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

Technology appraisal committee D [9 July 2025]

For presentation – confidential information redacted

Chair: Raju Reddy

Lead team: Carole Pitkeathley, Salman Waqar, Will Sulivan

External assessment group: Newcastle University

Technical team: Lauren Elston, Rachel Williams, Lorna Dunning

Company: Accord Healthcare

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on small-cell lung cancer

Extensive-stage SCLC is an aggressive cancer with limited treatment options and poor prognosis

- Small-cell lung cancer (SCLC) grows rapidly and spreads quickly to other parts of the body.
- 6.8% of lung cancer cases identified as SCLC (~2,500 people diagnosed in England, 2022).
- Tobacco use is a risk factor: 95% of patients have a positive smoking history.
- Common symptoms include: weight loss, malaise, bone pain, breathlessness and coughing up blood (haemoptysis).
- Around 70% of people with SCLC have extensive-stage disease (~1,750 based on 2022 figures):
    - cancer has spread beyond 1 lung and nearby lymph nodes.
    - poor prognosis; 5% overall survival rate at 5 years; treatment palliative in nature
    - limited treatment options – radiotherapy unsuitable.

Patient perspectives

SCLC in an aggressive, rapidly progressing cancer that has an obvious impact on the person with the disease, their families and carers

Submissions from Roy Castle Lung Cancer Foundation

- A diagnosis of SCLC is devastating; it's a particularly aggressive form of cancer that can be very symptomatic, rapidly progressive and prone to relapse after initial treatment.
- Poor prognosis has an obvious impact on people with SCLC and their family and carers.
- Symptoms (breathlessness, cough, weight loss) are difficult to treat without active anti-cancer therapy, and are distressing for loved ones to observe.
- Side effects associated with serplulimab could be a disadvantage.
- There are no direct comparisons of serplulimab with Atezolizumab or durvalumab in this indication.

"This is a rapidly progressive disease and as such, patients should be assessed quickly and systemic anticancer treatment started quickly."

"The outcome from current standard treatment, for this patient group, is poor. There is massive unmet need."

Clinical perspectives

SCLC is hard to treat and more options are needed; serplulimab would be an alternative delivered in a similar way to current treatments

Submissions from the Association of Respiratory Nurses (ARN) and Clinical Expert

- SCLC is hard to treat and there is a significant unmet need to improve survival outcomes for ES-SCLC.
- More treatment options needed; serplulimab plus carboplatin and etoposide will be an alternative treatment option but delivered in a similar way to current treatments.
- Aim of treatment: stop further disease progression, prolong survival, and improve quality of life and symptoms
- Effectiveness (and appropriateness) of treatment may depend on ECOG performance status and comorbidities.
- Side effects can be difficult for people taking treatment but can be managed with support.

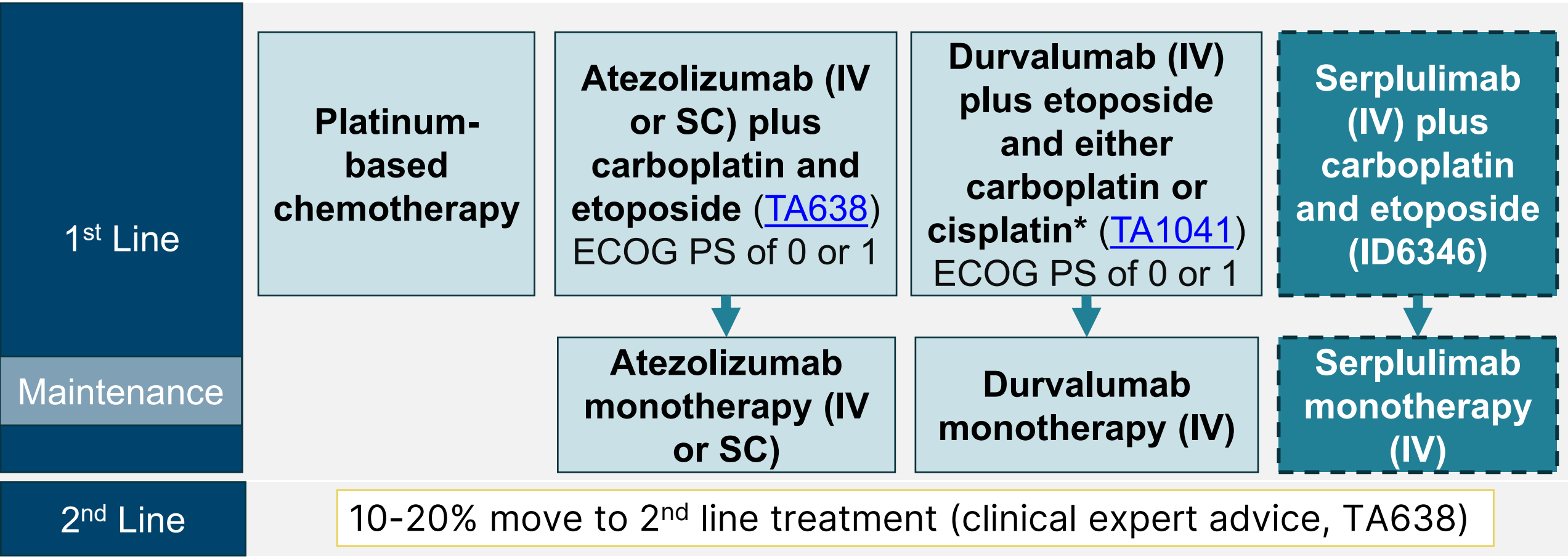
"Small cell lung cancer patients have limited treatment options. The more treatments available for patients, the better."

SCLC: small cell lung cancer; ECOG: Eastern Co-operative Oncology Group; ES-SCLC: extensive-stage small cell lung cancer

Equality considerations

- No equality considerations have been identified.

Treatment pathway for extensive-stage small cell lung cancer



NHS England: Currently >90% of people receive atezolizumab. Patients and Trusts generally prefer less invasive SC administration with lower healthcare resource needed

*Included in recommendation: Use the least expensive option of the available treatments (including durvalumab and atezolizumab).

ECOG: Eastern Cooperative Oncology Group; IV, intravenous; PS: performance status; SC, subcutaneous

Serplulimab (Hetronifly, Accord Healthcare)

Marketing authorisation	• Serplulimab in combination with carboplatin and etoposide is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
Mechanism of action	• Humanised monoclonal antibody that binds to PD-1 receptors on cancer cells, preventing the cancer cells from binding to PD-1 ligands on immune cells and causing immunosuppression.
Administration	• 4.5 mg/kg intravenously every 3 weeks until disease progression or unacceptable toxicity. • Dose escalation or reduction of serplulimab is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability.
Price	• £1,321.83 per vial (proposed list price) • Cost per treatment cycle: serplulimab £4,354 (list), carboplatin £30, etoposide £18. Total: £4,401 • Serplulimab has a PAS discount.

NICE

PAS: patient access scheme; PD-1: programmed cell death-1

Key issues

Key issues	ICER impact
Background characteristics of trial participants may not reflect characteristics of those in English clinical practice.	Unknown
PFS and OS parametric models for serplulimab and carboplatin + etoposide did not fit Kaplan-Meier curves well.	Moderate
Constant HRs for OS for atezolizumab versus serplulimab and for durvalumab versus serplulimab were assumed for duration of model.	Moderate
TTOT parametric model for serplulimab and carboplatin + etoposide did not fit Kaplan-Meier curves well.	Moderate
Average body weight and height in ASTRUM-005 lower than UK clinical practice.	Moderate

Other issues	ICER impact
Lead team issue: Health state utilities are least squared mean estimates and lack face validity	**Large**

HR, hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; TTOT: time-to-off treatment

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

- ❑ Background and key issues
- ✓ **Clinical effectiveness**
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Key clinical trials – designs (1/2)

Table: Clinical trial designs for ASTRUM-005, IMpower133 and CASPIAN

	ASTRUM-005 (n=585)	IMpower133 (n=403)	CASPIAN (n=537)
Design	Phase 3 RCT	Phase 3 RCT	Phase 3 RCT, open label
Population	People with ES-SCLC; no prior systemic therapy for ES-SCLC; ECOG PS 0/1	People with ES-SCLC; no prior systemic therapy for ES-SCLC; ECOG PS 0/1	People with ES-SCLC; no prior immune-mediated therapy; ES-SCLC; ECOG PS 0/1
Intervention	**Serplulimab + carboplatin + etoposide**	Atezolizumab + carboplatin + etoposide	Durvalumab + etoposide + either carboplatin OR cisplatin
Comparator	Placebo + carboplatin + etoposide	Placebo + carboplatin + etoposide	Carboplatin OR cisplatin, + etoposide
Median follow-up, months	OS and PFS: 42.38	OS: 22.9; PFS: 13.9	OS: 39.4; PFS: 14.2

ECOG: Eastern Cooperative Oncology Group; ES-SCLC: extensive-stage small cell lung cancer; OS: overall survival; PFS: progression-free survival; PS: performance status; n: number; RCT: randomised controlled trial

Key clinical trials – designs (2/2)

Table: Clinical trial designs for ASTRUM-005, IMpower133 and CASPIAN continued

See appendix for baseline patient characteristics

	ASTRUM-005 (n=585)	IMpower133 (n=403)	CASPIAN (n=537)
Primary outcome	OS	OS, investigator-assessed PFS	OS
Key secondary outcomes	PFS, ORR, DOR	ORR, DOR	PFS, ORR, DOR
Locations – see appendix	6 countries not including UK; predominantly China (n=400), Georgia, Poland, Russia, Turkey, and Ukraine.	21 countries in Europe (UK n=10), Asia, North and Central America and Australia	23 countries in Europe (not UK), Asia, North and South America

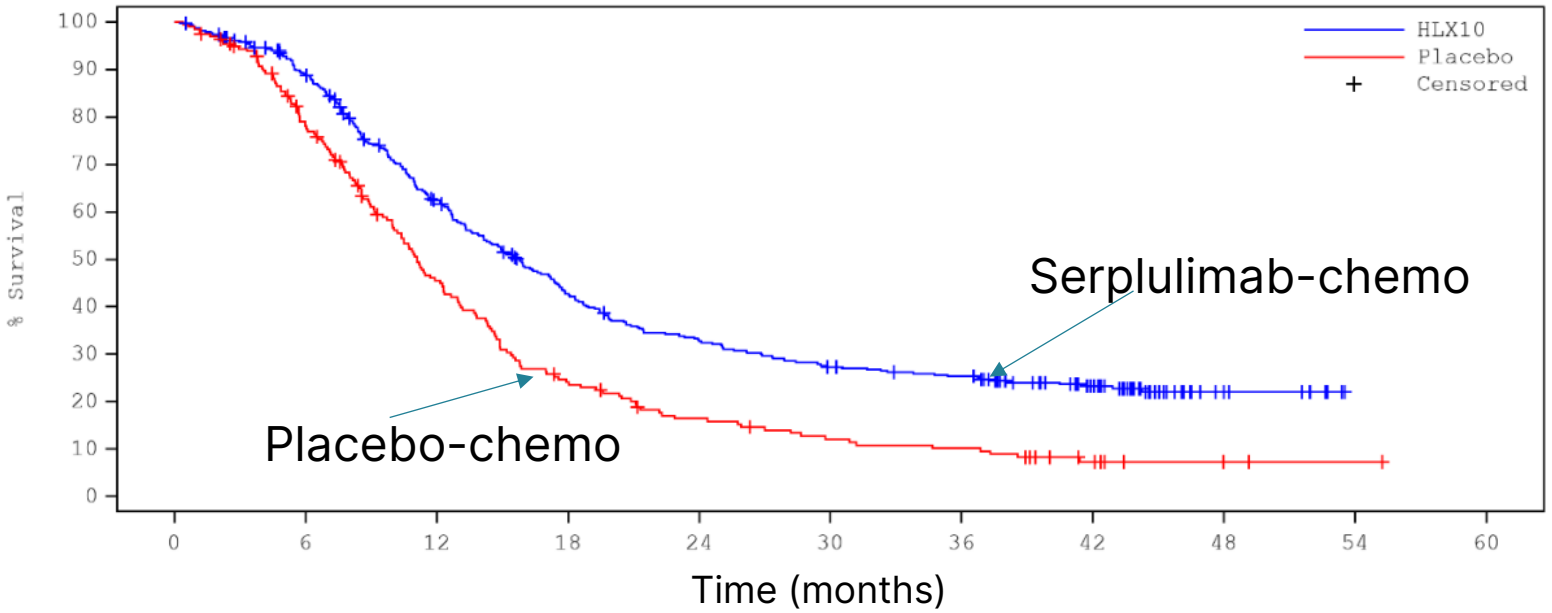
- ASTRUM-005 only included people with ECOG status 0 and 1 – is a restriction to the population according to ECOG status appropriate (as per TA638 and TA1041)?
  - Would restricting the recommendation result in any equalities issues?

DOR: duration of response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PS: performance status; n: number; RCT: randomised controlled trial

ASTRUM-005 results – overall survival

Significant reduction in risk of death with serplulimab compared with placebo

Figure: OS of ITT population (data cut-off 7 May 2024)



	Serplulimab-chemo (n=389)	Placebo-chemo (n=196)
Events (deaths), n (%)	280 (72.0)	166 (84.7)
Median OS (95% CI), mo	15.8 (13.9, 17.4)	11.1 (10.0, 12.4)
Stratified HR (95% CI); p-value	0.60 (0.49, 0.73); p<0.001	

Table: Number at risk (censored)

	0	6	12	18	24	30	36	42	48	54	60
Serp.	389 (0)	335 (12)	227 (22)	151 (27)	115 (28)	95 (29)	85 (32)	53 (58)	9 (101)	0 (109)	-
Placebo	196 (0)	146 (8)	81 (14)	42 (15)	27 (17)	19 (18)	16 (18)	7 (23)	2 (28)	1 (29)	0 (30)

NICE

CI: confidence interval; ITT: intent-to-treat; n: number; OS: overall survival

ASTRUM-005 results – progression free survival

Significant reduction in risk of progressive disease or death with serplulimab compared with placebo

Figure: PFS of ITT population (data cut-off 7 May 2024)

	Serplulimab-chemo (n=389)	Placebo-chemo (n=196)
Events (PFS), n (%)	[redacted]	[redacted]
Median OS (95% CI), mo	5.82 (5.552, 6.932)	4.34 (4.205, 4.435)
Stratified HR (95% CI); p-value	0.47 (0.380, 0.572); p<0.001	

Table: Number at risk (censored)

	0	6	12	18	24	30	36	42	48	54
Serp.	[redacted]									
Placebo	[redacted]									

NICE

CI: confidence interval; ITT: intent-to-treat; n: number; PFS: progression-free survival

Indirect treatment comparison

- Company undertook anchored matching-adjusted indirect comparisons (MAICs).
- Baseline characteristics for ASTRUM-005 ITT population were adjusted to the aggregate data of IMpower133 and CASPIAN.
- Cox proportional hazards were applied to estimate the relative efficacy between serplulimab and the comparator.

EAG comments

- 5 covariates included for atezolizumab MAIC (age, ECOG, smoking status, brain metastases, liver metastases – see appendix) and 4 for durvalumab MAIC (age, smoking status, brain metastases, liver metastases – see appendix); others with imbalances between trials were not adjusted for. EAG acknowledge a lack of data for some variables, but uncertainty remains.
- Adjustment for race and previous cancer treatment led to excessively low ESS, indicating a relatively small overlap between trial populations – see appendix.
- Results dependent upon PH assumption, which is uncertain (see later slide).
- Prefer an ML-NMR using IPD from ASTRUM-005 with aggregate data from IMpower133 and CASPIAN, as it allows more flexibility to generate population-adjusted ITC estimates across larger treatment networks.

NICE

ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size; IPD: individual patient data; ITC: indirect treatment comparison; ITT: intent to treat: MAIC: match-adjusted indirect comparison; ML-NMR: multi-level network meta regression PH: proportional hazards

Indirect treatment comparison - results

Company: serplulimab plus carboplatin-etoposide improves PFS and OS, with or without adjustment of baseline variables. Improvements in PFS were statistically significant.

Both before and after matching HRs were tested in cost effectiveness model scenarios

	Bucher ITC, HR (95% CI)	MAIC, HR (95% CI)
Versus atezolizumab[a]		
PFS	[redacted]	[redacted]
OS		
ASTRUM-005 ESS	Serplulimab: n=389 Placebo: n=196	Serplulimab: n=240 Placebo: n=126
Versus durvalumab[b]		
PFS	[redacted]	[redacted]
OS		
ASTRUM-005 ESS	Serplulimab: n=389 Placebo: n=196	Serplulimab: n=256 Placebo: n=134

Source: [a]Table 26, CS Section B.2.8.5; [b]Clarification response, Question B8

Abbreviations: CI: confidence interval; ESS, effective sample size; HR: hazard ratio; ITC: indirect treatment comparison; MAIC: matching-adjusted indirect comparison; PFS: progression free survival; OS: overall survival.

Key issues: Generalisability of trial populations to NHS (1/2)

Background

- Clinical effectiveness evidence derived from ASTRUM-005, IMpower133 and CASPIAN; similar designs but there are notable differences in patient characteristics (see appendix) and subsequent treatments; potential impact on outcomes uncertain.

EAG comments

- Compared to NHS, more patients were male (all 3 trials, highest in ASTRUM-005). In ASTRUM-005, majority (68.5%) were Asian and a high proportion (19.8%) were never smokers.
- Clinical advice to EAG in TA638 suggests 10-20% patients move to 2L but [redacted] in ASTRUM-005, ~55% in IMpower133, 43% in CASPIAN had subsequent treatments.
- Multilevel network meta regression (ML-NMR) may address some uncertainties around between-study variation and precision of treatment relative effect estimates (requested at clarification).
  - Acknowledge limited population overlap demonstrated by application of MAICs, and so ML-NMR would also be subject to potential limitation of clinical heterogeneity.

MAIC: match-adjusted indirect comparison; ML-NMR: multi-level network meta regression

Key issues: Generalisability of trial populations to NHS (2/2)

Company (at clarification)

- Clinical expert opinion agreed subgroup analyses show no differences in OS and PFS between Asian and non-Asian, so results from ASTRUM-005 are generalisable to NHS.
- MAIC offers robust methodology by addressing between-trial differences in baseline characteristics through matching and re-weighting baseline data; reduces bias of ITCs.
- MAIC suitable when the number of studies and data structure are not suitable for a full ML-NMR approach.

Are the trial populations and results generalisable to the NHS population? Is the MAIC approach to ITC appropriate?

ITC: indirect treatment comparison; MAIC: match-adjusted indirect comparison; ML-NMR: multi-level network meta regression; OS: overall survival; PFS: progression-free survival.

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

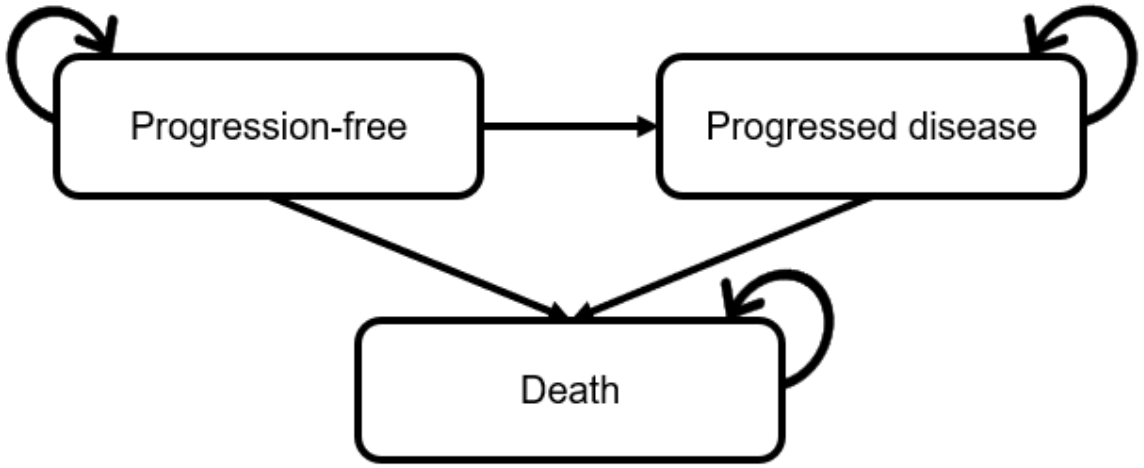
- ❑ Background and key issues
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Company's model overview

Partitioned survival model with three health states: progression-free, progressed disease, and death

Figure: Model structure



EAG comments

- Markov model generally preferred over partitioned survival model because better survival predictions may be obtained; but a high proportion of patients had died by the end of follow-up in ASTRUM-005, so uncertainty in survival predictions versus carboplatin+etoposide not significant.
- However, situation is different when modelling outcomes of atezolizumab and duvalumab (see later slides).

Key issues: Extrapolation of PFS and OS (serplulimab, carboplatin + etoposide)

Background

- Company selected log-logistic parametric model fitted independently for PFS and OS for both serplulimab and carboplatin + etoposide.
- EAG requested more flexible modelling options at clarification.

Company (at clarification)

- Provided 1, 2 and 3 knot spline models; 2/3 knots have best statistical fit and fit closely to Kaplan-Meier curves for OS, 3 knots best fit for PFS but provide implausible long-term estimates (cross with OS curves).
- Based on clinical input, long-term OS predictions overestimated (>5% of patients predicted to survive to year 20 in serplulimab arm).

EAG comments

- EAG preferred 3 knot spline models fitted until last timepoint when number at risk was at least 10. Adjustments then made due to uncertainty in long-term extrapolations

Which extrapolation is more appropriate for PFS and OS of serplulimab and carboplatin + etoposide? (log-logistic or 3 knot spline)

NIC

OS: overall survival; PFS: progression-free survival

Key issues: Extrapolation of PFS and OS

	PFS		OS	
	Serplulimab with carboplatin + etoposide	Carboplatin + etoposide	Serplulimab with carboplatin + etoposide	Carboplatin + etoposide
Company base case	Parametric: log-logistic	Parametric: log-logistic	Parametric: log-logistic	Parametric: log-logistic
EAG base case	3 knot spline until 3.5 years, then HR assumed to linearly increase to 1 at 6.5 years	3 knot spline until 1 year, then exponential	3 knot spline until 3.5 years, then HR[a] assumed to linearly increase from [redacted] at 3.5 years to 1 at 6.5 years	3 knot spline until 1.5 years, then exponential.
EAG scenario	-	-	3 knot spline until 3.5 years, then exponential[b]	-

EAG rationale: [a] HR may get closer to 1 over time with patients off treatment; [b] exponential used so OS at 10 years same as predicted using company's log-logistic

Which extrapolation is more appropriate for PFS and OS of serplulimab and carboplatin + etoposide? (log-logistic or 3 knot spline)

HR, hazard ratio; OS: overall survival; PFS: progression-free survival

Key issues: Extrapolation of PFS and OS

See appendix for OS estimates over time

Figure: Overall survival curves modelled for serplulimab and carboplatin + etoposide

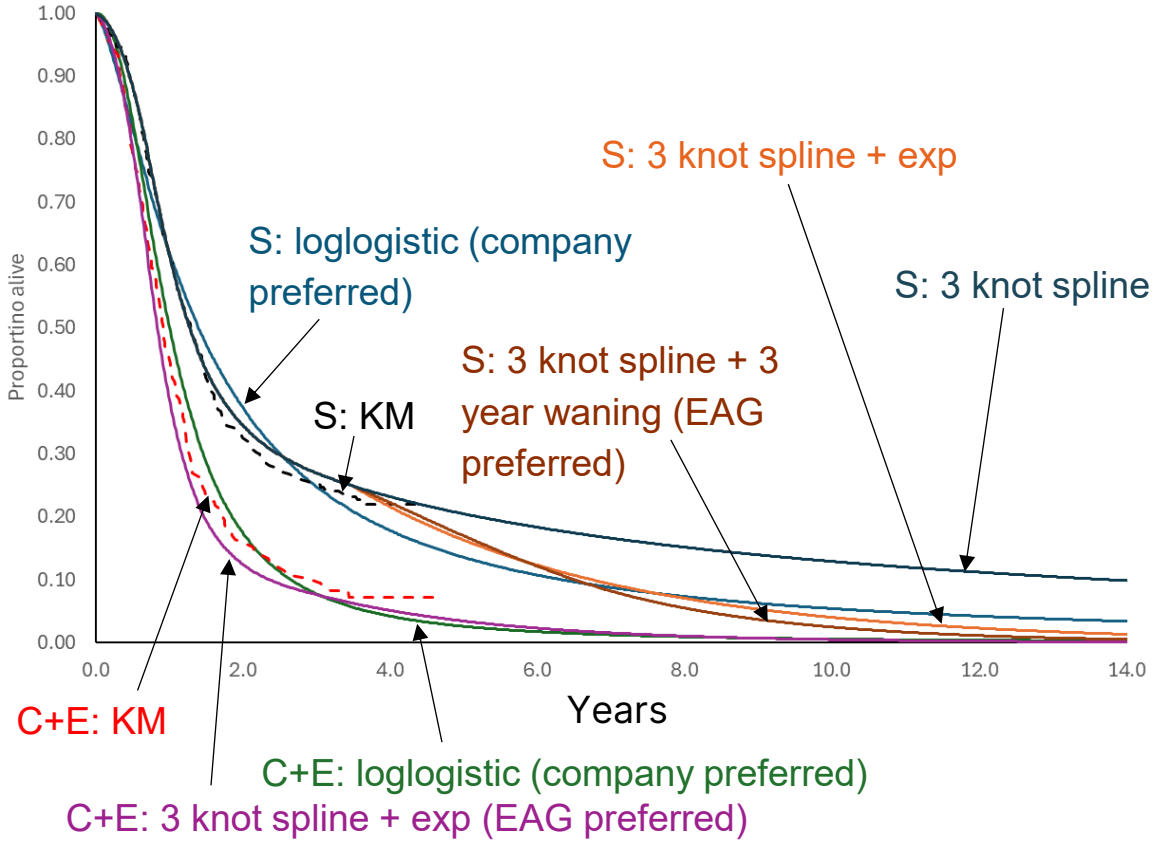


Figure: Progression-free survival curves modelled for serplulimab and carboplatin + etoposide

[redacted]

C+E, carboplatin + etoposide arm; exp, exponential; KM, Kaplan-Meier; OS: overall survival; PFS: progression-free survival; S, serplulimab arm

Key issues: Constant OS hazard ratios (vs atezolizumab, durvalumab)

Background

- OS HRs for serplulimab versus atezolizumab and serplilumab versus durvalumab were assumed constant over duration of company's model.

EAG comments

- Constant HR may not reflect clinical reality; people receiving treatment would eventually experience disease progression and come off treatment.
- HR from 3 knot spline models fairly constant over first 18 months, but HR would get closer to 1 over time.
- PFS and OS specific mortality hazard rates could be estimated and a semi-Markov model developed, but IPD for atezolizumab and durvalumab may not be available to conduct this analysis.
- EAG base case for HRs (serplulimab versus atezolizumab, and versus durvalumab):
  - OS: 3-year waning assumption applied from MAIC HR at 3.5 years to HR reaching 1 at 6.5 years, for all 3 comparisons.
  - PFS: HRs assumed to remain constant for duration of model.

Should the OS HRs for comparisons with atezolizumab and durvalumab be constant or should waning be considered? How should the PFS HRs be modelled?

HR: hazard ratio; IPD: individual patient data; OS: overall survival; PFS: progression-free survival

Key issues: Extrapolation for time-to-off-treatment (serplulimab, carboplatin + etoposide) (1/2)

Background

- Company used independent log-logistic TTOT curves for both serplulimab and placebo arms
- In the trial, serplulimab could be given post progression. In model, % patients on treatment assumed independent of disease progression status (EAG: limited impact on ICER).
- RDI applied to all arms based on ASTRUM-005 for carboplatin ([redacted]), etoposide ([redacted]) and serplulimab ([redacted]), TA638 for atezolizumab (92.10%) and TA1041 for durvalumab (95.4%).

EAG comments

- Company TTOT curve for serplulimab did not fit Kaplan-Meier curve well; proportion of people on treatment may be overestimated earlier in model and underestimated later.
- Association between treatment cost and effectiveness from trials should be retained.
- KM curves could reflect time on treatment more accurately; but good fitting parametric model is adequate and helps derive TTOT curves for atezolizumab and durvalumab.
- EAG base case: 3 knot spline model until 3.5 years (as for OS), then proportion on treatment limited to percentage on treatment in PFS and PD states in previous cycle, applied to PFS and PD numbers in current cycle.

ICER, incremental cost effectiveness ratio; OS: overall survival; PD, progressed disease; PFS: progression-free survival; RDI, relative dose intensity; TTOT: time to off treatment.

Key issues: Extrapolation for time-to-off-treatment (serplulimab, carboplatin + etoposide) (2/2)

Figure: Kaplan Meier curves for OS, PFS and TTOT for serplulimab + carboplatin + etoposide and placebo with carboplatin + etoposide from ASTRUM-005

[redacted]

Figure 4.6: Kaplan Meier curves and TTOT curves in EAG and company models for serplulimab + carboplatin + etoposide

[redacted]

Which extrapolation is more appropriate for TTOT of serplulimab and placebo (with carboplatin + etoposide)? (log-logistic or 3 knot spline)

Note: TToT curve for carboplatin + etoposide represents discontinuation of placebo. Costs for carboplatin + etoposide were for 4 cycles in model.

C+E, placebo (with carboplatin + etoposide) arm; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; S, serplulimab arm; TTOT, time to off treatment.

Key issues: Average weight and height in ASTRUM-005

Background

- Dosing of serplilumab and chemotherapy treatments based on weight and BSA.
- Company used mean body weight of 68.4 kg and height of 167 cm, from ASTRUM-005.
- In ASTRUM-005: 67.4% were Asian and 80% were male
- Using the SD, distribution of weight in target population derived using a normal distribution

EAG comments

- In England: ~49.8% of people with SCLC in England are female (National Lung Cancer Audit); Median age at diagnosis is 70 years (National Lung Cancer Audit); average weight and height for 69-74 years is 79.3 kg and 166.8 cm (Health Survey for England)
- Treatment effectiveness is independent of dose per unit of patient size. Using lower weight/height that in NHS may underestimate drug costs for same expected effectiveness.
- EAG base case: average height and weight in England age group 65-74 years (assumed same SD for weight as company).
- Scenario: average height (171.29 cm) and weight (78.84 kg) from non-Asian population in ASTRUM-005.

What height and weight should be used in the model?

BSA: body surface area; SCLC, small-cell lung cancer; SD, standard deviation

Lead team issue: Health state utilities (1/2)

Background

- Progression-based utility values in company base case informed by ASTRUM-005 EQ-5D-5L data, mapped to EQ-5D-3L
- Company scenarios: utilities based on treatment status and TTD approach – see appendix
- Health state utility values computed using least square means method

Company

- Acknowledge TA638 committee's conclusion that TTD approach should not be considered standard in ES-SCLC
- Acknowledge progression-based, on-treatment utility values from ASTRUM-005 are near the general population
- Potential overestimation of EQ-5D in oncology trials studied in literature; can be due to adaptation of patients to disease and inability of EQ-5D domains to fully capture AEs associated with chemotherapy, and its insensitivity to dimensions such as fatigue, cognitive functioning or social well-being

Source	Utility value	
	PFS	Progressed
ASTRUM-005	0.838	0.805
Nafees et al. 2008 (NSCLC)	0.673	0.473
Chouaid et al. 2013 (NSCLC)	0.71	0.67

AE, adverse event; PFS, progression-free survival; TTD, time to death

Lead team issue: Health state utilities (2/2)

Lead team comments

- Least squared mean estimates are subject to attrition bias
- Company's utility values notably higher than values from NSCLC patients, and are around levels expected for general population
- Ideally, company would have (i) provided completion rates across data points for EQ-5D data, (ii) estimated PFS and PD utility values using a linear mixed effects model with progression as an explanatory variable, and (iii) explored scenarios with values from alternative data sources

EAG comments

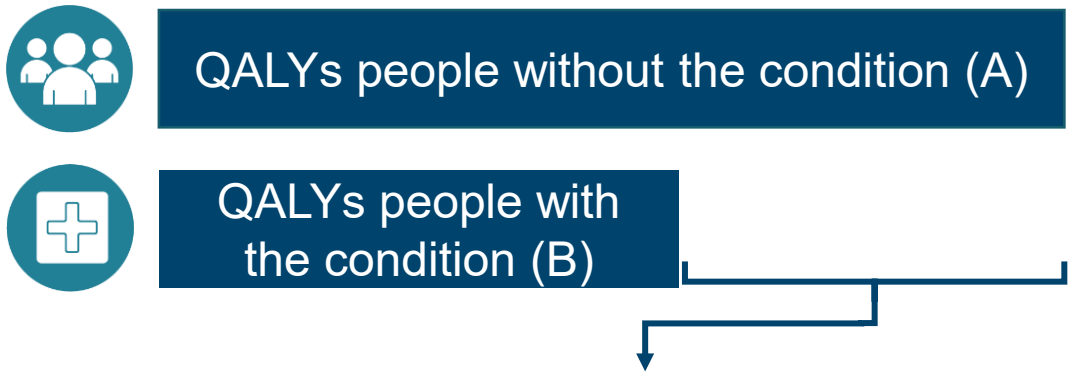
- Utility values in company base case higher than in similar NICE appraisals and other sources; e.g. Nafees et al. 2008 (most common source of utility identified in company's literature search; NSCLC population)
- If trial utility values higher than in NHS practice, may impact ICER estimates.
- EAG scenario: alternative utility values from Nafees 2008 and Chouaid et al. 2013

Are the utility values in the company base case appropriate for decision making?

ICER, incremental cost effectiveness ratio; NSCLC, non-small cell lung cancer; PFS: progression-free survival; PD, progressed disease

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

QALY, quality-adjusted life year

QALY weightings for severity (2/2)

Company

- QALY weight 1.2 based on atezolizumab model predictions for standard care.

EAG comments

- All comparators meet proportional QALY shortfall criteria for severity modifier of 1.2 in company and EAG base cases
- Although company approach to calculate QALYs in the general population follows NICE guidance, there's inconsistency in the mapping value sets for people with the condition (ASTRUM-005 EQ-5D-5L mapped to EQ-5D-3L).

QALYs of people without condition	Current treatment	QALYs with the condition on current treatment	Proportional QALY shortfall (has to be >0.85)	
			Company base case	EAG base case
11.91	Atezolizumab	1.25	0.90	0.89
	Durvalumab	1.36	0.89	0.89
	Carboplatin + etoposide	1.01	0.92	0.91

Does the committee agree it is appropriate to apply a QALY weighting for severity? If so, what QALY weighting should be used?

QALY, quality-adjusted life year

Summary of company and EAG base case assumptions (1/2)

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Utilities	PF: 0.838; PD: 0.805 (source: ASTRUM-005)	
Extrapolation of OS	Log-logistic	Serplulimab: 3 knot spline model up to 3.5 years, then linear increase of HR to 1 at 6.5 years Carboplatin + etoposide: 3 knot spline model up to 18 months, then exponential curve
Extrapolation of PFS	Log-logistic	Serplulimab: 3 knot spline model up to 3.5 years, then linear increase of HR to 1 at 6.5 years. Carboplatin + etoposide: 3 knot spline model up to 12 months, then exponential curve.

OS: overall survival; PFS: progression-free survival

Summary of company and EAG base case assumptions (2/2)

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
OS HRs	Constant HRs	Linear trend towards 1 from 3.5 to 6.5 years
Extrapolation of TTOT	Log-logistic	Same approach as OS; in addition, after 3.5 years percentage of people on treatment was limited to the PFS/PD states of previous cycle.
% on treatment across PFS/PD states – see appendix	Assumed the same in the PFS and PD states	People in PD state on serplulimab capped at 20%
Height and weight	ASTRUM-005 trial: 167.27 cm and 68.4kg	UK averages: 168.4 cm* and 79.3 kg
QALY weighting	1.2	1.2

*EAG: 168.4 cm (average height across all adults) modelled in error as 166.8 cm (for 65–74 age group) preferred but has negligible impact on ICERs

HR: hazard ratios; PD: progressed disease; PFS: progression-free survival; QALY: quality-adjusted life-year; TTOT: time to off treatment

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts for comparators

When using confidential prices, both the company and EAG base cases are over £30,000 per QALY gained for all pairwise comparisons, with and without a 1.2 QALY weighting

Scenarios explored	ICER impact (on EAG base case)
HRs from MAIC (before matching)	Large ↑
Serplulimab OS curve: 3 knot spline, then exponential	Small
Alternative health state utility values	Large ↑
Alternative % caps for people on treatment in PD state	Small
Administration costs for atezolizumab (SC versus IV in company base case)	Small

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Other considerations (1/2)

Uncaptured benefits

- NICE tech team: Alternative administration of atezolizumab
  - Atezolizumab may be administered by IV or SC. Serplulimab (and durvalumab) are administered by IV.
  - Company and EAG models cost 100% of atezolizumab using IV administration
  - Scenarios explored include: for atezolizumab monotherapy in maintenance phase, 75% of patients receive SC administration (N10AF cost code; £111) and 25% receive IV (SB12Z cost code; £217)

- No other uncaptured benefits raised.

- How should the administration of atezolizumab be modelled?
- Are there any uncaptured benefits?

IV, intravenous; SC, subcutaneous

Other considerations (2/2)

Managed access

- The committee can make a recommendation with managed access if:
  - the technology cannot be recommended for use because the evidence is too uncertain
  - the technology has the plausible potential to be cost effective at the currently agreed price
  - new evidence that could sufficiently support the case for recommendation is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
  - data could feasibly be collected within a reasonable timeframe (up to a maximum of 5 years) without undue burden.
- Company has not submitted a managed access proposal.

- What are the uncertainties, and can they be resolved with further data collection?

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Key issues	ICER impact
Background characteristics of trial participants may not reflect characteristics of those in English clinical practice.	Unknown
PFS and OS parametric models for serplulimab and carboplatin + etoposide did not fit Kaplan-Meier curves well.	Moderate
Constant HRs for OS for atezolizumab versus serplulimab and for durvalumab versus serplulimab were assumed for duration of model.	Moderate
TTOT parametric model for serplulimab and carboplatin + etoposide did not fit Kaplan-Meier curves well.	Moderate
Average body weight and height in ASTRUM-005 lower than UK clinical practice.	Moderate
Other issues	**ICER impact**
Lead team issue: Health state utilities are least squared mean estimates and lack face validity	**Large**

HR, hazard ratio; ICER: incremental cost-effectiveness ratio; OS: overall survival; PFS: progression-free survival; TTOT: time-to-off treatment

Ivosidenib for treating IDH1 R132 positive cholangiocarcinoma after at least 1 therapy [ID6164]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Key clinical trials – Locations

Table: Locations for ASTRUM-005, IMpower133 and CASPIAN

	ASTRUM-005 (n=585)	IMpower133 (n=403)	CASPIAN (n=537)
Locations	China (n=400), Georgia (n=50), Turkey (n=45), Russia (n=42), Ukraine (n=41), Poland (n=7)	United States of America (n=86), Poland (n=45), Japan (n=42), Russia (n=30), Spain (n=25), Austria (n=20), Hungary (n=19), Czech Republic (n=17), South Korea (n=17), Italy (n=15), Serbia (n=15), Australia (n=11), Greece (n=11), United Kingdom (n=10), Germany (n=9), Taiwan (n=9), France (n=7), Chile (n=6). Brazil (n=4), Mexico (n=4), China (n=1)	23 countries in Europe (not UK), Asia, North and South America

Key clinical trials – baseline patient characteristics (1/2)

Table: Patient characteristics of ASTRUM-005, IMpower133, CASPIAN

	ASTRUM-005		IMpower133		CASPIAN	
	Serplulimab	Control	Atezolizumab	Control	Durvalumab	Control
Age group (≥65 yr), %	39.6	39.3	44.8	47.5	37.7	41.6
Sex (male), %	**81.5**	**83.7**	**64.2**	**65.3**	**70.9**	**68.4**
Race (Asian), %	**67.4**	**70.9**	**16.4**	**17.8**	**13.4**	**15.6**
Disease stage (IV), %	81.7	79.1	NR	NR	89.6	91.1
ECOG (PS 1), %	**81.7**	**83.7**	**63.7**	**66.8**	**63.1**	**66.5**
Smoking status (Current/former smoker), %	**79.2**	**82.1**	**95.5**	**98.5**	**91.8**	**94.4**
Brain metastases (Yes), %	12.9	14.3	8.5	8.9	10.4	10.0

Notable imbalances between trials are emphasised in bold.

Back to clinical trial designs

NICE

ECOG: Eastern Cooperative Oncology Group; ES-SCLC: extensive-stage small cell lung cancer; PD-L1: programmed cell death-1 ligand; PS: performance status; n: number; NR: not reported.

Key clinical trials – baseline patient characteristics (2/2)

Table: Patient characteristics of ASTRUM-005, IMpower133, CASPIAN

	ASTRUM-005		IMpower133		CASPIAN	
	Serplulimab	Control	Atezolizumab	Control	Durvalumab	Control
Liver metastases (Yes), %	**25.4**	**26.0**	**38.8**	**35.6**	**40.3**	**38.7**
Blood-based tumour mutational burden ≥10 mutations/Mb, %	**11.3 (195 pts)**	**3.6 (110 pts)**	**59.0 (173 pts)**	**61.8 (178 pts)**	**NR**	**NR**
PD-L1 TPS >1%, %	16.4 (379 pts)	18.3 (186 pts)	NR	NR	NR	NR
Previous anticancer treatments, %	**2.6**	**2.6**	**32.8**	**32.2**	**NR**	**NR**

Back to clinical trial designs

NICE ECOG: Eastern Cooperative Oncology Group; ES-SCLC: extensive-stage small cell lung cancer; PD-L1: programmed cell death-1 ligand; PS: performance status; n: number; NR: not reported.

Key clinical trials – adjusted characteristics for MAIC atezolizumab

Table: Population variables adjusted and rationale, IMpower133

	Adjusted	Rationale
Age group (≥65 yr)	Yes	Imbalance in patient age between ASTRUM-005 and IMpower133.
Sex	No	Subgroup analysis in ASTRUM-005 showed no impact of sex on treatment effect.
Race	No	Adjustment would lead to excessively low ESS resulting in unreliable outcomes, furthermore subgroup analysis in ASTRUM-005 showed no impact of race on treatment effect.
Disease stage	No	Not reported in IMpower133.
ECOG	Yes	Imbalance in patient ECOG status between ASTRUM-005 and IMpower133.
Smoking status	Yes	Imbalance in patient smoking status between ASTRUM-005 and IMpower133.
Brain metastases	Yes	Imbalance in the presence of brain metastases between ASTRUM-005 and IMpower133.
Liver Metastases	Yes	Imbalance in the presence of liver metastases between ASTRUM-005 and IMpower133.
Blood-based tumor mutational burden	No	Not tested in all participants.
PD-L1	No	Not reported in IMpower133.
Previous anticancer treatments	No	Adjustment would lead to excessively low ESS resulting in unreliable outcomes.

Sensitivity analyses for matching variables - MAIC atezolizumab

Matching Baseline Characteristics Variables	[redacted]
(1) Age Group; ECOG; Smoking Status; Brain Metastases; Liver Metastases	
(1), excluding ECOG	
(1), including Sex	
(1) including Disease Stage	
(1) including Disease Stage, excluding Brain Metastasis and Liver Metastasis	
(1), excluding all never-smokers from ASTRUM-005	
(1), including Baseline Tumour Burden	
(1), including Race	
(1), only including non-Asians from ASTRUM-005	
(1), but only retain cases with available TMB values	

NICE

ESS, effective sample size: HR, hazard ratio; IPD, individual patient data; MAIC, matched adjusted indirect comparison; NA, not available; OS, overall survival; TMB, tumour mutational burden

Key clinical trials – adjusted characteristics for MAIC atezolizumab

Table: Population variables adjusted and rationale, IMpower133

Baseline Variables	ASTRUM-005		ASTRUM-005 - Adjusted		IMpower133	
	Serplulimab (N = 389)	Placebo (N = 196)	Serplulimab (ESS = 240)	Placebo (ESS = 126)	Placebo (N = 202)	Atezolizumab (N = 201)
Age Group, n (%)						
≥ 65 years	154 (39.6)	77 (39.3)	108 (44.8)	60 (47.5)	96 (47.5)	90 (44.8)
< 65 years	235 (60.4)	119 (60.7)	132 (55.2)	66 (52.5)	106 (52.5)	111 (55.2)
Sex, n (%)						
Male	317 (81.5)	164 (83.7)	216 (90.2)	117 (92.9)	132 (65.3)	129 (64.2)
Female	72 (18.5)	32 (16.3)	24 (9.8)	9 (7.1)	70 (34.7)	72 (35.8)
Race, n (%)						
Asian	262 (67.4)	139 (70.9)	150 (62.6)	84 (66.4)	36 (17.8)	33 (16.4)
Non-Asian	127 (32.6)	57 (29.1)	90 (37.4)	42 (33.6)	166 (82.2)	168 (83.6)
Disease Stage, n (%)						
IV	318 (81.7)	155 (79.1)	204 (84.8)	100 (79.3)	NR	NR
III or other	71 (18.3)	41 (20.9)	36 (15.2)	26 (20.7)	NR	NR
ECOG, n (%)						
PS 1	318 (81.7)	164 (83.7)	153 (63.7)	84 (66.8)	135 (66.8)	128 (63.7)
PS 0	71 (18.3)	32 (16.3)	87 (36.3)	42 (33.2)	67 (33.2)	73 (36.3)

ESS, effective sample size: MAIC, matched adjusted indirect comparison

Back to ITCs

Key clinical trials – adjusted characteristics for MAIC atezolizumab

Table: Population variables adjusted and rationale, IMpower133 cont.

Baseline Variables	ASTRUM-005		ASTRUM-005 - Adjusted		IMpower133	
	Serplulimab (N = 389)	Placebo (N = 196)	Serplulimab (ESS = 240)	Placebo (ESS = 126)	Placebo (N = 202)	Atezolizumab (N = 201)
Smoking Status, n (%)						
Current/former smoker	308 (79.2)	161 (82.1)	229 (95.5)	124 (98.5)	199 (98.5)	192 (95.5)
Never	81 (20.8)	35 (17.9)	11 (4.5)	2 (1.5)	3 (1.5)	9 (4.5)
Brain Metastasis, n (%)						
Yes	50 (12.9)	28 (14.3)	20 (8.5)	11 (8.9)	18 (8.9)	17 (8.5)
No	339 (87.1)	168 (85.7)	220 (91.5)	115 (91.1)	184 (91.1)	184 (91.5)
Liver Metastasis, n (%)						
Yes	99 (25.4)	51 (26.0)	92 (38.3)	45 (35.6)	72 (35.6)	77 (38.3)
No	290 (74.6)	145 (74.0)	148 (61.7)	81 (64.4)	130 (64.4)	124 (61.7)
Tumor Mutational Burden, n (%)						
≥10 mutations/Mb	22/195 (11.3)	4/110 (3.6)	13/120 (10.5)	2/71 (2.7)	110/178 (61.8)	102/173 (59.0)
<10 mutations/Mb	173/195 (88.7)	106/110 (96.4)	107/120 (89.5)	69/71 (97.3)	68/178 (38.2)	71/173 (41.0)
Previous Anticancer Treatments, n (%)						
Yes	10 (2.6)	5 (2.6)	6 (2.4)	3 (2.0)	65 (32.2)	66 (32.8)
No	379 (97.4)	191 (97.4)	234 (97.6)	123 (98.0)	137 (67.8)	135 (67.2)

N

ESS, effective sample size; MAIC, matched adjusted indirect comparison

Back to ITCs

Key clinical trials – adjusted characteristics for MAIC versus durvalumab

Table: Population variables adjusted and rationale, CASPIAN

Variable	Adjusted	Rationale
Age group (≥65 yr)	No	Patient age in ASTRUM-005 and CASPIAN were balanced.
Sex	No	Subgroup analysis in ASTRUM-005 and CASPIAN showed no impact of sex on treatment effect.
Race	No	Adjustment would lead to excessively low ESS resulting in unreliable outcomes, furthermore subgroup analysis in ASTRUM-005 showed no impact of race on treatment effect.
Disease stage	No	Cases of stage III or others accounted for about 10% or less of the total cases in CASPIAN and nearly balanced across studies.
ECOG	Yes	Imbalance in patient ECOG status between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Smoking status	Yes	Imbalance in patient smoking status between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Brain metastases	Yes	Imbalance in the presence of brain metastases between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Liver Metastases	Yes	Imbalance in the presence of liver metastases between ASTRUM-005 and CASPIAN and anticipated to impact treatment effect.
Blood-based tumour mutational burden	No	Not reported in CASPIAN.
PD-L1	No	Not reported in CASPIAN.
Previous anticancer treatments	No	Not reported in CASPIAN.

Key clinical trials – adjusted characteristics for MAIC versus durvalumab

Table: Patient characteristics in matched analysis

Baseline variables	ASTRUM-005		ASTRUM-005: Adjusted		CASPIAN	
	Serplulimab (n=389)	Placebo (n=196)	Serplulimab (ESS=256)	Placebo (ESS=134)	Control (n=269)	Durvalumab (n=268)
Age group, n (%)						
≥ 65 years	154 (39.6)	77 (39.3)	93 (36.5)	52 (38.5)	112(41.6)	101 (37.7)
< 65 years	235 (60.4)	119 (60.7)	163 (63.5)	82 (61.5)	157 (58.4)	167 (62.3)
Sex, n (%)						
Male	317 (81.5)	164 (83.7)	228 (89.1)	122 (91.0)	184 (68.4)	190 (70.9)
Female	72 (18.5)	32 (16.3)	28 (10.9)	12 (9.0)	85 (31.6)	78 (29.1)
Race, n (%)						
Asian	262 (67.4)	139 (70.9)	159 (62.1)	88 (65.9)	42 (15.6)	36 (13.4)
Non-Asian	127 (32.6)	57 (29.1)	97 (37.9)	46 (34.1)	227 (84.4)	232 (86.6)
Disease stage, n (%)						
IV	318 (81.7)	155 (79.1)	217 (84.9)	106 (79.4)	245 (91.1)	240 (89.6)
III or other	71 (18.3)	41 (20.9)	39 (15.1)	28 (20.6)	24 (8.9)	28 (10.4)
ECOG, n (%)						
PS 1	318 (81.7)	164 (83.7)	162 (63.1)	89 (66.5)	179 (66.5)	169 (63.1)
PS 0	71 (18.3)	32 (16.3)	94 (36.9)	45 (33.5)	90 (33.5)	99 (36.9)

NICE

ESS, effective sample size: MAIC, matched adjusted indirect comparison

Back to ITCs

Key clinical trials – adjusted characteristics for MAIC versus durvalumab

Table: Patient characteristics in matched analysis cont.

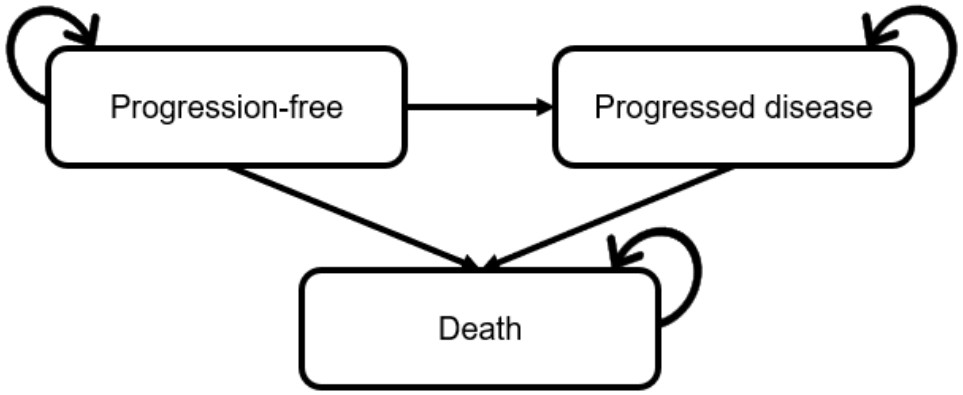
Baseline variables	ASTRUM-005		ASTRUM-005: Adjusted		CASPIAN	
	Serplulimab (n=389)	Placebo (n=196)	Serplulimab (ESS=256)	Placebo (ESS=134)	Control (n=269)	Durvalumab (n=268)
Smoking status, n (%)						
Current/former smoker	308 (79.2)	161 (82.1)	235 (91.8)	126 (94.4)	254 (94.4)	246 (91.8)
Never	81 (20.8)	35 (17.9)	21 (8.2)	8 (5.6)	15 (5.6)	22 (8.2)
Brain metastasis, n (%)						
Yes	50 (12.9)	28 (14.3)	27 (10.4)	13 (10.0)	27 (10.0)	28 (10.4)
No	339 (87.1)	168 (85.7)	229 (89.6)	121 (90.0)	242 (90.0)	240 (89.6)
Liver metastasis, n (%)						
Yes	99 (25.4)	51 (26.0)	103 (40.3)	52 (38.7)	104 (38.7)	108 (40.3)
No	290 (74.6)	145 (74.0)	153 (59.7)	82 (61.3)	165 (61.3)	160 (59.7)
Tumour mutational burden, n (%)						
≥10 mutations/Mb	22/195 (11.3)	4/110 (3.6)	14/128 (10.8)	2/75 (3.0)	NR	NR
<10 mutations/Mb	173/195 (88.7)	106/110 (96.4)	114/128 (89.2)	73/75 (97.0)	NR	NR
Previous anticancer treatments, n (%)						
Yes	10 (2.6)	5 (2.6)	6 (2.5)	4 (2.8)	NR	NR
No	379 (97.4)	191 (97.4)	250 (97.5)	130 (97.2)	NR	NR

ESS, effective sample size; MAIC, matched adjusted indirect comparison

Back to RTCs

Company's model overview

Model structure



Technology affects **costs** by:

- The time on treatment (acquisition and admin);
- Increasing the adverse events due to longer time on treatment;
- The number of patients receiving subsequent treatment;
- The delayed occurrence of palliative care costs.

Technology affects **QALYs** by:

- Increasing median life years;
- Increasing time in the PFS and progressed disease (PD) states;
- Increasing the adverse events due to longer time on treatment.

Assumptions with greatest ICER effect:

- The parametric curves selected for OS for serplulimab and carboplatin + etoposide;
- The parametric curve selected for TTOT for serplulimab;
- The assumption that the OS HRs serplulimab vs atezolizumab, and for serplulimab vs. durvalumab derived from MAICs are constant for the duration of the model;
- The average weight and height of patients with ES-SCLC in England matches the average weight and height in England of 65-74 year olds;
- The EQ-5D utility estimates for PD and PFS from ASTRUM-005 are generalisable to the England ES-SCLC population.

Key issues: Extrapolation of OS

	OS - Serplulimab		OS - carboplatin + etoposide	
Year	Loglogistic (company preferred)	3 knot spline + 3 year waning (EAG preferred)	Loglogistic (company preferred)	3 knot spline + exponential (EAG preferred)
0.5	0.85	0.88	0.78	0.81
1	0.64	0.62	0.46	0.45
2	0.36	0.33	0.17	0.15
3	0.22	0.25	0.08	0.10
5	0.11	0.15	0.03	0.04
10	0.04	0.02	0.01	0.01

OS, overall survival

Key issues: Extrapolation of PFS and OS, EAG base case

Figure: Overall survival curves modelled for serplulimab and carboplatin + etoposide, EAG base case

Figure: Progression-free survival curves modelled for serplulimab and carboplatin + etoposide, EAG base case

Key issues: Extrapolation of PFS and OS, company base case

Figure: OS parametric models for the serplulimab arm, company base case

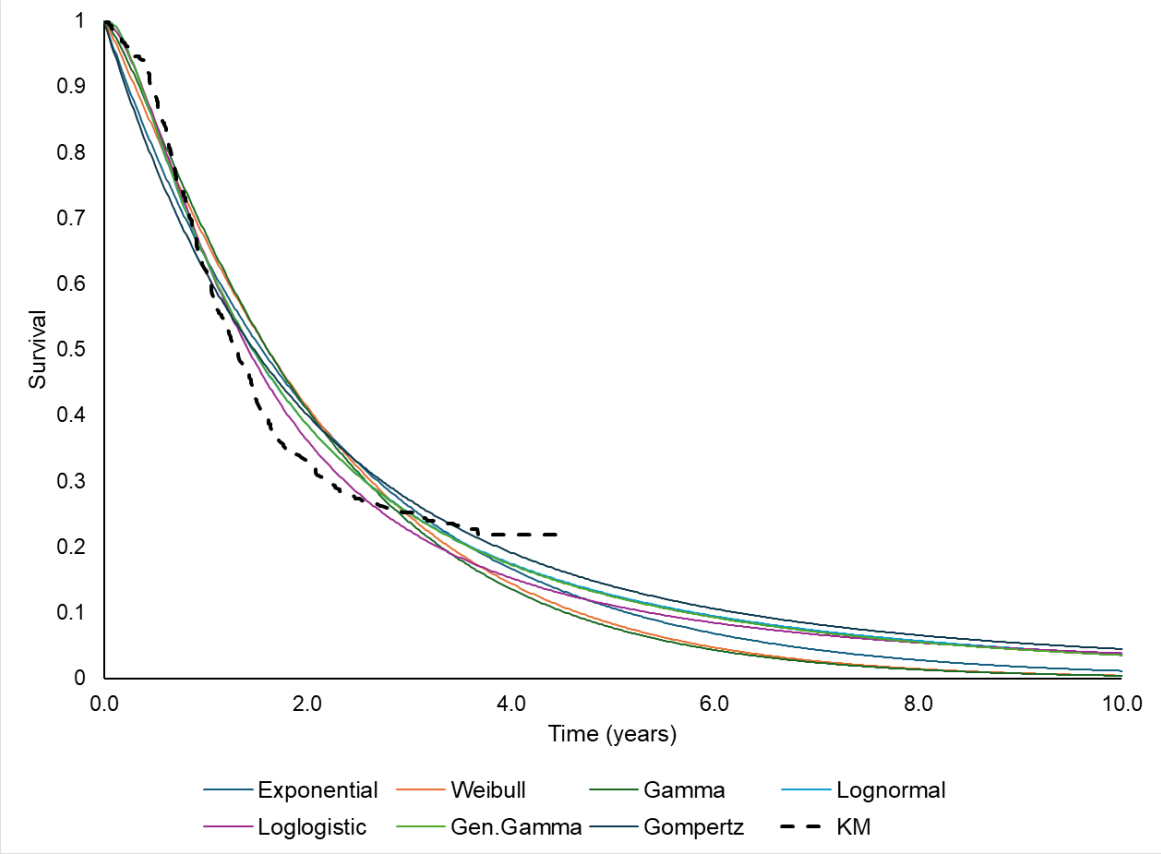


Figure: PFS parametric models for the serplulimab arm, company base case

[redacted]

Health state utilities - scenarios

Health state	ASTRUM-005 utility
PFS on-treatment	0.855
PFS off-treatment	0.757
Progressed disease on-treatment	0.836
Progressed disease off-treatment	0.786

Health state	ASTRUM-005: Actual model-based time to death estimate in the economic model	TA638 time to death estimate
On-treatment		
0-≤5 weeks	0.680	0.65
>5-≤15 weeks	0.778	0.73
>15-≤30 weeks	0.809	0.72
>30 weeks	0.859	0.73
Off-treatment		
0-≤5 weeks	0.432	0.33
>5-≤15 weeks	0.673	0.53
>15-≤30 weeks	0.770	0.70
>30 weeks	0.828	0.75

% on treatment across PFS/PD states

Proportion of PFS patients on treatment in company model and EAG scenarios

Proportion of PD patients on treatment in company model and EAG scenarios

Background

EAG believes company's assumption of equal percentages across states on treatment is unlikely given that disease has progressed. Consequently, EAG have taken a simple approach to exploring lower percentages of PD patients on treatment.

PD, progressed disease; PFS: progression-free survival

Back to base case assumptions