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Efficacy and safety of PD-1 inhibitors plus chemotherapy with or without endostatin for stage IV lung squamous cancer: a retrospective study

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Background: The study aimed to analyze the efficacy and safety of PD-1 inhibitors plus chemotherapy with or without endostatin for stage IV lung squamous cell carcinoma (LUSC).

Methods: A total of 219 patients with stage IV LUSC were included. 120 received PD-1 inhibitors plus chemotherapy with or without endostatin (IC ± A), of which 39 received endostatin (IC+A) and 81 did not receive endostatin (IC-A). 99 received chemotherapy with or without endostatin (C ± A). Endpoints included overall survival (OS), progression-free survival (PFS), adverse events (AEs), and immune-related adverse events (irAEs).

Results: The median PFS in the IC ± A group versus the C ± A group was 8 and 4 months ($P < 0.001$), and the median OS was 17 and 9 months ($P < 0.001$). There was no significant difference in any grade AEs between the IC ± A and C ± A groups ($P > 0.05$). The median PFS in the IC+A group versus the IC-A group was 11 and 7 months ($P = 0.024$), and the median OS was 34 and 15 months ($P = 0.01$). There was no significant difference between the IC+A group and the IC-A group for all grade AEs and irAEs ($P > 0.05$). The subgroup analysis showed that patients with LIPI = 0 had significant OS and PFS benefits in IC+A group, while for patients with LIPI = 1–2, there was no significant difference in OS and PFS benefits between the IC+A group and IC-A group.

Conclusions: PD-1 inhibitors plus chemotherapy with endostatin might be first-line treatment for patients with stage IV LUSC.

KEYWORDS

lung squamous cell carcinoma, PD-1 inhibitor, chemotherapy, endostatin, lung immune prognostic index

1 Introduction

Stage IV lung squamous cell carcinoma (LUSC) typically carries a poor prognosis (1, 2). However, survival rates among LUSC patients have improved with the application of immune checkpoint inhibitors (ICIs), particularly PD-1 inhibitors. Consequent to data unearthed from several clinical studies, the combination of PD-1 inhibitors with chemotherapy has emerged as the standard first-line treatment for stage IV driver gene-negative LUSC (3–6). While this combination enhances survival rates in patients with advanced LUSC, the emergence of drug resistance remains a critical concern, limiting the potential benefits (7, 8).

Endostatin (recombinant human vascular endostatin), targeting the endothelial cells of tumor vasculature, inhibits neovascularization, thereby impeding nutrient supply to tumor cells and curbing their proliferation and metastasis (9). As an anti-angiogenic agent, endostatin influences the tumor immune microenvironment similarly to PD-1 inhibitors, providing a rationale for their concurrent use (9, 10). A retrospective clinical study has demonstrated that the combination of ICIs with endostatin offers greater efficacy and safety than the combination of ICIs with chemotherapy in treating advanced non-small cell lung cancer (NSCLC) (11). Furthermore, Phase II clinical trials in the Lung-MAP S1800A study have shown that combining pembrolizumab with ramucirumab leads to improved efficacy and survival outcomes for patients with advanced LUSC (12).

Our research focuses on determining the potential of endostatin to enhance the efficacy of PD-1 inhibitors in conjunction with chemotherapy for treating stage IV LUSC. Given the insufficient clinical evidence to support the combined usage of PD-1 inhibitors, chemotherapy, and endostatin, our study is designed to evaluate the efficacy and safety of this treatment regimen. Specifically, we aim to elucidate endostatin's impact on the outcome and adverse effects when simultaneously administered with PD-1 inhibitors and chemotherapy in stage IV LUSC patients.

2 Methods

2.1 Patients

This retrospective study included patients diagnosed with stage IV LUSC at our hospital from 2018 to 2023 who were first-line received PD-1 inhibitor combined with chemotherapy or chemotherapy alone with or without endostatin therapy. Inclusion criteria: (1) pathological diagnosis was LUSC; (2)

clinical stage was stage IV; (3) Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0–2. Exclusion criteria: (1) patients' age less than 18 years or over 85 years; (2) patients with other primary malignancies; (3) lack of clinical hematological and imaging data. All patients were clinically staged using the 8th edition of the American Joint Committee on Cancer (AJCC) TNM staging system. According to the inclusion and exclusion criteria, 219 patients with stage IV LUSC were finally enrolled.

2.2 Data collections

Clinical data included baseline data before receiving anti-tumor therapy: gender, age, ECOG PS, smoking history, histological type, clinical stage, distant metastatic (brain, liver, bone), PD-L1 expression level, and Lung Immune Prognostic Index (LIPI). LIPI is based on the derived neutrophil to lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH), $dNLR = \text{baseline neutrophil count} / (\text{white blood cell} - \text{neutrophil count})$, and is calculated as 1 point for dNLR greater than 3 or LDH greater than normal. Patients are divided into two groups with good (0 points) and poor (1–2 points) prognosis (13, 14). Other relevant clinical data: anti-tumor drugs, chemotherapy cycle, survival events, treatment efficacy, AEs and irAEs.

2.3 Treatment regimen

IC ± A group received PD-1 inhibitor plus chemotherapy with or without endostatin, IC + A group received PD-1 inhibitor plus chemotherapy plus endostatin, IC-A group received PD-1 inhibitor plus chemotherapy without endostatin, C ± A group received chemotherapy with or without endostatin. PD-1 inhibitors: pembrolizumab (200 mg iv q3w d1) or sintilimab (200 mg iv q3w d1) or camrelizumab (200 mg iv q3w d1) or tislelizumab (200 mg iv q3w d1). Chemotherapy: paclitaxel (175 mg/m² iv q3w d1) plus carboplatin (400 mg/m² iv q3w d1) or cisplatin (100 mg/m² iv q3w d1). Endostatin: (15 mg qd iv q3w d0–6) was given intravenously at a dose of 15 mg for 3 hours once daily for 7 days. All patients received two cycles of treatment at least.

2.4 Outcomes

Overall survival (OS) is defined as the time between the first treatment and death from any cause or the last follow-up. Progression-free survival (PFS) is the time from the first treatment to disease progression, death from any cause, or the last follow-up. Objective response rate (ORR) is defined as the proportion of patients who achieve complete response (CR) or partial response (PR). Disease control rate (DCR) is defined as the proportion of patients who achieve CR, PR, and stable disease (SD). RECIST1.1 solid tumor evaluation criteria were used for short-term efficacy evaluation. All patients were followed up until September 2023.

Abbreviations: LUSC, lung squamous cell carcinoma; ICIs, immune checkpoint inhibitors; LIPI, lung immune prognostic index; dNLR, derived neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; PFS, progression-free survival; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; AEs, adverse events; irAEs, immune-related adverse events; ORR, objective response rate; DCR, disease control rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

2.5 Adverse events

Adverse events (AEs) and immune-related adverse events (irAEs) occurred during treatment were collected through the medical record system. AEs included anemia, neutropenia, thrombocytopenia, alanine aminotransferase (ALT) elevation, creatinine elevation, nausea, vomiting, decreased appetite, bronchial or pulmonary infection, rash, diarrhea, pain, and insomnia. irAEs included hyperthyroidism, hypothyroidism, adrenocortical insufficiency, pneumonia, severe skin reaction, hepatitis, nephritis, colitis, myocarditis, hypophysitis, pancreatitis, arthritis, peripheral neuropathy, and cardiac arrhythmias. All adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 5.0).

2.6 Statistical analysis

We used Pearson's chi-square test or Fisher's exact test to compare categorical variables. The Kaplan-Meier method was used to plot survival curves, and the log-rank test was used for differences between survival curves. Variables with a P value ≤ 0.05 in univariate Cox analysis were included in the multivariate Cox analysis. Multivariate Cox analysis was used to determine independent prognostic factors affecting OS and PFS. Therefore, a statistical result P value < 0.05 was considered statistically significant. All analyses were performed using SPSS 25.0 (IBM, Armonk, NY, USA) for all of the above statistical analyses.

3 Result

3.1 Patient characteristics

A total of 219 patients with stage IV LUSC were enrolled in our study. The baseline characteristics are shown in **Tables 1, 2**. There were 120 patients in the IC \pm A group and 99 patients in the C \pm A group. There were 39 patients in the IC+A group and 81 patients in the IC-A group. The IC \pm A group and the C \pm A group, the IC+A group and the IC-A group were mostly male, ECOG PS 0–1, smoking history, stage IVA, no brain metastasis, no liver metastasis, no bone metastasis, and the chemotherapy cycle ≥ 4 . Except for the PD-L1 expression status, there were no statistical differences in other baseline characteristics between the IC \pm A group and the C \pm A group. There was no statistical difference in baseline characteristics between the IC+A group and the IC-A group.

3.2 Outcome and efficacy analysis

Until September 2023, 105 PFS events (87.5%) and 76 OS events (63.4%) occurred in the IC \pm A group and 99 PFS events (100%) and 96 OS events (97%) occurred in the C \pm A group. The median OS was 17 (95% CI: 15–19) and 9 (95% CI: 6.6–11.4) months ($P < 0.001$, **Figure 1A**), and the median PFS of the IC \pm A group and the

TABLE 1 Baseline characteristics of IC \pm A and C \pm A.

Characteristics	IC \pm A group (n=120)	C \pm A group (n=99)	P value
Age			0.308
≤65	76 (63.3%)	56 (56.6%)	
>65	44 (36.7%)	43 (43.4%)	
Gender			0.505
Male	112 (93.3%)	90 (90.9%)	
Female	8 (6.7%)	9 (9.1%)	
ECOG PS			0.837
0-1	103 (85.8%)	84 (84.8%)	
2	17 (14.2%)	15 (15.2%)	
Smoking history			0.747
Yes	99 (82.5%)	80 (80.8%)	
No	21 (17.5%)	19 (19.2%)	
PD-L1			< 0.001
Negative	26 (21.7%)	15 (15.2%)	
1-49%	31 (25.8%)	6 (6.1%)	
$\geq 50\%$	13 (10.8%)	4 (4%)	
Unknown	50 (41.7%)	74 (74.7%)	
Clinical stage			0.487
IVA	99 (82.5%)	78 (78.8%)	
IVB	21 (17.5%)	21 (21.2%)	
Brain metastases			0.523
No	117 (97.5%)	94 (94.9%)	
Yes	3 (2.5%)	5 (5.1%)	
Liver metastases			0.898
No	106 (88.3%)	88 (88.9%)	
Yes	14 (11.7%)	11 (11.1%)	
Bone metastases			0.493
No	95 (79.2%)	82 (82.8%)	
Yes	25 (20.8%)	17 (17.2%)	
Endostatin therapy			0.896
Yes	39 (32.5%)	33 (33.3%)	
No	81 (67.5%)	66 (66.7%)	
Chemotherapy cycle			0.305
2-3	19 (15.8%)	21 (21.2%)	
≥ 4	101 (84.2%)	78 (78.8%)	
LIPI			0.557
0	69 (57.5%)	53 (53.5%)	
1-2	51 (42.5%)	46 (46.5%)	

C \pm A group was 8 (95% CI: 6.9–9.1) and 4 (95% CI: 3.2–4.8) months respectively ($P < 0.001$, **Figure 1B**). The IC \pm A group had longer median PFS and median OS than the C \pm A group. In addition, 2 patients (1.6%) achieved CR, 57 patients (47.5%) achieved PR, 44 patients (36.7%) achieved SD, and 17 patients (14.2%) achieved PD in the IC \pm A group, with an ORR of 49.2% and a DCR of 85.8%. In the C \pm A group, 33 patients (30.3%) achieved PR, 45 patients (45.5%) achieved SD, and 29 patients (29.3%) achieved PD, with an ORR of 25.3% and a DCR of 70.7% (**Table 3**). The ORR ($P < 0.001$) and DCR ($P = 0.006$) were better in the IC \pm A group than in the C \pm A group.

Thirty-nine patients in the IC+A group had PFS events in 33 (84.6%) and OS events in 20 (51.2%). Eighty-one patients in the IC-A group had PFS events in 72 (88.8%) and OS events in 56 (69.1%). The median OS was 34 (95% CI: 9.6–58.4) and 15 (95% CI: 13.1–16.9)

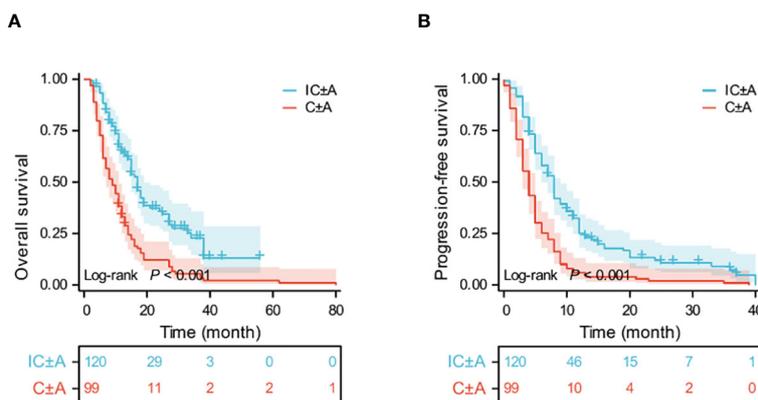


FIGURE 1

Kaplan-Meier estimates of OS (A) and PFS (B) in the IC ± A and C ± A population; IC ± A, PD-1 inhibitor plus chemotherapy with or without endostatin; C ± A, chemotherapy with or without endostatin; OS, overall survival; PFS, progression-free survival; Time, month.

months ($P = 0.01$, Figure 2A), and the median PFS in the IC+A group and the IC-A group was 11 (95% CI: 7.8–14.2) and 7 (95% CI: 5.5–8.5) months respectively ($P = 0.024$, Figure 2B), and The median PFS and median OS of the IC+A group were longer than those of the IC-A. In the IC+A group, 1 patient (2.6%) achieved CR, 23 patients (59%) achieved PR, 9 patients (23.1%) achieved SD, and 6 patients (15.4%) achieved PD, with an ORR of 61.5% and a DCR of 84.6%. In the IC-A group, 1 patient (1.2%) achieved CR, 34 patients (42%) achieved PR, 35 patients (43.2%) achieved SD, and 11 patients (13.6%) achieved PD, with an ORR of 43.2% and a DCR of 86.4% (Table 3). There was no statistical difference in ORR and DCR between the IC+A group and the IC-A group.

3.3 Predictors affecting efficacy in the IC ± A group

Multivariate analysis showed that ECOG PS (HR:2.718, 95% CI:1.491–4.953, $P = 0.001$), PD-L1 $\geq 50\%$ (HR:0.260, 95%CI:0.076–0.889, $P = 0.032$), plus endostatin (HR:0.501, 95%CI:0.289–0.867, $P = 0.014$), chemotherapy cycle ≥ 4 (HR:0.238, 95%CI: 0.124–0.458, $P < 0.001$), LIPI 0 score (HR:1.672, 95%CI:1.012–2.761, $P = 0.045$) were independent prognostic factors for OS (Table 4). In addition, PD-L1 $\geq 50\%$ (HR:0.392, 95%CI:0.170–0.904, $P = 0.028$), chemotherapy cycle ≥ 4 (HR:0.312, 95%CI:0.183–0.531, $P < 0.001$), LIPI 0 score (HR:1.821, 95%CI:1.176–2.822, $P = 0.007$) were independent prognostic factors for PFS (Table 5).

3.4 Subgroup analysis

Subgroup analysis of IC ± A and C ± A groups showed that IC ± A had an OS benefit in all subgroups except women ($P = 0.68$), ECOG PS score 2 ($P = 0.322$), no history of smoking ($P = 0.212$), PD-L1 expression 1–49% ($P = 0.338$), brain metastases ($P = 0.51$), and LIPI score 1–2 ($P = 0.08$) (Figure 3A). Subgroup analysis in the IC ± A and C ± A groups showed that IC ± A had a PFS benefit, except for women ($P = 0.966$), no history of smoking ($P = 0.194$), PD-L1

expression 1–49% ($P = 0.082$), brain metastases ($P = 0.856$), and LIPI scores 1–2 ($P = 0.347$) (Figure 3B).

The results of the subgroup analysis of IC+A and IC-A are shown in Figure 4. Patients with age ≤ 65 ($P = 0.017$), male ($P = 0.018$), ECOG PS = 0–1 ($P = 0.021$), smoking history ($P = 0.011$), stage IVA ($P = 0.004$), no brain metastasis ($P = 0.017$), no liver metastasis ($P = 0.012$), no bone metastasis ($P = 0.01$), chemotherapy cycles 2–3 ($P = 0.042$), chemotherapy cycles ≥ 4 ($P = 0.03$), and LIPI score of 0 ($P = 0.021$) had better OS when receiving IC+A treatment (Figure 4A). Patients who were male ($P = 0.043$), history of smoking ($P = 0.038$), IVA ($P = 0.03$), no brain metastasis ($P = 0.04$), no liver metastasis ($P = 0.02$), no bone metastasis ($P = 0.02$), chemotherapy cycles ≥ 4 ($P = 0.03$), and LIPI score of 0 ($P = 0.029$) had a better PFS when treated with IC+A (Figure 4B).

3.5 Safety and adverse events

The adverse events in each group are shown in Tables 6, 7, and the chi-square test for adverse events in each group is shown in Table 8. There were 116 (96.6%) any grade AEs and 72 (60%) grade 3–4 AEs in the IC ± A group, while there were 93 (93.9%) any grade AEs and 59 (59.5%) grade 3–4 AEs in the IC-A group. There was no statistical difference in any grade AEs and grade 3–4 AEs between IC ± A and C ± A groups ($P > 0.05$). In addition, there were 38 (97.4%) and 78 (96.2%) any grade AEs, 24 (61.5%) and 48 (59.2%) grade 3–4 AEs, 14 (35.9%) and 25 (30.9%) any grade irAEs, and 4 (10.2%) and 8 (9.9%) grade 3–4 irAEs in the IC+A group and the IC-A group, respectively. No statistical differences were observed in all AEs, grade 3–4 AEs, any grade irAEs and grade 3–4 irAEs between IC + A and IC-A groups.

Incidence rates for all adverse events (AEs) were comparable between the IC+A and IC-A cohorts. Common grade 3–4 AEs for patients undergoing IC+A versus IC-A treatment were as follows: anemia (25.6% vs 18.5%, $P = 0.252$), neutropenia (23.0% vs 14.8%, $P = 0.194$), thrombocytopenia (12.8% vs 6.1%, $P = 0.187$), and ALT elevation (5.1% vs 6.1%, $P = 0.59$). Regarding immune-

TABLE 2 Baseline characteristics of IC+A and IC-A.

Characteristics	IC+A group (n=39)	IC-A group (n=81)	P value
Age			0.082
≤65	29 (74.4%)	47 (58%)	
>65	10 (25.6%)	34 (42%)	
Gender			0.714
Male	36 (92.3%)	76 (93.8%)	
Female	3 (7.7%)	5 (6.2%)	
ECOG PS			0.769
0-1	34 (87.2%)	69 (85.2%)	
2	5 (12.8%)	12 (14.8%)	
Smoking history			0.147
Yes	35 (89.7%)	64 (79%)	
No	4 (10.3%)	17 (21%)	
PD-L1			0.206
Negative	7 (17.9%)	19 (23.5%)	
1-49%	12(30.9%)	19(23.5%)	
≥50%	7 (17.9%)	6 (7.4%)	
Unknown	13 (33.3%)	37 (45.6%)	
Clinical stage			0.147
IVA	35(89.7%)	64 (79%)	
IVB	4 (10.3%)	17 (21%)	
Brain metastases			0.553
No	39(100%)	78 (96.3%)	
Yes	0 (0%)	3 (3.7%)	
Liver metastases			0.524
No	36 (92.3%)	70 (86.4%)	
Yes	3 (7.7%)	11 (13.6%)	
Bone metastases			0.308
No	33 (84.6%)	62 (76.5%)	
Yes	6 (15.4%)	19 (23.5%)	
Chemotherapy cycle			0.660
2-3	7 (17.9%)	12 (14.8%)	
≥4	32 (82.1%)	69 (85.2%)	
LIPI			0.310
0	25 (64.1%)	44 (54.3%)	
1-2	14 (35.9%)	37 (45.7%)	
PD-1 inhibitors			0.938
Pembrolizumab	12(30.8%)	29(35.8%)	
Tislelizumab	9(23.1%)	17(21.0%)	
Sintilimab	11(28.2%)	23(28.4%)	
Camrelizumab	7(17.9%)	12(14.8%)	
Chemotherapy			0.692
Carboplatin	26(66.7%)	51(62.9%)	
Cisplatin	13(33.4%)	30(37.1%)	

related adverse events (irAEs), the prevalences in patients treated with IC+A versus IC-A were hypothyroidism (15.3% vs 11.1%, $P = 0.328$), hyperthyroidism (7.6% vs 6.1%, $P = 0.514$), and pneumonia (10.2% vs 6.1%, $P = 0.325$).

TABLE 3 Evaluation of outcomes in 219 patients with Stage IV LUSC.

Characteristics	IC ± A (n=120)	C ± A (n=99)	P value
Best response, n (%)			0.001
CR	2 (1.7%)	0 (0%)	
PR	57 (47.5%)	25 (25.3%)	
SD	44 (36.7%)	45 (45.5%)	
PD	17 (14.2%)	29 (29.3%)	
ORR, n (%)	59 (49.2%)	25 (25.3%)	< 0.001
DCR, n (%)	103 (85.8%)	70 (70.7%)	0.006
Characteristics	IC-A (n=81)	IC+A (n=39)	P value
Best response, n (%)			0.183
SD	35 (43.2%)	9 (23.1%)	
PD	11 (13.6%)	6 (15.4%)	
PR	34 (42%)	23 (59%)	
CR	1 (1.2%)	1 (2.6%)	
ORR, n (%)	35 (43.2%)	24 (61.5%)	0.060
DCR, n (%)	70 (86.4%)	33 (84.6%)	0.791

4 Discussion

In patients with early-stage LUSC, the combination of PD-1 inhibitors and chemotherapy markedly decreases recurrence rates and improves prognosis. Similarly, for patients with locally advanced unresectable LUSC, this combined therapeutic approach reduces the risk of metastasis and enhances prognosis. However, the majority of patients present with advanced-stage disease at diagnosis, and the median OS for those receiving first-line PD-1 inhibitors and chemotherapy is only 17.2 months (1–3). Endostatin, an antiangiogenic agent, has been demonstrated in preclinical studies to synergistically enhance the impact of PD-1 inhibitors on lung tumor suppression (15). However, clinical evidence is sparse regarding the additional survival benefits conferred by endostatin in patients with stage IV LUSC, who are also receiving PD-1 inhibitors and chemotherapy. Thus, our research represents the initial effort to substantiate the applicability of combining a PD-1 inhibitor with chemotherapy and endostatin for first-line treatment in this patient population. Our findings indicate that the median OS and PFS for this regimen were 34 months and 11 months, respectively. Overall, AEs and irAEs were within acceptable safety margins and manageable. These results imply that incorporating endostatin with PD-1 inhibitors and chemotherapy may offer a novel first-line therapeutic option for stage IV LUSC.

In advanced LUSC, the combination of PD-1 inhibitors with chemotherapy has become a standard approach in clinical settings. Data from several clinical trials have established that this combination therapy provides superior ORR, DCR, PFS, and OS compared with chemotherapy alone (3–6). Our study aligns with

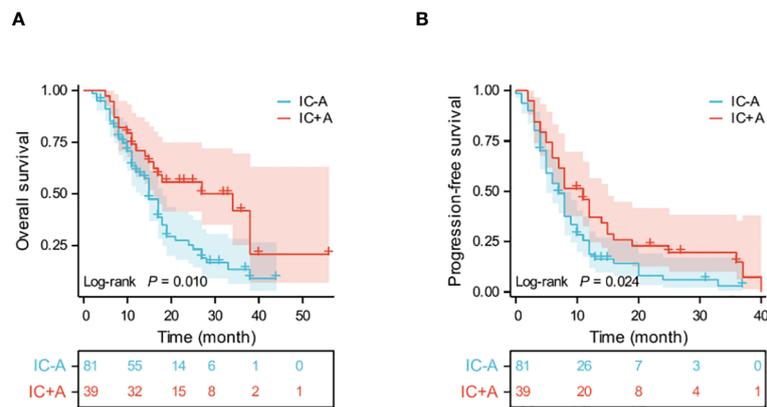


FIGURE 2 Kaplan-Meier estimates of OS (A) and PFS (B) in the IC+A and IC-A population; IC+A,PD-1 inhibitor plus chemotherapy with endostatin; IC-A,PD-1 inhibitor plus chemotherapy without endostatin; OS, overall survival; PFS, progression-free survival; Time, month.

TABLE 4 Univariate and multivariate Cox analysis of OS in the IC±A group.

Characteristics		Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age	≤65	Reference			
	>65	1.279 (0.811-2.017)	0.290		
Gender	Female	Reference			
	Male	0.665 (0.288-1.538)	0.340		
ECOG PS	0-1	Reference		Reference	
	2	2.669 (1.551-4.595)	<0.001	2.718 (1.491-4.953)	0.001
Smoking history	No	Reference			
	Yes	0.959 (0.535-1.720)	0.888		
PD-L1	Negative	Reference		Reference	
	1-49%	0.914 (0.498-1.678)	0.771	1.083 (0.582-2.012)	0.802
	≥50%	0.192 (0.057-0.648)	0.008	0.260 (0.076-0.889)	0.032
	Unknown	0.759 (0.431-1.337)	0.340	0.654 (0.364-1.176)	0.156
Clinical stage	IVA	Reference			
	IVB	1.190 (0.665-2.128)	0.558		
Brain metastases	No	Reference			
	Yes	1.489 (0.467-0.750)	0.501		
Liver metastases	No	Reference			
	Yes	0.952 (0.473-1.914)	0.889		
Bone metastases	No	Reference			
	Yes	0.826 (0.475-1.436)	0.497		
Endostatin therapy	No	Reference		Reference	
	Yes	0.524 (0.313-0.878)	0.014	0.501 (0.289-0.867)	0.014
Chemotherapy cycle	2-3	Reference		Reference	

(Continued)

TABLE 4 Continued

Characteristics		Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
	≥4	0.329 (0.180-0.603)	<0.001	0.238 (0.124-0.458)	<0.001
LIPI	0	Reference		Reference	
	1-2	2.266 (1.408-3.646)	0.001	1.672 (1.012-2.761)	0.045
PD-1 inhibitors	Pembrolizumab	Reference			
	Tislelizumab	1.250 (0.640-2.441)	0.513		
	Sintilimab	1.300 (0.623-2.713)	0.485		
	Camrelizumab	1.296 (0.595-2.821)	0.514		
Chemotherapy	Carboplatin	Reference			
	Cisplatin	0.999 (0.626-1.595)	0.998		

TABLE 5 Univariate and multivariate Cox analysis of PFS in the IC±A group.

Characteristics		Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Age	≤65	Reference			
	>65	1.254 (0.845-1.860)	0.261		
Gender	Female	Reference			
	Male	0.547 (0.264-1.133)	0.105		
ECOG PS	0-1	Reference		Reference	
	2	1.909 (1.131-3.221)	0.015	1.453 (0.812-2.601)	0.208
Smoking history	No	Reference			
	Yes	0.843 (0.516-1.377)	0.496		
PD-L1	Negative	Reference		Reference	
	1-49%	0.606 (0.348-1.056)	0.077	0.623 (0.355-1.094)	0.100
	≥50%	0.289 (0.128-0.650)	0.003	0.392 (0.170-0.904)	0.028
	Unknown	0.627 (0.385-1.021)	0.060	0.552 (0.334-0.913)	0.021
Clinical stage	IVA	Reference			
	IVB	0.924 (0.549-1.556)	0.766		
Brain metastases	No	Reference			
	Yes	1.533 (0.483-4.871)	0.468		
Liver metastases	No	Reference			
	Yes	0.949 (0.518-1.736)	0.864		
Bone metastases	No	Reference			
	Yes	0.752 (0.460-1.227)	0.254		
Endostatin therapy	No	Reference		Reference	
	Yes	0.631 (0.413-0.965)	0.034	0.671 (0.427-1.055)	0.084
Chemotherapy cycle	2-3	Reference		Reference	
	≥4	0.337 (0.202-0.562)	<0.001	0.312 (0.183-0.531)	<0.001

(Continued)

TABLE 5 Continued

Characteristics		Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
LIPI	0	Reference		Reference	
	1-2	2.079 (1.380-3.133)	<0.001	1.821 (1.176-2.822)	0.007
PD-1 inhibitors	Pembrolizumab	Reference			
	Tislelizumab	1.182 (0.655-2.134)	0.578		
	Sintilimab	1.556 (0.840-2.883)	0.160		
Chemotherapy	Carboplatin	Reference			
	Cisplatin	0.909 (0.611-1.354)	0.640		

these findings, demonstrating that, regardless of PD-L1 expression levels, the incorporation of PD-1 inhibitors with chemotherapy confers a greater survival advantage in the first-line management of stage IV LUSC. Despite these improvements, the survival benefit of anti-PD-1 therapy in combination with chemotherapy remains modest for patients with stage IV LUSC.

In 1971, Judah Folkman pioneered the concept of tumor treatment by inhibiting angiogenesis, proposing the theory that tumor proliferation depends on the formation of new blood vessels to supply essential nutrients. He posited that interrupting the tumor's blood supply could effectively starve the tumor (16). As an angiogenesis inhibitor, endostatin has undergone extensive clinical trials, demonstrating its capacity to target neovascular endothelial cells and suppress tumor growth (17). Notably, one case study reported that the addition of endostatin to PD-1 inhibitors and chemotherapy yielded significant results in treating stage IV LUSC (18). Furthermore, the combination has been attributed with promising

efficacy and acceptable safety in the primary treatment of advanced NSCLC (10, 19). Consequently, our retrospective analysis scrutinized the efficacy and safety of PD-1 inhibition with chemotherapy, both with and without the addition of endostatin, in stage IV LUSC treatment. The addition of endostatin was found to markedly enhance OS and PFS in patients. Multivariate Cox regression analysis reinforced the view that endostatin's synergistic use constitutes an independent prognostic indicator for stage IV LUSC patients undergoing PD-1 inhibitor and chemotherapy treatment. These findings endorse the combination of PD-1 inhibitors, chemotherapy, and endostatin as an emergent first-line treatment modality for stage IV LUSC, meriting adoption in clinical practice.

It is unclear whether the combination of PD-1 inhibitors with chemotherapy and endostatin is effective for all stage IV LUSC patients. Our study conducted a subgroup stratification analysis and found that, in most subgroups—including male patients, smokers, those with an ECOG PS 0–1, stage IVA, and patients without liver,

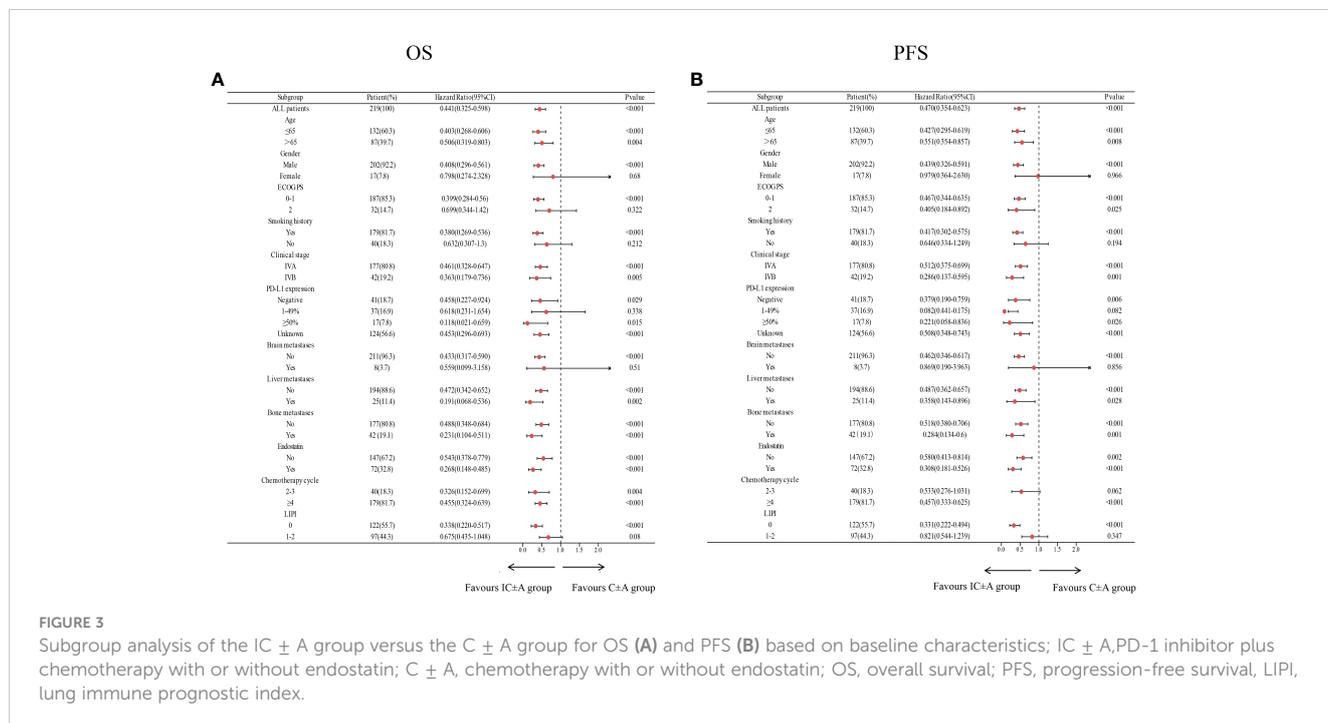


FIGURE 3

Subgroup analysis of the IC ± A group versus the C ± A group for OS (A) and PFS (B) based on baseline characteristics; IC ± A, PD-1 inhibitor plus chemotherapy with or without endostatin; C ± A, chemotherapy with or without endostatin; OS, overall survival; PFS, progression-free survival, LIPI, lung immune prognostic index.

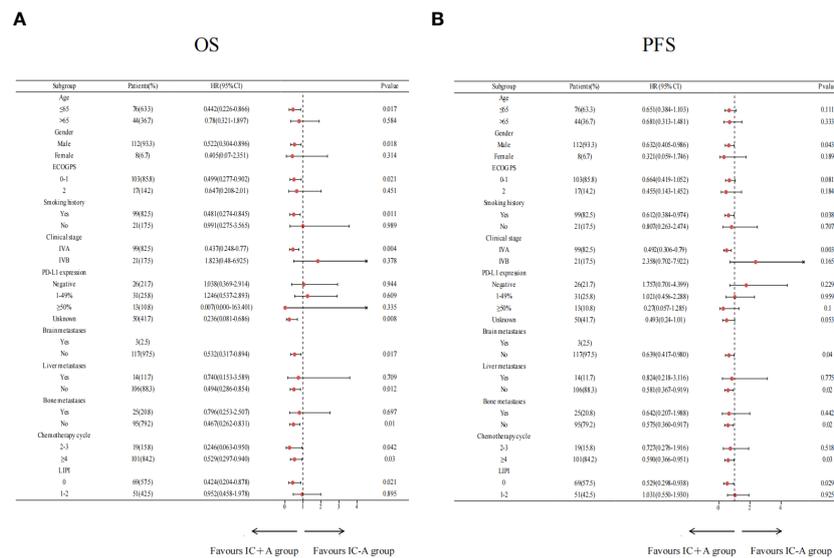


FIGURE 4 Subgroup analysis of the IC+A group versus the IC-A group for OS (A) and PFS (B) based on baseline characteristics; IC+A,PD-1 inhibitor plus chemotherapy with endostatin; IC-A,PD-1 inhibitor plus chemotherapy without endostatin; OS, overall survival; PFS, progression-free survival, LIPI, lung immune prognostic index.

TABLE 6 Adverse events in group IC±A and group C±A.

Event, n(%)	IC±A (n=120)		C±A (n=99)	
	All	Grade 3-4	All	Grade 3-4
Any	116(96.6)	72(60)	93(93.9)	59(59.5)
Anemia	70(58.3)	25(20.8)	51(51.5)	19(19.1)
Neutropenia	31(25.8)	21(17.5)	29(29.2)	16(16.1)
Thrombocytopenia	20(16.6)	10(8.3)	27(27.2)	10(10.1)
ALT elevation	23(19.1)	7(5.8)	22(22.2)	5(5.1)
Creatinine elevation	14(11.6)	2(1.6)	4(4)	1(1)
Nausea	58(48.3)	6(5)	51(51.5)	4(4)
Decreased appetite	36(30)	3(2.5)	22(22.2)	2(2)
Bronchial or pulmonary infection	40(33.3)	3(2.5)	41(41.4)	3(3)
Rash	21(17.5)	1(0.8)	10(10.1)	1(1)
Vomiting	13(10.8)	1(0.8)	9(9.1)	1(1)
Diarrhea	37(30.8)	4(3.3)	21(21)	3(3)
Pain	25(20.8)	1(0.8)	27(27.2)	1(1)
Insomnia	9(7.5)	1(0.8)	3(3)	1(1)
Immune-related AEs				
Any	39(32.5)	12(10)	/	/
Hypothyroidism	15(12.5)	2(1.6)	/	/
Hyperthyroidism	8(6.7)	1(0.8)	/	/
Pneumonitis	9(7.5)	5(4.1)	/	/
Severe skin reaction	3(2.5)	1(0.8)	/	/

(Continued)

TABLE 6 Continued

Event	IC±A (n=120)		C±A (n=99)	
	All	Grade 3-4	All	Grade 3-4
Adrenocortical insufficiency	3(2.5)	1(0.8)	/	/
Hypophysitis	2(1.6)	1(0.8)	/	/
Hepatitis	2(1.6)	2(1.6)	/	/
Nephritis	1(0.8)	1(0.8)	/	/
Colitis	1(0.8)	1(0.8)	/	/
Myocarditis	1(0.8)	1(0.8)	/	/
Arthritis	1(0.8)	1(0.8)	/	/
Pancreatitis	1(0.8)	1(0.8)	/	/
Peripheral neuropathy	1(0.8)	1(0.8)	/	/
Cardiac arrhythmias	1(0.8)	1(0.8)	/	/

/, not available.

brain, or bone metastases—the OS and PFS were more favorable with the combined treatment of PD-1 inhibitors, chemotherapy, and endostatin than without endostatin. Interestingly, patients with a LIPI score of 0 showed a benefit from the combined treatment, whereas those with LIPI scores of 1–2 did not experience significant advantages from the addition of endostatin. LIPI is assessed on the basis of two hematologic markers, LDH and dNLR, which reflect the systemic immune response to cancer-related inflammation (13, 14, 20). High levels of LDH are associated with cancer cell invasion and metastasis, and patients who have high levels of LDH before immunotherapy have relatively short PFS and OS (21–24). The dNLR reflects the body’s neutrophil levels, which are associated with immunosuppression and promote cancer cell metastasis (25–27).

TABLE 7 Adverse events in group IC+A and group C-A.

Event, n (%)	IC+A (n=39)		IC-A (n=81)	
	All	Grade 3-4	All	Grade 3-4
Any	38 (97.4)	24 (61.5)	78 (96.2)	48 (59.2)
Anemia	19 (48.7)	10 (25.6)	51 (62.9)	15 (18.5)
Neutropenia	12 (30.7)	9 (23)	19 (23.4)	12 (14.8)
Thrombocytopenia	7 (17.9)	5 (12.8)	13 (16)	5 (6.1)
ALT elevation	8 (20.5)	2 (5.1)	15 (18.5)	5 (6.1)
Creatinine elevation	5 (12.8)	1 (2.5)	9 (11.1)	1 (1.2)
Nausea	20 (51.2)	2 (5.1)	38 (46.9)	4 (4.9)
Decreased appetite	13 (33.3)	1 (2.5)	23 (28.3)	2 (2.4)
Bronchial or pulmonary infection	14 (35.8)	1 (2.5)	26 (32.1)	2 (2.4)
Rash	7 (17.9)	1 (2.5)	14 (17.2)	0
Vomiting	6 (15.3)	0	7 (8.6)	1 (1.2)
Diarrhea	13 (33.3)	1 (2.5)	24 (29.6)	3 (3.7)
Pain	7 (17.9)	0	18 (22.2)	1 (1.2)
Insomnia	3 (7.6)	1 (2.5)	6 (7.4)	0
Immune-related AEs				
Any	14 (35.9)	4 (10.2)	25 (30.9)	8 (9.9)
Hypothyroidism	6 (15.3)	1 (2.5)	9 (11.1)	1 (1.2)
Hyperthyroidism	3 (7.6)	1 (2.5)	5 (6.1)	0
Pneumonitis	4 (10.2)	2 (5.1)	5 (6.1)	3 (3.7)
Severe skin reaction	2 (5.1)	0	1 (1.2)	1 (1.2)
Adrenocortical insufficiency	2 (5.1)	0	1 (1.2)	1 (1.2)
Hypophysitis	1 (2.5)	0	1 (1.2)	1 (1.2)
Hepatitis	1 (2.5)	0	1 (1.2)	1 (1.2)
Nephritis	0	0	1 (1.2)	1 (1.2)
Colitis	0	0	1 (1.2)	1 (1.2)
Myocarditis	0	0	1 (1.2)	1 (1.2)
Arthritis	1 (2.5)	1 (2.5)	0	0
Pancreatitis	0	0	1 (1.2)	1 (1.2)
Peripheral neuropathy	0	0	1 (1.2)	1 (1.2)
Cardiac arrhythmias	0	0	1 (1.2)	1 (1.2)

An exploratory pooled analysis of data from 4914 metastatic non-small cell lung cancer patients from 11 randomized multinational clinical trials showed that LIPI is important for predicting the prognosis of patients with metastatic non-small cell lung cancer, and represents a different prognosis by its stratification, which is particularly significant in patients receiving ICIs therapy (14). Consequently, the LIPI score is a vital prognostic marker for

TABLE 8 Chi-square test of adverse events in each group.

Event, n(%)	IC±A vs C±A P value		IC+A vs IC-A P value	
	All	grade 3-4	All	grade 3-4
Any	0.261	0.531	0.608	0.486
Anemia	0.191	0.449	0.1	0.252
Neutropenia	0.337	0.469	0.261	0.194
Thrombocytopenia	0.041	0.412	0.492	0.187
ALT elevation	0.348	0.521	0.488	0.59
Creatinine elevation	0.034	0.572	0.501	0.546
Nausea	0.37	0.499	0.4	0.638
Decreased appetite	0.126	0.59	0.364	0.696
Bronchial or pulmonary infection	0.137	0.564	0.415	0.696
Rash	0.085	0.701	0.558	/
Vomiting	0.423	0.701	0.209	/
Diarrhea	0.073	0.605	0.417	0.608
Pain	0.17	0.701	0.388	/
Insomnia	0.125	0.701	0.609	/
Immune-related AEs				
Any	/	/	0.221	0.59
Hypothyroidism	/	/	0.328	0.546
Hyperthyroidism	/	/	0.514	/
Pneumonitis	/	/	0.325	0.525
Severe skin reaction	/	/	0.246	/
Adrenocortical insufficiency	/	/	0.246	/
Hypophysitis	/	/	0.546	/
Hepatitis	/	/	0.546	/
Nephritis	/	/	/	/
Colitis	/	/	/	/
Myocarditis	/	/	/	/
Arthritis	/	/	/	/
Pancreatitis	/	/	/	/
Peripheral neuropathy	/	/	/	/
Cardiac arrhythmias	/	/	/	/

/, not available.

immunotherapy and a significant guide for optimizing anti-PD-1 therapy with chemotherapy and endostatin in clinical practice.

Our study is subject to several limitations. Primarily, it is single-centered and retrospective in nature, characterized by a limited sample size, and incomplete detection of PD-L1 expression levels across the study population is a notable deficiency. Moreover, the incidence of survival events was not ubiquitously observed within our cohort, necessitating extended follow-up to amass comprehensive data on survival and adverse events, which would enable a more precise

evaluation of the combined efficacy and toxicity of PD-1 inhibitors and chemotherapy with endostatin. Consequently, to elucidate the therapeutic potential of this combination, prospective clinical trials with more extensive participant numbers are indispensable.

5 Conclusions

Endostatin, administered concomitantly with chemotherapy and PD-1 inhibitors, yield substantial benefits in OS and PFS and are associated with manageable adverse events. This combination therapy is anticipated to become the preferred initial treatment option for stage IV LUSC, particularly in patients presenting with a LIPI score of 0.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Fujian Medical University Union Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because The requirement for informed consent of the patients was waived due to the retrospective nature of this study.

Author contributions

CL: Conceptualization, Data curation, Methodology, Software, Writing – original draft, Writing – review & editing. YW:

Conceptualization, Data curation, Methodology, Software, Writing – original draft, Writing – review & editing. WG: Data curation, Formal analysis, Investigation, Visualization, Writing – review & editing. BD: Data curation, Formal analysis, Investigation, Visualization, Writing – review & editing. NY: Resources, Software, Validation, Writing – review & editing. YZ: Resources, Software, Validation, Writing – review & editing. JZ: Resources, Software, Validation, Writing – review & editing. YH: Data curation, Formal analysis, Investigation, Visualization, Writing – review & editing. JL: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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