Original Article

Efficacy and safety of first-line immunotherapy-based regimens for patients with extensive-stage small cell lung cancer: a systematic review and network meta-analysis

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Background: Combination regimens of immunotherapy plus chemotherapy have been approved as the first-line and standard of care for extensive-stage small cell lung cancer (ES-SCLC). Novel regimens are continuously being explored, with the ETER701 study being the representative randomized controlled trial (RCT). ETER701 study has assessed the efficacy and safety of chemotherapy with or without anlotinib (multi-target angiogenesis inhibitor) + benmelstobart (programmed cell death ligand 1 inhibitor) (Anl/Ben/CT). There is no evidence-based medicine available proving that Anl/Ben/CT is the optimal regimen due to the lack of direct or indirect comparisons among varying immunotherapy-based regimens. In this study, we aimed to identify the optimal regimen to assist in clinical decision-making.

Methods: The eligible RCTs were identified by searching PubMed, Embase, Cochrane Library databases, and major international conferences. Then, the network meta-analysis was analyzed to compare the efficacy and safety among 15 first-line regimens in ES-SCLC. The Cochrane Risk of Bias Tool was used to assess the risk of bias in included studies.

Results: A total of 12 immunotherapy-related RCTs covering 15 interventions and 6,178 patients with ES-SCLC were included. Overall, most RCTs exhibited a low risk of bias across multiple domains. The results indicated that most immunotherapy-based regimens could significantly prolong progression-free survival (PFS) compared with chemotherapy alone, especially Anl/Ben/CT [hazard ratio (HR) 0.32, 95% confidence interval (CI): 0.25–0.40]. Similar results were observed regarding overall survival (OS), that is, most immunotherapy-related regimens dramatically reduced the risk of death in ES-SCLC, with Anl/Ben/CT being the most prominent (HR 0.61, 95% CI: 0.47–0.80). The Bayesian ranking probabilities showed that Anl/Ben/CT ranked first and serplulimab plus chemotherapy ranked second in both PFS and OS among 15 regimens. Regarding safety, Anl/Ben/CT ranked 3rd, and serplulimab plus chemotherapy ranked 7th.

Conclusions: Adding anlotinib and benmelstobart to chemotherapy significantly improved PFS and OS compared with chemotherapy alone or chemotherapy plus immunotherapy, with an acceptable safety profile in patients with ES-SCLC. In conclusion, Anl/Ben/CT could be a new, preferable first-line treatment option but further clinical studies are needed to validate its efficacy and safety.

Keywords: Small cell lung cancer (SCLC); immunotherapy; anlotinib; benmelstobart; network meta-analysis

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Introduction

Small cell lung cancer (SCLC) is characterized as the most aggressive form of lung cancer, accounting for approximately 15% of all cases within the lung cancer spectrum (1). The epidemiologic data indicates that nearly two-thirds of patients with SCLC are diagnosed at an extensive stage (ES) (2). SCLC is characterized by a higher sensitivity to chemotherapy, thereby making chemotherapy with a platinum-based agent plus etoposide the standard first-line treatment for ES-SCLC over the past few decades (3,4). Nevertheless, the median survival of patients with ES-SCLC treated with standard first-line chemotherapy is only approximately 10 months, with a 5-year survival rate of only 7% (5).

Over recent years, immunotherapy, represented by targeting programmed cell death (ligand) 1 [PD-(L)1] and cytotoxic T lymphocyte-associated antigen-4, has made landmark progress in the area of cancer therapy (6,7). Multiple randomized controlled trials (RCTs) regarding combination regimens of immunotherapy plus chemotherapy versus chemotherapy alone have been widely explored in the first-line treatment of ES-SCLC (8,9). Phase III trial of IMpower133 showed that the addition of atezolizumab to chemotherapy resulted in significantly longer median overall survival (OS) (12.3 months *vs.* 10.3 months) than chemotherapy alone in ES-SCLC (3). Results from RCT of CASPIAN indicated that first-line durvalumab plus platinum-etoposide significantly prolonged OS compared to treatment with platinum-etoposide alone (10). Other representative RCTs include RATIONALE-312, ASTRUM-005, and CAPSTONE-1, etc. (11-13). Based on these RCT results, multiple combination regimens of distinct immune checkpoint inhibitors plus chemotherapy have been globally authorized for first-line treatment of ES-SCLC (14). Nevertheless, the combination of immunotherapy and chemotherapy treatment also inevitably yielded resistance, and improving long-term survival remains an unmet need. The result of the ETER701 study from the 2023 World Conference on Lung Cancer (WCLC), a phase III RCT comparing the efficacy and safety of the regimen with adding anlotinib to benmelstobart & chemotherapy (Anl/Ben/CT) versus chemotherapy alone, demonstrated that the four-agent regimen was dramatically superior to chemotherapy alone in terms of survival prolongation (15). It is noteworthy that the Anl/Ben/CT regimen demonstrates the most significant prolongation of survival compared to other contemporary first-line treatment modalities (15,16). The above trials consistently indicate that immunotherapy-based combination treatments have superior anti-tumor effects compared to chemotherapy alone, with a higher but acceptable incidence of adverse events Despite the promising results, a direct head-to-head comparison between the Anl/Ben/CT regimen and immunotherapy plus chemotherapy treatments remains elusive. This lack of direct evidence makes it difficult to conclusively determine if Anl/Ben/CT offers a distinct advantage over the immunotherapy combination chemotherapy approaches. Consequently, further research is warranted to clarify the relative efficacy of these treatment strategies.

In this paper, a network meta-analysis (NMA) incorporating the most comprehensive RCTs was conducted to evaluate the efficacy and safety of 15 varying regimens in ES-SCLC, with the aim of identifying the optimal regimen to assist in clinical decision-making. We present this article in accordance with the PRISMA reporting checklist (available at https://tlcr.amegroups.com/article/

Highlight box

Key findings

- Our study demonstrated for the first time that adding anlotinib and benmelstobart to chemotherapy significantly improved progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone or chemotherapy plus immunotherapy, with an acceptable safety profile in patients with extensive-stage small cell lung cancer (ES-SCLC).

What is known and what is new?

- Immunotherapy plus chemotherapy is now the standard first-line treatment for ES-SCLC. ETER701 study has assessed the efficacy and safety of chemotherapy supplemented with anlotinib and benmelstobart (Anl/Ben/CT), yet there has been a gap in evidence-based medicine that definitively positions Anl/Ben/CT as the superior regimen due to the absence of comparative studies among diverse immunotherapy-based treatments.
- Our study introduces a network meta-analysis that synthesizes the most comprehensive randomized controlled trials (RCTs) to compare the efficacy and safety of 15 distinct regimens for ES-SCLC. It is proved that Anl/Ben/CT could be a new and clinically preferable first-line treatment option for ES-SCLC.

What is the implication, and what should change now?

- The findings underscore the importance of considering the Anl/Ben/CT regimen in clinical practice for the treatment of ES-SCLC patients. The demonstrated superiority of this regimen in enhancing survival outcomes without compromising safety underscores the need for a reevaluation of current treatment protocols.

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Methods

Search strategy and selection criteria

The review protocol was prospectively registered in PROSPERO (CRD42023481850). We systematically searched PubMed, Embase, Cochrane Library, and major international conferences to retrieve relevant RCTs published up to 28 December 2023. The detailed search strategies are described in Table S1. The inclusion criteria and exclusion criteria were as follows:

The inclusion criteria:

(I) Studies were RCTs in phase II or phase III.
(II) Eligible patients were newly diagnosed with treatment-naive histologically or cytologically documented ES-SCLC.
(III) RCTs that used immunotherapy-based combination treatment as first-line treatment settings.
(IV) Any of the following outcomes: progression-free survival (PFS), OS, objective response rate (ORR), and grade 3 or higher adverse events, were available.

The exclusion criteria:

(I) Trials in which the treatment was administered as adjuvant or neoadjuvant therapy.
(II) RCTs that were based on overlapping patients.

Data extraction and quality assessment

Data extraction and quality assessment were independently conducted by two investigators (W.G.Z. and X.Y.Z.). The main information extracted from the original research included study ID, therapy regimens, and outcomes [e.g., PFS, OS, ORR, and grade 3 or higher adverse events (≥3 AEs)]. In this NMA, the Cochrane Risk of Bias Tool was utilized to assess the risk of bias in individual studies in Review Manager 5.3 software. The assessment included seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

Sensitivity analysis

Sensitivity analysis was performed by excluding phase II RCTs.

Statistical analysis

The NMA was performed using a Markov Chain Monte Carlo simulation technique within the GEMTC and the JAGS package in R software (17). There were 150,000 sample iterations generated with 100,000 burn-ins and a thinning interval of 1 for PFS and OS. The thinning interval was increased to 10 to minimize auto-correlation for ORR and ≥3 AEs. Fixed-effects consistency model was used in this NMA to guarantee the model's robustness. Deviance information criteria (DIC) were calculated to compare and evaluate the fixed and random effect models (18). The convergence adequacy (reaching a stable equilibrium distribution) was tested by visually inspecting the trace plots and estimating the values of the Brooks–Gelman–Rubin statistic (19). The ranking of each regimen was compared based on the surface under the cumulative ranking curve (SUCRA) (20). In this study, it was considered a statistical significance if the 95% confidence interval did not cross 1. All statistical analyses were conducted by R software (version 4.1.3) and Stata software (version 16.0).

Results

Clinical traits

As shown in *Figure 1*, the PubMed, Embase, Cochrane Library, and major international conferences were systematically and comprehensively retrieved. After a rigorous screening with inclusion and exclusion criteria, a final 12 RCTs were included in this NMA (11-13,15,21-28). The regimens included chemotherapy (CT), Anl/Ben/CT, serplulimab plus chemotherapy (Ser/CT), tislelizumab plus CT (Tis/CT), atezolizumab plus CT (Ate/CT), nivolumab plus CT (Niv/CT), adebrelimab plus CT (Ade/CT), toripalimab plus CT (Tor/CT), durvalumab plus CT (Dur/CT), pembrolizumab plus CT (Pem/CT), Ipi plus CT (Ipi/CT), concurrent Ipi plus CT (Con-Ipi/CT), phased Ipi plus CT (Pha-Ipi/CT), durvalumab plus tremelimumab plus CT (Dur/Tre/CT), and Niv plus Ipi plus CT (Niv/Ipi/CT). The characteristics of enrolled RCTs are described in *Table 1*. The risk of bias evaluation is shown in Figure S1.

NMA

PFS and OS

As depicted in *Figure 2A*, the network plots of PFS and OS were shown. All 12 RCTs included were available both in

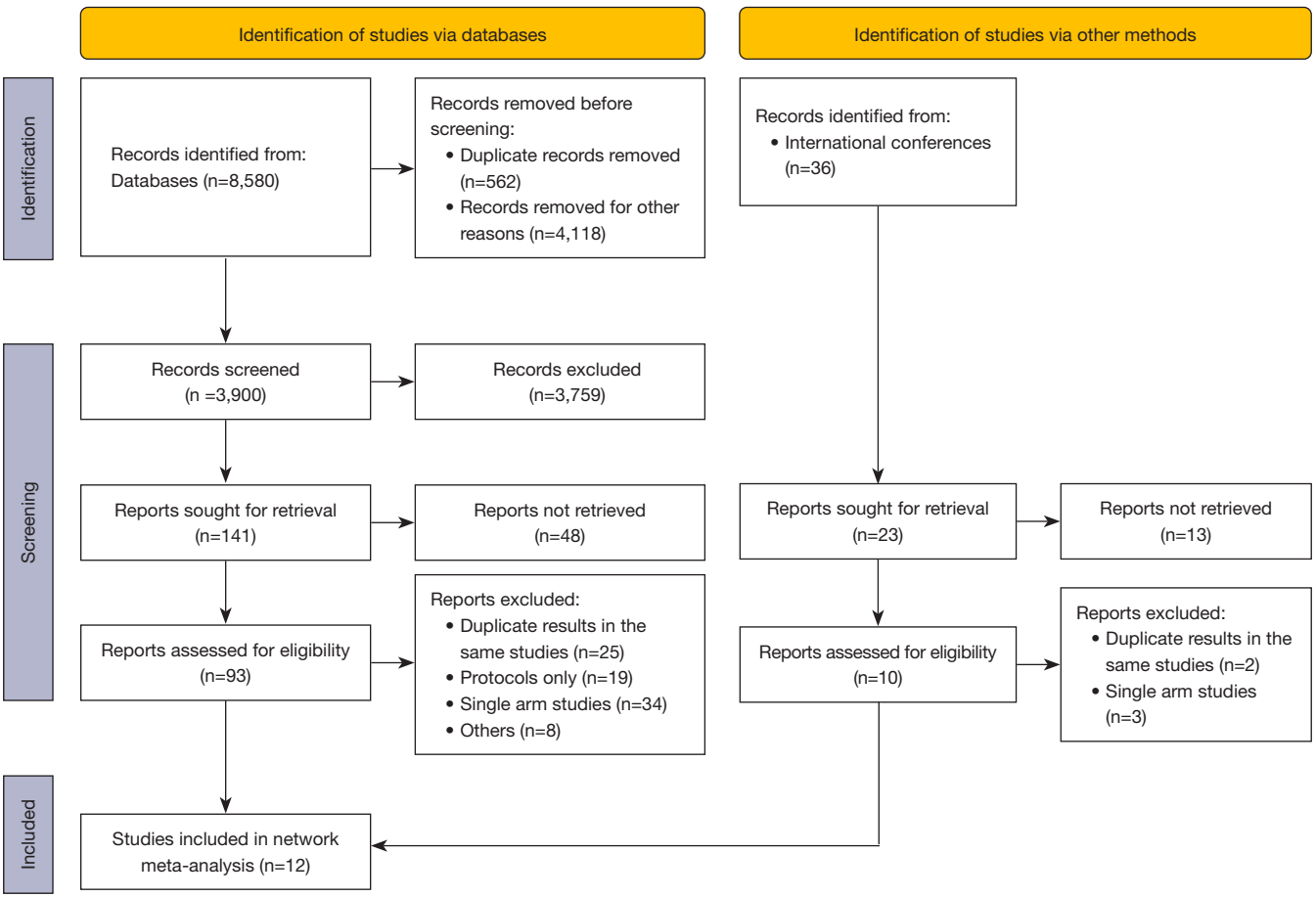


Figure 1 Flow diagram of literature retrieval and selection.

PFS and OS analyses involving 6,178 ES-SCLC individuals.

Regarding PFS, the NMA result showed that most immunotherapy-based combination regimens significantly reduced the risk of cancer progression versus chemotherapy alone [Anl/Ben/CT, Ser/CT, Tis/CT, Niv/CT, Tor/CT, Ade/CT, Niv/Ipi/CT, Pem/CT, Ate/CT, Dur/CT, Ipi/CT *vs.* CT: all hazard ratio (HRs) <1 and 95% CIs did not cross 1], with the exception of Pha-Ipi/CT (HR 0.64, 95% CI: 0.40–1.02), Con-Ipi/CT (HR 0.75, 95% CI: 0.48–1.18) and Dur/Tre/CT (HR 0.84, 95% CI: 0.70–1.01). Among immunotherapy-based regimens, significant prolongation of PFS was observed for ES-SCLC with Anl/Ben/CT compared to the others (all HR <1 and 95% CIs did not cross 1) (*Figure 2B*). Besides, Ser/CT could be a superior regimen following Anl/Ben/CT (Ser/CT *vs.* the other regimens except for Anl/Ben/CT: all HRs <1 and most 95% CIs did not cross 1). A pronounced PFS prolongation was also observed in both Tis/CT (HR 0.74, 95% CI: 0.58–0.95) and Niv/CT (HR 0.78, 95% CI: 0.64–0.96) when compared with Ipi/CT. Notably, Tis/CT was superior to the three-drug regimen of Dur/Tre/CT (HR 0.75, 95% CI: 0.57–0.99).

Regarding OS, similar results to PFS were obtained, that is, most immunotherapy-based regimens were superior in comparison with CT alone (all HR <1 and most 95% CI did not cross 1) (*Figure 2B*). Among immunotherapy-based regimens, Anl/Ben/CT exhibited superiority over the others in extending OS (all HR <1), especially relative to Niv/Ipi/CT (HR 0.68, 95% CI: 0.49–0.95) and Ipi/CT (HR 0.65, 95% CI: 0.48–0.88) (*Figure 2B*). Similar to its efficacy in PFS prolongation, Ser/CT was inferior only to Anl/Ben/CT in prolonging OS among all immunotherapy-based regimens. With specific regard, Ser/CT was demonstrated to be significantly superior to Niv/Ipi/CT (HR 0.7, 95% CI: 0.51–0.97) and Ipi/CT (HR 0.67, 95% CI: 0.50–0.90). Additionally, Ade/CT was observed to be more favorable than Ipi/CT (HR 0.77, 95% CI: 0.59–1.0) (*Figure 2B*).

Table 1 Baseline characteristics of trials included in the network meta-analysis of patients with extensive-stage small cell lung cancer

Trial	Year	Phase	Clinical trial number	Sample size	Median age (years)	Sex		Treatment strategy
						Female	Male	
RATIONALE-312	2023	III	NCT0400571					
Intervention arm				227	63	41	186	Tis 200 mg + Car (AUC5)/Cis 75 mg/m^2 + Eto 100 mg/m^2/3W (4C)-Tis 200 mg/3W maintenance
Control arm				230	62	44	186	Car (AUC5)/Cis 75 mg/m^2 + Eto 100 mg/m^2/3W (4C)
EXTENTORCH	2023	III	NCT04012606					
Intervention arm				223	62	40	183	Tor 240 mg + Eto + Cis/Car/3W (4-6C) + Tor 240 mg maintenance
Control arm				219	63	36	183	Eto + Cis/Car/3W (4-6C)
ETER701	2023	III	NA					
Intervention arm				246	62	37	209	Ben + Anl + Eto + Cis/Car/3W (4C)-Ben + Anl maintenance
Control arm				247	63	40	207	Eto + Cis/Car/3W (4C)
CAPSTONE-1	2022	III	NCT03711305					
Intervention arm				230	62	46	184	Ade 20 mg/kg + Car (AUC5) + Eto (100 mg/m^2) (4-6C)-Ade 20 mg/kg maintenance
Control arm				232	62	44	188	Car (AUC5) + Eto 100 mg/m^2 (4-6C)
ASTRUM-005	2022	III	NCT04063163					
Intervention arm				389	63	72	317	Ser 4.5 mg/kg + Car (AUC5) + Eto 100 mg/m^2/3W (4C)-Ser 4.5 mg/kg maintenance
Control arm				196	62	32	164	Car (AUC5) + Eto 100 mg/m^2/3W (4C)
CheckMate-451	2021	III	NCT02538666					
Arm 1				279	64	99	180	CT (≤4C)-Niv 1 mg/kg + Ipi 3 mg/kg/3W-Niv 240 mg/2W maintenance
Arm 2				280	65	103	177	CT (≤4C)-Niv 240 mg/2W maintenance
Arm 3				275	64	100	175	CT (≤4C)
KEYNOTE-604	2020	III	NCT03066778					
Intervention arm				228	64	76	152	Car (AUC5)/Cis 75 mg/m^2 + Eto 100 mg/m^2/3W (4C)-Pem 200 mg maintenance
Control arm				225	65	83	142	Car (AUC5)/Cis 75 mg/m^2 + Eto 100 mg/m^2/3W (4C)
ECOG-ACRIN EA5161	2020	II	NCT03382561					
Intervention arm				80	NA	NA		Niv 360 mg + Eto + Cis/Car/3W (4C)-Niv 240 mg/2W
Control arm				80	NA	NA		Eto + Cis/Car/3W (4C)
CASPIAN	2019	III	NCT03043872					
Arm 1				268	63	66	202	Dur 1,500 mg + Tre 75 mg + Car (AUC5-6)/Cis 75-80 mg/m^2 + Eto 80–100 mg/m^2/3W (4C)-Dur 1,500 mg maintenance
Arm 2				268	62	78	190	Dur 1,500 mg + Car (AUC5-6)/Cis 75–80 mg/m^2 + Eto 80–100 mg/m^2/3W (4C)-Dur 1,500 mg maintenance
Arm 3				269	63	85	184	Car (AUC5-6)/Cis 75–80 mg/m^2 + Eto 80–100 mg/m^2/3W (4C)

Table 1 *(continued)*

Table 1 *(continued)*

Trial	Year	Phase	Clinical trial number	Sample size	Median age (years)	Sex		Treatment strategy
						Female	Male	
Impower133	2018	III	NCT02763579					
Intervention arm				201	64	72	129	Ate 1,200 mg + Car (AUC5) + Eto 100 mg/m^2/3W (4C)-Ate 1,200 mg maintenance
Control arm				202	64	70	132	Car (AUC5) + Eto 100 mg/m^2/3W (4C)
CA184-156	2016	III	NCT01450761					
Intervention arm				478	62	161	317	Ipi 10 mg/kg + Car (AUC5)/Cis 75 mg/m^2 + Eto 100 mg/m^2/3W (4C)-Ipi 10 mg/kg/12W maintenance
Control arm				476	63	150	326	Car (AUC5)/Cis 75 mg/m^2 + Eto 100 mg/m^2/3W (4C)
CA184-041	2013	II	NCT00527735					
Arm 1				43	57	10	33	Concurrent-Ipi 10 mg/kg + Pac 175 mg/m^2 + Car (AUC6) (4-6C)
Arm 2				42	59	10	32	Phased-Ipi 10 mg/kg + Pac 175 mg/m^2 + Car (AUC6) (4-6C)
Arm 3				45	58	12	33	Pac 175 mg/m^2 + Car (AUC6) (4-6C)

Ade, adebrelimab; Anl, anlotinib; Ate, atezolizumab; Ben, benmelstobart; Car, carboplatin; Cis, cisplatin; CT, chemotherapy; Dur, durvalumab; Eto, etoposide; Ipi, ipilimumab; NA, not available; Niv, nivolumab; Pac, paclitaxel; Pem, pembrolizumab; Ser, serplulimab; Tis, tislelizumab; Tor, toripalimab; Tre, tremelimumab.

ORR

As shown in *Figure 3A*, ORR was available in 11 RCTs, involving 14 regimens and 5,691 ES-SCLC patients. When compared with CT, most immunotherapy-based treatments can provide patients with a higher ORR [Anl/Ben/CT, Ser/CT, Niv/CT, Pem/CT, Dur/CT *vs.* CT: all odds ratio (ORs) >1 and 95% CIs did not cross 1] (*Figure 3B*). Among all immunotherapy-based regimens, Anl/Ben/CT exhibited higher ORR versus the other regimens, e.g., in comparison with Ade/CT (OR 1.76, 95% CI: 1–3.14), Con-Ipi/CT (OR 2.61, 95% CI: 1.02–6.76), Ate/CT (OR 2.6, 95% CI: 1.46–4.66), Dur/Tre/CT (OR 2.16, 95% CI: 1.26–3.71), and Ipi/CT (OR 2.18, 95% CI: 1.33–3.59) (*Figure 3B*). Significantly higher ORR was observed for Ser/CT when compared with Ate/CT (OR 2.04, 95% CI: 1.15–3.59), and Ipi/CT (OR 1.71, 95% CI: 1.06–2.74). Additionally, Niv/CT showed an increase in ORR in ES-SCLC versus Con-Ipi/CT (OR 2.62, 95% CI: 1–6.93), Ate/CT (OR 2.6, 95% CI: 1.41–4.84), Dur/Tre/CT (OR 2.16, 95% CI: 1.21–3.86), and Ipi/CT (OR 2.18, 95% CI: 1.29–3.74) (*Figure 3B*).

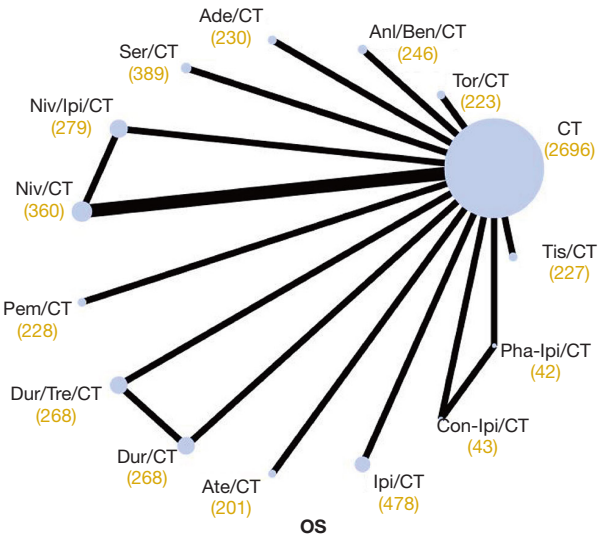
≥3 AEs

All the 12 RCTs included were available for the NMA of ≥3 AEs (*Figure 3C*). Compared with CT alone, ≥3 AEs were higher for 5 immunotherapy-based regimens, including Anl/Ben/CT (OR 2.03, 95% CI: 1.11–3.86), Niv/CT (OR 1.73, 95% CI: 1.12–2.7), Pha-Ipi/CT (OR 2.43, 95% CI: 1–6.07), Niv/Ipi/CT (OR 13.52, 95% CI: 8.66–21.63), and Dur/Tre/CT (OR 1.51, 95% CI: 1.04–2.2) (*Figure 3B*). Of importance, Niv/Ipi/CT resulted in significantly higher ≥3 AEs than other immunotherapy-based regimens (all OR >1 and 95% CIs did not cross 1) (*Figure 3B*). Besides, regarding Anl/Ben/CT, it did not significantly increase the incidence of ≥3 AEs compared with other immunotherapy-based regimens except Tis/CT (OR 2.36, 95% CI: 1.01–5.69) and Dur/CT (OR 2.08, 95% CI: 1.03–4.33) (*Figure 3B*). For Ser/CT, no significant differences in ≥3 AEs were identified, either compared with the other immunotherapy-based regimens or with CT (*Figure 3B*).

Rank probabilities

As shown in *Figure 4A* and Figure S2, it was showed the Bayesian rank probabilities of all comparable therapies in terms of PFS, OS, ORR, and ≥3 AEs. Significantly, the probability of Anl/Ben/CT ranking first was the highest among all regimens, regardless of PFS (98.9%), OS (41.4%), or ORR (23.5%) (*Figure 4A*). In contrast, CT had the highest probability of ranking last in both PFS (82.1%) and OS (32.1%) (Figure S3). With respect to Ser/CT, the probability of PFS (78.6%) and OS (27.7%) being ranked second is the highest (*Figure 4A*). Regarding ≥3 AEs, ranking first and second with the highest probability were Niv/Ipi/CT (99.9%) and Pha-Ipi/CT (47.3%), respectively.

A



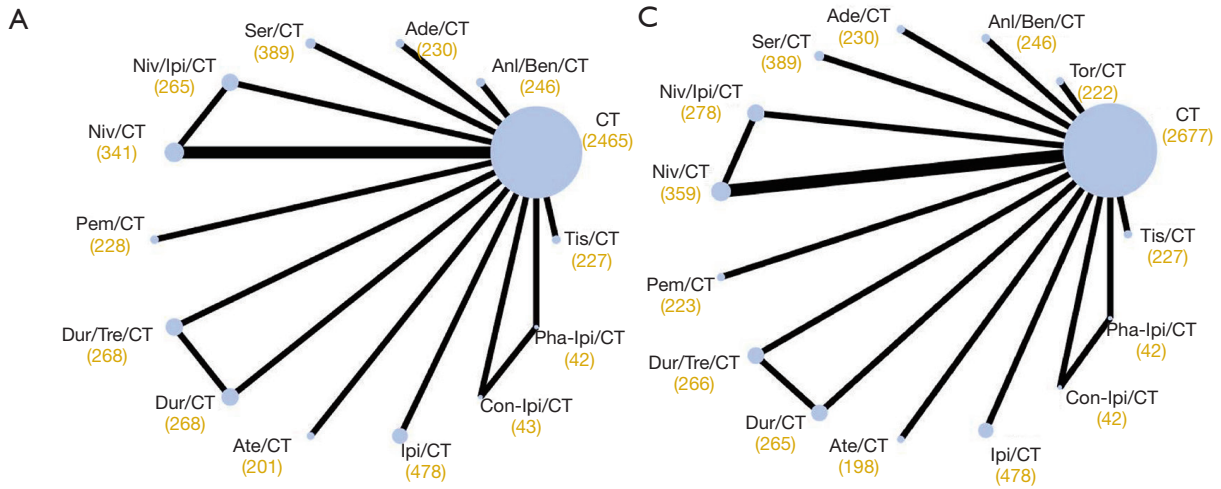
B

OS

PFS														
Anl/Ben/CT	0.97 (0.67, 1.41)	0.81 (0.58, 1.14)	0.76 (0.55, 1.05)	0.81 (0.46, 1.42)	0.76 (0.54, 1.08)	0.85 (0.6, 1.2)	0.68 (0.49, 0.95)	0.64 (0.37, 1.11)	0.76 (0.54, 1.08)	0.8 (0.56, 1.14)	0.81 (0.58, 1.13)	0.74 (0.53, 1.04)	0.65 (0.48, 0.88)	0.61 (0.47, 0.8)
0.67 (0.49, 0.92)	Ser/CT	0.84 (0.6, 1.17)	0.79 (0.58, 1.07)	0.84 (0.48, 1.46)	0.79 (0.57, 1.1)	0.87 (0.62, 1.23)	0.7 (0.51, 0.97)	0.66 (0.38, 1.14)	0.79 (0.56, 1.1)	0.83 (0.59, 1.17)	0.84 (0.61, 1.16)	0.77 (0.56, 1.06)	0.67 (0.5, 0.9)	0.63 (0.49, 0.81)
0.51 (0.37, 0.69)	0.76 (0.56, 1.03)	Tis/CT	0.94 (0.72, 1.23)	1 (0.59, 1.7)	0.94 (0.7, 1.26)	1.04 (0.77, 1.41)	0.83 (0.63, 1.11)	0.79 (0.47, 1.33)	0.94 (0.7, 1.26)	0.99 (0.73, 1.34)	1 (0.76, 1.32)	0.91 (0.69, 1.21)	0.8 (0.62, 1.03)	0.75 (0.61, 0.92)
0.48 (0.36, 0.64)	0.72 (0.55, 0.95)	0.95 (0.72, 1.24)	Niv/CT	1.07 (0.63, 1.8)	1 (0.77, 1.32)	1.11 (0.84, 1.47)	0.89 (0.72, 1.09)	0.84 (0.51, 1.41)	1 (0.76, 1.32)	1.05 (0.79, 1.41)	1.07 (0.82, 1.38)	0.98 (0.75, 1.26)	0.85 (0.68, 1.07)	0.8 (0.67, 0.95)
0.5 (0.3, 0.84)	0.75 (0.45, 1.26)	0.98 (0.59, 1.65)	1.04 (0.63, 1.7)	Pha-Ipi/CT	0.94 (0.55, 1.6)	1.04 (0.61, 1.79)	0.83 (0.49, 1.41)	0.79 (0.41, 1.53)	0.94 (0.55, 1.6)	0.99 (0.57, 1.7)	1 (0.59, 1.7)	0.92 (0.54, 1.55)	0.8 (0.48, 1.34)	0.75 (0.46, 1.23)
0.48 (0.35, 0.65)	0.72 (0.53, 0.98)	0.94 (0.7, 1.27)	1 (0.76, 1.3)	0.96 (0.57, 1.6)	Tor/CT	1.11 (0.82, 1.5)	0.89 (0.66, 1.18)	0.84 (0.5, 1.41)	1 (0.74, 1.34)	1.05 (0.77, 1.43)	1.06 (0.8, 1.41)	0.97 (0.73, 1.29)	0.85 (0.66, 1.1)	0.8 (0.65, 0.98)
0.48 (0.35, 0.65)	0.72 (0.53, 0.97)	0.94 (0.69, 1.27)	0.99 (0.76, 1.3)	0.96 (0.57, 1.6)	0.99 (0.74, 1.35)	Ade/CT	0.8 (0.6, 1.07)	0.76 (0.45, 1.28)	0.9 (0.66, 1.22)	0.95 (0.69, 1.3)	0.96 (0.72, 1.29)	0.88 (0.66, 1.18)	0.77 (0.59, 1)	0.72 (0.58, 0.9)
0.45 (0.33, 0.6)	0.67 (0.5, 0.89)	0.88 (0.66, 1.16)	0.93 (0.77, 1.11)	0.89 (0.54, 1.47)	0.93 (0.7, 1.23)	0.93 (0.71, 1.24)	Niv/Ipi/CT	0.95 (0.56, 1.59)	1.13 (0.84, 1.5)	1.18 (0.88, 1.6)	1.2 (0.91, 1.58)	1.1 (0.83, 1.45)	0.96 (0.75, 1.23)	0.9 (0.74, 1.1)
0.43 (0.26, 0.71)	0.64 (0.39, 1.06)	0.84 (0.51, 1.39)	0.89 (0.55, 1.44)	0.85 (0.46, 1.6)	0.89 (0.54, 1.47)	0.89 (0.54, 1.48)	0.96 (0.59, 1.56)	Con-Ipi/CT	1.19 (0.7, 2.01)	1.25 (0.73, 2.13)	1.27 (0.75, 2.12)	1.16 (0.69, 1.95)	1.01 (0.61, 1.67)	0.95 (0.59, 1.54)
0.43 (0.32, 0.58)	0.64 (0.48, 0.86)	0.84 (0.63, 1.12)	0.89 (0.69, 1.15)	0.85 (0.51, 1.42)	0.89 (0.66, 1.19)	0.89 (0.67, 1.2)	0.96 (0.73, 1.25)	1 (0.61, 1.64)	Pem/CT	1.05 (0.77, 1.44)	1.07 (0.8, 1.42)	0.98 (0.73, 1.3)	0.85 (0.66, 1.1)	0.8 (0.65, 0.99)
0.42 (0.31, 0.56)	0.62 (0.46, 0.84)	0.82 (0.61, 1.1)	0.86 (0.67, 1.12)	0.83 (0.5, 1.38)	0.87 (0.65, 1.16)	0.87 (0.65, 1.17)	0.93 (0.71, 1.22)	0.97 (0.59, 1.6)	0.97 (0.73, 1.3)	Ate/CT	1.01 (0.75, 1.37)	0.93 (0.69, 1.25)	0.81 (0.61, 1.06)	0.76 (0.6, 0.96)
0.4 (0.3, 0.54)	0.6 (0.45, 0.8)	0.79 (0.59, 1.05)	0.83 (0.65, 1.07)	0.8 (0.48, 1.32)	0.83 (0.63, 1.11)	0.84 (0.63, 1.11)	0.9 (0.69, 1.16)	0.94 (0.57, 1.53)	0.94 (0.71, 1.23)	0.96 (0.73, 1.27)	Dur/CT	0.91 (0.75, 1.12)	0.8 (0.63, 1.02)	0.75 (0.62, 0.91)
0.38 (0.28, 0.51)	0.57 (0.43, 0.76)	0.75 (0.57, 0.99)	0.79 (0.62, 1.01)	0.76 (0.46, 1.26)	0.79 (0.6, 1.05)	0.8 (0.6, 1.06)	0.85 (0.66, 1.1)	0.89 (0.55, 1.46)	0.89 (0.68, 1.17)	0.92 (0.7, 1.21)	0.95 (0.79, 1.15)	Dur/Tre/CT	0.87 (0.68, 1.11)	0.82 (0.68, 0.99)
0.38 (0.29, 0.49)	0.56 (0.44, 0.73)	0.74 (0.58, 0.95)	0.78 (0.64, 0.96)	0.75 (0.46, 1.22)	0.78 (0.61, 1.01)	0.79 (0.61, 1.01)	0.84 (0.68, 1.05)	0.88 (0.55, 1.42)	0.88 (0.7, 1.12)	0.91 (0.71, 1.15)	0.94 (0.75, 1.18)	0.99 (0.79, 1.24)	Ipi/CT	0.94 (0.81, 1.09)
0.32 (0.25, 0.4)	0.48 (0.39, 0.6)	0.63 (0.51, 0.78)	0.67 (0.57, 0.78)	0.64 (0.4, 1.02)	0.67 (0.54, 0.82)	0.67 (0.54, 0.83)	0.72 (0.6, 0.86)	0.75 (0.48, 1.18)	0.75 (0.61, 0.92)	0.77 (0.63, 0.94)	0.8 (0.66, 0.96)	0.84 (0.7, 1.01)	0.85 (0.75, 0.97)	CT

Figure 2 Network meta-analysis of comparisons of PFS and OS in patients with extensive-stage small cell lung cancer. (A) Network diagrams of comparisons on PFS and OS in patients with extensive-stage small cell lung cancer. Each circular node represents a type of treatment. Each line represents a type of head-to-head comparison. The size of the node and the thickness of the line are weighted according to the number of studies evaluating each treatment and direct comparison, respectively. The total number of patients receiving a treatment is shown in brackets. (B) Pooled HR (95% CI) for OS (upper triangle) and PFS (lower triangle). Data in each cell are HR (95% CI) for the comparison of row-defining treatment versus lower column-defining treatment. HR <1 favor row-defining treatment. Significant results are highlighted in red. PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Furthermore, the ranking of each regimen was evaluated based on the SUCRA. The results are generally consistent with the NMAs calculated by HRs. Anl/Ben/CT ranked first in both PFS, OS, and ORR among 15 regimens (*Figure 4B*). Ser/CT ranked second in PFS and OS, and Niv/CT ranked second in ORR. Regarding safety, ranked first and second for ≥3 AEs were Niv/Ipi/CT and Pha-Ipi/CT, respectively.



B

ORR

≥3 AEs	Anl/Ben/CT	Ser/CT	Tis/CT	Niv/CT	Pha-Ipi/CT	Tor/CT	Ade/CT	Niv/Ipi/CT	Con-Ipi/CT	Pem/CT	Ate/CT	Dur/CT	Dur/Tre/CT	Ipi/CT	CT
Anl/Ben/CT	1.28 (0.72, 2.28)	1.63 (0.92, 2.89)	1 (0.53, 1.86)	0.98 (0.36, 2.6)		1.76 (1, 3.14)	1.18 (0.56, 2.5)	2.61 (1.02, 6.76)	1.46 (0.82, 2.59)	2.6 (1.46, 4.66)	1.42 (0.82, 2.45)	2.16 (1.26, 3.71)	2.18 (1.33, 3.59)	2.17 (1.44, 3.32)
1.56 (0.75, 3.26)	Ser/CT	1.28 (0.73, 2.21)	0.78 (0.42, 1.43)	0.76 (0.28, 2.02)		1.38 (0.79, 2.41)	0.93 (0.45, 1.93)	2.05 (0.81, 5.24)	1.14 (0.65, 2)	2.04 (1.15, 3.59)	1.11 (0.65, 1.89)	1.69 (1, 2.85)	1.71 (1.06, 2.74)	1.71 (1.14, 2.53)
2.36 (1.01, 5.69)	1.52 (0.75, 3.1)	Tis/CT	0.61 (0.33, 1.12)	0.6 (0.22, 1.57)		1.08 (0.62, 1.88)	0.73 (0.35, 1.5)	1.61 (0.64, 4.09)	0.9 (0.52, 1.56)	1.6 (0.91, 2.8)	0.87 (0.52, 1.47)	1.32 (0.79, 2.22)	1.34 (0.84, 2.14)	1.34 (0.91, 1.97)
1.18 (0.55, 2.55)	0.76 (0.42, 1.35)	0.5 (0.24, 1.05)	Niv/CT	0.98 (0.35, 2.66)		1.76 (0.96, 3.25)	1.18 (0.68, 2.08)	2.62 (1, 6.93)	1.46 (0.8, 2.69)	2.6 (1.41, 4.84)	1.42 (0.79, 2.55)	2.16 (1.21, 3.86)	2.18 (1.29, 3.74)	2.18 (1.38, 3.49)
0.84 (0.28, 2.5)	0.54 (0.2, 1.41)	0.35 (0.12, 1.04)	0.71 (0.26, 1.92)	Pha-Ipi/CT		1.81 (0.69, 4.92)	1.21 (041, 3.67)	2.67 (1.1, 6.83)	1.5 (0.57, 4.07)	2.67 (1, 7.27)	1.45 (0.56, 3.91)	2.21 (0.85, 5.92)	2.24 (0.89, 5.83)	2.23 (0.92, 5.6)
1.97 (0.82, 4.81)	1.27 (0.62, 2.63)	0.83 (0.35, 1.97)	1.68 (0.79, 3.6)	2.36 (0.8, 7.09)	Tor/CT									
1.92 (0.86, 4.36)	1.23 (0.65, 2.35)	0.81 (0.37, 1.79)	1.63 (0.83, 3.22)	2.29 (0.82, 6.56)	0.97 (0.43, 2.18)	Ade/CT	0.67 (0.32, 1.39)	1.48 (0.58, 3.76)	0.83 (0.48, 1.44)	1.47 (0.84, 2.59)	0.8 (0.47, 1.36)	1.22 (0.72, 2.06)	1.24 (0.77, 1.98)	1.23 (0.83, 1.83)
0.15 (0.07, 0.33)	0.1 (0.05, 0.17)	0.06 (0.03, 0.13)	0.13 (0.08, 0.19)	0.18 (0.07, 0.5)	0.08 (0.04, 0.16)	0.08 (0.04, 0.16)	Niv/Ipi/CT	2.21 (0.78, 6.3)	1.23 (0.6, 2.55)	2.2 (1.05, 4.56)	1.2 (0.59, 2.43)	1.82 (0.9, 3.67)	1.84 (0.94, 3.59)	1.84 (0.99, 3.39)
1.13 (0.38, 3.36)	0.72 (0.27, 1.92)	0.48 (0.16, 1.4)	0.96 (0.35, 2.6)	1.35 (0.56, 3.22)	0.57 (0.19, 1.69)	0.59 (0.21, 1.64)	7.5 (2.7, 20.51)	Con-Ipi/CT	0.56 (0.22, 1.41)	0.99 (0.39, 2.53)	0.54 (0.22, 1.36)	0.83 (0.33, 2.06)	0.83 (0.34, 2.01)	0.83 (0.36, 1.93)
1.82 (0.89, 3.82)	1.17 (0.69, 2)	0.77 (0.38, 1.56)	1.55 (0.87, 2.78)	2.17 (0.83, 5.86)	0.92 (0.45, 1.91)	0.95 (0.5, 1.81)	12.12 (6.76, 22.11)	1.62 (0.61, 4.37)	Pem/CT	1.78 (1.01, 3.13)	0.97 (0.57, 1.65)	1.48 (0.87, 2.49)	1.49 (0.93, 2.4)	1.49 (1.01, 2.21)
2 (0.96, 4.25)	1.28 (0.74, 2.23)	0.84 (0.41, 1.74)	1.7 (0.94, 3.09)	2.38 (0.9, 6.47)	1.01 (0.48, 2.11)	1.04 (0.54, 2.01)	13.28 (7.27, 24.6)	1.77 (0.67, 4.8)	1.1 (0.63, 1.9)	Ate/CT	0.55 (0.32, 0.94)	0.83 (0.49, 1.41)	0.84 (0.52, 1.36)	0.84 (0.56, 1.26)
2.08 (1.03, 4.33)	1.34 (0.8, 2.25)	0.88 (0.44, 1.77)	1.77 (1, 3.12)	2.49 (0.95, 6.64)	1.05 (0.51, 2.15)	1.08 (0.58, 2.04)	13.83 (7.8, 24.86)	1.84 (0.71, 4.94)	1.14 (0.68, 1.92)	1.04 (0.61, 1.78)	Dur/CT	1.52 (1.07, 2.17)	1.54 (0.99, 2.4)	1.53 (1.08, 2.19)
1.35 (0.66, 2.83)	0.87 (0.51, 1.48)	0.57 (0.28, 1.16)	1.15 (0.64, 2.05)	1.61 (0.61, 4.34)	0.68 (0.33, 1.41)	0.7 (0.37, 1.33)	8.97 (5.01, 16.31)	1.2 (0.46, 3.22)	0.74 (0.43, 1.26)	0.68 (0.39, 1.17)	0.65 (0.45, 0.94)	Dur/Tre/CT	1.01 (0.66, 1.56)	1.01 (0.72, 1.42)
1.78 (0.92, 3.54)	1.14 (0.73, 1.81)	0.75 (0.39, 1.44)	1.51 (0.91, 2.52)	2.12 (0.84, 5.51)	0.9 (0.46, 1.76)	0.93 (0.52, 1.66)	11.81 (7.08, 20.12)	1.58 (0.62, 4.09)	0.98 (0.62, 1.54)	0.89 (0.55, 1.43)	0.85 (0.55, 1.33)	1.32 (0.84, 2.07)	Ipi/CT	1 (0.77, 1.3)
2.03 (1.11, 3.86)	1.31 (0.9, 1.92)	0.86 (0.47, 1.57)	1.73 (1.12, 2.7)	2.43 (1, 6.07)	1.03 (0.55, 1.91)	1.06 (0.63, 1.79)	13.52 (8.66, 21.63)	1.81 (0.74, 4.52)	1.12 (0.77, 1.63)	1.02 (0.68, 1.52)	0.98 (0.68, 1.4)	1.51 (1.04, 2.2)	1.14 (0.89, 1.48)	CT

Figure 3 Network meta-analysis of comparisons on ORR and ≥3 AEs in patients with extensive-stage small cell lung cancer. (A) Network diagrams of comparisons on ORR. (B) Pooled estimates of the network meta-analysis of ORR and ≥3 AEs. Data in each cell are OR (95% CI) for the comparison of row-defining treatment versus column column-defining treatment. OR more than 1 favours row-defining treatment. Significant results were highlighted in red (Each circular node represents a type of treatment. Each line represents a type of head-to-head comparison. The size of the nodes and the thickness of the lines are weighted according to the number of studies evaluating each treatment and direct comparison, respectively. The total number of patients receiving treatment was shown in brackets). (C) Network diagrams of comparisons on ≥3 AEs. ORR, objective response rate; AE, adverse event; OR, odds ratio; CI, confidence interval.

Sensitivity analyses

The sensitivity analysis was performed by excluding Phase II RCTs in order to examine the reliability and robustness of the NMA. The results of the sensitivity analysis were nearly identical to the originals (*Figure 4B*).

Consistency assessment

It is demonstrated that the fit of the consistency model was similar to that of the inconsistency model (Table S2). Figures S3-S6 show the trace plot and the Brooks-Gelman-Rubin diagnostic plot, indicating the excellent stability of the model convergence.

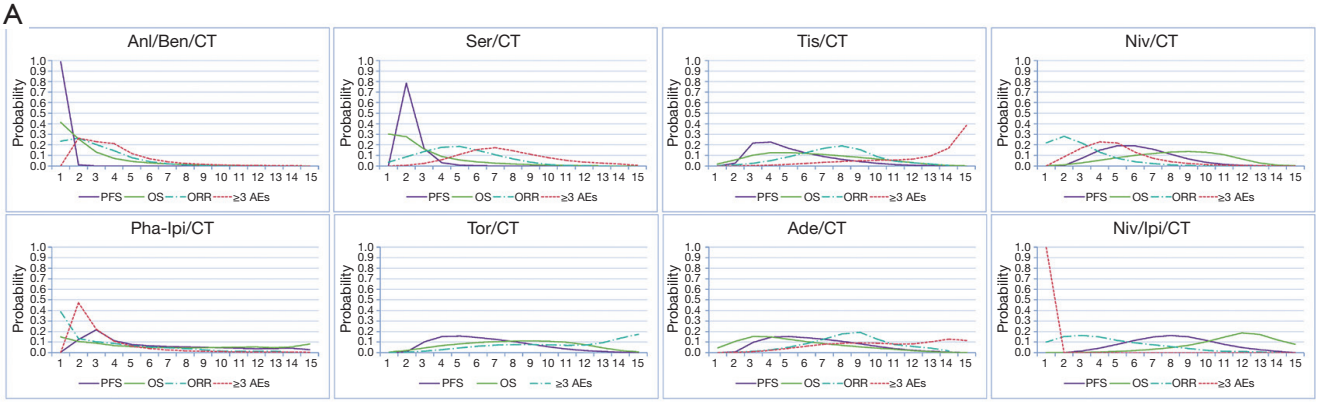
Discussion

To the best of our knowledge, our study is currently the NMA that incorporates the most comprehensive RCT involving immunotherapy for ES-SCLC. This NMA demonstrated for the first time that Anl/Ben/CT is the most efficacious regimen for extending survival in ES-SCLC, highlighting its potential as a preferred first-line treatment option for this patient population.

Currently, the standard first line of care for ES-SCLC is chemotherapy combined with immunotherapy (14). Adding immunotherapy to chemotherapy in the first-line treatment of ES-SCLC is approved by the Food and Drug Administration based on multiple RCTs. IMpower133, a multinational, phase III RCT, has evaluated the synergistic effect of the addition of atezolizumab to chemotherapy in the first-line treatment of ES-SCLC (29). It was shown that the median OS was 12.3 months and 10.3 months in the atezolizumab group and the placebo group, respectively (29). The primary objective of the CAPSTONE-1 study was to evaluate the effectiveness and safety of incorporating adebrelimab into conventional chemotherapy regimens as first-line treatment for ES-SCLC (13). As expected, a significantly improved OS (15.3 months *vs.* 12.8 months) was obtained, and the safety profile was acceptable (13). ASTRUM-005 is a phase III RCT evaluating the efficacy of the programmed cell death protein 1 (PD-1) inhibitor serplulimab plus chemotherapy compared with placebo plus chemotherapy for ES-SCLC in the first-line setting (12). The median OS was significantly longer in the serplulimab group (15.4 months) than in the placebo group (10.9 months) (12). Out of all regimens of immunotherapy combined with chemotherapy, serplulimab plus chemotherapy yielded the longest median OS (12). It remains uncertain whether the combination of serplulimab and chemotherapy offers a superior therapeutic outcome compared to alternative regimens, given the absence of RCTs directly assessing the comparative efficacy of these treatment approaches. To identify the optimal regimen, Zhang *et al.* compared the efficacy of varying combination strategies by NMA, demonstrating that Ser/CT was optimal (30). Consistently, our NMA demonstrated that Ser/CT was optimal in prolonging both PFS and OS with acceptable ≥3 AEs among immunotherapy-combination chemotherapy regimens.

In fact, the use of immunotherapy in conjunction with chemotherapy, despite its benefits, can result in the development of resistance, which is a persistent challenge for achieving sustained long-term survival. Enhancing long-term survival rates in this context continues to be an area where further advancements are required (6). Differing from other tumors, the tumor microenvironment (TME) of SCLC is mostly of a cold TME-enriched phenotype (a.k.a. the immunosuppressive microenvironment), which is featured by more Tregs, more exhausted CD8+ T-cells, and fewer activated CD8+ T-cells, and markedly attenuates the efficacy of immunotherapy (31). Angiogenesis and vascularization play essential roles in the development of a cold TME (32). Tumor vessel normalization and TME reprogramming can transform cold tumors into hot tumors, thereby potentially exerting synergistic anti-tumor effects with immunotherapy (32). Vascular abnormalities stem from the increased levels of proangiogenic factors (VEGFR, PDGFR, and FGFR) and proangiogenic factors (33). The antiangiogenic drug anlotinib targets angiogenesis pathways such as VEGFR, FGFR, and PDGFR (34). Expectedly, anlotinib can inhibit tumor angiogenesis and normalize blood vessels, thereby reprogramming the immunosuppressive TME into an immunostimulatory TME characterized by increased immune cell extravasation and enhanced antigen presentation function (33). Moreover, clinical trials have substantiated the synergistic impact of co-administering anlotinib with immunotherapy in the treatment of non-SCLC (35). The antitumor effects of anlotinib have been deemed significant, and its safety profile has been found to be acceptable in the context of SCLC (36). Based on the sufficient evidence above, ETER701 has explored the efficacy and safety of adding anlotinib to the combination of immunotherapy with chemotherapy, with the result showing a significant prolongation of OS compared to its control chemotherapy alone (19.3 *vs.*

A



B

	PFS	OS	ORR	≥3 AEs	Sensitivity analysis PFS	OS	ORR	≥3 AEs
Anl/Ben/CT	1	1	1	3	1	1	2	2
Ser/CT	2	2	5	7	2	2	4	5
Tis/CT	3	5	8	15	3	5	7	13
Niv/CT	4	9	2	4	4	10	1	4
Pha-Ipi/CT	5	7	3	2	NA	NA	NA	NA
Tor/CT	6	8	NA	11	5	7	NA	9
Ade/CT	7	3	9	10	6	3	8	8
Niv/Ipi/CT	8	13	4	1	7	11	3	1
Con-Ipi/CT	9	12	13	5	NA	NA	NA	NA
Pem/CT	10	10	7	9	8	8	6	7
Ate/CT	11	6	14	12	9	6	12	10
Dur/CT	12	4	6	13	10	4	5	12
Dur/Tre/CT	13	11	10	6	11	9	9	3
Ipi/CT	14	14	11	8	12	12	10	6
CT	15	15	12	14	13	13	11	11

Figure 4 Bayesian ranking profiles of comparable regimens on efficacy and safety for extensive-stage small cell lung cancer. (A) Profiles indicate the probability of each comparable regimen being ranked from first to last on OS, PFS, ORR, and grade ≥3 adverse events (≥3 AEs) (the X-axis represents different rankings, and the Y-axis corresponds to the probability of each ranking). (B) Number in each cell indicates the probability of each regimen being ranked from first to last on OS, PFS, ORR, and ≥3 AEs according to the surface under the cumulative ranking curve. PFS, progression-free survival; OS, overall survival; ORR, objective response rate; AE, adverse event.

11.9 months) (15). Up to now, Anl/Ben/CT is the regimen that yields the historically longest OS for ES-SCLC (15). No RCT has yet compared Anl/Ben/CT with other combination regimens, particularly with Ser/CT. Therefore, no evidence-based medicine is available indicating that Anl/Ben/CT is superior to other regimens despite its median OS being the longest. In this study, we conducted the NMA by enrolling all immunotherapy-based RCTs in first-line therapy, and the results showed that Anl/Ben/CT was optimal concerning PFS, OS, and ORR. Regarding safety, notwithstanding the third ranking for ≥3 AEs, HR-based NMA results showed no significant difference in ≥3 AEs for Anl/Ben/CT compared with other immunotherapy-based regimens, except for Tis/CT and Dur/CT. Collectively, our study for the first time confirmed that Anl/Ben/CT is historically the most efficacious regimen with tolerable and manageable safety profile for ES-SCLC, and provided evidence for its use as a new preferred option in the first-line setting.

Several limitations must be taken into account in this study. Firstly, some RCTs incorporated in this research

were sourced from conference reports, notably the ETER701 study presented at the 2023 WCLC and 2024 European Lung Cancer Congress, wherein subgroup analysis results were not accessible, thereby precluding the execution of subgroup analysis in the NMA. Therefore, it is still uncertain whether the efficacy of each regimen across the prespecified subgroups is consistent with the overall analysis. Secondly, the chemotherapy regimens among the included RCTs were not exactly identical, and we merged multiple chemotherapy regimens into one regimen to facilitate NMA in this study, potentially causing bias. Thirdly, our study confirmed that anlotinib can significantly enhance the antitumor effect in the regimen of PD-L1 inhibitor benmelstobart plus chemotherapy, whereas it requires corresponding RCTs to investigate whether anlotinib can also enhance the efficacy of regimens of other PD-(L)1 inhibitor plus chemotherapy. In addition, our study did not include non-English language research, which may introduce a potential bias in the analysis.

Conclusions

Adding anlotinib to the regimen of benmelstobart plus chemotherapy significantly improved PFS and OS compared with chemotherapy alone or chemotherapy plus immunotherapy, with an acceptable safety profile in patients with ES-SCLC. In conclusion, Anl/Ben/CT could be the new and clinically preferable first-line treatment option for ES-SCLC.

Acknowledgments

The study was submitted in abstract form to the World Lung Cancer Congress (EP.13B.01).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-636/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-636/prf

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-636/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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