Systematic Literature Review of Efficacy, Health-Related Quality of Life, and Safety of the First-Line Treatments of Extensive-Stage Small Cell Lung Cancer

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CONCLUSIONS

- This SLR identified multiple high-quality RCTs reporting efficacy and safety outcomes in patients with ES-SCLC receiving 1L treatment
- Across immuno-chemotherapies identified by the SLR, OS ranged from 9.1 months to 16.4 months and median PFS ranged from 3.9 months to 6.4 months
- Rates of treatment-related SAEs ranged from 13% to 31.3% across included immuno-chemotherapies
- Subsequently, a feasibility assessment and ITC are being conducted, focusing on the comparability of study populations, interventions, and outcome measures

INTRODUCTION

- Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers, and nearly all cases are attributable to cigarette smoking[1-3]
- Extensive-stage SCLC (ES-SCLC) is an incurable, aggressive form of lung cancer with early development of metastases and poor prognosis[4]
- Approximately two-thirds of patients with SCLC have extensive disease at diagnosis, where the cancer is no longer confined to the ipsilateral hemithorax[5,6]
- Patients with ES-SCLC typically receive chemotherapy plus immunotherapy, followed by maintenance immunotherapy until progression or unacceptable toxicities[5,7-9]
- In the past decade, programmed death ligand-1 (PD-L1) inhibitors such as atezolizumab and durvalumab have received regulatory approval for use in ES-SCLC, forming the backbone of current immuno-chemotherapy regimens[6]
- While these agents have improved survival outcomes, they are associated with immune-mediated adverse events (AEs) including pneumonitis, colitis, dermatitis, myositis, and hypothyroidism[6,8,9]
- The objective of this analysis was to systematically identify published clinical studies reporting on efficacy outcomes, including overall survival (OS) and progression-free survival (PFS), as well as safety and health-related quality of life (HRQoL) outcomes for first-line (1L) treatments in ES-SCLC, and to determine the feasibility of conducting an indirect treatment comparison (ITC) of immuno-chemotherapy regimens

METHODS

- Embase, MEDLINE, and Cochrane electronic databases (October 7, 2024), as well as recent oncology conference proceedings and previous health technology assessments (HTAs) (October 14, 2024), were searched according to best practice guidelines.[10-15] No date limits were applied to searches
- Titles/abstracts and full-text publications were screened by two independent reviewers according to prespecified eligibility criteria
- Data from relevant publications were extracted by one reviewer into standardized, piloted data extraction tables, and all extracted information was quality-checked by a second independent reviewer
- To assess the risk of bias, quality assessment of randomized controlled trials (RCTs) was conducted using the Cochrane Risk of Bias 2 checklist[16]
- Prespecified eligibility criteria included adults with histologically or cytologically confirmed ES-SCLC, who had received no prior systemic treatment for ES-SCLC
- Outcomes of interest were OS, PFS, objective response rate (ORR), duration of response (DoR), disease control rate (DCR), AEs, and HRQoL
- Full inclusion criteria are presented in **Table 1**

Table 1. PICOS Inclusion Criteria

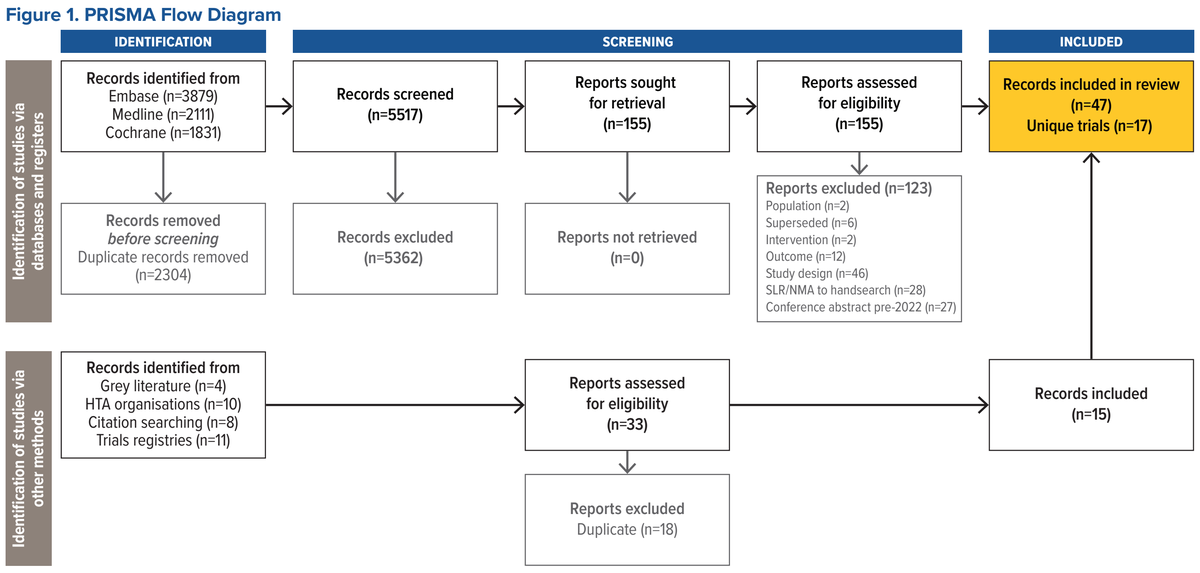
Characteristics	Inclusion Criteria		
Population	Adults (aged ≥18 years) with histologically or cytologically confirmed ES-SCLC, who have received no prior systemic treatment for ES-SCLC		
Interventions	Chemotherapy plus immunotherapies, including, but not limited to: • Tislelizumab • Nivolumab • Pembrolizumab • Atezolizumab	• Durvalumab • Tremelimumab • Ipilimumab • Serplulimab	• Toripalimab • Sintilimab • Benmelstobart
Comparators	• Chemotherapy plus immunotherapy • Platinum-based chemotherapy, such as, but not limited to: – Cisplatin – Carboplatin	• Topoisomerase inhibitors such as, but not limited to: – Etoposide – Irinotecan – Amrubicin	• Taxanes, such as, but not limited to: – Paclitaxel
Outcomes	• OS • PFS • ORR	• DoR • DCR • AEs	• HRQoL
Study design	RCTs (phase 2 and above) with ≥2 relevant arms		
Date limits	No restriction		
Countries	No restriction		
Languages	English language publications		

Abbreviations: AE, adverse event; DCR, disease control rate; DoR, duration of response; ES-SCLC, extensive-stage small cell lung cancer; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PICOS, Population, Intervention, Comparison, Outcome, Study design; RCT, randomized controlled trial.

RESULTS

- Of 7854 records retrieved through electronic database searches and hand searching, 47 publications corresponding to 17 unique RCTs were included (**Figure 1**)
- Of the 47 publications included, 20 were journal articles, 12 were conference abstracts, 11 were clinical trial records, two were HTA submissions, and one was a clinical study report
- Five of the 17 RCTs were phase 2 and 12 were phase 3. All RCTs utilized double-blinding except for three studies, which employed an open-label design
- The overall risk of bias judgement was low for nine of the 11 RCTs eligible for bias assessment. CASPIAN[17] and NCT01450761[18] RCTs were considered at some risk and high-risk of bias, respectively, due to potential deviations from intended interventions (domain two)

Figure 1. PRISMA Flow Diagram



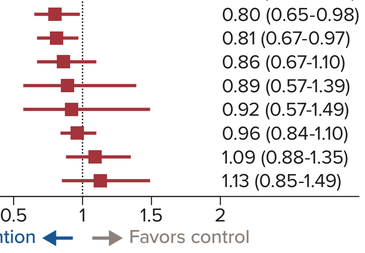
Abbreviations: HTA, health technology assessments; NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Overall Survival

- All 17 RCTs reported OS outcomes (**Figure 2**)
- Across all intervention arms, median OS ranged from 9.1 months to 19.3 months, which includes immuno-chemotherapy combined with other classes, such as tyrosine kinase inhibitors
- Across immuno-chemotherapy arms, OS ranged from 9.1 months to 16.4 months
- Across platinum-based chemotherapy comparators, median OS ranged from 8.1 months to 13.5 months
- The strongest OS benefit across all interventions compared with platinum-based chemotherapy alone was seen with an immuno-chemotherapy + targeted therapy combination (19.3 months vs 11.9 months; hazard ratio [HR]: 0.61; 95% confidence interval [CI]: 0.47-0.79; *P*=0.0002)
- Most intervention arms demonstrated similar improvements in OS, typically no more than 2-3 months, and varied in terms of statistical significance

Figure 2. Overall Survival in Included Publications[a]

Study	Intervention	Control	HR (95% CI)
ETER-701	BEN + ANLO + ETOP + CARB	PBO + ETOP + CARB	0.61 (0.47-0.79)
ASTRUM-005	SERPU + ETOP + CARB	PBO + ETOP + CARB	0.62 (0.50-0.76)
NCT04702880	BMS-986012 + NIVO + ETOP + CARB	NIVO + ETOP + CARB	0.71 (0.44-1.16)
CASPIAN	DURV + platinum-ETOP	Platinum-ETOP	0.71 (0.60-0.86)
CAPSTONE-1	ADEB + CARB + ETOP	PBO + ETOP + CARB	0.72 (0.58-0.90)
IMpower133	ATEZO + ETOP + CARB	PBO + ETOP + CARB	0.76 (0.60-0.95)
KEYNOTE-604	PEMBRO + ETOP + CARB/CIS	PBO + ETOP + CARB/CIS	0.76 (0.63-0.93)
NCT00527735	Phased IPIL + PAX + CARB	PBO + PAX + CARB	0.76 (0.48-1.19)
RATIONALE-312	TISLE + ETOP + CARB/CIS	PBO + ETOP + CARB/CIS	0.78 (0.63-0.95)
EXTENTORCH	TORI + ETOP + CARB/CIS	PBO + ETOP + CARB/CIS	0.80 (0.65-0.98)
CASPIAN	TREM + DURV + platinum-ETOP	Platinum-ETOP	0.81 (0.67-0.97)
ETER-701	ANLO + ETOP + CARB	PBO + ETOP + CARB	0.86 (0.67-1.10)
NCT00527735	Concurrent IPIL + PAX + CARB	PBO + PAX + CARB	0.89 (0.57-1.39)
NCT03041311	TRIL + ATEZO + ETOP + CARB	PBO + ATEZO + ETOP + CARB	0.92 (0.57-1.49)
NCT01450761	IPIL + ETOP + CARB/CIS	PBO + ETOP + CARB/CIS	0.96 (0.84-1.10)
SKYSCRAPER-02	TIRA + ATEZO + ETOP + CARB	PBO + ATEZO + ETOP + CARB	1.09 (0.88-1.35)
BEAT-SC	BEVA + ATEZO + platinum-ETOP	PBO + ATEZO + platinum-ETOP	1.13 (0.85-1.49)



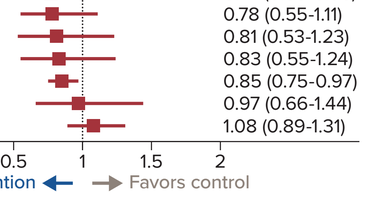
[a]Hazard ratios displayed for the latest analysis timepoint available at the time of the SLR. Where multiple populations and cohorts were reported in a trial, only one cohort has been presented. Where available, data for global (non-regional) cohorts evaluated by an independent review committee were presented. Data in bold indicate significant results (*P*<0.05).
Abbreviations: ADEB, adebrelimab; ANLO, anlotinib; ATEZO, atezolizumab; BEN, benmelstobart; BEVA, bevacizumab; CARB, carboplatin; CI, confidence interval; CIS, cisplatin; DURV, durvalumab; ETOP, etoposide; HR, hazard ratio IPIL, ipilimumab; NIVO, nivolumab; PAX, paclitaxel; PBO, placebo; PEMBRO, pembrolizumab; SERPU, serplulimab; SOCA, socazolimab; TIRA, tiragolumab; TISLE, tislelizumab; TORI, toripalimab; TREM, tremelimumab; TRIL, trilaciclib.

Progression-Free Survival

- Sixteen of the 17 included RCTs reported PFS outcomes (**Figure 3**)
- Across all intervention arms, median PFS ranged from 3.9 months to 8.2 months
- Across immuno-chemotherapy arms, median PFS ranged from 3.9 months to 6.4 months
- Across platinum-based chemotherapy arms, median PFS ranged from 4.2 months to 5.7 months
- Similar to the findings for OS, the strongest median PFS benefit compared with platinum-based chemotherapy alone was with an immuno-chemotherapy + targeted therapy combination (6.9 months vs 4.2 months; HR: 0.32 [95% CI: 0.26-0.41]; *P*<0.0001)
- Among the other treatments that improved median PFS, increased time to first progression event ranged from 0.2 months to 1.4 months

Figure 3. Progression-Free Survival in Included Studies[a]

Study	Intervention	Control	HR (95% CI)
ETER-701	BEN + ANLO + ETOP + CARB	PBO + ETOP + CARB	0.32 (0.26-0.41)
ETER-701	ANLO + ETOP + CARB	PBO + ETOP + CARB	0.44 (0.36-0.55)
ASTRUM-005	SERPU + ETOP + CARB	PBO + ETOP + CARB	0.47 (0.38-0.58)
NCT00527735	Phased IPIL + PAX + CARB	PBO + PAX + CARB	0.64 (0.40-1.02)
RATIONALE-312	TISLE + ETOP + CIS/CARB	PBO + ETOP + CIS/CARB	0.64 (0.52-0.78)
EXTENTORCH	TORI + ETOP + CIS/CARB	PBO + ETOP + CIS/CARB	0.67 (0.54-0.82)
CAPSTONE-1	ADEB + ETOP + CARB	PBO + ETOP + CARB	0.67 (0.54-0.83)
KEYNOTE-604	PEMBRO + ETOP + CIS/CARB	PBO + ETOP + CIS/CARB	0.70 (0.57-0.85)
CASPIAN	TREM + DURV + platinum-ETOP	Platinum-ETOP	0.72 (0.49-1.07)
BEAT-SC	BEVA + ATEZO + platinum-ETOP	PBO + ATEZO + platinum-ETOP	0.73 (0.58-0.93)
NCT00527735	Concurrent IPIL + PAX + CARB	PBO + PAX + CARB	0.75 (0.48-1.19)
IMpower133	ATEZO + ETOP + CARB	PBO + ETOP + CARB	0.77 (0.63-0.95)
ECOG-ACRIN EA5161	NIVO + ETOP + CIS/CARB	ETOP + CIS/CARB	0.78 (0.55-1.11)
NCT04702880	BMS-986012 + NIVO + ETOP + CARB	NIVO + ETOP + CARB	0.81 (0.53-1.23)
NCT03041311	TRIL + ATEZO + ETOP + CARB	PBO + ATEZO + ETOP + CARB	0.83 (0.55-1.24)
NCT01450761	IPIL + ETOP + CIS/CARB	PBO + ETOP + CIS/CARB	0.85 (0.75-0.97)
CASPIAN	DURV + platinum-ETOP	Platinum-ETOP	0.97 (0.66-1.44)
SKYSCRAPER-02	TIRA + ATEZO + ETOP + CARB	PBO + ATEZO + ETOP + CARB	1.08 (0.89-1.31)



[a]Hazard ratios displayed for the latest analysis timepoint available at the time of the SLR. Where multiple populations and cohorts were reported in a trial, only one cohort has been presented. Where available, data for global (non-regional) cohorts evaluated by an independent review committee were presented. Data in bold indicate significant results (*P*<0.05).
Abbreviations: ADEB, adebrelimab; ANLO, anlotinib; ATEZO, atezolizumab; BEN, benmelstobart; BEVA, bevacizumab; CARB, carboplatin; CI, confidence interval; CIS, cisplatin; DURV, durvalumab; ETOP, etoposide; HR, hazard ratio; IPIL, ipilimumab; NIVO, nivolumab; PAX, paclitaxel; PBO, placebo; PEMBRO, pembrolizumab; SERPU, serplulimab; TIRA, tiragolumab; TISLE, tislelizumab; TORI, toripalimab; TREM, tremelimumab; TRIL, trilaciclib.

Treatment Response

- Twelve of the included RCTs reported ORR outcomes
- Across all intervention arms, ORR ranged from 33% to 81.3%
- Across immuno-chemotherapy intervention arms, ORR ranged from 33% to 79%
- Across platinum-based chemotherapy arms, ORR ranged from 49% to 80%. Comparative measures of ORR improvement were infrequently reported (n=4). The highest ORR across all interventions compared with platinum-based chemotherapy alone was with an immunechemotherapy + targeted therapy (81.3% vs 66.8%; odds ratio: not reported; *P*=0.0001)
- Other treatments were associated with improvements in ORR ranging from +6.6% to +10%

Safety Outcomes

- Rates of all-cause treatment-emergent AEs (TEAEs) were reported in 11 RCTs and ranged from 90.9% to 100%
  - Four RCTs reported all patients experiencing a TEAE: durvalumab + platinum-etoposide, benmelstobart + anlotinib + carboplatin + etoposide, atezolizumab + carboplatin + etoposide, and pembrolizumab + etoposide + carboplatin/cisplatin
- Rates of treatment-related serious AEs (SAEs) were reported in nine RCTs and ranged from 1.9% to 38.7%
- Across immuno-chemotherapy therapies, treatment-related SAEs ranged from 13% to 31.3%
- Across platinum-based chemotherapy arms, treatment-related SAEs ranged from 9% to 28.4%
- Deaths due to AEs ranged from 0% to 10.9% across all RCTs, a range that was also observed in RCTs of immuno-chemotherapy combinations
  - The fewest deaths due to AEs (0%) occurred in the durvalumab + platinum-etoposide arm of the Japanese cohort enrolled in the CASPIAN trial (n=18) over a median follow-up of 12.5 months
  - The most deaths (10.9%) also occurred in the CASPIAN trial, but within the tremelimumab + durvalumab + platinum-etoposide arm of the global cohort (n=266) over a longer median follow-up of 39.4 months

Health-Related Quality of Life Outcomes

- Only six RCTs reported HRQoL outcomes: four RCTs used the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), one RCT used the Functional Assessment of Cancer Therapy General (FACT-G) scale, and one RCT used the EQ-5D visual analogue scale (VAS)
  - Two RCTs reported mean change from baseline in EORTC QLQ-C30 global scale with scores ranging from 4.2 to 11.3. The largest improvement was observed in patients treated with tislelizumab + etoposide + cisplatin/carboplatin
  - In the one RCT that used the FACT-G scale, no statistically significant benefits in HRQoL were observed in comparison to platinum-based chemotherapy
  - In the one RCT reporting EQ-5D VAS, no statistically significant benefits in HRQoL were observed for atezolizumab + carboplatin + etoposide compared with platinum-based chemotherapy

DISCUSSION

- Included RCTs were generally assessed to be of good quality according to the Cochrane Risk of Bias 2 checklist. The overall risk of bias judgement was low for nine RCTs
- Immuno-chemotherapy combinations exhibited similar efficacy benefits, while safety outcomes were more variable across treatment groups
- Significant evidence gaps in patient-reported outcomes exist for ES-SCLC populations, with only six of the 17 RCTs reporting on HRQoL
  - Within these six RCTs, reported outcomes were heterogeneous in terms of the scales used, measurement methods and timepoints

REFERENCES

1. What is lung cancer? American Cancer Society. Updated January 24, 2024. Accessed September 22, 2025. https://www.cancer.org/cancer/types/lung-cancer/about/what-is.html
2. Alberg AJ, et al. *Chest.* 2003;123(suppl 1):21S-49S.
3. Lung cancer risk factors. American Cancer Society. Updated January 24, 2024. Accessed September 22, 2025. https://www.cancer.org/cancer/types/lung-cancer/causes-risks-prevention/risk-factors.html
4. Tan W. Medscape. Small cell lung cancer (SCLC) treatment and management. Updated December 18, 2024. Accessed September 22, 2025. https://emedicine.medscape.com/article/280104-treatment?form=fpf
5. NCCN. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf
6. Small cell lung cancer. BMJ Best Practice. Updated April 29, 2025. Accessed September 22, 2025. https://bestpractice.bmj.com/topics/en-gb/1081
7. Dingemans AC, et al. *Ann Oncol.* 2021;32(7):839-853.
8. Goldman JW, et al. *Lancet Oncol.* 2021;22(1):51-65.
9. Horn L, et al. *N Engl J Med.* 2018;379(23):2220-2229.
10. Higgins JPT, et al. Cochrane Handbook. Version 6.4. Cochrane. 2023.
11. Page MJ, et al. *BMJ.* 2021;372:n71.
12. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance. University of York, 2009.
13. EUnetHTA. Guideline on information retrieval. Version 2.0. 2019.
14. NICE health technology evaluation: the manual. NICE (PMG36). Updated July 14, 2025. Accessed September 22, 2025. https://www.nice.org.uk/process/pmg36
15. Single technology appraisal and highly specialised technologies evaluation: user guide for company evidence submission template. NICE (PMG24). Updated December 3, 2024. Accessed September 22. 2025. https://www.nice.org.uk/process/pmg24
16. Sterne, et al. *BMJ.* 2019;366:l4898.
17. Paz-Ares, et al. *Lancet.* 2019;394(10212):1929-1939.
18. Reck, et al. *J Clin Oncol.* 2016;34(31):3740-3748.8

DISCLOSURES

EP and **JN:** employees of BeOne Medicines. **AMR** and **RH:** employees of Source Health Economics.

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