



# Adding immune checkpoint inhibitors to chemotherapy confers modest survival benefit in patients with small cell lung cancer and brain metastases: a retrospective analysis

Baishen Zhang<sup>1^</sup>, Jing Chen<sup>2</sup>, Hui Yu<sup>2</sup>, Meichen Li<sup>2</sup>, Likun Chen<sup>2</sup>

<sup>1</sup>Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China; <sup>2</sup>Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, Guangzhou, China

**Contributions:** (I) Conception and design: B Zhang, L Chen; (II) Administrative support: L Chen; (III) Provision of study materials or patients: L Chen; (IV) Collection and assembly of data: B Zhang, J Chen, H Yu, M Li; (V) Data analysis and interpretation: B Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

**Correspondence to:** Likun Chen, PhD. Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Guangdong Provincial Clinical Research Center for Cancer, 651 Dongfeng East Road, Yuexiu District, Guangzhou 510060, China. Email: chenlk@sysucc.org.cn.

**Background:** Brain metastases (BM) are highly prevalent and associated with a poor prognosis in patients with small cell lung cancer (SCLC). However, the evidence regarding the efficacy of immune checkpoint inhibitors (ICIs) in combination with chemotherapy for patients with SCLC and BM remains limited. Therefore, the objective of this study is to evaluate whether the addition of ICIs confers survival benefits for patients with SCLC and BM.

**Methods:** This retrospective study enrolled patients with SCLC and BM at the Sun Yat-sen University Cancer Center between January 2018 and December 2022. Clinical characteristics were extracted from medical records. Depending on whether ICIs were added to the first-line treatment, the patients were categorized into the chemotherapy group and the chemoimmunotherapy group. The efficacy of these two treatment approaches was analyzed and compared.

**Results:** A total of 165 patients were enrolled, with 85 in the chemotherapy group and 80 in the chemoimmunotherapy group. The chemoimmunotherapy group showed a tendency towards prolonged intracranial [6.6 *vs.* 5.9 months, hazard ratio (HR) =0.77; P=0.14] and extracranial (6.9 *vs.* 6.5 months, HR =0.73; P=0.12) progression-free survival (PFS) and overall survival (OS) (15.6 *vs.* 14.5 months, HR =0.98; P=0.93) compared to the chemotherapy group. Cox regression analysis identified liver metastases and local treatment for BM as independent prognostic factors for OS in patients. Furthermore, the chemotherapy group and the chemoimmunotherapy group demonstrated similar patterns of initial disease progression.

**Conclusions:** Adding ICIs to chemotherapy confers modest survival benefits in patients with SCLC and BM.

**Keywords:** Small cell lung cancer (SCLC); brain metastasis; immune checkpoint inhibitors (ICIs); intracranial and extracranial efficacy

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<sup>^</sup> ORCID: 0000-0002-9222-4882.

## Introduction

Lung cancer is a prevalent malignancy worldwide, with small cell lung cancer (SCLC) representing the most aggressive subtype and accounting for approximately 14% of all cases (1). Due to the highly aggressive nature of SCLC, distant metastases are commonly observed upon diagnosis. Notably, the brain serves as a frequent site for metastatic spread in patients with SCLC (2). Studies have reported a high incidence rate of brain metastases (BM), ranging from 40% to 50%, in individuals with SCLC during diagnosis and treatment (3,4). Furthermore, patients with SCLC and BM exhibit significantly poorer prognosis, characterized by a dismal 2-year survival rate below 2% and a median overall survival (OS) time limited to merely 6 months (5-7).

In the era of immunotherapy, immune checkpoint inhibitors (ICIs) have emerged as a crucial component in the treatment of extensive-stage SCLC (ES-SCLC) (8,9). The addition of ICIs to chemotherapy has been demonstrated to significantly prolong median OS by 2 to 4 months in patients with ES-SCLC (10). As such, the combination of chemotherapy and ICIs has become the standard of care for patients with this disease (11). However, the role of ICIs in patients with SCLC and BM remains controversial. In the IMpower133 (12) trials, the addition of ICIs to SCLC first-line treatment resulted in a median OS extension of approximately 2 months, but did not benefit patients with

BM [hazard ratio (HR) =1.07; 95% confidence interval (CI): 0.47–2.43]. On the contrary, the CASPIAN study (13) demonstrated for the first time that adding ICIs to chemotherapy could be beneficial for patients with SCLC and BM. Specifically, combining durvalumab and chemotherapy prolonged both median OS (HR =0.79; 95% CI: 0.44–1.41) and median progression-free survival (PFS) (HR =0.73; 95% CI: 0.42–1.29) compared to chemotherapy alone in these patients. Similarly, in the ASTRUM-005 trial (14), ICIs also improved outcomes for patients with SCLC and BM by prolonging their median OS compared to those receiving chemotherapy alone (HR =0.61; 95% CI: 0.33–1.13). Of note, the numbers of patients with baseline BM in the several pivotal studies were small, and adding ICIs showed only a trend toward improving survival without reaching statistical significance. In addition, several studies (CAPSTONE-1, RATIONALE-312 and EXTENTORCH) included too few patients with BM to perform efficacy analysis (15-17). Therefore, the available evidence regarding the efficacy of ICIs in patients with SCLC and BM is currently insufficient, necessitating further exploration.

Therefore, this retrospective study aims to enroll patients with SCLC and BM at diagnosis and compare the treatment efficacy between chemotherapy combined with ICIs and chemotherapy alone. The objective is to evaluate whether the addition of ICIs confers survival benefits for patients with SCLC and BM. We present this article in accordance with the STROBE reporting checklist (available at <https://tldr.amegroups.com/article/view/10.21037/tlcr-24-335/rc>).

### Highlight box

#### Key findings

- Adding immune checkpoint inhibitors to chemotherapy confers modest survival benefits in patients with small cell lung cancer (SCLC) and brain metastases (BM).

#### What is known and what is new?

- Chemoimmunotherapy is a primary treatment for SCLC. Nevertheless, its efficacy in patients with BM remains a topic of debate.
- Our study presented real-world evidence regarding the efficacy of chemoimmunotherapy in patients with SCLC and BM. Furthermore, we compared the intracranial and extracranial efficacy differences observed in patients with BM.

#### What is the implication, and what should change now?

- BM are not immune-privileged sites where chemoimmunotherapy fails to exert its therapeutic effect. Nonetheless, the efficacy of chemoimmunotherapy in patients with SCLC and BM remains suboptimal, necessitating further exploration and development of additional therapeutic modalities.

## Methods

### Study design

This retrospective study enrolled patients with histologically confirmed SCLC at Sun Yat-sen University Cancer Center from January 2018 to December 2022, with their BM being verified through magnetic resonance imaging at baseline. The clinical characteristics of patients were extracted from medical records. Based on whether the first-line treatment regimen included ICIs, the patients were stratified into two groups: the chemoimmunotherapy group and the chemotherapy group. In both groups, patients received the same chemotherapy regimen consisting of etoposide in combination with platinum. Within the chemoimmunotherapy group, the ICIs utilized included durvalumab (n=39), atezolizumab (n=24), pembrolizumab

(n=2), sintilimab (n=5), tislelizumab (n=3), camrelizumab (n=3), serplulimab (n=3), and toripalimab (n=1).

This study was reviewed and approved by the ethics and research committee of Sun Yat-sen University Cancer Center (approval number: B2023-489-01), and it was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients' individual consent for this retrospective analysis was waived.

### *Efficacy assessments*

Extracranial lesions (lesions in the lungs and liver) were evaluated using enhanced computed tomography scans, while intracranial lesions were evaluated using enhanced magnetic resonance imaging at baseline and after every second treatment cycle (6–8 weeks). Treatment efficacy assessments were conducted by experienced oncologists. According to the revised Response Evaluation Criteria in Solid Tumors version 1.1 guidelines, the number of target lesions for intracranial disease has been expanded to up to 5, and the number of target lesions for extracranial disease has also been expanded to up to 5.

### *Endpoint*

The primary endpoint of this study was OS, defined as the duration from treatment initiation to death due to any cause. The secondary endpoints were PFS for intracranial tumor lesions and PFS for extracranial tumor lesions. PFS for intracranial tumor lesions was defined as the period from the first treatment for intracranial tumor lesions until the occurrence of lesion progression, whereas PFS for extracranial tumor lesions referred to the period between initiation of systemic treatment and onset of lesion progression.

### *Statistical analysis*

Descriptive statistics were used to summarize all variables in the study. Categorical variables were analyzed using appropriate statistical tests, such as the chi-square test or Fisher's exact test. Survival data was estimated using the Kaplan-Meier curve and compared using the log-rank test. Cox proportional hazards regression models were utilized to assess the risk of disease progression and death, with HRs and 95% CIs calculated. Univariate and multivariate Cox proportional hazards regression analyses were conducted to evaluate the prognostic value of each factor for OS.

Variables with  $P < 0.20$  in the univariable Cox regression were included in the multivariable Cox regression. The survival package in R software (version 4.0) was used for fitting survival regression, while visualization of results was achieved through the survminer package and ggplot2 package. Statistical analyses were performed using SPSS (version 25). A two-sided  $P$  value  $< 0.05$  was considered statistically significant. The last follow-up date was December 15, 2023.

## **Results**

### *Baseline characteristics*

A total of 165 patients diagnosed with SCLC and BM were enrolled in this study. The median age of patients was 62 years. Most of the patients were male and had a history of smoking. Depending on whether the first-line treatment regimen included ICIs, patients were divided into the chemotherapy group and the chemoimmunotherapy group. The baseline clinical characteristics between the two treatment groups were well-matched, and the specific baseline characteristics are summarized in *Table 1*.

### *Survival outcomes*

During a median follow-up period of 34.7 months, 75 out of 85 patients in the chemotherapy cohort died, whereas 62 out of 80 patients in the chemoimmunotherapy cohort died. For intracranial lesions, there was a trend toward prolonged median PFS in the chemoimmunotherapy group than in the chemotherapy group (6.6 vs. 5.9 months, HR =0.77;  $P=0.14$ ) (*Figure 1A*). Similarly, for extracranial lesions, there was a trend towards an extended median PFS in the chemoimmunotherapy group relative to the chemotherapy group (6.9 vs. 6.5 months, HR =0.73;  $P=0.12$ ) (*Figure 1B*). Furthermore, no significant difference in median OS was observed between the chemotherapy and chemoimmunotherapy groups (15.6 vs. 14.5 months, HR =0.98;  $P=0.93$ ) (*Figure 1C*). Within the chemotherapy cohort, 26 patients underwent subsequent treatment with ICI. After excluding these 26 patients, the chemoimmunotherapy group demonstrated a trend of prolonged OS compared to the chemotherapy group (15.6 vs. 11.6 months, HR =0.79;  $P=0.21$ ) (*Figure 1D*). Additionally, subgroup analysis based on clinical characteristics indicated that the addition of ICIs to the first-line treatment regimen resulted in a favorable trend of OS benefit across the majority of subgroups (*Figure S1*).

**Table 1** Baseline characteristics for SCLC patients with brain metastasis

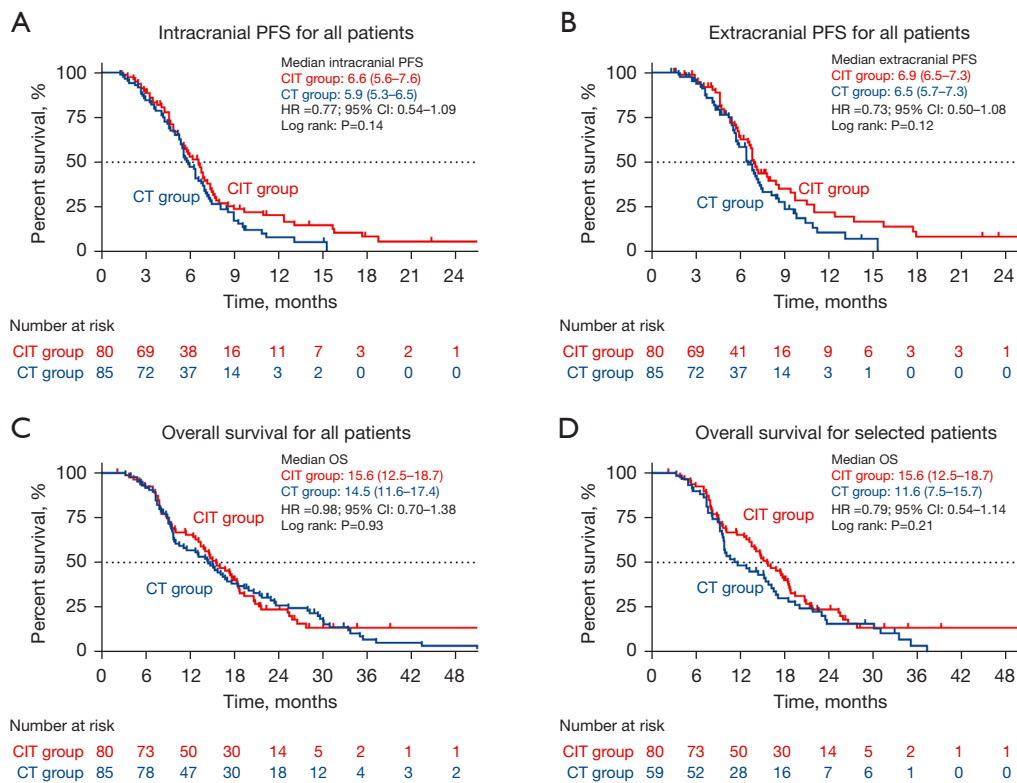
Characteristics	Patients			P value
	Total (n=165)	Chemotherapy (n=85)	Chemoimmunotherapy (n=80)	
Age (years), median	62	61	63	0.63
<60	65 (39.4)	35 (41.2)	30 (37.5)	
≥60	100 (60.6)	50 (58.8)	50 (62.5)	
Sex				0.15
Female	11 (6.7)	8 (9.4)	3 (3.8)	
Male	154 (93.3)	77 (90.6)	77 (96.3)	
Smoking history				>0.99
Non-smoker	33 (20.0)	17 (20.0)	16 (20.0)	
Smoker	132 (80.0)	68 (80.0)	64 (80.0)	
ECOG PS				0.64
0–1	65 (39.4)	32 (37.6)	33 (41.3)	
≥2	100 (60.6)	53 (62.4)	47 (58.8)	
Lung metastases				0.43
No	102 (61.8)	55 (64.7)	47 (58.8)	
Yes	63 (38.2)	30 (35.3)	33 (41.3)	
Liver metastases				0.70
No	130 (78.8)	68 (80.0)	62 (77.5)	
Yes	35 (21.2)	17 (20.0)	18 (22.5)	
Bone metastases				0.95
No	111 (67.3)	57 (67.1)	54 (67.5)	
Yes	54 (32.7)	28 (32.9)	26 (32.5)	
Intracranial tumor <sup>†</sup>				0.79
1–3	89 (53.9)	45 (52.9)	44 (55.0)	
≥4	76 (46.1)	40 (47.1)	36 (45.0)	
Intracranial tumor size <sup>‡</sup> (mm)				0.56
<20	74 (44.8)	40 (47.1)	34 (42.5)	
≥20	91 (55.2)	45 (52.9)	46 (57.5)	
Symptoms of brain metastases				0.26
Asymptomatic	90 (54.5)	50 (58.8)	40 (50.0)	
Symptomatic	75 (45.5)	35 (41.2)	40 (50.0)	

**Table 1** (continued)

Table 1 (continued)

Characteristics	Patients			P value
	Total (n=165)	Chemotherapy (n=85)	Chemoimmunotherapy (n=80)	
Local treatment for brain metastases <sup>†</sup>				0.46
No	75 (45.5)	41 (48.2)	34 (42.5)	
Yes	90 (54.5)	44 (51.8)	46 (57.5)	

Data are presented as n (%). <sup>†</sup>, intracranial tumor characteristics were evaluated according to baseline-enhanced brain magnetic resonance imaging; <sup>‡</sup>, local treatment for brain metastases includes surgery (n=4), SRS (n=23), and WBRT (n=63). In the chemotherapy group, 2 patients received surgery, 13 received SRS, and 29 received WBRT for their brain metastases. In the chemoimmunotherapy group, 2 received surgery, 10 received SRS, and 34 received WBRT for their brain metastases. SCLC, small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.



**Figure 1** Kaplan-Meier estimates for patient survival. (A) The intracranial PFS of patients receiving CT compared to CIT. (B) The extracranial PFS of patients receiving CT compared to CIT. (C) The OS of patients receiving CT compared to CIT. (D) Assessing the OS of patients receiving CT vs. CIT after excluding 26 patients who received the cross-therapeutic approach. PFS, progression-free survival; CIT, chemoimmunotherapy; CT, chemotherapy; HR, hazard ratio; CI, confidence interval; OS, overall survival.

**Response**

When it comes to the intracranial response of patients, among the 85 patients in the chemotherapy group, the objective response rate (ORR) was 68.2% (58/85), while the disease control rate (DCR) was 89.4% (76/85).

Furthermore, 8 patients (9.4%) achieved a complete response (CR), 50 patients (58.8%) achieved a partial response (PR), 18 patients (21.2%) had stable disease (SD), and 9 patients (10.6%) experienced progressive disease (PD). In contrast, among the 80 patients in the

**Table 2** Response of patients

Variables	Intracranial response				Extracranial response			
	CT, n (%)	CIT, n (%)	OR (95% CI)	P value	CT, n (%)	CIT, n (%)	OR (95% CI)	P value
Complete response	8 (9.4)	11 (13.8)	NA	NA	0	0	NA	NA
Partial response	50 (58.8)	49 (61.3)	NA	NA	62 (72.9)	63 (78.8)	NA	NA
Stable disease	18 (21.2)	14 (17.5)	NA	NA	19 (22.4)	15 (18.8)	NA	NA
Progressive disease	9 (10.6)	6 (7.5)	NA	NA	4 (4.7)	2 (2.5)	NA	NA
Objective response rate	58 (68.2)	60 (75.0)	0.72 (0.36–1.42)	0.34	62 (72.9)	63 (78.8)	0.73 (0.36–1.49)	0.39
Disease control rate	76 (89.4)	74 (92.5)	0.69 (0.23–2.02)	0.49	81 (95.3)	78 (97.5)	0.52 (0.09–2.92)	0.46

Treatment efficacy was evaluated according to Response Evaluation Criteria in Solid Tumors v1.1 criteria. CT, chemotherapy; CIT, chemoimmunotherapy; OR, odds ratio; CI, confidence interval; NA, not applicable.

chemoimmunotherapy group, the ORR was 75.0% (60/80), while the DCR was 92.5% (74/80). Specifically, 11 patients (13.8%) achieved a CR, 49 patients (61.3%) achieved a PR, 14 patients (17.5%) had SD, and 6 patients (7.5%) experienced PD (Table 2).

As for the extracranial response of patients, among the 85 patients in the chemotherapy group, an ORR of 72.9% (62/85) and a DCR of 95.3% (81/85) were observed. Furthermore, 62 patients (72.9%) achieved a PR, 19 patients (22.4%) had SD, and 4 patients (4.7%) experienced PD. In contrast, among the 80 patients in the chemoimmunotherapy group, an ORR of 78.8% (63/80) and a DCR of 97.5% (78/80) were noted. Specifically, 63 patients (78.8%) achieved a PR, 15 patients (18.8%) had SD, and 2 patients (2.5%) experienced PD (Table 2).

### Predictive factor

Cox regression analysis was performed to further distinguish the predictors associated with OS in patients with SCLC and BM. It was found that Eastern Cooperative Oncology Group performance status (ECOG PS), liver metastases, bone metastases, and local treatment for BM were prognostic factors for OS in univariate analysis. Furthermore, multivariate analysis confirmed that local treatment for BM was an independent prognostic factor for OS in patients with BM (Table 3).

The survival analysis demonstrated a significant improvement in OS for patients with BM from SCLC who received local treatment for BM compared to those who did not receive such treatment (Figure S2A). Furthermore, there was no statistically significant difference in survival outcomes observed between patients receiving first-line

treatment compared to those receiving second-line or subsequent-line local treatment (17.1 vs. 15.7 months, HR =0.97; P=0.90) (Figure S2B). Subgroup analysis in Figure S3 indicated that local treatment for BM improved OS in patients aged over 60 years, males, smokers, those with liver metastases, those without bone metastases, those with brain lesions larger than 20 mm, and symptomatic patients.

### Pattern of initial progression

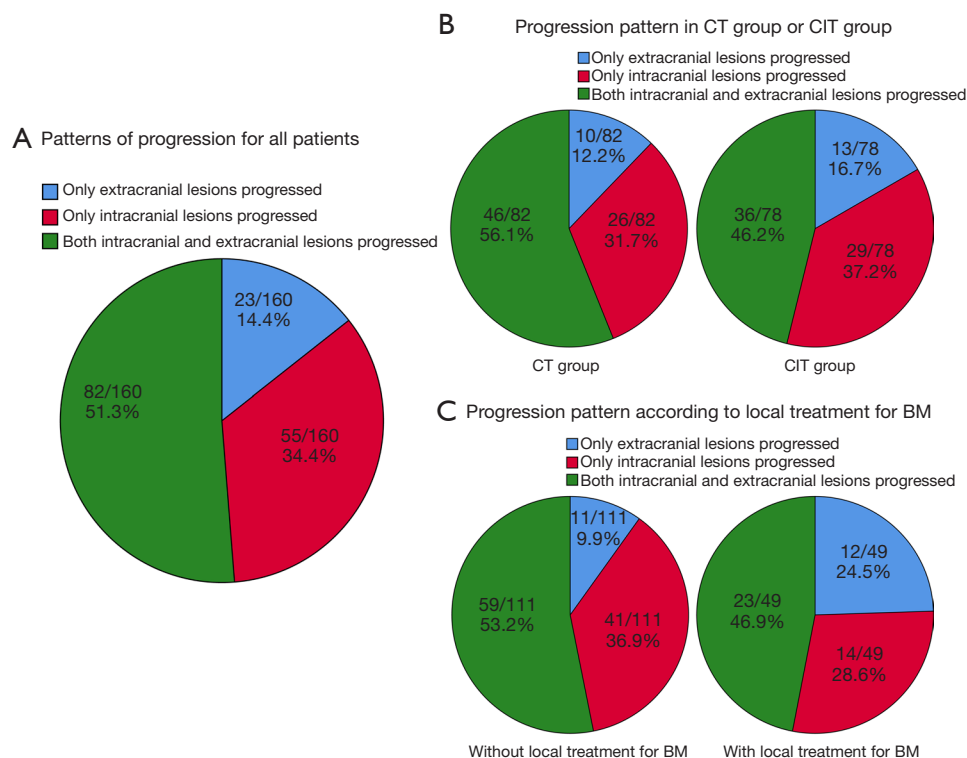
During the follow-up period, 5 patients showed no signs of disease progression. Among the remaining 160 patients who experienced disease progression, 82 (51.3%) had simultaneous initial progression of both intracranial and extracranial lesions, 55 (34.4%) demonstrated initial progression limited to intracranial lesions, and 23 (14.4%) showed initial progression confined to extracranial lesions (Figure 2A and Table S1). Of the 82 patients with disease progression in the chemotherapy group, 46 (56.1%) displayed simultaneous initial progression of both intracranial and extracranial lesions, 26 (31.7%) had initial progression of intracranial lesions only, and 10 (12.2%) had initial progression of extracranial lesions only. On the other hand, of the 78 patients with disease progression in the chemoimmunotherapy group, 36 (46.2%) had simultaneous initial progression of both intracranial and extracranial lesions, 29 (37.2%) had initial progression of intracranial lesions only, and 13 (16.7%) had initial progression of extracranial lesions only (Figure 2B and Table S1).

Among patients who received first-line treatment with local therapy targeting brain lesions, disease progression was observed in 49 out of 52 cases. Among these cases, 23 (46.9%) experienced initial progression involving both

**Table 3** Cox regression models on overall survival

Characteristics	N	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (years)					
<60	55	Reference		–	–
≥60	84	0.98 (0.67–1.43)	0.92	–	–
Sex					
Female	5	Reference		–	–
Male	134	0.74 (0.30–1.81)	0.50	–	–
Smoking history					
Non-smoker	25	Reference		–	–
Smoker	114	0.78 (0.49–1.26)	0.32	–	–
ECOG PS					
0–1	55	Reference		Reference	
≥2	84	1.30 (0.89–1.91)	0.17*	1.34 (0.91–1.97)	0.14
Lung metastases					
No	86	Reference		–	–
Yes	53	0.93 (0.63–1.36)	0.70	–	–
Liver metastases					
No	107	Reference		Reference	
Yes	32	1.49 (0.97–2.29)	0.07*	1.55 (0.97–2.46)	0.07
Bone metastases					
No	93	Reference		Reference	
Yes	46	1.38 (0.94–2.03)	0.11*	1.09 (0.71–1.66)	0.70
Intracranial tumor					
1–3	76	Reference		–	–
≥4	63	1.08 (0.74–1.56)	0.70	–	–
Intracranial tumor size (mm)					
<20	60	Reference		–	–
≥20	79	1.08 (0.74–1.56)	0.71	–	–
Symptoms of brain metastases					
Asymptomatic	77	Reference		–	–
Symptomatic	62	1.05 (0.72–1.51)	0.81	–	–
Local treatment for brain metastases					
No	65	Reference		Reference	
Yes	74	0.69 (0.48–0.99)	0.046*	0.64 (0.44–0.95)	0.03*
With ICIs					
No	80	Reference		–	–
Yes	59	0.79 (0.54–1.14)	0.21	–	–

\*, statistically significant values. P values were calculated with the log-rank test. Variables with P<0.20 in the univariable Cox regression were included in the multivariable Cox regression. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ICIs, immune checkpoint inhibitors.



**Figure 2** The pattern of initial progression in intracranial and extracranial lesions. (A) The initial progression pattern of all patients. (B) The initial progression pattern of all patients with or without ICIs. (C) The initial progression pattern of all patients with or without local treatment for BM. BM, brain metastases; CT, chemotherapy; CIT, chemoimmunotherapy; ICIs, immune checkpoint inhibitors.

intracranial and extracranial lesions, 14 (28.6%) experienced initial progression limited to intracranial lesions, and 12 (24.5%) experienced initial progression limited to extracranial lesions. In contrast, among patients who received first-line treatment without local therapy targeting brain lesions, disease progression occurred in 111 out of 113 cases. Among these cases, 59 (53.2%) showed initial progression involving both intracranial and extracranial lesions, 41 (36.9%) displayed initial progression limited to intracranial lesions only, and 11 (9.9%) manifested initial progression restricted to extracranial lesions (*Figure 2C* and *Table S1*).

## Discussion

BM is frequently observed in patients with ES-SCLC (3,4). However, due to the association of BM with poor outcomes, several SCLC-related trials have either excluded or limited the inclusion of patients with BM, resulting in a lack of evidence regarding the efficacy of ICIs in this population. Our study aims to provide valuable real-world insight

into the efficacy of ICIs in patients with SCLC and BM. It was found that the incorporation of ICIs into first-line chemotherapy regimens in patients with SCLC and BM might lead to a trend of prolonged PFS and OS benefits.

In recent years, it has become widely recognized that BM in cancer patients (not specifically SCLC) can also derive benefits from immunotherapy. Theoretically, ICIs exert their anti-tumor effects by activating peripheral T cells (18), which can traverse the blood-brain barrier or enter the cerebrospinal fluid, thereby enabling control of intracranial tumors (19). Several clinical studies have also confirmed the anti-tumor efficacy of ICIs in tumors such as non-small cell lung cancer (NSCLC) and melanoma that harbor BM (20,21). In the context of SCLC, our study revealed a trend toward improved PFS in both intracranial and extracranial lesions when utilizing first-line chemoimmunotherapy compared to chemotherapy. Similarly, the intracranial ORR in the chemoimmunotherapy group exhibited a slight increase relative to the chemotherapy group. These findings demonstrate that ICIs also possess appropriate anti-tumor activity in intracranial lesions within SCLC patients.



In our study, although the addition of ICIs showed a trend toward survival benefit, there was no statistically significant difference observed (*Figure 1*). A plausible explanation is that the benefit conferred by ICIs in patients with SCLC and BM may not be substantial, thus requiring a larger sample size to attain statistically significant results. Similarly, some studies have concluded that ICIs do not confer a survival benefit in patients with SCLC and BM (12,17), which may be attributed to the limited number of cases included in these studies.

The limited benefits of ICIs in patients with SCLC and BM can be attributed to several potential reasons. Firstly, the efficacy of ICIs in SCLC, whether with or without BM, is not particularly remarkable. For instance, the addition of ICIs to first-line chemotherapy in advanced NSCLC has been shown to extend OS by 6–12 months (22–24), whereas in advanced SCLC, the extension is only 2–4 months (10). The diminished benefit of the chemoimmunotherapy approach in SCLC compared to metastatic NSCLC can be attributed to the intrinsic immunosuppressive phenotype of SCLC (25). Secondly, the brain represents a highly immune-specific environment, and there exists a unique immunosuppressive microenvironment in BM lesions (26,27). The intricate interplay between tumor cells and the brain microenvironment creates a complex and challenging immune landscape, potentially limiting the full potential of ICIs. Last but not least, SCLC inherently exhibits a high degree of heterogeneity, with tumor cells within the intracranial and extracranial lesions potentially possessing distinct characteristics and immune evasion mechanisms (28,29), influencing the efficacy of immunotherapy.

In SCLC (regardless of the presence of BM), whether the combination of programmed cell death 1 ligand 1 (PD-L1) inhibitors or programmed death receptor 1 (PD-1) inhibitors is more effective has always been a hot topic. A meta analysis suggests that chemotherapy plus PD-1 inhibitors seem to outperform chemotherapy plus PD-L1 inhibitors in PFS (30). However, in patients with SCLC and BM, there is a lack of data on the superiority of PD-1 inhibitors or PD-L1 inhibitors. Through our data analysis, we found that chemotherapy plus PD-1 inhibitors seem to have a trend towards prolonged PFS (both intracranial and extracranial PFS) compared to chemotherapy plus PD-L1 inhibitors (*Figure S4A,S4B*), but there was no difference in OS between the two groups (*Figure S4C*). In the future, some prospective clinical studies will be needed to further explore this topic. Notably, our study highlighted the critical role of local therapy for BM in SCLC patients. The incorporation

of local therapy for BM into the first-line treatment strategy resulted in noteworthy alterations in the initial progression pattern, leading to a substantial decrease in the occurrence of brain progression (*Figure 2C*). Furthermore, local therapy for BM demonstrated a significant enhancement in OS and emerged as an independent prognostic factor for OS in multivariate analysis (*Table 3*). Research has unequivocally established the efficacy of local treatment for BM, encompassing surgical interventions and radiotherapy, in significantly reducing the progression rate of brain lesions and establishing better conditions for subsequent therapies (31,32). Moreover, local radiotherapy exhibits a synergistic interaction with immunotherapy. In our study, among patients who received local intracranial therapy, there was a trend towards prolonged intracranial PFS in the chemoimmunotherapy group compared to the chemotherapy group (HR =0.55, P=0.10) (*Figure S5A*). In terms of extracranial efficacy, the survival curves remained relatively close between the two treatment groups (HR =0.77, P=0.47) (*Figure S5B*), which also indirectly reflects the synergistic effect between radiation therapy and immunotherapy. Mechanistically, radiotherapy amplifies the release and presentation of tumor antigens, facilitates the infiltration of effector T cells into tumor tissues, and upregulates the expression of tumor PD-L1 and major histocompatibility complex class I (MHC-I), thereby augmenting the efficacy of immunotherapy (33–35). This provides a solid theoretical foundation for the concurrent utilization of immunotherapy and radiotherapy in the management of cancer. Consequently, we strongly advocate for the comprehensive implementation of diverse treatment modalities for patients with SCLC and BM, along with timely consideration of local therapy for brain lesions based on individual conditions.

Based on the findings of our study, we would like to underscore several key points. Firstly, in the management of patients with SCLC and BM, the combination of chemotherapy and ICIs should be regarded as the preferred systemic treatment. Nevertheless, in situations where access or affordability pose concerns, chemotherapy alone may serve as a viable alternative due to the limited incremental benefit associated with the addition of ICIs. Secondly, it is imperative to actively contemplate local brain-directed therapies, such as whole-brain radiotherapy or stereotactic radiosurgery, for these patients. Thirdly, there exists a pressing need to pursue biomarkers that can effectively predict the efficacy of immunotherapy in patients with SCLC and BM. Lastly, given the unfavorable prognosis

and constrained efficacy of current interventions for this patient cohort, the ongoing development of novel therapies designed specifically for targeting SCLC with BM is of paramount importance.

There are some limitations to be acknowledged in this study. Firstly, due to its retrospective design, the presence of missing information and potential analytical biases could not be completely eliminated. Secondly, patients who receive chemoimmunotherapy might have better economic status compared to those who receive chemotherapy alone, and thus receive better care, which might also affect patient prognosis. Finally, the ICIs utilized in the chemoimmunotherapy group were not the same ones, and different agents may yield distinct survival outcomes. Notwithstanding these limitations, our study offered valuable insight into the real-world treatment efficacy for patients with SCLC and BM. Future prospective studies involving larger cohorts should be undertaken to thoroughly assess the efficacy of immunotherapy in this specific patient population.

## Conclusions

In summary, our study findings indicate that the current first-line regimen consisting of the combination of chemotherapy and ICIs provides modest survival benefits for patients with SCLC and BM. Nonetheless, given the abysmal prognosis associated with BM in SCLC, there remains room for further enhancements in the efficacy of existing treatment protocols. Hence, it is imperative to undertake the exploration of novel therapeutic agents tailored specifically to this particular patient cohort, while simultaneously employing a comprehensive treatment strategy, in order to substantively ameliorate their prognostic outcomes.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <https://tldr.amegroups.com/article/view/10.21037/tldr-24-335/rc>

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was reviewed and approved by the ethics and research committee of Sun Yat-sen University Cancer Center (approval number: B2023-489-01), and it was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients' individual consent for this retrospective analysis was waived.

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