

Immune checkpoint inhibitor-based vs. non-immunotherapy subsequent treatment after progression on first-line chemoimmunotherapy in extensive-stage small cell lung cancer: A meta-analysis

CHUAN LONG*, YINGDING RUAN*, AIMING YANG, SUWEI XU and JIANWEI HAN

Department of Thoracic Surgery, The First People's Hospital of Jiande, Jiande, Zhejiang 311600, P.R. China

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Abstract. First-line chemoimmunotherapy is currently a standard treatment for extensive-stage small cell lung cancer (ES-SCLC), but the value of immune checkpoint inhibitor (ICI)-based subsequent treatment after progression remains uncertain. The present meta-analysis assessed the efficacy and safety of ICI-based vs. non-immunotherapy subsequent treatment after progression on first-line chemoimmunotherapy. The present systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement. The PubMed, Embase, Web of Science Core Collection, Scopus and Cochrane Library databases were searched from their respective dates of inception to May 8, 2026. Comparative studies evaluating ICI-based vs. non-immunotherapy subsequent treatment after progression on first-line chemoimmunotherapy in ES-SCLC were eligible for inclusion. The primary outcomes were overall survival (OS) and progression-free survival (PFS). Secondary outcomes included objective response rate (ORR), disease control rate (DCR) and grade ≥ 3 adverse events (AEs) or treatment-related AEs (TRAEs). Hazard ratios (HRs) and risk

ratios (RRs) with 95% CIs were pooled using random-effects models. A total of 10 non-randomized comparative studies, including nine retrospective clinical real-world cohorts and one retrospective translational cohort analysis, were included. Among these, six studies contributed to the primary OS and PFS meta-analyses, whereas the remaining four were included in qualitative synthesis or sensitivity analyses because of incomplete eligibility alignment or non-poolable estimates. Compared with non-immunotherapy subsequent treatment, ICI-based subsequent treatment was associated with longer OS (HR, 0.62; 95% CI, 0.51-0.74; $P < 0.00001$) and PFS (HR, 0.51; 95% CI, 0.38-0.69; $P < 0.0001$). The survival associations remained stable in sensitivity analyses using unmatched estimates or additional partially aligned datasets. ICI-based subsequent treatment was also associated with higher ORR (RR, 2.31; 95% CI, 1.61-3.32; $P < 0.00001$) and DCR (RR, 1.51; 95% CI, 1.16-1.98; $P = 0.003$). No significant increase in grade ≥ 3 AEs or TRAEs was observed (RR, 0.89; 95% CI, 0.56-1.40; $P = 0.61$). To conclude, these findings suggest that ICI-based subsequent treatment was associated with more favorable survival and tumor-response outcomes after progression on first-line chemoimmunotherapy in ES-SCLC, without evidence of a clear increase in severe toxicity. However, given that all included studies were non-randomized comparative studies, with potential treatment-selection bias and regimen heterogeneity, the present findings require prospective validation.

Correspondence to: Dr Jianwei Han, Department of Thoracic Surgery, The First People's Hospital of Jiande, 55 Yanzhou Street, Jiande, Zhejiang 311600, P.R. China
E-mail: hihjw@163.com

*Contributed equally

Abbreviations: AE, adverse event; DCR, disease control rate; ES, extensive-stage; HR, hazard ratio; ICI, immune checkpoint inhibitor; RECIST, Response Evaluation Criteria in Solid Tumors; NOS, Newcastle-Ottawa Scale; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PSM, propensity score matching; RR, risk ratio; SCLC, small cell lung cancer; TRAE, treatment-related adverse event

Key words: ES-SCLC, ICI, chemoimmunotherapy, treatment beyond progression, meta-analysis

Introduction

Worldwide, small cell lung cancer (SCLC) accounts for 10-15% of all lung cancer cases and is associated with a 5-year overall survival rate of $< 10\%$, reflecting its aggressive clinical course characterized by rapid growth, early dissemination and frequent relapse after an initial response to treatment (1,2). The majority of patients with SCLC first present with extensive-stage (ES) disease, for which systemic therapy is the principal treatment modality and largely determines the subsequent clinical course (2). Platinum plus etoposide has remained the first-line backbone for ES-SCLC. However, it has only conferred modest survival improvements (2). The advent of immune checkpoint inhibitors (ICIs) has reshaped this long-static therapeutic landscape. Landmark trials, including

IMpower133 and CASPIAN, established atezolizumab or durvalumab plus platinum-etoposide as first-line chemoimmunotherapy standards (3-5). Subsequent phase III studies, including CAPSTONE-1 and ASTRUM-005, extended this approach to additional programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors and in turn consolidated the role of chemoimmunotherapy in ES-SCLC (6,7). Despite these advances, most patients ultimately experience disease progression after first-line chemoimmunotherapy, underscoring the need for effective post-progression strategies (3-7).

The post-progression setting remains an important clinical gap. Conventional subsequent-line options include topotecan, a topoisomerase I inhibitor, and lurbinectedin, a transcription inhibitor that binds preferentially to guanine-rich DNA sequences; both agents have demonstrated antitumor activity in selected patients with relapsed SCLC, but generally provide modest and short-lived disease control (8,9). As first-line chemoimmunotherapy has become routine, clinicians increasingly encounter patients who relapse after prior PD-1 or PD-L1 blockade. Whether subsequent treatment should retain an ICI component through continuation, rechallenge, switching or combination with chemotherapy and/or antiangiogenic agents remains uncertain. This is no longer a purely theoretical question, such that it is now a practical treatment decision in everyday ES-SCLC care.

A plausible but unproven rationale supports ICI-based treatment after progression. Resistance to immunotherapy may be heterogeneous rather than absolute, which may involve tumor-intrinsic immune escape, altered antigen presentation, IFN-pathway changes and remodeling of the tumor microenvironment (10). Recent proteogenomic profiling of SCLC has identified subtype-specific immune and therapeutic vulnerabilities (11). Recent real-world studies have begun to evaluate ICI-containing subsequent strategies after progression on chemoimmunotherapy, including ICI continuation and rechallenge, but their findings remain heterogeneous and lack consensus because of differences in patient selection, treatment combinations, endpoint definitions and the use of adjusted or propensity score-matched analyses (12,13). These observations provide a rationale for further evaluating continued or rechallenged ICI-containing therapy in selected patients, particularly in combination with chemotherapy or antiangiogenic treatment, while also underscoring the need for quantitative synthesis of the available comparative evidence.

Given these uncertainties, the current systematic review and meta-analysis was conducted to evaluate whether ICI-based subsequent treatment is associated with more favorable outcomes compared with non-immunotherapy subsequent treatment after progression on first-line chemoimmunotherapy in ES-SCLC. The primary outcomes were overall survival (OS) and progression-free survival (PFS), whereas the secondary outcomes were objective response rate (ORR), disease control rate (DCR) and grade ≥ 3 adverse events (AEs) or treatment-related adverse events (TRAEs).

Materials and methods

Protocol and reporting standard. The present systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and

Meta-Analyses (PRISMA) 2020 statement (14) and the methodological guidance of the Cochrane Handbook for Systematic Reviews of Interventions (15). The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (registration no. CRD420261392088). The review question, eligibility criteria, outcome hierarchy, data-extraction strategy and quantitative synthesis plan were defined before data pooling. The present study focused on comparative evidence evaluating whether ICI-based subsequent treatment after progression on first-line chemoimmunotherapy is associated with more favorable outcomes in patients with ES-SCLC.

Search strategy. The PubMed/MEDLINE (<https://pubmed.ncbi.nlm.nih.gov/>), Embase (<https://www.embase.com/>), Web of Science Core Collection (<https://www.webofscience.com/>), Scopus (<https://www.scopus.com/>) and Cochrane Library (<https://www.cochranelibrary.com/>) databases were systematically searched from their respective dates of inception to May 8, 2026. The search combined terms related to SCLC, ICI, post-progression treatment, ICI continuation, ICI discontinuation, rechallenge, retreatment and comparative study designs. As post-progression immunotherapy strategies have been described inconsistently across studies, terms, such as ‘immunotherapy beyond progression’, ‘ICI rechallenge’, ‘continuous immunotherapy’, ‘second-line immunotherapy’ and ‘post-progression treatment’, were included to maximize sensitivity during retrieval. Search strategies were adapted to the syntax of each database. Reference lists of eligible studies and relevant reviews were also screened manually. The complete database-specific search strategies are provided in Table S1.

Inclusion and exclusion criteria. Studies were eligible if they fulfilled all of the following criteria: i) Included patients with ES-SCLC or advanced/metastatic SCLC in a treatment setting consistent with ES disease, defined for the purposes of the present study as disease requiring systemic therapy because it was not amenable to definitive local treatment alone; ii) evaluated patients who had experienced disease progression after first-line chemoimmunotherapy, typically platinum-etoposide chemotherapy combined with a PD-1 or PD-L1 inhibitor; iii) compared ICI-based subsequent treatment with non-immunotherapy subsequent treatment; iv) used a comparative design, including retrospective, prospective or randomized studies; and v) reported at least one extractable comparative outcome, including OS, PFS, ORR, DCR or safety outcomes.

For operational purposes, ICI-based subsequent treatment included continuation of the same ICI, switching to another ICI, ICI rechallenge, ICI plus chemotherapy, ICI plus antiangiogenic therapy or ICI plus chemotherapy and antiangiogenic therapy. These strategies were grouped pragmatically according to whether an ICI component was retained after progression. This grouping was not intended to imply pharmacological or clinical interchangeability among different ICI-containing regimens. The comparator, defined as non-immunotherapy subsequent treatment, consisted of patients who did not receive further ICI-containing therapy after progression and instead received chemotherapy, antiangiogenic therapy, chemotherapy plus antiangiogenic therapy or another non-ICI systemic treatment.

Studies would be excluded if they were single-arm studies, case reports, case series without a comparator, reviews, editorials, letters, comments, meta-analyses or conference abstracts with insufficient extractable data. In addition, mixed non-SCLC (NSCLC)/SCLC population studies would be excluded unless SCLC-specific data could be extracted separately. Studies were also excluded if first-line chemoimmunotherapy was not clearly documented, if ICI-based and non-immunotherapy subsequent treatments could not be distinguished or if no comparative efficacy or safety outcome could be extracted. When overlapping cohorts were suspected, the most complete or most relevant dataset would be prioritized for the primary analysis.

To further minimize potential double-counting, potentially overlapping retrospective multicenter cohorts were cross-checked during full-text review and data extraction. The cross-check considered reported participating institutions or study centers, enrollment periods, authorship groups, cohort sizes, eligibility criteria, first-line treatment exposure, subsequent-treatment definitions and outcome datasets. When complete center-level information was not reported, potential overlap was assessed as far as possible from the available study-level information and considered when interpreting the findings.

Study selection. In total, two reviewers (CL and YR) independently performed screening in two sequential stages. After duplicates were removed, titles and abstracts were assessed for potential eligibility. The full texts of potentially relevant reports were then reviewed against the prespecified inclusion and exclusion criteria. Disagreements were resolved through discussion, but a third reviewer was consulted when consensus could not be achieved.

Data extraction. A total of two reviewers independently extracted data using a standardized form. The extracted information included first author, publication year, country, study design, study period, participating institutions or study centers when reported, eligibility criteria, sample size, first-line treatment, subsequent ICI-containing strategy, non-ICI comparator strategy, follow-up or data cut-off and reported outcomes.

The primary outcomes were OS and PFS. OS was defined as the time from initiation of the subsequent treatment under evaluation, or from the time origin specified in the original study, to death from any cause. PFS was defined as the time from initiation of the subsequent treatment under evaluation, or from the time origin specified in the original study, to disease progression or death. For time-to-event endpoints, hazard ratios (HRs) and corresponding 95% CIs were extracted when available. For PFS-related endpoints, the original endpoint definitions were audited before pooling. Endpoints were included in the PFS meta-analysis only if they measured disease control during the post-progression or subsequent-treatment period. In oncology trials, PFS2 commonly refers to the time from initial first-line treatment initiation or randomization to second disease progression or death; however, the term was not used uniformly across the retrospective studies included in the present review. When a study used the term 'PFS2' but defined it as the time from first-line progression to subsequent progression or as PFS during ICI rechallenge or second-line

chemotherapy, the endpoint was treated as a post-progression PFS construct rather than as conventional first-line-origin PFS2. Estimates corresponding to true PFS2 measured from initial first-line treatment initiation or randomization were not pooled directly with second-line or post-progression PFS. The secondary outcomes were ORR, DCR and grade ≥ 3 AEs or TRAEs. Specific toxicities, including pneumonitis, hematological toxicity, hepatic toxicity, hypothyroidism and rash, were summarized descriptively when reported, but were not pooled because definitions and reporting patterns varied across studies.

When multiple estimates were available from the same study, adjusted or propensity score-matched estimates were prioritized over crude or unmatched estimates. Multivariable Cox estimates were preferred over unadjusted Kaplan-Meier estimates. If both an entire-cohort estimate and a propensity score-matched estimate were available, the matched estimate was used in the primary analysis, while the unmatched estimate was considered in sensitivity analysis. The same patient cohort was not entered more than once in any single pooled analysis.

Quality assessment. The methodological quality of the included non-randomized studies was assessed independently by two reviewers (CL and YR) using the Newcastle-Ottawa Scale (NOS) for cohort studies, which is available from the Ottawa Hospital Research Institute website (https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS assesses the following three domains: i) Selection of study groups; ii) cohort comparability; and iii) outcome assessment. The NOS assesses selection (maximum 4 points), comparability (maximum 2 points) and outcome assessment (maximum 3 points), for a total score of 0-9. Studies scoring 7-9 points were classified as high quality, 5-6 points as moderate quality and 0-4 points as low quality. Discrepancies in quality assessment were resolved through discussion with a third reviewer.

Statistical analysis. All meta-analyses were performed using Review Manager version 5.4.0 (RevMan 5; The Cochrane Collaboration; <https://revman.cochrane.org>). For time-to-event outcomes, HRs were pooled using the generic inverse-variance method after conversion to log (HR) and standard error values. For dichotomous outcomes, risk ratios (RRs) with 95% CIs were estimated using the Mantel-Haenszel method. Random-effects models were applied for all pooled analyses because clinical and methodological heterogeneity was expected across retrospective real-world cohorts, including differences in subsequent treatment regimens, ICI agents, endpoint definitions and use of propensity score matching (PSM).

Statistical heterogeneity was assessed using the I^2 statistic. I^2 values $>50\%$ were considered to indicate substantial heterogeneity. Sensitivity analyses were conducted when alternative estimates were available or when studies showed partial alignment with the main Population, Intervention, Comparator and Outcomes (PICO) framework. These analyses included replacing propensity score-matched estimates with unmatched entire-cohort estimates and where appropriate, adding studies with extractable SCLC subgroup data from mixed populations. A conservative PFS sensitivity analysis was also performed by

excluding studies that used the label ‘PFS2’, regardless of the audited endpoint definition, to examine whether the primary PFS estimate depended on PFS2-labelled endpoints. In addition, a leave-one-out sensitivity analysis was performed for the primary OS and PFS outcomes by sequentially omitting one contributing study at a time and recalculating the pooled estimates. This analysis was used to assess whether the main survival results were disproportionately driven by any single study. Strategy-specific subgroup analyses and formal publication-bias assessment were considered as conditional analyses and were performed only when sufficient study-level data were available. Two-sided $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Study selection and characteristics. From database inception to May 8, 2026, the search identified 614 records, including 139 from PubMed, 164 from Embase, 87 from Web of Science Core Collection, 119 from Scopus and 105 from the Cochrane Library. After 248 duplicate records were removed, 366 records underwent title and abstract screening. Of these, 356 records were excluded, including three non-English publications, 27 reviews, 92 conference abstracts or proceedings and seven case reports, the remaining 227 records were excluded because they did not address ES-SCLC, post-progression ICI-based treatment after first-line chemoimmunotherapy or a comparative ICI-based vs. non-immunotherapy subsequent-treatment framework. A total of 10 full-text reports were retrieved and assessed for eligibility, all of which met the inclusion criteria. Finally, 10 comparative studies were included in the qualitative synthesis (Fig. 1) (16-25).

Quantitative synthesis was performed according to outcome availability and PICO alignment. The primary survival meta-analyses were restricted to studies that provided directly poolable comparative HRs aligned with the main PICO framework and were included in the primary OS and PFS meta-analyses (Figs. 2 and 3). The remaining four studies were not included in the primary survival meta-analyses because Cheng *et al* (16) provided SCLC subgroup data from a mixed NSCLC/SCLC cohort, Shang *et al* (19) did not provide a directly poolable all-cohort survival HR, Wang *et al* (21) reported subgroup estimates that were not used for primary survival pooling, and Zhang *et al* (25) included mixed first-line ICI exposure without a directly poolable main-PICO HR. These studies were therefore retained for qualitative synthesis or, when analytically appropriate, prespecified sensitivity analyses (Figs. S1-S4). Binary response and safety outcomes were pooled when comparable event counts were available (Figs. 4-6), and all extracted comparative outcomes are summarized in Table SII.

All included studies were non-randomized comparative studies; nine were retrospective clinical real-world cohorts and one was a retrospective translational cohort analysis. The aforementioned studies evaluated subsequent treatment strategies after progression on first-line chemoimmunotherapy or closely related first-line ICI-based regimens in patients with ES-SCLC or extractable SCLC subgroups. The main comparison was ICI-based vs. non-immunotherapy subsequent treatment. However, alignment with the prespecified

PICO framework varied across studies. Six studies directly evaluated patients with ES-SCLC after progression on first-line chemoimmunotherapy (18,20-24), whereas one study provided extractable estimates for patients initially treated with first-line immunotherapy within a broader cohort (17). In total, one study included a mixed NSCLC/SCLC cohort from which SCLC-specific subgroup data were extracted (16). A total of two studies required more cautious interpretation. Namely, one translational cohort analysis incorporated data from IMpower133 alongside a real-world validation cohort (19), whereas the other included patients with mixed first-line immunotherapy exposure (25). Consequently, the studies included in each quantitative synthesis varied according to outcome availability and eligibility criteria.

Potential cohort overlap was assessed across retrospective multicenter Chinese studies with overlapping enrollment periods, particularly Peng *et al* (18), Sun *et al* (20), Wang *et al* (21), Wang *et al* (22) and Zhang *et al* (23,24). Reported study periods, participating centers when available, authorship groups, cohort sizes, eligibility criteria, treatment definitions and outcome datasets were compared. No definite duplicate analytical cohort could be identified. However, Peng *et al* (18), Sun *et al* (20), Wang *et al* (21) and Zhang *et al* (23,25) did not provide patient-level identifiers, and some multicenter reports did not provide exhaustive center lists; therefore, unrecognized partial overlap across regional real-world networks could not be ruled out with absolute certainty.

The key study characteristics are summarized in Table I. Additional eligibility details, cohort definitions, treatment strategies, follow-up information and restriction notes are provided in Table SIII. As shown in Table SIII, the ICI-based arms were heterogeneous and included ICI continuation or rechallenge alone, ICI plus chemotherapy, ICI plus antiangiogenic therapy and triplet regimens. Because seven cohorts combined more than one ICI-containing strategy within the same intervention arm (16,17,20-24), the pooled analyses should be interpreted as assessing an ICI-containing treatment framework rather than any single post-progression regimen. Extracted comparative efficacy and safety outcomes are presented in Table SII. Study quality was assessed with the NOS. NOS scores ranged from 6-9, with seven of the 10 studies scoring 8 or 9 (17,18,20-24). These scores indicated acceptable reporting, cohort comparability and outcome assessment in most studies. However, they should not be interpreted as removing residual confounding inherent to non-randomized real-world comparisons (Table II). Accordingly, the pooled estimates should be interpreted as associations rather than causal treatment effects, because residual confounding and treatment-selection bias may remain even after multivariable adjustment or PSM.

Primary outcomes

OS. In total, six studies were included in the primary meta-analysis of OS (17,18,20,22-24). Using a random-effects model and prioritizing the propensity score-matched estimate where available, ICI-based subsequent treatment was associated with longer OS compared with that after non-immunotherapy subsequent treatment (HR, 0.62; 95% CI, 0.51-0.74; $P < 0.00001$; Fig. 2). Heterogeneity was low to moderate across studies ($I^2 = 33\%$).

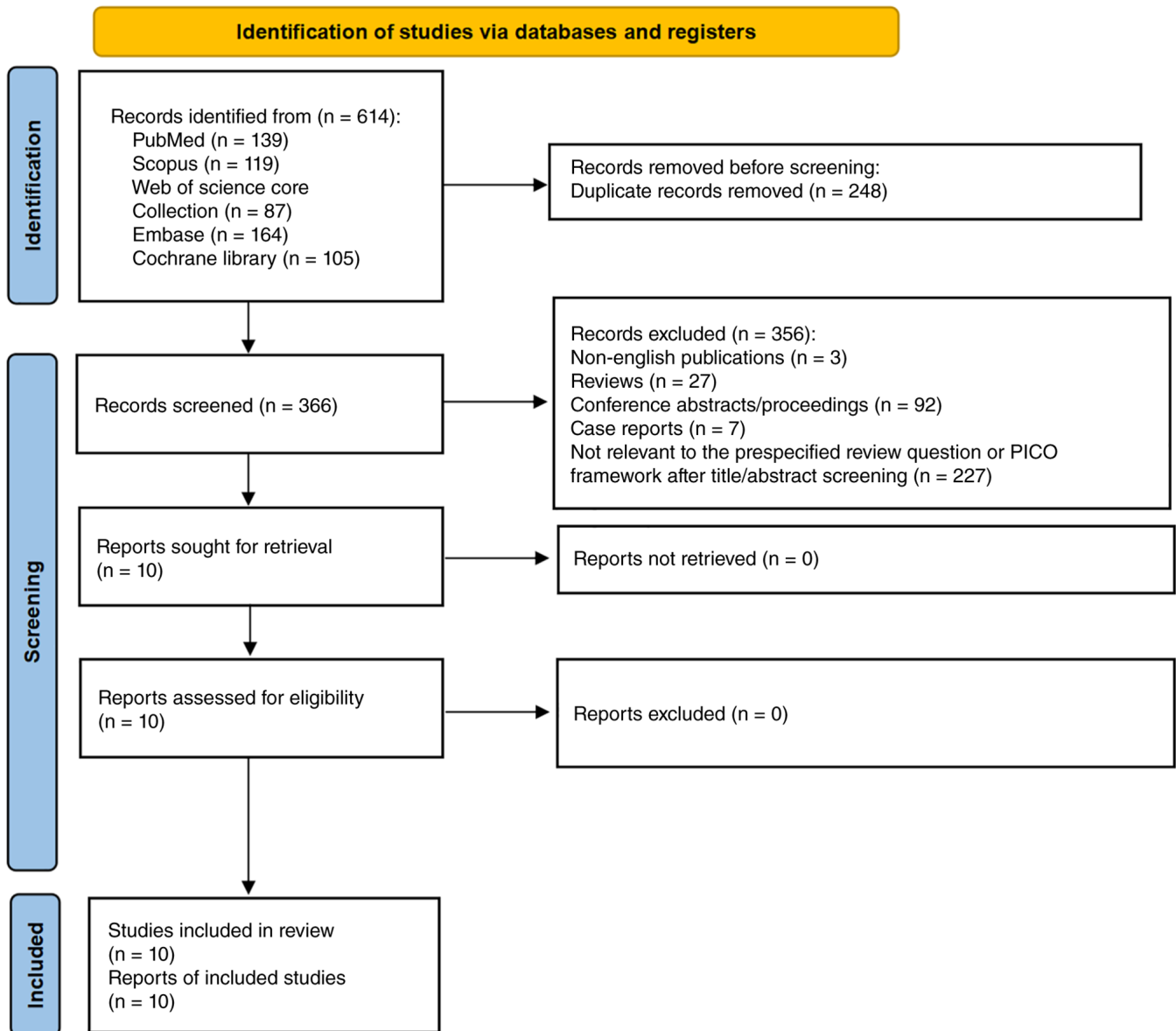


Figure 1. PRISMA flow diagram displaying the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PICO, Population, Intervention, Comparator and Outcomes.

A sensitivity analysis using the unmatched entire-cohort estimate from the same PSM study instead of the matched estimate yielded a nearly identical result (HR, 0.62; 95% CI, 0.52-0.75; $P < 0.00001$; Fig. S1), with similarly low-to-moderate heterogeneity ($I^2 = 35\%$). These findings indicate that the OS association observed with ICI-based subsequent treatment was not materially affected by the choice of matched vs. unmatched estimates.

PFS. In total, six studies were included in the primary meta-analysis of PFS (17,18,20,22-24). Before pooling, the definitions of PFS-related endpoints were audited. A total of two studies used the label PFS2 (20,22). In Sun *et al* (20), PFS2 was defined from progression on first-line treatment to progression on second-line treatment, whilst in Wang *et al* (22), PFS2 referred to PFS for ICI rechallenge or second-line chemotherapy. Therefore, these endpoints were considered to measure disease control during the post-progression or subsequent-treatment period rather than conventional

first-line-origin PFS2. Using a random-effects model and prioritizing the propensity score-matched estimate where available, ICI-based subsequent treatment was associated with longer PFS compared with that after non-immunotherapy subsequent treatment (HR, 0.51; 95% CI, 0.38-0.69; $P < 0.0001$; Fig. 3). Substantial heterogeneity was observed ($I^2 = 77\%$), although the direction of effect consistently favored ICI-based subsequent treatment.

Sensitivity analyses supported this result. When the unmatched entire-cohort estimate from the PSM study (23) was used instead of the matched estimate, the pooled effect remained unchanged (HR, 0.51; 95% CI, 0.38-0.69; $P < 0.0001$; $I^2 = 77\%$; Fig. S2). A further sensitivity analysis that included additional studies with extractable SCLC subgroup data or partial alignment with the main PICO framework (16,25) also yielded a consistent result favoring ICI-based subsequent treatment (HR, 0.50; 95% CI, 0.38-0.67; $P < 0.00001$; $I^2 = 73\%$; Fig. S3). These results suggest that the observed PFS association

Table I. Main characteristics of the studies included in the present systematic review and meta-analysis.

First author, year	Country	Study design	Population characteristics	IL treatment	Total, n ^a	ICI-based, n	Non-IO, n	Subsequent treatment comparison	Outcomes	(Refs.)
Cheng <i>et al</i> , 2025	China	Retrospective single-center cohort	Advanced SCLC subgroup with PD after 1L ICI-based therapy and SCLC data separately extractable	IO + ChT ± A	39	31	8	IBP vs. NIBP	PFS, OS, ORR, DCR and safety	(16)
Li <i>et al</i> , 2022	China	Retrospective multicenter cohort	ES-SCLC after PD on PD-1/PD-L1 inhibitor + ChT and 1L subgroup available	PD-1/PD-L1 inhibitor + ChT	100	45	55	RIBP vs. DIBP	PFS, OS, ORR, DCR and DCB	(17)
Peng <i>et al</i> , 2025	China	Retrospective multicenter cohort	ES-SCLC after PD on 1L PD-L1 inhibitor + ChT	PD-L1 inhibitor + EP/EC	150	86	64	IBP vs. non-IBP	PFS, OS, ORR, DCR and safety	(18)
Shang <i>et al</i> , 2024	International/China	Retrospective translational cohort analysis	ES-SCLC after progression on 1L ICI, and ^b IMpower133 and Shandong cohorts	1L ICI-based therapy	125/161	54/89	71/72	Atezolizumab/CI Irretreatment vs. non-ICI treatment	OS, subgroup analysis and TME analysis	(19)
Sun <i>et al</i> , 2026	China	Retrospective multicenter cohort	ES-SCLC after PD on 1L PD-1/PD-L1 inhibitor + ChT	PD-1/PD-L1 inhibitor + EP/EC	489	298	191	Continuing IO vs. control	PFS2, OS and safety	(20)
Wang <i>et al</i> , 2026	China	Retrospective multicenter cohort	ES-SCLC with disease control followed by PD after 1L anti-PD-1/PD-L1 + ChT and primary resistance excluded for 2L analysis	Anti-PD-1/PD-L1 + EP/EC	206	149	57	Continuous IO-containing strategies vs. non-ICI strategies	2L PFS, OS and safety	(21)
Wang <i>et al</i> , 2026	China	Retrospective single-center cohort	ES-SCLC after PD on 1L chemoimmunotherapy	Anti-PD-1/PD-L1 + platinum-based ChT	151	100	51	ICI rechallenge vs. single-agent ChT	PFS2, OS, ORR, DCR and safety	(22)
Zhang <i>et al</i> , 2025	China	Retrospective multicenter cohort with PSM	ES-SCLC after PD on 1L chemoimmunotherapy	1L chemoimmunotherapy	211	118	93	ICIs continuation vs. discontinuation	PFS, OS, ORR, DCR and safety	(23)
Zhang <i>et al</i> , 2025	China	Retrospective multicenter cohort	ES-SCLC receiving 2L therapy after progression on 1L chemoimmunotherapy	1L chemoimmunotherapy	103	53	50	2L ICIs vs. 2L non-ICIs	2L PFS, OS, ORR, DCR and safety	(24)

Table I. Continued.

First author, year	Country	Study design	Population characteristics	IL treatment	Total, n ^a	ICI-based, Non-IO, n	Subsequent treatment comparison	Outcomes	(Refs.)
Zhang <i>et al.</i> , 2025	China	Retrospective multicenter cohort	ES-SCLC after progression on 1L EP ± PD-L1 inhibitor; IL ICI subgroup available	EP ± PD-L1 inhibitor	389	211	ICI + A or ICI + ChT vs. ChT	PFS, OS, ORR, DCR and safety	(25)

^aTotal n refers to the analytic cohort used for the comparative extraction. bFor Shang *et al.*, two cohorts are shown as IMpower133/Shandong. 1L, first line; 2L, second line; A, anti-angiogenic therapy; ChT, chemotherapy; DCR, durable clinical benefit; DCR, disease control rate; DIBP, discontinuation of immunotherapy beyond progression; EP/EC, etoposide plus platinum/carboplatin; ES, extensive-stage; IBP, immunotherapy beyond progression; ICI, immune checkpoint inhibitor; IO, immunotherapy; NIBP, non-immunotherapy beyond progression; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PSM, propensity score matching; RIBP, rechallenging of immunotherapy beyond progression; SCLC, small cell lung cancer; TME, tumor microenvironment.

was not substantially altered by the alternative handling of matched estimates or by the inclusion of additional partially aligned datasets. In the conservative sensitivity analysis that excluded the two studies that used the label PFS2 (20,22), the PFS association remained statistically significant and heterogeneity was no longer observed (HR, 0.48; 95% CI, 0.39-0.59; $P<0.00001$; $I^2=0\%$; Fig. S4).

Additional robustness analyses. A leave-one-out sensitivity analysis was conducted for the six studies contributing to the primary OS and PFS meta-analyses (17,18,20,22-24). After sequential omission of each individual study, both OS and PFS estimates remained statistically significant, with recalculated HRs ranging from 0.57-0.68 for OS and from 0.45-0.55 for PFS (all $P<0.001$; Table SIV). In the PFS analysis, heterogeneity decreased from $I^2=77\%$ in the primary analysis to $I^2=0\%$ when Sun *et al.* (20) was omitted, suggesting that this large multicenter cohort contributed substantially to between-study heterogeneity. However, the direction of association remained favorable to ICI-based subsequent treatment. These findings provided additional support for the stability of the primary survival analyses, whilst reinforcing the need for cautious interpretation because all analyses were based on non-randomized study-level data.

Secondary outcomes

ORR. In total, four studies were included in the meta-analysis of ORR (18,22-24). Using a random-effects model and prioritizing the PSM dataset where available, ICI-based subsequent treatment was associated with a higher ORR compared with that after non-immunotherapy subsequent treatment (RR, 2.31; 95% CI, 1.61-3.32; $P<0.00001$; Fig. 4). No heterogeneity was observed ($I^2=0\%$).

DCR. In total, four studies were included in the meta-analysis of DCR (18,22-24). Using a random-effects model and prioritizing the propensity score-matched dataset where available, ICI-based subsequent treatment was associated with a higher DCR than non-immunotherapy subsequent treatment (RR, 1.51; 95% CI, 1.16-1.98; $P=0.003$; Fig. 5). Substantial heterogeneity was observed ($I^2=69\%$). The direction of effect generally favored ICI-based subsequent treatment, although the magnitude of DCR improvement varied across studies.

Grade ≥ 3 AEs/TRAES. In total, two studies were included in the meta-analysis of grade ≥ 3 AEs or TRAES (18,22). Using a random-effects model, ICI-based subsequent treatment was not associated with an increased risk of grade ≥ 3 AEs/TRAES compared with non-immunotherapy subsequent treatment (RR, 0.89; 95% CI, 0.56-1.40; $P=0.61$; Fig. 6). No heterogeneity was observed ($I^2=0\%$). Because only two studies reported comparable overall grade ≥ 3 AE/TRAES data, no sensitivity analysis was performed for this outcome.

Discussion

In the present systematic review and meta-analysis of comparative studies, ICI-based subsequent treatment after progression on first-line chemoimmunotherapy was associated with more favorable clinical outcomes in patients with ES-SCLC. This association was observed across both major survival endpoints, with pooled estimates favoring ICI-based

Table II. NOS for assessing the quality of non-randomized studies included in the present study.

First author, year	Country	Type of article	NOS ^a			Total score (Refs.)
			Selection	Comparability	Outcome	
Cheng <i>et al</i> , 2025	China	Single-center, retrospective cohort study	3	1	2	6 (16)
Li <i>et al</i> , 2022	China	Multicenter, retrospective cohort study	4	2	2	8 (17)
Peng <i>et al</i> , 2025	China	Multicenter, retrospective cohort study	4	2	3	9 (18)
Shang <i>et al</i> , 2024	International/ China	Retrospective translational cohort analysis	3	1	2	6 (19)
Sun <i>et al</i> , 2026	China	Multicenter, retrospective cohort study	4	1	3	8 (20)
Wang <i>et al</i> , 2026	China	Multicenter, retrospective real-world study	4	2	3	9 (21)
Wang <i>et al</i> , 2026	China	Single-center, retrospective real-world study	4	2	3	9 (22)
Zhang <i>et al</i> , 2025	China	Multicenter, retrospective cohort study with propensity score matching	4	2	3	9 (23)
Zhang <i>et al</i> , 2025	China	Multicenter, retrospective cohort study	4	2	3	9 (24)
Zhang <i>et al</i> , 2025	China	Multicenter, retrospective cohort study	3	1	3	7 (25)

^aNOS was applied using the cohort-study domains: Selection, comparability and outcome. The maximum score was 9 points, with 1 point in comparability indicating adjustment for the most important prognostic confounder(s), while 2 points indicating additional adjustment for other relevant clinicopathological confounders. NOS, Newcastle-Ottawa Scale.

subsequent treatment for OS and PFS. Response outcomes pointed in the same direction, as patients receiving ICI-based subsequent treatment had higher ORR and DCR compared with those treated with non-immunotherapy strategies. Importantly, this apparent efficacy signal was not accompanied by a clear increase in grade ≥ 3 AEs/TRAEs, although the safety dataset was smaller than the efficacy dataset; the toxicity findings should therefore be interpreted in the context of established guidance for the recognition and management of immune-related AEs (26,27). Collectively, the present findings suggest that ICI-based subsequent treatment after first-line chemoimmunotherapy progression may have clinical value in selected patients. Despite this, the evidence should be interpreted as comparative real-world evidence rather than definitive proof of causal benefit, as all included studies were non-randomized and treatment allocation was not controlled.

OS is the most clinically stringent endpoint in this setting, and the observed OS association therefore warrants particular attention. In ES-SCLC, relapse after first-line chemoimmunotherapy typically marks the beginning of a brief and refractory disease course. Conventional second-line options, including topotecan and lurbinectedin, have activity in selected patients but generally provide only modest and frequently transient disease control (2,8,9). Earlier attempts to prolong immunotherapy exposure in SCLC, such as maintenance nivolumab with or without ipilimumab after first-line chemotherapy, also failed to establish a clear OS advantage (28). The δ -like ligand 3-targeted tarlatamab has produced clinically meaningful antitumor activity in previously treated SCLC, reflected by durable objective responses and disease control in a subset of patients (29) and in a randomized setting, an OS benefit after platinum-based chemotherapy was observed for this drug (30). However, these data address a different therapeutic question from whether subsequent therapy should retain a PD-L1

blockade component after progression on a PD-L1-containing first-line regimen. In the present context, the pooled OS estimate in the present analysis (HR, 0.62; 95% CI, 0.51-0.74) is clinically relevant, but it remains an association derived from non-randomized comparative evidence rather than definitive proof of treatment efficacy. The low-to-moderate heterogeneity ($I^2=33\%$) and the nearly unchanged result after replacing the PSM estimate with the unmatched estimate also support the stability of the OS finding (17,18,20,22-24). Therefore, the OS association does not appear to be dependent on a single analytical choice or one influential matched cohort, although it should still be interpreted within the limitations of non-randomized treatment selection.

The present PFS result complements the aforementioned OS result by suggesting improved post-progression disease control with ICI-based subsequent therapy. The pooled estimate favored ICI-based subsequent treatment (HR, 0.51; 95% CI, 0.38-0.69) and this direction remained consistent in sensitivity analyses, including use of unmatched estimates and inclusion of additional partially aligned datasets (16-18,20,22-24). However, the substantial heterogeneity in the PFS analysis ($I^2=77\%$) should not be overlooked. Importantly, this heterogeneity appears to reflect variation in effect magnitude rather than conflicting treatment directions. This is clinically plausible, because PFS-related endpoints were not described using identical terminology across studies. Endpoint-definition audit indicated that the PFS2-labelled studies captured disease control during the post-progression or second-line treatment period, rather than conventional PFS2 measured from initial first-line treatment initiation. Despite this, differences in endpoint terminology, time origin within the post-progression period, assessment schedule and censoring rules may still have contributed to heterogeneity. The conservative sensitivity analysis excluding PFS2-labelled studies yielded a consistent PFS

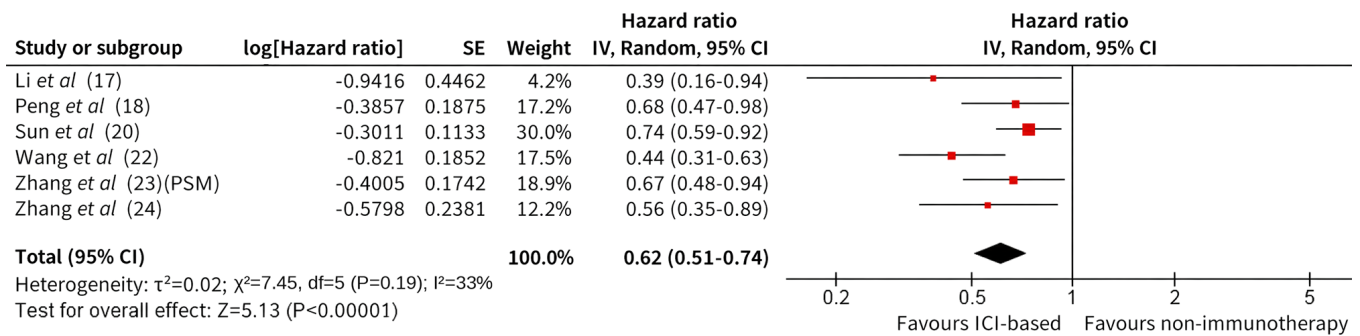


Figure 2. Random-effects meta-analysis of overall survival comparing ICI-based subsequent treatment with non-immunotherapy subsequent treatment after first-line chemoimmunotherapy progression in extensive-stage small cell lung cancer, shown as a forest plot. PSM, propensity score matching; ICI, immune checkpoint inhibitor; HR, hazard ratio; CI, confidence interval; IV, inverse variance; SE, standard error; df, degrees of freedom.

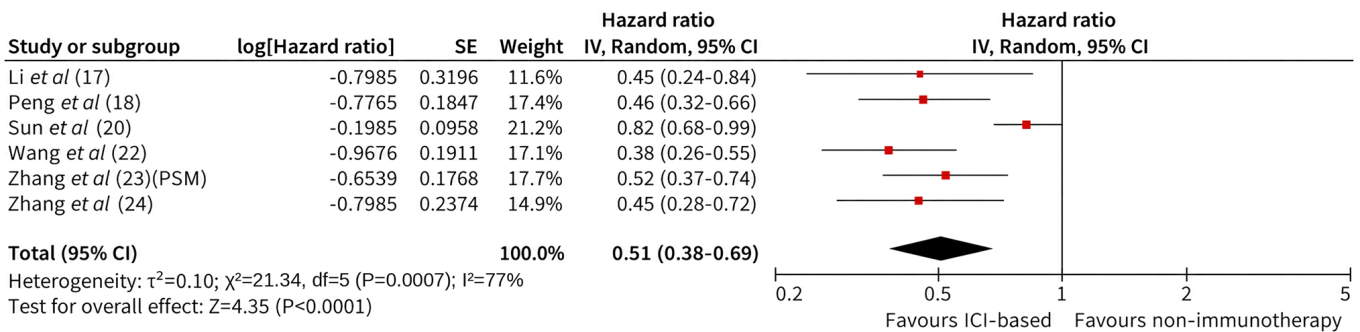


Figure 3. Random-effects meta-analysis of progression-free survival comparing ICI-based subsequent treatment with non-immunotherapy subsequent treatment after first-line chemoimmunotherapy progression in extensive-stage small cell lung cancer, shown as a forest plot. PSM, propensity score matching; ICI, immune checkpoint inhibitor; HR, hazard ratio; CI, confidence interval; IV, inverse variance; SE, standard error; df, degrees of freedom.

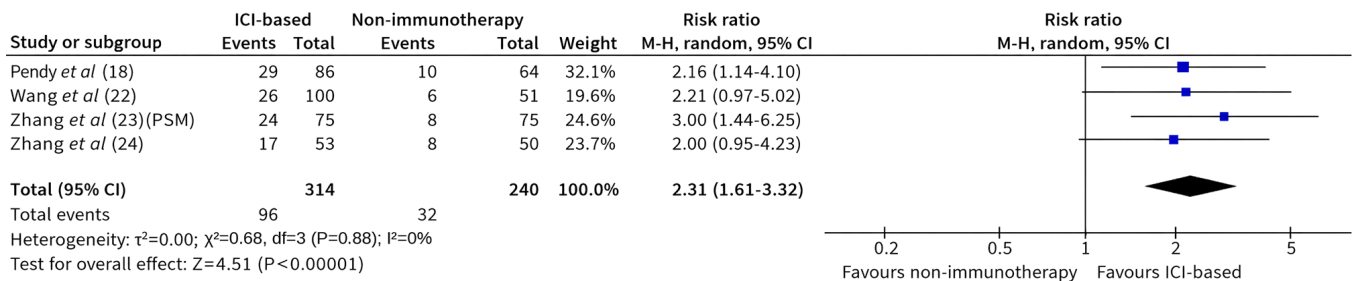


Figure 4. Random-effects meta-analysis of objective response rate comparing ICI-based subsequent treatment with non-immunotherapy subsequent treatment after first-line chemoimmunotherapy progression in extensive-stage small cell lung cancer, shown as a forest plot. PSM, propensity score matching; ICI, immune checkpoint inhibitor; RR, risk ratio; CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.

association with reduced heterogeneity, supporting that the primary PFS result was not driven by endpoint-origin misalignment. Treatment heterogeneity likely added a second layer of variability. Across the included studies, ICI-based subsequent treatment was delivered through different strategies, including ICI continuation or rechallenge, ICI plus chemotherapy, ICI plus antiangiogenic therapy and ICI plus chemotherapy and antiangiogenic therapy (18,22-24). These strategies should not be considered clinically interchangeable, because isolated ICI continuation or rechallenge and ICI-containing combination regimens address different therapeutic questions. The phase III ATLANTIS trial of lurbinectedin plus doxorubicin vs. physician's choice of chemotherapy in relapsed SCLC also illustrates the broader difficulty of producing uniform survival

gains in this disease setting (31). Therefore, the PFS result is best interpreted as a consistent indicator of improved disease control across heterogeneous real-world post-progression pathways, not as evidence that all ICI-based post-progression strategies have equivalent efficacy.

The response outcomes provide supportive but non-definitive evidence for the survival findings. In the ORR analysis, ICI-based subsequent treatment was associated with a higher objective response than non-immunotherapy subsequent treatment (RR, 2.31; 95% CI, 1.61-3.32), without observed heterogeneity ($I^2=0\%$) (18,22-24). This consistency indicates that the objective tumor-response finding was relatively stable across the contributing cohorts. By contrast, while the DCR analysis also favored ICI-based subsequent treatment (RR,

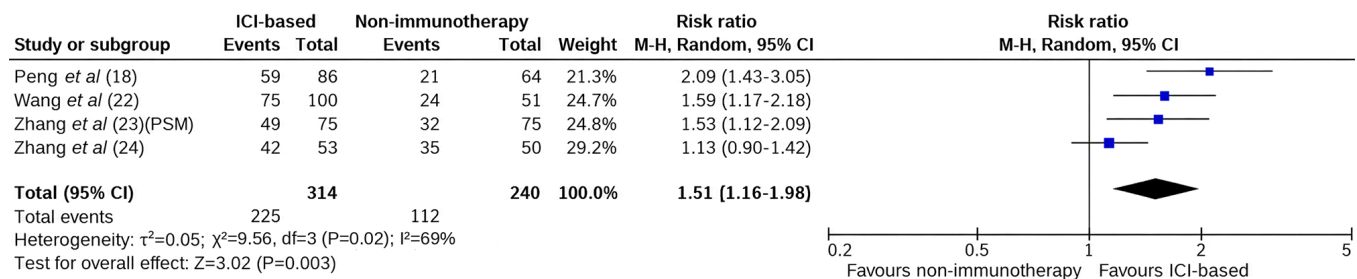


Figure 5. Random-effects meta-analysis of disease control rate comparing ICI-based subsequent treatment with non-immunotherapy subsequent treatment after first-line chemoimmunotherapy progression in extensive-stage small cell lung cancer, shown as a forest plot. PSM, propensity score matching; ICI, immune checkpoint inhibitor; RR, risk ratio; CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.

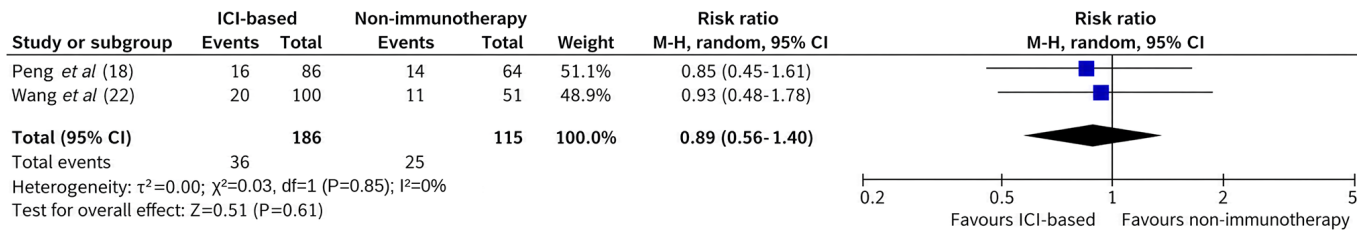


Figure 6. Random-effects meta-analysis of grade ≥ 3 adverse events or treatment-related adverse events comparing ICI-based subsequent treatment with non-immunotherapy subsequent treatment after first-line chemoimmunotherapy progression in extensive-stage small cell lung cancer, shown as a forest plot. ICI, immune checkpoint inhibitor; RR, risk ratio; CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.

1.51; 95% CI, 1.16-1.98), the heterogeneity was substantial ($I^2=69\%$) (18,22-24). This difference is clinically plausible. ORR is associated with measurable tumor shrinkage, whereas DCR also incorporates stable disease, a category more sensitive to imaging intervals, timing of response assessment, censoring and the balance among chemotherapy, antiangiogenic therapy and ICI-containing combinations. Standard response frameworks, such as Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and immune RECIST, provide a structured basis for response assessment, but they do not eliminate the practical variability introduced by retrospective imaging schedules and heterogeneous treatment pathways (32,33). In addition, ORR and DCR should not be interpreted as substitutes for OS or PFS. Contemporary trial-level analyses across advanced solid tumors have shown that ORR is at best an imperfect surrogate for OS, with surrogacy varying by tumor type and treatment class (34). Therefore, the response results strengthen the biological plausibility of the survival signal, but they remain secondary and supportive rather than independently practice changing.

Biologically, the observed association is plausible but should not be overinterpreted. Progression during PD-L1-based therapy may reflect spatially heterogeneous or partial resistance rather than complete immune insensitivity. Acquired resistance can emerge through defects in antigen presentation, IFN-pathway remodeling, activation of alternative immune checkpoints and changes in the tumor microenvironment (10,35). This concept is particularly relevant in SCLC, a disease marked by biological plasticity, molecular heterogeneity and subtype-specific immune phenotypes (11,36). Single-cell analyses have further shown that SCLC contains plastic, metastatic and immunosuppressive cellular states, suggesting that immune responsiveness may vary across lesions and disease

phases rather than being uniformly lost at progression (37). In this context, subsequent combination therapy may restore or amplify residual immune sensitivity in selected patients. Chemotherapy can promote antigen release and immunogenic cell death, whereas antiangiogenic therapy may improve immune-cell trafficking through vascular normalization and remodeling of the tumor microenvironment (38,39). The translational cohort by Shang *et al* (19) also suggested that selecting patients with ES-SCLC exhibiting lower metastatic burden may benefit from ICI rechallenge through tumor microenvironment reshaping. However, this rationale has an important boundary, whereby rapid clonal evolution and immune escape remain central features of SCLC. ICI-based subsequent treatment is therefore biologically plausible for selected patients, but it is unlikely to benefit all patients uniformly.

The real-world nature of the included evidence in the present study is both a strength and a limitation. On the one hand, these cohorts capture the treatment decisions that clinicians face after first-line chemoimmunotherapy progression, including ICI rechallenge, ICI switching, ICI plus chemotherapy, ICI plus antiangiogenic therapy and combined regimens. This breadth is clinically beneficial because rigid trial-defined treatment pathways typically do not reflect the fragmented and individualized post-progression management of ES-SCLC. The inclusion of comparative real-world cohorts also provides more informative evidence than single-arm rechallenge series, particularly when adjusted or propensity score-matched estimates are available (23,40-42). However, real-world comparisons are intrinsically vulnerable to bias. Patients selected for ICI-based subsequent treatment may have had improved performance status, a more indolent disease course, lower metastatic burden, improved prior response or greater physician-perceived suitability for further

immunotherapy. These factors can create selection bias, confounding by indication and a possible fit-patient effect, since the clinical reasons for choosing ICI-based subsequent treatment may themselves be prognostic (43,44). Time-related bias is another concern. Patients must survive sufficiently and remain sufficiently fit to receive subsequent ICI-containing therapy, which can introduce immortal time bias if treatment assignment and follow-up time are not aligned carefully (45). Although multivariable adjustment and PSM can improve balance in measured covariates, they cannot remove unmeasured confounding, differences in imaging frequency, follow-up intensity or institution-specific treatment practices (40,46). This is particularly relevant in the present study, as one included study was a mixed NSCLC/SCLC cohort with extractable SCLC subgroup data (16), one sensitivity analysis depended on matched vs. unmatched estimates from a PSM study (23) and another included mixed first-line immunotherapy exposure (25). Therefore, the present findings should be viewed as hypothesis-strengthening comparative evidence rather than a substitute for prospective randomized evaluation.

Clinically, the current findings should not be interpreted as supporting indiscriminate ICI-based treatment in all patients after progression. Rather, ICI-based subsequent treatment may be considered as a potential strategy for selected patients with preserved Eastern Cooperative Oncology Group performance status, prior disease control on first-line chemoimmunotherapy, a longer progression-free interval, a more indolent disease course, limited progression or lower metastatic burden and no prohibitive history of immune-related toxicity. This patient-selection framework is consistent with the broader relapsed SCLC literature, in which post-progression treatment choice is shaped not only by the available drug but also by platinum sensitivity, treatment-free interval, disease burden, symptoms and fitness for further systemic therapy (2,8,47,48). In the present evidence base, this interpretation is also supported by the observation that a number of the included cohorts evaluated ICI rechallenge or continuation in clinically selected populations rather than unselected patients progressing after first-line therapy (17-19,23).

Conversely, patients with primary resistance to first-line chemoimmunotherapy, explosive tumor progression, rapidly progressive multi-organ disease, poor performance status, uncontrolled comorbidities or prior severe immune-related AEs are unlikely to be appropriate candidates for routine ICI-based subsequent treatment. The toxicity issue is particularly important. Although the pooled grade ≥ 3 AE/TRAE analysis did not show a clear excess risk, the safety dataset was small, and immune-related toxicities may recur after rechallenge in a clinically meaningful proportion of patients (26,27,49-51). Current guidelines still prioritize established subsequent-line options, including topotecan, lurbinectedin, platinum rechallenge in selected platinum-sensitive relapse, clinical trial enrollment and best supportive care when appropriate. They do not define ICI-based subsequent treatment after progression as a universal post-progression standard (2,8,9,47). Therefore, the practical implication of the present meta-analysis is not to change the standard of care immediately, but to identify a clinically plausible subgroup in whom prospective evaluation of ICI-containing subsequent therapy is justified.

The current study has several strengths. The research question was deliberately narrow and clinically actionable, namely whether patients with ES-SCLC who progress after first-line chemoimmunotherapy may benefit from ICI-based subsequent treatment compared with non-immunotherapy subsequent treatment. This framing avoids conflating the analysis with broader questions of first-line immunotherapy efficacy or isolated single-arm rechallenge outcomes. The exclusive inclusion of comparative studies also provides a more interpretable evidence base than descriptive single-arm series. In addition, adjusted, multivariable or PSM estimates were prioritized when available, and sensitivity analyses were used to evaluate whether alternative handling of matched vs. unmatched data changed the main findings. Studies with partial alignment to the main PICO framework were not indiscriminately pooled into every primary analysis. Instead, their contribution was handled according to outcome availability and analytical suitability. Finally, the analysis considered survival, response, disease control and severe toxicity together, allowing a more balanced view of potential benefit and clinical decisions.

However, several limitations should be acknowledged. The primary limitation is the non-randomized nature of all the included studies. Even when multivariable adjustment or PSM was used, residual confounding remained likely. Patients selected for ICI-based subsequent treatment may have differed from controls in performance status, disease tempo, metastatic burden, prior response to first-line therapy or physician-perceived suitability for further immunotherapy. Therefore, the overall certainty of evidence should be considered low. The effective evidence base was also limited for each pooled outcome: In total, 6 studies contributed to the primary OS and PFS analyses, while 4 studies contributed to ORR and DCR and only 2 studies contributed to the pooled grade ≥ 3 AE/TRAE analysis. This limited statistical power, precluded formal assessment of publication bias and prevented robust subgroup analyses according to ICI class, treatment combination, progression pattern or patient-selection factors. In addition, although reported study periods, participating centers when available and cohort characteristics were cross-checked, the possibility of unrecognized partial patient overlap among retrospective multicenter cohorts could not be completely excluded because exhaustive patient-level identifiers were unavailable. The included studies also used heterogeneous subsequent treatment regimens, including ICI continuation or rechallenge, ICI switching, ICI plus chemotherapy, ICI plus antiangiogenic therapy and combined or triplet strategies. Since the majority of studies reported only aggregate estimates for mixed ICI-based arms, reliable strategy-specific subgroup analyses were not possible. Although endpoint-definition audit did not identify conventional first-line-origin PFS2 estimates in the primary PFS analysis, PFS-related endpoints remained imperfectly standardized. Differences in terminology, time origin within the post-progression period, imaging assessment schedule and censoring rules may still have contributed to the substantial heterogeneity observed in the PFS analysis. Safety evidence was limited, particularly for specific immune-related toxicities and treatment discontinuation.

In clinical practice, ICI-based subsequent treatment after progression on first-line chemoimmunotherapy should be viewed as a potential strategy for selected patients with ES-SCLC rather than as a universal post-progression standard. The present meta-analysis suggests a favorable association with survival

and tumor control, without a clear indication of excess severe toxicity. However, the evidence remains comparative, retrospective and vulnerable to treatment-selection bias. This distinction is important. The current data support further clinical exploration, not unselective use of immunotherapy-based treatment for every patient after progression. Future prospective studies should therefore focus on defining the patients most likely to benefit from ICI-containing therapy after progression, clarifying the optimal ICI-containing regimens, standardizing post-progression endpoints and toxicity reporting. Biomarker-informed and clinically stratified designs will be particularly important to determine whether continued immune pressure can translate into a reproducible benefit-risk advantage in this setting.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CL participated in conceptualization, methodology, investigation, data curation, writing of the original draft, reviewing and editing. YR contributed to methodology, investigation and data curation. AY and SX were involved in investigation and data curation. JH participated in conceptualization, methodology, supervision and writing (reviewing and editing). CL and JH confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Rudin CM, Brambilla E, Faivre-Finn C and Sage J: Small-cell lung cancer. *Nat Rev Dis Primers* 7: 3, 2021.
- Dingemans AC, Früh 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* 32: 839-853, 2021.
- Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, *et al*: First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 379: 2220-2229, 2018.
- Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair MJ, Özgüroğlu M, Ji JH, *et al*: Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): A randomised, controlled, open-label, phase 3 trial. *Lancet* 394: 1929-1939, 2019.
- Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair MJ, Özgüroğlu M, Ji JH, *et al*: Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): Updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 22: 51-65, 2021.
- Wang J, Zhou C, Yao W, Wang Q, Min X, Chen G, Xu X, Li X, Xu F, Fang Y, *et al*: Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 23: 739-747, 2022.
- Cheng Y, Han L, Wu L, Chen J, Sun H, Wen G, Ji Y, Dvorkin M, Shi J, Pan Z, *et al*: Effect of first-line serplulimab vs placebo added to chemotherapy on survival in patients with extensive-stage small cell lung cancer: The ASTRUM-005 randomized clinical trial. *JAMA* 328: 1223-1232, 2022.
- Ganti AKP, Loo BW Jr, Badiyan S, Bassetti M, Bestvina C, Chiang A, Choudhury N, D'Avella CA, Daly M, Dowlati A, *et al*: NCCN guidelines® insights: Small cell lung cancer, version 2.2026. *J Natl Compr Canc Netw* 24: e260002, 2026.
- Trigo J, Subbiah V, Besse B, Moreno V, López R, Sala MA, Peters S, Ponce S, Fernández 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* 21: 645-654, 2020.
- Schoenfeld AJ and Hellmann MD: Acquired resistance to immune checkpoint inhibitors. *Cancer Cell* 37: 443-455, 2020.
- Liu Q, Zhang J, Guo C, Wang M, Wang C, Yan Y, Sun L, Wang D, Zhang L, Yu H, *et al*: Proteogenomic characterization of small cell lung cancer identifies biological insights and subtype-specific therapeutic strategies. *Cell* 187: 184-203.e28, 2024.
- Liu L, Liu T, Wang X, Wang J, Wang J, Yuan M, Yang Y, Zhang Y, Wang H, Hu P and Zhang J: Patterns of treatment failure for PD-(L)1 refractory extensive-stage small cell lung cancer in continued PD-(L)1 treatment. *Transl Oncol* 33: 101687, 2023.
- Liu F, Yin G, Tao Y and Pan Y: The efficacy of ICIs rechallenge in advanced small cell lung cancer after progression from ICIs plus chemotherapy: A real-world study. *Int Immunopharmacol* 152: 114372, 2025.
- Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 372: n71, 2021.
- Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ and Welch VA: *Cochrane handbook for systematic reviews of interventions* version 6.3 (updated February 2022). Chichester: Cochrane, 2022. Available from: <https://training.cochrane.org/handbook/current>. Accessed May 9, 2026.
- Cheng J, Kang W, Chen Y, Pan L, Han H and Lv T: Continuous immunotherapy beyond disease progression in patients with advanced non-small cell and small cell lung cancer. *Cancer Immunol Immunother* 74: 124, 2025.
- Li L, Liu T, Liu Q, Mu S, Tao H, Yang X, Li Y, Xiong Q, Wang L and Hu Y: Rechallenge of immunotherapy beyond progression in patients with extensive-stage small-cell lung cancer. *Front Pharmacol* 13: 967559, 2022.
- Peng J, Zhai X, Liu X, Huang Z, Wang Y, Wu P, Gao R and Meng X: Beyond first-line therapy: Efficacy and safety outcomes of continuing immunotherapy in extensive stage small cell lung cancer after PD-L1 inhibitor progression. *Transl Oncol* 52: 102249, 2025.
- Shang X, Zhang C, Lv Y, Zhang X, Guo K, Li H and Wang H: Patients with extensive-stage small cell lung cancer harboring less than 4 metastatic sites may benefit from immune checkpoint inhibitor rechallenge by reshaping tumor microenvironment. *Immunotargets Ther* 13: 571-583, 2024.
- Sun Z, Tian Y, Lu S, Niu J, Dong Q and Zhu H: Continuing immunotherapy beyond progression prolongs the survival of patients with extensive-stage small-cell lung cancer: A multicenter retrospective analysis. *Cancer Med* 15: e71607, 2026.

21. Wang C, Xuan T, Wang Y, Yang C, Zhao W, Zhang R, Meng X and Li J: Clinical outcomes and safety of continuous immunotherapy beyond progression in patients with extensive-stage small cell lung cancer: A retrospective real-world study. *Front Immunol* 16: 1681545, 2026.
22. Wang J, Zhong Y, Chen B, Xu Y, Xu L, Li J, Xu F, Wang Q, Li K, Kong Y, *et al*: Immunotherapy rechallenge in extensive-stage small cell lung cancer: A real-world retrospective study. *Lung Cancer* 215: 109369, 2026.
23. Zhang J, Zi R, Zhang HX, Lv Y, Zhao LJ and Wang Y: Immune checkpoint inhibitors continuation beyond progression as second-line treatment for extensive-stage small-cell lung cancer: A real-world, multicenter analysis. *Front Immunol* 16: 1666373, 2025.
24. Zhang B, Bao H, Li Z, Chen J, Yu H, Li M, Cai M and Chen L: Continuing immune checkpoint inhibitors after progression: Real-world patterns of care and outcomes in second-line treatment for extensive-stage small-cell lung cancer. *Lung Cancer* 199: 108021, 2025.
25. Zhang J, Wu Z, Wang S, Sun Y, Wu J, Wang D, Ge Y, Li J, Sun H, Cheng Q, *et al*: Efficacy of PD-(L)1 inhibitors plus anlotinib in the second-line treatment of extensive-stage small cell lung cancer. *BMC Cancer* 25: 1070, 2025.
26. Schneider BJ, Naidoo J, Santomaso BD, Lacchetti C, Adkins S, Anadkat M, Atkins MB, Brassil KJ, Caterino JM, Chau I, *et al*: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol* 39: 4073-4126, 2021.
27. Haanen J, Obeid M, Spain L, Carbone F, Wang Y, Robert C, Lyon AR, Wick W, Kostine M, Peters S, *et al*: Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol* 33: 1217-1238, 2022.
28. Owonikoko TK, Park K, Govindan R, Ready N, Reck M, Peters S, Dakhil SR, Navarro A, Rodríguez-Cid J, Schenker M, *et al*: Nivolumab and ipilimumab as maintenance therapy in extensive-disease small-cell lung cancer: CheckMate 451. *J Clin Oncol* 39: 1349-1359, 2021.
29. Ahn MJ, Cho BC, Felip E, Korantzis I, Ohashi K, Majem M, Juan-Vidal O, Handzhiev S, Izumi H, Lee JS, *et al*: Tarlatamab for patients with previously treated small-cell lung cancer. *N Engl J Med* 389: 2063-2075, 2023.
30. Mountzios G, Sun L, Cho BC, Demirci U, Baka S, Gümüş M, Lugini A, Zhu B, Yu Y, Korantzis I, *et al*: Tarlatamab in small-cell lung cancer after platinum-based chemotherapy. *N Engl J Med* 393: 349-361, 2025.
31. Aix SP, Ciuleanu TE, Navarro A, Cousin S, Bonanno L, Smit EF, Chiappori A, Olmedo ME, Horvath I, Grohé 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* 11: 74-86, 2023.
32. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009.
33. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, Lin NU, Litière S, Dancey J, Chen A, *et al*: iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol* 18: e143-e152, 2017.
34. Shahnam A, Hitchen N, Nindra U, Manoharan S, Desai J, Tran B, Solomon B, Luen SJ, Hui R, Hopkins AM and Sorich MJ: Objective response rate and progression-free survival as surrogates for overall survival treatment effect: A meta-analysis across diverse tumour groups and contemporary therapies. *Eur J Cancer* 198: 113503, 2024.
35. Dagogo-Jack I and Shaw AT: Tumour heterogeneity and resistance to cancer therapies. *Nat Rev Clin Oncol* 15: 81-94, 2018.
36. Gay CM, Stewart CA, Park EM, Diao L, Groves SM, Heeke S, Nabat BY, Fujimoto J, Solis LM, Lu W, *et al*: Patterns of transcription factor programs and immune pathway activation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell* 39: 346-360.e7, 2021.
37. Chan JM, Quintanal-Villalonga Á, Gao VR, Xie Y, Allaj V, Chaudhary O, Masilionis I, Egger J, Chow A, Walle T, *et al*: Signatures of plasticity, metastasis, and immunosuppression in an atlas of human small cell lung cancer. *Cancer Cell* 39: 1479-1496.e18, 2021.
38. Galluzzi L, Humeau J, Buqué A, Zitvogel L and Kroemer G: Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat Rev Clin Oncol* 17: 725-741, 2020.
39. Fukumura D, Kloepper J, Amoozgar Z, Duda DG and Jain RK: Enhancing cancer immunotherapy using antiangiogenics: Opportunities and challenges. *Nat Rev Clin Oncol* 15: 325-340, 2018.
40. Concato J and Corrigán-Curay J: Real-world evidence-where are we now? *N Engl J Med* 386: 1680-1682, 2022.
41. Saesen R, Van Hemelrijck M, Bogaerts J, Booth CM, Cornelissen JJ, Dekker A, Eisenhauer EA, Freitas A, Gronchi A, Hernán MA, *et al*: Defining the role of real-world data in cancer clinical research: The position of the European organisation for research and treatment of cancer. *Eur J Cancer* 186: 52-61, 2023.
42. Castelo-Branco L, Pellat A, Martins-Branco D, Valachis A, Derksen JWG, Suijkerbuijk KPM, Dafni U, Dellaporta T, Vogel A, Prelaj A, *et al*: ESMO guidance for reporting oncology real-world evidence (GROW). *Ann Oncol* 34: 1097-1112, 2023.
43. Hernán MA, Wang W and Leaf DE: Target trial emulation: A framework for causal inference from observational data. *JAMA* 328: 2446-2447, 2022.
44. Matthews AA, Danaei G, Islam N and Kurth T: Target trial emulation: Applying principles of randomised trials to observational studies. *BMJ* 378: e071108, 2022.
45. Agarwal P, Moshier E, Ru M, Ohri N, Ennis R, Rosenzweig K and Mazumdar M: Immortal time bias in observational studies of time-to-event outcomes: Assessing effects of postmastectomy radiation therapy using the national cancer database. *Cancer Control* 25: 1073274818789355, 2018.
46. Sendor R and Stürmer T: Core concepts in pharmacoepidemiology: Confounding by indication and the role of active comparators. *Pharmacoepidemiol Drug Saf* 31: 261-269, 2022.
47. 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* 21: 1224-1233, 2020.
48. Owonikoko TK: SCLC classification by platinum sensitivity in the era of immunotherapy: Mere relic or a valuable treasure to keep? *J Thorac Oncol* 19: 193-195, 2024.
49. Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, Fedrizzi S, Chrétien B, Da-Silva A, Plane AF, *et al*: Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. *JAMA Oncol* 6: 865-871, 2020.
50. Allouchery M, Lombard T, Martin M, Rouby F, Sassier M, Bertin C, Atzenhoffer M, Miremont-Salame G, Perault-Pochat MC and Puyade M: French Network of Regional Pharmacovigilance Centers: Safety of immune checkpoint inhibitor rechallenge after discontinuation for grade ≥ 2 immune-related adverse events in patients with cancer. *J Immunother Cancer* 8: e001622, 2020.
51. Inno A, Roviello G, Ghidini A, Luciani A, Catalano M, Gori S and Petrelli F: Rechallenge of immune checkpoint inhibitors: A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 165: 103434, 2021.



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