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Research article

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

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ABSTRACT

Objective: In recent years, the introduction of immune checkpoint inhibitors (ICIs) has revolutionized the treatment of extensive-stage small cell lung carcinoma (ES-SCLC), but the optimal combination of ICI and standard chemotherapy strategy is yet to be established. The aim of this network meta-analysis (NMA) was to identify which first-line combination strategy is optimal for patients with ES-SCLC.

Methods: PubMed, Embase, Cochrane Library, and the proceedings of international conferences, including American Society of Clinical Oncology and European Society for Medical Oncology meetings, were searched for randomized controlled trials (RCTs) published through October 31, 2022. The collected primary outcomes were overall survival (OS), progression-free survival (PFS), and grade 3–5 treatment-related adverse events (TRAEs).

Results: Our NMA study included six phase 3 and three phase 2 RCTs including 4037 patients and 10 first-line regimens. Regarding effectiveness, the addition of programmed cell death 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors to standard chemotherapy provided greater efficacy than chemotherapy alone. However, cytotoxic T lymphocyte-associated antigen-4 inhibitors were not associated with satisfactory prognoses. Serplulimab plus carboplatin–etoposide (vs. standard chemotherapy, hazard ratio [HR] = 0.63; 95% CI = 0.49–0.82) and nivolumab plus platinum–etoposide (HR = 0.65; 95% confidence interval [CI] = 0.46–0.91) displayed the greatest benefit regarding OS. In terms of PFS, serplulimab plus carboplatin–etoposide yielded the best benefit of all treatments (HR = 0.48; 95% CI = 0.39–0.6). The combination of ICIs and chemotherapy caused more toxicity in general, but durvalumab plus platinum–etoposide (odds ratio [OR] = 0.98; 95% CI = 0.68–1.4), atezolizumab plus carboplatin–etoposide (OR = 1.04; 95% CI = 0.68–1.6), and adebrelimab plus platinum–etoposide (OR = 1.02; 95% CI = 0.52–2) displayed similar safety as standard chemotherapy. Subgroup analysis by race illustrated that serplulimab plus carboplatin–etoposide was associated with the best OS in Asian patients. And in non-Asian patients, the combination of PD-1/PD-L1 inhibitors and chemotherapy (pembrolizumab plus platinum–etoposide, durvalumab plus platinum–etoposide, and durvalumab and tremelimumab plus platinum–etoposide) displayed superiority to standard chemotherapy.

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Conclusions: The results of our NMA study suggested that serplulimab plus carboplatin–etoposide and nivolumab plus platinum–etoposide are associated with the best OS as first-line treatments for patients with ES-SCLC. Serplulimab plus carboplatin–etoposide was associated with the best PFS. In Asian patients, serplulimab plus carboplatin–etoposide had the best OS.
Systematic review registration: This study is registered with PROSPERO, number CRD42022345850.

1. Introduction

In 2020, lung cancer accounted for approximately 1 in 10 new cases of cancer and 1 in 5 deaths, making it the second most common cancer globally [1]. Small cell lung carcinoma (SCLC) accounts for 14% of all lung cancer cases [2]. SCLC is characterized by an early doubling time and early extensive metastases, distinguishing this malignancy from non-small cell lung cancer (NSCLC) [3]. Therefore, at the time of first diagnosis, the majority of patients (60%–70%) have extensive-stage (ES)-SCLC (defined as cancer that cannot be included in a single radiation therapy field) [3]. SCLC has an exceptionally poor prognosis, and cigarette smoking and second-hand smoke are the most common causes of this disease [4]. Because of smoking signatures caused by prolonged exposure to smoke, SCLC is among the malignancies with the highest tumor mutational burden (TMB) and lowest immunogenicity [5].

The first-line chemotherapy for ES-SCLC has consisted of a platinum agent (cisplatin or carboplatin) together with etoposide [6]. In patients with ES-SCLC, numerous randomized phase III studies revealed statistically significant advantages of adding an immune checkpoint inhibitor (ICI) to first-line treatment. These studies implied that ICIs double the 2-year survival rate from 11% to 22%. Furthermore, atezolizumab plus carboplatin–etoposide and durvalumab plus platinum–etoposide have been included in the National Comprehensive Cancer Network guideline as first-line treatments for ES-SCLC, providing median overall survival (OS) of approximately 12.3–12.9 months. However, chemoimmunotherapy is associated with higher rates of adverse effects, such as neutropenia, anemia, and thrombocytopenia [7–13].

With the increasing number of studies of ICIs, concerns have been raised regarding the relative effectiveness and safety of any two of the numerous first-line therapies. It is necessary to use network meta-analysis (NMA), which synthesizes data from direct and indirect comparisons, to identify the most effective currently accessible treatments. Future clinical studies with head-to-head comparisons might also benefit from using this NMA in their design.

In our study, we aimed to compare all currently accessible ICIs with chemotherapy for the first-line treatment of adults with ES-SCLC and offer thorough evidence for selecting the optimal chemoimmunotherapy option.

2. Methods

2.1. Search strategy

Based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) for NMA guidelines [14], we performed this systematic review and NMA. The PRISMA checklist is provided in Table S1. Without linguistic constraints, we searched Embase, the Cochrane Central Register of Controlled Trials, PubMed, and the proceedings of international conferences, including American Society of Clinical Oncology and European Society for Medical Oncology meetings, for studies published through October 31, 2022. The keywords of the search queries were “Small Cell Lung Carcinoma, Immunotherapy, Immune Checkpoint Inhibitors, PD-1, PD-L1, CTLA-4, pembrolizumab, ipilimumab, atezolizumab, nivolumab, durvalumab, tremelimumab, camrelizumab and serplulimab".

2.2. Inclusion criteria

The inclusion criteria were as follows: 1) a primary diagnosis of ES-SCLC obtained via histological examination; 2) randomized controlled trials (RCTs) including phase 2 or phase 3 trials; 3) available data on OS, progression-free survival (PFS), and treatment-related adverse events (TRAEs); 4) comparison of treatment with least one ICI (programmed cell death 1 [PD-1], programmed cell death ligand 1 [PD-L1], and cytotoxic T lymphocyte-associated antigen-4 [CTLA-4] inhibitors) plus standard chemotherapy versus standard chemotherapy alone; and 5) included only first-line treatments for ES-SCLC.

2.3. Exclusion criteria

Studies that only compared different doses of an ICI and crossover trials, non-randomized trials, and observational studies were excluded.

2.4. Definition of outcomes

Our primary outcomes were efficacy (OS, the period from randomization to death with any causes) and safety (TRAEs, identified and ranked in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events). The secondary

outcome was PFS (the period between the start of treatment and the observation of disease progression or death from any cause in patients with oncologic disease).

2.5. Data extraction

When duplicate data were obtained, the study reporting the most detailed and informative data was included. We estimated summary hazard ratios (HRs) and odds ratios (ORs) for dichotomous outcomes using pairwise meta-analysis and NMA. In NMA, we used group-level data, whereas the binomial likelihood was used for dichotomous outcomes.

2.6. Risk of bias assessment

The risk of bias of each study was assessed using the Cochrane risk of bias assessment tool. The tool includes random sequence generation; selective outcome reporting; blinding of participants, personnel, and outcome assessors; incomplete outcome data; allocation concealment; and other biases. Each item was labeled as low, unclear, or high risk of bias according to the evaluation criteria

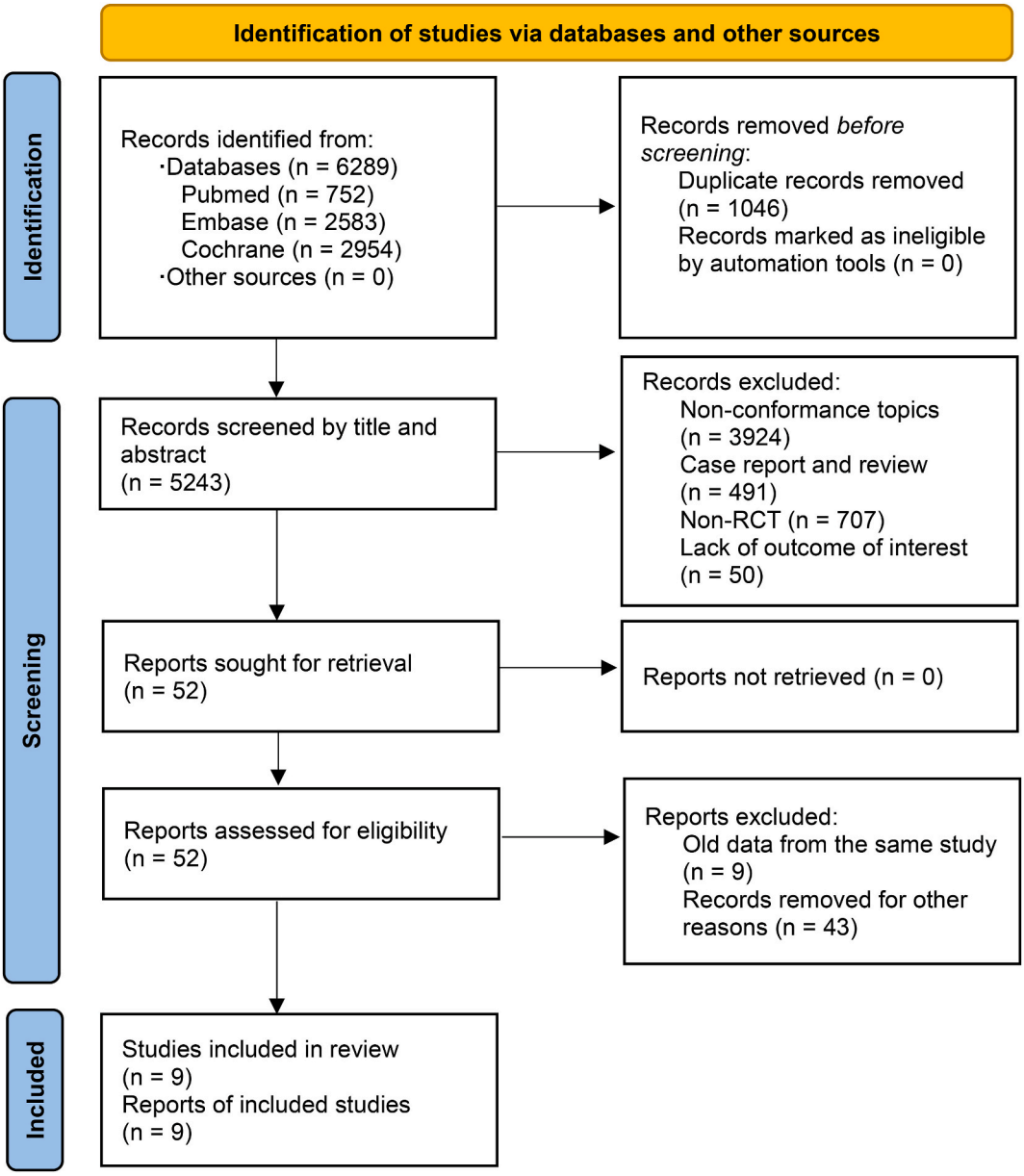

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of literature search and selection.

[15]. Independently, two researchers (JD, LL) chose the studies, read the primary reports and supplemental materials, obtained the pertinent data from the included trials, and estimated the risk of bias. Any disagreements were arbitrated by a third investigator (LF) and settled by consensus.

2.7. Statistical analysis

Cochrane's Q and the inconsistency statistic (I^2) were used to describe heterogeneity and inconsistency among the studies [16]. A fixed-effects NMA model was then used to synthesize the study effect sizes, presuming that the degree of heterogeneity was the same in all treatment comparisons. The surface under the cumulative ranking curve (SUCRA) was employed as a major assessment criteria to rate the treatments regarding each outcome [17]. For the SUCRA score, the therapy with a score of 1 is unquestionably the best, and that with a score of 0 is unquestionably the worst [17].

All models were fitted in R (version 4.2.0) using the binomial likelihood for dichotomous outcomes.

Visual inspection of four chains and consideration of the Brooks–Gelman–Rubin diagnostic were used to confirm model convergence. A fixed-effects network under a Bayesian framework using Markov chain Monte Carlo methods was built in R (version 4.2.0). For each outcome, we used a random-effects consistency model using four independent Markov chains with a step size of 10 and adapted 10,000 times for each chain in 100,000 sample iterations. NMAs of the primary outcomes were generated using the gemtc package in R (version 4.2.0), and the assessment of risk of bias was performed using RevMan (version 5.3).

3. Results

3.1. Study selection and characteristics

In total, 6289 citations were identified by the initial search, and 52 potentially eligible articles were retrieved for full text review (Fig. 1). Eventually, 9 RCTs that fulfilled the selection criteria were included for NMA. Two included studies were published as meeting abstracts, and the other studies were full articles. Table 1 summarizes the characteristics of the included studies. Fig. 2 presents the

Table 1
Baseline characteristics of the trials included in this network meta-analysis.

Trial	Phase	Regimen	Patients	Median OS	HR	Median PFS	HR	Numbers of
			numbers	(months)	(95% CI)	(months)	(95% CI)	TRAE 3-5
ASTRUM-005 2022	III	Serplulimab plus Carboplatin-Etoposide	389	15.4	0.63 (0.49, 0.82)	5.7	0.48 (0.38, 0.59)	129/389
		Carboplatin-Etoposide	196	10.9		4.3		54/196
CA184-156 2016	III	Ipilimumab plus Platinum-Etoposide	478	11	0.94 (0.81, 1.09)	4.6	0.85 (0.75, 0.97)	391/478
		Platinum-Etoposide	476	10.9		4.4		361/476
CAPSTONE-1 2022	III	Adebrelimab plus Platinum-Etoposide	230	15.3	0.72 (0.58, 0.90)	5.8	0.67 (0.54, 0.83)	197/230
		Platinum-Etoposide	232	12.8		5.6		197/232
CASPIAN 2019	III	Durvalumab plus Tremelimumab plus Platinum–Etoposide	268	10.4	0.82 (0.68, 0.99)	4.9	0.84 (0.70, 1.01)	85/266
		Durvalumab plus Platinums Platinum	268	12.9	0.75 (0.62, 0.91)	5.1	0.80 (0.66, 0.96)	64/265
		Platinum-Etoposide	269	10.5		5.4		88/266
EA5161	II	Nivolumab plus Platinum–Etoposide	80	11.3	0.67 (0.46, 0.98)	5.5	0.65 (0.46, 0.91)	62/80
		Platinum–Etoposide	80	8.5		4.6		50/80
IMpower133 2018	III	Atezolizumab plus Carboplatin-Etoposide	201	12.3	0.76 (0.60, 0.96)	5.2	0.77 (0.62, 0.96)	138/198
		Carboplatin-Etoposide	202	10.3		4.3		135/196
KEYNOTE-604 2020	III	Pembrolizumab plus Platinum-Etoposide	228	10.8	0.80 (0.65, 0.99)	4.5	0.75 (0.61, 0.92)	185/223
		Platinum-Etoposide	225	9.7		4.3		181/223
NCT00527735 2013	II	Ipilimumab plus Paclitaxil/Carboplatin (phased)	42	12.94	0.75 (0.46, 1.23)	6.44	0.64 (0.40, 1.02)	29/42
		Ipilimumab plus Paclitaxil/Carboplatin (concurrent)	43	9.13	0.95 (0.59, 1.54)	5.68	0.75 (0.48, 1.19)	31/42
		Paclitaxil/Carboplatin	45	9.92		5.26		26/44
REACTION 2020	II	Pembrolizumab plus Platinum-Etoposide	61	12.3	0.73 (0.46, 1.17)	4.7	0.84 (0.57, 1.25)	26/61
		Platinum-Etoposide	64	10.4		5.4		23/64

network of eligible comparisons for efficacy and safety.

The studies were published between 2013 and 2022, and the mean study sample size was 490 participants. In total, 2248 participants were randomly assigned to the immunotherapy plus chemotherapy experimental arm, and 1789 were randomly assigned to the chemotherapy control arm. Of all studies, CASPIAN and NCT00527735 were three-arm trials, and the others were two-arm trials. Two arms were combined in NCT00527735 because the same types of drugs were used, albeit in different orders. The experimental arms included serplulimab plus carboplatin–etoposide (n = 1) [18], ipilimumab plus platinum–etoposide (n = 1) [19], adebrelimab plus platinum–etoposide (n = 1) [20], durvalumab and tremelimumab plus platinum–etoposide (n = 1) [8], durvalumab plus platinum–etoposide (n = 1) [8], nivolumab plus platinum–etoposide (n = 1) [21], atezolizumab plus carboplatin–etoposide (n = 1) [22], pembrolizumab plus platinum–etoposide (n = 2) [12,23], and ipilimumab plus paclitaxel–carboplatin (n = 1) [10].

3.2. Methodological quality of the studies

In general, all of the trials of high methodological quality. Of the studies, six had a double-blind design, one trial had a triple-blind design, and the others were open-label studies. Furthermore, all but two studies (EA5161 and REACTION) utilized random sequence generation for allocation. The risk of bias of each trial is presented in Fig. S1.

3.3. Pairwise meta-analysis

For OS, head-to-head comparisons revealed that ipilimumab plus platinum–etoposide (HR = 0.94; 95% confidence interval [CI] = 0.81–1.09) did not improve OS versus standard chemotherapy. OS was improved in the combination treatment arm in the other trials (Fig. S2). The forest plot of OS is provided in Fig. S2. For PFS, ipilimumab plus paclitaxel–carboplatin did not improve outcomes versus standard chemotherapy (Fig. S3). In terms of TRAEs, no combination regimens had lower risks of TRAEs than standard chemotherapy, as presented in Fig. S4.

3.4. NMA

Regarding OS, the results of indirect comparisons are presented in Fig. 3A. Serplulimab plus carboplatin–etoposide significantly improved survival versus chemotherapy (HR = 0.63; 95% CI = 0.49–0.82), ipilimumab plus platinum–etoposide (HR = 0.67; 95% CI = 0.5–0.9). Serplulimab plus carboplatin–etoposide produced similar outcomes as nivolumab plus platinum–etoposide (HR = 0.97; 95% CI = 0.63–1.49).

The findings of the indirect comparison for PFS are also presented in Fig. 3A. Serplulimab plus carboplatin–etoposide yielded the

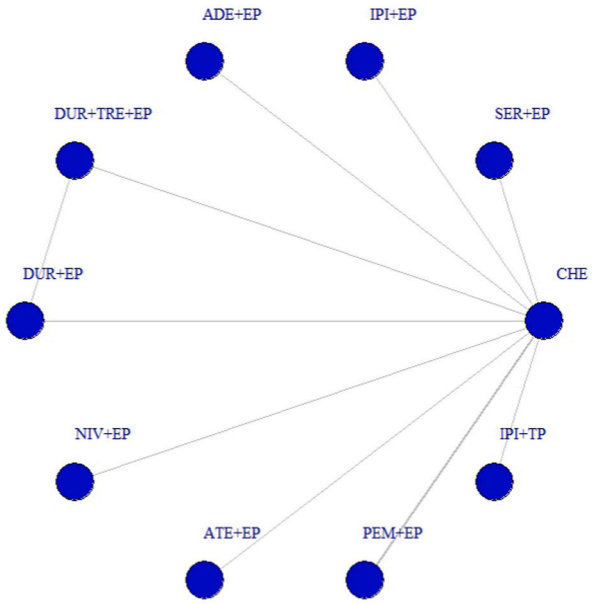

Fig. 2. Network of immunotherapies used in the first-line treatment of extensive-stage small cell lung carcinoma. Network geometry uses nodes to represent interventions, lines to indicate direct comparisons, and line thickness to illustrate the number of randomized controlled trails evaluating these immunotherapies. SER + EP: serplulimab plus carboplatin-etoposide; IPI + EP: ipilimumab plus platinum-etoposide; ADE + EP: adebrelimab plus platinum-etoposide; DUR + TRE + EP: durvalumab plus tremelimumab plus platinum-etoposide; DUR + EP: durvalumab plus platinum-etoposide; NIV + EP: nivolumab plus platinum-etoposide; ATE + EP: atezolizumab plus carboplatin-etoposide; PEM + EP: pembrolizumab plus platinum-etoposide; IPI + TP: ipilimumab plus paclitaxil/carboplatin; CHE: chemotherapy.

best benefit among all treatments versus chemotherapy (HR = 0.48; 95% CI = 0.39–0.6), ipilimumab plus paclitaxel–carboplatin (HR, 0.52; 95% CI 0.35–0.77), ipilimumab plus platinum–etoposide (HR = 0.56; 95% CI = 0.44–0.73), durvalumab and tremelimumab plus platinum–etoposide (HR = 0.57; 95% CI = 0.43–0.76), durvalumab plus platinum–etoposide (HR = 0.6; 95% CI = 0.45–0.8), pembrolizumab plus platinum–etoposide (HR = 0.62; 95% CI = 0.46–0.85), atezolizumab plus carboplatin–etoposide (HR = 0.63 95% CI = 0.47–0.83), and adebrelimab plus platinum–etoposide (HR = 0.72; 95% CI = 0.53–0.96).

Regarding TRAEs, compared with the findings for chemotherapy alone, no combination of immunotherapy and standard chemotherapy had an obviously lower incidence of TRAEs. Durvalumab plus platinum–etoposide (OR = 0.98; 95% CI = 0.68–1.4), atezolizumab plus carboplatin–etoposide (OR = 1.04; 95% CI = 0.68–1.6), and adebrelimab plus platinum–etoposide (OR = 1.02; 95% CI = 0.52–2) had a similar incidence of TRAEs as standard chemotherapy (Fig. 3B).

3.5. Subgroup analysis

Concerning the outcomes in Asian and non-Asian patients (IMpower 133 only provided data for Japanese patients; CAPSTONE-1 was only conducted in China) [13,24], only OS network meta-analysis could be performed, and eight and six treatments could be compared in Asian and non-Asian patients, respectively (Fig. 4).

Overall Survival

CHE	0.94 (0.81, 1.09)	0.85 (0.6, 1.2)	**0.82 (0.68, 0.99)**	**0.79 (0.65, 0.96)**	**0.76 (0.6, 0.95)**	**0.75 (0.62, 0.91)**	**0.72 (0.58, 0.9)**	**0.65 (0.46, 0.91)**	**0.63 (0.49, 0.82)**
	IPI+EP	0.91 (0.62, 1.32)	0.87 (0.68, 1.11)	0.84 (0.66, 1.07)	0.81 (0.61, 1.06)	0.8 (0.63, 1.02)	**0.77 (0.59, 1)**	**0.69 (0.48, 1)**	**0.67 (0.5, 0.9)**
		IPI+TP	0.96 (0.65, 1.43)	0.93 (0.63, 1.37)	0.89 (0.59, 1.35)	0.88 (0.59, 1.31)	0.85 (0.57, 1.27)	0.77 (0.47, 1.24)	0.74 (0.48, 1.14)
SER+EP			DUR+TRE+EP	0.96 (0.73, 1.26)	0.93 (0.69, 1.25)	0.91 (0.75, 1.12)	0.88 (0.65, 1.17)	0.79 (0.54, 1.17)	0.77 (0.56, 1.06)
0.74 (0.49, 1.11)	NIV+EP			PEM+EP	0.96 (0.71, 1.3)	0.95 (0.73, 1.25)	0.91 (0.68, 1.22)	0.83 (0.56, 1.22)	0.8 (0.58, 1.1)
0.72 (0.53, 0.97)	0.97 (0.65, 1.45)	ADE+EP			ATE+EP	0.99 (0.73, 1.33)	0.95 (0.69, 1.3)	0.86 (0.57, 1.28)	0.83 (0.59, 1.17)
0.63 (0.47, 0.83)	0.85 (0.57, 1.24)	0.87 (0.66, 1.15)	ATE+EP			DUR+EP	0.96 (0.72, 1.28)	0.87 (0.59, 1.28)	0.84 (0.61, 1.15)
0.62 (0.46, 0.85)	0.84 (0.56, 1.27)	0.87 (0.64, 1.18)	1 (0.76, 1.33)	PEM+EP			ADE+EP	0.9 (0.6, 1.35)	0.87 (0.62, 1.23)
0.6 (0.45, 0.8)	0.81 (0.55, 1.2)	0.84 (0.63, 1.11)	0.96 (0.72, 1.29)	0.96 (0.74, 1.24)	DUR+EP			NIV+EP	0.97 (0.63, 1.49)
0.57 (0.43, 0.76)	0.77 (0.53, 1.14)	0.8 (0.6, 1.06)	0.92 (0.69, 1.22)	0.91 (0.71, 1.18)	0.95 (0.79, 1.15)	DUR+TRE+EP			SER+EP
0.56 (0.44, 0.73)	0.77 (0.53, 1.1)	0.79 (0.61, 1.01)	0.91 (0.7, 1.16)	0.9 (0.73, 1.12)	0.94 (0.75, 1.18)	0.99 (0.79, 1.24)	IPI+EP		
0.52 (0.35, 0.77)	0.7 (0.43, 1.12)	0.72 (0.49, 1.06)	0.83 (0.56, 1.23)	0.83 (0.57, 1.2)	0.86 (0.59, 1.25)	0.9 (0.62, 1.31)	0.91 (0.65, 1.3)	IPI+TP	
0.48 (0.39, 0.6)	**0.65 (0.46, 0.92)**	**0.67 (0.54, 0.83)**	**0.77 (0.62, 0.96)**	**0.77 (0.64, 0.92)**	**0.8 (0.66, 0.97)**	0.84 (0.7, 1.01)	**0.85 (0.75, 0.97)**	0.93 (0.67, 1.28)	CHE

Progression-free Survival

(A)

DUR+EP									
0.94 (0.54, 1.65)	ATE+EP								
0.92 (0.49, 1.72)	0.98 (0.5, 1.91)	ADE+EP							
0.82 (0.48, 1.41)	0.87 (0.49, 1.59)	0.89 (0.46, 1.7)	PEM+EP						
0.74 (0.44, 1.26)	0.79 (0.45, 1.4)	0.81 (0.42, 1.54)	0.91 (0.52, 1.57)	SER+EP					
0.68 (0.42, 1.1)	0.72 (0.42, 1.23)	0.74 (0.4, 1.35)	0.83 (0.5, 1.38)	0.91 (0.56, 1.49)	IPI+EP				
0.65 (0.45, 0.94)	0.69 (0.39, 1.22)	0.7 (0.37, 1.33)	0.79 (0.46, 1.38)	0.87 (0.51, 1.49)	0.95 (0.59, 1.55)	DUR+TRE+EP			
0.56 (0.24, 1.32)	0.6 (0.25, 1.44)	0.61 (0.24, 1.55)	0.69 (0.29, 1.64)	0.75 (0.32, 1.77)	0.83 (0.36, 1.9)	0.87 (0.37, 2.06)	IPI+TP		
0.47 (0.21, 1.02)	0.5 (0.22, 1.11)	0.51 (0.21, 1.21)	0.57 (0.25, 1.26)	0.63 (0.28, 1.38)	0.69 (0.32, 1.46)	0.72 (0.32, 1.58)	0.83 (0.29, 2.33)	NIV+EP	
0.98 (0.68, 1.4)	1.04 (0.68, 1.6)	1.02 (0.52, 2)	1.12 (0.59, 2.15)	1.1 (0.64, 1.92)	1.1 (0.67, 1.78)	1.51 (1.04, 2.19)	1.73 (0.81, 3.75)	**2.09 (1.05, 4.26)**	CHE

Grade ≥ 3 Adverse Events

(B)

Fig. 3. Pooled estimates of the network meta-analysis. (A) The data present hazard ratios (HRs) and 95% confidence intervals (CIs, in parentheses) for overall survival (upper triangle in green) and progression-free survival (lower triangle in yellow) in the column-defining treatment compared with the row-defining treatment. HR < 1 indicates a survival benefit. (B) Odds ratio (OR) and 95% CI (in parentheses) for grade 3–5 treatment-related adverse events (upper triangle in green). Bold numbers indicate statistical significance. OR < 1 indicates better tolerance. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

In Asian patients, serplulimab plus carboplatin–etoposide displayed a significant benefit versus ipilimumab plus platinum-etoposide (HR = 0.5; 95% CI = 0.32–0.79), and standard chemotherapy (HR = 0.58; 95% CI = 0.43–0.79).

For non-Asian patients, the combination of PD-1/PD-L1 inhibitors and chemotherapy produced superior outcomes versus chemotherapy among the comparable treatments (pembrolizumab plus platinum-etoposide vs. chemotherapy: HR = 0.74; 95% CI = 0.59–0.92; durvalumab plus platinum–etoposide vs. chemotherapy: HR = 0.75; 95% CI = 0.61–0.92; durvalumab and tremelimumab plus platinum–etoposide vs. chemotherapy: HR = 0.81; 95% CI = 0.66–1). Serplulimab plus carboplatin–etoposide was not showed a significant statistic result.

3.6. Ranking of all treatments

Fig. 5 illustrates the comparative effectiveness of therapies regarding OS, PFS, and TRAEs based on the treatment ranking probability and SUCRA value. The detailed SUCRA values are presented in Table 2. The SUCRA value was approximately consistent with the ranking probabilities. Concerning OS, serplulimab plus carboplatin–etoposide had the highest SUCRA value (0.869). Regarding PFS, serplulimab plus platinum–etoposide also had the highest SUCRA value (0.990). Concerning TRAEs, chemotherapy had the highest SUCRA value (0.800).

4. Discussion

This NMA included six phase 3 and three phase 2 RCTs. The effectiveness and safety of various immunotherapy–chemotherapy combinations were compared in patients with ES-SCLC. Several important conclusions were drawn from this NMA. The SUCRA value was used to rank the safety and efficacy of different regimens. Regarding OS, the ranking of all regimens was [1] serplulimab plus carboplatin–etoposide [2], nivolumab plus platinum–etoposide [3], adebrelimab plus platinum–etoposide [4], durvalumab plus platinum–etoposide [5], atezolizumab plus carboplatin–etoposide [6], pembrolizumab plus platinum–etoposide [7], durvalumab and tremelimumab plus platinum–etoposide [8], ipilimumab plus paclitaxel–carboplatin, and [9] ipilimumab plus platinum–etoposide. For PFS, the ranking was [1] serplulimab plus carboplatin–etoposide [2], nivolumab plus platinum–etoposide [3], adebrelimab plus platinum–etoposide [4], atezolizumab plus carboplatin–etoposide [5], pembrolizumab plus platinum–etoposide [6], durvalumab plus platinum–etoposide [7], durvalumab and tremelimumab plus platinum–etoposide [8], ipilimumab plus platinum–etoposide, and [9] ipilimumab plus paclitaxel–carboplatin. Concerning TRAEs, the combination of ICIs and chemotherapy was generally more toxic than chemotherapy alone.

In a previous study [25] of the best treatment option for ES-SCLC, PD-L1 inhibitors plus standard chemotherapy provided the best OS. The findings of this NMA contradicted this conventional thinking. Serplulimab, a novel *anti*-PD-1 antibody, plus standard chemotherapy provided the best PFS and OS versus chemotherapy alone. Specifically, the combination prolonged OS by 4.5 months compared with the control arm. Both PD-L1 and PD-1 inhibitors displayed promising PFS. Some characteristics of SCLC could explain the results of those studies. Because of the patients' high TMB, SCLC cells are expected to trigger potent T-cell responses [6]. Patients

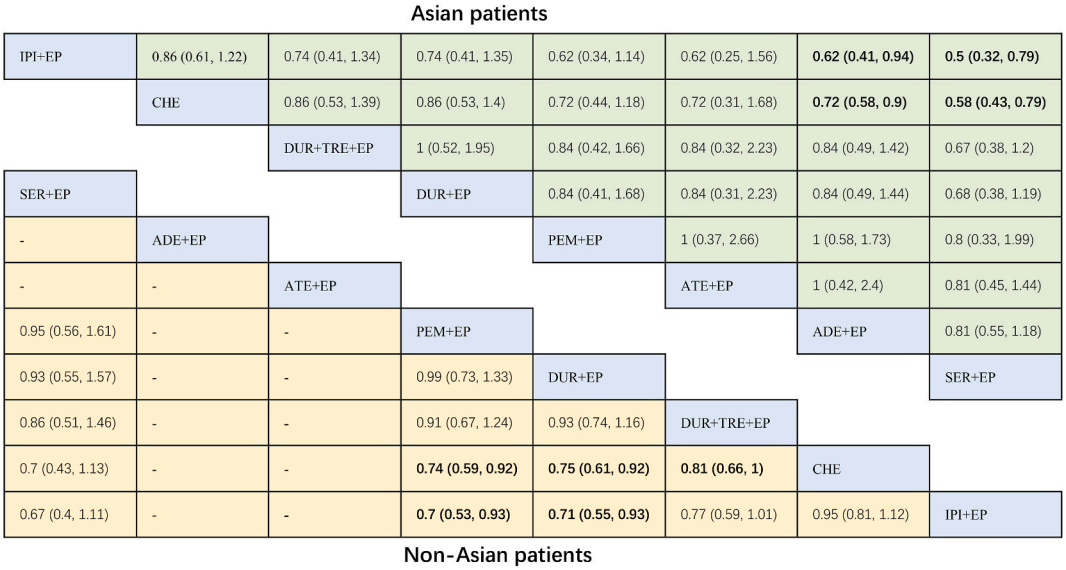

Fig. 4. Pooled estimates of subgroup analysis. Hazard ratios (95% confidence intervals) for overall survival among Asian (upper triangle in green) and non-Asian patients (lower triangle in yellow). The results present a comparison between the column-defining treatment and the row-defining treatment. Hazard ratio <1 denotes a survival benefit. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

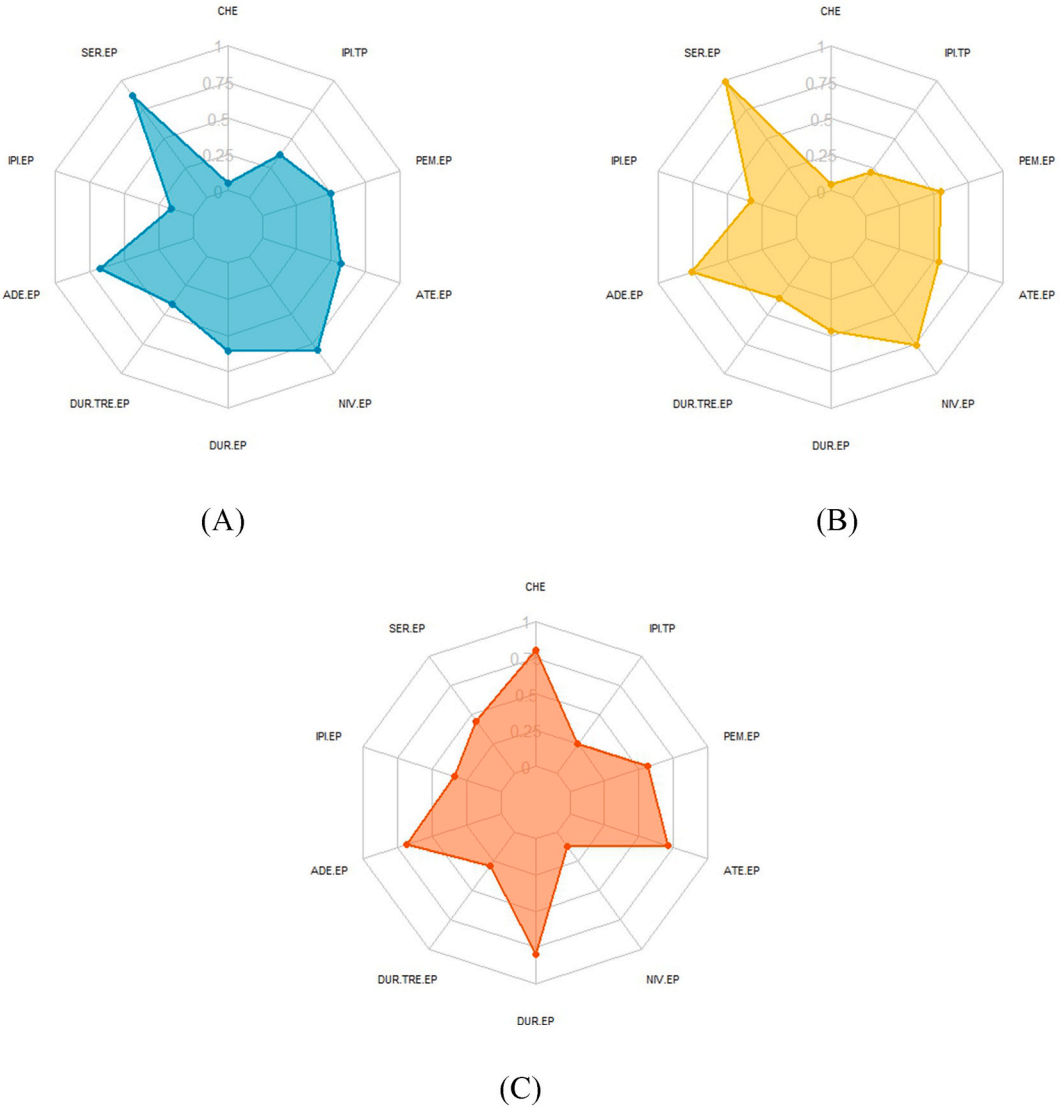

Fig. 5. Surface under the cumulative ranking curve (SUCRA) values for (A) overall survival, (B) progression-free survival, and (C) treatment-related adverse events. SUCRA values close to 1 denote better effects, and values close to 0 indicate worse effects. SER. EP: serplulimab plus carboplatin-etoposide; IPI. EP: ipilimumab plus platinum-etoposide; ADE. EP: adebrelimab plus platinum-etoposide; DUR. TRE.EP: durvalumab plus tremelimumab plus platinum-etoposide; DUR. EP: durvalumab plus platinum-etoposide; NIV. EP: nivolumab plus platinum-etoposide; ATE. EP: atezolizumab plus carboplatin-etoposide; PEM. EP: pembrolizumab plus platinum-etoposide; IPI. TP: ipilimumab plus paclitaxil/carboplatin; CHE: chemotherapy.

with paraneoplastic neurological syndromes whose tumor cells exhibited strong immune activity typically had better outcomes than those without these syndromes [26].

Although survival is prolonged in patients with SCLC who receive immunotherapy, the benefit of immunotherapy is less significant than that in melanoma. The limited effects of ICIs might be explained by the following mechanisms. First, the expression of major histocompatibility complex class I molecules on the surface of SCLC is low [27]. Second, immune evasion might be aided by the presence of immune cells with suppressive characteristics, such as regulatory T cells, in the SCLC tumor microenvironment [28]. A meta-analysis revealed that PD-1/CTLA-4 inhibitor combinations have a limited role in the treatment of patients with advanced NSCLC and low or high PD-L1 levels, whereas they might be effective and tolerable treatment options in certain PD-L1–negative populations [29]. Additionally, PD-L1 expression does not appear to be a correlate of immunotherapy benefit in SCLC [8,12,20].

A meta-analysis revealed that both PD-1 and PD-L1 inhibitors provided modest advantages over anti–CTLA-4 drugs in terms of efficacy [30]. A similar conclusion was drawn in our study. CTLA-4 inhibitors (tremelimumab or ipilimumab) plus standard chemotherapy did not produce significant benefits regarding OS or PFS. It is unclear why CTLA-4 inhibitors did not confer additional benefits over standard chemotherapy alone. One rationale is that without equivalent T-cell activation in the tumor microenvironment,

Table 2
Surface under the cumulative ranking curve values for overall survival (OS), progression-free survival (PFS), and treatment-related adverse events (TRAEs).

Outcome	Treatment	SUCRA
OS	CHE	0.048
	SER + EP	0.869
	IPI + EP	0.163
	ADE + EP	0.675
	DUR + TRE + EP	0.407
	DUR + EP	0.604
	NIV + EP	0.801
	ATE + EP	0.571
	PEM + EP	0.496
	IPI + TP	0.367
PFS	CHE	0.044
	SER + EP	0.990
	IPI + EP	0.328
	ADE + EP	0.761
	DUR + TRE + EP	0.355
	DUR + EP	0.467
	NIV + EP	0.758
	ATE + EP	0.534
	PEM + EP	0.547
	IPI + TP	0.215
TRAEs	CHE	0.800
	SER + EP	0.447
	IPI + EP	0.336
	ADE + EP	0.683
	DUR + TRE + EP	0.289
	DUR + EP	0.798
	NIV + EP	0.122
	ATE + EP	0.715
	PEM + EP	0.561
	IPI + TP	0.249

CTLA-4 inhibitors, which promote peripheral T-cell activation, may not establish a sufficiently potent antitumor response in ES-SCLC. Furthermore, concurrent chemotherapy might worsen immunosuppression, which might be related to a limited level of T-cell activation and proliferation [8,19].

The combination of ICIs and standard chemotherapy had similar overall safety profiles as standard chemotherapy, including a decreased incidence of additional serious side effects, such as neutropenia, anemia, nausea, and diarrhea.

To date, three traditional meta-analyses have compared the effectiveness and safety of ICIs (including pembrolizumab, durvalumab, ipilimumab, and atezolizumab) plus standard chemotherapy with standard chemotherapy alone in patients with ES-SCLC [30–32]. Additionally, only one NMA has evaluated the differences in the efficacy and safety profiles of durvalumab, ipilimumab, and atezolizumab in patients with untreated ES-SCLC [25]. In contrast to previous studies investigating first-line treatments for patients with ES-SCLC, our NMA assessed all currently accessible ICIs (serplulimab, ipilimumab, adebrelimab, durvalumab, atezolizumab, nivolumab, pembrolizumab, and tremelimumab) as part of regimens used to treat ES-SCLC. In addition, this is the first study to evaluate outcomes by race. The effect of ICI therapy as a maintenance treatment for ES-SCLC is controversial. Our study included only patients who received first-line treatment, and no follow-up ICI maintenance therapy was permitted.

With continued studies of ICIs, numerous randomized studies have confirmed the advantages of ICICs plus chemotherapy as first-line treatments for ES-SCLC. There is a need to establish the best chemoimmunotherapy regimen. From our study, serplulimab plus carboplatin–etoposide might be the optimal treatment, especially in Asian populations. However, researchers must perform head-to-head RCTs (serplulimab versus other ICIs) to provide solid evidence to support the selection of the best chemoimmunotherapy option.

Limitations existed in our NMA study. First, the control chemotherapy regimens differed and included both platinum–etoposide (n = 8) and paclitaxel–carboplatin (n = 1). The effectiveness and safety of platinum–etoposide have proven to be better than those of other chemotherapies in patients with ES-SCLC. This combination might provide various synergistic effects when combined with different chemotherapies. Second, some drugs were not approved by all regulatory agencies. Third, second- or third-treatments were received by some patients with tumor progression, which influenced survival. Unfortunately, we could not collect these data from individual clinical studies. In addition, some comparisons in ICIs plus standard chemotherapy were indirect. Consequently, additional direct studies are needed.

5. Conclusions

In summary, our NMA revealed that serplulimab plus carboplatin–etoposide provided better OS and PFS than other regimens in patients with ES-SCLC. However, this regimen was not associated with lower rates of TRAEs. Serplulimab plus carboplatin–etoposide appears to be superior first line treatment choices for patients with ES-SCLC, and were preferentially recommended to Asian patients.

Our findings add to current evidence for the selection of first-line treatments for patients with ES-SCLC. However, large-scale and head-to-head RCTs are needed for patients with ES-SCLC because of the limitations of NMA.

Author contribution statement

Jincheng Du: Conceived and designed the experiments; Wrote the paper.
Xinyu Wang: Performed the experiments.
Xinyuan Shan; Muyao Li: Performed the experiments; Analyzed and interpreted the data.
Liwen Fan: Contributed reagents, materials, analysis tools or data.
Linlin Liu: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

The authors do not have permission to share data.

Declaration of competing interest

All of the authors declare that they have no competing interests or conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e14794.

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