Efficacy of immune checkpoint inhibitors in advanced large cell neuroendocrine carcinoma of the lung: A single-institution experience

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Abstract. Large cell neuroendocrine carcinoma (LCNEC) is a rare and highly invasive lung cancer subtype with an overall poor prognosis. Due to its low incidence rate and unusual pathological features, the clinical management of LCNEC remains controversial. The present study aimed to assess the effect of immune checkpoint inhibitors (ICIs) on treatment response and survival outcomes in patients with advanced LCNEC. The clinical data from 148 patients with LCNEC treated with ICIs at The First Affiliated Hospital of Zhengzhou University (Zhengzhou, China) between January 2019 and September 2021 were retrospectively analyzed. Kaplan-Meier and multivariable Cox regression analyses were used to evaluate associations between clinicopathological variables and patient outcomes. Patients treated with ICIs demonstrated extended median overall survival (mOS) times [23.5 months; 95% confidence interval (CI), 18.524-28.476] compared with patients who did not receive ICIs (11.2 months; 95% CI, 4.530-18.930) (P<0.001). Univariate analysis revealed that histological subtype (P=0.043), lymph node metastases (P=0.032) and number of metastatic organs (P=0.009) were associated with a poor prognosis. The heterogeneity of pathological components was associated with prognosis, and the mOS time was shorter for mixed LCNEC than that for pure LCNEC (P=0.043). The median progression-free survival (mPFS) (9.78 vs. 9.37 months; P=0.82) and mOS (20.70 vs. 25.79 months; P=0.181) times showed no significant association with regard to different regimens of immuno-based combination therapy (chemotherapy combined with ICIs vs. anti-angiogenic agents combined with ICIs). Poor Eastern Cooperative Oncology Group performance status score (P=0.04), multiple organ metastases (P=0.02) and high cancer antigen 125 levels (P=0.01) were independent risk factors of a poor prognosis. The present findings offer valuable insights into potential prognostic markers and highlight the favorable impact of ICIs on OS in advanced LCNEC. Prospective clinical studies are required to validate the therapeutic value of ICIs in LCNEC.

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Introduction

Pulmonary large cell neuroendocrine carcinoma (LCNEC) is a rare disease, accounting for ~3% of all lung cancer cases (1,2). The cancer is highly invasive, with rapid development and hidden symptoms, and is difficult to diagnose early (3). In total, ~40% of patients with LCNEC are initially diagnosed at stage IV, with no opportunity for surgery. Hence, the overall prognosis is poor, with a median overall survival (mOS) time of only 8-12 months (4). In 2015, the World Health Organization defined LCNEC as a unique subtype of lung neuroendocrine neoplasms and one of the subtypes of non-small cell lung cancer (NSCLC) (5). However, its biological and clinical characteristics, and prognostic factors, are similar to those of SCLC (6). Next-generation sequencing has revealed molecular heterogeneity among patients with LCNEC that could be roughly divided into two subtypes: The SCLC-like subtype that mainly co-occurs with *TP53* and *RB1* mutations, and the NSCLC-like subtype that is mainly associated with *KRAS*, *STK11*/*KEAP1* and/or *TP53* mutations (7,8). Studies have shown that the NSCLC-like and SCLC-like subsets have no differences in terms of mOS and median progression-free survival (mPFS) (7). However, Zhuo *et al* (9) demonstrated that genomic subtype analysis plays a role in the prognostic and therapeutic decisions for patients with LCNEC.

The clinical management of LCNEC is controversial due of its low incidence rate and unusual pathological features. Radical surgical resection is primarily recommended for

early stage LCNEC (10), with reported OS benefits for patients with resectable LCNEC (11-13). Postoperative platinum-based single-agent or multi-agent adjuvant chemotherapy can prolong survival time (14,15); however, utilizing preoperative neoadjuvant chemotherapy remains controversial due to uncertain efficacy (3). Currently, no standardized treatment strategy exists for the multi-disciplinary and comprehensive treatment of advanced LCNEC, with most regimens relying on chemotherapy. Existing evidence supports the efficacy of drugs commonly used in the treatment of SCLC, such as platinum-etoposide (SCLC-like regimen), and advanced LCNEC (16-18). The selection of a first-line treatment for metastatic LCNEC poses challenges due to the predominantly small scale and retrospective nature of available studies, with some yielding conflicting results, as some choose SCLC-like regimens, while other select NSCLC-like regimens (4).

Immune checkpoint inhibitors (ICIs) targeting programmed death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) have transformed treatment planning for patients with driver mutation-negative advanced NSCLC (19,20). Due to the lack of prospective evidence, the efficacy of immunotherapy in LCNEC remains unestablished. Data from existing case reports and small retrospective studies are promising, indicating that the mPFS time of patients with advanced LCNEC using ICIs was 4.2-14.2 months, while the mOS time was 11.8 months (21-24). However, the efficacy and safety of ICIs in patients with LCNEC remain controversial. Therefore, further assessment is necessary to validate the effect of LCNEC on ICI efficacy in a more homogeneous patient subgroup, especially given that the treatment regimen may considerably affect outcomes. The present study aimed to evaluate the effect of ICIs on treatment response and survival outcomes in patients with advanced LCNEC.

Materials and methods

Patient selection and clinical data. The present retrospective study included patients with pathologically confirmed advanced LCNEC (stage IV; poorly differentiated, large cell, abundant cytoplasm and multiple necrosis) who visited The First Affiliated Hospital of Zhengzhou University (Zhengzhou, China) between January 1, 2019, and September 9, 2021. The main inclusion criteria were as follows: i) Pathologically confirmed LCNEC, mixed LCNEC and SCLC, and mixed LCNEC and NSCLC with a predominant LCNEC component; and ii) the presence of at least one observable or measurable lesion. The exclusion criteria were as follows: i) The presence of non-primary lung cancer; ii) previous or current malignant tumors of other types; and iii) uncontrolled dysfunction of any major organ. After obtaining approval from the Institutional Ethical Review Board of the First Affiliated Hospital of Zhengzhou University (approval no. 2022-KY-0592-002), baseline demographic [including age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS score) (25), and smoking history], clinical, pathological and treatment characteristics, were retrospectively collected, in addition to toxicity and outcome data.

Study design and treatment methods. Patients were divided into group A (patients who received ICIs as any treatment line; n=73) and group B (patients who did not receive ICIs; n=75). Group A was further divided into group C (patients who received chemotherapy combined with ICIs; n=34) and group D (patients who received anti-angiogenic agents combined with ICIs; n=32) for analysis. Additionally, patients were divided into pure LCNEC and mixed LCNEC (squamous cell carcinoma, adenocarcinoma and small-cell carcinoma) based on the pathological type.

Chemotherapy consisted of etoposide (80-100 mg/m^2, administered on days 1-3 of each 21-day cycle), pemetrexed (500 mg/m^2), docetaxel (75 mg/m^2) or paclitaxel (175 mg/m^2) (administered on day 1 of each cycle), with or without carboplatin (area under the curve, 4-6), cisplatin (75-80 mg/m^2) or nedaplatin (80-100 mg/m^2) (administered on day 1 of each 21-day cycle), based on the investigator's judgment. Patients in groups A and C received 4-6 cycles of chemotherapy plus ICIs, followed by maintenance ICIs every 3 weeks. Anti-angiogenic therapy consisted of anlotinib (8-12 mg, taken orally once a day for 2 weeks with a 1-week break), apatinib (250 mg, taken continuously) and bevacizumab (15 mg/kg, administered on day 1 of each 21-day cycle). ICIs consisted of pembrolizumab (200 mg), camrelizumab (200 mg), sintilimab (200 mg), toripalimab (240 mg), tislelizumab (200 mg), atezolizumab (1,200 mg) or durvalumab (1,500 mg, administered on day 1 of each 21-day cycle). Patients continued treatment until disease progression based on investigator assessment, unacceptable toxicity or other discontinuation criteria. Continuation of the study's treatment regimen following disease progression was permitted if clinical benefit was proven. Group C was comprised of 34 patients as follows: Patients with NSCLC who received pemetrexed-platinum (n=1), paclitaxel-platinum (n=5), docetaxel-platinum (n=2) and gemcitabine-platinum (n=2), and patients with SCLC who received etoposide-platinum (n=20) (4 patients received thoracic radiotherapy and 1 patient received palliative radiotherapy for brain metastasis) and irinotecan-platinum (n=4). In total, 32 patients were included in group D, and the following anti-angiogenesis drugs were used: Anlotinib, apatinib and bevacizumab. A single patient with brain metastasis received palliative radiotherapy.

Evaluation of efficacy. The revised Response Evaluation Criteria in Solid Tumors, version 1.1 (26), was used to evaluate the treatment efficacy, including complete response, partial response (PR), stable disease (SD) and progressive disease (PD) statuses. PFS was defined as the time from the start of ICI treatment to the date of disease progression or death due to any cause. Overall survival (OS) was defined as the time from advanced disease diagnosis until death or censored at the last follow-up visit. Immune-related adverse events (irAEs) were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0 (27). Duration of follow-up was calculated from the time of advanced disease diagnosis until the last follow-up visit or censored at death. The cut-off date for data collection was June 14, 2022.

Statistical analysis. Categorical variables are presented as numbers and percentiles. Medians and ranges are reported for continuous variables. Fisher's exact and χ^2 tests were used

to compare the baseline demographic, clinical and pathological characteristics (except for age, tumor size and Ki-67 values, which are continuous variables that were tested using an independent sample t-test). The Kaplan-Meier method was used to estimate survival rates and the log-rank test was used to analyze between-group survival differences. Case characteristics were regarded as independent prognostic factors if they showed a significant association (P<0.05) in the multivariable regression with a Cox proportional hazards model. Statistical analyses were conducted using SPSS 26.0 (IBM Corp). P<0.05 was used to indicate a statistically significant difference.

Results

Demographic and clinical characteristics. In total, 174 patients with histologically confirmed LCNEC were diagnosed at The First Affiliated Hospital of Zhengzhou University between January 1, 2019, and September 9, 2021. A total of 26 patients with early stage disease were excluded. Thus, 148 patients were clinically evaluated (Fig. 1). The baseline demographic, clinical and pathological characteristics of the 148 patients are summarized in Table I, and the detailed treatment regimens and outcomes for all patients are presented in Table II. All patients in the clinical analysis underwent follow-up from the time of pathological diagnosis to June 14, 2022, or until death.

The patients had a median age of 67 years (age range, 32-86 years), were mostly men (88.5%) and had a history of smoking (58.8%). Patients with an ECOG PS score ≥2 at diagnosis accounted for 20.3% of the population. LCNEC occurred in the lung lobe, and no significant differences were observed in the distribution of LCNEC between the left and right lungs. All the patients had stage IV LCNEC at diagnosis, while 20.3% had brain metastases, 13.5% had liver metastases and 14.9% had bone metastases. Moreover, 104 patients (70.3%) had pure LCNEC and 44 had combined LCNEC (mixed LCNEC and SCLC, 22.3%; mixed LCNEC and NSCLC, 7.4%). The positive rate of serum tumor marker cytokeratin 19 fragment antigen 21-1 (CYFRA21-1) was the highest (65.5%), followed by neuron-specific enolase (NSE) (61.5%), and the positivity rates for carcinoembryonic antigen (CEA) and cancer antigen (CA)-125 were low. The levels of peripheral blood markers such as the neutrophil/lymphocyte ratio (NLR), cholesterol and triglyceride were low, while the lactate dehydrogenase (LDH) level was higher than normal in ~66.2% of patients. The median Ki-67 level was 80.0% [inter-quartile range (IQR), 66.2-80.0%]. Group B had more patients with increased NSE and CA125 levels (P=0.033 and P=0.020, respectively) than group A. All patients received chemotherapy, anti-angiogenic therapy or immunotherapy according to their condition, and some patients received radiotherapy. Of these, 73 patients received ICIs (group A) and 75 patients did not receive ICIs (group B). In group A, 7 patients (9.6%) received immunotherapy alone, 34 patients (46.6%) received chemotherapy combined with immunotherapy and 32 patients (43.8%) received anti-angiogenic combined immunotherapy (Tables I, II, and Fig. 2).

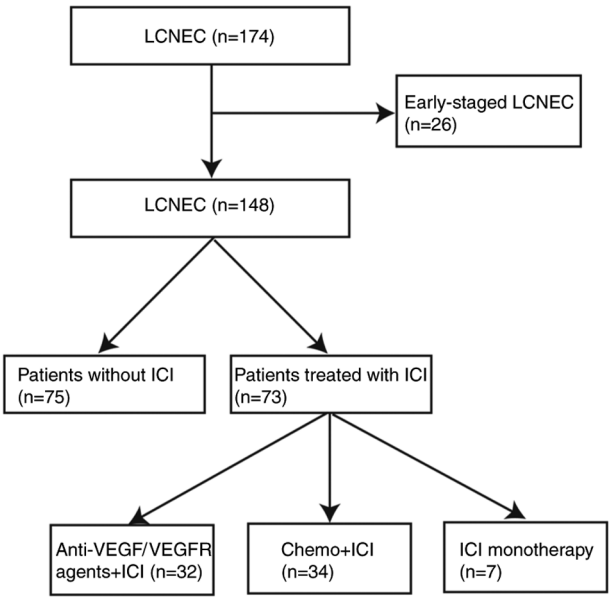

Figure 1. Consolidated Standards of Reporting Trials diagram with the inclusion and exclusion parameters. LCNEC, large cell neuroendocrine carcinoma; ICI, immune checkpoint inhibitor.

Patient outcomes

Efficacy of ICI based on LCNEC. The primary endpoint of this study was OS. The mean follow-up duration was 18.18 months (IQR, 1.8-56.13 months) in group A and 12.56 months (IQR, 0.43-40.37 months) in group B. By the end of follow-up, 34 patients (46.6%) in group A and 50 patients (66.7%) in group B had died. The mOS time of group A was 23.500 months [95% confidence interval (CI), 18.524-28.476] and that of group B was 11.230 months (95% CI, 4.530-18.930). The survival time of group A was significantly longer than that of group B (P=0.001) (Fig. 3A). In the univariate analysis, ICI administration (P<0.001), histological type (P=0.043), lymph node metastases (P=0.032) and number of metastatic organs (P=0.009) demonstrated a significant association with OS (Fig. 3A-D; Table III). However, sex, smoking status, ECOG PS score, presence of brain, liver and bone metastases, and levels of NLR, CEA, CA125, CYFRA21-1, LDH, cholesterol and triglycerides did not demonstrate any significant associations with OS (all P>0.05) (Table III). In the multivariate Cox regression analysis model, which incorporated all factors significantly associated with OS from the univariate analysis, ICI administration (P<0.001), pathological type (P=0.005), lymph node metastases (P=0.030) and number of metastatic organs (P=0.011) were significantly associated with OS (Table III).

Efficacy analysis of combination therapy based on immunotherapy

Comparison of the survival rate. Since different treatment regimens were used in group A (patients who received ICIs), it was subdivided into group C (patients who received chemotherapy combined with ICIs; n=34) and group D (patients who received anti-angiogenic agents combined with ICIs; n=32). A total of 7 patients who received monotherapy with an anti-PD-1/PD-L1 agent were not included in the analysis.

Table I. Baseline clinical, pathological and treatment characteristics of patients with advanced large cell neuroendocrine carcinoma of divided according to exposure to ICI.

Characteristics	Patients treated with ICI (group A; n=73)	Patients not treated with ICI (group B; n=75)	P-value	All patients (n=148)
Median age (range), years	67 (32-84)	66 (34-86)	0.892	67 (32-86)
Sex, n (%)			0.405	
Male	63 (86.3)	68 (90.7)		131 (88.5)
Female	10 (13.7)	7 (9.3)		17 (11.5)
Smoking history, n (%)			0.716	
Current/former smoker	44 (60.3)	43 (57.3)		87 (58.8)
Never smoker	29 (39.7)	32 (42.7)		61 (41.2)
ECOG PS at diagnosis, n (%)			0.934	
0-1	58 (79.5)	60 (80.0)		118 (79.7)
≥2	15 (20.5)	15 (20.0)		30 (20.3)
Primary tumor location, n (%)			0.509	
Left	39 (53.4)	36 (48.0)		75 (50.7)
Right	34 (46.6)	39 (52.0)		73 (49.3)
Median primary tumor size (IQR), mm	38.5 (27.5-57.0)	42.0 (27.4-59.0)	0.324	40.9 (27.5-58.0)
Median Ki-67 (IQR)	80 (67.3-80.0)	80.0 (60.0-80.0)	0.680	80.0 (66.2-80.0)
Histological subtype, n (%)			0.782	
LCNEC	50 (68.5)	54 (72.0)		104 (70.3)
Mixed LCNEC + NSCLC	5 (6.8)	6 (8.0)		11 (7.4)
Mixed LCNEC + SCLC	18 (24.7)	15 (20.0)		33 (22.3)
Lymph node metastases, n (%)			0.370	
Yes	65 (89.0)	63 (84.0)		128 (86.5)
No	8 (11.0)	12 (16.0)		20 (13.5)
N, n (%)			0.483	
N0	8 (11.0)	12 (16.0)		20 (12.5)
N1	6 (8.2)	4 (5.3)		10 (6.8)
N2	33 (45.2)	39 (52.0)		72 (38.6)
N3	26 (35.6)	20 (26.7)		46 (31.1)
M, n (%)			0.420	
M0	30 (41.1)	26 (34.7)		56 (37.8)
M1	43 (58.9)	49 (65.3)		92 (62.2)
Number of metastatic organs, n (%)			0.959	
0	39 (53.4)	41 (54.7)		80 (54.1)
1	21 (28.8)	20 (26.7)		41 (27.7)
≥2	13 (17.8)	14 (18.7)		27 (18.2)
Brain metastases, n (%)			0.368	
Yes	17 (23.3)	13 (17.3)		30 (20.3)
No	56 (76.7)	62 (82.7)		118 (79.7)
Liver metastases, n (%)			0.948	
Yes	10 (13.7)	10 (13.3)		20 (13.5)
No	63 (86.3)	65 (86.7)		128 (86.5)
Bone metastases, n (%)			0.188	
Yes	8 (11.0)	14 (18.7)		22 (14.9)
No	65 (89.0)	61 (81.3)		126 (85.1)
NLR, n (%)			0.722	
<5	61 (83.6)	61 (81.3)		122 (82.4)
≥5	12 (16.4)	14 (18.7)		26 (17.6)

Table I. Continued.

Characteristics	Patients treated with ICI (group A; n=73)	Patients not treated with ICI (group B; n=75)	P-value	All patients (n=148)
CEA, n (%)			0.233	
<5 ng/ml	46 (63.0)	40 (53.3)		86 (58.1)
≥5 ng/ml	27 (37.0)	35 (46.7)		62 (41.9)
NSE, n (%)			0.020[a]	
<16.3 ng/ml	35 (47.9)	22 (29.3)		57 (38.5)
≥16.3 ng/ml	38 (52.1)	53 (70.7)		91 (61.5)
CA125, n (%)			0.033[a]	
<35 U/ml	63 (86.3)	54 (72.0)		117 (79.1)
≥35 U/ml	10 (13.7)	21 (28.0)		31 (20.9)
CYFRA21-1, n (%)			0.325	
<3.3 ng/ml	28 (38.4)	23 (30.7)		51 (34.5)
≥3.3 ng/ml	45 (61.6)	52 (69.3)		97 (65.5)
LDH, n (%)			0.355	
<240 U/l	22 (30.1)	28 (37.3)		50 (33.8)
≥240 U/l	51 (69.9)	47 (62.7)		98 (66.2)
Cholesterol, n (%)			0.063	
<5.2 mg/dl	67 (91.8)	61 (81.3)		128 (86.5)
≥5.2 mg/dl	6 (8.2)	14 (18.7)		20 (13.5)
Triglycerides, n (%)			0.951	
<1.7 mg/dl	64 (87.7)	66 (88.0)		130 (87.8)
≥1.7 mg/dl	9 (12.3)	9 (12.0)		18 (12.2)
Treatment details, n (%)				
ICI alone	7 (9.6)			
Chemotherapy + ICI	34 (46.6)			
Anti-angiogenesis + ICI	32 (43.8)			
Name of ICI, n (%)				
Durvalumab	6 (9.1)			
Toripalimab	3 (4.5)			
Camrelizumab	45 (62.1)			
Sintilimab	11 (15.2)			
Atezolizumab	1 (1.5)			
Tislelizumab	5 (6.1)			
Pembrolizumab	2 (1.5)			

[a]P<0.05. ICI, immune checkpoint inhibitor; LCNEC, large cell neuroendocrine carcinoma of the lung; IQR, inter-quartile range; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; NLR, neutrophil/lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; CA125, cancer antigen 125; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; LDH, lactate dehydrogenase.

No differences were found in baseline characteristics between the two groups, except for age (P=0.026), and the clinical and pathological characteristics of the patients are summarized in Table IV.

Among the 66 response evaluable patients, 22 (33.3%) patients achieved a confirmed PR, 35 (53.0%) patients achieved SD and 9 (13.6%) patients experienced PD. The disease control rate (DCR) was 86.4% (n=57/66) (Tables II and V). No significant differences were found in the DCR between the two groups (χ^2=0.730, P=0.460) (Table V).

The median follow-up period was 13.7 months in group C (IQR, 9.25-18.95 months) and 18.97 months in group D (IQR, 12.38-35.33 months). At the end of the study period, 16 patients (47.1%) in group C and 15 patients (46.9%) in group D had died. The median OS times were 20.70 months (95% CI, 12.065-29.335) and 25.97 months (95% CI, 19.095-32.839) in groups C and D, respectively (P=0.181; Fig. 4). The PFS times

Table II. Details of treatment in 73 patients who underwent different treatment regimens.

Case no.	Systemic treatment lines	Treatment details	Radiotherapy	Efficacy
1	1st-line	Etoposide + carboplatin + durvalumab	Whole-brain radiotherapy	SD
2	1st-line	Etoposide + cisplatin + durvalumab		PR
3	1st-line	Etoposide + lobaplatin + camrelizumab		PR
4	1st-line	Etoposide + carboplatin + camrelizumab	Thoracic radiotherapy	PR
5	1st-line	Etoposide + carboplatin + camrelizumab	Thoracic radiotherapy	PR
6	1st-line	Irinotecan + nedaplatin + durvalumab		PR
7	1st-line	Etoposide + carboplatin + camrelizumab		PR
8	1st-line	Etoposide + cisplatin + durvalumab		SD
9	1st-line	Paclitaxel + tislelizumab		SD
10	1st-line	Etoposide + carboplatin + camrelizumab		SD
11	1st-line	Etoposide + cisplatin + durvalumab		SD
12	1st-line	Etoposide + nedaplatin + tislelizumab		PR
13	1st-line	Etoposide + cisplatin + camrelizumab	Thoracic radiotherapy	SD
14	1st-line	Paclitaxel + nedaplatin + sintilimab		SD
15	1st-line	Etoposide + carboplatin + camrelizumab		PR
16	1st-line	Etoposide + cisplatin + camrelizumab		PD
17	1st-line	Etoposide + nedaplatin + atezolizumab	Thoracic radiotherapy	PR
18	1st-line	Etoposide + nedaplatin + sintilimab		PR
19	1st-line	Etoposide + lobaplatin + camrelizumab		PR
20	2nd-line	Etoposide + nedaplatin + camrelizumab		PR
21	2nd-line	Docetaxel + camrelizumab		PR
22	2nd-line	Paclitaxel + carboplatin + camrelizumab		SD
23	2nd-line	Gemcitabine + cisplatin + camrelizumab		SD
24	2nd-line	Irinotecan + toripalimab		PD
25	2nd-line	Etoposide + nedaplatin + camrelizumab		SD
26	2nd-line	Etoposide + camrelizumab		SD
27	2nd-line	Docetaxel + sintilimab		SD
28	2nd-line	Irinotecan + lobaplatin + camrelizumab		SD
29	2nd-line	Irinotecan + sintilimab		PD
30	2nd-line	Paclitaxel + carboplatin + camrelizumab		PR
31	3rd-line	Gemcitabine + carboplatin + tislelizumab		PD
32	3rd-line	Paclitaxel + carboplatin + camrelizumab		SD
33	3rd-line	Pemetrexed + carboplatin + camrelizumab		SD
34	3rd-line	Etoposide + lobaplatin + camrelizumab		SD
35	1st-line	Sintilimab + anlotinib		PR
36	1st-line	Camrelizumab + apatinib		PR
37	2nd-line	Camrelizumab + anlotinib		SD
38	2nd-line	Sintilimab + anlotinib		SD
39	2nd-line	Camrelizumab + apatinib		PR
40	2nd-line	Camrelizumab + anlotinib		SD
41	2nd-line	Camrelizumab + anlotinib		SD
42	2nd-line	Durvalumab + anlotinib		SD
43	2nd-line	Camrelizumab + anlotinib		PR
44	2nd-line	Camrelizumab + anlotinib		SD
45	2nd-line	Camrelizumab + anlotinib		PD
46	2nd-line	Camrelizumab + bevacizumab		SD
47	2nd-line	Sintilimab + anlotinib		PR
48	2nd-line	Camrelizumab + apatinib		SD
49	2nd-line	Sintilimab + anlotinib		SD
50	2nd-line	Camrelizumab + anlotinib		SD
51	2nd-line	Camrelizumab + apatinib		PR

Table II. Continued.

Case no.	Systemic treatment lines	Treatment details	Radiotherapy	Efficacy
52	2nd-line	Camrelizumab + anlotinib		PD
53	2nd-line	Camrelizumab + anlotinib		SD
54	2nd-line	Toripalimab + anlotinib		PR
55	3rd-line	Tislelizumab + anlotinib		SD
56	3rd-line	Camrelizumab + apatinib		SD
57	3rd-line	Toripalimab + anlotinib		SD
58	3rd-line	Pembrolizumab + anlotinib	Whole-brain radiotherapy	SD
59	3rd-line	Camrelizumab + anlotinib		PD
60	3rd-line	Camrelizumab + anlotinib		PD
61	3rd-line	Sintilimab + anlotinib		PR
62	4th-line	Sintilimab + anlotinib		PD
63	4th-line	Camrelizumab + anlotinib		SD
64	5th-line	Camrelizumab + anlotinib		SD
65	5th-line	Camrelizumab + anlotinib		SD
66	6th-line	Camrelizumab + bevacizumab		SD
67	2nd-line	Camrelizumab		SD
68	2nd-line	Camrelizumab		PD
69	2nd-line	Camrelizumab		PD
70	2nd-line	Pembrolizumab		SD
71	3rd-line	Tislelizumab		SD
72	3rd-line	Camrelizumab		PR
73	3rd-line	Sintilimab		SD

SD, stable disease; PR, partial response; PD, progressive disease.

Table III. Univariate and multivariate Cox regression analyses of overall survival since the diagnosis of advanced disease in patients with advanced large cell neuroendocrine carcinoma.

	Univariate analysis		Multivariate analysis	
Parameters	HR (95% CI)	P-value	HR (95% CI)	P-value
ICI (yes vs. no)	0.453 (0.292-0.703)	<0.001[a]	0.377 (0.235-0.607)	<0.001[a]
Sex (male vs. female)	0.969 (0.501-1.875)	0.636		
Smoking (yes vs. no)	0.894 (0.579-1.380)	0.613		
ECOG PS (0-1 vs. ≥2)	0.920 (0.546-1.551)	0.754		
Number of metastatic organs (0-1 vs. ≥2)	0.429 (0.227-0.812)	0.009[a]	2.595 (1.246-5.403)	0.011[a]
Lymph node metastases (yes vs. no)	0.542 (0.314-0.934)	0.032[a]	0.537 (0.306-0.942)	0.030[a]
Brain metastases (yes vs. no)	1.318 (0.790-2.199)	0.290		
Liver metastases (yes vs. no)	1.091 (0.578-2.058)	0.789		
Bone metastases (yes vs. no)	1.571 (0.867-2.845)	0.136		
Histological subtype (pure vs. no)	1.573 (1.015-2.439)	0.043[a]	1950 (1.222-3.110)	0.005[a]
NLR (<5 vs. ≥5)	0.895 (0.516-1.552)	0.693		
CEA (<5 vs. ≥5 ng/ml)	1.099 (0.711-1.699)	0.670		
NSE (<16.3 vs. ≥16.3 ng/ml)	1.515 (0.946-2.425)	0.084		
CA125 (<35 vs. ≥35 U/ml)	1.463 (0.905-2.365)	0.121		
CYFRA21-1 (<3.3 vs. ≥3.3 ng/ml)	1.248 (0.793-1.965)	0.338		
LDH (<240 vs. ≥240 U/l)	1.315 (0.818-2.114)	0.258		
Cholesterol (<5.2 vs. ≥5.2 mg/dl)	1.711 (0.925-3.165)	0.087		
Triglycerides (<1.7 vs. ≥1.7 mg/dl)	1.157 (0.613-2.186)	0.653		

[a]P<0.05. ICI, immune checkpoint inhibitor; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil/lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; CA125, cancer antigen 125; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; LDH, lactate dehydrogenase.

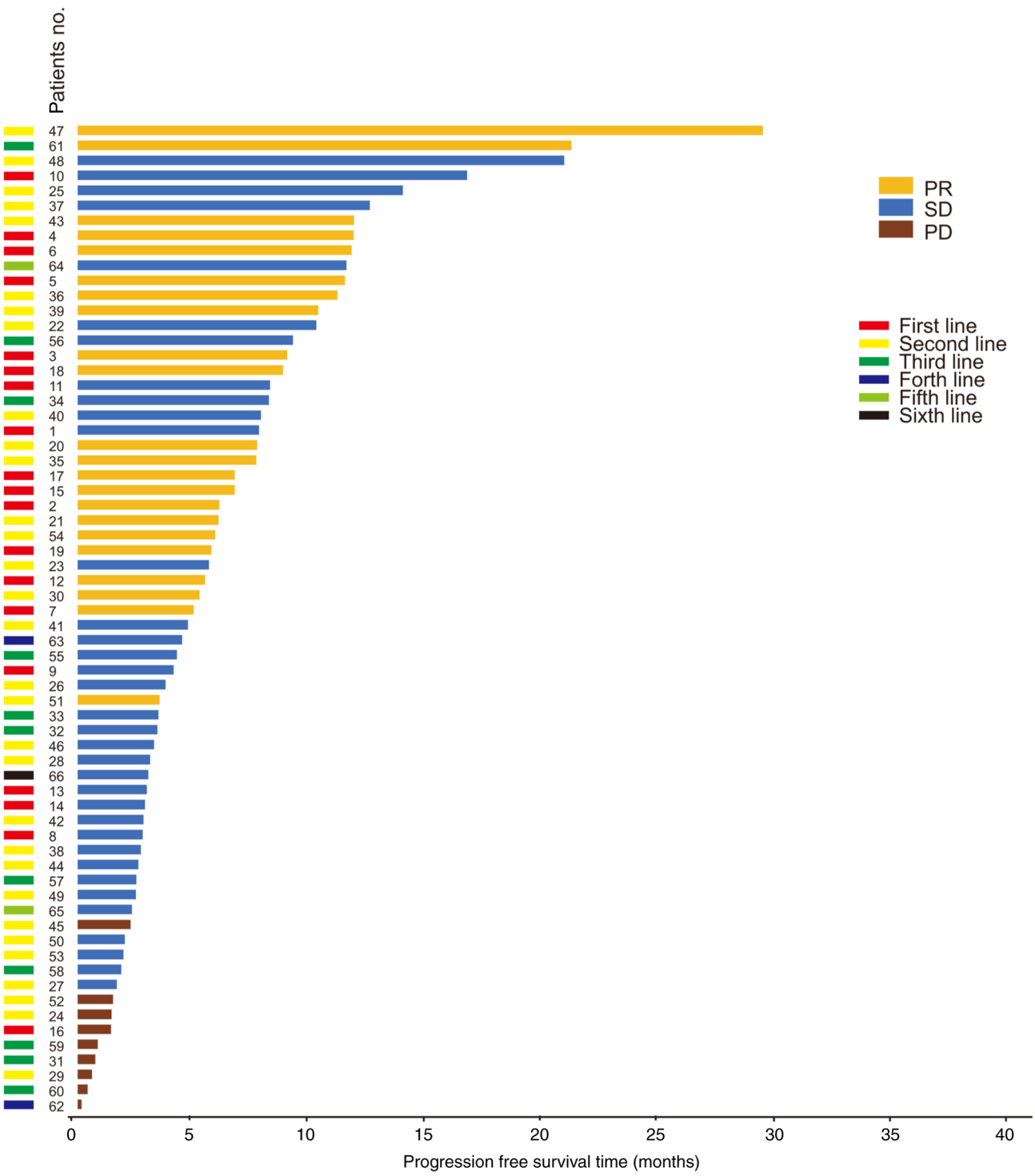

Figure 2. Swimming plots for 66 patients receiving immune checkpoint inhibitor combinations. PR, partial response; SD, stable disease; PD, progressive disease.

were 9.77 months (95% CI, 4.991-14.542) and 9.37 months (95% CI, 2.015-16.718) in groups C and D, respectively (P=0.82; Fig. 4). Immuno-based combination therapy (group C vs. group D) exhibited no significant association with regard to mPFS and mOS. Univariate analysis showed that the ECOG PS score (P=0.045), number of metastatic organs (P=0.02), and CA125 level (P=0.01) exhibited a significant association with regard to mOS but not mPFS (Fig. 4; Table VI). In addition, age, sex, smoking status, pathological type (pure LCNEC vs. mixed LCNEC), presence of brain, liver and bone metastases, and levels of NLR, CEA, CYFRA21-1, LDH, cholesterol and triglycerides were also not associated with OS (all P>0.05). However, in the multivariate Cox regression analysis, no statistical significance was observed between the CA125 level and OS (P=0.070) (Table VI).

irAEs. No statistically significant differences were observed between the development of irAEs and the use of combined immunotherapy regimen (group C vs. group D, P=0.48). The

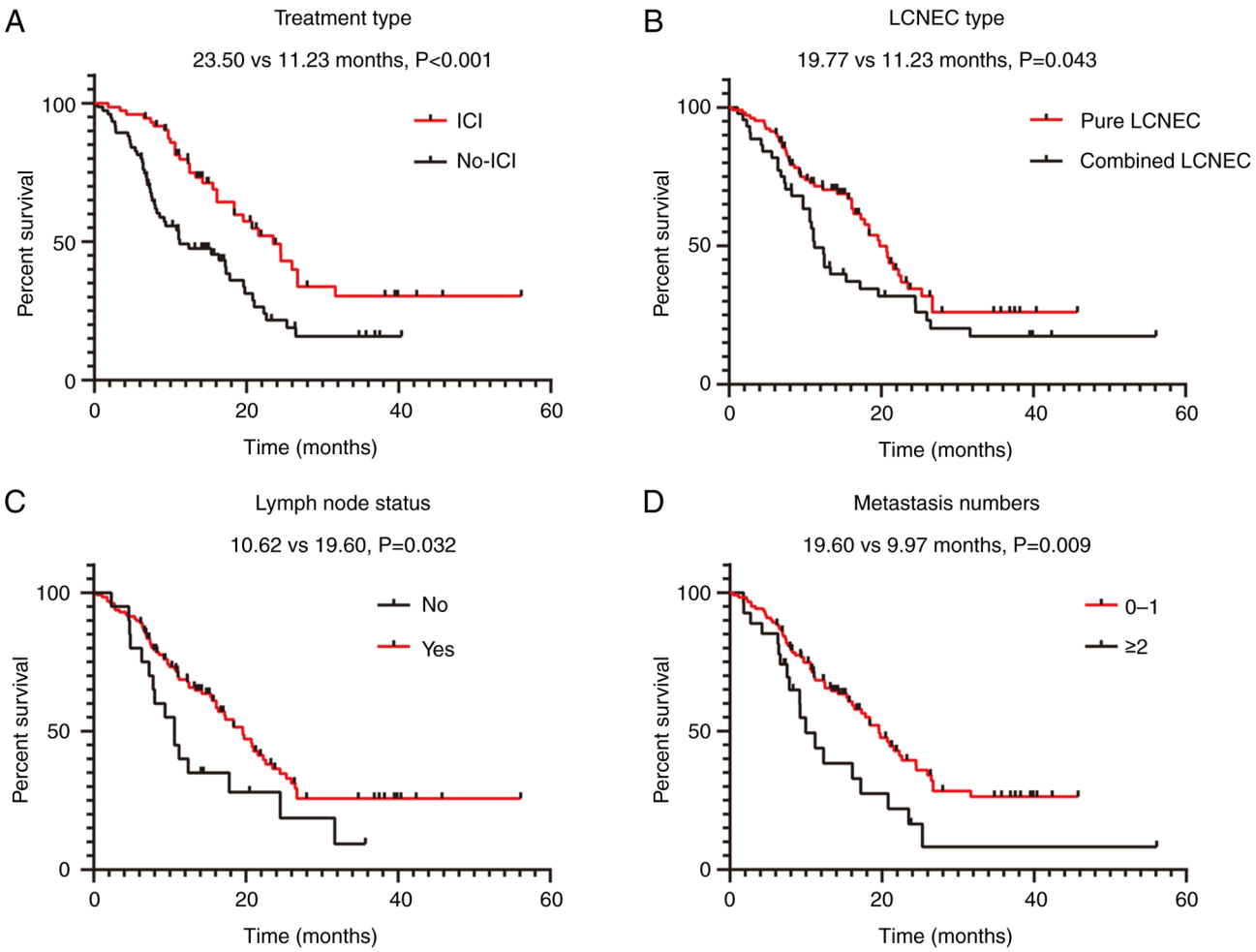

Figure 3. Kaplan-Meier estimates of overall patient survival. (A) Comparison of patient survival based on the effect of ICI exposure. (B) Patient survival based on the histological subtype. (C) Patient survival based on lymph node metastases. (D) Patient survival based on the number of metastatic organs. ICI, immune checkpoint inhibitor.

frequency of corticosteroid use was significantly higher in group C than that in group D (P=0.001). The most common irAEs were hypothyroidism (n=5) and immune-associated pneumonitis (n=3). No statistically significant differences were observed with regard to irAE grade (P=0.49) and permanent treatment discontinuation due to irAEs (P=0.65) between the two groups (Table VII).

Discussion

The prognosis of patients with LCNEC is generally poor, and the 5-year survival rate of those with advanced stage disease is as low as 8% (28). Currently, the first-line treatment of metastatic LCNEC is still controversial, and the chemotherapy regimen for advanced LCNEC tends to be the same regimen as that for SCLC. Based on the results of the present study and those of current small-scale and retrospective studies, the prognosis remains poor, with an mOS time of 8-12 months (17,29). The combination of immunotherapy with etoposide-platinum chemotherapy has been identified as the standard first-line treatment for advanced SCLC (30,31). However, due to the rarity of LNCEC and the lack of prospective evidence, the efficacy of immunotherapy in LCNEC has not been determined. According to the present findings, the mOS of the ICI group was 23.500 months, which was double that of the non-ICI group (11.230 months). The results of univariate and multivariate analyses further supported the positive effect of ICI on the OS time of patients with advanced LCNEC. The present results are in line with the previously reported data on LCNEC (21), suggesting that immunotherapy is a superior treatment and providing valuable insight regarding possible therapeutic options for advanced LCNEC. For instance, a recent retrospective study (24) assessed the efficacy and safety of ICIs in 37 patients with advanced LCNEC and concluded that patients receiving mono-immunotherapy or a combination of different ICIs exhibited a favorable prognosis with an objective response rate of 33%, an mPFS time of 4.2 months and a mOS time of 11.8 months. In addition, a real-world study (21) showed that ICIs had a positive impact on OS, with mOS time of 12.4 months in patients who received ICIs and 6.0 months in patients who did not. Agar *et al* (22) reported that the mOS time of patients administered nivolumab treatment was 12.1 months (95% CI, 7.10-14.20), indicating that nivolumab as a second-line treatment or beyond showed a high level of tumor response and prolonged OS time in patients with advanced LCNEC. This result is consistent with the present finding that ICI administration is associated with prolonged OS time in patients with LCNEC.

Table IV. Baseline clinical, pathological and treatment characteristics of patients with advanced large cell neuroendocrine carcinoma of the lung by treatment regimen.

Characteristics	Chemo + ICI (group C; n=34)	Anti-VEGF + ICI (group D; n=32)	P-value
Age, n (%)			0.044[a]
<67 years	19 (55.9)	10 (31.3)	
≥67 years	15 (44.1)	22 (68.8)	
Sex, n (%)			>0.999
Male	30 (88.2)	28 (87.5)	
Female	4 (11.8)	4 (12.5)	
Smoking history, n (%)			0.05
Current/past smoker	22 (64.7)	13 (40.6)	
Never smoker	12 (35.3)	19 (59.4)	
ECOG PS at diagnosis, n (%)			0.384
0-1	28 (82.4)	23 (71.9)	
≥2	6 (17.6)	9 (28.1)	
Histological subtype, n (%)			0.561
LCNEC	24 (70.6)	20 (62.5)	
Mixed LCNEC + NSCLC	2 (5.9)	3 (9.4)	
Mixed LCNEC + SCLC	8 (23.5)	9 (28.1)	
N, n (%)			0.813
N0	3 (8.8)	3 (9.4)	
N1	1 (2.9)	4 (12.5)	
N2	18 (52.9)	12 (37.5)	
N3	12 (35.3)	13 (40.6)	
M, n (%)			0.66
M0	12 (35.3)	13 (40.6)	
M1	22 (64.7)	19 (59.4)	
Brain metastases, n (%)			0.578
Yes	10 (29.4)	7 (21.9)	
No	24 (70.6)	25 (78.1)	
Liver metastases, n (%)			0.505
Yes	4 (11.8)	6 (18.8)	
No	30 (88.2)	26 (81.3)	
Bone metastases, n (%)			0.106
Yes	6 (17.6)	1 (3.1)	
No	28 (82.4)	31 (96.9)	
NLR, n (%)			0.104
<5	31 (91.2)	24 (75.0)	
≥5	3 (8.8)	8 (25.0)	
CEA, n (%)			>0.999
<5 ng/ml	21 (61.8)	20 (62.5)	
≥5 ng/ml	13 (38.2)	12 (37.5)	
NSE, n (%)			0.631
<16.3 ng/ml	17 (50.0)	14 (43.8)	
≥16.3 ng/ml	17 (50.0)	18 (56.3)	
CA125, n (%)			0.734
<35 U/ml	28 (82.4)	28 (87.5)	
≥35 U/ml	6 (17.6)	4 (12.5)	
CYFRA21-1, n (%)			0.802
<3.3 ng/ml	13 (38.2)	11 (34.4)	
≥3.3 ng/ml	21 (61.8)	21 (65.6)	

Table IV. Continued.

Characteristics	Chemo + ICI (group C; n=34)	Anti-VEGF + ICI (group D; n=32)	P-value
LDH, n (%)			0.185
<240 U/l	13 (38.2)	7 (21.9)	
≥240 U/l	21 (61.8)	25 (78.1)	
Cholesterol, n (%)			0.673
<5.2 mg/dl	30 (88.2)	30 (93.8)	
≥5.2 mg/dl	4 (11.8)	2 (6.2)	
Triglycerides, n (%)			0.151
<1.7 mg/dl	27 (79.4)	30 (93.8)	
≥1.7 mg/dl	7 (20.6)	2 (6.3)	

[a]P<0.05. ICI, immune checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil/lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; CA125, cancer antigen 125; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; LDH, lactate dehydrogenase

Table V. Efficacy of different treatment regimens.

Response	Chemo + ICI	Anti-VEGF + ICI	P-value	ICI alone
Complete response, n (%)	0 (0.0)	0 (0.0)		0 (0.0)
Partial response, n (%)	14 (41.2)	8 (25.0)		1 (14.3)
Stable disease, n (%)	16 (47.0)	19 (59.4)		4 (57.1)
Progressive disease, n (%)	4 (11.8)	5 (15.6)		2 (28.6)
DCR, %	88.2	84.4	0.460	

DCR, disease control rate; chemo, chemotherapy; ICI, immune checkpoint inhibitor.

In population-based studies, age, sex, primary tumor size, lymph node metastasis and tumor stage have been identified as prognostic factors for lung cancer survival (32,33). Previous studies have shown that LCNEC is highly prevalent in elderly men with a history of smoking (3). In the present study, the median age of patients was 67 years, with a predominance of men. Among them, 58.8% had a history of smoking and 100% had stage IV LCNEC at the time of diagnosis, with distant metastases mainly in the brain, liver and bones. Serum tumor markers such as CEA, NSE, CA125 and CYFRA21-1 are important indicators of an auxiliary diagnosis of lung cancer (34). In the present study, CYFRA21-1 had the highest positivity rate, followed by NSE, while the positivity rates of CEA and CA125 were low. Studies have shown that peripheral blood markers such as NLR and LDH are high-risk factors for a poor prognosis in patients with NSCLC (35). In the present study, 61.5 and 66.2% of the patients had elevated NLR and LDH levels, respectively, but univariate and multivariate analyses showed no statistical association between these markers and OS. Considering the presence of differences in baseline and treatment characteristics favoring patients treated with ICIs in the present cohort, further analysis after elimination of confounding factors is required. A recent retrospective study of 251 patients with LCNEC after surgical resection (36) showed that only lymphatic infiltration was an independent prognostic factor. The present study showed a significant association between OS and lymph node metastasis and the number of metastatic organs. Patients with lymph node metastasis and >2 metastatic organs had a poor prognosis. Thus, lymphatic invasion affects surgical efficacy in the early stage and functions as an independent risk factor of poor prognosis in patients with advanced LCNEC. In addition, distant metastasis is an indicator of prognosis.

In clinical practice, the incidence of LCNEC with other lung cancer subtypes (e.g., SCLC, adenocarcinoma and squamous cell carcinoma) is ~10% (37,38). However, the differences in clinical characteristics, prognosis and treatment between pure LCNEC and mixed LCNEC remain unclear. Zhang *et al* (16) showed that the mOS time of patients with pure LCNEC was significantly greater than that of patients with combined LCNEC (P=0.083). The present study explored the difference in prognosis between pure and combined LCNEC. The results of the univariate and multivariate analyses showed that the histological type of LCNEC was significantly associated with the mOS time, and the difference in the mOS time between patients with pure LCNEC and combined LCNEC was statistically significant. Therefore, the prognosis of mixed LCNEC was worse than that of pure LCNEC. However, the retrospective nature and limited sample size of the present study may impact the ability to draw a definite conclusion. Nevertheless, the data indicate that the heterogeneity of pathological components may be related to prognosis.

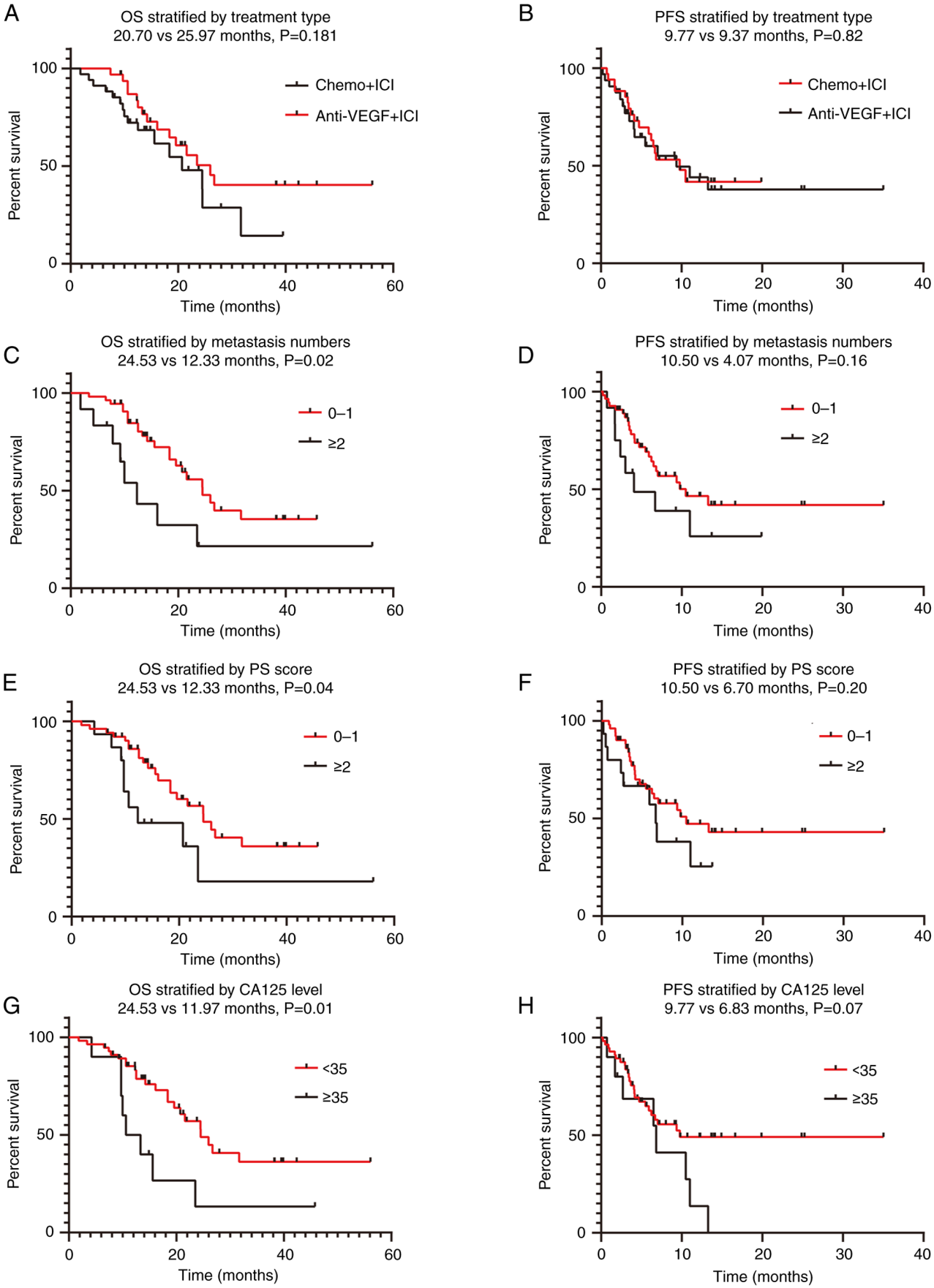

Figure 4. Effect of ICI exposure on OS and PFS times in patients with advanced large cell neuroendocrine carcinoma of the lung in selected subgroups. (A) OS and (B) PFS of patients treated with different treatment regimens (chemo + ICI vs. anti-VEGF + ICI). (C) OS and (D) PFS of patients with different numbers of metastatic organs (0-1 vs. ≥2). (E) OS and (F) PFS of patients with different ECOG PS scores (0-1 vs. ≥2). (G) OS and (H) PFS of patients with different CA125 levels (<35 vs. ≥35). ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; CA125, cancer antigen 125; chemo, chemotherapy.

Table VI. Univariate and multivariate Cox regression analyses of overall survival in patients with advanced LCNEC by treatment regimen.

	Univariate analysis		Multivariate analysis	
Parameters	HR (95% CI)	P-value	HR (95% CI)	P-value
Treatments (chemo + ICI vs. anti-VEGF)	0.617 (0.302-1.263)	0.187		
Age (<67 vs. ≥67 years)	0.949 (0.468-1.924)	0.884		
Sex (male vs. female)	1.255 (0.437-3.606)	0.673		
Smoking (yes vs. no)	0.738 (0.363-1.500)	0.401		
ECOG PS (0-1 vs. ≥2)	2.238 (1.019-4.915)	0.045[a]	1.356 (0.511-3.599)	0.541
Number of metastatic organs (0-1 vs. ≥2)	2.531 (1.125-5.697)	0.025[a]	1.856 (0.692-4.982)	0.220
Lymph node metastases (yes vs. no)	0.558 (0.214-1.456)	0.233		
Brain metastases (yes vs. no)	1.165 (0.520-2.609)	0.710		
Liver metastases (yes vs. no)	0.976 (0.373-2.555)	0.961		
Bone metastases (yes vs. no)	1.411 (0.426-4.671)	0.573		
Histological subtype (pure vs. no)	1.212 (0.584-2.515)	0.607		
NLR (<5 vs. ≥5)	1.029 (0.438-2.415)	0.948		
CEA (<5 vs. ≥5 ng/ml)	0.845 (0.396-1.801)	0.662		
NSE (<16.3 vs. ≥16.3 ng/ml)	1.049 (0.507-2.167)	0.898		
CA125 (<35 vs. ≥35 U/ml)	2.699 (1.199-6.075)	0.016[a]	2.207 (0.938-5.191)	0.070
CYFRA21-1 (<3.3 vs. ≥3.3 ng/ml)	1.078 (0.518-2.245)	0.840		
LDH (<240 vs. ≥240 U/l)	1.214 (0.542-2.718)	0.637		
Cholesterol (<5.2 vs. ≥5.2 mg/dl)	2.744 (0.807-9.328)	0.106		
Triglycerides (<1.7 vs. ≥1.7 mg/dl)	1.396 (0.479-4.067)	0.541		

[a]P<0.05. ICI, immune checkpoint inhibitor; LCNEC, large cell neuroendocrine carcinoma of the lung; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil/lymphocyte ratio; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; CA125, cancer antigen 125; CYFRA21-1, cytokeratin 19 fragment antigen 21-1; LDH, lactate dehydrogenase.

Anti-angiogenic agents can regulate the tumor immune microenvironment and exert synergistic action when combined with ICIs (38,39), highlighting the potential of the combined application of antitumor therapy as a new treatment strategy for advanced LCNEC. In a multicenter, open-label, single-arm, phase II clinical study of surufatinib in combination with toripalimab in patients with advanced neuroendocrine carcinoma (NCT04169672) (40), 21 patients received combination therapy. Among 20 tumor evaluable patients, the objective response rate (4 patients achieved confirmed PR and 10 patients achieved SD) and DCR were 20 and 70%, respectively. The median PFS time was 3.94 months (95% CI, 1.31 to unknown). Based on these findings, the present study further analyzed the efficacy and influencing factors of combined chemotherapy and anti-angiogenesis therapy on the basis of immunotherapy. In the present study, the difference in the DCR between the two groups was not statistically significant. Moreover, immuno-based combination therapy (chemotherapy vs. anti-vascular endothelial growth factor therapy) was not significantly associated with the mPFS or mOS time. Further analysis showed that the ECOG PS score, number of metastatic organs and CA125 level were significantly associated with a poor prognosis, but not with PFS time. In the multivariate Cox regression analysis, CA125 level was still significantly associated with the mOS time. No statistically significant differences were found with regard to the effects of ICI combination therapy on mOS time among patients with elevated levels of NLR, CEA, CYFRA21-1, LDH, cholesterol and triglycerides. Furthermore, patients with advanced LCNEC in the enrolled cohort with a better ECOG PS score, fewer metastatic organs and lower CA125 levels had better outcomes after ICI-based systemic therapy than their counterparts. Considering that 34 and 32 patients were included in groups C and D, respectively, in this retrospective study, the influence of the small sample size and selection bias, and other related factors, could not be excluded. Therefore, expanding the sample size to conduct a multi-cohort study is necessary to verify the findings.

This single-center retrospective study had several limitations. First, no centralized histological review of the enrolled patients was present. LCNEC may be difficult to diagnose, and a small biopsy is usually insufficient; thus, a surgical lung biopsy is usually required (3,4). In the present study, the diagnosis of patients depended on findings from histological examinations, and only some patients underwent next-generation sequencing to determine the pathological type. Second, comprehensive molecular tumor characteristic data that could be applied to most patients were lacking, and the PD-L1 status of some patients was unknown. Therefore, the study did not analyze the prognostic correlation between PD-L1 expression levels and ICI treatment, which needs to be analyzed in future

Table VII. Safety analysis of the total study population based on advanced large cell neuroendocrine carcinoma of the lung.

Parameter	Chemo + ICI (n=34)	Anti-VEGF + ICI (n=32)	P-value	ICI alone (n=7)
Any irAEs, n (%)			0.48	
Yes (n=20)	7 (35.0)	9 (45.0)		4 (20.0)
No (n=53)	27 (50.9)	23 (43.4)		3 (5.7)
irAEs Grade, n (%)			0.49	
2 (n=7)	3 (42.9)	4 (57.1)		0 (0.0)
3 (n=11)	3 (27.3)	5 (45.5)		3 (27.3)
4-5 (n=2)	1 (50.0)	0 (0.0)		1 (50.0)
Treatment permanent discontinuation, n (%)			0.65	
Yes (n=10)	4 (40.0)	5 (50.0)		1 (10.0)
No (n=63)	30 (47.6)	27 (42.9)		6 (11.1)
Systemic corticosteroid use, n (%)			0.001	
Yes (n=35)	24 (68.6)	9 (25.7)		2 (5.7)
No (n=38)	10 (26.3)	23 (60.5)		5 (13.2)
irAE type, n (%)				
Dermatitis (n=2)	0 (0.0)	1 (11.1)		1 (25.0)
Reactive cutaneous capillary endothelial proliferation (n=2)	1 (14.3)	1 (11.1)		0 (0.0)
Hypothyroidism (n=5)	2 (28.5)	2 (22.3)		1 (25.0)
Hyperthyroidism (n=1)	0 (0.0)	1 (11.1)		0 (0.0)
Autoimmune diabetes mellitus (n=1)	1 (14.3)	0 (0.0)		0 (0.0)
Adrenocortical dysfunction (n=1)	0 (0.0)	1 (11.1)		0 (0.0)
Hypophysitis (n=2)	1 (14.3)	1 (11.1)		0 (0.0)
Pneumonitis (n=3)	1 (14.3)	1 (11.1)		1 (25.0)
Immune myocarditis (n=2)	0 (0.0)	1 (11.1)		1 (25.0)
Anaphylactic shock (n=1)	1 (14.3)	0 (0.0)		0 (0.0)

ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; chemo, chemotherapy.

studies. Lastly, other limitations to the present study included its retrospective design, lack of a central pathology assessment and a small sample size of patients receiving ICIs. Overall, the results of the present study suggest that ICIs are a reasonable choice for the treatment of advanced LCNEC in the absence of other treatment options, but prospective clinical studies are needed to confirm the value of ICIs in the treatment of LCNEC.

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Availability of data and materials

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

Authors' contributions

NY, SG, SS and XL conceived and designed the study. Administrative support was provided by NY and XL. SG, ZZ and SS provided study materials or patients. Collection and assembly of data was performed by NY and SG. Data analysis and interpretation was performed by NY, SG, ZZ and SS. NY, SG, SS and XL confirm the authenticity of all the raw data. All authors helped to write the manuscript. All authors have read and approved the manuscript.

Ethics approval and consent to participate

The Ethics Committee of the First Affiliated Hospital of Zhengzhou University approved this study (approval no. 2022-KY-0592-002). The requirement for informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University due to the retrospective design and use of anonymized patient information. All procedures have been performed in accordance with the Declaration of Helsinki.

Patient consent for publication

The requirement for informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (approval no. 2022-KY-0592-002).

Competing interests

The authors declare that they have no competing interests.

References

1. Takei H, Asamura H, Maeshima A, Suzuki K, Kondo H, Niki T, Yamada T, Tsuchiya R and Matsuno Y: Large cell neuroendocrine carcinoma of the lung: A clinicopathologic study of eighty-seven cases. J Thorac Cardiovasc Surg 124: 285-292, 2002.
2. Iyoda A, Hiroshima K, Toyozaki T, Haga Y, Fujisawa T and Ohwada H: Clinical characterization of pulmonary large cell neuroendocrine carcinoma and large cell carcinoma with neuroendocrine morphology. Cancer 91: 1992-2000, 2001.
3. Corbett V, Arnold S, Anthony L and Chauhan A: Management of large cell neuroendocrine carcinoma. Front Oncol 11: 653162, 2021.
4. Andrini E, Marchese PV, De Biase D, Mosconi C, Siepe G, Panzuto F, Ardizzoni A, Campana D and Lamberti G: Large cell neuroendocrine carcinoma of the lung: Current understanding and challenges. J Clin Med 11: 1461, 2022.
5. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, *et al*: The 2015 World Health Organization classification of lung tumors: Impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 10: 1243-1260, 2015.
6. Ferrara MG, Stefani A, Simbolo M, Pilotto S, Martini M, Lococo F, Vita E, Chiappetta M, Cancellieri A, D'Argento E, *et al*: Large cell Neuro-Endocrine carcinoma of the lung: Current treatment options and potential future opportunities. Front Oncol 11: 650293, 2021.
7. Rekhtman N, Pietanza MC, Hellmann MD, Naidoo J, Arora A, Won H, Halpenny DF, Wang H, Tian SK, Litvak AM, *et al*: Next-Generation sequencing of pulmonary large cell neuroendocrine carcinoma reveals small cell carcinoma-like and non-small cell carcinoma-like subsets. Clin Cancer Res 22: 3618-3629, 2016.
8. George J, Walter V, Peifer M, Alexandrov LB, Seidel D, Leenders F, Maas L, Müller C, Dahmen I, Delhomme TM, *et al*: Integrative genomic profiling of large-cell neuroendocrine carcinomas reveals distinct subtypes of high-grade neuroendocrine lung tumors. Nat Commun 9: 1048, 2018.
9. Zhuo M, Guan Y, Yang X, Hong L, Wang Y, Li Z, Chen R, Abbas HA, Chang L, Gong Y, *et al*: The prognostic and therapeutic role of genomic subtyping by sequencing tumor or cell-free DNA in pulmonary large-cell neuroendocrine carcinoma. Clin Cancer Res 26: 892-901, 2020.
10. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, Escriu C and Peters S; ESMO Guidelines Committee: Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 28 (Suppl_4): iv1-iv21, 2017.
11. Welter S, Aigner C and Roesel C: The role of surgery in high grade neuroendocrine tumours of the lung. J Thorac Dis 9 (Suppl 15): S1474-S1483, 2017.
12. Moon JY, Choi SH, Kim TH, Lee J, Pyo JH, Kim YT, Lee SJ, Yoon HI, Cho J and Lee CG: Clinical features and treatment outcomes of resected large cell neuroendocrine carcinoma of the lung. Radiat Oncol J 39: 288-296, 2021.
13. Gu J, Gong D, Wang Y, Chi B, Zhang J, Hu S and Min L: The demographic and treatment options for patients with large cell neuroendocrine carcinoma of the lung. Cancer Med 8: 2979-2993, 2019.
14. Wakeam E, Adibfar A, Stokes S, Leighl NB, Giuliani ME, Varghese TK Jr and Darling GE: Defining the role of adjuvant therapy for early-stage large cell neuroendocrine carcinoma. J Thorac Cardiovasc Surg 159: 2043-2054.e9, 2020.
15. Iyoda A, Hiroshima K, Moriya Y, Takiguchi Y, Sekine Y, Shibuya K, Iizasa T, Kimura H, Nakatani Y and Fujisawa T: Prospective study of adjuvant chemotherapy for pulmonary large cell neuroendocrine carcinoma. Ann Thorac Surg 82: 1802-1807, 2006.
16. Zhang JT, Li Y, Yan LX, Zhu ZF, Dong XR, Chu Q, Wu L, Zhang HM, Xu CW, Lin G, *et al*: Disparity in clinical outcomes between pure and combined pulmonary large-cell neuroendocrine carcinoma: A multi-center retrospective study. Lung Cancer 139: 118-123, 2020.
17. Le Treut J, Sault MC, Lena H, Souquet PJ, Vergnenegre A, Le Caer H, Berard H, Boffa S, Monnet I, Damotte D and Chouaid C: Multicentre phase II study of Cisplatin-Etoposide chemotherapy for advanced large-cell neuroendocrine lung carcinoma: the GFPC 0302 study. Ann Oncol 24: 1548-1552, 2013.
18. Rossi G, Cavazza A, Marchioni A, Longo L, Migaldi M, Sartori G, Bigiani N, Schirosi L, Casali C, Morandi U, *et al*: Role of chemotherapy and the receptor tyrosine kinases KIT, PDGFRalpha, PDGFRbeta, and Met in large-cell neuroendocrine carcinoma of the lung. J Clin Oncol 23: 8774-8785, 2005.
19. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, *et al*: Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375: 1823-1833, 2016.
20. Hanna NH, Robinson AG, Temin S, Baker S, Brahmer JR, Ellis PM, Gaspar LE, Haddad RY, Hesketh PJ, Jain D, *et al*: Therapy for Stage IV non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol 39: 1040-1091, 2021.
21. Dudnik E, Kareff S, Moskovitz M, Kim C, Liu SV, Lobachov A, Gottfried T, Urban D, Zer A, Rotem O, *et al*: Real-world survival outcomes with immune checkpoint inhibitors in large-cell neuroendocrine tumors of lung. J Immunother Cancer 9: e001999, 2021.
22. Agar C, Geier M, Léveiller G, Lamy R, Bizec JL, Tiercin M, Bernier C, Robinet G, Léna H, Ricordel C and Corre R: Brief report on the efficacy of nivolumab in patients with previously treated advanced large-cell neuroendocrine cancer of the lung. JTO Clin Res Rep 2: 100129, 2021.
23. Chauhan A, Arnold SM, Kolesar J, Thomas HE, Evers M and Anthony L: Immune checkpoint inhibitors in large cell neuroendocrine carcinoma: Current status. Oncotarget 9: 14738-14740, 2018.
24. Sherman S, Rotem O, Shochat T, Zer A, Moore A and Dudnik E: Efficacy of immune check-point inhibitors (ICPi) in large cell neuroendocrine tumors of lung (LCNEC). Lung Cancer 143: 40-46, 2020.
25. Yates JW, Chalmer B and McKegney FP: Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 45: 2220-2224, 1980.
26. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al*: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009.
27. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.
28. Lowczak A, Kolasinska-Cwikla A, Osowiecka K, Glinka L, Palucki J, Rzepko R, Doboszynska A and Cwikla JB: Outcomes of patients with pulmonary large cell neuroendocrine carcinoma in I-IV stage. Medicina (Kaunas) 57: 118, 2021.
29. Fujiwara Y, Sekine I, Tsuta K, Ohe Y, Kunitoh H, Yamamoto N, Nokihara H, Yamada K and Tamura T: Effect of platinum combined with irinotecan or paclitaxel against large cell neuroendocrine carcinoma of the lung. Jpn J Clin Oncol 37: 482-486, 2007.
30. Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, Huemer F, Losonczy G, Johnson ML, Nishio M, *et al*: First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 379: 2220-2229, 2018.
31. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair MJ, Özgüroğlu M, Ji JH, *et al*: Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): Updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 22: 51-65, 2021.
32. Yang Q, Xu Z, Chen X, Zheng L, Yu Y, Zhao X, Chen M, Luo B, Wang J and Sun J: Clinicopathological characteristics and prognostic factors of pulmonary large cell neuroendocrine carcinoma: A large population-based analysis. Thorac Cancer 10: 751-760, 2019.

33. He Y, Liu H, Wang S and Chen Y: Prognostic nomogram predicts overall survival in pulmonary large cell neuroendocrine carcinoma. PLoS One 14: e0223275, 2019.
34. Chen ZQ, Huang LS and Zhu B: Assessment of seven clinical tumor markers in diagnosis of non-small-cell lung cancer. Dis Markers 2018: 9845123, 2018.
35. Peng L, Wang Y, Liu F, Qiu X, Zhang X, Fang C, Qian X and Li Y: Peripheral blood markers predictive of outcome and immune-related adverse events in advanced non-small cell lung cancer treated with PD-1 inhibitors. Cancer Immunol Immunother 69: 1813-1822, 2020.
36. Roesel C, Welter S, Kambartel KO, Weinreich G, Krbek T, Serke M, Ibrahim M, Alnajdawi Y, Plönes T and Aigner C: Prognostic markers in resected large cell neuroendocrine carcinoma: A multicentre retrospective analysis. J Thorac Dis 12: 466-476, 2020.
37. Miyoshi T, Umemura S, Matsumura Y, Mimaki S, Tada S, Makinoshima H, Ishii G, Udagawa H, Matsumoto S, Yoh K, *et al*: Genomic profiling of large-cell neuroendocrine carcinoma of the lung. Clin Cancer Res 23: 757-765, 2017.
38. Liang H and Wang M: Prospect of immunotherapy combined with anti-angiogenic agents in patients with advanced non-small cell lung cancer. Cancer Manag Res 11: 7707-7719, 2019.
39. Yi M, Jiao D, Qin S, Chu Q, Wu K and Li A: Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. Mol Cancer 18: 60, 2019.
40. Shen L, Yu X, Lu M, Zhang X, Cheng Y, Zhang Y, Li Z, Xu J, Weng D, Wu C, *et al*: Surufatinib in combination with toripalimab in patients with advanced neuroendocrine carcinoma: Results from a multicenter, open-label, single-arm, phase II trial. J Clin Oncol 39: e16199, 2021.