided in Appendix A. Based on a synthesis of the best available data, serplulimab is estimated to be a cost-effective treatment for ES-SCLC compared to atezolizumab and durvalumab, resulting in significant patient benefits in a population with high disease burden.

Insert extra rows as needed

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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. Horn, L., et al., *First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer.* N Engl J Med, 2018. **379**(23): p. 2220-2229.
3. Paz-Ares, L., et al., *Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial.* Lancet, 2019. **394**(10212): p. 1929-1939.
4. Chen, L. and X. Han, *Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future.* J Clin Invest, 2015. **125**(9): p. 3384-91.
5. Issafras, H., et al., *Structural basis of HLX10 PD-1 receptor recognition, a promising anti-PD-1 antibody clinical candidate for cancer immunotherapy.* PLoS One, 2021. **16**(12): p. e0257972.
6. Philips, E.A., et al., *The structural features that distinguish PD-L2 from PD-L1 emerged in placental mammals.* J Biol Chem, 2020. **295**(14): p. 4372-4380.
7. Herbst, R.S., et al., *Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients.* Nature, 2014. **515**(7528): p. 563-7.
8. Liu, Y., et al., *Navigating first-line therapies for extensive-stage small-cell lung cancer: a frequentist network meta-analysis and systematic review.* Future Oncol, 2024. **20**(28): p. 2109-2122.
9. Wang, S., et al., *Efficacy and safety of first-line immune checkpoint inhibitors combined with chemotherapy for extensive-stage small cell lung cancer: A network meta-analysis.* Lung Cancer, 2023. **178**: p. 47-56.
10. Zhang, T., et al., *Efficacy and safety of first-line immunotherapy plus chemotherapy in treating patients with extensive-stage small cell lung cancer: a Bayesian network meta-analysis.* Front Immunol, 2023. **14**: p. 1197044.
11. Zhu, Y., et al., *Comparative efficacy and safety of novel immuno-chemotherapy for extensive-stage small-cell lung cancer: a network meta-analysis of randomized controlled trial.* Ther Adv Med Oncol, 2023. **15**: p. 17588359231206147.
12. Zhang, Y., et al., *Insights into the mechanisms of serplulimab: a distinctive anti-PD-1 monoclonal antibody, in combination with a TIGIT or LAG3 inhibitor in preclinical tumor immunotherapy studies.* MAbs, 2024. **16**(1): p. 2419838.
13. Du, J., et al., *Effectiveness and safety of first-line immune checkpoint inhibitors for patients with extensive-stage small cell lung carcinoma: A systematic review and network meta-analysis.* Heliyon, 2023. **9**(4): p. e14794.
14. Yang, C., et al., *Efficacy and safety of novel immune checkpoint inhibitor-based combinations versus chemotherapy as first-line treatment for patients with extensive-stage small cell lung cancer: A network meta-analysis.* Thorac Cancer, 2024. **15**(15): p. 1246-1262.
15. Cheng, Y., et al., *Serplulimab vs. placebo combined with chemotherapy as first-line treatment for extensive-stage small-cell lung cancer: Extended follow-up results and patient-reported outcomes from the international phase 3 ASTRUM-005 study.* Journal of Clinical Oncology, 2024. **42**(16_suppl): p. 8100-8100.

Appendix A

Additional scenarios and revised model base case

Deterministic results from the additional model scenarios requested by the Committee are presented at list price and PAS price in Table 1 and Table 2, respectively. Each of the scenarios was applied individually on the original company base case. Deterministic and probabilistic results for the revised base case are also presented. The key assumptions in the revised base care are:

- Height and weight inputs based on the Non-Asian population from ASTRUM-005 reweighted to be 50% female, to better reflect the NHS population with ES-SCLC
- Utility values based on the ITT population from ASTRUM-005 and estimated using a linear mixed effects approach
- Independent log-logistic distributions were selected for modelling OS and PFS for serplulimab and carboplatin-etoposide; for atezolizumab and durvalumab, hazard ratios from the MAIC were applied to the serplulimab extrapolations
- The original base case approach for modelling time on treatment directly based on the time to off-treatment curves from ASTRUM-005 is maintained. Independent log-logistic distributions were selected for serplulimab and carboplatin-etoposide; for atezolizumab and durvalumab OS hazard ratios from the MAIC were applied to the serplulimab time on treatment extrapolation

Deterministic sensitivity analyses (DSA) were performed to explore the effect of uncertainty associated with varying individual model inputs in the revised base case. The inputs with the greatest impact on the ICER against atezolizumab, durvalumab, and carboplatin-etoposide are presented in descending order as tornado plots in Figure 1, Figure 2, and Figure 3, respectively.

Table 1: Additional scenarios requested by the Committee and revised company base case – list price (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 1 – Height/weight from Non-Asian population reweighted to be 50% female							
Serplulimab	£84,613	2.47	2.10	-	-	-	-
Durvalumab	£80,063	1.87	1.64	£4,550	0.60	0.46	£9,794
Atezolizumab	£54,721	1.74	1.50	£29,891	0.74	0.60	£50,044
Carboplatin-etoposide	£21,603	1.38	1.21	£63,009	1.09	0.89	£70,558
Scenario 2 – Updated health state utility values from linear mixed effects model							
Serplulimab	£79,427	2.47	2.08	-	-	-	-
Durvalumab	£80,009	1.87	1.62	-£582	0.60	0.46	Dominant
Atezolizumab	£54,671	1.74	1.49	£24,756	0.74	0.59	£41,855
Carboplatin-etoposide	£21,561	1.38	1.19	£57,866	1.09	0.88	£65,435
Scenario 3 – Time to off-treatment assumed to be equivalent to progression-free survival							
Serplulimab	£112,094	2.47	2.04	-	-	-	-
Durvalumab	£99,315	1.87	1.61	£12,778	0.60	0.43	£29,463
Atezolizumab	£70,864	1.74	1.45	£41,229	0.74	0.59	£70,066
Carboplatin-etoposide	£21,579	1.38	1.19	£90,514	1.09	0.85	£106,457
Scenario 4 – Gap between time to off-treatment and progression-free survival 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 progression-free survival extrapolations							
Serplulimab	£120,142	2.47	2.03	-	-	-	-

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Durvalumab	£108,480	1.87	1.59	£11,662	0.60	0.43	£26,890
Atezolizumab	£77,362	1.74	1.43	£42,780	0.74	0.59	£71,938
Carboplatin-etoposide	£21,135	1.38	1.17	£99,007	1.09	0.86	£115,623
Scenario 5 – The trial-observed ratios of median progression-free survival to median time to off-treatment, applied to the progression-free survival curves to generate the time-on-treatment curves, per treatment arm							
Serplulimab	£100,569	2.47	2.06	-	-	-	-
Durvalumab	£112,661	1.87	1.59	-£12,093	0.60	0.47	Dominant
Atezolizumab	£65,902	1.74	1.47	£65,902	0.74	0.61	£58,381
Carboplatin-etoposide	£21,148	1.38	1.20	£79,420	1.09	0.86	£92,596
Revised company base case – deterministic							
Serplulimab	£84,613	2.47	2.08	-	-	-	-
Durvalumab	£80,063	1.87	1.62	£4,550	0.60	0.46	£9,889
Atezolizumab	£54,721	1.74	1.49	£29,891	0.74	0.59	£50,537
Carboplatin-etoposide	£21,603	1.38	1.19	£63,009	1.09	0.88	£71,252
Revised company base case – probabilistic							
Serplulimab	£87,252	2.47	2.07	-	-	-	-
Durvalumab	£83,869	1.93	1.65	£3,383	0.54	0.42	£8,055
Atezolizumab	£58,691	1.81	1.53	£28,562	0.66	0.54	£52,719
Carboplatin-etoposide	£23,232	1.39	1.20	£64,021	1.08	0.88	£72,987

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.*
***Notes**: Discounted costs and QALYs are presented. 1.2x QALY weight are applied to the total/incremental QALYs.*

Table 2: Additional scenarios requested by the Committee and revised company base case - PAS price (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 1 – Height/weight from Non-Asian population reweighted to be 50% female							
Serplulimab	[redacted]	2.47	2.10	-	-	-	-
Durvalumab	£80,063	1.87	1.64	[redacted]	0.60	0.46	[redacted]
Atezolizumab	£54,721	1.74	1.50	[redacted]	0.74	0.60	[redacted]
Carboplatin-etoposide	£21,603	1.38	1.21	[redacted]	1.09	0.89	[redacted]
Scenario 2 – Updated health state utility values from linear mixed effects model							
Serplulimab	[redacted]	2.47	2.08	-	-	-	-
Durvalumab	£80,009	1.87	1.62	[redacted]	0.60	0.46	[redacted]
Atezolizumab	£54,671	1.74	1.49	[redacted]	0.74	0.59	[redacted]
Carboplatin-etoposide	£21,561	1.38	1.19	[redacted]	1.09	0.88	[redacted]
Scenario 3 – Time to off-treatment assumed to be equivalent to progression-free survival							
Serplulimab	[redacted]	2.47	2.04	-	-	-	-
Durvalumab	£99,315	1.87	1.61	[redacted]	0.60	0.43	[redacted]
Atezolizumab	£70,864	1.74	1.45	[redacted]	0.74	0.59	[redacted]

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Carboplatin-etoposide	£21,579	1.38	1.19	[redacted]	1.09	0.85	[redacted]
Scenario 4 – Gap between time to off-treatment and progression-free survival 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 progression-free survival extrapolations							
Serplulimab	[redacted]	2.47	2.03	-	-	-	-
Durvalumab	£108,480	1.87	1.59	[redacted]	0.60	0.43	[redacted]
Atezolizumab	£77,362	1.74	1.43	[redacted]	0.74	0.59	[redacted]
Carboplatin-etoposide	£21,135	1.38	1.17	[redacted]	1.09	0.86	[redacted]
Scenario 5 – The trial-observed ratios of median progression-free survival to median time to off-treatment, applied to the progression-free survival curves to generate the time-on-treatment curves, per treatment arm							
Serplulimab	[redacted]	2.47	2.06	-	-	-	-
Durvalumab	£112,661	1.87	1.59	[redacted]	0.60	0.47	[redacted]
Atezolizumab	£65,902	1.74	1.47	[redacted]	0.74	0.61	[redacted]
Carboplatin-etoposide	£21,148	1.38	1.20	[redacted]	1.09	0.86	[redacted]
Revised company base case – deterministic							
Serplulimab	[redacted]	2.47	2.08	-	-	-	-
Durvalumab	£80,063	1.87	1.62	[redacted]	0.60	0.46	[redacted]
Atezolizumab	£54,721	1.74	1.49	[redacted]	0.74	0.59	[redacted]
Carboplatin-etoposide	£21,603	1.38	1.19	[redacted]	1.09	0.88	[redacted]
Revised company base case – probabilistic							
Serplulimab	[redacted]	2.49	2.08	-	-	-	-
Durvalumab	£84,046	1.93	1.65	[redacted]	0.57	0.43	[redacted]
Atezolizumab	£59,332	1.84	1.55	[redacted]	0.65	0.53	[redacted]
Carboplatin-etoposide	£22,831	1.39	1.19	[redacted]	1.10	0.89	[redacted]

***Abbreviations**: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.*
***Notes**: Discounted costs and QALYs are presented. 1.2x QALY weight are applied to the total/incremental QALYs.*

Utility models

A summary of the mixed linear effects models used to derive health state utilities are presented in Table 3; the updated utility values presented in Table 4.

Table 3: Summary of mixed linear effects models for health state utilities

	Progression state	Progression state and on/off-treatment status	Time to death and on/off-treatment status
	Regression coefficients (95% CI)		
Intercept	0.8302 (0.8179, 0.8426)	0.8351 (0.8228, 0.8475)	0.6363 (0.5914, 0.6813)
Progression status (progressed vs progression-free)	-0.0343 (-0.0454, -0.0232)	-0.0074 (-0.0204, 0.0057)	-
Treatment status (off vs on treatment)	-	-0.0491 (-0.0619, -0.0364)	-0.0385 (-0.0499, -0.0270)

Time to death (reference: ≤5 weeks)			
> 5 to ≤ 15 weeks	-	-	0.1615 (0.1167, 0.2062)
> 15 to ≤ 30 weeks	-	-	0.1906 (0.1464, 0.2347)
> 30 weeks	-	-	0.2071 (0.1622, 0.2520)
	Model fit		
AIC	-4822.576	-4868.652	-4932.662
BIC	-4797.274	-4837.025	-4888.388

Abbreviations: *AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; CI, confidence interval*

Table 4: Updated health state utility values

Health state	**Utility value (95% CI)**
By disease progression state (base case)	
Progression-free	0.830 (0.818, 0.843)
Progressed disease	0.796 (0.781, 0.811)
By disease progression and on/off-treatment status	
On-treatment	
Progression-free	0.835 (0.823, 0.847)
Progressed disease	0.828 (0.811, 0.845)
Off-treatment	
Progression-free	0.786 (0.769, 0.803)
Progressed disease	0.779 (0.763, 0.794)
By time to death and on/off-treatment status	
On-treatment	
> 30 weeks	0.843 (0.831, 0.856)
> 15 to ≤ 30 weeks	0.827 (0.810, 0.844)
> 5 to ≤ 15 weeks	0.798 (0.774, 0.822)
0 to ≤ 5 weeks	0.636 (0.591, 0.681)
Off-treatment	
> 30 weeks	0.805 (0.789, 0.821)
> 15 to ≤ 30 weeks	0.788 (0.770, 0.807)
> 5 to ≤ 15 weeks	0.759 (0.737, 0.782)
0 to ≤ 5 weeks	0.598 (0.555, 0.641)

Abbreviations: *CI, confidence interval*

Figure 4: Tornado plot of sensitive parameters in the deterministic sensitivity analysis – comparator atezolizumab

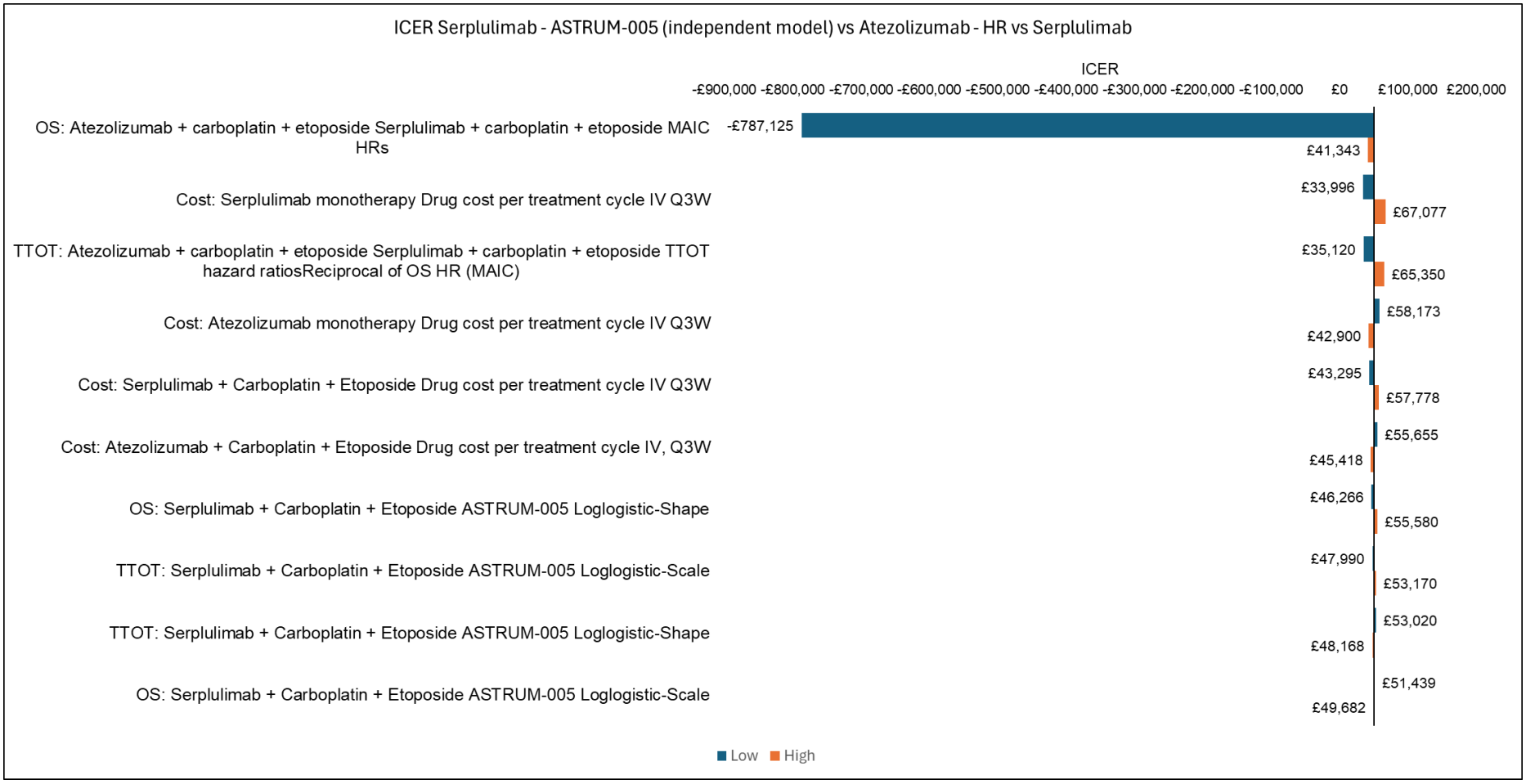


Figure 5: Tornado plot of sensitive parameters in the deterministic sensitivity analysis – comparator durvalumab

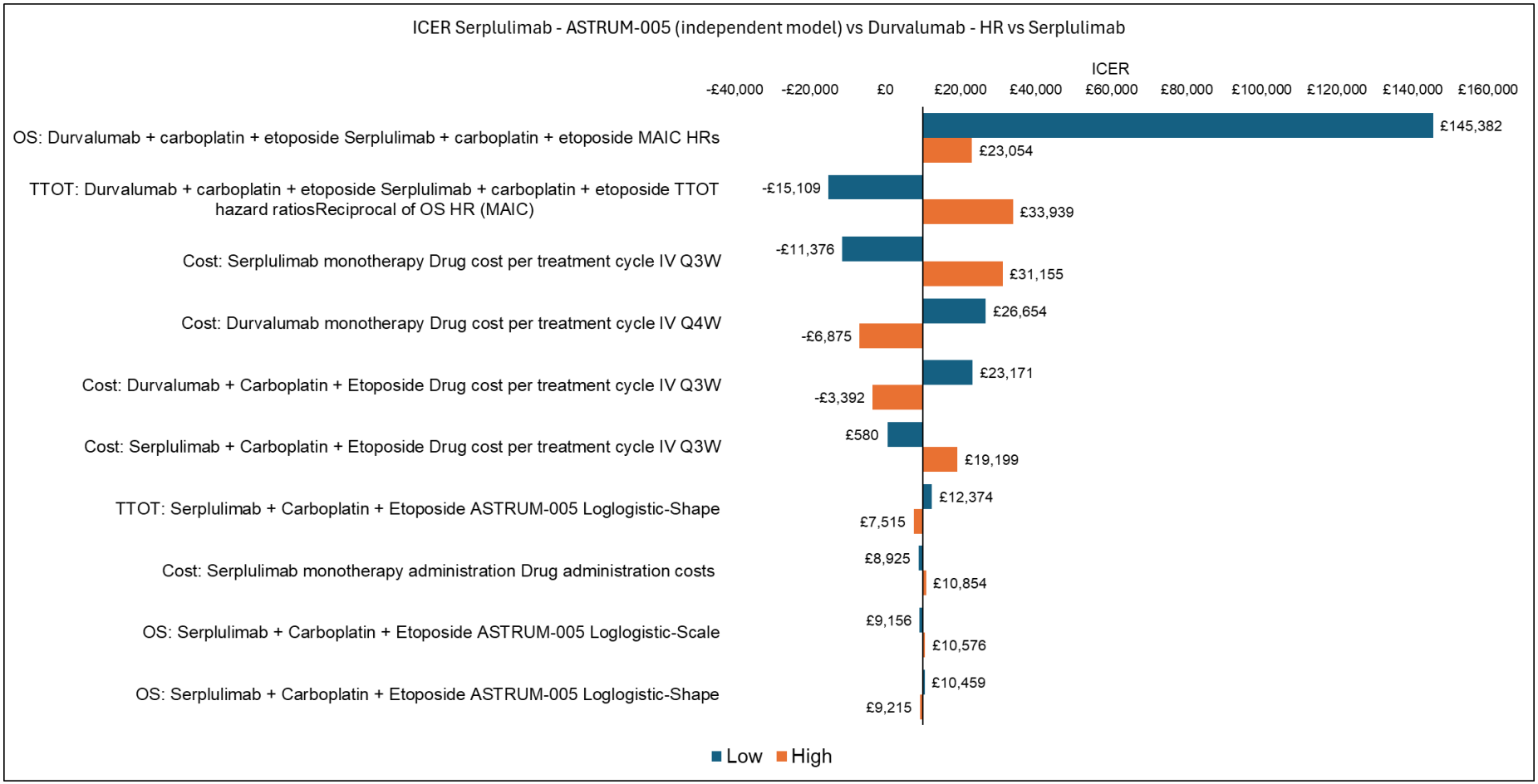
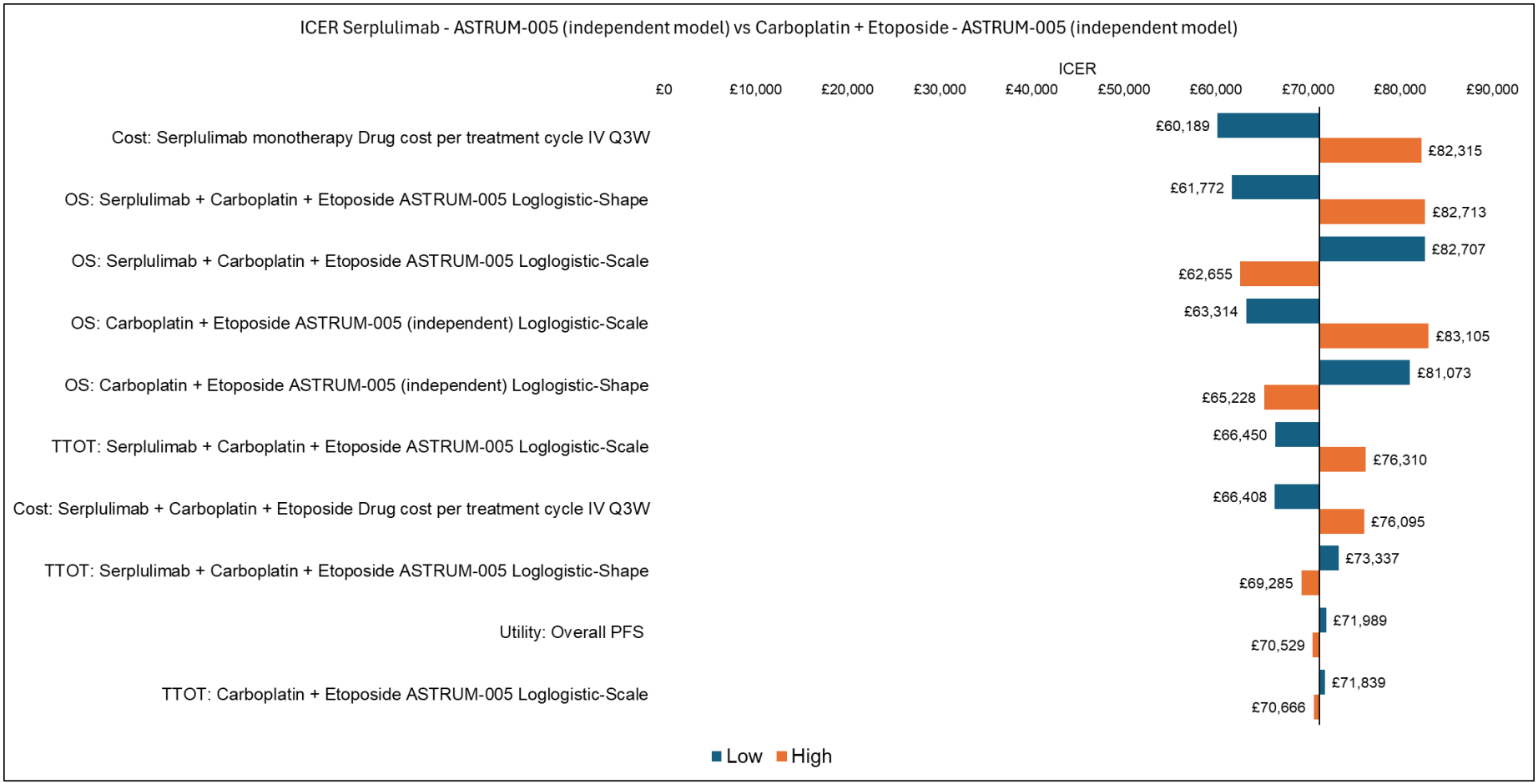


Figure 6: Tornado plot of sensitive parameters in the deterministic sensitivity analysis – comparator carboplatin plus etoposide



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

Draft Guidance Comments Appendix B: Indirect treatment comparison updates

Contents

Introduction

This document outlines the methods and results of supplementary indirect treatment comparisons (ITCs) conducted to support the appraisal of serplulimab with carboplatin and etoposide for patients with untreated extensive-stage small-cell lung cancer (ES-SCLC). In response to the draft guidance issued by NICE, further analyses were undertaken to compare serplulimab, atezolizumab, and durvalumab using a network meta-analysis (NMA) approach that allows for time-varying hazard ratios.

Methods

Fractional polynomial (FP) NMAs were used to model time-to-event outcomes for overall survival (OS) and progression-free survival (PFS). FP NMAs are a flexible, time-varying method that allows hazard rates to change over time, addressing potential violations of the proportional hazards assumption.

Data requirements

FP NMAs require individual patient-level time-to-event data across all trial arms in the network. For this analysis, patient-level data from ASTRUM-005 were used, alongside pseudo-IPD for IMPower133 (1) and CASPIAN (2, 3) generated from digitized Kaplan–Meier curves using the method described by Guyot et al. (2012) (4).

Following methods described by Jansen (2011)(5), survival data were divided into discrete time intervals and within each interval, the number of events and patients at risk were estimated to inform the model. The choice of time intervals was based on exploratory analyses of the outcome data (inspection of Kaplan-Meier (KM) curves and hazard plots). The choice of time interval in FP models involves a trade-off: intervals are required to be short enough that the hazard of an event is constant, but choosing too short intervals increases uncertainty due to fewer events, while longer intervals reduce uncertainty but rely on stronger structural assumptions.

Proportional hazard assumption

The proportional hazard (PH) assumptions were assessed using the patient-level data from ASTRUM-005 and pseudo-IPD from comparator trials (IMPower133 and CASPIAN). The PH assumption was evaluated using log-cumulative hazard plots, Schoenfeld residuals, and the Schoenfeld individual test to determine whether the PH assumption can be rejected (based on nominal $p < 0.05$).

Fractional polynomial network meta-analyses

FP models allow evidence synthesis of time-to-event data based on FP models. Fixed effects FP NMA models within a Bayesian NMA of first and second order were fitted to the endpoints OS and PFS. Fixed effects models were chosen due to the small network of evidence, which makes estimating between study heterogeneity often unreliable and there was no evidence of strong heterogeneity in the network. Therefore, fixed effect models were anticipated to be more stable and interpretable in this setting.

The analysis followed the approach described by Jansen (2011)(5) using FP models to flexibly model time-to-event data, by expressing the log-hazard as a polynomial function of time. First and second-order FP models were analysed with the log-hazard expressed as:

- First-order: $\ln(h_{jkt}) = \beta_0 + \beta_1 t^{\,p_1}$
- Second-order: $\ln(h_{jkt}) = \beta_0 + \beta_1 t^{p_1} + \beta_2 t^{p_2}$

First order models were fitted with power p_1 from the set (-2, -1, -0.5, 0, 0.5, 1, 2), with $t^0 = \ln t$. Second order models were fitted using the best fitting p_1 from the first order models, with p_2 from the set (-2, -1, -0.5, 0, 0.5, 1, 2).

FP NMA estimates relative treatment effects by comparing differences in model parameters (e.g. β_0 and β_1 for first-order models) across trials using a multivariate NMA framework. For trial j, the first-order FP model for treatment k versus reference treatment b for the hazard at time t is:

$$\ln(h_{jkt}) = \beta_{0\mathrm{jk}} + \beta_{1\mathrm{jk}} t^{p_1}$$

Where:

$$\begin{pmatrix}\beta_{0jk}\\ \beta_{1jk}\end{pmatrix} = \begin{cases}\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}, if\ k = b\ and\ b \in \{A, B, C, \dots\}\\ \begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix} + \begin{pmatrix}\delta_{0jbk}\\ \delta_{1jbk}\end{pmatrix}, if\ k \neq b\end{cases}$$

Where $\begin{pmatrix}\mu_{0jb}\\ \mu_{1jb}\end{pmatrix}$ is the vector of true underlying baseline effects for the β parameters for the reference treatment b in trial j and $\begin{pmatrix}\delta_{0jbk}\\ \delta_{1jbk}\end{pmatrix}$ represents the trial-specific, true underlying relative treatment effects for treatment k versus the baseline comparator b of that trial. In the fixed-effects model, relative effects for treatment k are expressed as $\begin{pmatrix}\delta_{0jbk}\\ \delta_{1jbk}\end{pmatrix} = \begin{pmatrix}d_{0Ak} - d_{0Ab}\\ d_{1Ak} - d_{1Ab}\end{pmatrix}$, where *A* is the overall reference treatment.

Second-order FP models are similarly defined as:

$$\ln(h_{jkt}) = \beta_{0\mathrm{jk}} + \beta_{1\mathrm{jk}} t^{p_1} + \beta_{2\mathrm{jk}} t^{p_2}.$$

Models were fitted using Bayesian Markov Chain Monte Carlo methods via JAGS, implemented through R, specifically the gemtcPlus R package.(6) For the model in gemtcPlus, the reference treatment used was the control arm of the trials, placebo added to chemotherapy (carboplatin plus etoposide) and the reference study was ASTRUM-005.

For each endpoint, the preferred FP NMA model was evaluated based on:

- Deviance Information Criterion (DIC) values, which allow comparison across models using the same input data
- Visual fit of the estimated survival curves to observed Kaplan–Meier curves and clinical plausibility of extrapolated survival

Results

Proportional hazard assessment

[redacted]

Fractional polynomial network meta-analyses

[redacted]

[redacted]

OS

[redacted]

Table 1: Model fit - OS first and second order FP NMAs fixed effects models

Power (p_1)	Power (p_2)	DIC	pD	meanDev
[redacted]				

[a] Corresponding to Weibull distribution for hazard over time; [b] Corresponding to Gompertz distribution for hazard over time.

Abbreviations: DIC, deviance information criterion; FP, fractional polynomials; meanDev, posterior mean residual deviance; NMA, network meta-analysis; pD, effective number of parameters ;PFS, progression-free survival.

[redacted]

Figure 1: OS first order FP NMA model ($\mathbf{p_1 = -2}$) hazard ratio over time serplulimab vs comparator treatments

[redacted]

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; OS, overall survival.

Figure 2: OS first order FP NMA model ($\mathbf{p_1 = -2}$) estimated survival curves

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; OS, overall survival.

Figure 3: OS first order FP NMA model ($p_1 = -2$) survival estimates with KM overlays

Abbreviations: FP, fractional polynomials; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival.

PFS

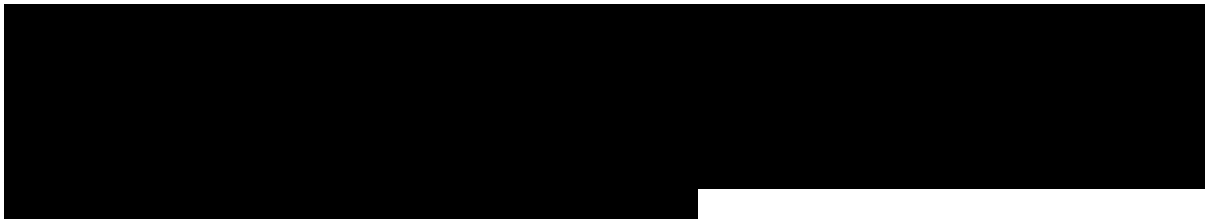


Table 2: Model fit - PFS first and second order FP NMAs fixed effects model

Power (p_1)	Power (p_2)	DIC	pD	meanDev
[redacted]				

[a] Corresponding to Weibull distribution for hazard over time; [b] Corresponding to Gompertz distribution for hazard over time

Abbreviations: DIC, deviance information criterion; FP, fractional polynomials; meanDev, posterior mean residual deviance; NMA, network meta-analysis; pD, effective number of parameters ;PFS, progression-free survival.

Figure 4: PFS first order FP NMA model ($p_1 = -2$) hazard ratio over time serplulimab vs comparator treatments

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; PFS, progression-free survival.

Figure 5: PFS first order FP NMA model ($p_1 = -2$) survival estimates

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; PFS, progression-free survival.

Figure 6: PFS first order FP NMA model ($p_1 = -2$) survival estimates with KM overlays

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; PFS, progression-free survival.

Conclusion

References

1. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. New England Journal of Medicine. 2018;379(23):2220-9.
2. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. The Lancet Oncology. 2021;22(1):51-65.
3. Paz-Ares L, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO open. 2022;7(2):100408.
4. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC medical research methodology. 2012;12(1):9.
5. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC medical research methodology. 2011;11(1):61.
6. Gsteiger S, Howlett N, Ashlee B. gemtcPlus: Provides a suite of extension functions for NMA using the `gemtc` package. R package version 1.0.0 ed2022.

Appendix

Appendix: Proportional hazards assessments

[redacted]

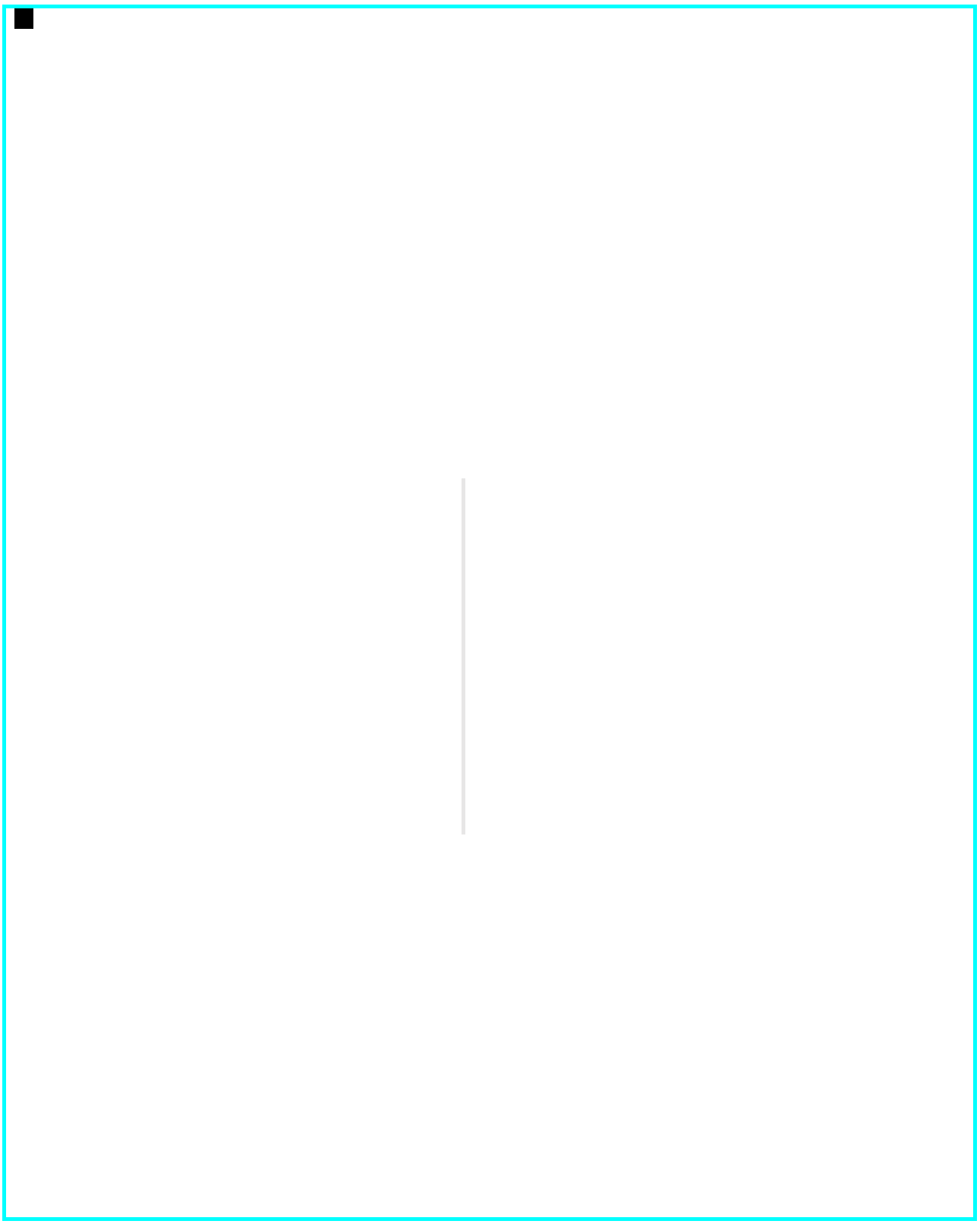
Table 3: Summary of proportional hazard assumption assessment

Trial	Endpoint	Assessment of PH
[redacted]		

Abbreviations: OS, overall survival; PFS, progression-free survival; PH, proportional hazards.

[redacted]

[redacted]



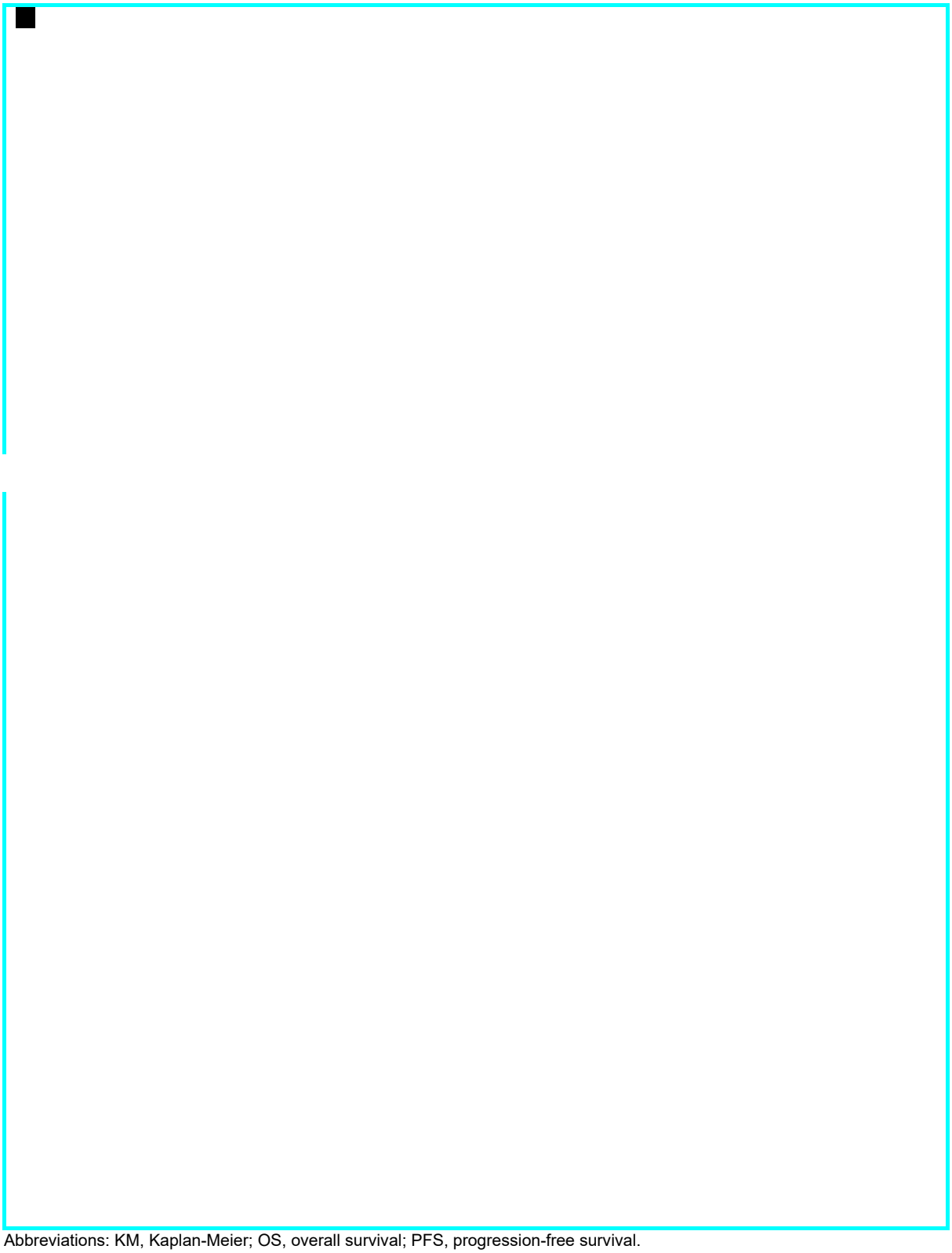
Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

[redacted]

[redacted]

Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

[redacted]



Abbreviations: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

Appendix: Second order FP NMA model results

Figure 7: OS second order FP NMA model ($p_1 = -2, p_2 = 0.5$) hazard ratio over time serplulimab vs comparator treatments

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; OS, overall survival

Figure 8: OS second order FP NMA model ($\mathrm{p}_1 = -2, \mathrm{p}_2 = 0.5$) estimated survival curves

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; OS, overall survival

Figure 9: OS second order FP NMA model ($p_1 = -2, p_2 = 0.5$) survival estimates with KM overlays

Abbreviations: FP, fractional polynomials; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival

Figure 10: PFS second order FP NMA model ($p_1 = -2, p_2 = 1$) hazard ratio over time serplulimab vs comparator treatments

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; PFS, progression-free survival

Figure 11: PFS second order FP NMA model ($p_1 = -2, p_2 = 1$) survival estimates

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; PFS, progression-free survival

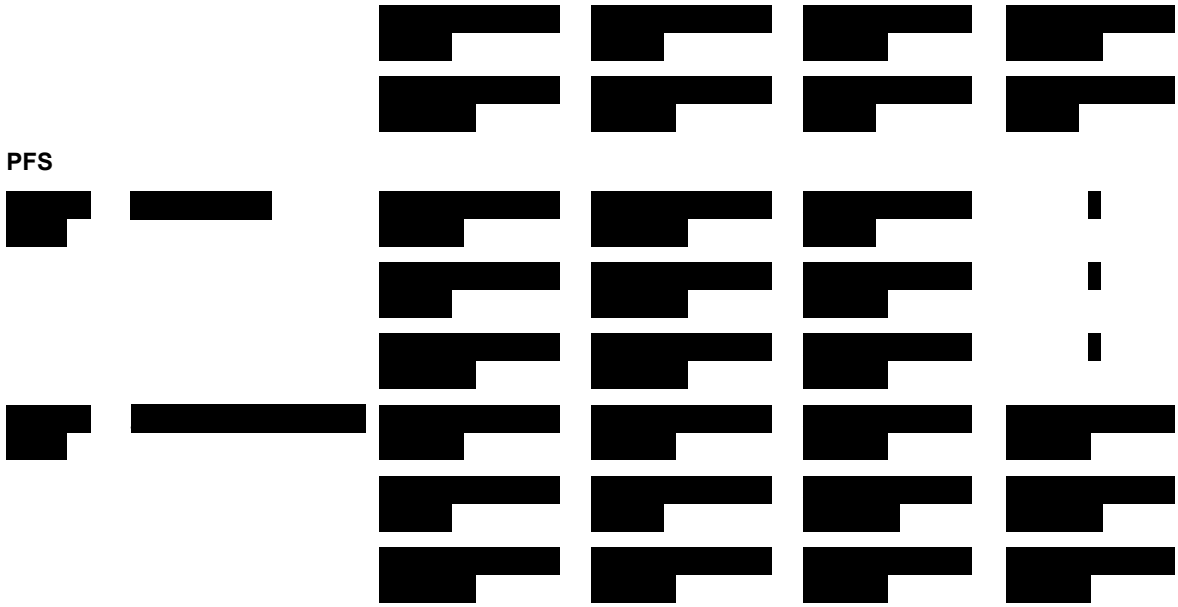
Figure 12: PFS second order FP NMA model ($p_1 = -2, p_2 = 1$) survival estimates with KM overlays

Abbreviations: FP, fractional polynomials; KM, Kaplan-Meier; NMA, network meta-analysis; PFS, progression-free survival.

Appendix: FP NMA model parameters

Table 4: FP NMA model parameter estimates

FP NMA Model	Powers	Comparison	Estimated coefficients – median of posterior distribution (95% credible intervals)		
			β_0	β_1	β_2
OS					
					
					
					
					



Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

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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Report reference:	
Report key:	[redacted]

1 Serplulimab as a clinically relevant alternative

In the company submission (CS) document draft guidance (DG) comments,[1] the company reiterate the distinct mode of action and molecular structure of serplulimab compared to other PD-L1 inhibitors and PD-1 inhibitors, respectively. The EAG acknowledge the molecular evidence for serplulimab disrupting both PDL1 and PDL2 through binding to the PD1, which may lead to greater suppression of T-cell inhibition, thus enabling a greater anti-tumour response. However, the company did not present any direct evidence from ASTRUM-005 demonstrating that PDL1 expression, nor PDL2 expression was associated with an improvement in outcome in patients receiving serplulimab treatment. Thus, while these preclinical findings from cell and animal models provide valuable insights, direct clinical evidence is needed to confirm whether serplulimab treatment in patients with ES-SCLC leads to the dual disruption of PDL1 and PDL2 and subsequent T-cell activation, and that this translates into clinically meaningful outcomes. The EAG agrees that serplulimab presents a safe and clinically effective profile for patients with ES-SCLC and with the clinical expert view from the committee meeting that serplulimab would offer an alternative first-line immunotherapy option in combination with chemotherapy. However, indications of superiority of serplulimab treatment over currently recommended treatments for ES-SCLC should be interpreted with caution, owing to the differences in patient characteristics and settings of the trials being compared and to the NHS population.

2 Generalisability of clinical trials

The company have reiterated that ASTRUM-005, the pivotal trial in this appraisal, is a large, Phase 3 randomised controlled trial with pre-planned subgroup analysis. The EAG acknowledge that the quality and rigor of ASTRUM-005 was acceptable, providing evidence for the efficacy and safety of serplulimab in patients with ES-SCLC. However, the trial enrolled mostly Asian patients (68.5% of the total trial population)[2] and was not powered to detect differences in treatment efficacy between races. While the EAG agree the fractional polynomial network meta-analysis (FP-NMA) conducted by the company[1, 3] may address some concerns over violations of the proportional hazards assumption, this additional network meta-analysis (NMA) does not address uncertainties surrounding the generalisability of the trial population to the NHS patient population. The limited overlap in patient populations would still present a recurring issue in alternative methods such as a multilevel network meta-regression (ML-NMR), however, such alternatives may have offered further insight for decision making.

Furthermore, the company state that very few patients are fit enough to progress to subsequent lines of treatment in clinical practice. While this is reflected in UK clinical practice and was validated by clinical experts to the EAG, in ASTRUM-005 [redacted] and [redacted] of participants had subsequent treatment after first disease progression in the serplulimab and placebo arms, respectively.[4] The impact of subsequent treatments on overall survival was not accounted for in the trial analysis or in the indirect treatment comparisons presented in the CS. Therefore, uncertainty still remains as to whether these subsequent treatments confounded outcomes in the trial including the effectiveness estimates.

3 Extrapolation of progression-free survival and overall survival

In the draft guidance, the committee requested a comparison of the base case model predictions with the trial Kaplan-Meier (KM) curves.[5]

For this purpose, the company produced pseudo individual patient data (pseudo IPD) from the atezolizumab arm in IMPower133 and pseudo IPD from the durvalumab arm in CASPIAN to extrapolate survival (PFS and OS) for atezolizumab and durvalumab respectively (Table 3.1). The predictions from the original company model were observed to slightly overestimate the median OS and median PFS when compared to the estimates from the pseudo IPD from trials.[6]

Table 3.1: Median PFS and median OS (Model predicted and trial-observed)

	Serplulimab	Atezolizumab	Durvalumab
OS			
Model Prediction	16.90	13.45	14.14
Trial-Observed	15.77	12.30	12.90
PFS			
Model Prediction	7.70	5.86	5.63
Trial-Observed	5.82	5.2	5.1

Source: Company DG comments form[1]
Abbreviations: OS = Overall survival, PFS = Progression free survival

The plot comparing the model predictions to the trial KM curves for OS is reproduced in Figure 3.1 and for PFS is reproduced in Figure 3.2.

For durvalumab, the model prediction curve crosses below the trial KM curve in the latter stages. It is possible the model prediction curve underestimates long-term PFS and OS, but the number of patients at risk is quite low later on in the KM curve.

For atezolizumab, the model prediction curve is marginally higher than the KM curve for the time period of the KM curve.

Figure 1: Extrapolation for OS – serplulimab, durvalumab and atezolizumab

Source: Figure 7, CS document[7], DG Comments form[1]

Figure 2: Extrapolation for PFS – serplulimab, durvalumab and atezolizumab

Source: Figure 8, CS document[7], Company DG comments form[1]

4 Constant hazard ratios

In the CS, MAICs were performed to derive the relative effect estimates for the model. However, due to uncertainties surrounding the validity of proportional hazards (PH) assumption between serplulimab and atezolizumab and between serplulimab and durvalumab the Committee requested further analyses that model serplulimab, atezolizumab, and durvalumab using a network meta-analysis (NMA) with time-varying hazard ratios (HRs). In response, the company ran fixed effect first-order and second-order fractional polynomial NMAs (FP-NMA) across a standard range, following methods described by Jansen (2011).[8] The first-order models are similar to fitting standard parametric survival models in an NMA. The second order models provide greater curve shape flexibility. The company reported that there were some concerns regarding the PH assumption in the CASPIAN and Impower133 trials, and these FP-NMA models do not make the PH assumption.

See Section 9 for the EAG selection of ITC for a revised EAG base case and an accompanying explanation.

The EAG considers fixed effect models to be appropriate given the few trials in the network. The FP-NMA models, PH diagnostic tests, FP-NMA model diagnostics conducted (summarised, not presented), and FP-NMA performance statistics and plots all seemed to be appropriate.

The summary and commentary below focus on OS. However, similar statements can be made for PFS (see the company consultation document and Appendix B).[1, 3]

The company reported that the first-order FP-NMA models were a poor fit to the trials in the network for both PFS and OS. The Deviance Information Criterion (DIC) values (Table 1, page 5 in the company consultation document Appendix B[3]) were much higher for the first-order FP-NMA models than for the second-order models. The best-fitting first-order FP was reported to be p = -2. The fit of the p = -2 FP NMA to the KM curves has been reproduced in Figure 4.1. The original plot of the parametric survival curves from the CS for ASTRUM005 is reproduced in Figure 4.2. The EAG considers the loglogistic distribution used in the company base case may be a better fit than the p = -2 FP-NMA model.

Figure 3. OS first order FP NMA model ($p_1 = -2$) survival estimates with KM overlays

Abbreviations: FP, fractional polynomials; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival.

Source: Figure 3, CS document, DG Comments Appendix B[3]

Figure 4 [redacted]

Abbreviations**:** KM, Kaplan-Meier.

Source: Figure 23, CS Document B[7]

How well the model fits to the KM curve in ASTRUM005 or the other trials is not the only consideration. The FP-NMA models do not make the PH assumption, whereas the MAICs conducted in the CS estimated a single HR value.

Based on the p = -2 FP-NMA model, the HR was roughly constant over time. See Figure 4.3. The estimated HRs were not dissimilar to the HRs estimated using the MAICs. For OS, the MAIC estimate was [redacted] for serplulimab versus atezolizumab[7] and [redacted] for serplulimab versus durvalumab.[4]

Figure 5 OS first order FP NMA model ($p_1 = -2$) hazard ratio over time serplulimab vs comparator treatments

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; OS, overall survival.

Source: Figure 1, CS document, DG Comments appendix B.[3]

The EAG notes that the company clinical experts considered the more flexible 3 knot survival models produced in response to the clarification letter to predict survival that was unreasonably high in the long-term. There is no additional clinical expert commentary in this new company evidence, but it does not seem unreasonable to suppose that the same comment may be made for these predictions.

Figure 6 OS second order FP NMA model ($p_1 = -2, p_2 = 0.5$) survival estimates with KM overlays

Abbreviations: FP, fractional polynomials; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival

Source: Figure 12, CS, DG comments appendix B.[3]

Figure 7 OS second order FP NMA model ($p_1 = -2, p_2 = 0.5$) hazard ratio over time serplulimab vs comparator treatments

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; OS, overall survival

Source: Figure 10, CS, DG comments appendix B.[3]

Figure 8 OS second order FP NMA model ($\mathbf{p_1 = -2, p_2 = 0.5}$) estimated survival curves

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; OS, overall survival

Source: Figure 11, CS, DG comments Appendix B.[3]

The company concluded the MAIC results offer the most plausible available effectiveness estimates for use in their base case. FP-NMA models were included in the revised model. The company stated that the best-fitting first-order FP-NMA model produced similar cost-effectiveness results to the company's original base case. The company did not report the cost-effectiveness results for either the best-fitting first-order or second-order FP-NMA model. The EAG expects that there would be greater uncertainty in the cost and QALY estimates using the best-fitting second-order model; for the total costs and QALYs to be greater; and for the cost-effectiveness of serplulimab to be greater compared to atezolizumab and worse compared to durvalumab.

5 Extrapolating time to off-treatment

The committee requested:

- Time-to-off treatment data across trials
- Additional scenarios for time-to-off treatment

Time-to-off treatment data

The company reported data on TTOT values for serplulimab, atezolizumab and durvalumab from ASTRUM-005, IMPower133 and CASPIAN trials, respectively, presented in Table 5.1. The company commented that durvalumab had the longest median TTOT (28 weeks) since it was administered every 4 weeks unlike 3 weeks in other treatments.

Table 5.1: TTOT data from trials

Treatment	Trial	Median TTOT	No. of Doses
Serplulimab	ASTRUM-005	22 weeks	8
Atezolizumab	IMPower133	4.7 months (20.4 weeks)	7
Durvalumab	CASPIAN	28 weeks	7

Source: Company DG comment form[1]
Abbreviations: TTOT = time to off treatment.

Scenario analyses (scenarios numbered according to the company report)

Scenario 3- Time-to-off treatment assumed to be equivalent to progression-free survival

The company commented that it is likely that this scenario will overestimate time on treatment as people will likely discontinue treatment for reasons other than disease progression. The EAG notes that some patients do continue on treatment after disease progression, but that the KM curve for TTOT for serplulimab was lower than the PFS KM curve up until about 24 months when the TTOT curve remains higher than the PFS curve.

Scenario 4- The gap between time to off-treatment and progression-free survival 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 progression-free survival extrapolations

The company commented that applying the same gap observed from ASTRUM-005 to the atezolizumab and durvalumab arms leads to an imbalance in the costs and efficacy for these arms, particularly for durvalumab as a longer time on treatment was observed in CASPIAN; therefore, this approach underestimates time on treatment for durvalumab. The EAG notes that, since the PFS curve for durvalumab is lower than the PFS curve for serplulimab, the company's argument may be true.

Scenario 5- The trial-observed ratios of median progression-free survival to median time to off-treatment, applied to the progression-free survival curves to generate the time-on-treatment curves, per treatment arm

The company commented that this scenario is simplistic since, for the durvalumab arm, the median time on treatment in CASPIAN was greater than median PFS. The EAG does not know why that would be a problem, as multiplying the PFS by a value greater than 1 will result in a TTOT curve that should reflect greater time on treatment, which is consistent with the evidence. This is reflected in the greater total costs for durvalumab in Scenario 5 than in the other scenarios. The EAG notes that the company multiplied the PFS probability by the ratio, while ensuring that the percentage on treatment was never impossibly high.

The EAG considered additional scenarios:

- Scenario 6- Multiplying the serplulimab TTOT hazard rates by the median TTOT for atezolizumab/durvalumab over serplulimab
- Scenario 7- Multiplying the atezolizumab/durvalumab PFS hazard rates by the ratio of the median TTOT over the median PFS for atezolizumab/durvalumab. This is another way of applying the ratio used in Scenario 5.

In the EAG revised base case, Scenario 7 was adopted, where the ratio of median TTOT to median PFS was multiplied with the PFS hazard rates for atezolizumab and durvalumab. See Section 9. The results of the scenario analyses with different assumptions around TTOT are presented in Table 5.2. These are based on the original company base case. In Scenario 4, where the gap between TTOT and PFS for different arms had been modelled to account for treatment beyond progression, had the highest impact on ICER. The EAG is of the opinion that the company explored all the scenarios around TTOT assumptions, which were requested by the committee.

Due to a lack of time, the company base case assumption was adopted where the percentage of patients receiving treatment was the same in both the progression-free and disease progression states.

The TTOT curves for different scenarios are presented for serplulimab, atezolizumab and durvalumab in Figures 9, 10 and 11.

Figure 9: Company base case serplulimab TTOT and PFS curves

Figure 10: Atezolizumab TTOT curves

Figure 11: Durvalumab TTOT curves

For completeness, the proportion of patients in the progression-free (PF) and disease progression (PD) states are presented in the Appendix. But the distribution across PF and PD states does not have a significant effect on the ICER.

The TTOT curves used in the EAG base case in the EAG report are presented in Figure 12. In the original EAG base case, an approach similar to the extrapolation of PFS and OS was used. A 3 knot spline model was fit to the KM data and then after a specific point in time, an exponential distribution was used to calibrate the predicted TTOT at a certain time point to what would be predicted using a log-logistic survival model.

Figure 12: TTOT curves in EAG model and TTOT and KM curves for serplulimab + carboplatin + etoposide in company model

Source: Produced by EAG from the company economic model
Abbreviations: Serplulimab: serplulimab + carboplatin + etoposide; KM: Kaplan-Meier

Table 5.2: Scenario Analysis with assumptions around TTOT – using serplulimab PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 3 – Time to off-treatment assumed to be equivalent to progression-free survival							
Serplulimab	[redacted]	2.47	2.04	-	-	-	-
Durvalumab	£99,315	1.87	1.61	[redacted]	0.60	0.43	[redacted]
Atezolizumab	£70,864	1.74	1.45	[redacted]	0.74	0.59	[redacted]
Carboplatin-etoposide	£21,579	1.38	1.19	[redacted]	1.09	0.85	[redacted]
Scenario 4 – Gap between time to off-treatment and progression-free survival 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 progression-free survival extrapolations							
Serplulimab	[redacted]	2.47	2.03	-	-	-	-
Durvalumab	£108,480	1.87	1.59	[redacted]	0.60	0.43	[redacted]
Atezolizumab	£77,362	1.74	1.43	[redacted]	0.74	0.59	[redacted]
Carboplatin-etoposide	£21,135	1.38	1.17	[redacted]	1.09	0.86	[redacted]
Scenario 5 – The trial-observed ratios of median progression-free survival to median time to off-treatment, applied to the progression-free survival curves to generate the time-on-treatment curves, per treatment arm							
Serplulimab	[redacted]	2.47	2.06	-	-	-	-
Durvalumab	£112,661	1.87	1.59	[redacted]	0.60	0.47	[redacted]
Atezolizumab	£65,902	1.74	1.47	[redacted]	0.74	0.61	[redacted]
Carboplatin-etoposide	£21,148	1.38	1.20	[redacted]	1.09	0.86	[redacted]

Source: Company DG comment form[1]
Abbreviations: LYG = life years gained; QALY = quality-adjusted life years; ICER = incremental cost-effectiveness ratio.

6 Choice of height and weight in the economic model

The committee requested weight and height values that reflected the NHS population.

The company revised the model so that data from the non-Asian subgroup of ASTRUM-005 were reweighted to assume a 50% female patient population, consistent with the expected gender distribution in England. In the ASTRUM-005, females had an average weight and height of 73.06 kg and 160.83 cm, while males averaged 79.71 kg and 172.86 cm. Reweighting these values produced overall averages of 76.38 kg and 166.85 cm. The EAG thinks that is reasonable.

Table 6.1 shows the impact of reweighting height and weight in the revised model of the company at the serplulimab PAS price. This scenario is based on the original company base case. (Please see the company consultation document Appendix A for the serplulimab list price results).

Table 6.1: Height/weight from Non-Asian population reweighted to be 50% female/ revised company base case - PAS price (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 1 – Height/weight from Non-Asian population reweighted to be 50% female							
Serplulimab	[redacted]	2.47	2.10	-	-	-	-
Durvalumab	£80,063	1.87	1.64	[redacted]	0.60	0.46	[redacted]
Atezolizumab	£54,721	1.74	1.50	[redacted]	0.74	0.60	[redacted]
Carboplatin-etoposide	£21,603	1.38	1.21	[redacted]	1.09	0.89	[redacted]

Source: Table 2, CS document, DG Comments Appendix A.[9]
Abbreviations: LYG = life years gained; QALY = quality-adjusted life years

7 Choice of health-state utility values in the economic model

The committee requested a mixed linear effects approach to estimate health-state utility values for SCLC using the whole patient population from ASTRUM-005 trial. The company adopted least square mean estimates for the health state utilities in the initial company submission.

The company provided the mixed linear effects estimates as per the committee request and these are labelled as updated health-state utility values in Table 7.1, alongside the original CS utility estimates. The EAG notes that the updated and original utility estimates are similar for PFS and PD states. However, the lack of face validity that the company was concerned about regarding the on-off treatment PFS and PD estimates no longer applies. As mentioned in the EAG report, the utility values are higher than some published values for SCLC patients.

The company presented a scenario based on the original company base case with the utility estimates derived using the mixed linear effect method. The results are reported in Table 7.2.

Table 7.1: Health-state utility values

Health state	Original Utility values (95% CI)- least square mean	Updated Utility values (95% CI)- mixed linear effects
By disease progression state (base case)		
Progression-free	0.838 (0.826, 0.849)	0.830 (0.818, 0.843)
Progressed disease	0.805 (0.785, 0.825)	0.796 (0.781, 0.811)
By disease progression and on/off-treatment status		
On-treatment		
Progression-free	0.855 (0.843, 0.866)	0.835 (0.823, 0.847)
Progressed disease	0.836 (0.813, 0.859)	0.828 (0.811, 0.845)
Off-treatment		
Progression-free	0.757 (0.741, 0.773)	0.786 (0.769, 0.803)
Progressed disease	0.786 (0.760. 0.812)	0.779 (0.763, 0.794)
By time to death and on/off-treatment status		
On-treatment		
> 30 weeks	0.849 (0.785, 0.913)	0.843 (0.831, 0.856)
> 15 to ≤ 30 weeks	0.825 (0.799, 0.852)	0.827 (0.810, 0.844)
> 5 to ≤ 15 weeks	0.836 (0.819, 0.854)	0.798 (0.774, 0.822)
0 to ≤ 5 weeks	0.862 (0.851, 0.873)	0.636 (0.591, 0.681)
Off-treatment		
> 30 weeks	0.464 (0.361, 0.567)	0.805 (0.789, 0.821)
> 15 to ≤ 30 weeks	0.697 (0.640, 0.753)	0.788 (0.770, 0.807)
> 5 to ≤ 15 weeks	0.765 (0.718, 0.812)	0.759 (0.737, 0.782)
0 to ≤ 5 weeks	0.817 (0.785, 0.850)	0.598 (0.555, 0.641)

Source: Table 39 and table 40, CS document[7], DG Comments Appendix A.[9]
Abbreviations: CI = Confidence Interval

Table 7.2: Updated health state utility values from linear mixed effects model - PAS price (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 2 – Updated health state utility values from linear mixed effects model							
Serplulimab	[redacted]	2.47	2.08	-	-	-	-
Durvalumab	£80,009	1.87	1.62	[redacted]	0.60	0.46	[redacted]
Atezolizumab	£54,671	1.74	1.49	[redacted]	0.74	0.59	[redacted]
Carboplatin-etoposide	£21,561	1.38	1.19	[redacted]	1.09	0.88	[redacted]

Source: Table 2, CS document[7], DG Comments Appendix A.[9]
Abbreviations: LYG = life years gained; QALY = quality-adjusted life years; ICER = incremental cost-effectiveness ratio.

8 Revised company base case results

The company reported the revised base case assumptions as follows:

- Height and weight inputs based on the Non-Asian population from ASTRUM-005 reweighted to be 50% female, to better reflect the NHS population with ES-SCLC
- Utility values based on the ITT population from ASTRUM-005 and estimated using a linear mixed effects approach
- Independent log-logistic distributions were selected for modelling OS and PFS for serplulimab and carboplatin-etoposide; for atezolizumab and durvalumab, hazard ratios from the MAIC were applied to the serplulimab extrapolations
- The original base case approach for modelling time on treatment directly based on the time to off-treatment curves from ASTRUM-005 is maintained. Independent log-logistic distributions were selected for serplulimab and carboplatin-etoposide; for atezolizumab and durvalumab OS hazard ratios from the MAIC were applied to the serplulimab time on treatment extrapolation

The deterministic and probabilistic results of the revised company base case are reported in Table 8.1, using the serplulimab PAS price. Please see the company consultation document Appendix A for the serplulimab list price results. The company did not present the additional scenarios listed in previous sections in this document or any other scenarios based on the revised base case. The EAG was able to replicate the original company base case deterministic results in the new company model.

The company presented Tornado diagrams for the sensitivity analysis results for serplulimab versus each comparator. The EAG is not confident in these Tornado plots as the base case ICER for serplulimab versus atezolizumab is given as a positive number when serplulimab dominates atezolizumab in the base case.

The EAG notes a small but likely insignificant error in the company model where the TTOT while in post progression disease (PD) is calculated using the half cycle corrected PFS but the half cycle uncorrected TTOT.

Table 8.1: Revised company base case – serplulimab PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs x1.2	Incremental costs (£)	Incremental LYG	Incremental QALYs x1.2	ICER versus baseline (£/QALY) x1.2
Revised company base case – deterministic							
Serplulimab	[redacted]	2.47	2.08	-	-	-	-
Durvalumab	£80,063	1.87	1.62	[redacted]	0.60	0.46	[redacted]
Atezolizumab	£54,721	1.74	1.49	[redacted]	0.74	0.59	[redacted]
Carboplatin-etoposide	£21,603	1.38	1.19	[redacted]	1.09	0.88	[redacted]
Revised company base case – probabilistic							
Serplulimab	[redacted]	2.49	2.08	-	-	-	-
Durvalumab	£84,046	1.93	1.65	[redacted]	0.57	0.43	[redacted]*
Atezolizumab	£59,332	1.84	1.55	[redacted]	0.65	0.53	[redacted]*
Carboplatin-etoposide	£22,831	1.39	1.19	[redacted]	1.10	0.89	[redacted]*

Source: Table 2, CS document, DG Comments Appendix A.[9]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.
Notes: Discounted costs and QALYs are presented. 1.2x QALY weight are applied to the total/incremental QALYs.
*the ICER associated with the severity modifier that applies for the comparator

9 EAG Additional commentary and analyses

The NICE technical team made a number of requests to the EAG and this section provides the requested information.

9.1 Choice of serplulimab + C/E and carboplatin + etoposide survival model for EAG revised base case

In the EAG base case in the EAG report, the EAG used the 3 knot spline survival model combined with an exponential model from a specific time point that ensured that the PFS and OS predictions matched the log-logistic parametric model used in the company base case. The EAG only slightly preferred the 3 knot spline survival model, but accepted the clinical expert opinion that PFS and OS were overestimated in the long-term when extrapolated, and the shape of the survival curve is uncertain given the low numbers of patients at risk towards the end of the KM curves.

The NICE committee stated it preferred the log-logistic parametric model, and this has been adopted for serplulimab + C/E and carboplatin + etoposide in a revised EAG base case.

9.2 Choice of ITC for EAG revised base case

There were some concerns regarding the differences in the countries included in the different clinical trials. However, the company noted the similarity in the adjusted and unadjusted effectiveness estimates compared to atezolizumab and durvalumab. The NICE committee accepted that the Bucher ITC results were most appropriate.

The EAG has considered the following four factors.

(1) Population: If it is assumed that the populations are comparable across trials when considering effect modifiers then Bucher ITC, simulated ITCs, MAICs, NMAs, and ML-NMAs should produce similar results. The MAIC and Bucher results are fairly similar.

(2) Multiple comparators: When there are multiple comparators evaluated in a full incremental cost-effectiveness analysis, then Bucher, simulated ITCs and ML-NMAs are preferred to MAICs because they either assume a similar population (Bucher, NMA) or they adjust to a common population (simulated ITCs, ML-NMAs). When combining these two considerations of population and consistent evidence for a multi-comparator economic evaluation, the EAG agrees the Bucher ITC is a suitable method for use in the base case.

(3) Proportional hazards:

The log-cumulative hazard plots, the Schoenfeld residual plots and Schoenfeld test for proportional hazards all indicated that the proportional hazard assumption was appropriate in the ASTRUM005 trial.

The company log-cumulative hazard plots indicate that it is possible that the proportional hazard assumption may not hold in IMPower133 and CASPIAN due to crossing curves. The curves do not always look parallel. This is reflected in the Shoendfeld residual plots where the curves are not perfectly horizontal. However, in the log-cumulative hazard plots the curves

cross early on in time (the horizontal axis distorts the time frame). It is only the PFS for CASPIAN where the curves cross significantly later in time, proportionally speaking. And this is reflected in the fact that the Schoenfeld test for proportional hazards was only statistically significant ($p < 0.05$) for PFS in CASPIAN. The Schoenfeld test for proportional hazards was not statistically significant for PFS in IMPower133 nor for OS in CASPIAN and IMPower133.

[redacted]

Accounting for these factors, in the new EAG base case, the following hazard ratios are used:

- PFS atezolizumab: ITC
- OS atezolizumab: ITC
- PFS durvalumab: 2nd order FP-NMA (p_1=-2, p_2=1)
- OS durvalumab: ITC

Another plausible approach that has been included in a scenario analysis is to use the 2nd order FP-NMA estimates for PFS and OS for both atezolizumab and durvalumab. In the company submission, there was a scenario where treatment waning was included. The predicted survival curves for atezolizumab and its control from the FP-NMA indicate that the hazard ratio likely falls over time and the hazard ratio versus serplulimab changes over time. There is greater uncertainty in the extrapolated estimates, and that may reflect reality. When the FP-NMA estimates are used to derive the survival predictions from the log-logistic model for serplulimab, the survival estimates are plausible given the clinical expert opinion in the company submission.

9.3 Serplulimab + C/E and carboplatin + etoposide time to off treatment (TTOT) assumptions for EAG revised base case

See Figure 12, page 19, for the TTOT curves used in the original EAG base case.

Now that a log-logistic survival model is used to model PFS and OS in the revised EAG base case, a log-logistic model is also used to model TTOT in the revised EAG base case. Just as a 3 knot spline model may overestimate PFS and OS in the tail of the KM curve and in extrapolation beyond the end of the KM curve, the same may also be said for TTOT.

Due to a lack of time, the EAG revised base case retains the company approach to determining the number of patients on treatment in both the progression-free and post-progression disease states. The company multiples the percentage of patients receiving treatment to the number of patients in the PFS and PD states to derive the number of patients in the PFS and PD states on treatment.

9.4 Atezolizumab and durvalumab time to off treatment (TTOT) assumptions for EAG revised base case

In the company base case and the original EAG base case the OS HR for the comparator versus serplulimab was multiplied by the hazard rate of discontinuation for serplulimab. In the revised EAG base case, the company scenario 5 was implemented differently: the PFS hazard rates were multiplied by the ratio (see Section 5). The company's scenario 5 approach to TTOT has been used in Section 9.8 (S2). The company base case approach of using the OS HR is used in S3, reported in Section 9.9.

9.5 Utility assumptions for EAG revised base case

The EAG has adopted the mixed linear effects utility estimates for progression free and post progression states in the model. These are likely more accurate than the original OLS estimates although they are similar. See Section 7.

9.6 Height and weight

The EAG has adopted the approach taken by the company in the revised company base case. See Section 6.

9.7 (S1) Revised EAG base case post ACM1 results

The only differences between the revised EAG base case and the revised company base case are

- The selection of ITC estimates. The company used the MAIC estimates. The EAG used the estimates stated in Section 9.2.
- Atezolizumab and durvalumab TTOT curves. The company used the OS HRs to derive the TTOT curves from the serplulimab TTOT curve; the EAG also used that approach in the EAG base case in the EAG report. In this revised EAG base case the ratio of the median TTOT to median PFS is used to derive the TTOT curves from the comparator PFS curves (company scenario 5), but implementing it differently: multiplying the PFS hazard rates by the ratio.

In the EAG base case in the EAG report, the percentage of people post-progression who were on treatment was capped at 20% and this was varied in scenario analysis. The EAG has not had time to edit the company model to incorporate that for this report. The company base case assumption was made where the percentage of people on treatment was the same in the progression-free and post-progression states.

Table 9.1: Revised EAG base case post ACM1

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.73						
durvalumab + carboplatin + etoposide	[redacted]	2.01	1.43	[redacted]	0.46	0.30	0.36	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.84	1.31	[redacted]	0.63	0.42	0.51	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	1.09	0.74	0.88	[redacted]	[redacted]
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year *the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis									

9.8 (S2) EAG scenario with company method of applying ratio of median TTOT to median PFS

Table 9.2: EAG scenario with company method of applying ratio of median TTOT to median PFS

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.73						
durvalumab + carboplatin + etoposide	[redacted]	2.01	1.42	[redacted]	0.46	0.31	0.37	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.84	1.28	[redacted]	0.63	0.45	0.54	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	1.09	0.74	0.88	[redacted]	[redacted]
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year *the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis									

9.9 (S3) EAG scenario with OS HRs used to derive TTOT curves for atezolizumab and durvalumab

The only difference from the company base case in this scenario is the selection of Bucher ITC/FP-NMA effectiveness estimates.

Table 9.3: EAG scenario with OS HRs used to derive TTOT curves

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.73						
durvalumab + carboplatin + etoposide	[redacted]	2.01	1.43	[redacted]	0.46	0.30	0.36	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.84	1.31	[redacted]	0.52	0.42	0.51	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	1.09	0.74	0.88	[redacted]	[redacted]
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year *the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis									

9.10 (S4) EAG scenario with all Bucher ITC hazard ratio estimates

Table 9.4: All ITC estimates

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.73						
durvalumab + carboplatin + etoposide	[redacted]	2.01	1.43	[redacted]	0.46	0.31	0.37	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.84	1.31	[redacted]	0.63	0.42	0.51	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	1.09	0.74	0.88	[redacted]	[redacted]
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year *the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis									

9.11 (S5) EAG scenario with OS and PFS effectiveness estimated using first-order FP NMA

Table 9.5: EAG scenario with OS and PFS effectiveness estimated using first-order FP NMA

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.73						
durvalumab + carboplatin + etoposide	[redacted]	1.92	1.37	[redacted]	0.55	0.36	0.43	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.47	1.07	[redacted]	1.00	0.66	0.80	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	1.09	0.74	0.88	[redacted]	[redacted]
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year *the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis									

9.12 (S6) EAG scenario with OS and PFS effectiveness estimated using second-order FP NMA

Table 9.6: EAG scenario with OS and PFS effectiveness estimated using second-order FP NMA

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	Lys	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.73						
durvalumab + carboplatin + etoposide	[redacted]	2.50	1.7	[redacted]	-0.03	0.028	0.034	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.51	1.10	[redacted]	0.97	0.63	0.76	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	Lys	QALYs x1	QALYs x1.2		
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	1.09	0.74	0.88	[redacted]	[redacted]
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year *the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis									

9.13 (S7) EAG scenario with TTOT equal to PFS (company scenario 3)

Table 9.7: EAG scenario with TTOT equal to PFS (company scenario 3)

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.73						
durvalumab + carboplatin + etoposide	[redacted]	2.01	1.43	[redacted]	0.46	0.30	0.36	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.84	1.27	[redacted]	0.63	0.42	0.51	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	1.09	0.74	0.88	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year *the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis									

9.14 (S8) EAG scenario with equal TTOT-PFS time gap across comparators (company scenario 4)

Table 9.8: EAG scenario with equal TTOT-PFS time gap across comparators (company scenario 4)

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.47	1.73						
durvalumab + carboplatin + etoposide	[redacted]	2.01	1.42	[redacted]	0.46	0.31	0.38	[redacted]	[redacted]
atezolizumab + carboplatin + etoposide	[redacted]	1.84	1.28	[redacted]	0.63	0.45	0.54	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	1.09	0.74	0.88	[redacted]	[redacted]
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year									

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
*the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis									

9.15 (S9) EAG scenario with treatment waning from 5 years to 10 years

Table 9.9: EAG scenario with treatment waning from 5 years to 10 years

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide**	[redacted]	2.44	1.72						
durvalumab + carboplatin + etoposide	[redacted]	2.01	1.43	[redacted]	0.43	0.29	0.34	[redacted]	[redacted]
serplulimab + carboplatin + etoposide**	[redacted]	2.43	1.71						
atezolizumab + carboplatin + etoposide	[redacted]	1.84	1.31	[redacted]	0.59	0.41	0.49	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	1.05	0.72	0.86	[redacted]	[redacted]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year
*the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis
**there are two serplulimab rows because the treatment waning
is modelled to effect the serplulimab arm versus the comparator (atezolizumab/ durvalumab)

9.16 (S10) EAG scenario with 2nd FP-NMA and treatment waning from 5 years to 10 years

Table 9.10: EAG scenario with 2nd FP-NMA and treatment waning from 5 years to 10 years

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.55	1.77						
durvalumab + carboplatin + etoposide	[redacted]	2.50	1.7	[redacted]	0.05	0.065	0.078	[redacted]	[redacted]

Technologies	Total			Incremental				ICER (£/QALY) x1	ICER (£/QALY) x1.2
	Costs	Lys	QALYs	Costs	LYs	QALYs x1	QALYs x1.2		
serplulimab + carboplatin + etoposide	[redacted]	2.25	1.62						
atezolizumab + carboplatin + etoposide	[redacted]	1.51	1.10	[redacted]	0.75	0.52	0.62	[redacted]	[redacted]
carboplatin + etoposide	[redacted]	1.38	1.00	[redacted]	0.87	0.63	0.75	[redacted]	[redacted]

Abbreviations: CS = company submission; EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year
*the next most cost-effective comparator; the ICER for serplulimab in a full cost-effectiveness analysis

9.17 Severity modifier

In the results tables, the * indicates which severity modifier result (x1 or x1.2) is applicable for each comparator. In every case, the 1.2 severity modifier applies. More detail is presented below.

In the updated company base-case, the QALYs accumulated in the atezolizumab arm are 1.24 (discounted at 3.5% across a lifetime horizon). So, the QALY calculated for the general population using QALY shortfall calculator is 11.92. The general population's QALY is the same with respect to EAG base-case.

Table below shows the total QALY thresholds for the comparator to meet the severity modifier criteria

For example, if the total QALYs for one of the comparators is between 0.6 and 1.79 then the severity modifier of x1.2 can be selected.

Multiplier	Proportional shortfall	
	Criteria	Comparator total QALYs threshold
x1	<0.85	>1.79
x1.2	0.85–0.95	1.79-0.60
x1.7	≥0.95	≤0.60

The absolute QALY threshold is irrelevant in this case because the general population QALY (11.91) is less than the absolute QALY shortfall criteria (less than 12). A severity modifier of x1 would always be selected using the absolute shortfall criteria. Hence, only the proportional QALY shortfall should be considered in this case.

The table below shows the total discounted QALY and the corresponding proportional QALY of different comparators. All the comparators met the severity modifier of **x1.2 criteria** in the Company base case and in the EAG base case.

Comparator	Total QALY without Severity Modifier	Proportional QALY	Severity Modifier qualification		Severity Modifier applied in model
			Absolute QALY Shortfall	Proportional QALY Shortfall	
Revised company base-case					
Serplulimab + Carboplatin + Etoposide	1.73	0.85	NA	Yes	Yes

Atezolizumab + Carboplatin + Etoposide	1.24	0.90	NA	Yes	Yes
Durvalumab + Carboplatin + Etoposide	1.35	0.89	NA	Yes	Yes
Carboplatin + Etoposide	1.00	0.92	NA	Yes	Yes
Revised EAG base-case					
Serplulimab + Carboplatin + Etoposide	1.73	0.85	NA	Yes	Yes
Atezolizumab + Carboplatin + Etoposide	1.31	0.89	NA	Yes	Yes
Durvalumab + Carboplatin + Etoposide	1.43	0.88	NA	Yes	Yes
Carboplatin + Etoposide	1.00	0.92	NA	Yes	Yes

10 References

1 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.

2 Cheng Y, Han L, Wu L, Chen J, Sun H, Wen G, et al. Effect of First-Line Serplulimab vs Placebo Added to Chemotherapy on Survival in Patients With Extensive-Stage Small Cell Lung Cancer: The ASTRUM-005 Randomized Clinical Trial. JAMA. 2022 Sep 27;328(12):1223-32.

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

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

5 NICE. Serplulimab with carboplatin and etoposide for untreated extensive-stage small-cell lung cancer. [ID6346]. Single technology appraisal. Draft guidance consultation: NICE; 2025.

6 Accord. Serplulimab with carboplatin and etoposide for untreated extensive-stage small cell lung cancer [ID6346]. Single technology appraisal. Company evidence submission: CEM clarification addendum 20042025. Barnstaple: Accord; 2025.

7 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.

8 Jansen J. Network meta-analysis of survival data with fractional polynomials. BMC Medical Research Methodology. 2011;11:61.

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

11 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 13: Atezolizumab PFS, proportion on treatment

Figure 14: Atezolizumab PD, proportion on treatment

Figure 15: Durvalumab PFS, proportion on treatment

Figure 16: Durvalumab PD, proportion on treatment