

Original Study

Chemoimmunotherapy Versus Chemotherapy for Extensive-Stage Small Cell Lung Cancer in the Real-World Setting: Retrospective Study of 904 Patients



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ABSTRACT

In this retrospective study of 904 patients with extensive-stage small cell lung cancer (ES-SCLC), first-line chemoimmunotherapy improved overall survival compared with chemotherapy alone in routine clinical practice. Thoracic and brain radiotherapy were associated with additional survival benefit, and immune-related adverse events correlated with better outcomes. These findings support chemoimmunotherapy as the preferred first-line treatment in ES-SCLC.

Background: Small-cell lung cancer (SCLC) is an aggressive malignancy accounting for approximately 15% of all lung cancers, with over 70% of patients diagnosed at the extensive stage (ES). Phase III studies have shown significantly improved overall survival (OS) with the addition of PD-(L)1 inhibitors to platinum-based chemotherapy (CT), establishing chemoimmunotherapy (CIT) as the new first-line standard. This study investigates the real-world efficacy of CIT compared to alternative first-line regimens in patients with ES SCLC.

Methods: In this retrospective study, we analyzed 904 patients with newly diagnosed ES SCLC treated at a specialized thoracic cancer center between 2010 and 2022. The primary endpoints were OS and progression-free survival (PFS). Secondary endpoints included the impact of baseline brain metastases (BM), brain and thoracic radiotherapy (RT), and immune-related adverse events (irAEs).

Results: CIT ($n = 203$) resulted in longer OS than both platinum-based CT ($n = 530$) and nonplatinum CT ($n = 171$; median OS 10.2 vs. 9.4 vs. 3.6 months, $P < .001$). PFS under CIT and platinum-based CT was significantly longer compared to nonplatinum CT (median PFS 5.3 vs. 5.6 vs. 2.6 months, $P < .001$). Compared to platinum-based CT, CIT significantly reduced the risk of death or progression (OS HR 0.73, 95% CI, 0.62–0.87; $P < .001$; PFS HR 0.79, 95% CI, 0.67–0.93; $P = .006$), whereas nonplatinum CT was associated with a 2x higher risk (OS HR 2.19, 95% CI, 1.84–2.61; PFS HR 2.28, 95% CI, 1.91–2.72; both $P < .001$). Thoracic RT was an independent predictor of longer survival across the entire cohort (OS HR 0.57, 95% CI, 0.48–0.69; $P < .001$ in multivariable analysis [MVA] including sex, age, ECOG performance status, type of systemic treatment, and presence of baseline BM). While the presence of BM at diagnosis was prognostically neutral, brain RT among patients with baseline BM was also associated with longer survival (OS HR 0.47, 95% CI, 0.35–0.65; $P < .001$ in MVA). Immune-related adverse

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events (iAEs) were associated with longer OS and PFS (OS HR 0.67, 95% CI, 0.46–0.97; $P = .032$; PFS HR 0.68, 95% CI 0.47–0.97; $P = .035$ in MVA), while treatment discontinuation due to iAEs did not compromise survival. **Conclusion:** Chemoimmunotherapy confers a clear OS advantage over conventional chemotherapy in real-world ES-SCLC. Local radiotherapy is associated with additional survival improvement, while the occurrence of iAEs may correlate with treatment efficacy.

Introduction

Lung cancer remains one of the most common and lethal malignancies, with approximately 56,500 new cases diagnosed annually in Germany.¹ Small-cell lung cancer (SCLC) accounts for about 15% of all lung cancers and usually (70%) presents in extensive-stage (ES) with particularly aggressive tumor biology and poor prognosis.^{2,3} Despite intensive research, therapeutic advances in ES-SCLC have remained limited for decades with platinum-based Chemotherapy (CT) as the standard first-line treatment since the mid1980s.⁴ Only recently, the approval of PD(L)1 inhibitors, like atezolizumab (IMpower133, 2018), durvalumab (CASPIAN, 2019), serplulimab (ASTRUM-005, 2022) or tislelizumab (RATIONALE-312, 2024) each in combination with platinum-etoposide, demonstrated longer overall survival (OS) in several randomized phase 3 trials and established a new standard of care.^{5–8} The aim of this study was to evaluate the effectiveness of CT combined with immune checkpoint inhibitors (ICIs) versus other first-line regimens in an unselected real-world ES-SCLC patient population.

Methods

Study Population and Inclusion Criteria

This retrospective study included patients with newly diagnosed ES-SCLC treated at a specialized thoracic cancer center between 2010 and 2022. Patients were identified through search in the tumor registry of the hospital. Eligible patients required histological and radiologic confirmation of ES-SCLC as well as initiation of first-line systemic therapy. Between 2010 and 2019, all patients with ES-SCLC were included, while after 2019—when immunotherapy became available—only patients receiving CIT were analyzed in this study, in order to avoid the potential selection bias associated with omission of immunotherapy despite its availability. The histopathological diagnosis of SCLC was established by expert pathologists according to the WHO criteria.⁹ Patients with combined histological features—such as additional components of non-small cell lung cancer (NSCLC) or large cell neuroendocrine lung carcinoma (LCNEC)—were included if the SCLC component was histologically predominant and treatment decisions were guided by the SCLC phenotype. Patients who did not receive systemic therapy (eg, were managed with best supportive care) due to severely reduced ECOG performance status (PS) were excluded from the analysis (Figure 1). Treatment monitoring followed standardized institutional protocols and typically included thoracic and abdominal computerized tomography imaging at baseline as well as every 2 treatment cycles (approximately 6 weeks), along with brain magnetic resonance imaging (MRI) every 6 to 12 weeks. CT was continued until radiologic progression or completion of a maximum of 6 cycles. Patients with stable disease (SD) or partial response (PR) after 4 cycles of CIT proceeded to maintenance therapy with ICI, which was continued until disease progression or unacceptable toxicity. Radiologic progression disease (PD) was assessed according to response evaluation criteria in solid tumors (RECIST) v1.1 criterion and confirmed by the investigators through own review of radiologic images for this study. Other patient, tumor characteristics, as well as treatment type and outcomes were extracted from the medical records. The primary endpoints were progression-free survival (PFS, defined as the time from initiation of therapy to radiologically confirmed PD or death from any cause), and overall survival (OS, defined as the time from treatment initiation to death from any cause), while patients without events were censored

at the time of last follow-up. Secondary endpoints included the association of clinical variables—such as baseline brain metastases, radiotherapy, and immune-related adverse events (irAEs) graded according to the common terminology criteria for adverse events (CTCAE)—on OS and PFS.

Treatment Stratification

The total cohort of consecutive patients was retrospectively stratified into 3 groups according to the type of administered first-line therapy: Group A with platinum-based CT (cisplatinum-etoposide or carboplatinum-etoposide) in combination with an ICI; Group B with PE (ie, cisplatinum/carboplatinum-etoposide) without an ICI; Group C with nonplatinum-based CT, predominantly administered in patients with contraindications to platinum-based CT, including frailty due to advanced age or comorbidities, poor ECOG PS, or special comorbidities precluding the use of platinum (eg, renal insufficiency).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics v29 (IBM Corp., Armonk, NY). Descriptive statistics included the median, and interquartile range (IQR), as well as cross-tabulations. Categorical variables were compared using the Pearson chi-square test, and ordinal variables were compared using the Kruskal–Wallis test. A P -value $< .05$ was considered statistically significant. Median follow-up time was estimated using the reverse Kaplan–Meier method. In the nonplatinum chemotherapy group, in which no patients were censored, follow-up was descriptively summarized using median and interquartile range (IQR).

Survival outcomes were analyzed according to Kaplan–Meier, and comparisons between groups were performed using the log-rank test. Associations of OS and PFS with other parameters were evaluated using Cox regression. Variables with statistically significant results in univariable analyses were analyzed further with multivariable models. 95% confidence intervals (CI) are given for the results whenever appropriate.

Results

Characteristics of Study Population

Among 1486 ES-SCLC patients identified in the hospital registry, 582 were excluded due to limited stage (LS, $n = 483$) or best supportive care (BSC, $n = 99$). The remaining 904 patients were stratified between CIT ($n = 203$, 22.5%), PE ($n = 530$, 58.6%), and nonplatinum-based CT ($n = 171$, 18.9%) (Figure 1). CIT patients received carboplatinum ($n = 201$; 99%) or cisplatinum ($n = 2$; 1%; Table 1) with etoposide and an immune checkpoint inhibitor (ICI), which was most commonly atezolizumab ($n = 184$; 90.6%; Table 1). Other ICIs included ipilimumab ($n = 14$; 6.9%), pembrolizumab ($n = 3$; 1.5%), and durvalumab ($n = 2$; 1.0%; Table 1). PE patients received also mainly carboplatinum ($n = 407$; 76.8%; Table 1) due to its more favourable toxicity profile.^{10,11} Among patients with nonplatinum-based chemotherapies, predominant was vincristine-etoposide (VE, 98.8%), which is typically selected in case of significant comorbidities, advanced age, or poor ECOG PS.¹¹

At the time of data cutoff (April 16, 2024), the median follow-up was 3.3 years (95% CI, 2.4–4.2) in the CIT group and 8.8 years (95% CI,

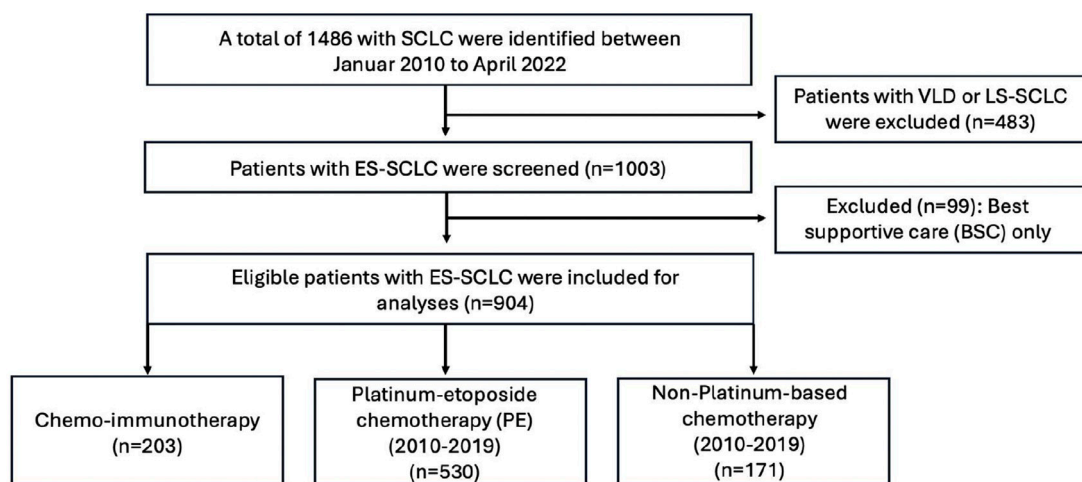


Figure 1. Flow diagram of patient selection. A total of 1486 patients with small cell lung cancer (SCLC) were identified from electronic medical records. Among them, 483 patients diagnosed with very limited disease (VLD) or limited-stage (LS) disease were excluded. An additional 99 patients who received best supportive care (BSC) only were also excluded. The remaining 904 patients with extensive-stage (ES) disease were stratified into the following treatment groups: chemoimmunotherapy ($n = 203$), platinum-etoposide (PE) chemotherapy ($n = 530$), and nonplatinum-based chemotherapy ($n = 171$). Following the implementation of CIT as the standard first-line treatment in 2019, all patients treated from 2019 onward received CIT and were therefore assigned to the CIT cohort. BSC = best supportive care; ES = extensive stage; LS = limited stage; PE = platinum-etoposide; SCLC = small cell lung cancer; VLD = very limited disease.

Table 1
Patient Characteristics by Type of Systemic Treatment.

Characteristic	All Patients $n = 904$	Chemo-immunotherapy $n = 203$	PE Chemotherapy $n = 530$	Nonplatinum Chemotherapy $n = 171$	P-Value
Median age, y (IQR)	63 (57-70)	63 (57-70)	62 (56-69)	68 (61-74)	< .001 ^b
Age group, y (%)					< .001 ^a
< 65	501 (55.4%)	117 (57.6%)	333 (62.8%)	51 (29.8%)	
≥ 65	403 (44.6%)	86 (42.4%)	197 (37.2%)	120 (70.2%)	
Sex					.620 ^a
Men	336 (37.2%)	80 (39.4%)	197 (37.2%)	59 (34.5%)	
Women	568 (62.8%)	123 (60.6%)	333 (62.8%)	112 (65.5%)	
Smoking history					.125 ^a
Ever-smoker	872 (96.5%)	100 (98%)	512 (96.6%)	161 (94.2%)	
Never-smoker	32 (3.5%)	4 (2.0%)	18 (3.4%)	10 (5.8%)	
ECOG, median (IQR)	1 (0-2)	1 (0-2)	1 (0-1)	2 (1-3)	< .001 ^b
ECOG 0-1	86%	93.1%	92%	59.6%	< .001 ^a
Histology					.250 ^a
SCLC	844 (93.4%)	194 (95.6%)	490 (92.5%)	160 (93.6%)	
SCLC + nonsquamous	19 (2.1%)	6 (3%)	9 (1.7%)	4 (2.3%)	
SCLC + squamous	15 (1.7%)	1 (0.5%)	12 (2.3%)	2 (1.2%)	
SCLC + LCLC	26 (2.9%)	2 (1.0%)	19 (3.6%)	5 (2.9%)	
Chemotherapy					
Carboplatinum + etoposide		201 (99%)	407 (76.8%)	-	
Cisplatinum + etoposide		2 (1%)	123 (13.2%)	-	
Vincristine + etoposide		-	-	169 (98.8%)	
Immunotherapy, PD(L)1 inhibitors					
Atezolizumab		184 (90.6%)			
Ipilimumab		14 (6.9%)			
Pembrolizumab		3 (1.5%)			
Durvalumab		2 (1.0%)			
Brain metastases (%)	279 (30.9%)	50 (24.6%)	183 (34.5%)	46 (26.9%)	.016 ^a
Brain radiotherapy (%)	223 (24.7%)	42 (20.7%)	152 (28.7%)	29 (17%)	.007 ^a
WBRT	206 (22.8%)	33 (16.3%)	145 (27.4%)	28 (16.4%)	< .001 ^a
SRT	17 (1.9%)	9 (4.4%)	7 (1.3%)	1 (0.6%)	< .001 ^a
Thoracic radiotherapy (%)	150 (16.6%)	33 (16.3%)	109 (20.6%)	8 (4.7%)	< .001 ^a
cTRT	81 (54.0%)	17 (9.1%)	63 (13%)	1 (0.6%)	< .001 ^a
10 × 3 Gy - 15 × 3 Gy (45%), 17 × 3 Gy - 20 × 3 Gy (55%)					
palliative/Salvage-Radiotherapy	69 (46%)	16 (8.6%)	46 (9.9%)	7 (4.1%)	.069 ^a
10 × 3 Gy - 15 × 3 Gy (35%), 17 × 3 Gy - 20 × 3 Gy (65%)					

Abbreviations: cTRT = consolidative thoracic radiotherapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IQR = interquartile range; PD(L)1 = programmed death (Ligand) 1; PE = platinum-etoposide; SCLC = small-cell lung cancer; SRT = stereotactic radiotherapy; WBRT = whole-brain radiotherapy.

^a Pearson chi-square test.

^b Kruskal–Wallis test.

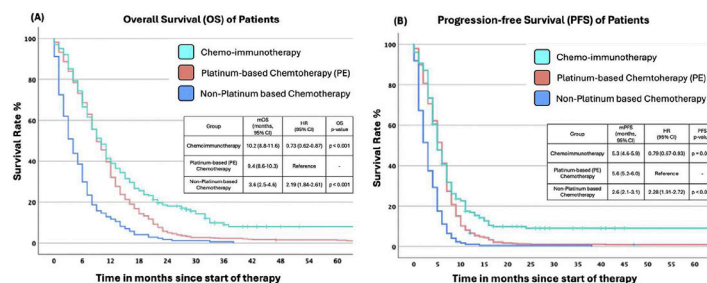


Figure 2. Kaplan–Meier survival curves for overall survival (OS; A) and progression-free survival (PFS; B) stratified by treatment group. (A) In the OS analysis, patients treated with chemoimmunotherapy achieved the longest median OS (10.2 months; 95% CI, 8.8–11.6), followed by PE chemotherapy (9.4 months; 95% CI, 8.6–10.3), while the shortest median OS was observed in the nonplatinum chemotherapy group (3.6 months; 95% CI, 2.5–4.6). The between-group difference was highly significant (log-rank $P < .001$). (B) Median PFS was 5.3 months (95% CI, 4.6–5.9) in the chemoimmunotherapy group, 5.6 months (95% CI, 5.2–6.0) in the PE chemotherapy group, and 2.6 months (95% CI, 2.1–3.1) in the nonplatinum chemotherapy group, with a highly significant difference across groups (log-rank $P < .001$). OS = overall survival; PFS = progression-free survival.

6.7–10.9) in the PE group. In the nonplatinum chemotherapy group, the median follow-up was 2.5 months (IQR 1.0–6.1).

Baseline demographics and smoking history were generally well balanced across treatment groups (Table 1). The median age at treatment initiation was 63 years (IQR 57–70) but was significantly higher among patients receiving nonplatinum CT (median 68 years, IQR 61–74; $P < .001$; Table 1). Although ECOG PS was 0–1 for most patients (86%), patients in the nonplatinum cohort had significantly poorer baseline performance status (ECOG PS 0–1: 59.6%; $P < .001$; Table 1). Accordingly, ECOG PS 2 (33.9%) and ECOG PS 3–4 (6.5%) were more common in this group (Supplemental Figure 1). Mixed SCLC histologies were encountered in < 10% of patients and evenly distributed among the 3 patient groups ($P = .25$, Table 1). Baseline brain metastases (BM, 30.9%) and the use of brain radiotherapy (BRT, 24.7%) were more common in the PE group (34.5% and 28.7%) than in the CIT (24.6% and 20.7%) and nonplatinum groups (26.9% and 17.0%, $P = .016$ and $P = .007$, respectively, Table 1). Among patients with BM receiving BRT, stereotactic radiotherapy (SRT) was rare (<5%), but more frequent in the CIT (4.4%) compared to the PE (1.3%) and nonplatinum cohorts (0.6%), in which whole-brain radiotherapy (WBRT) predominated ($P < .001$; Table 1). Thoracic radiotherapy (TRT) was also least frequent in the nonplatinum cohort (4.7%) and more common in the PE (20.6%) and CIT groups (16.3%, $P < .001$; Table 1), with no difference between the latter 2 ($P = .186$). Thoracic radiotherapy was administered either as consolidative thoracic radiotherapy (cTRT) after response to systemic therapy, or as palliative or salvage radiotherapy for symptom control or thoracic disease progression. cTRT was rare in the nonplatinum CT group (0.6%; $n = 1$) but more frequent in the CIT (9.1%; $n = 17$) and PE groups (13.0%; $n = 63$; $P < .001$; Table 1), with no difference between the latter 2 ($P = .159$). The frequency of palliative/salvage TRT was similar in the CIT (8.6%; $n = 16$) and PE groups (9.9%; $n = 46$) and did not differ significantly from that in the nonplatinum CT group (4.1%; $n = 7$; $P = .069$; Table 1).

Patient Survival and Prognostic Factors

CIT was associated with a longer median OS (10.2 months; CI 8.8–11.6; HR 0.73; 95% CI, 0.62–0.87; $P < .001$) than PE (9.4 months; 95% CI, 8.6–10.3), or nonplatinum CT (3.6 months; 95% CI, 2.5–4.6; log-rank $P < .001$; HR 2.19 vs. PE, $P < .001$; Supplemental Table 1 and Figure 2). Median PFS was 5.3 months (95% CI, 4.6–5.9; HR 0.79 vs. PE; 95% CI, 0.67–0.93; $P = .006$) under CIT, 5.6 months (95% CI, 5.2–6.0) under PE, and 2.6 months (95% CI, 2.1–3.1) under nonplatinum CT (log-rank $P < .001$; HR 2.28 vs. PE; $P < .001$ Supplemental Table 1 and Figure 2).

Furthermore, a longer OS of study patients was significantly associated with female sex (HR 1.35 for male; 95% CI, 1.18–1.55; $P < .001$; Supplemental Table 1), younger age (HR 1.32 for ≥ 65 years; 95% CI, 1.16–1.52; $P < .001$) and better ECOG PS 0–1 (HR 2.23 for PS 2–4; 95%

CI, 1.84–2.71; $P < .001$). Along the same lines, PFS was longer for female patients (HR 1.25 for male; 95% CI, 1.09–1.44; $P = .001$), younger age (HR 1.20; 95% CI, 1.05–1.38; $P = .006$) and a better ECOG PS 0–1 (HR 1.89 for PS 2–4; 95% CI, 1.55–2.29; $P < .001$; Supplemental Table 1). Among patient characteristics, ECOG PS showed the strongest prognostic impact, while smoking status, histological subtype, and the presence of BM at diagnosis were not significantly associated with survival outcomes. Receipt of BRT was also associated with substantial improvements in both OS (HR 0.41; 95% CI, 0.30–0.56) and PFS (HR 0.52; 95% CI, 0.39–0.71; both $P < .001$; Supplemental Table 1). Among irradiated patients, SRT was associated with superior outcomes compared to WBRT (OS: HR 0.40; 95% CI, 0.23–0.69; $P = .001$; PFS: HR 0.51; 95% CI, 0.29–0.88; $P = .016$; Supplemental Table 1). TRT was likewise associated with significantly longer OS (HR 0.54; 95% CI, 0.45–0.64) and PFS (HR 0.54; 95% CI, 0.45–0.65; both $P < .001$; Supplemental Table 1). Palliative/salvage radiotherapy was associated with improved OS (HR 0.67; 95% CI, 0.52–0.86; $P = .002$), but not PFS (HR 0.81; 95% CI, 0.63–1.05; $P = .108$; Supplemental Table 1), whereas cTRT after initial response improved PFS (HR 0.77; 95% CI, 0.59–0.99; $P = .043$), but not OS (HR 0.85; 95% CI, 0.65–1.09; $P = .201$; Supplemental Table 1). Finally, the occurrence of immune-related adverse events (irAE) was also associated with improved OS (HR 0.66; 95% CI, 0.46–0.95; $P = .025$; Supplemental Table 1) and longer PFS (HR 0.66; 95% CI, 0.46–0.94; $P = .022$; Supplemental Table 1).

Multivariable analysis revealed that all aforementioned patient characteristics except for age and baseline BM were independently associated with OS and PFS ($P < .05$; Table 2). Patients receiving CIT showed the most favourable outcomes (OS HR 0.72 vs. PE, 95% CI, 0.60–0.85; $P < .001$; PFS HR 0.77 vs. PE, 95% CI, 0.65–0.92; $P = .003$; Table 2), while prognosis under nonplatinum CT was poor (OS HR 1.78 vs. PE, 95% CI, 1.47–2.13; $P < .001$; PFS HR 1.93 vs. PE, 95% CI, 1.60–2.33; $P < .001$; Table 2). In prespecified subgroup analyses comparing CIT with PE, the survival benefit of CIT was generally consistent across most evaluated subgroups (Supplemental Figure 2 and Supplemental Figure 3). A diminished benefit of CIT was observed only in patients with ECOG PS 2–4, which was not statistically significant ($P = .64$; Supplemental Figure 2). Furthermore, no statistically significant interactions were observed between the type of systemic treatment and sex, age, or ECOG PS (Supplemental Table 2).

TRT emerged in multivariable analysis as an additional independent prognostic factor associated with longer OS (HR 0.57, 95% CI, 0.48–0.69; $P < .001$) and PFS (HR 0.59, 95% CI, 0.49–0.70; $P < .001$; Table 2) without significant interaction by the type of systemic treatment (HR 0.84, 95% CI, 0.52–1.34; $P = .458$, Supplemental Table 2). Among patients with an initial response to systemic therapy, cTRT was administered to 81 patients (22.6%) and independently predicted improved OS (HR 0.76; 95% CI, 0.59–1.00; $P = .048$; Supplemental Table 3). Simi-

Table 2
Multivariable Analysis of Overall and Progression-Free Survival.

Group	n	n	OS HR (95% CI)	OS P-Value	PFS HR (95% CI)	PFS P-Value
Variable	Reference					
Sex						
male	568	female	1.34 (1.16-1.54)	< .001	1.25 (1.10-1.44)	.001
Age						
≥ 65	403	< 65	1.14 (0.99-1.31)	.073	1.03 (0.90-1.18)	.68
ECOG PS 2-4	121	ECOG PS 0-1	1.85 (1.51-2.19)	< .001	1.50 (1.22-1.83)	< .001
Chemo-immunotherapy	203	PE-Chemotherapy	0.72 (0.60-0.85)	< .001	0.77 (0.65-0.92)	.003
Non platinum based CHT	171		1.78 (1.47-2.13)	< .001	1.93 (1.60-2.33)	< .001
Baseline BM						
Yes	279	no	1.12 (0.97-1.30)	.12	1.05 (0.91-1.21)	.54
Thoracic radiotherapy						
Yes	150	no	0.57 (0.48-0.69)	< .001	0.59 (0.49-0.70)	< .001

The model included patient-related characteristics (sex, age, and ECOG performance status), treatment-related factors with significant associations in univariable analyses (type of systemic treatment and thoracic radiotherapy), as well as clinically relevant covariates regardless of univariable significance, including the presence of brain metastases at initial diagnosis. A hazard ratio (HR) > 1 indicates an increased risk, whereas an HR < 1 indicates a reduced risk.

Abbreviations: BM = brain metastases; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; OS = overall survival; PE = platinum-etoposide; PFS = progression-free survival.

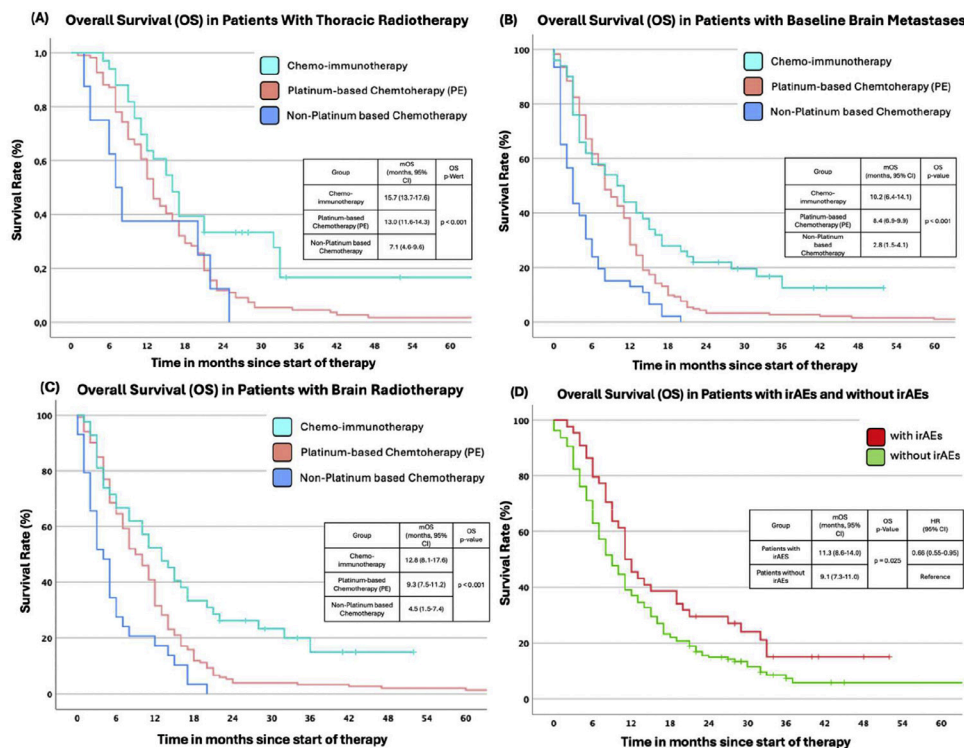


Figure 3. Kaplan-Meier curves of overall survival (OS). (A) Patients receiving thoracic radiotherapy; (B) patients with brain metastases at initial diagnosis; (C) patients with brain metastases receiving brain radiotherapy, all stratified by treatment group. (D) patients treated with chemoimmunotherapy stratified by the presence or absence of immune-related adverse events (irAEs). (A) Among patients receiving thoracic radiotherapy, median OS was 15.7 months (95% CI, 13.7-17.6) with chemoimmunotherapy, 13.0 months (95% CI, 11.6-14.3) with platinum-etoposide (PE), and 7.1 months (95% CI, 4.6-9.6) with nonplatinum-based chemotherapy (log-rank $P < .001$). (B) In patients with brain metastases at initial diagnosis, median OS was 10.2 months (95% CI, 6.4-14.1), 8.4 months (95% CI, 6.9-9.9), and 2.8 months (95% CI, 1.5-4.1), respectively (log-rank $P < .001$). (C) Among patients with brain metastases receiving brain radiotherapy, median OS was 12.8 months (95% CI, 8.1-17.6), 9.3 months (95% CI, 7.5-11.2), and 4.5 months (95% CI, 1.5-7.4), respectively (log-rank $P < .001$). (D) In the chemoimmunotherapy cohort, patients who developed immune-related adverse events (irAEs) had longer OS than those without irAEs (11.3 vs. 9.1 months; HR 0.66, 95% CI, 0.45-0.95; $P = .025$). CI = confidence interval; irAEs = immune-related adverse events; OS = overall survival; PE = platinum-etoposide.

larly, palliative/salvage RT was administered to 69 patients (7.6% of the total cohort) and was independently associated with improved OS (HR 0.75; 95% CI, 0.58-0.97; $P = .028$; Supplemental Table 4). Among patients who received TRT, OS was significantly longer for patients who received CIT (median 15.7 months, 95% CI, 13.7-17.6 months) compared to PE (13.0 months, 95% CI, 11.6-14.3 months) and nonplatinum-based CT (7.1 months, 95% CI, 4.6-9.6 months, $P < .001$; Figure 3). Simi-

larly, among patients with baseline BM, OS was significantly longer under CIT (median 10.2 months, 95% CI, 6.4-14.1) than PE (8.4 months, 95% CI, 6.9-9.9) and nonplatinum-based CT (2.8 months, 95% CI, 1.5-4.1, $P < .001$, Figure 3) without interaction among the presence of BM and effect of different systemic therapies (HR 0.75, 95% CI, 0.52-1.34; $P = .150$, Supplemental Table 2). Among patients with BM, BRT emerged as an additional independent prognostic factor in multivariable analysis

and was associated with longer OS (HR 0.47; 95% CI, 0.35–0.65; $P < .001$) and PFS (HR 0.58; 95% CI, 0.43–0.78; $P < .001$; Supplementary Table 6). Furthermore, among patients with BM who received BRT, OS was much longer under CIT (12.8 months, 95% CI, 8.1–17.6) than PE (9.3 months, 95% CI, 7.5–11.2) and nonplatinum-based CT (4.5 months, 95% CI, 1.5–7.4, $P < .001$; Figure 3). Here, a significant interaction was noted suggesting a stronger benefit from BRT from patients receiving CIT vs. PE (HR 0.26; 95% CI, 0.11–0.62; $P = .002$, Supplemental Table 2). Furthermore, among patients with BM receiving BRT, SRT was independently associated with longer OS compared to WBRT (HR 0.48; 95% CI, 0.27–0.85; $P = .012$; Supplemental Table 7).

Among patients receiving CIT, irAE occurred in 44/203 (21.7%) and lead to treatment discontinuation in 28/44 (63.6%) (Supplemental Figure 4). Detailed organ-specific distributions and CTCAE grades of irAEs are summarized in Supplemental Table 10. Multivariable analysis including irAE alongside the same covariates as in the overall cohort (sex, age, ECOG PS, TRT, and baseline BM) demonstrated that irAE occurrence was independently associated with longer OS (HR 0.67, 95% CI, 0.46–0.97; $P = .032$; 11.3 vs. 9.1 months for patients without irAE; $P = .025$; Supplemental Table 8 and Figure 3) and PFS (HR 0.68, 95% CI, 0.47–0.95; $P = .035$; 7.2 vs. 4.8 months for patients without irAE; $P = .022$; Supplemental Table 8 and Supplemental Figure 5). Notably, neither OS (11.3 vs. 10.9 months; $P = .99$; Supplemental Figure 5) nor PFS (7.2 vs. 7.0 months $P = .51$; Supplemental Figure 5) differed significantly according to whether immunotherapy was discontinued or continued after occurrence of irAEs in study patients.

Discussion

Our study results confirm the superiority of CIT over PE alone in the real-world setting with an OS difference of almost 1 month (10.2 vs. 9.4, HR 0.73 vs. PE; $P < .001$), consistent with the results of several registrational phase III trials.^{5–8} The markedly poorer outcomes in the nonplatinum group, with median OS of only 3.6 months, likely reflect not only the inferior antitumor activity of platinum-free regimens but also the presence of adverse baseline characteristics, including advanced age, comorbidities, and poorer ECOG PS. Nevertheless, we intentionally included this subgroup because it represents a clinically relevant and vulnerable real-world population with limited therapeutic options that is often excluded from prospective studies. Including these patients allowed a more comprehensive representation of routine clinical practice. Chemoimmunotherapy also conferred a consistent and significant advantage in PFS in univariable Cox regression analysis (5.3 vs. 5.6 months, HR 0.79, 95% CI, 0.67–0.93; $P = .006$; Supplemental Table 1), a pattern closely resembling the results observed in CASPIAN (5.1 vs. 5.4, HR 0.78, 95% CI, 0.65–0.94), although the magnitude of benefit was smaller than that observed for OS—a well-recognized characteristic of immunotherapy.⁵ Likewise, similar to the CASPIAN and IMPower133 trials, the CIT cohort in our study was predominantly treated with PD-L1 inhibitor, with most patients receiving atezolizumab. Therefore, the observed outcomes may predominantly reflect the efficacy and safety profile of PD-L1 inhibitors and may not be fully generalizable to other PD-1 inhibitors. Of note, a large recent study from France demonstrated comparable outcomes among patients with ES-SCLC treated with either of the 2 approved PD-L1 inhibitors, atezolizumab or durvalumab.¹² A similar pattern was observed in the phase III DeLLphi-304 trial, in which tarlatamab significantly improved OS (median OS 13.6 vs. 8.3 months; HR, 0.60; 95% CI, 0.47–0.77; $P < .001$) despite only modest gains in PFS (median progression-free survival 5.3 vs. 4.3 months, HR 0.71, 95% CI, 0.59–0.86; $P = .002$), particularly among responders.¹³ Taken together, these findings reinforce that OS remains the most clinically meaningful and robust endpoint for evaluating the efficacy of immuno-oncologic therapies in ES-SCLC.

Furthermore, TRT emerged as an independent predictor of longer OS and PFS for our ES-SCLC patients in all multivariable analyses, irrespective of systemic therapy type and other relevant patient characteristics.

This benefit remained consistent among patients with an initial response to systemic therapy, cTTR was independently associated with improved OS (HR 0.76; 95% CI, 0.59–0.98; $P = .048$; Supplemental Table 3) and the palliative/salvage radiotherapy was also independently associated with improved OS compared with no TRT. (OS HR 0.75; 95% CI, 0.58–0.97; $P = .028$; Supplemental Table 4). The marked improvement in OS with TRT among CIT-treated patients (15.7 vs. 8.2 months; $P = .002$; Supplemental Table 9) provides concrete clinical evidence to support continued use of TRT for selected ES-SCLC patients beyond the potential immunomodulatory synergy suggested by translational evidence.¹⁴ This is important for the field, as the results of previous studies have been contradictory with significant benefit from TRT in some retrospective series^{15,16} but increased toxicity in a prospective trial (TREASURE).^{17,18} Ongoing studies continue to investigate the integration of thoracic radiotherapy into modern immuno-oncological treatment strategies.¹⁹

Similarly, for patients with baseline BM, CIT was also associated with a significantly longer OS than PE (HR 0.62; 95% CI, 0.44–0.88; $P = .006$; Supplemental Table 5), consistent with similar observations in the ASTRUM-005 (HR 0.61; 95% CI, 0.33–1.13) and other randomized studies.^{7,8,19} Furthermore, the survival advantage from BRT among ES-SCLC patients with BM was especially pronounced for those receiving CIT with a significant interaction between BRT and CIT (HR 0.26, 95% CI, 0.11–0.62; $P = .002$; Supplemental Table 2). These results underscore the importance of integrating BRT for BM into first-line treatment—particularly with CIT—and the potential benefit of ES-SCLC patients from a multimodal treatment approach. Besides, they also offer an explanation why presence of baseline BM has limited prognostic impact in ES-SCLC, as they were not associated with worse survival in any of our univariable and multivariable analyses, either in the overall cohort or within treatment subgroups in the current study. On the other hand, the apparent benefit from SRT in our study needs to be interpreted with caution, as their number was very small (SRT, $n = 17$; WBRT, $n = 206$) and some selection bias is likely.

Finally, irAEs were observed in approximately 22% of patients and represented an additional independent factor strongly associated with longer OS and PFS among CIT-treated patients (HR 0.67, 95% CI, 0.46–0.97; $P = .032$; Supplemental Table 8). These findings are consistent with recent real-world analyses in both SCLC^{20,21} and NSCLC,²² suggesting that the occurrence of irAEs may be associated with effective antitumor immunity and improved clinical outcomes. Notably, despite treatment discontinuation due to irAEs in a substantial proportion of patients (63.6%), no significant differences in OS or PFS were observed compared with patients who continued immunotherapy (OS: 11.3 vs. 10.9 months, $P = .99$; PFS: 7.2 vs. 7.0 months, $P = .51$; Supplemental Figure 5). These findings suggest that treatment discontinuation due to severe irAEs may not necessarily compromise long-term oncologic outcomes. Rather, the data indicate that even limited exposure to immunotherapy may be sufficient to induce a sustained antitumor immune response and durable clinical benefit. These aspects should be considered in individualized risk-benefit assessments and may support a watch-and-wait approach following serious irAEs, such as colitis or pneumonitis, that require prolonged treatment interruption, rather than early re-exposure to immunotherapy, which may compromise favorable outcomes through recurrence of toxicity. Nevertheless, given the retrospective real-world design of our study, underreporting and incomplete assessment of irAEs cannot be excluded. Therefore, the association between irAEs and treatment efficacy should be interpreted cautiously and requires further prospective validation.

In conclusion, our study confirms chemoimmunotherapy as a superior first-line approach for ES-SCLC in real-world clinical practice, demonstrating significant survival benefits over chemotherapy alone. Our results further highlight the critical importance of multimodal treatments, including brain and thoracic radiotherapy, in further enhancing patient outcomes. Importantly, the occurrence of irAEs correlated with improved prognosis, and treatment discontinuation due to irAEs did not adversely impact survival, underscoring their potential as clinical corre-

lates of therapeutic efficacy. Nevertheless, due to the retrospective nature of the study and the potential for selection bias, as well as the lack of data regarding treatment dose modifications, and socioeconomic or financial factors, these findings should be interpreted with caution and warrant further prospective validation.

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Kyriaki Dimitriou: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Shuo Shi:** Writing – review & editing. **Antonia Marginenau:** Writing – review & editing. **Miriam Blasi:** Writing – review & editing. **Farastuk Bozorgmehr:** Writing – review & editing. **Laura V. Klotz:** Writing – review & editing. **Florian Eichhorn:** Writing – review & editing. **Marc A. Schneider:** Writing – review & editing. **Michael Allgäuer:** Writing – review & editing. **Rajiv Shah:** Writing – review & editing. **Helge Bischoff:** Writing – review & editing. **Fabian Weykamp:** Writing – review & editing. **Albrecht Stenzinger:** Writing – review & editing. **Michael Thomas:** Resources, Writing – review & editing. **Petros Christopoulos:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Conceptualization.

Supplementary materials

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