



# Effectiveness and safety of bevacizumab in extensive-disease small cell lung cancer: a systemic review and meta-analysis

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**Background:** Small cell lung cancer (SCLC) is highly invasive and poorly prognostic. The effects of chemotherapy with bevacizumab are promising on other tumors but unclear in extensive-disease SCLC (ED-SCLC). A systemic review and meta-analysis were performed to investigate the efficacy and toxicity in ED-SCLC patients.

**Methods:** A review of current studies was performed on electronic databases and other sources to identify publications of ED-SCLC patients who received bevacizumab. Endpoints included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and complications.

**Results:** Nine relevant articles with six single-arm and three two-arm studies were identified. Four hundred seventy-six patients were included, of which 368 and 108 were untreated and relapse patients. Most patients were performance status 0–1 (71.6%) and male (58.1%). The comparisons showed CT/bevacizumab slightly prolonged OS (HR =0.84) but significantly improved PFS (HR =0.74). The ORRs of untreated and relapse patients were 71% and 19%, though no significant difference was observed than CT/placebo. The most grade 3–4 complication and bevacizumab-associated complications were neutropenia and hypertension, whose rates were 33% and 6%. Patients who received CT/bevacizumab had a higher hypertension rate than CT/placebo (6% vs. 2%). No different complication rate was observed between high and low dose groups.

**Discussion:** The present study suggests that bevacizumab in the combination of standard chemotherapy provides better PFS than chemotherapy alone. Although the combined regimen is well-tolerated, no superiority in OS or response rate is observed.

**Keywords:** Small cell lung cancer (SCLC); chemotherapy; bevacizumab; prognosis

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## Introduction

Small cell lung cancer (SCLC) is one of the pathological subtypes of lung cancer characterized as highly invasive, poorly prognostic, and easily metastatic. It currently accounts for 12–15% of respiratory malignancies (1,2). A more significant proportion of SCLC patients are primarily diagnosed as extensive-disease (ED-SCLC) at presentation, which is defined as the presence of overt metastatic disease by imaging or physical examination.

Platinum-based etoposide regimen (EP) has been recommended as the first-line treatment for ED-SCLC for the last decades (3), which can yield up to 80% response rate and ten months of survival (4). Other studies reported that the irinotecan/platinum regimen showed a slightly superior or similar effect to the traditional regimen (5–8), which is still unsatisfactory.

Given that vascular endothelial growth factor (VEGF) has been proved to be associated with growth in tumors (9,10) including SCLC (11,12), anti-angiogenic medication is considered a potentially effective treatment in the combination of chemotherapy. Bevacizumab, a humanized monoclonal VEGF antibody, was developed and proved to improve survival in various tumors, including gastric cancer (13), colorectal cancer (14), breast cancer (15), glioblastoma multiforme (16), and non-squamous non-small cell lung cancer (NSCLC). Previous studies on SCLC revealed the ideal survival and response of bevacizumab in both naïve and relapsed SCLC patients (17–22). Besides, some two-arm studies compared the survival outcomes and adverse events (AEs) of SCLC patients who received chemotherapy (CT) with/without bevacizumab (23–25). However, no consensus has been reached on the efficacy of bevacizumab in the combination of CT for treating ED-SCLC.

We, therefore, performed a systemic review and meta-analysis to assess the efficacy and safety of CT/bevacizumab in both untreated and relapse ED-SCLC patients. Besides, the comparisons of survival outcomes and AEs between patients who received CT/bevacizumab and CT/placebo were also analyzed. We present the following article in accordance with the PRISMA reporting checklist (available at <https://dx.doi.org/10.21037/atm-21-963>).

## Methods

### *Literature search strategy and selection criteria*

The initial search for potential publications was performed in four electronic bibliography databases, including

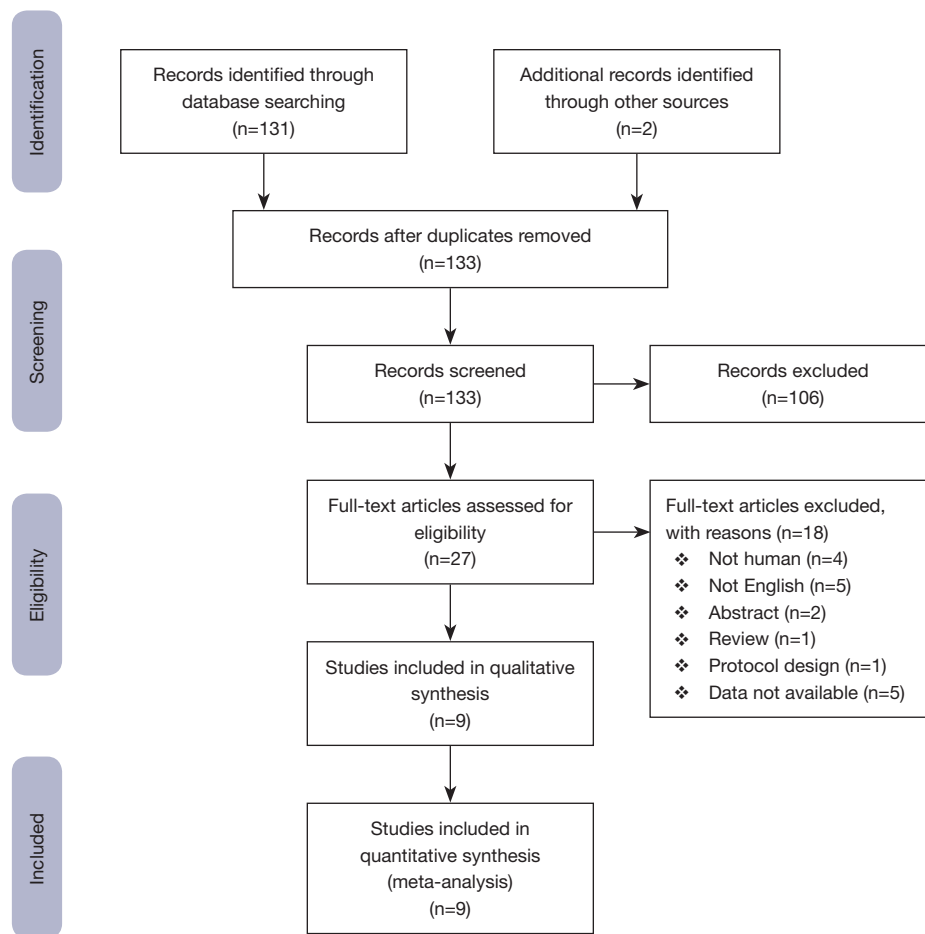
MEDLINE, Web of Science, Embase, and Cochrane Central Register of Controlled Trials from the earliest to March 2020. Unpublished studies and data from other sources were also identified for different screening. Search terms were “small cell lung cancer” and synonyms “chemotherapy” and “Bevacizumab”. The titles and abstracts of publications were initially screened. The full-text evaluation was performed after the exclusion of irrelevant studies. Both single-arm and two-arm studies were included. Review, abstract, brief report, comment, protocol design, or editorial publications were excluded. Language and species were restricted in English and human only, respectively. Publications with duplicate or unavailable data were eventually excluded from data extraction in further evaluation. Two independent individuals finished the initial search. The senior investigators reviewed the final included publications. A total of 27 publications were eligible for full-text assessment. After further evaluation, 18 candidates were excluded for various reasons, and nine studies were selected for meta-analysis (*Figure 1*).

### *Data extraction*

All the data were independently extracted from the articles, tables, figures, and supplements of the publications by two inspectors. The clinical characteristics, numbers of AEs, and time-to-event data, including median overall survival (OS) hazard ratio (HR), progression-free survival (PFS) HR, survival rate, objective response rate (ORR), and disease control rate (DCR) were reviewed and extracted. Some time-to-event data were collected from the Kaplan-Meier curve and its P value (26). ORR is defined as the proportion of complete response and partial response patients, while DCR is defined as the proportion of complete response, partial response, and stable disease patients. Discrepancies in search and selection would be resolved after the discussion with other group members.

### *Statistical analysis*

A systemic review and meta-analysis were performed to evaluate the 1-year survival rate, ORR, DCR, and AE incidence. Besides, OS and PFS comparisons between CT/bevacizumab and CT/placebo were estimated by hazard ratio (HR). AE incidence was evaluated by risk ratio (RR).  $\chi^2$  tests were conducted to assess the fit of distribution.  $I^2$  test was used to estimate the variation across the studies instead of the Q test, whose results were closely related to the



**Figure 1** The flow diagram of study selection process.

number of included studies. The formula calculated the  $I^2$ :  $I^2 = 100\% \times (Q - df) / Q$ ;  $Q$  stood for a heterogeneity statistic, and  $df$  was defined as the degree of freedom ( $df = \text{total number of trials} - 1$ ). The heterogeneity was defined as low (25–49%), moderate (50–74%), or severe (>75%). A random-effect analysis model would be used to calculate the endpoints when the heterogeneity was >50%.  $Z$ -test was performed to calculate the  $p$ -value, which was two-sided and defined as statistically different when  $P < 0.05$ . Funnel plots were used to evaluate the publication bias of the included studies. The statistical analysis was conducted via R (Version 3.6.2).

## Results

### Characteristics of enrolled studies

A total of 133 articles were identified in the initial screening, including 131 from the electronic databases and two from

other sources. Of these articles, 106 were excluded as irrelevant studies. The full-text screening was conducted on 27 publications. Nine publications were eventually selected for data extraction and meta-analysis (17–25) (Figure 1). Three studies were two-arm randomized control trials (23–25) and 6 were single-arm studies (17–22) (Table 1).

A total of 666 patients were included in the cohort. All of them were diagnosed as ED-SCLC, of which 458 previously untreated patients were administered platinum-based doublet regimens, while 108 relapse patients were given topotecan, paclitaxel, or irinotecan. The median ages of patients ranged from 61 to 66 years old. A total of 477 patients received bevacizumab treatment. Most of them (436/477, 71.6%) had performance status (PS) 0–1. Male patients accounted for a larger proportion in the cohort (277/477, 58.1%). Referring to bevacizumab dosage, 229 patients in 4 studies received 15 mg/kg (17,19,21,24), 81 in 2 studies received 10 mg/kg

**Table 1** Overview of the included both single/two-arm studies of ED-SCLC patients received chemotherapy with/without bevacizumab

Study	Year	Study year	Regimen	Primary endpoint	Size	Study type	Randomization
Horn	2009	2004–2006	Cisplatin + etoposide + bevacizumab	OS, PFS	63	Single-arm	Non-randomized
Spigel	2009	2006–2007	Carboplatin + irinotecan + bevacizumab	OS, TTP	51	Single-arm	Non-randomized
Ready	2011	2005–2006	Cisplatin + irinotecan + bevacizumab	OS, PFS	64	Single-arm	Non-randomized
Spigel	2011	2007–2008	Carboplatin + irinotecan ± bevacizumab	OS, PFS	102	Two-arm	Prospective
Mountzio	2012	2007–2010	Paclitaxel + bevacizumab	OS, TTP	30	Single-arm	Non-randomized
Spigel	2013	2008–2010	Topotecan + bevacizumab	OS, PFS	50	Single-arm	Non-randomized
Pujol	2015	2009–2011	Cisplatin + etoposide/cisplatin + etoposide + epioxorubicin + cyclophosphate ± bevacizumab	OS, PFS	74	Two-arm	Prospective
Trafalis	2016	2010–2014	Irinotecan + bevacizumab	OS, PFS	28	Single-arm	Non-randomized
Tiseo	2017	2009–2015	Cisplatin + etoposide ± bevacizumab	OS, PFS	204	Two-arm	Prospective

ED-SCLC, extensive-disease small cell lung cancer; OS, overall survival; PFS, progression-free survival.

**Table 2** The characteristics of patients received bevacizumab in the included studies

Study	Cancer type	Age, median [range]	Performance status		Sex		Bevacizumab dosage (mg/kg)	Cycles	Efficacy	
			0–1	2	Male	Female			ORR	DCR
Horn 2009	Untreated	65 [45–83]	57	6	27	36	15	6	40	50
Spigel 2009	Untreated	66 [46–81]	51	0	29	22	10	6	43	45
Ready 2011	Untreated	62 [38–81]	57	7	31	33	15	6	48	59
Spigel 2011	Untreated	63 [38–82]	45	7	26	26	15	6	30	46
Mountzio 2012	Relapse	64 [43–82]	27	3	27	3	10	4	6	11
Spigel 2013	Relapse	62.5 [28–80]	46	4	24	26	15	8	8	28
Pujol 2015	Untreated	61 [43–75]	33	3	25	12	7.5	6	32	32
Trafalis 2016	Relapse	63.5 [48–73]	25	5	19	9	7.5	6	7	25
Tiseo 2017	Untreated	63 [41–81]	95	6	69	32	7.5	6	59	68

ORR, objective response rate; DCR, disease control rate.

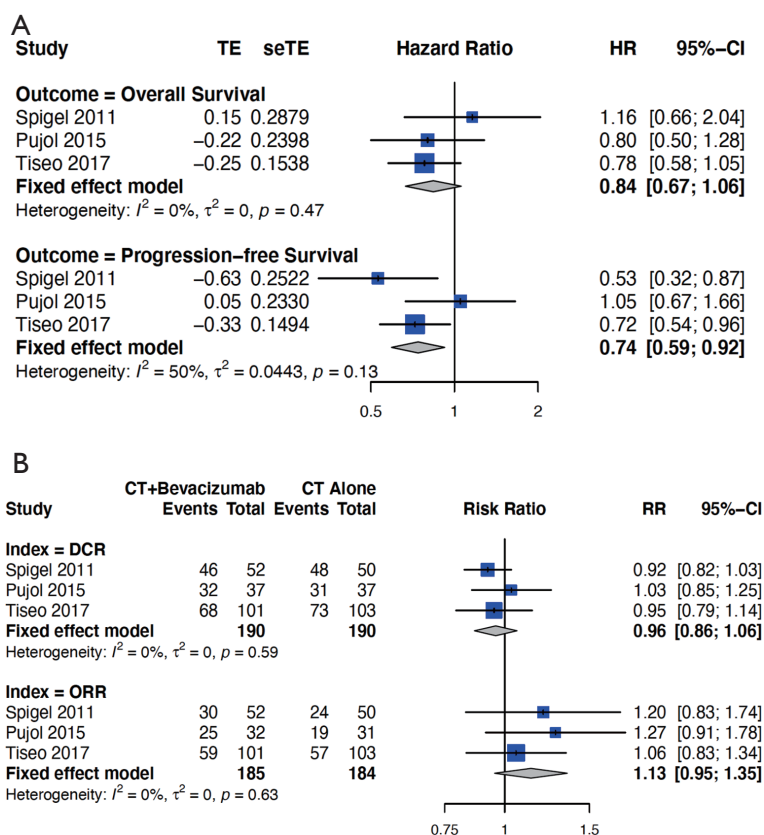
(18,20) and 167 patients in 3 studies received 7.5 mg/kg (22,23,25). Most of the patients in studies received six cycles (17,19,20,22–25) of treatments while others received 4 and 8 cycles in 2 studies (18,21) (Table 2).

### Assessment of the efficacy of bevacizumab

The comparison of CT/bevacizumab versus CT/placebo showed that bevacizumab improved OS of ED-SCLC though it was not significant (HR =0.84, 95% CI: 0.67–1.06, P=0.14). A significantly improved PFS in the bevacizumab

group was shown (HR =0.74, 95% CI: 0.59–0.92, P=0.007) (Figure 2A). The total 1-year survival rate was 32% (95% CI: 21–44%). The relapse ED-SCLC patients had a 15% (95% CI: 7–30%) 1-year survival rate, whereas untreated patients had 40% (95% CI: 31–50%) (Figure S1A). The 6-month PFS rates of relapse and untreated patients were 18% (95% CI: 7–38%) and 51% (95% CI: 37–64%), respectively. The total PFS rate was 38% (95% CI: 24–55%) (Figure S1B).

Although there was no difference in DCR between the bevacizumab and placebo group (RR =0.96, 95% CI:



**Figure 2** Forest plot of the clinical outcomes of chemotherapy (CT)/bevacizumab versus CT alone in the treatment of extensive-disease small cell lung cancer (ED-SCLC). (A) The estimate hazard ratio (HR) of overall survival (OS) and progression-free survival (PFS) between two groups; (B) the estimate relative risk (RR) of disease-control rate (DCR) and objective-response rate (ORR) between two groups.

0.86–1.06,  $P=0.41$ ), the bevacizumab group seemed to have better ORR than the placebo group ( $RR = 1.13$ , 95% CI: 0.95–1.35,  $P=0.13$ ). The overall ORR and DCR were 55% (95% CI: 35–73%) and 79% (95% CI: 67–90%), respectively (Figure 2B). The relapse patients had lower ORR than the untreated patients (19% vs. 71%), while the DCRs of relapse and untreated patients were 63% and 84%, respectively (Figure S2).

**Assessment of the safety of bevacizumab**

Grade 5 AEs were reported in 14 patients in the bevacizumab cohort (14/477, 2.9%), while 402 cases of Grade 3–4 AEs were reported. In the two-arm studies, no difference of Grade 3–5 AE was observed between bevacizumab and the placebo group. Among AEs, 172 cases of neutropenia and 22 cases of hypertension were the most chemotherapy-associated and bevacizumab-associated complications. No

hypertension case was reported in the relapse ED-SCLC patients (Table 3). Patients who received CT/bevacizumab had a higher risk of hypertension than patients who received CT alone ( $RR = 3.26$ , 95% CI: 1.02–10.42,  $P < 0.01$ ). However, no significant risk of neutropenia was observed between these groups ( $RR = 1.0$ , 95% CI: 0.79–1.27) (Figure 3). In detail, the neutropenia rates were 18% (95% CI: 9–31%) in relapse patients and 41% (95% CI: 33–50%) in untreated patients (Figure 4A), while the total hypertension rate was 6% (95% CI: 4–9%) (Figure 4B). The summary of bias was shown in the funnel plots and the risk of bias plots (Figures S1,S2).

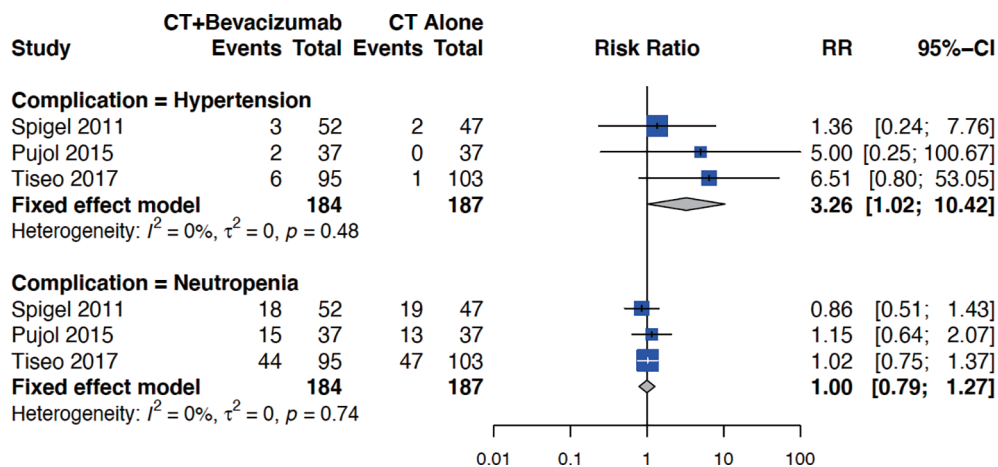
**Discussion**

SCLC is an invasive malignancy with a poor prognosis, though it accounts for a small proportion of lung cancer. Surgical treatment with adjuvant chemotherapy or chemotherapy with cranial irradiation has been proved to

**Table 3** Overview of prognosis, disease response and complications of included studies

Study	OS		PFS		Complication			
	Median (months)	12-month rate	Median (months)	6-month rate	Grade		Neutropenia	Hypertension
					3-4	5		
Horn 2009	10.9	38.1	4.7	30.2	47	2	37	5
Spigel 2009	12.1	51	9.13	76	74	1	20	0
Ready 2011	11.6	43.8	7	63	41	3	17	6
Spigel 2011	9.4	32.4	5.45	40.3	36	2	18	3
Mountzio 2012	6.3	26.7	-	33	19	0	5	0
Spigel 2013	7.4	18	4.02	22	71	3	14	0
Pujol 2015	11.1	59.5	5.3	34.4	54	3	15	2
Trafalis 2016	6	3.6	3	3.6	8	0	2	0
Tiseo 2017	9.8	25	6.7	57.4	52	0	44	6

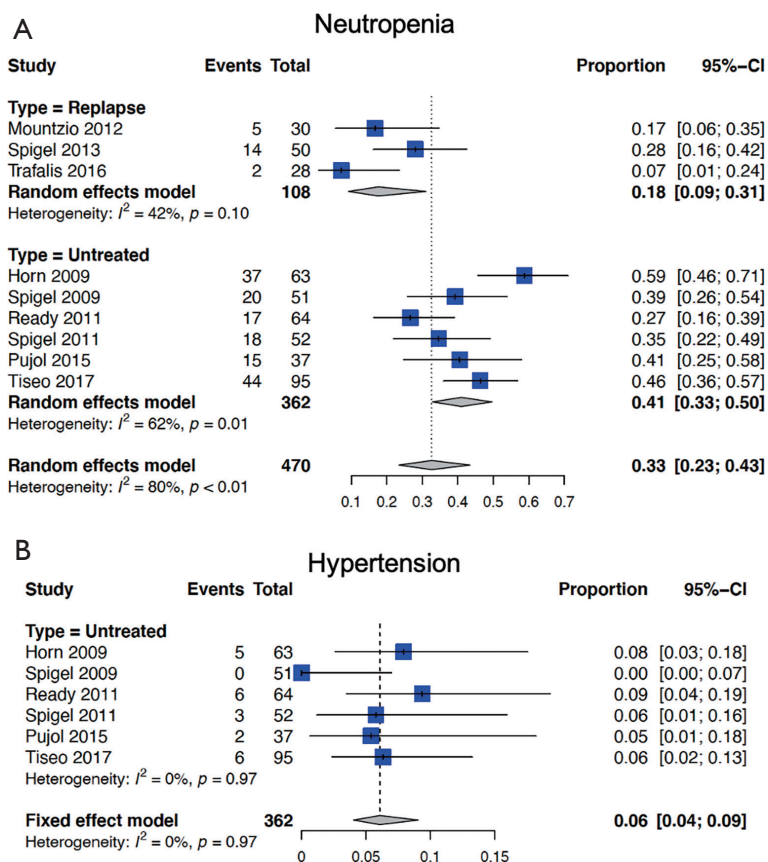
OS, overall survival; PFS, progression-free survival.



**Figure 3** Forest plot of the major complications of chemotherapy (CT)/bevacizumab versus CT alone in the treatment of extensive-disease small cell lung cancer (ED-SCLC).

be effective for limited-disease SCLC (LD-SCLC) (27). Despite the chemotherapy and radiation, ED-SCLC is considered incurable (28). Since the initial recommendation of platinum-based EP, new medications or regimens have not yielded a remarked improvement in ED-SCLC. Anti-angiogenic treatment improves prognostic outcomes in various tumors in the combination of standard regimens and becomes a new recommendation in their treatment guidelines. Based on its pronounced effect in non-squamous NSCLC (29,30), several studies have been performed to verify its role in SCLC.

Three two-arm RCTs were included in the studies comparing the efficacy of first-line CT/bevacizumab to CT alone (23,24,31). Although the prognostic advantage of CT/bevacizumab was not significantly on OS, it could improve PFS. Our study indicated that the total 1-year OS rate and 6-month PFS rates of untreated patients who received CT/bevacizumab were higher than those who received regular CT (32-34). Two studies were performed to verify the effect of irinotecan/cisplatin versus etoposide/cisplatin. They reported that both arms' median survival ranged from 9.1–10.2 months, while the median time to progression was 4.1–5.6 months (7,8).



**Figure 4** Forest plot of the summarized major complications of chemotherapy (CT)/bevacizumab in the treatment of extensive-disease small cell lung cancer (ED-SCLC). (A) The summarized rate of neutropenia in CT/Bevacizumab group including the untreated and the relapsed patients; (B) the summarized rate of hypertension in CT/Bevacizumab group.

Our study showed that the median survival of patients who received bevacizumab was 9.4–12.1 months, and the median time to progression was 4.7–9.13 months, which indicated the survival outcomes of CT/bevacizumab patients were better or at least tended to be better than the patients received CT alone. Improvements in ORR could also be observed in this study, which was favorable compared to other CT alone studies (8,35).

In terms of relapse cases, O'Brien *et al.* reported that oral topotecan as a second-line treatment for relapse SCLC could yield 5.8 months of median survival time and 18% ORR (36). Another study compared the efficacy of oral and intravenous topotecan as second-line therapy. It showed no difference between oral and intravenous administration that single topotecan provided 18.3–21.9% ORR and 8.3–8.8 months of median survival time (37). In our analysis, no significant superiority was observed by adding bevacizumab to CT but a slightly higher ORR.

The most reported Grade 3–4 complications and bevacizumab-associated complications in these studies are neutropenia and hypertension, respectively. More hypertension cases were observed in the bevacizumab group than the control group, but no difference in neutropenia. The overall neutropenia risks were 41% and 18% in untreated and relapsed patients, consistent with regular chemotherapies without bevacizumab in other reports (7,8,35-37). Sandler *et al.* performed an RCT on paclitaxel/carboplatin with or without bevacizumab in NSCLC patients. They reported that 7% of patients in the experiment group had Grade 3–4 hypertension (38). Meanwhile, Hurwitz and his colleagues stated that 11% of colon cancer patients who received bevacizumab had Grade 3 hypertension (14). However, only 6% of patients were reported Grade 3–4 hypertension in the untreated group, and no case was reported in the relapse group. The results indicated that the standard regimens with bevacizumab had

tolerable toxicities in ED-SCLC, which were at least not more significant than other cancers.

The bevacizumab dosages in the included studies varied from 7.5 to 15 mg/kg. It is believed that higher dosage is associated with a higher risk of complications. We, therefore, explored the Grade 3–4 hypertension rates among different dosage subgroups. Nevertheless, no significant difference was noticed in the severe hypertension rate between the 15 mg/kg subgroup and the 7.5 mg/kg subgroup. No other advantage was observed in the 15 mg/kg subgroup. These results indicated that higher bevacizumab dosage in ED-SCLC might not bring remark benefit.

The effects of other anti-angiogenic medications on SCLC patients are also investigated. Vandetanib, a tyrosine kinase inhibitor of multiple receptors including VEGFR, EGFR, and RET, was examined in SCLC patients in a phase II RCT. It showed that it could improve PFS of SCLC patients and significantly prolong OS in LD-SCLC. Unfortunately, ED-SCLC patients in the vandetanib group had shorter survival than the placebo group (39). Sunitinib, another multitarget tyrosine kinase inhibitor, was administered to ED-SCLC patients for maintenance therapy. Both improved OS and PFS were observed in this study, which was up to 3.7 and 9 months, respectively (40). Some researchers tried to verify the effect of thalidomide in SCLC, but no benefit from either PFS or OS was observed in the studies (41,42).

On the other hand, thalidomide was seldom used because of its potential teratogenic effect (43). Only a few studies compared CT/bevacizumab to CT alone in SCLC patients. We, therefore, performed both comparative and single-arm integrated meta-analysis to investigate the efficacy and safety of the additional administration of bevacizumab. A total of three comparative studies were eligible for analysis, which might be inconclusive because of few candidates.

The current recommended standard treatment for ED-SCLC is the combination of platinum-based chemotherapy and atezolizumab, which showed significant improvement compared to the chemotherapy alone. Meanwhile, the bevacizumab plus atezolizumab have been proved to yield better survival outcomes in other tumors (e.g., hepatocellular carcinoma, renal cell carcinoma) than monotherapy (44,45). The roles of anti-angiogenesis treatment with immunotherapy are worth verifying in ED-SCLC. A phase II single-arm study of carboplatin plus etoposide with bevacizumab and atezolizumab in ED-SCLC patients is ongoing in Europe (NCT04730999).

Besides, another phase III randomized study of bevacizumab combined with carboplatin or cisplatin + etoposide + atezolizumab compared with carboplatin or cisplatin + etoposide + atezolizumab in untreated ED-SCLC patients is recruiting patients in Japan (JapicCTI-195034). These trials would provide some new ideas for using bevacizumab in the presence of immunotherapy in SCLC.

In conclusion, the effects of anti-angiogenic medication in SCLC patients are not completely clear. The present study suggests that bevacizumab in the combination of standard chemotherapy provides similar OS and slightly improved PFS than chemotherapy alone. Although the response rate is not remarkably superior, this regimen is well tolerable. It also indicates that 7.5 mg/kg dosage of bevacizumab provides a similar effect to ED-SCLC patients with a lower risk of bevacizumab-associated complication. Further investigations on the dosage and cost-effectiveness are warranted to figure out its application. The roles of anti-angiogenesis treatment in the combination with IO is also expected to be verified.

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## Footnote

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*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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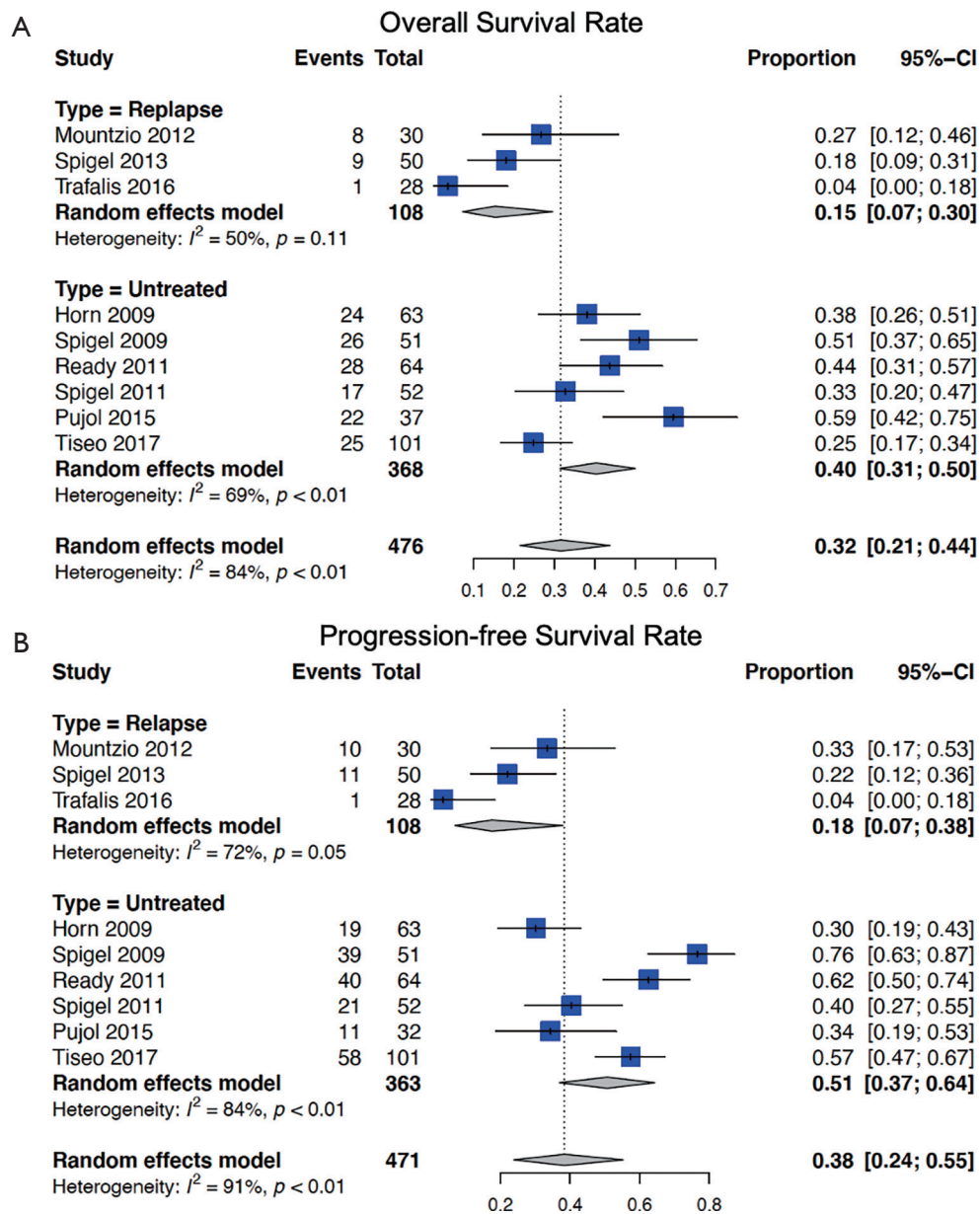
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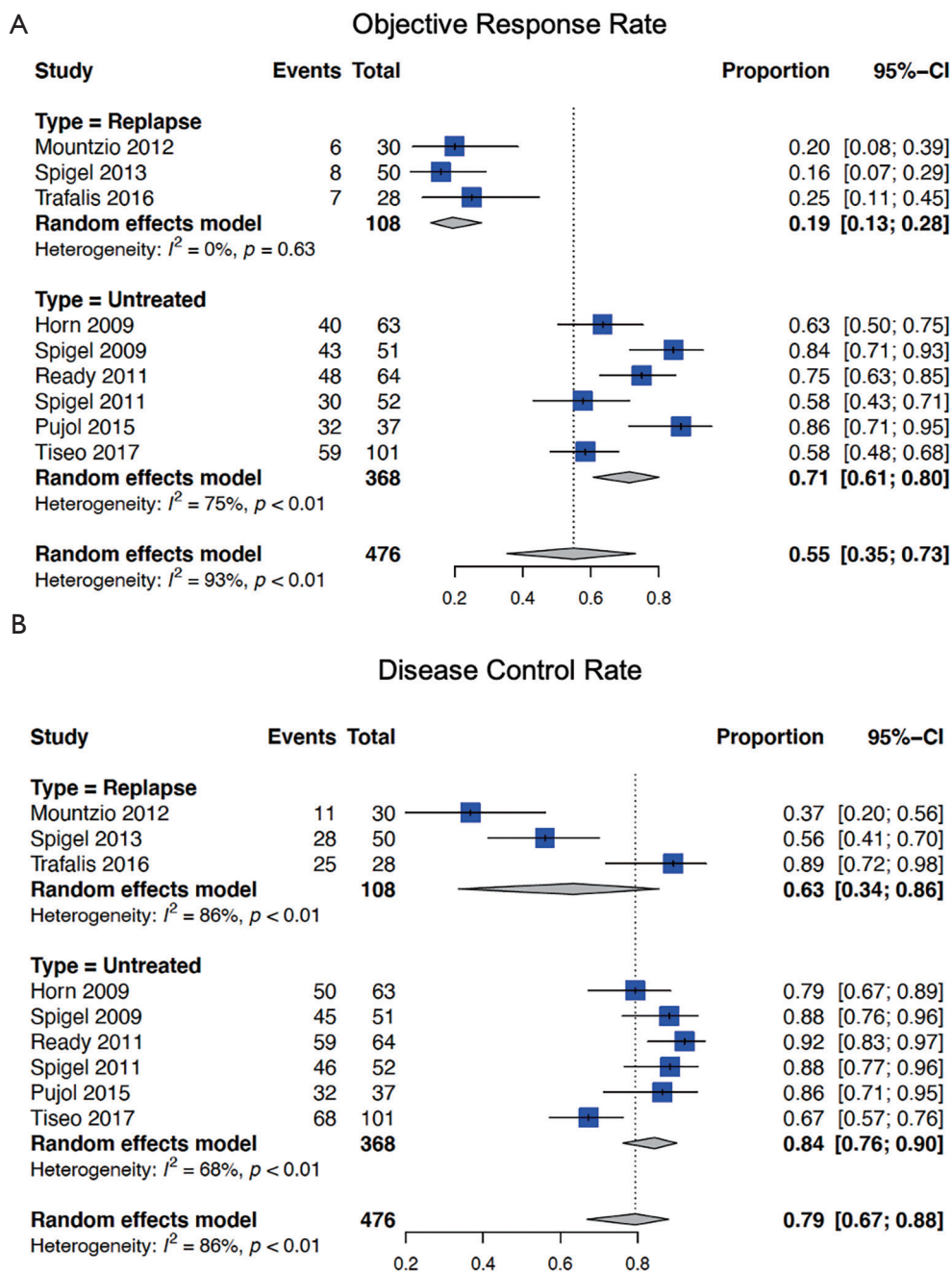
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**Figure S1** Forest plot of the summarized clinical outcomes of chemotherapy (CT)/bevacizumab in the treatment of extensive-disease small cell lung cancer (ED-SCLC) including the untreated and the relapsed patients. (A) The summarized overall survival (OS) of CT/bevacizumab group; (B) the summarized progression-free survival (PFS) of CT/bevacizumab group.



**Figure S2** Forest plot of the summarized clinical outcomes of chemotherapy (CT)/bevacizumab in the treatment of extensive-disease small cell lung cancer (ED-SCLC) including the untreated and the relapsed patients. (A) The summarized objective response rate (ORR) of CT/bevacizumab group; (B) the summarized disease control rate (DCR) of CT/bevacizumab group.