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Efficacy and safety of novel immune checkpoint inhibitor-based combinations versus chemotherapy as first-line treatment for patients with extensive-stage small cell lung cancer: A network meta-analysis

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Abstract

Background: Patients with extensive-stage small cell lung cancer (ES-SCLC) have an exceptionally poor prognosis and immune checkpoint inhibitors (ICIs) combined with etoposide-platinum is recommended as standard first-line therapy. However, which combination pattern is the best still remains unknown. This network meta-analysis was performed to compare the efficacy and safety of currently available patterns including an antiangiogenic agent containing regimen and probed into the most appropriate therapy for patients.

Methods: Hazard ratios (HRs) and odds ratios (ORs) were generated using R software. The outcomes of overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events of grade 3 or higher (grade ≥ 3 adverse events [AEs]) were analyzed.

Results: A total of 10 randomized controlled trials (RCTs) involving 5544 patients were included for analysis. Drug combination patterns included adebrelimab, atezolizumab, durvalumab, durvalumab plus tremelimumab, ipilimumab, pembrolizumab, serplulimab, benmelstobart plus anlotinib, tislelizumab, tiragolumab plus atezolizumab and toripalimab in combination with chemotherapy. The novel antiangiogenic agent containing regimen benmelstobart + anlotinib + chemotherapy showed the highest possibility to present the best PFS and OS versus chemotherapy. Compared with ICI plus chemotherapy, it also achieved significantly better PFS and presented a tendency of OS benefit. As for safety and toxicity, patients treated with benmelstobart + anlotinib + chemotherapy and durvalumab + tremelimumab + chemotherapy suffered a higher likelihood of more grade ≥ 3 AEs without unexpected AEs.

Conclusion: PD-1/PD-L1 inhibitors-based combinations are associated with significant improvement in both PFS and OS for treatment-naïve ES-SCLC patients. Benmelstobart plus anlotinib with chemotherapy (CT) yielded better survival benefit versus CT alone or other ICIs + CT with caution for more adverse effects along with the addition of an antiangiogenic agent.

KEYWORDS
angiogenesis, chemotherapy, immunology, network meta-analysis, small cell lung cancer

Chuang Yang and Tiantian Xuan contributed equally to this work.

INTRODUCTION

Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer death in 2020, representing approximately one in 10 (11.4%) cancers diagnosed and one in five (18.0%) deaths, with an estimated 2.2 million new cancer cases and 1.8 million deaths worldwide.[1] Small cell lung cancer (SCLC) accounts for about 15% of all lung cancer cases,[2] which is a high-grade neuroendocrine carcinoma arising predominantly in current or former smokers with an exceptionally poor prognosis.[3] The Veterans Administration Lung Cancer Study Group (VALSG) staging system is widely used in both designing clinical trials and presenting data of SCLC as it effectively distinguishes patients treated primarily with chemoradiotherapy (limited-stage disease) from those treated with systemic chemotherapy or chemoimmunotherapy (extensive-stage disease). At the time of diagnosis, about two-thirds of all cases of SCLC present with extensive-stage disease (ES-SCLC).[4] For over three decades, platinum-based (with etoposide or irinotecan) chemotherapy has remained the standard first-line treatment for ES-SCLC, which provides a limited median overall survival (OS) of only 9–11 months.[5–10]

SCLC is known to have a relatively high tumor mutational burden (TMB) with median ~8 mutations per megabase (mut/Mb),[11] which favors the development of immunogenic tumor clones and the elicitation of adaptive immune response.[12,13] Immune-checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 pathway have been extensively investigated in SCLC and several ICIs including atezolizumab,[14,15] durvalumab,[4,16] adebrelimab[17] and serplulimab[18] are approved for the first-line treatment of ES-SCLC.[19,20] For example, the phase III randomized trial Impower133 showed that adding atezolizumab to first-line platinum and etoposide chemotherapy significantly improved OS (12.3 vs. 10.3 months) of ES-SCLC patients compared with platinum plus etoposide only.[14,15] The CASPIAN trial is another randomized phase III trial that evaluated durvalumab with etoposide-platinum in comparison to etoposide-platinum as first-line therapy and proved the addition of durvalumab significantly improved OS.[4,16] Anti-PD-L1 antibodies atezolizumab or durvalumab in combination with etoposide-platinum are now recommended as standard first-line therapy by the National Comprehensive Cancer Network (NCCN) panel for patients with ES-SCLC. Other ICIs such as pembrolizumab,[21] ipilimumab,[22] tremelimumab,[16] adebrelimab,[17] serplulimab[18] and most recently tislelizumab and toripalimab have also been investigated in the first-line treatment of ES-SCLC and the latter four ICIs have been shown to significantly improve the OS of ES-SCLC in four RCTs in China.[23,24] The positive OS data of tislelizumab plus chemotherapy and toripalimab plus chemotherapy have just been reported in the World Conference of Lung Cancer (WCLC)[23] and Congress of the European Society for Medical Oncology (ESMO).[24]

Despite immunochemotherapy showing promise with a 2–4 months OS benefits in ES-SCLC compared with chemotherapy only,[4,14,17,25] improving long-term survival remains an unmet need for this lethal malignancy. The limited benefit might be attributed to the complicated tumor microenvironment in SCLC, which is characterized by immunosuppression and angiogenesis. Tumor microenvironment reprogramming and tumor vessel normalization could promote immune cell infiltration and induce synergistic antitumor effects with immunotherapy.[26–28] Recently, a pivotal study ETER701 explored the efficacy and safety of the combination of a PD-L1 antibody benmelstobart, an antiangiogenic agent anlotinib and chemotherapy in patients with ES-SCLC.[23] Anlotinib is a tyrosine kinase inhibitor of vascular endothelial growth factor receptor-2 (VEGFR-2) which has demonstrated antitumor effects in various cancers and has been approved for the later-line treatment of advanced NSCLC in China.[29–32] This combination of four drugs including an antiangiogenic agent is associated with a superior OS of 19.3 months as reported in WCLC 2023.[23] Until now, multiple studies have explored if ICI-based combinations could obtain improved efficacy, longer survival benefits and manageable safety in ES-SCLC in comparison to chemotherapy. However, the question which ICI or which combination pattern, such as atezolizumab, pembrolizumab, ipilimumab, tremelimumab, durvalumab, adebrelimab, serplulimab, tislelizumab, toripalimab, tiragolumab or benmelstobart plus anlotinib is the best agent for ES-SCLC still remains unknown.

Hereby, we conducted a Bayesian network meta-analysis to compare and rank the efficacy and safety of different ICIs with or without antiangiogenic agent plus chemotherapy as first-line treatments for patients with ES-SCLC and also investigated the best treatment for different clinically relevant subgroups, such as gender, age, and metastatic sites. The results of this network meta-analysis of 10 RCTs might provide more evidence and help to make better decisions for clinical practice in fighting this lethal malignancy.

METHODS

We followed the Preferred Reporting Items for Systemic Review and Meta-analyses (PRISMA) checklist when conducting this meta-analysis. The network meta-analysis (NMA) was conducted and reported in accordance with the PRISMA extension version (PRISMA-NMA) (Table S1). The study protocol has been duly registered on the international prospective register of systematic reviews (PROSPERO) under the registration no. CRD42023464813.

Retrieval method

The search terms used to gather the studies from Medline, Embase, PubMed, and the Cochrane Central Register of Controlled Trials databases were as follows: Immunotherapy, tremelimumab, nivolumab, pembrolizumab, atezolizumab, adebrelimab, ipilimumab, durvalumab, serplulimab,

tislelizumab, benmelstobart, toripalimab, small cell lung carcinoma, randomized controlled trial, extensive-stage and their related MeSH terms. The detailed search strategy is presented in Table S2.

Inclusion and exclusion criteria

Two researchers conducted separate searches and evaluations to determine the eligibility of each study. They reviewed the title and abstract, and in some cases, the full text, to make their assessments. The inclusion criteria for selecting studies were as follows: (1) Prospective, randomized, phase 3 and controlled clinical trials. (2) Patients who were eligible had recently been diagnosed with a histologically or cytologically confirmed SCLC and had not yet received any treatment. (3) Clinical trials that employed a combination of ICI treatments as the initial treatment option. (4) Clinical trials that employed a combination of ICI treatments or placebo treatment as the initial treatment option. The exclusion criteria for selecting studies were as follows: (1) Retrospective study, phase I or II clinical trials, single-arm studies. (2) Studies without complete survival data or of outdated treatment concept.

Data extraction

Overall survival (OS) was the primary outcome and the secondary outcomes included progression-free survival (PFS), objective response rate (ORR), and grade ≥ 3 adverse events (AEs). The data extraction process encompassed the HRs with 95% confidence intervals (CIs) for OS, PFS, and dichotomous data for ORR and AEs. The data regarding the year of publication, primary author, drugs used in studies, patients' age and sex distribution, smoking status, PD-L1 expression level, sample size and Eastern Cooperative Oncology Group (ECOG) performance status scores were all gathered. Data collection was conducted independently by two investigators (CY and TX) with any discrepancies resolved through consensus.

Assessment of quality

The studies included in the analysis were assessed using Review Manager 5.4 software. The process of data extraction was conducted independently by two investigators (CY and TX). In the event of any discrepancies, a consensus was reached through discussion and agreement.

Statistical analysis

Statistical significance was defined as two-sided $p < 0.05$. The meta-analyses were conducted using R software (version 4.3.1) and the gemtc R packages using Bayesian fixed-effect consistency models to compare treatments. For the use of R software, we set the number of iterations to 100 000 and considered the first 50 000 as a burnin sample. We employed the Bayesian fixed-effect consistency models to compare various immunotherapy treatments and utilized surfaces under the cumulative ranking (SUCRA) probabilities to present pairwise comparisons between regimens for OS, PFS, ORR, and grade ≥3 AEs. Furthermore, the software has the capability to calculate the likelihood of each intervention being ranked as the top choice. Chuang Yang and Xin Dai made the major contributions to the statistical analysis.

RESULTS

Basic information

Finally, a total of 10 studies involving 5544 patients matched our predetermined eligibility criteria (Figure 1). The basic information of the studies included for analysis is shown in Table 1. Except for the Glodman trial in 2021 which was a three-arm randomized trial that investigated durvalumab with or without tremelimumab plus chemotherapy (CT) versus CT alone, the other trials were all two-arm trials. For ICI-based combination arms, there were 3001 patients in total with 478, 228, 268, 268, 230, 201, 389, 243, 246, 227 and 223 patients receiving treatment with ipilimumab + EP, pembrolizumab + EP, durvalumab + EP, durvalumab + tremelimumab + EP, adebrelimab + EC, atezolizumab + EC, serplulimab + EC, tiragolumab + atezolizumab + EC, benmelstobart + anlotinib + EC, tislelizumab + EP and toripalimab + EP, respectively. CT alone was administered to 2543 patients in the control arms of all 10 studies. The network diagram is shown in Figure 2. The evaluation of potential bias is shown in Figure S1, which suggested a low risk of bias.

OS analysis

Based on the result of NMA analysis for OS (Figure 3a), the combination of benmelstobart, anlotinib and CT showed a statistically significantly better OS compared with ipilimumab + CT (HR = 0.65; 95% CI: 0.48–0.88) or CT alone (HR = 0.61; 95% CI: 0.47–0.80). Although benmelstobart + anlotinib + CT also achieved a better OS in comparison with pembrolizumab + CT (HR = 0.76; 95% CI: 0.54–1.07), durvalumab + tremelimumab + CT (HR = 0.74; 95% CI: 0.54–1.04), serplulimab + CT (HR = 0.97; 95% CI: 0.67–1.40), adebrelimab + CT (HR = 0.85; 95% CI: 0.60–1.20), durvalumab + CT (HR = 0.81; 95% CI: 0.58–1.13), atezolizumab + CT (HR = 0.80; 95% CI: 0.56–1.14), tislelizumab + CT (HR = 0.81; 95% CI: 0.58–1.14), tiragolumab + atezolizumab + CT (HR = 0.74; 95% CI: 0.49–1.11) or toripalimab + CT (HR = 0.76; 95% CI: 0.55–1.07), none of the differences were statistically significant. By

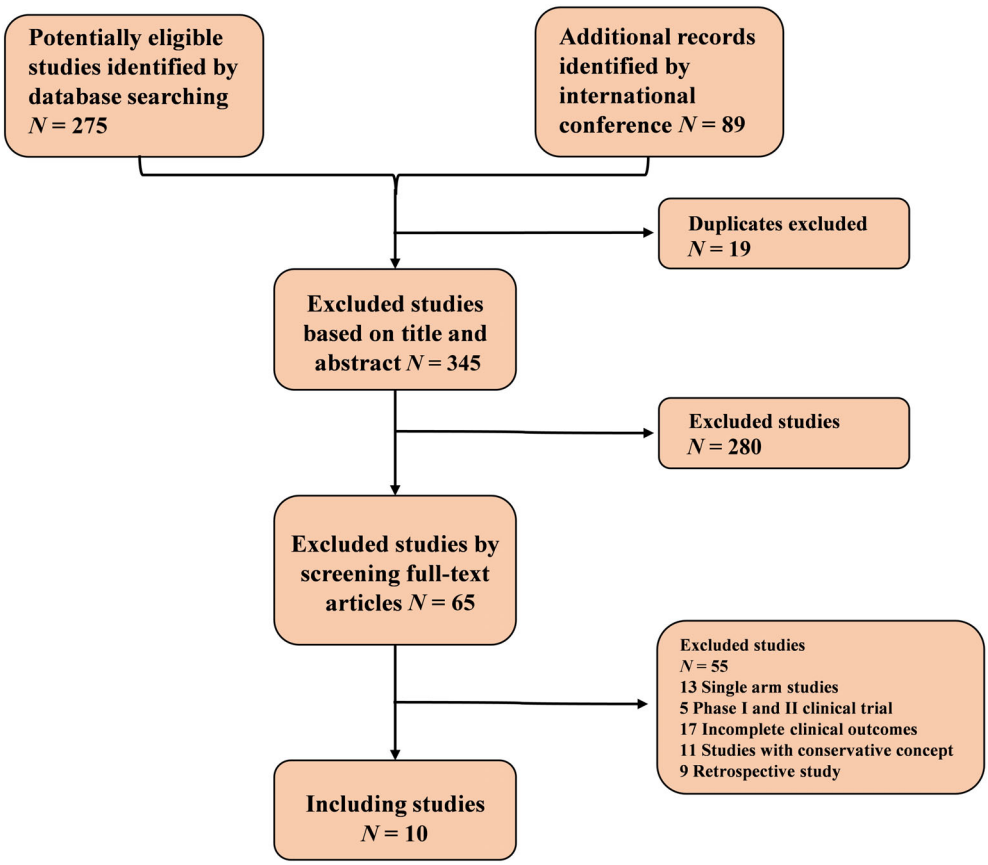

FIGURE 1 Flow chart of search, inclusion, and exclusion studies.

calculating the OS rate ORs of different ICI-based regimens at the third, sixth, ninth, 12th, 15th, 18th, 21st, and 24th months of treatment, we found that only serplulimab + CT (OR = 2.29; 95% CI: 1.40–3.75) significantly increased the sixth month OS rate (Table 2). At the 12th month, adebrelimab + CT (OR = 1.49; 95% CI: 1.03–2.17), atezolizumab + CT (OR = 1.67; 95% CI: 1.12–2.48), durvalumab + CT (OR = 1.74; 95% CI: 1.23–2.45), serplulimab + CT (OR = 1.6; 95% CI: 1.12–2.28), benmelstobart + anlotinib + CT (OR = 1.74; 95% CI: 1.21–2.5) all significantly increased the OS rate compared to CT alone. Benmelstobart + anlotinib + CT showed the best OS benefit at both the 15th month (OR = 2.28; 95% CI: 1.58–3.29) and the 18th month (OR = 3.1; 95% CI: 2.14–4.55). At the 24th month, except for atezolizumab + CT (OR = 1.34; 95% CI: 0.82–2.22) and ipilimumab + CT (OR = 1.46; 95% CI: 0.95–2.26), pembrolizumab + CT (OR = 2.31; 95% CI: 1.38–3.97), benmelstobart + anlotinib + CT (OR = 2.25; 95% CI: 1.53–3.34), adebrelimab + CT (OR = 2.25; 95% CI: 1.44–3.54), tislelizumab + CT (OR = 1.78; 95% CI: 1.17–2.73), durvalumab + tremelimumab + CT (OR = 1.73; 95% CI: 1.12–2.7), and durvalumab + CT (OR = 1.71; 95% CI: 1.09–2.68) all showed statistically significant OS benefit compared to CT (Table 2). Toripalimab + CT did not show a statistically significant OS benefit compared to CT at any time points. The OS rate information was condensed by creating a matrix plot that compared the effectiveness of each treatment regimen from the third to 24th months (Table S3). In the rank-heat plot for OS, the surface of each sector is colored based on the cumulative ranking (SUCRA) of monthly overall survival rate (Figure 4a). Compared with CT only over time, the benmelstobart + anlotinib + CT combination was associated with the strongest long-term overall survival benefit from the third to the 24th month among all combinations as a potential best choice as shown in Figure 4a.

PFS analysis

In terms of PFS (Figure 3b), benmelstobart + anlotinib + CT demonstrated the best survival benefit versus CT only with the smallest HR (HR = 0.32, 95% CI: 0.26–0.40). This combination also demonstrated statistically significant superiority when compared with other ICI-based regimens, including serplulimab + CT (HR = 0.67; 95% CI: 0.49–0.92), tislelizumab + CT (HR = 0.51; 95% CI: 0.37–0.69), adebrelimab + CT (HR = 0.48; 95% CI: 0.35–0.65), toripalimab + CT (HR = 0.48; 95% CI: 0.35–0.65), pembrolizumab + CT (HR = 0.43; 95% CI: 0.31–0.58), atezolizumab + CT (HR = 0.42; 95% CI: 0.31–0.56), durvalumab + CT (HR = 0.40; 95% CI: 0.30–0.54), durvalumab + tremelimumab + CT (HR = 0.38; 95% CI: 0.28–0.51), ipilimumab + CT (HR = 0.38; 95% CI: 0.29–0.49) and tiragolumab + atezolizumab + CT (HR = 0.38; 95% CI: 0.27–0.55). From the 1st month to the 3rd month, only serplulimab + CT showed a statistically significant

TABLE 1 The characteristics of studies enrolled in the network meta-analysis.

No.	Study	Author	Year	Intervention arm	No. of patients	Control arm	No. of patients	OS (HR; 95% CI)	PFS (HR;95% CI)
1	Reck et al.	Reck et al.	2016	Ipilimumab plus EP	478	Placebo plus EP	476	0.94 (0.81,1.09)	0.85 (0.75,0.97)
2	KEYNOTE-604	Rudin et al.	2020	Pembrolizumab plus EP	228	Placebo plus EP	225	0.80 (0.64,0.98)	0.75 (0.61,0.91)
3	CASPIAN	Goldman et al.	2021	Durvalumab plus EP, Durvalumab plus tremelimumab plus EP	268 268	EP	269	0.75 (0.62,0.91) 0.82 (0.68,1.00)	0.80 (0.66,0.96) 0.84 (0.70,1.01)
4	CAPSTONE-1	Wang et al.	2022	Adebrelimab plus chemotherapy	230	Placebo plus chemotherapy	232	0.72 (0.58,0.90)	0.67 (0.54,0.83)
5	IMpower133	Stephen, et al.	2022	Atezolizumab plus CP/ET	201	Placebo plus CP/ET	202	0.76 (0.60,0.95)	0.77 (0.63,0.95)
6	ASTRUM-005	Cheng et al.	2022	Serplulimab plus chemotherapy	389	Placebo plus chemotherapy	196	0.63 (0.49,0.82)	0.48 (0.38,0.59)
7	SKYSCRAPER-02	Rudin et al.	2023	Tiragolumab plus atezolizumab plus EC	243	Placebo plus atezolizumab plus EC	247	1.09 (0.88,1.35)	1.08 (0.89,1.31)
8	ETER701	Cheng et al.	2023	Benmelstobart plus anlotinib plus EC	246	Placebo plus Placebo plus EC	247	0.61 (0.46,0.79)	0.32 (0.26,0.41)
9	RATIONALE-312	Cheng et al.	2023	Tislelizumab plus EC	227	Placebo plus EC	230	0.75 (0.61,0.92)	0.63 (0.51,0.78)
10	EXTENTORCH	Cheng et al.	2023	Toripalimab plus EP	223	Placebo plus EP	219	0.80 (0.65,0.98)	0.67 (0.54,0.83)

Abbreviations: CI, confidence interval; EC, etoposide plus carboplatin; EP, etoposide plus cisplatin/carboplatin; HR, hazard ratio; No., number; OS, overall survival; PFS, progression-free survival.

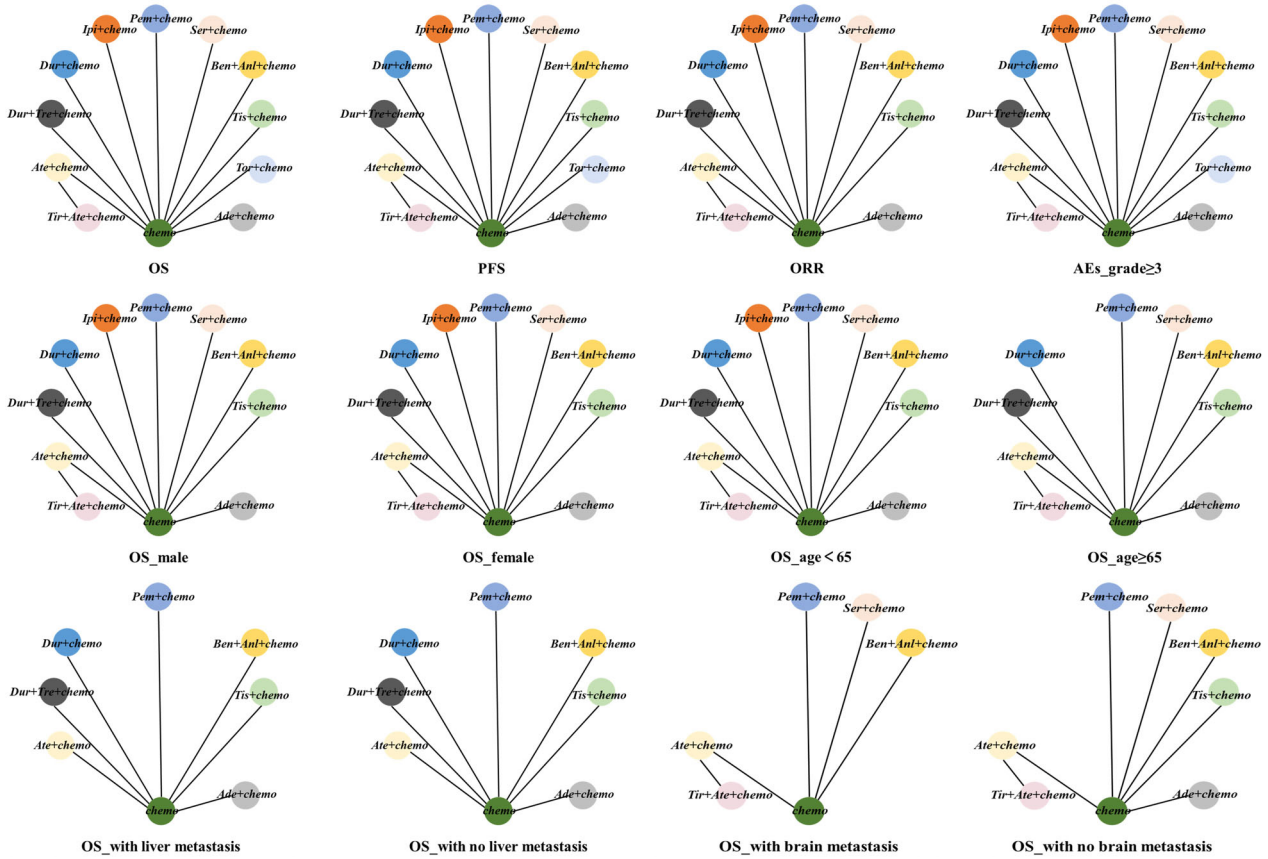

FIGURE 2 Network meta-analysis of first-line treatments for extensive-stage small cell lung cancer (ES-SCLC) patients in various groups that included overall survival, progression-free survival, and grades ≥3 adverse events of the ES-SCLC and different subgroups by age, gender, and metastasis. Each node represents a treatment, and the line between the two points represents a comparison between the two treatments. Chemo, chemotherapy; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; AEs, adverse events; Ade + chemo, adebrelimab + chemotherapy; Ate + chemo, atezolizumab + chemotherapy; Dur + Tre + chemo, durvalumab + tremelimuamb + chemotherapy; Dur + chemo, durvalumab + chemotherapy; Ipi + chemo, ipilimumab + chemotherapy; Pem + chemo, pembrolizumab + chemotherapy; Ser + chemo, serplulimab + chemotherapy; Ben + Anl + chemo, benmelstobart + anlotinib + chemotherapy; Tis + chemo, tislelizumab + chemotherapy; Tir + Ate + chemo, tiragolumab + atezolizumab + chemotherapy; Tor + chemo, toripalimab + chemotherapy.

difference in PFS rate versus CT (OR = 2.14; 95% CI: 1.29–3.53) as shown in Table 3. At the sixth month, only the combinations of atezolizumab + CT (OR = 1.46; 95% CI: 0.93–2.31), durvalumab + tremelimumab + CT (OR = 0.89; 95% CI: 0.63–1.25), durvalumab + CT (OR = 0.98; 95% CI: 0.7–1.37), ipilimumab + CT (OR = 1.28; 95% CI: 0.96–1.71) and toripalimab + CT (OR = 1.26; 95% CI: 0.86–1.86) failed to demonstrate PFS rate superiority, while benmelstobart + anlotinib + CT was associated with the best PFS benefit (OR = 6.22; 95% CI: 3.98, 10). From the ninth month to the 12th month, all ICI-based combinations but atezolizumab + CT and ipilimumab + CT increased the PFS rate with a statistically significant difference. Atezolizumab + CT only demonstrated improvement in PFS rate specifically during 10th and 12th months but not in the ninth and 11th months. Ipilimumab + CT only demonstrated improvement in PFS rate specifically during the ninth and 10th months but not in the 11th and 12th months. At the 12th month specifically, benmelstobart + anlotinib + CT once again demonstrated the best PFS rate among all combinations (OR = 44.9; 95% CI: 7.93, 1249) (Table 3). The PFS rate information was condensed by creating a matrix plot that compared the effectiveness of each treatment regimen from the 3rd to 12th months (Table S4). Based on the result of the rank-heat plot, it is evident that benmelstobart + anlotinib + CT exhibits the highest capacity in improving PFS, followed by serplulimab + CT and tislelizumab + CT as shown in Figure 4b.

ORR analysis

ORs for ORR from 10 regimens were calculated and compared with network meta-analysis. The results indicated that only four of all nine ICI-based combinations, benmelstobart + anlotinib + CT (OR = 2.17; 95% CI: 1.43–3.32), serplulimab + CT (OR = 1.70; 95% CI: 1.14–2.52), durvalumab + CT (OR = 1.54; 95% CI: 1.08–2.19) and pembrolizumab + CT (OR = 1.49; 95% CI: 1.01–2.21) demonstrated statistically significant ORR advantage versus CT

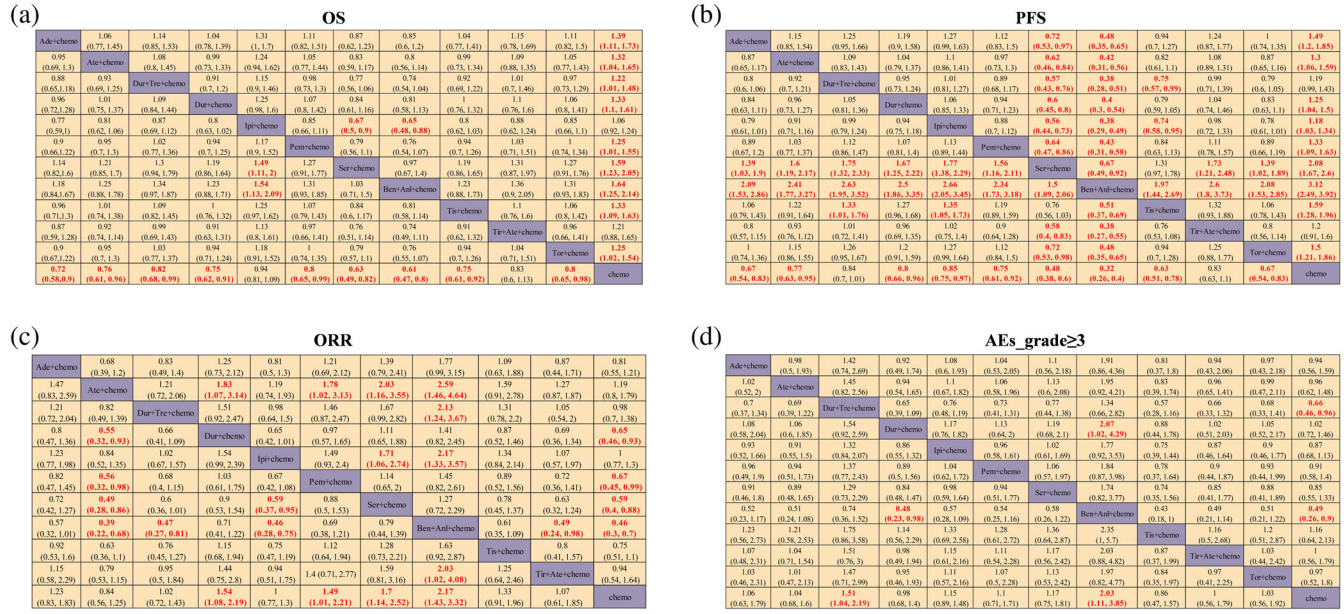

FIGURE 3 Efficacy and safety characteristics of Bayesian network meta-analysis in patients with extensive-stage small cell lung cancer (ES-SCLC). (a) Hazard ratios (HRs) and 95% confidence interval (CI) for overall survival (OS) in ES-SCLC patients. (b) HRs and 95% CI for progression-free survival (PFS) in ES-SCLC patients. (c) ORs and 95% CI for objective response rate (ORR) in ES-SCLC patients. (d) ORs and 95% CI for grades ≥3 adverse events (AEs_grade ≥3) in ES-SCLC patients. Significant results are shown in bold and red. Chemo, chemotherapy; Ade + chemo, adebrelimab + chemotherapy; Ate + chemo, atezolizumab + chemotherapy; Dur + Tre + chemo, durvalumab + tremelimuamb + chemotherapy; Dur + chemo, durvalumab + chemotherapy; Ipi + chemo, ipilimumab + chemotherapy; Pem + chemo, pembrolizumab + chemotherapy; Ser + chemo, serplulimab + chemotherapy; Ben + Anl + chemo, benmelstobart + anlotinib + chemotherapy; Tis + chemo, tislelizumab + chemotherapy; Tir + Ate + chemo, tiragolumab + atezolizumab + chemotherapy; Tor + chemo, toripalimab + chemotherapy.

only as shown in Figure 3c. Compared with other ICI-based combinations, benmelstobart + anlotinib + CT demonstrated superior ORR versus atezolizumab + CT (OR = 2.59; 95% CI: 1.46–4.64), ipilimumab + CT (OR = 2.17; 95% CI: 1.33–3.57), durvalumab + tremelimumab + CT (OR = 2.13; 95% CI: 1.24–3.67) and tiragolumab + atezolizumab + CT (OR = 2.03; 95% CI: 1.02–4.08).

Safety analysis

ORs for grade ≥3 AEs of 10 regimens were calculated to compare their safety. Compared with CT only, benmelstobart + anlotinib + CT (OR = 2.03; 95% CI:1.11–3.85) and durvalumab + tremelimumab + CT (OR = 1.51; 95% CI: 1.04–2.19) expressed a significantly higher likelihood causing more grade ≥ 3 adverse events (Figure 3d). Meanwhile, tislelizumab + CT (OR = 0.86; 95% CI: 0.47–1.57) and durvalumab + CT (OR = 0.98, 95% CI: 0.68–1.40) expressed lower possibility to cause grade ≥3 AEs versus CT but without statistically significant differences. Among ICI-based regimens, benmelstobart + anlotinib + CT caused more grade ≥3 AEs compared with durvalumab + CT (OR = 2.07, 95% CI: 1.02–4.29). The common reported adverse events of grade ≥3 for the immunotherapy combinations are shown in Table S5.

Subgroup-level NMA for OS

We performed a network meta-analysis to examine the impact of subgroup factors including, age, gender, smoking status, physical status and metastasis sites (Table S6) on the survival outcomes. In male patients, all ICI-based regimens but atezolizumab + CT (HR = 0.83; 95% CI: 0.63–1.1), durvalumab + tremelimumab + CT (HR = 0.83; 95% CI: 0.67–1.04), ipilimumab + CT (HR = 1.07; 95% CI: 0.89–1.28) and tiragolumab + atezolizumab + CT (HR = 0.92; 95% CI: 0.63–1.34) significantly improved OS versus CT (Figure 5a). However, in female patients only benmelstobart + anlotinib + CT (HR = 0.30; 95% CI: 0.12–0.75), atezolizumab + CT (HR = 0.64; 95% CI: 0.43–0.95) and durvalumab + CT (HR = 0.65; 95% CI: 0.45–0.94) demonstrated superior OS benefit versus CT, with statistically significant differences (Figure 5b). Among all ICI-based regimens, benmelstobart + anlotinib + CT was associated with the best OS HR in both genders.

In patients under the age of 65, all ICI-based regimens but atezolizumab + CT (HR = 0.94; 95% CI: 0.69–1.29), ipilimumab + CT (HR = 1.08; 95% CI: 0.89–1.3), pembrolizumab + CT (HR = 0.83; 95% CI: 0.61–1.12) and tiragolumab + atezolizumab + CT (HR = 1.02; 95% CI: 0.66–1.59) significantly improved OS versus CT, with serplulimab + CT (HR = 0.62; 95% CI:0.45–0.86) associated with the best HR (Figure 5c). Among patients aged 65 years or older, only benmelstobart + anlotinib + CT

TABLE 2 Comparing the OS rate of immunotherapy combinations to chemotherapy at the third, sixth, ninth, 12th, 15th, 18th, 21st, and 24th month, with ORs and 95% CI.

Time (months)	Ade + chemo	Ate + chemo	Dur + Tre + chemo	Dur + chemo	Ipi + chemo	Pem + chemo	Ser + chemo	Ben + Anl + chemo	Tis + chemo	Tor + chemo
Third	0.51 (0.17, 1.4)	1.48 (0.62, 3.7)	0.72 (0.39, 1.3)	0.99 (0.53, 1.85)	0.82 (0.34, 1.93)	0.49 (0.24, 0.98)	1.37 (0.55, 3.29)	1.27 (0.32, 5.36)	0.5 (0.19, 1.18)	0.82 (0.23, 2.79)
Sixth	0.75 (0.41, 1.36)	1.16 (0.67, 2)	0.8 (0.53, 1.2)	0.99 (0.65, 1.53)	1.22 (0.87, 1.73)	1.09 (0.71, 1.69)	**2.29 (1.4, 3.75)**	1.57 (0.89, 2.83)	0.99 (0.55, 1.75)	1.47 (0.81, 2.7)
Ninth	1.08 (0.71, 1.63)	1.22 (0.82, 1.84)	1.06 (0.75, 1.49)	**1.46 (1.03, 2.07)**	1.11 (0.86, 1.44)	1.06 (0.73, 1.54)	**1.71 (1.16, 2.51)**	1.31 (0.88, 1.97)	1.1 (0.73, 1.67)	1.35 (0.87, 2.11)
12th	**1.49 (1.03, 2.17)**	**1.67 (1.12, 2.48)**	1.19 (0.85, 1.68)	**1.74 (1.23, 2.45)**	1.07 (0.83, 1.38)	1.28 (0.88, 1.87)	**1.6 (1.12, 2.28)**	**1.74 (1.21, 2.5)**	1.19 (0.82, 1.75)	1.42 (0.97, 2.08)
15th	**1.61 (1.11, 2.33)**	**1.96 (1.3, 2.96)**	1.21 (0.85, 1.74)	**1.56 (1.1, 2.23)**	1.22 (0.92, 1.61)	**1.59 (1.07, 2.38)**	**1.92 (1.36, 2.71)**	**2.28 (1.58, 3.29)**	**1.46 (1.01, 2.11)**	1.43 (0.98, 2.08)
18th	**1.88 (1.27, 2.77)**	**1.92 (1.24, 3.02)**	1.38 (0.95, 2.03)	**1.48 (1.02, 2.15)**	1.24 (0.89, 1.73)	1.49 (0.98, 2.29)	**1.62 (1.14, 2.29)**	**3.1 (2.14, 4.55)**	1.45 (1, 2.14)	1.37 (0.93, 2.03)
21st	**1.97 (1.31, 2.97)**	1.51 (0.94, 2.44)	1.47 (0.98, 2.21)	1.44 (0.96, 2.16)	1.08 (0.73, 1.58)	**1.82 (1.14, 2.92)**	-	**2.49 (1.7, 3.68)**	**1.56 (1.05, 2.33)**	1.44 (0.95, 2.2)
24th	**2.25 (1.44, 3.54)**	1.34 (0.82, 2.22)	**1.73 (1.12, 2.7)**	**1.71 (1.09, 2.68)**	1.46 (0.95, 2.26)	**2.31 (1.38, 3.97)**	-	**2.25 (1.53, 3.34)**	**1.78 (1.17, 2.73)**	1.41 (0.9, 2.22)

Note: Results with statistically significant differences are shown in bold.

Chemo, chemotherapy; Ade + chemo, adebrelimab + chemotherapy; Ate + chemo, atezolizumab + chemotherapy; Dur + Tre + chemo, durvalumab + tremelimuamb + chemotherapy; Dur + chemo, durvalumab + chemotherapy; Ipi + chemo, ipilimumab + chemotherapy; Pem + chemo, pembrolizumab + chemotherapy; Ser + chemo, serplulimab + chemotherapy; Ben + Anl + chemo, benmelstobart + anlotinib + chemotherapy; Tis + chemo, tislelizumab + chemotherapy; Tor + chemo, toripalimab + chemotherapy.

Abbreviations: CI: confidence intervals; ORs: odds ratios; OS: overall survival.

(HR = 0.54; 95% CI: 0.36–0.82), atezolizumab + CT (HR = 0.59; 95% CI: 0.42–0.83) and serplulimab + CT (HR = 0.60; 95% CI: 0.40–0.89) significantly improved OS with the anlotinib containing regimen associated with the best OS HR (Figure 5d).

Subgroup survival data for patients with liver metastasis are available in six studies. In patients with liver metastasis, although some ICI-based regimens showed good OS, only tislelizumab + CT (HR = 0.65; 95%: 0.44–0.95) shown significantly superior OS versus CT (Figure 6a). Tislelizumab + CT also demonstrated a better OS tendency versus adebrelimab + chemotherapy (HR = 0.71; 95% CI: 0.42–1.19), durvalumab + tremelimumab + CT (HR = 0.72; 95% CI: 0.45–1.16), durvalumab + CT (HR = 0.75; 95% CI: 0.46–1.20), and benmelstobart + anlotinib + CT (HR = 0.82; 95% CI: 0.47–1.43), although there were no statistically significant differences observed. In patients without liver metastasis, only atezolizumab + CT (HR = 0.76; 95%: 0.57–1.02) and pembrolizumab + CT (HR = 0.82; 95%: 0.62–1.08) failed to demonstrate OS superiority versus CT, with benmelstobart + anlotinib + CT (HR = 0.51; 95%: 0.36–0.72) presenting the best OS HR (Figure 6b). Benmelstobart + anlotinib + CT also demonstrated significant better OS versus pembrolizumab + CT (HR = 0.62; 95%: 0.40–0.97) and tendency of superiority versus atezolizumab + CT (HR = 0.67; 95%: 0.43–1.06), durvalumab + tremelimumab + CT (HR = 0.69; 95%: 0.45–1.06), durvalumab + CT (HR = 0.75; 95%: 0.49–1.15) and tislelizumab + CT (HR = 0.68; 95%: 0.44–1.04).

Subgroup survival data for patients with brain metastasis were available in five studies. In patients with brain metastasis, no ICI-based regimens showed significantly superior OS versus CT (Figure 6c). But serplulimab + chemotherapy (HR = 0.61; 95%: 0.33–1.13) and benmelstobart + anlotinib + chemotherapy (HR = 0.64; 95%: 0.29–1.41) demonstrated a better OS tendency versus CT without statistically significant difference, which might be due to small sample size of patients with brains metastasis. In patients without brain metastasis, except for tiragolumab + atezolizumab + CT (HR = 0.87; 95% CI: 0.62–1.21), other ICI-based regimens all demonstrated superior OS versus CT with statistically significant differences, with benmelstobart + anlotinib + CT (HR = 0.60; 95%: 0.45–0.80) showing the best OS HR (Figure 6d). Benmelstobart + anlotinib + CT also showed the tendency of superiority versus pembrolizumab + CT (HR = 0.80; 95%: 0.56–1.14), tislelizumab + CT (HR = 0.80; 95%: 0.56–1.14) and tiragolumab + atezolizumab + CT (HR = 0.69; 95% CI: 0.45–1.08).

Rank possibility

It is important to acknowledge that the purpose of treatment ranking is primarily to provide support rather than definitive evidence for the final choice of treatment. The ranking profiles for the efficacy and safety of ICI-based combinations

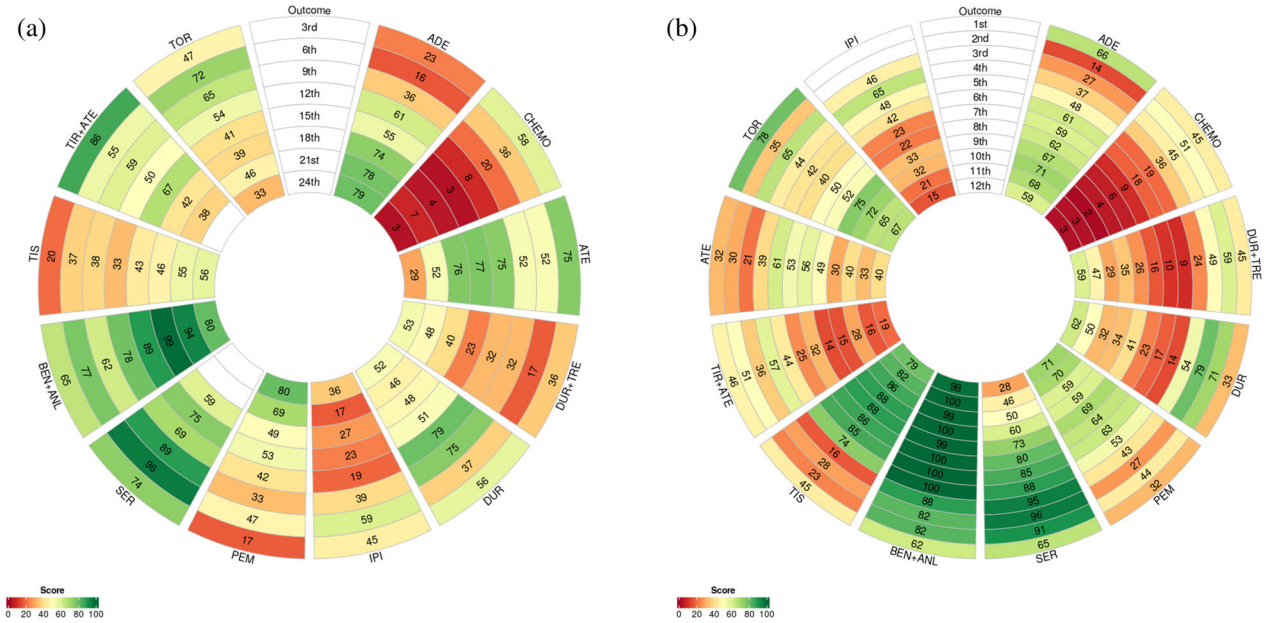

FIGURE 4 The rank-heat plot presented in this study illustrates the evaluation of various therapies used as first-line treatment for patients with extensive-stage small cell lung cancer (ES-SCLC). The sectors in the plot are color-coded based on the surface under the cumulative ranking (SUCRA) value, which represents the overall ranking of each treatment and outcome. (a) SUCRA values for overall survival (OS). (b) SUCRA values for progression-free survival (PFS). The circles in the plot represent the SUCRA values for OS at third, sixth, ninth, 12th, 15th, 18th, 21st, and 24th month for immunotherapy combinations compared to chemotherapy, as well as the SUCRA values for PFS at first, second, third, fourth, fifth, sixth, seventh, eighth, ninth, 10th, 11th, and 12th month. Chemo, chemotherapy; Ade, adebrelimab; Ate, atezolizumab; Dur + Tre, durvalumab + tremelimuamb; Dur, durvalumab; Ipi, ipilimumab; Pem, pembrolizumab; Ser, serplulimab; Ben + Anl, benmelstobart + anlotinib; Tis, tislelizumab; Tir + Ate, tiragolumab + atezolizumab; Tor, toripalimab.

and chemotherapy are shown in Figure 7. The cumulative probability in the first ranking (V1) indicated that benmelstobart + anlotinib + CT and serplulimab + CT had the highest (48.4%) and second highest (35.4%) possibilities of improving OS versus CT only. Benmelstobart + anlotinib + CT also had the highest possibility (99.4%) of improving PFS and the highest possibility (69.4%) of enhancing ORR. In various subgroups, benmelstobart + anlotinib + CT demonstrated the highest possibility of ranking first for OS improvement in female patients (79.7%), patients aged 65 years or older (43.7%), patients without liver metastasis (72.9%) and patients without brain metastasis (46.8%). For male patients, benmelstobart + anlotinib + CT (38.5%) and serplulimab + CT (38.2%) had similar possibilities of ranking first for OS improvement. Meanwhile, serplulimab + CT demonstrated the highest possibility of ranking first for OS improvement in patients under the age of 65 years (41.6%) and patients with brain metastasis (44.0%). For patients with liver metastasis, tislelizumab + CT demonstrated the highest possibility (48.8%) of ranking first for OS improvement. In terms of safety, tislelizumab + CT also demonstrated the highest (35.3%) possibility to rank first for causing less grade ≥3 AEs.

DISCUSSION

To date, several ICIs have already been approved as first-line therapies for ES-SCLC. However, ICIs as single agents or in combination with chemotherapy result in a prolonged benefit for only a small proportion of patients. There is an unmet need for survival improvement for SCLC patients and more novel regimens especially a combination of ICIs, to be investigated. Unfortunately, the addition of tiragolumab to atezolizumab and CT has failed to present survival improvement versus atezolizumab + CT at interim analysis for either PFS or OS in Skyscraper-02 study.[33,34] By contrast, inspiring results from the new study ETER701 on benmelstobart + anlotinib + CT reported in WCLC 2023 showed the historically best PFS of 6.93 months and best OS of 19.32 months. However, the benefits and safety of these ICI-based regimens as first-line agents have not been compared directly and the optimal agent for patients in different clinically relevant subgroups is as yet unknown, especially when much superior survival benefit versus CT has emerged. Thus, we carried out this NMA to compare the survival benefit and safety of currently available ICI-based regimens for ES-SCLC and probed into the most appropriate therapy for patients. To the best of our knowledge, herein we have analyzed all available results of ICIs (PD-1, PD-L1, and CTLA-4 inhibitors) in combination with platinum and etoposide from phase III RCTs. We included the results of three novel ICI-based combinations tislelizumab + CT, benmelstobart + anlotinib + CT and toripalimab + CT for the first time, which have not been included in previous ES-SCLC NMA.

In accordance with previous studies, the results of current NMA have suggested that both anti-PD-1/PD-L1

TABLE 3 Comparing the PFS rate of immunotherapy combinations to chemotherapy at the first, second, third, fourth, fifth, sixth, eighth, ninth, 10th, 11th and 12th month, with odds ratios and 95% CI.

Time (months)	Ade + chemo	Ate + chemo	Dur + Tre + chemo	Dur + chemo	Ipi + chemo	Pem + chemo	Ser + chemo	Ben + Anl + chemo	Tis + chemo	Tor + chemo
First	2.32 (0.18, 70.51)	0.8 (0.31, 2)	1 (0.4, 2.5)	0.8 (0.31, 2)	-	0.77 (0.27, 2.16)	1.58 (0.37, 6.23)	1.41 (0.55,3.74)	0.99 (0.17, 5.83)	3.92 (0.43113.15)
Second	0.56 (0.26, 1.12)	0.75 (0.38, 1.45)	1.1 (0.66, 1.84)	1.29 (0.76, 2.2)	-	0.92 (0.49, 1.7)	1.94 (0.95, 3.97)	1.57 (0.87, 2.9)	0.66 (0.32, 1.34)	0.79 (0.34, 1.79)
Third	0.81 (0.46, 1.42)	0.77 (0.47, 1.26)	1.04 (0.69, 1.57)	1.47 (0.95, 2.29)	1 (0.66, 1.53)	0.82 (0.5, 1.32)	**2.14 (1.29, 3.53)**	1.56 (0.98, 2.51)	0.83 (0.49, 1.39)	1.26 (0.72, 2.25)
Fourth	0.99 (0.61, 1.63)	1.02 (0.66, 1.59)	0.89 (0.6, 1.3)	1.15 (0.77, 1.71)	1.26 (0.93, 1.71)	1.04 (0.68, 1.58)	**2.03 (1.29, 3.17)**	**1.74 (1.15, 2.68)**	0.81 (0.52, 1.25)	1.06 (0.63, 1.79)
Fifth	1.29 (0.87, 1.92)	1.45 (0.98, 2.17)	0.86 (0.61, 1.2)	0.92 (0.66, 1.29)	1.28 (0.99, 1.66)	1.35 (0.93, 1.97)	**2.28 (1.6, 3.26)**	**4.08 (2.8, 5.95)**	**1.73 (1.19, 2.51)**	1.21 (0.81, 1.79)
Sixth	**1.64 (1.13, 2.38)**	1.46 (0.93, 2.31)	0.89 (0.63, 1.25)	0.98 (0.7, 1.37)	1.28 (0.96, 1.71)	**1.69 (1.12, 2.56)**	**2.6 (1.82, 3.72)**	**6.22 (3.98, 10)**	**2.65 (1.72, 4.13)**	1.26 (0.86, 1.86)
Seventh	**1.91 (1.29, 2.84)**	**1.81 (1.09, 3.03)**	1.06 (0.73, 1.55)	1.16 (0.8, 1.7)	1.17 (0.85, 1.62)	**2.08 (1.32, 3.35)**	**2.74 (1.9, 3.98)**	**6.68 (3.84, 12.33)**	**3.24 (2.02, 5.33)**	**1.68 (1.12, 2.55)**
Eighth	**2.23 (1.45, 3.45)**	**1.83 (1.07, 3.2)**	1.33 (0.89, 2.01)	**1.65 (1.11, 2.49)**	1.26 (0.89, 1.79)	**2.5 (1.51, 4.27)**	**2.62 (1.8, 3.82)**	**7.78 (4.3, 15.12)**	**3.92 (2.34, 6.79)**	**1.93 (1.24, 3.04)**
Ninth	**2.7 (1.65, 4.49)**	1.48 (0.83, 2.65)	**1.64 (1.05, 2.6)**	**1.62 (1.04, 2.54)**	**1.61 (1.07, 2.47)**	**2.4 (1.34, 4.45)**	**2.35 (1.62, 3.46)**	**15.2 (6.4, 45.68)**	**4.78 (2.66, 9.1)**	**3.19 (1.88, 5.57)**
10th	**3.26 (1.86, 5.92)**	**1.99 (1.05, 3.88)**	**1.71 (1.05, 2.79)**	**1.79 (1.12, 2.91)**	**1.79 (1.15, 2.84)**	**2.66 (1.43, 5.2)**	**2.28 (1.56, 3.38)**	**18.12 (6.25, 82.3)**	**4.8 (2.59, 9.54)**	**3.3 (1.86, 6.13)**
11th	**3.39 (1.91, 6.28)**	1.87 (0.96, 3.75)	**2.41 (1.42, 4.21)**	**2.54 (1.5, 4.39)**	1.53 (0.96, 2.5)	**3.61 (1.83, 7.74)**	**2.37 (1.61, 3.54)**	**28.34 (7.99, 200.28)**	**4.67 (2.52, 9.34)**	**3.26 (1.81, 6.17)**
12th	**3.85 (2.1, 7.54)**	**2.55 (1.16, 6.02)**	**3.84 (2.09, 7.48)**	**4.02 (2.21, 7.83)**	1.47 (0.85, 2.58)	**5.08 (2.3, 12.98)**	**2.1 (1.42, 3.16)**	**44.9 (7.93, 1249)**	**5.91 (3.01, 12.93)**	**4.45 (2.36, 9.14)**

Note: Results with statistically significant differences are shown in bold.

Chemo, chemotherapy; Ade + chemo, adebrelimab + chemotherapy; Ate + chemo, atezolizumab + chemotherapy; Dur + Tre + chemo, durvalumab + tremelimuamb + chemotherapy; Dur + chemo, durvalumab + chemotherapy; Ipi + chemo, ipilimumab + chemotherapy; Pem + chemo, pembrolizumab + chemotherapy; Ser + chemo, serplulimab + chemotherapy; Ben + Anl + chemo, benmelstobart + anlotinib + chemotherapy; Tis + chemo, tislelizumab + chemotherapy; Tor + chemo, toripalimab + chemotherapy.

Abbreviations: CI: confidence intervals; ORs: odds ratios; PFS: progression-free survival.

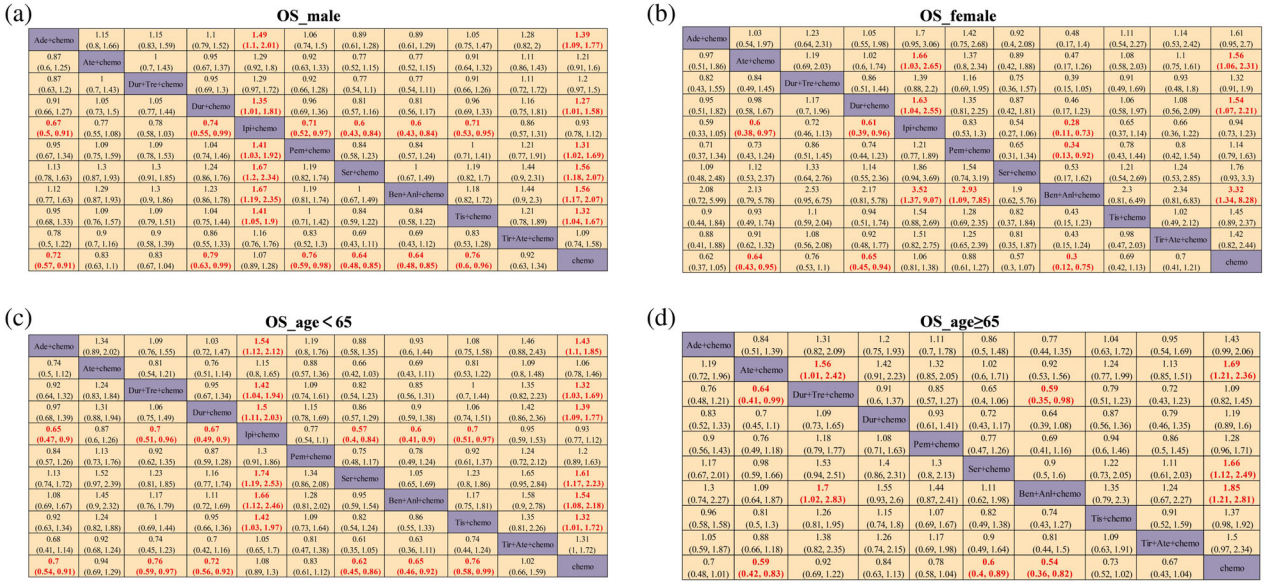

FIGURE 5 Efficacy and safety characteristics of Bayesian network meta-analysis in patients with extensive-stage small cell lung cancer (ES-SCLC). (a) Hazard ratios (HRs) and 95% confidence interval (CI) in male patients with ES-SCLC. (b) HRs and 95% CI in female patients with ES-SCLC. (c) HRs and 95% CI in patients aged <65 with ES-SCLC. (d) HRs and 95% CI in patients aged ≥65 with ES-SCLC. Significant results are shown in bold and red. Chemo, chemotherapy; Ade + chemo, adebrelimab + chemotherapy; Ate + chemo, atezolizumab + chemotherapy; Dur + Tre + chemo, durvalumab + tremelimuamb + chemotherapy; Dur + chemo, durvalumab + chemotherapy; Ipi + chemo, ipilimumab + chemotherapy; Pem + chemo, pembrolizumab + chemotherapy; Ser + chemo, serplulimab + chemotherapy; Ben + Anl + chemo, benmelstobart + anlotinib + chemotherapy; Tis + chemo, tislelizumab + chemotherapy; Tir + Ate + chemo, tiragolumab + atezolizumab + chemotherapy. OS, overall survival.

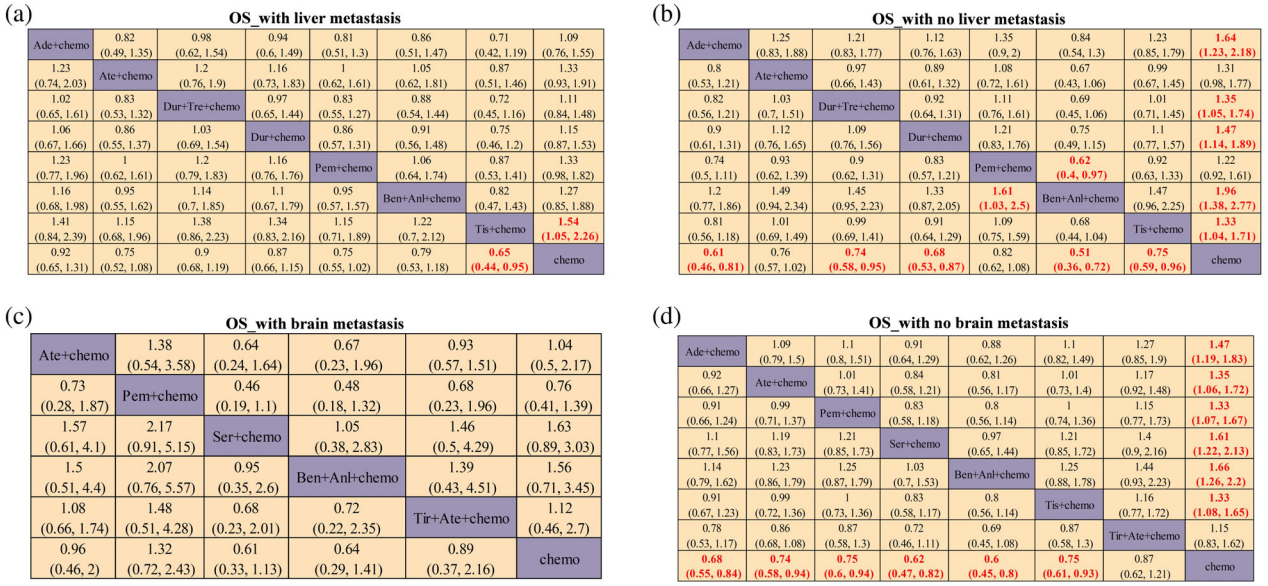

FIGURE 6 Efficacy and safety characteristics of Bayesian network meta-analysis in patients with extensive-stage small cell lung cancer (ES-SCLC). (a) Hazard ratios (HRs) and 95% confidence interval (CI) in ES-SCLC patients with liver metastasis. (b) HRs and 95% CI in ES-SCLC patients with no liver metastasis. (c) HRs and 95% CI in ES-SCLC patients with brain metastasis (d) HRs and 95% CI in ES-SCLC patients with no brain metastasis. Significant results are shown in bold and red. Chemo, chemotherapy; Ade + chemo, adebrelimab + chemotherapy; Ate + chemo, atezolizumab + chemotherapy; Dur + Tre + chemo, durvalumab + tremelimuamb + chemotherapy; Dur + chemo, durvalumab + chemotherapy; Ipi + chemo, ipilimumab + chemotherapy; Pem + chemo, pembrolizumab + chemotherapy; Ser + chemo, serplulimab + chemotherapy; Ben + Anl + chemo, benmelstobart + anlotinib + chemotherapy; Tis + chemo, tislelizumab + chemotherapy; Tir + Ate + chemo, tiragolumab + atezolizumab + chemotherapy. OS, overall survival.

antibodies plus chemotherapy strategy could significantly prolong PFS and OS versus CT alone. For the novel antiangiogenic agent containing combination, our NMA analysis showed for the first time that benmelstobart + anlotinib + CT achieved significantly better PFS and OS with the lowest HR of 0.32 and 0.61 versus CT, which was also

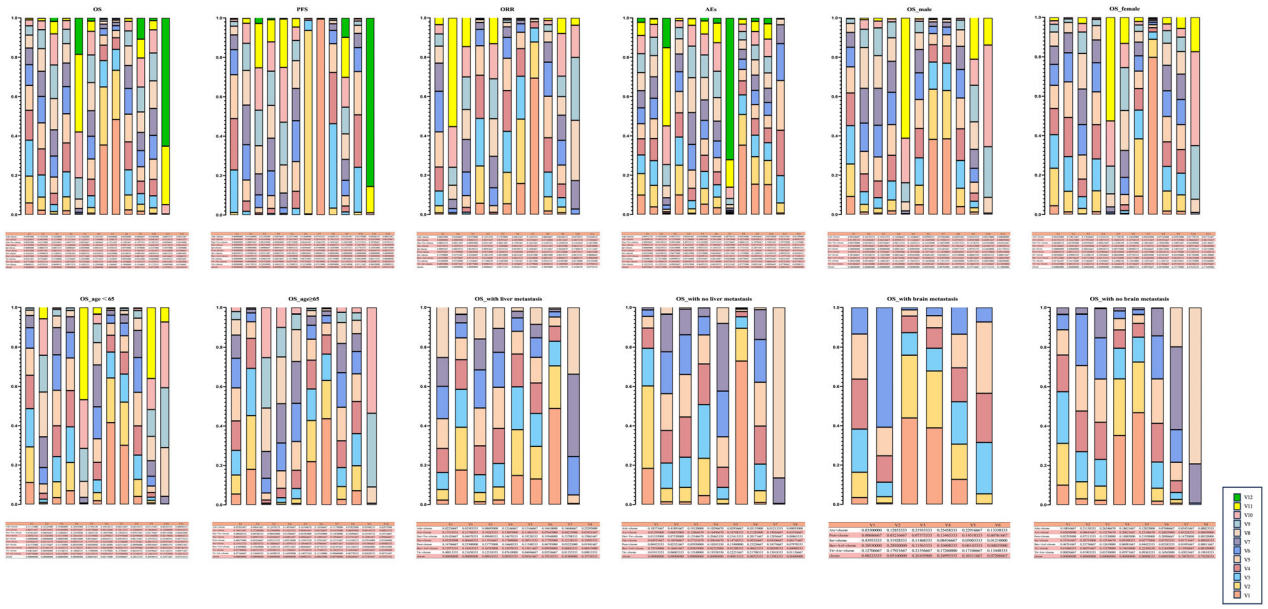

FIGURE 7 Bayesian ranking profiles from the most likely to the least likely to cause less grades ≥3 adverse events (AEs) or from the most effective to the least effective immunotherapies in the overall population. The top spot demonstrates the highest chances of improving overall survival (OS), extending progression-free survival (PFS), or being the most likely to cause less grades ≥3 AEs.

associated with the best ORR of 2.17 versus CT. In comparison to ICIs + CT, this regimen also presented a tendency of OS superiority, although the difference did not reach statistical significance, except for ipilimumab + CT with HR of 0.65. According to Bayesian ranking profiles, this novel combination showed the highest possibility to present the best PFS and OS versus CT. According to the subgroup analysis results, male patients were more likely to benefit from ICIs + CT than female patients and benmelstobart + anlotinib + CT showed better survival in both male and female subgroups. Younger patients might tend to achieve better overall survival through combination therapies, which may be due to their better physical condition. Benmelstobart + anlotinib + CT and serplulimab + CT significantly improved OS of both younger patients (age < 65) and elderly patients (age ≥ 65), while atezolizumab + CT only improved survival of older patients but with a good HR of 0.59. As for specific metastatic sites, although benmelstobart + anlotinib + CT achieved better efficacy in the total population and in most of the subgroups, it did not show significantly better OS versus CT in the liver or brain metastasis subgroups. In patients with liver metastasis, only tislelizumab + CT (HR = 0.65) shown superior OS versus CT, which might be preferred in patients with liver metastases. None of the combinations showed superiority in patients with brain metastasis, which might be due to the limited sample size of patients with brain metastasis. From the longitudinal perspective of survival improvement, we found that all ICI-based regimens but ipilimumab + CT improved 12th month PFS rate while atezolizumab, durvalumab, serplulimab, adebrelimab and benmelstobart plus anlotinib were first echelon agents versus placebo for OS at the 12th to 18th month. At the 24th month, only atezolizumab + CT, ipilimumab + CT and toripalimab + CT failed to showed better OS rate versus CT.

The combination of CT with ICIs allows for boosting of the immune system, which results in immunogenic tumor cell death and the release of immunogenic tumor-specific antigens, thereby activating the cytotoxic T cell antitumor response. For PD-1 monoclonal antibody studies in the first-line treatment of ES-SCLC, the failure of immunotherapy combinations such as pembrolizumab has led researchers to doubt the feasibility of PD-1 monoclonal antibody studies in ES-SCLC. Recently several studies have showed different results. These results suggest that PD-1 monoclonal antibody combined with chemotherapy may also be a standard treatment for ES-SCLC. As the immune response is dynamic, combination therapy may also further improve patient survival compared to monotherapy. Antiangiogenic agents, radiation therapy, and T cell modulation are all under investigation for combination with immunotherapy. Studies have revealed the synergistic effects of antiangiogenic agents with immunotherapy could reprogram the tumor microenvironment from being immunosuppressive to an immune permissive microenvironment, and thus could be an opportunity to overcome immunotherapy resistance.[35–37] Diverse combination regimens involving ICIs (PD-1, PD-L1, and CTLA-4 inhibitors) with inhibitors of vascular endothelial growth factor (VEGF) pathway such as anti-VEGF antibody, anti-VEGFR antibody, or VEGFR TKI have shown improved clinical benefit than ICIs or antiangiogenic monotherapy, providing a hopeful solution to

improve SCLC outcomes.[38–40] In our study, the superior efficacy of benmelstobart + anlotinib + CT further supported the underlying synergistic action of anti-PD-L1 antibody and antiangiogenic agent with chemotherapy combination, in which the reversal of VEGF-mediated immunosuppression by anlotinib and chemotherapy-induced cell death potentiated T cell-mediated killing activated by benmelstobart in tumor microenvironment. Another recently reported single-arm phase II trial explored if the addition of VEGF antibody bevacizumab to first-line atezolizumab-carboplatin-etoposide could improve survival in ES-SCLC. This combination presented with an improved 1-year OS rate of 61.8% but only with a median OS of 12.7 months and median PFS of 6.2, which might justify further studies of the ICI plus anti-angiogenesis combination.[41] These results might indicate that monoclonal antibodies and small molecules TKIs may not be exactly the same. Diverse results and mechanisms of different antiangiogenic drugs in combination with immunotherapy need to be studied further in the future. Clinicians also need to consider the patient eligibility criteria, molecular typing and risks of anti-angiogenic drugs when making decisions.

Tiragolumab is an anti-T cell immunoreceptor with Ig and ITIM domains (anti-TIGIT) antibody that was given breakthrough therapy designation by the US Food and Drug Administration (FDA) for treatment of PD-L1-high metastatic NSCLC, which was based off of the promising phase II CITYSCAPE study.[42] However, SKYSCRAPER-02 showed that the addition of tiragolumab to atezolizumab plus CT did not provide a PFS or OS benefit compared with atezolizumab and CT for ES-SCLC.[33,34] Comparing IMpower133 and Skyscraper-02, the control arm outperformed expectations in the Skyscraper-02 study, which is likely the cause of negative endpoints. Certainly, the reason for this is unclear and maybe related to the molecular subtypes of SCLC. Clarifying mechanisms of immune regulation within SCLC and its subtypes may improve the identification of patients who may derive benefit from TIGIT inhibition as part of an immunotherapy combination.[43]

The status of liver metastasis (LM) has been evaluated as a predictive biomarker in patients receiving ICIs, suggesting cancer patients with LM derive limited benefit from immunotherapy independent of other established biomarkers of response.[44] Mechanisms underlying hepatic immune tolerance include ineffective immune synapses resulting in T cell anergy, regulatory T cell induction or effector T cell elimination.[44] Hepatocellular carcinoma is associated with hypoxic tumor conditions, high VEGF expression, and increased angiogenesis, which can contribute to the induction of immunosuppressive immune-cell types (e.g., myeloid-derived suppressor cells and regulatory T cells), the promotion of immune tolerance in the tumor microenvironment,[45] and abrogate immunotherapy efficacy in preclinical models.[44] Antiangiogenic agents could reverse the VEGF-mediated immunosuppression as an underlying choice to enhance the antitumor activity of ICIs in patients with LM. Therefore, combination treatment with an ICI and an antiangiogenic agent has been an effective strategy for the treatment of primary hepatocellular carcinoma as well as many solid tumors with LM.[39,46,47] More importantly, LM from lung cancer have been shown to respond to treatment in a way to more like liver cancer than primary lung cancer.[48] For example, in the IMpower150 trial of NSCLC, the survival benefit of the atezolizumab + bevacizumab + CT regimen was more pronounced than bevacizumab + CT or atezolizumab + CT in patients with LM.[38] However, in the present study, among the nine combinations only tislelizumab + CT significantly improved OS of patients with LM. It is surprising that benmelstobart + anlotinib + CT failed to significantly prolong the OS of patients with LM (HR 0.79), in spite of its inspiring therapeutic effect in the whole experimental arm. However, the PFS of benmelstobart + anlotinib + CT in LM group are superior than CT (HR 0.36).[23] The explanation for these findings may lie in the immunosuppressive microenvironment within LM, which has been reported to undermine the efficacy of immunotherapy.[49] In addition, the results may also be influenced by the smaller sample size of LM subgroup and thus need further exploration.

More than 50% of SCLC patients may experience brain metastases (BM) during the disease course.[50] The prognosis of ES-SCLC with BM is dismal and only patients with asymptomatic BM or treated BM stable off steroids could be included in randomized controlled trials. Different clinical trials and retrospective studies have evaluated the effect of ICI alone or in combination with other interventions in lung cancer patients with BM suggesting the efficacy of ICI in patients with BM was worse than those without BM.[51] In addition, data from recent studies of ICIs in patients with NSCLC having brain metastases supported the notion that the brain was an immune privileged site.[52–54] Similarly, the current study also showed no survival benefit from ICIs + CT versus CT in patients with BM, even with anlotinib in combination, which may be due to the small sample size of enrolled patients with BM. However, recent updates from the CASPIAN study indicated that durvalumab plus EP prolonged the time to brain progression or cranial radiotherapy, suggesting that this combination may delay intracranial progression.[55] In our study, serplulimab + CT and benmelstobart + anlotinib + chemotherapy actually demonstrated a tendency toward better OS versus CT and the results might be different after expanding the sample size of patients with BM. It has been suggested that the combination of brain radiotherapy and ICIs has a synergistic effect,[56,57] thus the combination of brain radiotherapy and ICI-based regimens is worthy of further study in future.

In terms of safety and toxicity, the ICI + CT combinations were not associated with unexpected safety events and all adverse events were generally manageable as previously reported, among which tislelizumab + CT seemed to be the safest ICI + CT regimen. The incidence and type of treatment-related adverse events and treatment

discontinuation in patients receiving ICI + CT were similar with that observed in patients with NSCLC receiving ICI + CT.[58,59] However, patients treated with benmelstobart + anlotinib + CT and durvalumab + tremelimumab + CT suffered a higher likelihood of grade ≥3 AEs, which might be due to the additional adverse effects of four drug combinations. In the CASPIAN study, durvalumab + tremelimumab + CT was associated with a higher incidence of grade ≥3 AEs, serious adverse events, and adverse events leading to death or discontinuation.[16] Elevated adverse events reduced drug exposure and might thus ultimately impair overall survival in the durvalumab + tremelimumab + CT group. As for benmelstobart + anlotinib + CT, the additional AEs might be mainly induced by VEGFR2-TKI anlotinib, including hypertension, proteinuria and bleeding, which were generally easier to be manageable and tolerable in comparison to AEs induced by ICIs combination of durvalumab + tremelimumab.[16,23] The adverse events which led to discontinuation were 8.1% in the benmelstobart + anlotinib + CT group versus 21% in the durvalumab + tremelimumab + CT group, indicating the potentially better safety of ICI plus antiangiogenic agents compared with anti-CTL4A antibody.[16,23] In the benmelstobart + anlotinib + CT group, ≥3 grade AEs of platelet count decreased, hypertension, hypertriglyceridemia, palmar-plantar erythrodysesthesia syndrome were higher to those with chemotherapy alone. The adverse effects were predictable and most adverse events are manageable.

The advent of first-line immunochemotherapy as a new standard care for ES-SCLC is a remarkable hallmark of progress. However, it is disappointing that by now there have still been no broadly accepted biomarkers which could predict the limited benefit from ICI in ES-SCLC. In contrast to other solid tumors, PD-L1 expression level does not seem to be correlated with immunotherapy benefit in SCLC.[21] It is well known that SCLC has a high TMB which is predicted to be able to induce strong T cell responses. However, the role of TMB as a predictive biomarker of SCLC response to immunotherapy is also controversial as results from the Checkmate-032 study suggested a correlation but blood-based TMB analysis from Impower133 study showed no evident association.[14,60] Generally, to date, only limited efficacy from T cell-based immunotherapy has been achieved in this refractory and lethal malignancy, which could be explained by multiple mechanisms including the low expression of major histocompatibility complex (MHC) class I molecules on the surface of SCLC cells,[61] the low expression of PD-L1, poor tumor infiltration by effector T cells, presence of myeloid-derived suppressor cells and regulatory T lymphocytes which counteract the immune system activation by checkpoint inhibitors as well as hypoxia.[2,5,26,62] Recently, intensive clinical research has been focused on the exploration of complementary pathways leading to immune activation, including the blockade of alternative immune checkpoints and combination of antiangiogenic agents. The anlotinib containing four-drug combination has presented a historically best OS and PFS in ES-SCLC but whether the PD-L1 or TMB level could predict its efficacy has not been released in WCLC 2023, which is worthy of follow up.

By comparing the efficacy and safety profiles of novel ICI-based treatment combinations for ES-SCLC, this timely study aimed to provide instruction in order to choose the most appropriate immunotherapy agent and combination pattern for SCLC patients in the clinical work. The novel combination of ICI and antiangiogenic agent with chemotherapy yielded the best survival benefit for ES-SCLC patients, although it caused more adverse effects which are generally well manageable. With further follow up for its efficacy and safety, this therapy may become a mainstream option for patients with ES-SCLC in future. However, it is important to acknowledge that the purpose of treatment ranking is primarily to provide support rather than definitive evidence for the final choice of treatment. As an analysis for the data from phase III clinical trials, the current study has some innate limitations as follows. First, there might be publication bias and potential selection bias limitations because of the missing unpublished literature, though we have proposed a comprehensive retrieval strategy. Second, all the comparison between different ICI-based combinations were not head-to-head and relied on the transitivity and consistency assumptions of different clinical trials. Third, the number of studies that met the inclusion criteria was limited, and the small sample size of the enrolled population could increase the overall uncertainty of the results. Fourth, some data were extracted from slide images presented at meetings, which might be different from the real trial data. Meanwhile, the difference of patient races among trails should be considered. For example, most patients enrolled in the ETER701 study were Asian ES-SCLC patients and the superior efficacy of this novel anlotinib based combination might need to be verified in other populations.

In conclusion, considering OS, PFS, ORR, and safety profiles, the addition of PD-1/PD-L1 inhibitors to chemotherapy resulted in significant improvements in both PFS and OS with manageable safety profile for treatment-naive ES-SCLC patients. The novel antiangiogenic agent containing regimen benmelstobart, anlotinib and chemotherapy further improved survival and showed the highest possibility to present the best PFS and the best OS versus chemotherapy. It might be recommended as the better choice with caution for more but manageable adverse events along with the addition of an antiangiogenic agent.

AUTHOR CONTRIBUTIONS

Chuang Yang: Conceptualization (lead), data curation (lead), methodology (equal) and software (equal). Tiantian Xuan: Formal analysis (lead), methodology (equal), software (equal), writing – original draft (lead). Qing Gong: Methodology (equal), resources (equal), supervision (equal), validation (equal) and visualization (equal). Xin Dai: Methodology (lead), data curation (equal), software (equal), resources

(equal), supervision (equal), validation (equal) and visualization (equal). Chengjun Wang: Methodology (equal), resources (equal), supervision (equal), validation (equal) and visualization (equal). Rongyu Zhang: Methodology (equal), resources (equal), supervision (equal), validation (equal) and visualization (equal). Wen Zhao: Methodology (equal), resources (equal), supervision (equal), validation (equal) and visualization (equal). Jian Wang: Methodology (equal), resources (equal), supervision (equal), validation (equal) and visualization (equal). Weiming Yue: Investigation (lead), writing–review and editing (equal). Jiseeng Li: Funding acquisition (lead), project administration (lead), writing–review and editing (equal). All authors contributed to writing the manuscript and read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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