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Efficacy and toxicity of lurbinectedin in subsequent systemic therapy of extensive-stage small cell lung cancer: a meta-analysis

Jiayi Tang[1,2†], Tianlei Wang[1,2†], Hongwei Wu[1,2†], Xinrui Bao[1,2], Ke Xu[1,2*] and Tao Ren[1,2*]

Abstract

Objective This study aimed to systematically analyze the efficacy and toxicity of lurbinectedin as a second-line or subsequent treatment for extensive-stage small cell lung cancer (ES-SCLC).

Methods Candidate studies were identified in PubMed, Embase, Cochrane Library, ClinicalTrials.gov, CNKI, and Wanfang databases up to 1 May 2024. Objective remission rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs) were extracted, respectively. The efficacy and toxicity of lurbinectedin in ES-SCLC were analyzed by meta-analysis.

Results Six eligible prospective studies were included in this meta-analysis, including 536 patients with ES-SCLC who received second-line or subsequent treatment. In pooled analysis, the ORR of lurbinectedin was 35% (95% confidence interval [CI] 29–41), DCR was 67% (95%CI 58–76), DOR was 5.33 months (95%CI 4.51-6.16), PFS was 3.38 months (95%CI 2.59-4.17), and OS was 7.49 months (95%CI 5.11–9.87). The incidence of AEs and severe adverse events (SAEs) was 92% (95%CI 78–100) and 37% (95%CI 19–57), respectively. The most common AEs were leukopenia, neutropenia, anemia, and thrombocytopenia, with incidences of 81% (68–91), 74% (57–88), 73% (35–98) and 57% (46–68), respectively.

Conclusion As a promising alternative for second-line treatment for ES-SCLC, lurbinectedin has a certain level of efficacy and a favorable safety profile. The integration of lurbinectedin with other therapeutic modalities presents an emerging area warranting further investigation.

Keywords Lurbinectedin, Extensive-stage small cell lung cancer, Efficacy, Toxicity, Meta-analysis

†Jiayi Tang, Tianlei Wang and Hongwei Wu authors contributed equally to this work and should be considered co-first authors.

*Correspondence:
Ke Xu
xuke@cmc.edu.cn
Tao Ren
rentao509@cmc.edu.cn
[1]Clinical Medical College, Chengdu Medical College, Chengdu, Sichuan, China
[2]Department of Oncology, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan, China

Introduction

Small cell lung cancer (SCLC) is a highly invasive subtype of lung cancer, accounting for 15% of the lung cancer, and the 5-year survival rate of it is only 7% [1, 2]. The small cell lung cancer (SCLC) exhibits multidrug resistance, and is prone to recurrence and metastasis [3]. At present, etoposide combined with carboplatin or cisplatin, and atezolizumab or durvalumab is recommended for first-line treatment of ES-SCLC [3]. The relevant literature suggests that atezolizumab combined with etoposide and cisplatin extended median survival from 10.3 months to 12.3 months [4]. When patients are accompanied by tumor emergencies such as elevated intracranial pressure, spinal cord compression syndrome, or superior vena cava syndrome, local treatment based on radiotherapy could be considered to improve the symptoms of patients [3]. However, most patients with ES-SCLC always have problems of rapid recurrence and treatment resistance during treatment [5]. The therapeutic options for subsequent treatment are severely limited when patients experience relapse or progression following initial-line therapy. At present, common drugs include topotecan, irinotecan, paclitaxel, and gemcitabine; however, their efficacy is limited and they are associated with a high incidence of AEs, which pose challenges for subsequent treatment of ES-SCLC [6]. Most scholars considered that the survival of the disease could not be improved if only an effective therapeutic molecular target could be found in the therapeutic exploration of SCLC [7, 8].

The Food and Drug Administration (FDA) approved lurbinectedin as a second-line treatment for SCLC in 2020 [5]. Lurbinectedin is an inhibitor of RNA polymerase II, preferentially binds to guanine located in the GC-rich regulatory area of the DNA promoter, induces double-strand breaks by forming adducts, destroys DNA-protein interaction and RNA transcription, and causes DNA damage and apoptosis in tumor cells during mitosis. Finally, lurbinectedin inhibits the proliferation of tumor cells [9, 10]. Its other anti-tumor mechanisms include inducing immunogenic cell death (ICD), stimulating anticancer immunity, and reducing tumor-associated macrophages (TAM) in tumor microenvironment [11, 12]. In a recent multicenter, randomized, open-label phase III trial, the median duration of response (DOR) of lurbinectedin in relapsed SCLC was 5.7 months (95% CI 4.1–7.1), the median progression-free survival (PFS) was 3.3 months (95% CI 1.4–6.4), and the median overall survival (OS) was 8.6 months (95% CI 7.1–9.4). The efficacy of lurbinectedin combined with doxorubicin was similar to that of topotecan or CAV, but severe hematological toxicity (grade 3–4) was significantly lower, and there were fewer complications and supportive care needs [13]. The above results undoubtedly bring us a new treatment option for relapsed ES-SCLC. In order to more comprehensively and systematically elucidate the role of lurbinectedin in the second-line treatment of ES-SCLC, the published data was used to pooled-analyze through meta-analysis in this study. The purpose is to provide new evidence for second-line treatment of ES-SCLC from an evidence-based perspective.

Methods

Search strategy

A systematic search of the following databases, such as PubMed, Embase, Cochrane Library, ClinicalTrials.gov, Wanfang, and CNKI was performed to identify relevant articles published from 30 April 2013, to 1 May 2024. The search strategy used a combination of meSH and free words, including lurbinectedin, PM01183, small cell lung cancer, small cell lung tumor, and small cell lung carcinoma.

Inclusion criteria

(1) Studies including patients with a confirmed pathological diagnosis of SCLC.
(2) Studies evaluating second-line or subsequent treatment of ES-SCLC.
(3) Studies including patients administered with lurbinectedin.

Exclusion criteria

(1) Published papers must be original studies reporting on prospective clinical trials, not preclinical studies, retrospective studies, reviews, case reports, and other types of articles.
(2) Studies with no specific data on treatment response, efficacy, and toxicity.

Data extraction and management

All authors actively participated in the literature search. The researchers were divided into two groups, each comprising three members. The first group independently performed a literature screening, extracting, and data cross-checking. When disagreement arose among team members, the second group of researchers engaged in thorough discussions to identify optimal solutions. The following information was extracted from each study: first author, year of publication, country, sample size, treatment response, DOR, PFS, OS, and AEs.

Quality assessment

The quality of the literature was assessed by the second group, and the studies included in the assessment were quantitatively evaluated according to the Methodological

Index for Non-Randomized Studies (MINORS). In the event of a dispute regarding the research quality, a comprehensive team discussion will be conducted to achieve consensus.

Statistical analysis

This meta-analysis was conducted using STATA11.0 software (https://www.stata.com), a statistical analys is tool developed by StataCorp. ORR, DCR, the incidence of AEs and SAEs were calculated by pooled ratio method. The survival data were processed by median and mean approximation transformation statistical methods. $I^2 > 50\%$ or p-value < 0.05 was considered the existence of heterogeneity. Subgroup analyses and sensitivity analyses were used to trace the source of heterogeneity. Finally, Egger's linear regression tests were used to analyze publication bias. If p-value > 0.05, the publication bias was not considered significant.

Result

Literature inclusion and research quality assessment

A total of 473 papers were obtained through a comprehensive search of the databases. By excluding the ineligible papers, 6 studies were eventually included, including 1 phase III Randomized Controlled Trial (RCT) study, 2 phase II non-RCT studies, and 3 phase I non-RCT studies (Fig. 1) [13–18]. The quality of the included studies was evaluated using the MINORS method. The specific scores of the six studies were as follows: one study scored 21 points, and the other five studies scored 11 points (Table S1). Table 1 provides detailed information for each study.

Data extraction

A total of 536 patients were included in this meta-analysis. All enrolled participants had metastatic or relapsed ES-SCLC and were administered second-line or subsequent therapies. All six studies were prospective. 3 studies used lurbinectedin monotherapy and 3 studies adopted combination therapy with lurbinectedin and doxorubicin. All 6 studies provided data on PFS and ORR, 4 studies provided data on the incidence of AEs, 5 studies provided data on the incidence of SAEs, 4 studies provided data on DOR, and 4 studies provided data on OS.

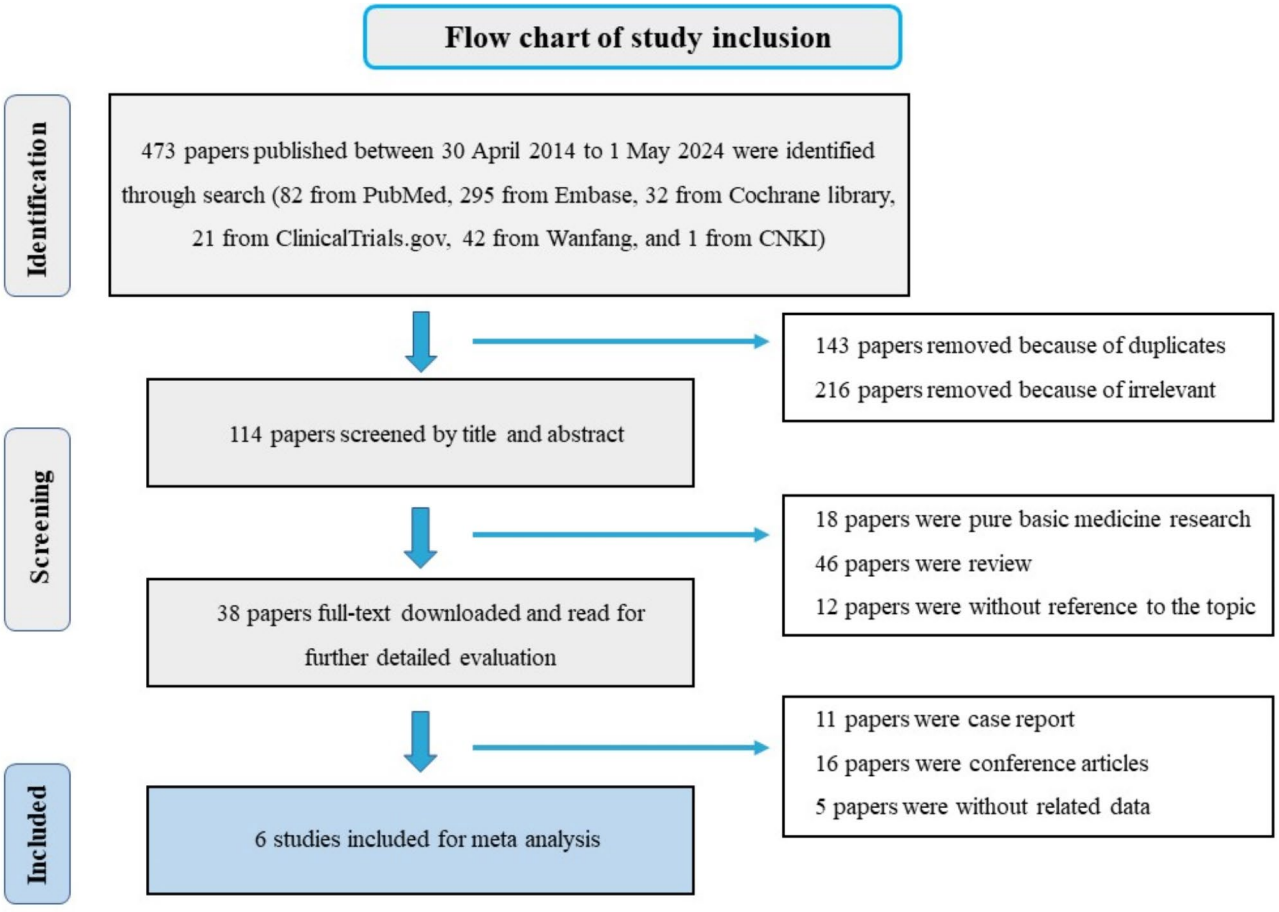

Fig. 1 Detailed process of literature identification and screening. CNKI, China National Knowledge Infrastructure

Table 1 Information on the clinical trials eligible for enrollment and their specific characteristics

Author	Year	Country	Trial design	Disease	Intervention/ treatment	Age	Total patients	CR	PR	SD	PD	NE	DOR, months (95% CI)	PFS, months (95% CI)	OS, months (95% CI)	AEs	SAEs	Grade ≥ 3 AEs	Efficacy evaluation criteria	AE evaluation criteria	MINORS score
Cheng Y	2024	CHINA	I/ non-RCT	Second Line of relapsed SCLC patients	Lurbinectedin 3.2 mg/m^2 d1; Q3W.	58 (52–69)	22	0	10	10	1	1	4.2 (2.7–inf)	5.6 (4.1–6.9)	11.0 (9.2–inf)	22	11	19	RECIST v1.1	CTCAE v5.0	11
Alexander M	2024	AUS	IIb/ non-RCT	SCLC second or subsequent line therapy	Lurbinectedin 3.2 mg/m^2, d1; Q3W.	67 (32–83)	46	1	12	7	20	6	NA	2.5 (1.8–2.9)	4.5 (3.5–7.2)	NA	NA	13	RECIST v1.1	NA	11
Aix SP	2023	USA	III/RCT	relapsed SCLC patients	Lurbinectedin 2.0 mg/m^2, d1; Doxorubicin, 40mg/m^2, d1; Q3W	63 (58–69)	307	8	89	111	74	25	5.7 (4.1–7.1)	4.0 (2.8–4.2)	8.6 (7.1–9.4)	268	126	145	RECIST v1.1	CTCAE v4.0	21
Olmedo ME	2021	USA	Ib/non-RCT	relapsed SCLC of Second line patients	Lurbinectedin 2.0 mg/m^2, d1; Doxorubicin, 40 mg/m^2, d1; Q3W	64 (49–77)	28	1	9	10	8	0	5.2 (1.0–6.9)	3.3 (1.4–6.2)	7.9 (4.2–11.5)	28	19	NA	RECIST v1.1	CTCAE v4.0	11
Trigo J	2020	USA	IIb/ non-RCT	relapsed SCLC after failure of platinum-based chemotherapy	Lurbinectedin 3.2 mg/m^2, d1; Q3W.	60 (54–68)	105	0	37	35	28	5	5.3 (4.1–6.4)	3.5 (2.6–4.3)	9.3 (6.3–11.8)	NA	11	11	RECIST v1.1	CTCAE v4.0	11
Calvo E	2017	USA	Ib/non-RCT	relapsed SCLC of Second, Third , Fourth-line patients	Lurbinectedin 4.0 mg FD, d1; Doxorubicin, 50 mg/m^2, d1; Q3W	62 (48–73)	28	2	13	3	8	2	4.5 (2.3–7.8)	4.1 (1.4–5.8)	NA	19	NA	NA	RECIST v1.1	CTCAE v4.0	11

CR, complete response; PR, partial response; SD, table disease; PD, progressive disease; NE, not evaluable; NA, not available; DOR, duration of response;

PFS, progression-free survival; OS, overall survival; AEs, Adverse Events; SAEs, Severe Adverse Events; FD, flat dose; Q3w, one time three week; RECIST, Response Evaluation Criteria in Solid Tumors; CTCAE, Common Terminology Criteria for Adverse Event

Efficacy and toxicity of lurbinectedin in the treatment of ES-SCLC

Pooled analyses showed that included patients with advanced or relapsed ES-SCLC had an ORR of 35% (95%CI 29–41) and a DCR of 67% (95%CI 58–76) at second-line or subsequent treatment with lurbinectedin. In terms of other efficacy evaluation indicators, DOR was 5.33 months (95%CI 4.51–6.16), PFS was 3.77 months (95%CI 2.84–4.69), and OS was 7.49 months (95%CI 5.11–9.87). In the safety evaluation, the incidence of total AEs and SAEs in all patients treated with lurbinectedin was 92% (95%CI 78–100) and 37% (95%CI 19–57), respectively (Fig. 2). The most frequent AEs and SAEs were related to hematotoxicity. Leukopenia, neutropenia, and anemia were the most common AEs, with incidences of 81% (68–91), 74% (57–88), and 73% (35–98), respectively (Table 2). Meanwhile, the most frequent SAEs were neutropenia, leukopenia, and thrombocytopenia, with an incidence of 63% (43–82), 40% (13–72), and 17% (9–26) (Table 2).

Subgroup analysis

Heterogeneities were found in the calculation of DCR, PFS, OS, and incidences of AEs and SAEs during the pooled analyses. To identify and analyze sources of data heterogeneity, subgroup analyses were performed using the following variables: country, treatment regimens, and clinical trial stages. First of all, the implementation of country-based grouping can effectively mitigate heterogeneity in the analysis of DCR, PFS, and OS. The four studies conducted in the United States had a DCR of 68% (95%CI 64–72), a PFS of 3.79 months (95%CI 3.28–4.30), and an OS of 8.64 months (95%CI 7.62–9.65). The above results had good homogeneity which can reflect the influence of the country on the heterogeneity of the data related to efficacy. However, for the incidence of AEs and SAEs, the intra-group heterogeneity could not be effectively reduced no matter which variables were used in subgroup analyses(Figure 3).

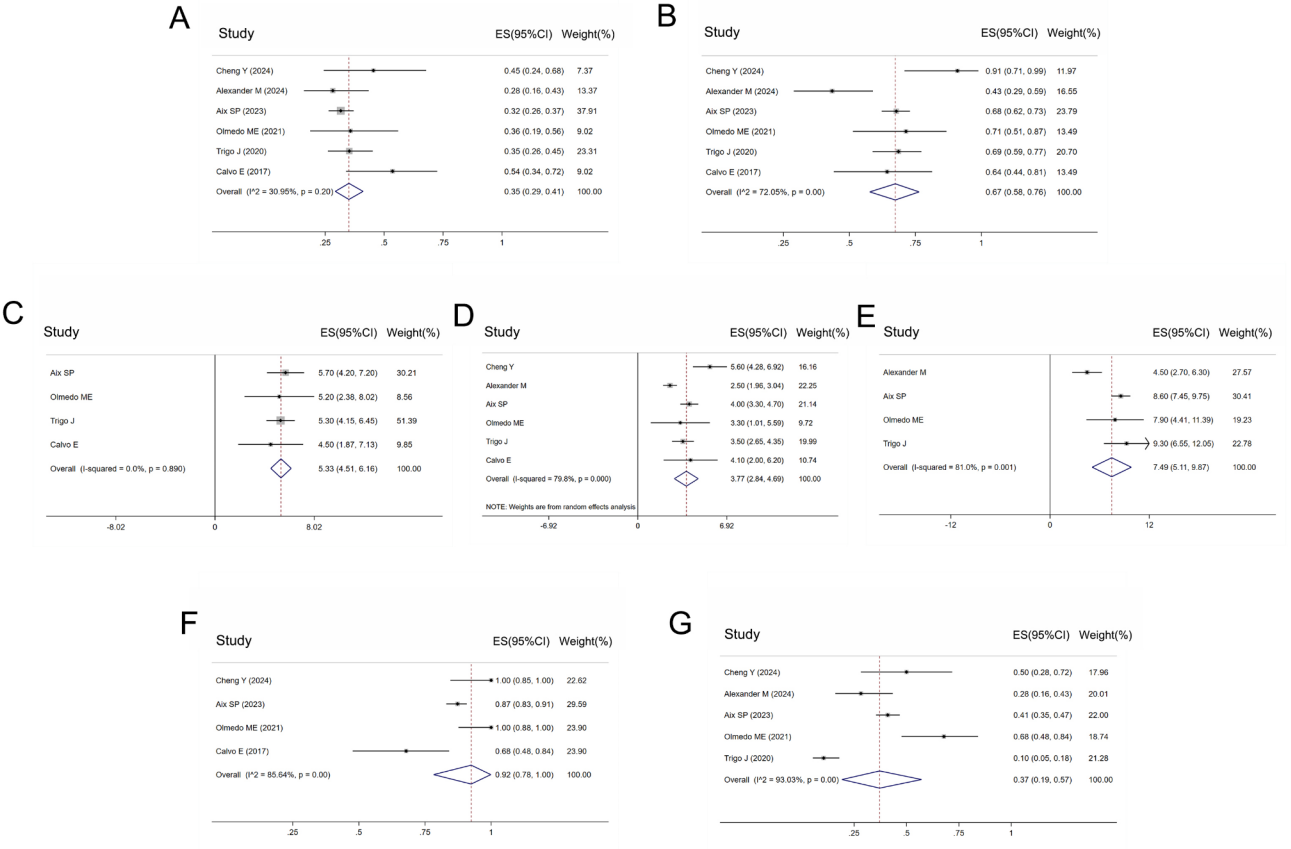

Fig. 2 Efficacy and toxicity of lurbinectedin in the treatment of extensive SCLC. **A**. ORR of lurbinectedin in second-line and above treatment of advanced or recurrent SCLC, **B**. DCR of lurbinectedin in patients with second-line and above advanced SCLC, **C**. DOR of lurbinectedin in patients with second-line and above advanced SCLC, **D**. PFS of lurbinectedin in patients with second-line and above advanced SCLC, **E**. OS of lurbinectedin in patients with second-line and above advanced SCLC, **F**. Incidence of AEs of lurbinectedin in patients with second-line and above advanced SCLC, **G**. Incidence of SAEs of lurbinectedin in patients with second-line and above advanced SCLC. SCLC, small cell lung cancer; ORR, Objective Response Rate; DCR, Disease control rate; DOR, Duration of response; PFS, Progression-Free Survival; OS, Overall Survival; AEs, Adverse Events; SAEs, Severe Adverse Events

Table 2 Incidence of AEs and sAEs caused by lurbinectedin

	AEs				sAEs			
	No. of clinical trials	Incidence % (95% CI)	I^2(%)	p value	No. of clinical trials	Incidence % (95% CI)	I^2%	p value
Anemia	5	73 (35–98)	98. 24	0.00	6	15 (8–24)	78.23	0.00
Febrile neutropenia	5	6 (3–11)	59.34	0.04	6	6 (3–10)	49.34	0.08
Thrombocytopenia	4	57 (46–68)	74.78	0.01	5	17 (9–26)	75.45	0.00
Leukopenia	3	81 (68–91)	64.73	0.06	4	40 (13–72)	93.42	0.00
Neutropenia	4	74 (57–88)	89.60	0.00	5	63 (43–82)	92.84	0.00
Decreased appetite	4	23 (9–41)	91.53	0.00	5	0 (0–1)	0.00	0.47
Diarrhea	3	14 (6–24)	77. 58	0.01	5	0 (0–1)	0.00	0.99
Fatigue	4	57 (44–70)	81.94	0.00	6	7 (2–12)	68.29	0.01
Mucositis	2	26 (16–39)	0.00	NA	3	1 (0–7)	48.36	0.14
Nausea	5	32 (16–50)	92.09	0.00	6	1 (0–3)	37.84	0.15
Alopecia	2	27 (16–39)	0.00	NA	2	0 (0–3)	0.00	NA
Pneumonia	3	5 (1–10)	65.08	0.06	5	3 (2–6)	0.00	0.51
Hypokalemia	2	7 (4–10)	0.00	0.82	5	2 (0–8)	74.14	0.00
Hypomagnesemia	4	0 (0–0)	NA	NA	4	0 (0–5)	62.06	0.05
ALT increased	2	36 (23–49)	0.00	NA	5	4 (0–12)	85.78	0.00
AST increased	2	27 (16–39)	0.00	NA	5	2 (0–7)	74.92	0.00

Sensitivity analysis and publication bias analysis

In the sensitivity analysis, ORR, DCR, DOR, PFS, OS and the incidence of AEs and SAEs were analyzed separately, and no study was identified as the source of heterogeneity. Therefore, no studies were excluded for data analysis (Fig. 4). Egger's linear regression method was used to analyze publication bias. The p values corresponding to ORR, DCR, DOR, PFS, OS, and the incidence of AEs and SAEs were 0.159, 0.989, 0.473, 0.851, 0.859, 0.892, and 0.875, respectively. These results indicated that there was no publication bias in the studies included in the present meta-analysis (Fig. 5).

Discussion

For a long time, there has been no milestone found in the second-line treatment of ES-SCLC. The therapeutic effect was limited and the survival of the patients was poor. Recent studies showed that there was a close relationship between the efficacy of second-line treatment for ES-SCLC and the relapse time interval. Relapsed small cell lung cancer (SCLC) is classified according to the chemotherapy-free interval of either 6 months or 3 months, as per the guidelines provided by the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO), respectively. These classifications offer slightly different second-line treatment options for patients [3, 19]. At present, re-treatment with platinum-based doublet is the preferred regimen, and other recommended regimens include topotecan, CAV, docetaxel, etoposide, gemcitabine, irinotecan, nivolumab, paclitaxel, temozolomide, and vinorelbine. In the 1980s, Korkmaz et al. reported a retrospective study about the efficacy of second-line chemotherapy in ES-SCLC. Platinum re-treatment patients had longer PFS and OS, and the patients receiving rechallenged platinum-based chemotherapy had a higher ORR [20–23]. In contrast, Wakuda et al. found that platinum-based rechallenge chemotherapy was no better than other chemotherapy regimens for ES-SCLC patients (median survival was 14.4 and 13.1 months in the rechallenge and other groups, respectively) [24]. In a recent study, 67 patients who received rechallenged platinum-based chemotherapy had an ORR of 52.2%, DCR of 82.1%, median PFS of 5.1 months (95%CI 4.3–5.4), and median OS of 10.8 months (95%CI 8.7–14.5), respectively [25]. Up to now, re-treatment with platinum-based doublet is still the preferred regimen in the updated version of the guidelines [25–27]. The application of other single-drug chemotherapy regimens such as paclitaxel, etoposide, vinorelbine, bendamustine, and gemcitabine has also been confirmed by some clinical studies. In several small sample size phase II clinical trials, it had been found that the ORR of paclitaxel monotherapy in second-line therapy was 24–29% [28, 29]. In a clinical trial that enrolled 22

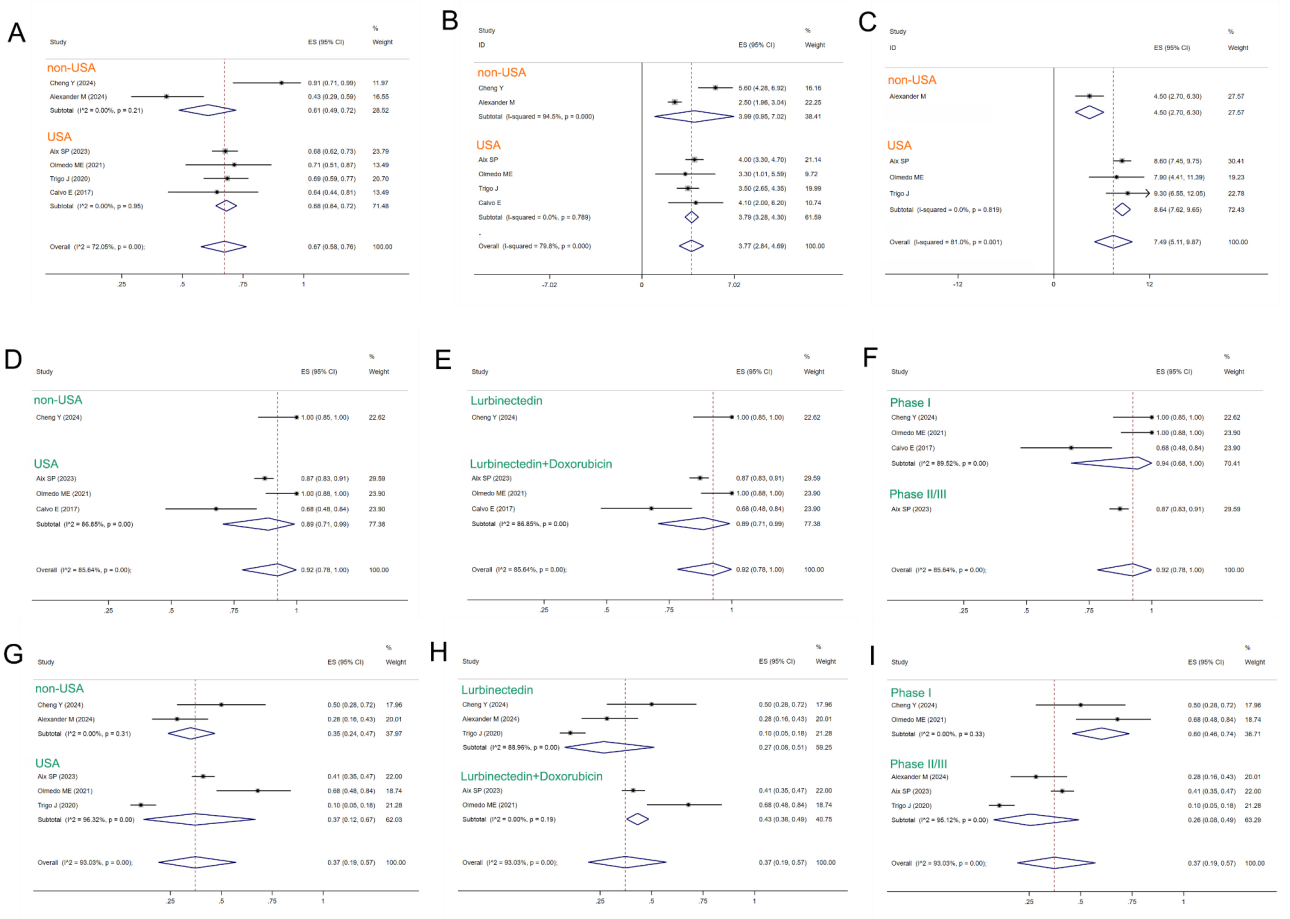

Fig. 3 lurbinectedin subgroup analysis of patients with SCLC. (**A**) DCR of SCLC in the United States and non-United States, (**B**) PFS of SCLC in the United States and non-United States, (**C**) OS of SCLC in the United States and non-United States, (**D**) Incidence of AEs in the United States and non-United States, (**E**) Incidence of AEs in lurbinectedin monotherapy or lurbinectedin combined with doxorubicin, (**F**) Incidence of AEs in phase I and non-phase I clinical trials, (**G**) Incidence of SAEs in the United States and non-United States, (**H**) Incidence of SAEs in lurbinectedin monotherapy or lurbinectedin combined with doxorubicin, (**I**) Incidence of SAEs in phase I and non-phase I clinical trials. SCLC, small cell lung cancer; DCR, Disease control rate; PFS, Progression-Free Survival; OS, Overall Survival; AEs, Adverse Events; SAEs, Severe Adverse Events;

relapsed SCLC patients, the ORR of oral etoposide used as a second-line chemotherapy regiment was 45%, and the median OS was 3.5 months [30]. In another clinical trial involving 24 patients with relapsed SCLC, vinorelbine monotherapy showed an ORR of 12.5% [31]. Bendamustine monotherapy was also reported to have an ORR of 26% and a median OS of 4.8 months (95% CI,3.8–6.3) [32]. Gemcitabine was found in a Phase II clinical study to have an ORR of 11.9% and a median OS of 7.1 months [33]. In addition, a phase III RCT was conducted to compare the efficacy and AEs of topotecan monotherapy with the CAV regimen in the subsequent treatment of relapsed SCLC. The ORR of topotecan monotherapy and CAV regimen were 24.3% and 18.3%, respectively. The median OS was 25.0 and 24.7 weeks, respectively. The incidence of grade 4 neutropenia induced by CAV combination was 51.4%, while that of topotecan was 37.8%. Compared with CAV, topotecan improved the symptoms of dyspnea, anorexia, hoarseness, and fatigue, suggesting that topotecan monotherapy can be safely used in the treatment of recurrent SCLC [34].

The role of immune checkpoint inhibitors (ICIs) was also evaluated in patients with relapsed SCLC [35–38]. CheckMate032 is a phase I/II trial evaluating the efficacy of nivolumab monotherapy ($n=147$) or nivolumab plus ipilimumab ($n=96$) in the treatment of relapsed SCLC [35, 38]. The updated data revealed that the objective response rate (ORR) in the nivolumab group was 11.6%, whereas it reached 21.9% in the group of nivolumab and ipilimumab. The Overall survival at 12 and 24 months was comparable between the nivolumab (30.5% and 17.9%, respectively) and the nivolumab+ipilimumab groups (30.2% and 16.9%, respectively). The incidence of grade 3–4 adverse events was 12.9% in the nivolumab group, while the nivolumab+ipilimumab group was 37.5%. Elevated levels of lipase and aspartate

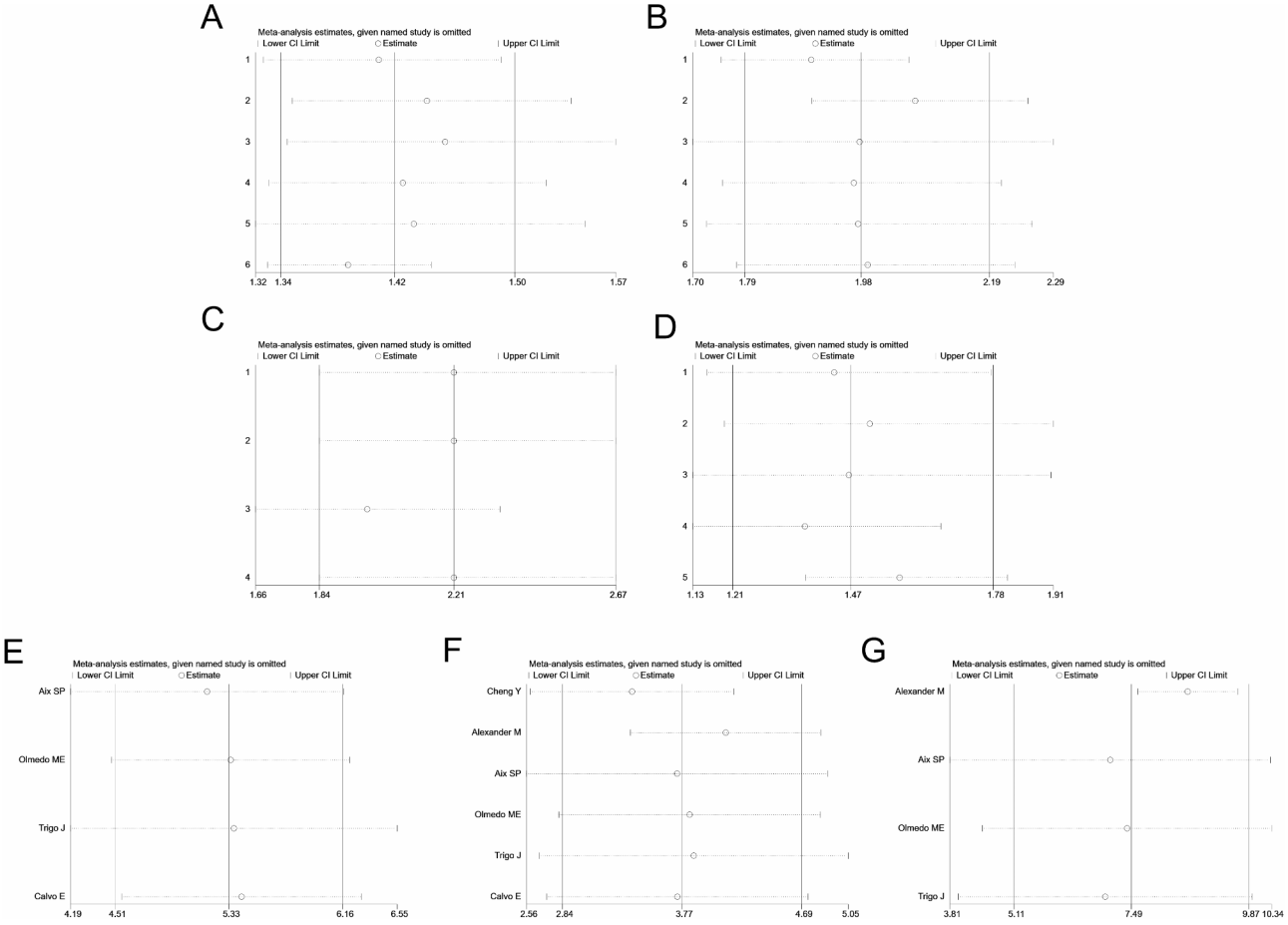

Fig. 4 Sensitivity analysis of ORR, DCR, AEs, SAEs, DOR, PFS, and OS. **A**. ORR, **B**. DCR, **C**. Incidence of AEs, **D**. Incidence of SAEs, **E**. DOR, **F**. PFS, **G**. OS. ORR, Objective Response Rate; DCR, Disease control rate; AEs, Adverse Events; SAEs, Severe Adverse Events; DOR, Duration of response; PFS, Progression-Free Survival; OS, Overall Survival

aminotransferase and pneumonia were the most common grade 3 or 4 treatment-related adverse events in the nivolumab monotherapy group. CheckMate331 was a randomized Phase III trial comparing the efficacy and adverse effects of monotherapy with nivolumab versus chemotherapy with topotecan or amrubicin in 569 patients with relapsed SCLC [39]. The median OS was 7.5 months in the nivolumab group, while it was 8.4 months (HR,0.86; 95%CI, 0.72–1.04; $p=0.11$) in the chemotherapy group. The response rate in the nivolumab group was 13.7%, while the chemotherapy group was 16.5%. 2 patients who received nivolumab monotherapy and 3 patients who received chemotherapy had treatment-related deaths. Only 14% of patients receiving nivolumab monotherapy experienced grade 3–4 adverse events, in contrast to the 73% incidence observed among patients treated with chemotherapy. Currently, nivolumab or pembrolizumab monotherapy is recommended as a viable option for second-line therapy in patients with a disease-free interval of less than 6 months and no prior exposure to ICIs [3].

A total of 536 patients with ES-SCLC were included in this meta-analysis, all of whom received lurbinectedin in second-line or subsequent treatment. Through this analysis, the ORR and DOR results were stable, with an ORR of 35% (95%CI 29–41), and a DOR of 5.33 months (95%CI 4.51–6.16). In order to reduce the heterogeneity of the results, subgroup analyses showed that the four studies conducted in the United States had a good homogeneity, with a DCR of 68% (95%CI-72), a PFS of 3.79 months (95%CI 3.28–4.30), and an OS of 8.64 months (95%CI 7.62–9.65). From the perspective of efficacy data, lurbinectedin has good application potential in the second-line treatment of ES-SCLC. In terms of safety, the incidence of total AEs and SAEs in lurbinectedin was 92% (95%CI 78–100) and 37% (95%CI 19–57), respectively. The most common AEs and SAEs were mainly hematotoxicity, while other AEs encompass fatigue, abnormal liver function, diarrhea, mucositis, and decreased appetite; however, these AEs were predominantly of grade 1–2 severity. In order to comprehensively assess the effectiveness and safety of lurbinectedin in second-line or

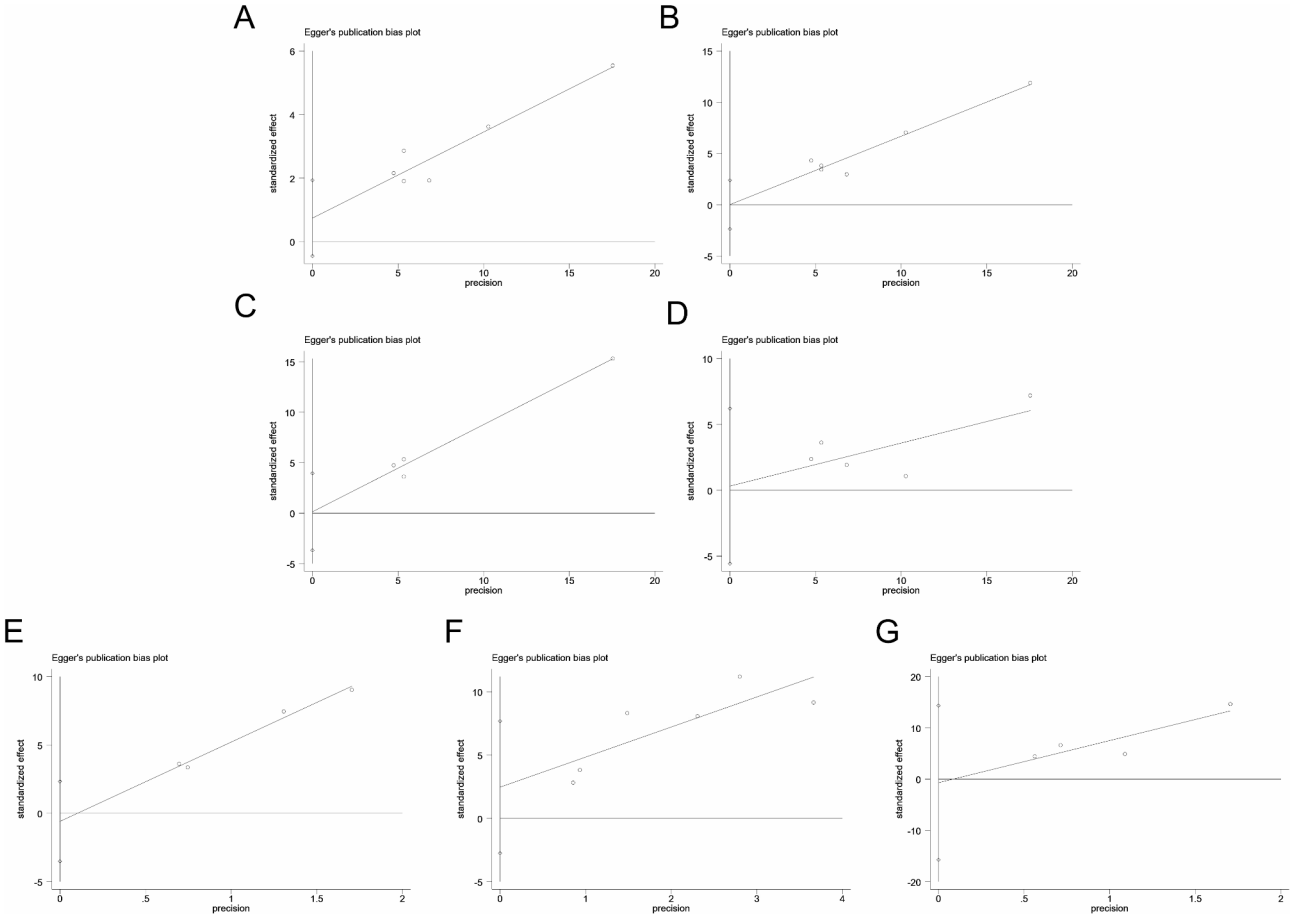

Fig. 5 Publication bias analysis of ORR, DCR, the incidence of AEs, the incidence of SAEs, DOR, PFS, OS. (**A**) ORR, (**B**) DCR, (**C**) Incidence of AEs, (**D**) Incidence of SAEs, (**E**) DOR, (**F**) PFS, (**G**) OS. ORR, Objective Response Rate; DCR, Disease control rate; DOR, Duration of response; PFS, Progression-Free Survival; OS, Overall Survival; AEs, Adverse Events; SAEs, Severe Adverse Events;

subsequent treatment of SCLC, the results of some real-world studies are also summarized here. Recently, a real-world study conducted in Canada demonstrated that the median OS for patients with relapsed SCLC treated with lurbinectedin was 9.3 months (95% CI 6.3–11.8 months) [40]. The results of this study closely align with those obtained in our subgroup analysis. However, another study showed lurbinectedin exhibited a median OS of 5.1 months in the second-line cohort and 5.6 months in the third-line or subsequent cohorts [41]. OS was worse compared to the result in our meta-analysis. From a safety perspective, the main AEs reported in real-world studies were related to the hematologic system, which is consistent with as findings. In terms of incidence, a study reported that 18% of patients in the second-line cohort and 21% in the ≥third-line cohort experienced≥grade 3 AEs. No treatment-related deaths or grade 5 toxicities were documented [41]. The incidence is marginally lower compared to our pooled analysis. This discrepancy may be attributed to a higher proportion of patients receiving dose reductions in real-world study.

In order to improve the prognosis of SCLC, the world is focusing on the research and development of new drugs and exploring new combination therapies. Recently, the research and development of new target inhibitors has progressed rapidly. For example, alisertib is a selective AURKA inhibitor, and it has been found in a randomized phase II clinical trial that its combination with paclitaxel treatment has a significant improvement in prognosis for some SCLC patients compared to paclitaxel plus placebo treatment. The main characteristics of this population are the presence of mutations in cell cycle regulation-related genes and high expression level of c-Myc [42]. The treatment of SCLC by inhibition of ATR has also been confirmed in preclinical studies. Currently, a randomized phase II clinical trial of topotecan combined with ATR inhibitor M6620 and topotecan is underway (NCT03896503) [43]. In a proof-of-concept study, the combination of M6620 and topotecan had an ORR of 36% in relapsed SCLC and still sustained tumor regression in one patient with platinum-resistant SCLC [44]. The mechanism of CDK7 inhibitors is similar to that

of inhibiting ATR, both of which can cause the reduction of replication stress. Researchers have found that the combination of CDK7 inhibitors and anti-PD-1 immune checkpoint inhibition can improve the survival rate of SCLC patients. Currently, the efficacy of CDK7 inhibitor CT7001 in patients with SCLC is also being investigated [45]. In addition, DLL-3 is an inhibitory protein of the NOTCH signaling pathway, which is highly expressed in SCLC and other high-grade neuroendocrine tumors, but low or not expressed in normal tissues [46, 47]. Rovalpituzumab tesirine is an antibody-drug conjugate targeting DLL3. The TRINITY phase II trial was performed to explore its efficacy in SCLC patients with DLL3 positive expression [48]. However, the results of phase III RCT have not yet confirmed its role in second-line or maintenance therapy for SCLC [49, 50]. Tarlatamab (AMG 757) is a bispecific T cell connector targeting tumor cells DLL3 and T cells CD3. A phase I clinical trial included relapsed or refractory SCLC had found that AMG757 had a good therapeutic efficacy and safety. The ORR was 23.4%, the median PFS and OS were 3.7 months and 13.2 months, respectively. Only 1 treatment-related death occurred in 102 patients, and the incidence of ≥grade 3 AEs was 30.8% [51]. Additionally, a Phase I clinical trial of AMG 119, a CART drug targeting DLL3, in advanced SCLC after the progression of platinum-based regimens is also underway (NCT03392064) [52]. Clinical trials on the targeted treatment of GD2 have also been progressively conducted, partial data from the Phase II/III clinical trial of the GD2 antibody dinutuximab in second-line SCLC treatment were reported. However, dinutuximab in combination with irinotecan did not provide a significant survival benefit compared with irinotecan or topotecan monotherapy [53]. LSD1 is a flavin adenine dinucleotide-dependent demethylase, which is highly expressed in SCLC. Preclinical studies have demonstrated that its inhibition can reduce tumor growth in SCLC [54]. Phase III clinical trials of the LSD1 inhibitor tiragolumab in combination with atezolizumab, carboplatin, and etoposide in first-line treatment of ES-SCLC are ongoing (NCT04256421) [55]. In terms of exploring the combination therapy model of lurbinectedin, researchers are also exploring the therapeutic effect of lurbinectedin combined with ICIs on relapsed or refractory SCLC (NCT04253145) (NCT04358237) (NCT04610658) [56–58]. Previous data found that the ORR of lurbinectedin combined with atezolizumab could achieve 57.7% [59], and the results of the later study are worthy of expectation. At the same time, researchers are also conducting phase III clinical trials investigating lurbinectedin alone or in combination with irinotecan in patients with relapsed SCLC (NCT05153239) [60]. It is believed that the exploration of important targets and target-based clinical trials will bring a turning point for the precision treatment of SCLC.

Lurbinectedin has been in development for less than four years, and many clinical trial data are still to be published. As a result, the number of clinical trials included in this study was relatively small, the sample size of the subjects was limited, and the clinical trials included were mostly distributed in the United States. In addition, most of the included studies were Phase I/II clinical trials, and only one Phase III RCT, which could not fully compare lurbinectedin with the current treatment regimens. According to the results of the analysis, there was some heterogeneity in the incidence of AEs and SAEs after pooled analyses, and the heterogeneity could not be traced through the analysis of factors such as study location, treatment regimens, and clinical trial stage. In the future, with the in-depth development of related clinical trials, it is believed that the clinical application of lurbinectedin will be more accurate.

Conclusion

The subsequent treatment in recurrence or progression of ES-SCLC has always been a complex and thorny problem in clinical treatment. Lurbinectedin, as a new second-line treatment option for ES-SCLC, has been shown to have definite efficacy and good safety. However, lurbinectedin still faces multiple challenges, including optimal dose selection and appropriate combination therapy. In addition, whether lurbinectedin can be used in first-line or maintenance therapy is also worthy of further evaluation.

Abbreviations

SCLC	Small cell lung cancer
ES-SCLC	Extensive-stage small cell lung cancer
FDA	The Food and Drug Administration
AEs	Adverse Events
SAEs	Severe Adverse Events
ORR	Objective Response Rate
DCR	Disease control rate
DOR	Duration of response
PFS	Progression-Free Survival
OS	Overall Survival
RNA	Ribonucleic Acid
DNA	Deoxyribonucleic Acid
ICD	Immunogenic Cell Death
TAM	Tumor-Associated Macrophages
CAV	Cisplatin + Adriamycin + Vincristine
CNKI	China National Knowledge Infrastructure
MINORS	Methodological Index for Non-Randomized Studies
95%CI	95% confidence interval
RCT	Randomized Controlled Trial
NCCN	National Comprehensive Cancer Network
ESMO	European Society for Medical Oncology
ICIs	Immune checkpoint inhibitors
AURKA	Aurora kinase A
ATR	Ataxia telangiectasia and Rad3-related
CDK	Cyclin-dependent kinase
PD	Programmed cell death protein
DLL3	Delta-like ligand 3
CART	Chimeric antigen receptor T cells

GD2 Glycosphingolipid 2
LSD1 Lysine specific demethylase 1

Supplementary Information

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Supplementary Material 1

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

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References

1. Pietanza MC, Byers LA, Minna JD, Rudin CM. Small cell lung cancer: will recent progress lead to improved outcomes? Clin Cancer Res. 2015;21(10):2244–55. https://www.ncbi.nlm.nih.gov/pubmed/25979931.
2. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward. Nat Rev Cancer. 2017;17(12):765. https://www.ncbi.nlm.nih.gov/pubmed/29123245.
3. Ganti AKP, Billy W, Loo J, Bassetti M, Chiang A, D'Avella CA, Dowlati A, Downey RJ, Edelman M, Florsheim C, Gold KA et al. Version 2.2024, NCCN Clinical Practice Guidelines in Oncology. In: Small Cell Lung Cancer.National Comprehensive Cancer Network. 2024. https://www.nccn.org/guidelines/nccn-guidelines. Accessed 21 Nov 2023.
4. Mansfield AS, Kazarnowicz A, Karaseva N, Sanchez A, De Boer R, Andric Z, Reck M, Atagi S, Lee JS, Garassino M, et al. Safety and patient-reported outcomes of atezolizumab, carboplatin, and etoposide in extensive-stage small-cell lung cancer (IMpower133): a randomized phase I/III trial. Ann Oncol. 2020;31(2):310–7. https://www.ncbi.nlm.nih.gov/pubmed/31959349.
5. Singh S, Jaigirdar AA, Mulkey F, Cheng J, Hamed SS, Li Y, Liu J, Zhao H, Goheer A, Helms WS, et al. FDA approval Summary: Lurbinectedin for the treatment of metastatic small cell Lung Cancer. Clin Cancer Res. 2021;27(9):2378–82. https://www.ncbi.nlm.nih.gov/pubmed/33288660.
6. Lambrecht L, Arnold P, Behr J, Mertsch P, Tufman A, Kauffmann-Guerrero D. Topotecan in a real-world small-cell Lung Cancer Cohort: prognostic biomarkers improve selection of patients for second-line treatment. Diagnostics (Basel). 2024, 14(14). https://www.ncbi.nlm.nih.gov/pubmed/39061709
7. Christensen CL, Kwiatkowski N, Abraham BJ, Carretero J, Al-Shahrour F, Zhang T, Chipumuro E, Herter-Sprie GS, Akbay EA, Altabef A, et al. Targeting transcriptional addictions in small cell lung cancer with a covalent CDK7 inhibitor. Cancer Cell. 2014;26(6):909–22. https://www.ncbi.nlm.nih.gov/pubmed/25490451.
8. Rudin CM, Poirier JT, Byers LA, Dive C, Dowlati A, George J, Heymach JV, Johnson JE, Lehman JM, MacPherson D, et al. Molecular subtypes of small cell lung cancer: a synthesis of human and mouse model data. Nat Rev Cancer. 2019;19(5):289–97. https://www.ncbi.nlm.nih.gov/pubmed/30926931.
9. Leal JF, Martinez-Diez M, Garcia-Hernandez V, Moneo V, Domingo A, Bueren-Calabuig JA, Negri A, Gago F, Guillen-Navarro MJ, Aviles P, et al. PM01183, a new DNA minor groove covalent binder with potent in vitro and in vivo anti-tumour activity. Br J Pharmacol. 2010;161(5):1099–110. https://www.ncbi.nlm.nih.gov/pubmed/20977459.
10. Santamaria Nunez G, Robles CM, Giraudon C, Martinez-Leal JF, Compe E, Coin F, Aviles P, Galmarini CM, Egly JM. Lurbinectedin specifically triggers the degradation of phosphorylated RNA polymerase II and the formation of DNA breaks in Cancer cells. Mol Cancer Ther. 2016;15(10):2399–412. https://www.ncbi.nlm.nih.gov/pubmed/27630271.
11. Belgiovine C, Bello E, Liguori M, Craparotta I, Mannarino L, Paracchini L, Beltrame L, Marchini S, Galmarini CM, Mantovani A, et al. Lurbinectedin reduces tumour-associated macrophages and the inflammatory tumour microenvironment in preclinical models. Br J Cancer. 2017;117(5):628–38. https://www.ncbi.nlm.nih.gov/pubmed/28683469.
12. Xie W, Forveille S, Iribarren K, Sauvat A, Senovilla L, Wang Y, Humeau J, Perez-Lanzon M, Zhou H, Martinez-Leal JF, et al. Lurbinectedin synergizes with immune checkpoint blockade to generate anticancer immunity. Oncoimmunology. 2019;8(11):e1656502. https://www.ncbi.nlm.nih.gov/pubmed/31646106.
13. Aix SP, Ciuleanu TE, Navarro A, Cousin S, Bonanno L, Smit EF, Chiappori A, Olmedo ME, Horvath I, Grohe C, et al. Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): a multicentre, randomised, open-label, phase 3 trial. Lancet Respir Med. 2023;11(1):74–86. https://www.ncbi.nlm.nih.gov/pubmed/36252599.
14. Calvo E, Moreno V, Flynn M, Holgado E, Olmedo ME, Lopez Criado MP, Kahatt C, Lopez-Vilarino JA, Siguero M, Fernandez-Teruel C, et al. Antitumor activity of lurbinectedin (PM01183) and doxorubicin in relapsed small-cell lung cancer: results from a phase I study. Ann Oncol. 2017;28(10):2559–66. https://www.ncbi.nlm.nih.gov/pubmed/28961837.
15. Trigo J, Subbiah V, Besse B, Moreno V, Lopez R, Sala MA, Peters S, Ponce S, Fernandez C, Alfaro V, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020;21(5):645–54. https://www.ncbi.nlm.nih.gov/pubmed/32224306.
16. Olmedo ME, Forster M, Moreno V, Lopez-Criado MP, Brana I, Flynn M, Doger B, de Miguel M, Lopez-Vilarino JA, Nunez R, et al. Efficacy and safety of lurbinectedin and doxorubicin in relapsed small cell lung cancer. Results from an expansion cohort of a phase I study. Invest New Drugs. 2021;39(5):1275–83. https://www.ncbi.nlm.nih.gov/pubmed/33704620.
17. Goto K, Ohe Y, Shibata T, Seto T, Takahashi T, Nakagawa K, Tanaka H, Takeda K, Nishio M, Mori K, et al. Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2016;17(8):1147–57. https://www.ncbi.nlm.nih.gov/pubmed/27312053.
18. Cheng Y, Wu C, Wu L, Zhao J, Zhao Y, Chen L, Xin Y, Zhang L, Pan P, Li X, et al. A pivotal bridging study of lurbinectedin as second-line therapy in Chinese patients with small cell lung cancer. Sci Rep. 2024;14(1):3598. https://www.ncbi.nlm.nih.gov/pubmed/38351146.
19. Dingemans AC, Fruh M, Ardizzoni A, Besse B, Faivre-Finn C, Hendriks LE, Lantuejoul S, Peters S, Reguart N, Rudin CM, et al. Small-cell lung cancer: ESMO Clinical Practice guidelines for diagnosis, treatment and follow-up(☆). Ann Oncol. 2021;32(7):839–53. https://www.ncbi.nlm.nih.gov/pubmed/33864941.
20. Giaccone G, Ferrati P, Donadio M, Testore F, Calciati A. Reinduction chemotherapy in small cell lung cancer. Eur J Cancer Clin Oncol. 1987;23(11):1697–9. https://www.ncbi.nlm.nih.gov/pubmed/2828074.

21. Postmus PE, Berendsen HH, van Zandwijk N, Splinter TA, Burghouts JT, Bakker W. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. Eur J Cancer Clin Oncol. 1987;23(9):1409–11. https://www.ncbi.nlm.nih.gov/pubmed/2824211.
22. Garassino MC, Torri V, Michetti G, Lo Dico M, La Verde N, Aglione S, Mancuso A, Gallerani E, Galetta D, Martelli O, et al. Outcomes of small-cell lung cancer patients treated with second-line chemotherapy: a multi-institutional retrospective analysis. Lung Cancer. 2011;72(3):378–83. https://www.ncbi.nlm.nih.gov/pubmed/20950888.
23. Korkmaz T, Seber S, Kefeli U, Sari E, Canhoroz M, Oven B, Yildirim E, Yasar N, Aydin D, Balvan O, et al. Comparison of second-line treatment outcomes between sensitive and refractory small cell lung cancer patients: a retrospective analysis. Clin Transl Oncol. 2013;15(7):535–40. https://www.ncbi.nlm.nih.gov/pubmed/23143955.
24. Wakuda K, Kenmotsu H, Naito T, Akamatsu H, Ono A, Shukuya T, Nakamura Y, Tsuya A, Murakami H, Takahashi T, et al. Efficacy of rechallenge chemotherapy in patients with sensitive relapsed small cell lung cancer. Am J Clin Oncol. 2015;38(1):28–32. https://www.ncbi.nlm.nih.gov/pubmed/23388567.
25. Naito Y, Yamada K, Imamura Y, Ishii H, Matsuo N, Tokito T, Kinoshita T, Azuma K, Hoshino T. Rechallenge treatment with a platinum-based regimen in patients with sensitive relapsed small-cell lung cancer. Med Oncol. 2018;35(5):61. https://www.ncbi.nlm.nih.gov/pubmed/29610997.
26. Genestreti G, Tiseo M, Kenmotsu H, Kazushige W, Di Battista M, Cavallo G, Carloni F, Bongiovanni A, Burgio MA, Casanova C, et al. Outcomes of platinum-sensitive small-cell lung Cancer patients treated with Platinum/Etoposide rechallenge: a multi-institutional retrospective analysis. Clin Lung Cancer. 2015;16(6):e223–228. https://www.ncbi.nlm.nih.gov/pubmed/25983005.
27. Baize N, Monnet I, Greillier L, Geier M, Lena H, Janicot H, Vergnenegre A, Crequit J, Lamy R, Auliac JB, et al. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2020;21(9):1224–33. https://www.ncbi.nlm.nih.gov/pubmed/32888454.
28. Yamamoto N, Tsurutani J, Yoshimura N, Asai G, Moriyama A, Nakagawa K, Kudoh S, Takada M, Minato Y, Fukuoka M. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. Anticancer Res. 2006;26(1B):777–81. https://www.ncbi.nlm.nih.gov/pubmed/16739353.
29. Smit EF, Fokkema E, Biesma B, Groen HJ, Snoek W, Postmus PE. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer. 1998;77(2):347–51. https://www.ncbi.nlm.nih.gov/pubmed/9461009.
30. Johnson DH, Greco FA, Strupp J, Hande KR, Hainsworth JD. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol. 1990;8(10):1613–7. https://www.ncbi.nlm.nih.gov/pubmed/2170589.
31. Furuse K, Kubota K, Kawahara M, Takada M, Kimura I, Fujii M, Ohta M, Hasegawa K, Yoshida K, Nakajima S, et al. Phase II study of vinorelbine in heavily previously treated small cell lung cancer. Japan Lung Cancer Vinorelbine Study Group. Oncology. 1996;53(2):169–72. https://www.ncbi.nlm.nih.gov/pubmed/8604245.
32. Lammers PE, Shyr Y, Li CI, Hutchison AS, Sandler A, Carbone DP, Johnson DH, Keedy VL, Horn L. Phase II study of bendamustine in relapsed chemotherapy sensitive or resistant small-cell lung cancer. J Thorac Oncol. 2014;9(4):559–62. https://www.ncbi.nlm.nih.gov/pubmed/24736081.
33. Masters GA, Declerck L, Blanke C, Sandler A, DeVore R, Miller K, Johnson D, Eastern Cooperative Oncology G. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol. 2003;21(8):1550–5. https://www.ncbi.nlm.nih.gov/pubmed/12697880.
34. von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, Stewart DJ, Clark PI, Palmer MC, Depierre A, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol. 1999;17(2):658–67. https://www.ncbi.nlm.nih.gov/pubmed/10080612.
35. Antonia SJ, Lopez-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, Jager D, Pietanza MC, Le DT, de Braud F, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016;17(7):883–95. https://www.ncbi.nlm.nih.gov/pubmed/27269741.
36. Horn L, Reck M, Spigel DR. The future of Immunotherapy in the treatment of small cell Lung Cancer. Oncologist. 2016;21(8):910–21. https://www.ncbi.nlm.nih.gov/pubmed/27354668.
37. Ott PA, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, Piperdi B, Mehnert JM. Pembrolizumab in patients with extensive-stage small-cell Lung Cancer: results from the phase ib KEYNOTE-028 study. J Clin Oncol. 2017;35(34):3823–9. https://www.ncbi.nlm.nih.gov/pubmed/28813164.
38. Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, Antonia SJ, Ascierto PA, Moreno V, Atmaca A, et al. Nivolumab Monotherapy and Nivolumab Plus Ipilimumab in Recurrent Small Cell Lung Cancer: results from the CheckMate 032 Randomized Cohort. J Thorac Oncol. 2020;15(3):426–35. https://www.ncbi.nlm.nih.gov/pubmed/31629915.
39. Spigel DR, Vicente D, Ciuleanu TE, Gettinger S, Peters S, Horn L, Audigier-Valette C, Pardo Aranda N, Juan-Vidal O, Cheng Y, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331(☆). Ann Oncol. 2021;32(5):631–41. https://www.ncbi.nlm.nih.gov/pubmed/33539946.
40. Boyne DJ, Dawe DE, Shakir H, Joe-Uzuegbu O, Farah E, Pabani A, Baratta C, Brenner DR, Cheung WY. Comparative effectiveness of Lurbinectedin for the treatment of relapsed small cell Lung Cancer in the Post-platinum setting: a real-world Canadian Synthetic Control Arm Analysis. Target Oncol. 2023;18(5):697–705. https://www.ncbi.nlm.nih.gov/pubmed/37656263.
41. Desai A, Smith CJ, Ashara Y, Orme JJ, Zanwar S, Potter A, Hocum C, Moffett JN, Schwecke AJ, Manochakian R, et al. Real-world outcomes with Lurbinectedin in Second-Line setting and beyond for extensive stage small cell Lung Cancer. Clin Lung Cancer. 2023;24(8):689–e695681. https://www.ncbi.nlm.nih.gov/pubmed/37880074.
42. Owonikoko TK, Niu H, Nackaerts K, Csoszi T, Ostoros G, Mark Z, Baik C, Joy AA, Chouaid C, Jaime JC, et al. Randomized Phase II study of Paclitaxel plus Alisertib versus Paclitaxel plus Placebo as Second-Line therapy for SCLC: primary and correlative biomarker analyses. J Thorac Oncol. 2020;15(2):274–87. https://www.ncbi.nlm.nih.gov/pubmed/31655296.
43. Randomized Trial of Topotecan With M6620. an ATR Kinase Inhibitor, in Small Cell Lung Cancers and Small Cell Cancers Outside of the Lungs [database on the Internet]2024. https://clinicaltrials.gov/study/NCT03896503?term=NCT03896503&rank=1
44. Thomas A, Takahashi N, Rajapakse VN, Zhang X, Sun Y, Ceribelli M, Wilson KM, Zhang Y, Beck E, Sciuto L, et al. Therapeutic targeting of ATR yields durable regressions in small cell lung cancers with high replication stress. Cancer Cell. 2021;39(4):566–e579567. https://www.ncbi.nlm.nih.gov/pubmed/33848478.
45. Sava GPFH, Coombes RC, Buluwela L, Ali S. CDK7 inhibitors as anticancer drugs. Cancer Metastasis Rev. 2020;39(3):805–23. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7497306
46. Saunders LR, Bankovich AJ, Anderson WC, Aujay MA, Bheddah S, Black K, Desai R, Escarpe PA, Hampl J, Laysang A, et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. Sci Transl Med. 2015;7(302):302ra136. https://www.ncbi.nlm.nih.gov/pubmed/26311731.
47. Rudin CM, Pietanza MC, Bauer TM, Ready N, Morgensztern D, Glisson BS, Byers LA, Johnson ML, Burris HA 3rd, Robert F, et al. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. Lancet Oncol. 2017;18(1):42–51. https://www.ncbi.nlm.nih.gov/pubmed/27932068.
48. Morgensztern D, Besse B, Greillier L, Santana-Davila R, Ready N, Hann CL, Glisson BS, Farago AF, Dowlati A, Rudin CM, et al. Efficacy and safety of Rovalpituzumab Tesirine in Third-Line and Beyond patients with DLL3-Expressing, Relapsed/Refractory small-cell Lung Cancer: results from the phase II TRINITY study. Clin Cancer Res. 2019;25(23):6958–66. https://www.ncbi.nlm.nih.gov/pubmed/31506387.
49. Blackhall F, Jao K, Greillier L, Cho BC, Penkov K, Reguart N, Majem M, Nackaerts K, Syrigos K, Hansen K, et al. Efficacy and safety of Rovalpituzumab Tesirine compared with Topotecan as second-line therapy in DLL3-High SCLC: results from the phase 3 TAHOE Study. J Thorac Oncol. 2021;16(9):1547–58. https://www.ncbi.nlm.nih.gov/pubmed/33607312.
50. Johnson ML, Zvirbule Z, Laktionov K, Helland A, Cho BC, Gutierrez V, Colinet B, Lena H, Wolf M, Gottfried M, et al. Rovalpituzumab Tesirine as a maintenance Therapy after First-Line platinum-based chemotherapy in patients with extensive-Stage-SCLC: results from the phase 3 MERU Study. J Thorac Oncol. 2021;16(9):1570–81. https://www.ncbi.nlm.nih.gov/pubmed/33823285.
51. Paz-Ares L, Champiat S, Lai WV, Izumi H, Govindan R, Boyer M, Hummel HD, Borghaei H, Johnson ML, Steeghs N, et al. Tarlatamab, a first-in-class DLL3-Targeted bispecific T-Cell engager, in recurrent small-cell lung Cancer: an Open-Label, phase I study. J Clin Oncol. 2023;41(16):2893–903. https://www.ncbi.nlm.nih.gov/pubmed/36689692.

52. A Phase 1 Study Evaluating the Safety. Tolerability and Efficacy of AMG 119 in Subjects With RR SCLC [database on the Internet]2023. https://clinicaltrials.gov/study/NCT03392064?term=NCT03392064&rank=1
53. Ganti AKP, Billy W, Loo J, Bassetti M, Chiang A, D'Avella CA, Dowlati A, Downey RJ, Edelman M, Florsheim C, Gold KA, et al. Randomized phase 3 study of the anti-disialoganglioside antibody dinutuximab and irinotecan vs irinotecan or topotecan for second-line treatment of small cell lung cancer. Lung Cancer. 2022;166:135–42. https://www.ncbi.nlm.nih.gov/pubmed/35278766.
54. Augert A, Eastwood E, Ibrahim AH, Wu N, Grunblatt E, Basom R, Liggitt D, Eaton KD, Martins R, Poirier JT et al. Targeting NOTCH activation in small cell lung cancer through LSD1 inhibition. Sci Signal. 2019, 12(567):eaau2922. https://www.ncbi.nlm.nih.gov/pubmed/30723171
55. A Study of Atezolizumab Plus. Carboplatin and Etoposide With or Without Tiragolumab in Patients With Untreated Extensive-Stage Small Cell Lung Cancer (SKYSCRAPER-02) [database on the Internet]2024. https://clinicaltrials.gov/study/NCT04256421?term=NCT04256421&rank=1
56. Study toA. Safety,Tolerability,Efficacy of PM01183 and Atezolizumab in Patients w/ Advanced Small Cell Lung Cancer. [database on the Internet]2023. https://clinicaltrials.gov/study/NCT04253145?term=NCT04253145&rank=1
57. Lurbinectedin (PM01183.) Combined With Pembrolizumab in Small Cell Lung Cancer. [database on the Internet]2024. https://clinicaltrials.gov/study/NCT04358237?term=NCT04358237&rank=1
58. Immune Checkpoint Inhibition With Lurbinectedin Relapsed/Recurrent SCLC [database on the Internet]2024. https://clinicaltrials.gov/study/NCT04610658?term=NCT04610658&rank=1
59. Russo-Cabrera JS, Ponce-Aix S, Cozar P, Luengo A, Mendivil AFN. 1050P sensitization to immunotherapy through manipulation of tumor transcription by lurbinectedin. Ann Oncol. 2023. https://doi.org/10.1016/j.jbc.2022.102153.
60. Clinical Trial of Lurbinectedin as. Single-agent or in Combination With Irinotecan Versus Topotecan or Irinotecan in Patients With Relapsed Small-cell Lung Cancer (LAGOON) [database on the Internet]2024. https://clinicaltrials.gov/study/NCT05153239?term=NCT05153239&rank=1

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