ORIGINAL ARTICLE

WILEY

Treatment patterns and outcomes of immunotherapy in extensive-stage small-cell lung cancer based on real-world practice

Yaning Yang[1] | Xin Ai[1] | Haiyan Xu[2] | Guangjian Yang[3] | Lu Yang[4] | Xuezhi Hao[1] | Ke Yang[5] | Yuling Mi[6] | Guizhen Wang[7] | Shuyang Zhang[1] | Siyu Lei[1] | Yan Wang[1]

[1]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[2]Department of Comprehensive Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[3]Department of Respiratory Medicine, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China

[4]Department of Medical Oncology and Radiation Sickness, Peking University Third Hospital, Beijing, China

[5]Department of Medical Oncology, Cancer Hospital of Huanxing, Beijing, China

[6]Department of Medical Oncology, Chaoyang Sanhuan Cancer Hospital, Beijing, China

[7]State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Correspondence
Yan Wang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No.17 Panjiayuan Street South, Chaoyang District, Beijing, 100021, China.
Email: wangyanyifu@163.com

Abstract

Background: The application of immune checkpoint inhibitors (ICIs) represents a breakthrough in the current landscape for the treatment of extensive-stage small-cell lung cancer (ES-SCLC), but the real-world outcome is limited. This study aimed to investigate the treatment options and efficacy evaluation of first-line, second-line, and subsequent-line immunotherapy in routine practice.

Methods: A retrospective analysis of ES-SCLC patients treated with ICIs was conducted between May 2016 and September 2021. Objective response rate, disease control rate, progression-free survival (PFS) and overall survival were assessed between groups to explore the value of ICIs at different treatment time periods. PFS1 and PFS2 were defined as the duration from initial therapy to disease progression or death in first-line or second-line treatment.

Results: Ninety-six patients with ES-SCLC were included. PFS1 was prolonged in patients treated with first-line ICIs-combined therapy (median PFS1 7.20 months vs. 5.30 months, hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.36–087, $p = 0.0085$). For patients who progressed after first-line ICIs treatment ($N = 22$), PFS1 + PFS2 was longer in the second-line ICIs continuation group with no significant difference (median PFS1 + PFS2 11.27 months vs. 7.20 months, HR 0.45, 95% CI 0.14–1.51, $p = 0.19$). For patients who experienced a progression event after first-line chemotherapy ($N = 50$), PFS2 and PFS1 + PFS2 were prolonged in patients who accepted second-line ICIs-combined therapy without significant difference (median PFS2 4.00 months vs. 2.43 months, HR 0.59, 95% CI 0.33–1.05, $p = 0.070$; median PFS1 + PFS2 11.30 months vs. 8.70 months, HR 0.53, 95% CI 0.29–0.98, $p = 0.056$).

Conclusion: First-line ICIs plus chemotherapy should be applied in the clinical practice of ES-SCLC. If patients did not receive ICIs plus chemotherapy in first-line treatment, therapies that include ICIs in second-line treatment should be considered.

KEYWORDS
immunotherapy, prognostication, small-cell lung carcinoma, survival

Yaning Yang and Xin Ai should be considered the joint first authors.

INTRODUCTION

Lung cancer is the malignant tumor with the highest incidence and mortality rate worldwide. Small-cell lung cancer

(SCLC), a high-grade neuroendocrine carcinoma, accounts for approximately 15% of lung malignancies and is commonly found in men with a history of smoking.[1] At the time of diagnosis, two-thirds of patients have distant metastases and are classified as extensive-stage small-cell lung cancer (ES-SCLC). More than 90% of ES-SCLC patients develop recurrence or progression within 2 years and have an extremely poor prognosis.[2]

For decades, the first-line treatment for ES-SCLC has been etoposide/irinotecan combined with cisplatin/carboplatin chemotherapy with a median progression-free survival (PFS) of less than 5 months and median overall survival (OS) of less than 9 months.[3] IMpower133 and CASPIAN, two landmark studies for ES-SCLC, showed a prolonged OS of chemotherapy plus programmed death-ligand 1 (PD-L1) inhibitors vs. chemotherapy alone with statistically significance.[4,5] Based on these studies, the addition of PD-L1 inhibitors to chemotherapy became the standard first-line therapy of ES-SCLC. However, real-world retrospective data on first-line combination therapy have been relatively scarce.

In the field of second-line immunotherapy for ES-SCLC, immune checkpoint inhibitors (ICIs) as monotherapy failed to exhibit meaningful benefit. The phase III CheckMate 331 study explored the efficacy of nivolumab vs. chemotherapy and obtained a negative OS of 7.5 months vs. 8.4 months, while the PFS of 1.4 months vs. 3.8 months was even worse.[6] The phase II IFCT-1603 study aimed at evaluating the efficacy of atezolizumab vs. chemotherapy. The OS of 9.5 months vs. 8.7 months did not significantly differ between groups, and a worse PFS of 1.4 months vs. 4.3 months was observed.[7] As for ICIs-combined therapy in the second-line setting, whether the addition of immunotherapy is beneficial remains inconclusive. In addition, the above prospective studies are all second-line explorations after first-line chemotherapy for ES-SCLC. In the current treatment pattern of first-line chemotherapy plus ICIs (C + I), there was no definitive conclusion in the second-line setting with high-level evidence. Whether immunotherapy beyond progression brings more benefits is worth exploring in depth.

This study presents a retrospective analysis of ES-SCLC patients under real-world conditions, mainly focused on the efficacy and survival benefit of ICIs in ES-SCLC at different treatment periods.

METHODS

Patients

A retrospective analysis of ES-SCLC patients was conducted at the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Eligible patients were adults with histologically or cytologically confirmed SCLC and assessed as ES-SCLC according to the Veterans Administration Lung Study Group (VALG) staging system from May 2016 to September 2021, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2,

and measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). All patients were treated with ICIs in first-line, second-line, or subsequent-lines treatment. The key exclusion criterion was patients without ICI application from initial treatment to last follow-up. The last follow-up ended on November 10, 2021.

Treatment and assessment

Most patients received C + I or chemotherapy as first-line treatment, following chemotherapy, immunotherapy, anti-angiogenesis therapy, and targeted therapy alone or in combination beyond progression. The selection and dosing of therapeutic agents were based on current guidelines and patient conditions. Patients underwent cervical, thoracic, and abdominal contrast-enhanced computed tomography (CT), cranial contrast-enhanced magnetic resonance imaging (MRI) and whole-bone scan, or whole-body positron emission tomography/computed tomography (PET-CT) and cranial contrast-enhanced MRI to clarify staging and measurable lesions before ES-SCLC treatment. We repeated necessary examinations as above every 6 weeks (two treatment cycles) to evaluate the efficacy of treatment according to RECIST 1.1. Objective response rate (ORR) was the percentage of complete response (CR) and partial response (PR), while disease control rate (DCR) was the percentage of CR, PR, and stable disease (SD). PFS was the time from initial treatment to disease progression or death, and OS was the time from initial treatment to death from any cause. PFS1 and PFS2 were defined as the duration from initial therapy to disease progression or death in first-line or second-line treatment. Chemotherapy-sensitive disease referred to relapse that occurred >90 days after completion of prior chemotherapy, while chemotherapy-resistant disease was defined as relapse that occurred ≤90 days after completion of prior chemotherapy.

Statistical analysis

Baseline characteristics were described as counts and percentages, and compared between groups using the chi-square test or Fisher's exact test. Survival was estimated by the Kaplan–Meier method, and differences were assessed with the log-rank test. The Cox proportional-hazards model was used to evaluate the effect of prognostic factors, including hazard ratio (HR) and 95% confidence interval (CI). SPSS version 25.0 (SPSS, IBM Corporation) was used for statistical analysis. R version 4.1.3 was used to present survival curves.

RESULTS

Patient characteristics

A total of 96 ES-SCLC patients with ICIs utility were included in this real-world study. The median follow-up

time was 23.87 months (95% CI 13.39–34.34 months). Eighty-one patients (84.38%) were male and 71 patients (73.96%) were current or former smokers. Thirty patients (31.25%) were diagnosed with limited-stage SCLC at first, while 66 patients (68.75%) were in extensive-stage at initial diagnosis. Only seven patients (7.29%) and five patients (5.21%) exhibited PD-L1 expression and tumor mutation burden (TMB) level, respectively (Table 1). Univariate analysis revealed that liver metastasis ($N = 30$, 31.25%) forecasted a poor PFS1 for ES-SCLC patients (median PFS1 5.00 months vs. 6.93 months, HR 2.20, 95% CI 1.36–3.55, $p = 0.001$), while no significant differences were observed between groups of age, gender, smoking status, family history, body mass index (BMI), central nervous system (CNS) or liver metastasis, or VALG staging at diagnosis on PFS1 (Supporting Information Table S1). Simultaneously, there were no significant differences in baseline characteristics on OS (Supporting Information Table S2).

Ninety-six patients presented accessible first-line treatment status. Forty-six patients (47.92%) who started immunotherapy in the first-line setting were assigned to the first-line ICIs-combined therapy group (1L-ICIs group) while the other 50 patients (52.08%) were placed in the first-line without ICIs group (1L-nonICIs group) (Supporting Information Figure S1). Baseline characteristics were balanced between the 1L-ICIs and 1L-nonICIs group (Table 1).

Seventy-two patients presented obtainable second-line treatment status, including 43 patients (59.72%) who accepted immunotherapy and 29 (40.28%) patients who received chemotherapy in a second-line setting. Among patients who received ICIs, 16 patients (37.21%) in the 1L-ICIs group who continued ICIs as second-line treatment were classified as the ICIs-beyond-progression group (ITBP group), while the other 27 patients (62.79%) who accepted immunotherapy for the first time in a second-line setting were placed in the second-line ICIs-combined therapy group (2L-ICIs group). Six patients (20.69%) discontinued immunotherapy after first-line ICIs progression and were assigned to the non-ICIs-beyond-progression group (nonITBP group). Twenty-three patients (79.31%) without ICI application in either first-line or second-line treatment started immunotherapy in subsequent-lines treatment. These patients were placed in the subsequent-lines ICIs-combined therapy group (SL-ICIs group) (Supporting Information

TABLE 1 Baseline characteristics of patients with first-line treatment

Baseline characteristics	Total ($N = 96$) N (%)	1L-ICIs group ($N = 46$) N (%)	1L-nonICIs group ($N = 50$) N (%)	p
Age (years)				0.69
<65	67 (69.79%)	33 (71.74%)	34 (68.00%)	
≥65	29 (30.21%)	13 (28.26%)	16 (32.00%)	
Gender				0.92
Male	81 (84.38%)	39 (84.78%)	42 (84.00%)	
Female	15 (15.62%)	7 (15.22%)	8 (16.00%)	
Smoking status				0.99
Smoker	71 (73.96%)	34 (73.91%)	37 (74.00%)	
Never-smoker	25 (26.04%)	12 (26.09%)	13 (26.00%)	
Family history				0.92
Yes	20 (20.84%)	10 (21.74%)	10 (20.00%)	
No	74 (77.08%)	36 (78.26%)	38 (76.00%)	
Unknown	2 (2.08%)	0 (0.0%)	2 (4.00%)	
BMI				0.24
≤24	38 (39.58%)	21 (45.65%)	17 (34.00%)	
>24	58 (60.42%)	25 (54.35%)	33 (66.00%)	
CNS metastasis				0.54
Yes	30 (31.25%)	13 (28.26%)	17 (34.00%)	
No	66 (68.75%)	33 (71.74%)	33 (66.00%)	
Liver metastasis				0.87
Yes	30 (31.25%)	14 (30.43%)	16 (32.00%)	
No	66 (68.75%)	32 (69.57%)	34 (68.00%)	
VALG staging at diagnosis				0.054
Limited-stage	30 (31.25%)	10 (21.74%)	20 (40.00%)	
Extensive-stage	66 (68.75%)	36 (78.26%)	30 (60.00%)	

Abbreviations: 1L-ICIs group, patients who started ICIs in first-line treatment; 1L-nonICIs group, patients who did not start ICIs in first-line treatment; BMI, body mass index; CNS, central nervous system; ICIs, immune checkpoint inhibitors; VALG, Veterans Administration Lung Study Group.

Figure S1). Baseline characteristics were balanced between the 1L-ICIs (N = 22), 2L-ICIs (N = 27) and SL-ICIs (N = 23) groups without significant differences (Supporting Information Table S3).

First-line treatment patterns and efficacy

The platinum-etoposide combination was the most common chemotherapy choice in both the 1L-ICIs and 1L-nonICIs

TABLE 2 First-line treatment and response as determined by RECIST v.1.1

Variants	1L-ICIs group (N = 46) N (%)	1L-nonICIs group (N = 50) N (%)
Chemotherapy choice	**(N = 45)**	**(N = 50)**
Etoposide-based therapy	40 (88.89%)	48 (96.00%)
Albumin-bound paclitaxel-based therapy	5 (11.11%)	2 (4.00%)
ICI choice	**(N = 46)**	**(N = 0)**
PD-1 inhibitors[a]	16 (34.78%)	NA
PD-L1 inhibitors[b]	30 (65.22%)	NA
Response	**(N = 46)**	**(N = 50)**
CR and PR	34 (73.91%)	38 (76.00%)
SD	9 (19.57%)	4 (8.00%)
PD	3 (6.52%)	6 (12.00%)
Not evaluable	0 (0.00%)	2 (4.00%)
ORR	34 (73.91%)	38 (79.17%)
DCR	43 (93.48%)	42 (87.50%)

Abbreviations: 1L-ICIs group, patients who started ICIs in first-line treatment; 1L-nonICIs group, patients who did not start ICIs in first-line treatment; CR, complete response; DCR, disease control rate; ICI, immune checkpoint inhibitor; NA, not available; ORR, objective response rate; PD, progressive disease; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a]Included pembrolizumab, nivolumab, sintilimab, camrelizumab, tislelizumab, and toripalimab.
[b]Included atezolizumab and durvalumab.

groups (N = 40, 88.89%; N = 48, 96.00%). With regard to the selection of ICIs in the 1L-ICIs group, 30 patients (65.22%) were treated with PD-L1 inhibitors, while 16 patients (34.78%) were given programmed cell death protein 1 (PD-1) inhibitors (Table 2). No significant difference for PFS1 and OS was observed between PD-L1 and PD-1 inhibitors in the first-line setting (median PFS1 7.20 months vs. 7.07 months, HR 0.90, 95% CI 0.44–1.83, p = 0.77; median OS 16.53 months vs. 19.70 months, HR 1.78, 95% CI 0.52–6.02, p = 0.35).

As for the treatment response of chemotherapy plus ICIs or not, the ORR was 73.91% (34/46) and 79.17% (38/48), while DCR was 93.48% (43/46) and 87.50% (42/48) in the 1L-ICIs and 1L-nonICIs groups, respectively (Table 2). A total of 34 patients (73.91%) in the 1L-ICIs group and 50 patients (100%) in the 1L-nonICIs group experienced a progression event after first-line treatment. PFS1 was longer in the 1L-ICIs group than in the 1L-nonICIs group with a significant difference (median PFS1 7.20 months vs. 5.30 months, HR 0.55, 95% CI 0.36–087, p = 0.0085) (Figure 1a). Although OS was prolonged in the 1L-ICIs group, the significance threshold was not met (median OS 19.70 months vs. 16.93 months, HR 0.93, 95% CI 0.50–1.73, p = 0.81) (Figure 1b). Comparing PFS between groups distinguished when immunotherapy was initially applied, as the PFS of immunotherapy in the first-line setting was longer than in the second-line and subsequent-lines setting (median PFS 7.20 months vs. 3.70 months, HR 0.46, 95% CI 0.30–0.74, p = 0.00074) (Figure 1c).

Second-line treatment patterns and efficacy

For patients who progressed after the first-line ICIs setting (N = 22), C + I was adopted by most patients (N = 14, 63.64%) with an ORR of 28.57% (4/14) and DCR of 78.57% (11/14) (Table 3). PFS1 + PFS2 was longer in the ITBP group (N = 16) than in the nonITBP group (N = 6), but the significance threshold was not met (median PFS1 + PFS2 11.27 months vs. 7.20 months, HR 0.45, 95% CI 0.14–1.51, p = 0.19) (Figure 2a).
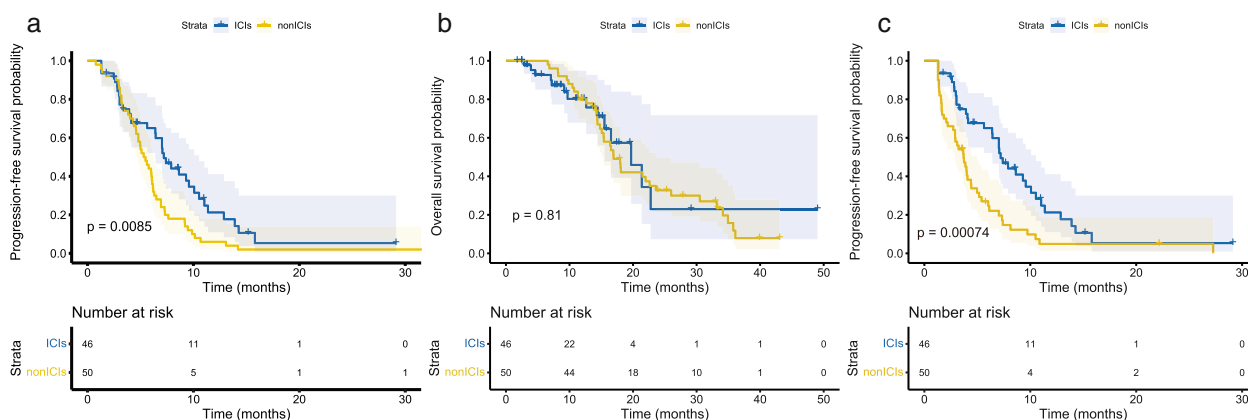

FIGURE 1 Kaplan–Meier curves of first-line treatment and survival outcomes between IL-ICIs and IL-nonICIs groups. (a) PFS1 of the IL-ICIs or IL-nonICIs groups. (b) OS of the IL-ICIs or IL-nonICIs groups. (c) PFS of immunotherapy between first-line setting and second-line + subsequent-lines setting

TABLE 3 Second-line treatment and response as determined by RECIST v.1.1

Variants	Total (N = 72) N (n%)	1L-ICIs group (N = 22) N (n%)	1L-nonICIs group (N = 50) N (n%)
Treatment mode	(N = 72)	(N = 22)	(N = 50)
Chemotherapy (C)	15 (20.83%)	2 (9.09%)	13 (26.00%)
Chemotherapy plus angiogenesis inhibitors (C + A)	8 (11.11%)	2 (9.09%)	6 (12.00%)
Chemotherapy plus ICIs (C + I)	35 (48.61%)	14 (63.64%)	21 (42.00%)
ICIs plus angiogenesis inhibitors (I + A)	6 (8.33%)	2 (9.09%)	4 (8.00%)
Angiogenesis inhibitors (A)	5 (6.94%)	1 (4.55%)	4 (8.00%)
EGFR inhibitor osimertinib (O)	1 (1.39%)	1 (4.55%)	0 (0%)
ICIs (I)[a]	2 (2.78%)	0 (0%)	2 (4.00%)
Chemotherapy choice of all patients	(N = 58)	(N = 18)	(N = 40)
Etoposide-based therapy	1 (1.72%)	0 (0%)	1 (2.50%)
Paclitaxel-based therapy	38 (65.52%)	11 (61.11%)	27 (67.50%)
Topoisomerase inhibitor-based therapy	17 (29.31%)	5 (27.78%)	12 (30.00%)
Paclitaxel and irinotecan-based therapy	2 (3.45%)	2 (11.11%)	0 (0%)
Chemotherapy choice of C + I patients	(N = 35)	(N = 14)	(N = 21)
Etoposide-based therapy	1 (2.86%)	0 (0%)	1 (4.76%)
Paclitaxel-based therapy	27 (77.14%)	9 (64.29%)	18 (85.71%)
Topoisomerase inhibitor-based therapy	5 (14.29%)	3 (21.43%)	2 (9.52%)
Paclitaxel and irinotecan-based therapy	2 (5.71%)	2 (14.29%)	0 (0%)
Chemotherapy plus ICIs response	(N = 35)	(N = 14)	(N = 21)
CR and PR	9 (25.71%)	4 (28.57%)	5 (23.81%)
SD	19 (54.29%)	7 (50.00%)	12 (57.14%)
PD	7 (20.00%)	3 (21.43%)	4 (19.05%)
ORR	9 (25.71%)	4 (28.57%)	5 (23.81%)
DCR	28 (80.00%)	11 (78.57%)	17 (80.95%)

Abbreviations: 1L-ICIs group, patients who started ICIs in first-line treatment; 1L-nonICIs group, patients who did not start ICIs in first-line treatment; CR, complete response; DCR, disease control rate; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a]Included PD-1 inhibitor alone or combined with CTLA-4 inhibitor.

Fifty patients experienced a progression event after first-line chemotherapy. C + I was the most popular choice (N = 21, 42.00%) with an ORR of 23.81% (5/21) and DCR of 80.95% (17/21) (Table 3). PFS2 and PFS1 + PFS2 was longer in the 2L-ICIs group (N = 27) than in the SL-ICIs group (N = 23) without a significant difference (median PFS2 4.00 months vs. 2.43 months, HR 0.59, 95% CI 0.33–1.05, p = 0.070; median PFS1 + PFS2 11.30 months vs. 8.70 months, HR 0.53, 95% CI 0.29–0.98, p = 0.056) (Figure 2b,c). PFS2 in the 2L-ICIs group was longer for first-line chemotherapy-resistant patients than for the SL-ICIs group without a significant difference (median PFS2 4.07 months vs. 1.77 months, HR 0.56, 95% CI 0.28–1.14, p = 0.10) (Figure 2d). Similar PFS2 was observed between first-line chemotherapy-sensitive and chemotherapy-resistant patients in the 2L-ICIs group (median PFS2 3.67 months vs. 4.07 months, HR 1.07, 95% CI 0.42–2.74, p = 0.89).

Among patients who accepted chemo-based therapy (N = 58) in a second-line setting, patients were treated with paclitaxel (N = 38, 65.52%) or topoisomerase inhibitors, including topotecan and irinotecan (N = 17, 29.31%)

(Table 3). The majority of patients (N = 35, 92.11%) in the paclitaxel group (PTX group) were treated with albumin-bound paclitaxel (nab-PTX). The ORR and DCR were 15.79% (6/38) and 71.05% (27/38) in the PTX group, and 23.53% (4/17) and 64.71% (11/17) in the topoisomerase-inhibitor group (TOPi group). No significant difference was observed between the PTX and TOPi groups in PFS2 (median PFS2 4.00 months vs. 3.47 months, HR 0.84, 95% CI 0.45–1.57, p = 0.58) (Figure 3a). Among patients treated with second-line C + I (N = 35), the ORR and DCR were 22.22% (6/27) and 81.48% (22/27) in the PTX group (N = 27), and 20.00% (1/5) and 60.00% (3/5) in the TOPi group (N = 5). The PFS2 of these groups was 4.40 months and 7.67 months with no statistical difference (HR 1.35, 95% CI 0.39–4.67, p = 0.63) (Figure 3b).

DISCUSSION

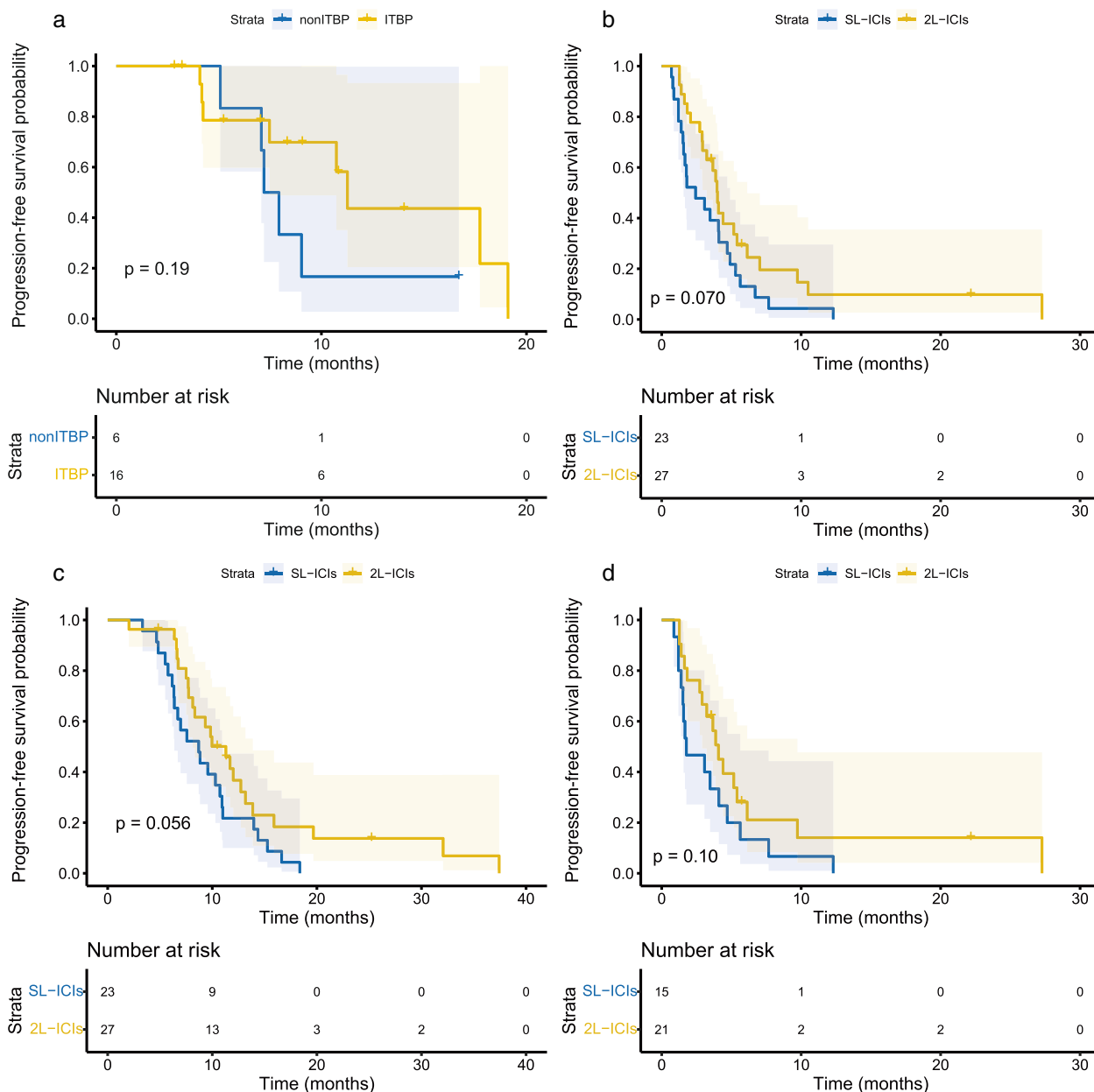The positive OS result of IMpower133 and CASPIAN established the preferred first-line PD-L1 inhibitors plus

FIGURE 2 Kaplan–Meier curves of second-line treatment and survival outcomes between different groups. (a) PFS1 + PFS2 of the ITBP or nonITBP groups. (b) PFS2 of the 2L-ICIs or SL-ICIs groups. (c) PFS1 + PFS2 of the 2L-ICIs or SL-ICIs groups. (d) PFS2 of the 2L-ICIs or SL-ICIs groups of first-line chemotherapy-resistant patients

chemotherapy of ES-SCLC in the National Comprehensive Cancer Network (NCCN) guideline.[8] In our study, the median PFS1 (7.20 months) and OS (19.70 months) of first-line ICIs-combined therapy were longer than the result of IMpower 133 and CASPIAN, which might be related to the inclusion of 10 patients with limited-stage initially. This more closely resembled real-world clinical practice, where some patients diagnosed with limited-stage but progressed rapidly.

The use of PD-1 inhibitors for first-line ES-SCLC has been controversial. Although there is no positive prospective evidence for pembrolizumab and nivolumab as first-line C + I therapy,[9,10] a recent abstract from the annual meeting of the American Society of Clinical Oncology (ASCO) presented an interim analysis of the PD-1 inhibitor serplulimab plus chemotherapy vs. chemotherapy in a first-line setting, with a prolonged median OS in the serplulimab group (median OS 15.4 months vs. 10.9 months, HR 0.63, 95% CI 0.49–0.82, $p < 0.001$).[11] In our retrospective cohort, 16 patients used PD-1 inhibitors as first-line ICIs due to their clinical accessibility and the economic situation. No significant difference in PFS1 and OS was observed between PD-L1 and PD-1 inhibitors, therefore, our study corroborates that PD-1 inhibitors can be considered as an alternative when PD-L1 inhibitors are not available.
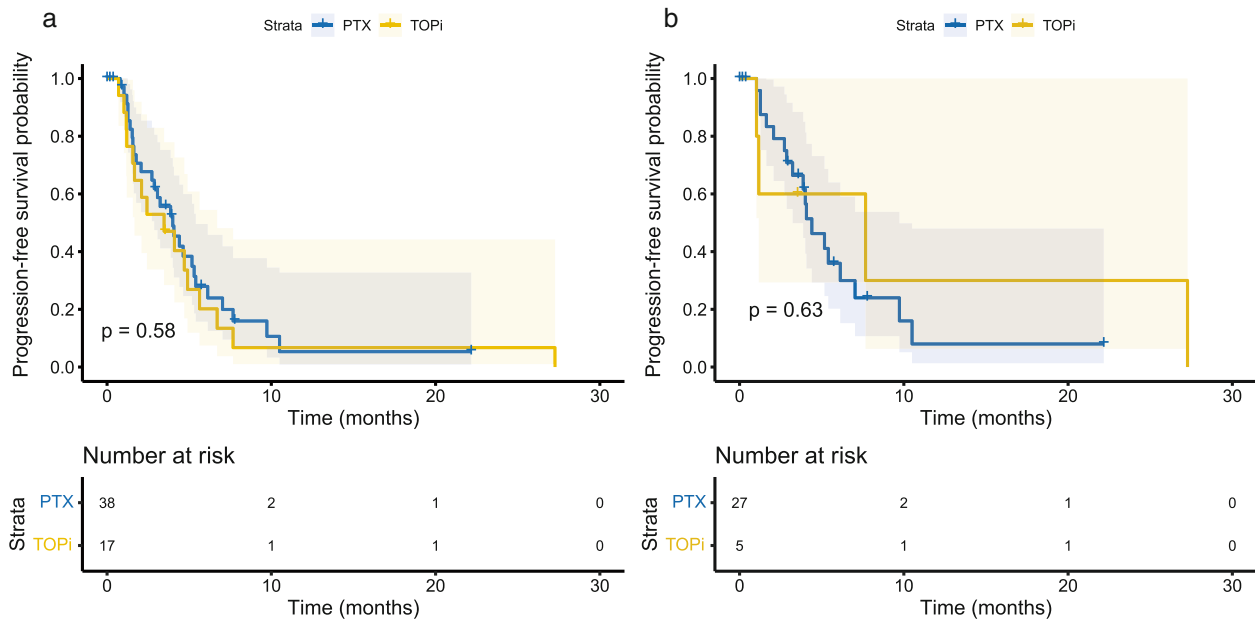
FIGURE 3 Kaplan–Meier curves of second-line paclitaxel-based therapy or topoisomerase inhibitor-based therapy. (a) PFS2 of patients treated with chemo-based therapy. (b) PFS2 of patients treated with C + I therapy

The current preferred second-line setting in the NCCN guidelines was topotecan or lurbinectedin.[8] All patients in the clinical trial of topotecan accepted chemotherapy alone before enrollment,[12] and only 8% of patients in the clinical trial of lurbinectedin received C + I as first-line treatment,[13] therefore the current evidence for the standard treatment of patients with relapsed SCLC is based on first-line chemotherapy. The choice of second-line treatment after resistance to first-line C + I is inconclusive. Many physicians choose to continue first-line ICIs due to the complimentary drug policy and adjust the paired medications in clinical practice, but research on this ITBP mode is relatively absent in SCLC. In advanced non-small-cell lung cancer (NSCLC), the phase III OAK study compared 168 patients of subsequent-lines atezolizumab beyond progression with 94 patients who switched to nonprotocol therapy after the progression of atezolizumab. The results showed a prolonged median post-progression OS of 12.7 months (95% CI 9.3–14.9) vs. 8.8 months (95% CI 6.0–12.1) and an 18 months OS rate of 37% vs. 20%, respectively.[14] Several retrospective analyses also suggested that the continuation of ICIs beyond progression might improve survival in NSCLC patients.[15,16] In this study, 16 patients continued ICIs-combined therapy with a prolonged PFS1 + PFS2, but the significance threshold was not met. Consequently, the continued application of immunotherapy can be an option after the progression of first-line C + I therapy. Future expansion of sample size, a continuation of follow-up, and attention to prospective data are necessary.

For ES-SCLC patients treated with first-line chemotherapy alone, the role of immunotherapy in second-line treatment remains unclear. The prospective research in the CheckMate 331 and IFCT-1603 studies did not show satisfied overall efficacy of ICIs monotherapy, with an even worse PFS.[6,7] Our retrospective analysis showed that PFS2

and PFS1 + PFS2 were prolonged in patients with ICIs, especially for first-line chemotherapy-resistant patients. Although the significance threshold was not met, the role of immunotherapy should not be underestimated in the second-line setting.

In contrast to the CheckMate 331, CheckMate 032, IFCT-1603, and KEYNOTE-028/158 clinical trials with poor median PFS of 1.4–2.0 months,[6,7,17,18] the vast majority of ICIs in our study combined with chemotherapy or angiogenesis inhibitors in second-line treatment, with median PFS of 4.00 months, therefore the prolonged PFS of immunotherapy was driven by a combination of ICIs and chemotherapy/angiogenesis inhibitors. In the exploration of second-line ICIs-combined therapy, the phase II clinical trial by Kim et al. evaluated the efficacy of pembrolizumab plus paclitaxel in 26 ES-SCLC patients who progressed after first-line chemotherapy, with an ORR of 23.1%, DCR of 80.7%, median PFS of 5.0 months (2.7–6.7 months), and median OS of 9.1 months (6.5–15.0 months).[19] Another phase II clinical trial by Fan et al. assessed the efficacy of camrelizumab plus apatinib in 59 ES-SCLC patients, with an ORR of 34.0%, DCR of 68.1%, median PFS of 3.6 months (1.9–4.6 months), and median OS of 8.4 months (4.7–12.3 months).[20] However, CheckMate 032 compared nivolumab plus ipilimumab with nivolumab monotherapy in 243 ES-SCLC patients as second-line or subsequent-lines treatment. Although ORR significantly increased (21.9% vs. 11.6%, $p = 0.03$), it did not translate into PFS or OS benefit (median PFS 1.4 months vs. 1.5 months, median OS 5.7 months vs. 4.7 months).[21] This phenomenon might be attributed to the immunodeficiency of SCLC patients from low PD-L1 expression, downregulation of major histocompatibility complex (MHC) molecules, a less immunogenic environment, and unique autocrine and paracrine regulation.[22] Consequently, C + I or

I + A might be better than single or double ICIs to improve clinical efficacy.

As for the choice of chemotherapy in the second-line setting, we observed a similar PFS2 between paclitaxel-based therapy and topoisomerase inhibitor-based therapy. While topotecan is preferred in the NCCN guidelines, there are no relevant studies of topoisomerase inhibitors plus ICIs reported in relapsed ES-SCLC, but there are several ongoing clinical trials to keep an eye on in the future (NCT05353439, NCT05027100, NCT04607954, and NCT04173325, etc., collected by ClinicalTrials.gov as of May 26, 2022). Among them, MC1923 (NCT04607954) is a phase II clinical trial of durvalumab and topotecan or lurbinectedin in ES-SCLC patients progressed after first-line C + I therapy. Beyond exploring the efficacy of combining two chemotherapeutic agents with immunotherapy, MC1923 compares the efficacy of lurbinectedin for platinum-sensitive and platinum-resistant patients, which is worth noting.[23]

The paclitaxel regimen showed antitumor activity in single-arm phase II studies of second-line ES-SCLC treatment and is also recommended in the NCCN guidelines.[8] Nab-PTX, a nanoparticle conjugate of paclitaxel and albumin, displays high efficiency and low toxicity compared with other paclitaxel therapies. However, a phase II NABSTER prospective trial of nab-PTX did not meet its primary endpoint, with an ORR of 11.8% and DCR of 30.9% in patients who progressed to first-line chemotherapy.[24] The results for nab-PTX alone for relapsed ES-SCLC from retrospective studies remained variable, with ORR of 5.6–29.4%, DCR of 44.4–81.1%, median PFS of 1.6–5.0 months, and median OS of 4.0–9.0 months, but lacking large sample data and drug comparisons.[25–28] It is therefore inconclusive whether or not nab-PTX alone can be used in second-line or subsequent-lines treatment. Similar to the clinical trial of pembrolizumab plus paclitaxel by Kim et al.,[19] our data for ICIs plus paclitaxel (mainly nab-PTX) also showed a favorable antitumor effect for ES-SCLC in second-line treatment. Several studies have shown a regulation role of paclitaxel in various immune cells,[29] which may complement ICI application. Our study therefore suggests that nab-PTX could be selected as a chemotherapy option for second-line C + I therapy, filling a gap in this area.

The present study has some limitations. First, the retrospective nature of data collection can introduce unavoidable selection bias and critical information is missing, especially for biomarkers of immunotherapy. Previous studies cast doubt on whether PD-L1 and TMB can be predictors of ICIs efficacy.[30] Because only a few patients were tested for PD-L1 expression and TMB level in our study, we were unable to conduct further analysis. Thus, since C + I in a first-line setting has only been applied in recent years, the insufficient follow-up time results in less mature OS data. Furthermore, future research will require a larger sample size to verify our results.

CONCLUSIONS

This research provided a comprehensive analysis of treatment patterns and outcomes of immunotherapy in ES-SCLC in real-world practice. First-line C + I should be applied in clinical practice based on prospective and retrospective evidence. If patients did not receive C + I in first-line therapy, ICIs-combination patterns in the second-line setting should be considered. Future prospective studies are expected to determine the optimal drug selection.

ORCID
Haiyan Xu https://orcid.org/0000-0002-0048-3191
Lu Yang https://orcid.org/0000-0002-4286-9586
Yan Wang https://orcid.org/0000-0002-1743-6383

REFERENCES
1. Hiddinga BI, Raskin J, Janssens A, Pauwels P, Van Meerbeeck JP. Recent developments in the treatment of small cell lung cancer. Eur Respir Rev. 2021;30(161):210079.
2. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primers. 2021;7(1):3.
3. Roth BJ, Johnson DH, Einhorn LH, Schacter LP, Cherng NC, Cohen HJ, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III

trial of the southeastern cancer study group. J Clin Oncol. 1992;10(2): 282–91.

4. Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018;379(23):2220–9.

5. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, 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. 2019;394(10212):1929–39.

6. Spigel DR, Vicente D, Ciuleanu TE, Gettinger S, Peters S, Horn L, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331. Ann Oncol. 2021;32(5):631–41.

7. Pujol JL, Greillier L, Audigier-Valette C, Moro-Sibilot D, Uwer L, Hureaux J, et al. A randomized non-comparative phase II study of anti-programmed cell death-ligand 1 Atezolizumab or chemotherapy as second-line therapy in patients with small cell lung cancer: results from the IFCT-1603 trial. J Thorac Oncol. 2019;14(5):903–13.

8. Ganti AKP, Loo BW, Bassetti M, Blakely C, Chiang A, D'Amico TA, et al. Small cell lung cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2021;19(12):1441–64.

9. Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csőszi T, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol. 2020; 38(21):2369–79.

10. Owonikoko TK, Kim HR, Govindan R, et al. Nivolumab (nivo) plus ipilimumab (ipi), nivo, or placebo (pbo) as maintenance therapy in patients (pts) with extensive disease small cell lung cancer (ED-SCLC) after first-line (1L) platinum-based chemotherapy (chemo): results from the double-blind, randomized phase III CheckMate 451 study. Ann Oncol. 2019;30:77–7.

11. Cheng Y, Han L, Wu L, Chen J, Sun H, Wen G, et al. Serplulimab, a novel anti-PD-1 antibody, plus chemotherapy versus chemotherapy alone as first-line treatment for extensive-stage small-cell lung cancer: an international randomized phase 3 study. J Clin Oncol. 2022;40-(16_suppl):8505–5.

12. von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol. 1999;17(2):658–67.

13. Trigo J, Subbiah V, Besse B, Moreno V, López R, Sala MA, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020;21(5):645–54.

14. Gandara DR, von Pawel J, Mazieres J, Sullivan R, Helland Å, Han JY, et al. Atezolizumab treatment beyond progression in advanced NSCLC: results from the randomized, phase III OAK study. J Thorac Oncol. 2018;13(12):1906–18.

15. Ge X, Zhang Z, Zhang S, Yuan F, Zhang F, Yan X, et al. Immunotherapy beyond progression in patients with advanced non-small cell lung cancer. Transl Lung Cancer Res. 2020;9(6):2391–400.

16. Stinchcombe TE, Miksad RA, Gossai A, Griffith SD, Torres AZ. Real-world outcomes for advanced non-small cell lung cancer patients treated with a PD-L1 inhibitor beyond progression. Clin Lung Cancer. 2020;21(5):389–394.e383.

17. Ready N, Farago AF, de Braud F, Atmaca A, Hellmann MD, Schneider JG, et al. Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Oncol. 2019;14(2):237–44.

18. Chung HC, Piha-Paul SA, Lopez-Martin J, Schellens JHM, Kao S, Miller WH Jr, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: results

from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol. 2020;15(4):618–27.

19. Kim YJ, Keam B, Ock CY, Song S, Kim M, Kim SH, et al. A phase II study of pembrolizumab and paclitaxel in patients with relapsed or refractory small-cell lung cancer. Lung Cancer. 2019;136:122–8.

20. Fan Y, Zhao J, Wang Q, Huang D, Li X, Chen J, et al. Camrelizumab plus apatinib in extensive-stage SCLC (PASSION): a multicenter, two-stage, phase 2 trial. J Thorac Oncol. 2021;16(2):299–309.

21. Ready NE, Ott PA, Hellmann MD, Zugazagoitia J, Hann CL, de Braud F, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. J Thorac Oncol. 2020;15(3):426–35.

22. Tian Y, Zhai X, Han A, Zhu H, Yu J. Potential immune escape mechanisms underlying the distinct clinical outcome of immune checkpoint blockades in small cell lung cancer. J Hematol Oncol. 2019;12(1):67.

23. Leventakos K, Dimou A, Foster NR, Flickinger LM, Tella SH, Molina JR, et al. MC1923 phase II clinical trial of durvalumab (MEDI4736) and topotecan or lurbinectedin in patients with relapsed extensive-stage small cell lung cancer previously treated with chemotherapy and immunotherapy. J Clin Oncol. 2022;40(16_suppl): TPS8604–4.

24. Gelsomino F, Tiseo M, Barbieri F, Riccardi F, Cavanna L, Frassoldati A, et al. Phase 2 study of NAB-paclitaxel in SensiTivE and refractory relapsed small cell lung cancer (SCLC) (NABSTER TRIAL). Br J Cancer. 2020;123(1):26–32.

25. Oi H, Matsuda T, Kimura T, Morise M, Yamano Y, Yokoyama T, et al. Weekly nanoparticle albumin-bound paclitaxel and paclitaxel for relapsed small cell lung cancer: a retrospective observational study. Medicine. 2022;101(6):e28863.

26. Wang Y, Li L, Xu C. Nanoparticle albumin bound paclitaxel in the third-line treatment of recurrent small cell lung cancer in real-world practice: a single center experience. Technol Cancer Res Treat. 2021; 20:15330338211050775.

27. Nakao M, Fujita K, Suzuki Y, et al. Nab-paclitaxel monotherapy for relapsed small cell lung cancer: retrospective analysis and review. Anticancer Res. 2020;40(3):1579–85.

28. Naito Y, Tamiya A, Tamiya M, Kimura Y, Hamaguchi M, Saijo N, et al. Efficacy of nanoparticle albumin-bound paclitaxel regimens for relapsed small cell lung cancer: a retrospective analysis. Medicine. 2017;96(35):e7884.

29. Zhu L, Chen L. Progress in research on paclitaxel and tumor immunotherapy. Cell Mol Biol Lett. 2019;24:40.

30. Ortega-Franco A, Ackermann C, Paz-Ares L, Califano R. First-line immune checkpoint inhibitors for extensive stage small-cell lung cancer: clinical developments and future directions. ESMO Open. 2021; 6(1):100003.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.