Original Article

Efficacy and safety of immune checkpoint inhibitors in lung large-cell neuroendocrine carcinoma

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Background: Lung large-cell neuroendocrine carcinoma (L-LCNEC) is a rare and highly aggressive neuroendocrine tumor. There is currently no standard therapeutic regimen, and systemic chemotherapy results in poor prognosis. Due to the rarity of L-LCNEC, the efficacy and safety of immune checkpoint inhibitors (ICIs) remain unclear.

Methods: This study included 34 L-LCNEC patients administered ICIs at Zhejiang Cancer Hospital, from February 6, 2018 to February 6, 2023. The treatment responses were evaluated. Fisher's exact test was used to compare categorical variables, and the Kaplan-Meier method was used for survival analyses. Cox regression was used for multivariate analysis.

Results: The objective response rate (ORR) of 34 patients was 29.4%, the disease control rate (DCR) was 82.4%, the median progression-free survival (PFS) was 6.30 months, and the median overall survival (OS) was 14.77 months. The ORRs of combined LCNEC (n=7) and pure LCNEC (n=27) were 14.3% and 33.3%; the DCRs were 100% and 77.8%; the median PFSs were 12.48 and 5.6 months (P=0.032); and the median OSs were 21.27 and 14.73 months, respectively (P=0.233). The observed incidence of immune-related adverse events (irAEs) was 61.8%, primarily occurring in grades 1/2 (58.8%) and grade 3 (5.9%). Elevated aminotransferases (14.7%), pneumonia (8.8%), and fatigue (8.8%) were the most common irAEs.

Conclusions: ICIs treatment showed efficacy and safety in advanced L-LCNEC, with the potential for greater benefits in the combined LCNEC subtype.

Keywords: Efficacy; immune checkpoint inhibitors (ICIs); immune-related adverse events (irAEs); lung large-cell neuroendocrine carcinoma (L-LCNEC); safety

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Introduction

Lung large-cell neuroendocrine carcinoma (L-LCNEC) is a rare and highly aggressive malignancy, representing approximately 2.0–3.5% of all primary lung cancers (1). In the 2021 World Health Organization (WHO) histological classification of lung tumors, L-LCNEC is classified as a neuroendocrine tumor with the following pathological criteria: non-small cell cytological features, neuroendocrine morphology, high mitotic rate, and positive expression of at least one marker including chromogranin-A, synaptophysin, or neural-cell adhesion molecule-1 (2). Additionally, about 10–25% of patients with LCNEC are diagnosed with combined LCNEC (c-LCNEC), characterized by the coexistence of LCNEC with adenocarcinoma (AC), squamous cell carcinoma (SCC), or other components (2-6). c-LCNEC typically indicates poorer prognosis compared to pure LCNEC (p-LCNEC), as associated with a higher incidence of lymph nodes and distant metastasis (1,7).

For L-LCNEC patients, even after early surgical resection, the postoperative recurrence is still high, with 63.9–82.0% of patient experiencing recurrence in 1 year (8-10). Currently, no standard therapeutic regimen exists for locally advanced or metastatic unresectable L-LCNEC. Due to its distinct biological characteristics, L-LCNEC is known to be more aggressive than non-small cell lung cancer (NSCLC) such as AC, and demonstrates a lower response rate to standard chemotherapy regimens used for small-cell lung cancer (SCLC). There is considerable debate regarding whether L-LCNEC should be approached and treated similarly to SCLC or NSCLC (11-13). In previous studies, the overall survival (OS) of advanced L-LCNEC patients receiving chemotherapy was approximately 7.0–12.6 months (14-18). Systemic chemotherapy appears to be of limited value to L-LCNEC patients. Therefore, it is necessary to develop more effective therapeutic regimens to treat L-LCNEC.

Immune checkpoint inhibitors (ICIs) have provided a major paradigm shift in the management of various cancers (19). For example, ICIs have been approved as a first-line treatment for NSCLC and SCLC, leading to significant improvements in prognoses (20,21). Despite the lack of prospective data correlating ICIs and L-LCNEC, several retrospective studies and case reports have been reported, providing insight into the effectiveness of ICIs for L-LCNEC (22-30). However, due to the rarity of L-LCNEC, the efficacy and safety of ICIs application remain unclear, and different pathological types may exhibit diverse treatment responses and prognoses.

This study therefore aimed to evaluate the efficacy and safety of ICIs on the treatment of advanced L-LCNEC. Moreover, we investigated the differences in the efficacy of ICIs application between pure and combined pathological types. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-348/rc).

Highlight box

Key findings

- Immune checkpoint inhibitors (ICIs) showed efficacy in lung large-cell neuroendocrine carcinoma (L-LCNEC) patients, with the potential for greater benefits in the combined LCNEC subtype.

What is known and what is new?

- Immunotherapy significantly improves the prognoses of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) patients. However, due to the rarity of L-LCNEC patients, the efficacy and safety in LCNEC remain unclear.
- In addition to evaluating the efficacy and safety of ICIs for the treatment of L-LCNEC, we also analyzed the difference in efficacy between treatments for combined and pure L-LCNEC patients.

What is the implication, and what should change now?

- ICIs is a promising potential therapeutic regimen for L-LCNEC. However, larger cohort studies, especially prospective studies, are needed to further investigate the effectiveness.

Methods

Study design

The medical records of ICI-treated L-LCNEC patients at Zhejiang Cancer Hospital (Hangzhou, Zhejiang) from February 6, 2018 to February 6, 2023 were retrospectively analyzed. All patients met 2021 WHO LCNEC pathological diagnostic criteria using pathological and immunohistochemical (IHC) analyses. Cases with diagnostic uncertainties or controversies were excluded from the analysis. In non-surgical cases, additional tissue sampling was often performed after the initial biopsy to ensure accurate pathological assessment. The final diagnosis was established by two experienced pathologists. According to pathological diagnoses and IHC analyses, LCNEC with AC, SCC, or other components were defined as c-LCNEC, while LCNEC without other components was defined as p-LCNEC (2). The 22C3 pharmDx companion diagnostic assay (Agilent Technologies, Santa Clara, CA, USA) was

utilized for IHC analysis of programmed cell death 1 ligand 1 (PD-L1) in formalin-fixed paraffin-embedded tissues. A tumor proportion score (TPS) of ≥1% was considered positive. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee at Zhejiang Cancer Hospital (No. IRB-2023-136) and individual consent for this retrospective analysis was waived.

Assessment of treatment responses

Data collection for this study involved comprehensive reviews of patients' medical and follow-up records. Therapeutic regimens consisted of monotherapy or combination therapy clinical efficacy was assessed via regular computed tomography scans, typically taking place every two cycles or in the event of significant disease progression.

A panel of at least two independent medical professionals assessed treatment efficacy using the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1). Disagreements among professionals were collaboratively resolved through information re-reviews and dialogues, and ultimately confirming both the objective response rate (ORR) and disease control rate (DCR). OS was defined as the time from advanced L-LCNEC diagnosis to death or the last follow-up. Progression-free survival (PFS) was defined as the time from the initial day of ICI treatment to disease progression or death, or to the last follow-up for surviving patients without disease progression.

Assessment of adverse events (AEs)

AEs and safety were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE V5.0). Immune-related adverse events (irAEs) were AEs associated with the activation of the immune system and had an immunological basis. All irAEs were diagnosed and graded from 1 to 5 by a panel of at least two independent medical professionals.

Statistical analysis

Statistical analysis was conducted using SPSS Statistics for Windows, Version 25.0 (IBM, Armonk, NY, USA) and Prism, Version 9.0 (GraphPad, San Diego, CA, USA). Categorical variables were compared using Fisher's exact test, and statistical significance was set at a two-sided probability (P) value <0.05. To estimate the PFS and OS, the Kaplan-Meier method was used, and the log-rank test was used to compare groups. Cox regression was used for multivariate analysis, and corresponding forest plots were generated. As of February 6, 2023, the last follow-up data were recorded.

Results

Patient characteristics

From February 6, 2018 to February 6, 2023, 34 ICI-treated L-LCNEC patients were included in this study. *Table 1* provides an overview of the patients' baseline characteristics. The median age of patients receiving ICI treatment was 64.5 years (range, 46–79 years), and the majority of patients were male (31/34, 91.2%) and former or current smokers (28/34, 82.4%). The Eastern Cooperative Oncology Group performance status was 2 in two patients (5.9%) and 0/1 in 32 (94.1%). Tumor-node, metastasis staging showed that most patients (29/34, 85.3%) were stage IV, and extrathoracic metastases were observed in 23 patients (23/34, 67.6%). Fifteen patients (15/34, 44.1%) had undergone early surgical resection with the median time to recurrence being 7.6 months (range, 1.3–68.9 months). Excluding these 15 patients, 15 of the remaining patients (44.1%) underwent percutaneous lung biopsy, and four underwent bronchial biopsy to confirm pathological diagnoses. Pathological examination revealed seven patients (7/34, 20.6%) were c-LCNEC, while 27 patients (27/34, 79.4%) were p-LCNEC. The median expression level of neuron-specific enolase (NSE) was 18.53 μg/L (range, 11.00–370.00 μg/L).

Table 2 summarizes the ICI treatment characteristics, where more than half of the patients (19/34, 55.9%) received second- or higher-line ICI treatments. Only two patients (5.9%) received ICI monotherapy, while 32 (94.1%) received ICIs in combination with chemotherapy. The most frequent ICI types were Tislelizumab (7/34, 20.6%), Sintilimab (7/34, 20.6%), and Camrelizumab (5/34, 14.7%). Of the 34 patients, 9 (26.5%) were tested for PD-L1 expression, and five patients (5/34, 14.7%) were PD-L1 positive. As of the last follow-up, the ICI treatments were ongoing in two patients (5.9%).

Treatment response and survival analysis

Among the 34 ICIs-treated L-LCNEC patients, 10 (29.4%)

Table 1 Baseline characteristics of 34 lung large-cell neuroendocrine carcinoma patients

Characteristics	LCNEC (n=34)
Sex, n (%)	
Male	31 (91.2)
Female	3 (8.8)
Age (years), median [range]	
At diagnosis	62.5 [45–78]
At the start of ICIs	64.5 [46–79]
Smoking history, n (%)	
Current/past smoker	28 (82.4)
Never smoker	6 (17.6)
ECOG PS at ICI initiation, n (%)	
0–1	32 (94.1)
2–3	2 (5.9)
TNM staging, n (%)	
III	5 (14.7)
IV	29 (85.3)
Diagnosis method, n (%)	
Surgery	15 (44.1)
Percutaneous lung biopsy	15 (44.1)
Bronchial biopsy	4 (11.8)
Histological subtype, n (%)	
Pure LCNEC	27 (79.4)
Combined LCNEC	7 (20.6)
NSE (μg/L), median [range]	18.53 [11.00–370.00]
Extrathoracic metastases, n (%)	
Yes	23 (67.6)
No	11 (32.4)
Previous surgery, n (%)	
Yes	15 (44.1)
No	19 (55.9)
Recurrence time (months), median [range]	7.6 [1.3–68.9]
Radiotherapy, n (%)	
Yes	22 (64.7)
No	12 (35.3)

LCNEC, large-cell neuroendocrine carcinoma; ICIs, immune checkpoint inhibitors; ECOG PS, Eastern Cooperative Oncology Group Performance Status; TNM, tumor, node, metastasis; NSE, neuron-specific enolase.

Table 2 Baseline characteristics of immune checkpoint inhibitor treatment of lung LCNEC patients

Characteristics	LCNEC (n=34)
Line of ICIs treatment, n (%)	
First	15 (44.1)
Second or more	19 (55.9)
ICIs regimens, n (%)	
Monotherapy	2 (5.9)
Combination treatment	32 (94.1)
ICI type, n (%)	
Tislelizumab/Sintilimab/ Camrelizumab	7/7/5 (20.6/20.6/14.7)
Durvalumab/Navulizumab/ Atezolizumab	4/3/3 (11.8/8.8/8.8)
Pembrolizumab/Toripalimab	3/2 (8.8/5.9)
PD-L1 status, n (%)	
Positive	5 (14.7)
Negative	4 (11.8)
NA	25 (73.5)
Best response, n (%)	
Partial response	10 (29.4)
Stable disease	18 (52.9)
Progressive disease	6 (17.7)
Reason for discontinuation, n (%)	
Progressive	31 (91.2)
Toxicity	1 (2.9)
Ongoing	2 (5.9)
Median PFS (95% CI) (months)	6.30 (4.33–8.27)
1-year PFS rate	17.6% (6/34)
Median OS (95% CI) (months)	14.77 (10.07–19.46)
1-year OS rate	64.7% (22/34)

LCNEC, large-cell neuroendocrine carcinoma; ICIs, immune checkpoint inhibitors; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; CI, confidence interval; OS, overall survival.

achieved partial response (PR), and 18 (52.9%) achieved stable disease (SD). The ORR of ICI treatment was 29.4% and the DCR was 82.4%. The median PFS was 6.30 months [95% confidence interval (CI): 4.33–8.27], the 1-year PFS was 17.6% (6/34), and the median OS was 14.77 months

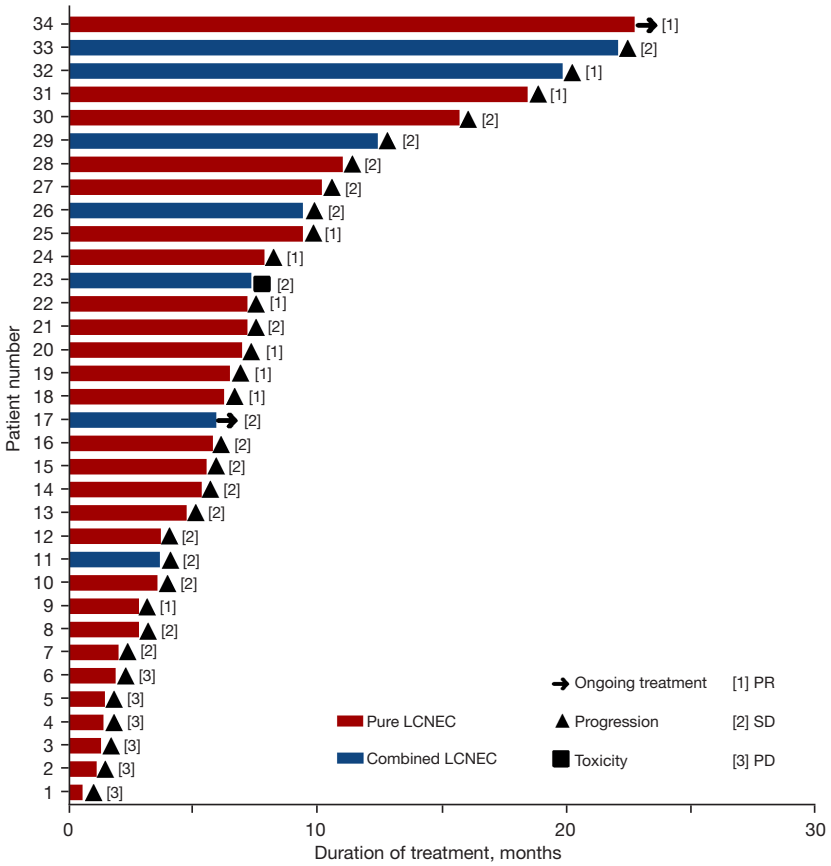

Figure 1 Swimmer plot of immune checkpoint inhibitors-treated lung LCNEC patients. LCNEC, large-cell neuroendocrine carcinoma; PR, partial response; SD, stable disease; PD, progressive disease.

(95% CI: 10.07–19.46), with a 1-year OS of 64.7% (22/34). *Figure 1* provides specifics on the ICI treatments.

According to the number of treatment lines, 34 patients were divided into first-line and second- or higher-line groups. Among the 15 patients (44.1%) in the first-line group, 8 (53.3%) achieved PR and 5 (33.3%) achieved SD. Of the 19 patients (55.9%) in the second- or higher-line group, 2 (10.5%) achieved PR, and 13 (68.4%) achieved SD. The ORR of ICIs as first-line treatment (53.3%, 8/15) was higher than that of the second- or higher-line (10.5%, 2/19), with a statistically significant difference (P=0.007). There was no significant difference in DCR between the first- and second- or higher-line groups (86.7%, 13/15 *vs.* 78.9%, 15/19, P=0.558). The median PFS and OS of the 15 patients receiving first-line treatment were 6.53 months (95% CI: 3.54–9.52) and 12.13 months (95% CI: 7.43–16.83), respectively. The median PFS and OS of the 19 patients receiving second- or higher-line treatment were 5.87 months (95% CI: 3.26–8.47) and 19.47 months (95% CI: 14.28–24.66), respectively. There was no significant difference in PFS between the two groups (P=0.949, *Figure 2A*), but the difference in OS was statistically significant (P=0.031, *Figure 2B*).

All L-LCNEC patients were further grouped into the c-LCNEC (7/34, 20.6%) and p-LCNEC (27/34, 79.4%) groups according to pathological types. Comparison of the characteristics between the two groups is listed in Table S1. The ORRs of the c-LCNEC and p-LCNEC groups were 14.3% (1/7) and 33.3% (9/37), respectively, with no significant difference (P=0.261). The DCRs of the two groups were 100% (7/7) and 77.8% (21/27), respectively, with no statistical difference (P=0.261). The median PFS and OS in the c-LCNEC group were 12.47 months (95% CI: 6.82–18.12) and 21.27 months (95% CI: 3.37–39.17), respectively. The median PFS and OS in the p-LCNEC group were 5.60 months (95% CI: 3.12–8.08) and 14.73 months (95% CI: 12.71–16.76), respectively. The PFS and OS survival curves (*Figure 2C,2D*) were separated

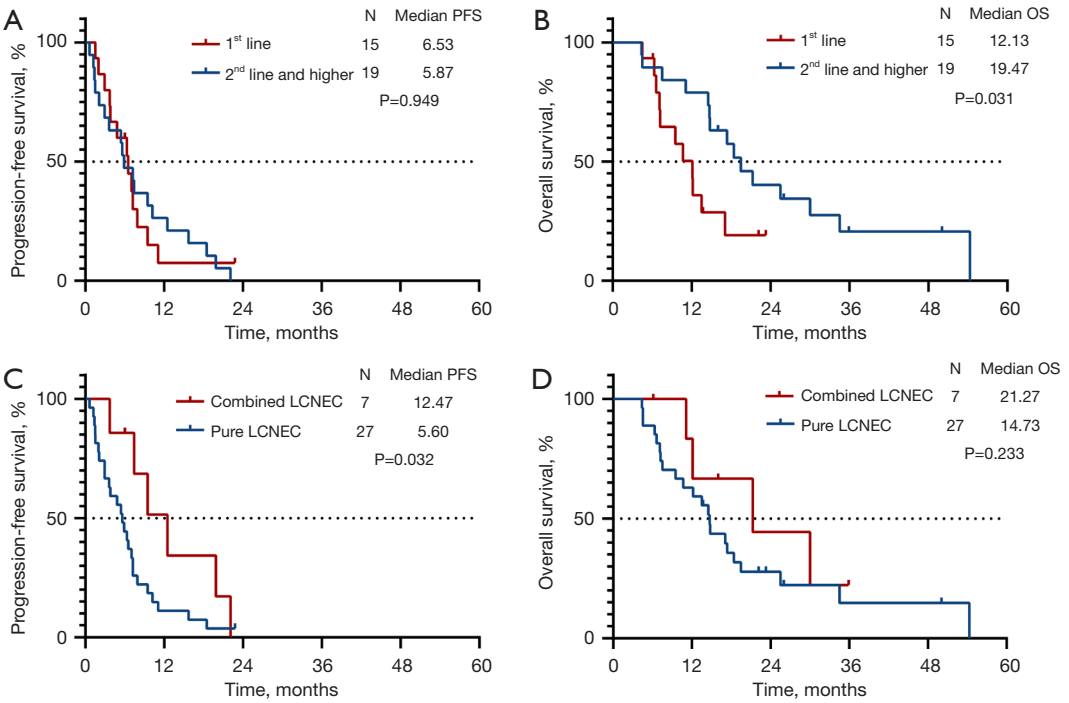

Figure 2 Kaplan-Meier curves of PFS and OS according to treatments and pathological types. (A) PFS of first-line *vs.* second- and higher-line treatments. (B) OS of first-line *vs.* second- and higher-line treatments. (C) PFS of combined LCNEC *vs.* pure LCNEC patients. (D) OS of combined LCNEC *vs.* pure LCNEC patients. PFS, progression-free survival; OS, overall survival; LCNEC, large-cell neuroendocrine carcinoma.

between the two groups, and the difference in PFS was statistically significant (P=0.032, *Figure 2C*), but the difference in OS was not statistically significant (P=0.233, *Figure 2D*).

Safety and toxicity evaluations

The 34 L-LCNEC patients included in the study were evaluated for treatment toxicity, and the irAEs of any grade are recorded in *Table 3*. Among the 34 patients, irAEs occurred in 21 patients (61.8%), mainly grades 1 (38.2%, 13/34) and 2 (20.6%, 7/34). The incidence of grade 3 irAE patients was 5.9% (2/34), and no irAE patients above grade 3 occurred. Elevated transaminases (14.7%, 5/34), pneumonia (8.8%, 3/34), and fatigue (8.8%, 3/34) were the most common irAEs. Two (5.9%) patients had grade 3 pneumonia, and 1 (2.9%) patient discontinued ICI treatment.

Discussion

Due to the rarity of L-LCNEC and the lack of relevant prospective studies, there is currently no consensus on an effective therapeutic regimen for advanced L-LCNEC (20). However, our results indicated that ICIs treatment showed efficacy in L-LCNEC patients, especially in c-LCNEC patients. Moreover, the toxicity of treatment was manageable. To the best of our knowledge, our study presents the first comparative analysis between c-LCNEC and p-LCNEC patients, and is the largest record of irAEs patients.

In our retrospective study, the ORRs and DCRs of 34 ICIs-treated L-LCNEC patients were 29.4% and 82.4%, respectively, and the median PFS and OS were 6.30 and 14.77 months, respectively. These results were consistent with comparable retrospective studies (Table S2). In two studies with sample sizes greater than 20, Dudnik *et al.* (28) reported a median OS of 12.4 months (95% CI: 10.7–23.4) in a cohort of 41 ICIs-treated L-LCNEC patients. Sherman *et al.* (27) reported an ORR of 33%, median PFS of 4.2 months, and median OS of 11.8 months in a cohort of 21 ICIs-treated L-LCNEC patients. Compared with their results, our results showed a longer PFS and OS, which may be attributed to the fact that we included more patients

Table 3 Immune-related adverse events of 34 lung large-cell neuroendocrine carcinoma patients

Immune-related adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonia	0	1	2	0	0
Elevated aminotransferases	3	2	0	0	0
Fatigue	2	1	0	0	0
Constipation	1	1	0	0	0
Cardiovascular toxicity	0	1	0	0	0
Nephritis	0	1	0	0	0
Nausea	2	0	0	0	0
Diarrhea	2	0	0	0	0
Arthritis	1	0	0	0	0
Thrombocytopenia	1	0	0	0	0
Fever	1	0	0	0	0

with PS 0/1 (32/34, 94.1%) and a higher proportion of ICIs combined with chemotherapy (32/34, 94.1%). In several other small sample studies (8–13 patients), the ORR was 9.1–75.0%, the PFS was 2.70–6.85 months, and the OS was 4.6–25.2 months (24-26). When comparing the first-line and later-line treatments, we observed a shorter OS in the first-line (12.13 months) compared to the latter (19.47 months, P=0.031), despite achieving a higher ORR in the first-line (53.3% *vs.* 10.5%, P=0.007). We speculate that these results may be attributed to the inclusion of relatively small sample size and the potential biases introduced by baseline characteristics, such as adjuvant chemotherapy after surgery, PD-L1 expression, and subsequent treatment regimens, which could have influenced the OS outcome. Although we could not directly compare our results with historical control studies, the above studies and our study still showed efficacy of ICIs for the treatment of L-LCNEC. Consequently, ICIs are a potential therapeutic regimen for L-LCNEC patients.

L-LCNEC can be classified as a combined or pure type according to its components (2). Our cohort included 7 c-LCNEC patients, with an occurrence rate of 20.6% falling within the range of 10–25% reported in previous studies (2-6). Most patients were diagnosed by surgery (85.7%) and c-LCNEC with AC (57.1%). Previous research consistently associates c-LCNEC with poorer prognosis and the occurrence of multiple metastases (1,7,12,31,32). In Zhang's study (12), in which we participated previously, a total of 220 p-LCNEC and 30 c-LCNEC patients were analyzed. The median OS was found to be significantly longer in p-LCNEC compared to c-LCNEC. However, Tsutsumi *et al.* (29) reported that a 73-year-old c-LCNEC patient with brain metastases achieved PR after receiving atezolizumab combined with carboplatin and nab-paclitaxel, which was maintained for 12 months. Xu *et al.* (30) reported a 54-year-old locally advanced c-LCNEC patient who was maintained with durvalumab after concurrent radiotherapy and chemotherapy, who achieved complete remission. The above cases suggested that c-LCNEC patients may exhibit favorable treatment response to ICIs. We therefore further analyzed the efficacy of different pathological types of ICI-treated L-LCNEC patients. Survival analysis revealed that c-LCNEC patients receiving ICI treatment had longer PFS compared to p-LCNEC patients (12.47 *vs.* 5.60 months, P=0.032), while OS showed a longer duration but did not reach statistical significance (21.27 *vs.* 14.73 months, P=0.233), possibly due to the small sample size. In subsequent multivariate analysis (Figure S1), pathological type (HR =0.281, 95% CI: 0.091–0.865, P=0.027) remained a significant factor affecting PFS, but not for OS. Additionally, in three cases mixed with AC, with an evaluable composition ratio, AC accounted for 80%, 30%, and 15%. The corresponding PFS times were 9.47, 6.00, and 3.73 months. Therefore, we propose the potential for greater benefit of ICIs to c-LCNEC, which may be related to the high tumor mutational burden (33) and the distinct biological characteristics of combined components, but more clinical evidence is still needed.

In addition, we recorded all observed irAEs. Overall, the toxicity profile of ICI treatment in L-LCNEC patients

was manageable, with grade 3 irAEs detected in only 5.9% of patients (2/34), and most irAEs were grade 1/2 (55.9%, 19/34). Elevated aminotransferases (14.7%, 5/34), pneumonia (8.8%, 3/34), and fatigue (8.8%, 3/34) were the most common irAEs. Specifically, pneumonia occurred in three patients, and one had to discontinue treatment accordingly. No patients died from ICI treatment.

Our study had several limitations. First, the rarity of L-LCNEC led to a small sample size, potentially limiting the generalizability of our findings. Second, as a retrospective study, our analysis depended on medical records, which might have introduced biases in data collection. Third, the absence of a centralized pathological revision could have resulted in the inclusion of certain c-LCNEC cases within the p-LCNEC group. Additionally, a considerable number of cases lacked PD-L1 assessment, which could introduce bias when evaluating the impact of treatment outcomes.

Conclusions

ICIs showed therapeutic efficacy in treating L-LCNEC patients, with the potential for greater benefits in the c-LCNEC subtype. However, larger cohort studies, especially prospective studies, are needed to further investigate their effectiveness.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-348/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-348/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-348/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-348/coif). ZS reports that this study was funded by the Medical Scientific Research Foundation of Zhejiang Province (No. 2022KY653). ZS was sponsored by Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Ethics Committee at Zhejiang Cancer Hospital (No. IRB-2023-136) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Comparison of the characteristics of combined LCNEC and pure LCNEC patients

Characteristics	Combined LCNEC (n=7)	Pure LCNEC (n=27)
Sex, n (%)		
Male	6 (85.7)	25 (92.6)
Female	1 (14.3)	2 (7.4)
Age (years), median [range]		
At the start of ICIs	68 [56–71]	62 [46–79]
Smoking history, n (%)		
Current/past smoker	6 (85.7)	22 (81.5)
Never smoker	1 (14.3)	5 (18.5)
ECOG PS at ICI initiation, n (%)		
0/1	6 (85.7)	26 (96.3)
2/3	1 (14.3)	1 (3.7)
TNM staging, n (%)		
III	1 (14.3)	4 (14.8)
IV	6 (85.7)	23 (85.2)
Diagnosis method, n (%)		
Surgery	6 (85.7)	9 (33.3)
Percutaneous lung biopsy	0 (0)	15 (55.5)
Bronchial biopsy	1 (14.3)	3 (11.1)
Histological subtype, n (%)		
LCNEC	–	27 (100.0)
LCNEC + AC	4 (57.1)	–
LCNEC + SCC	3 (42.9)	–
Extrathoracic metastases, n (%)		
Yes	5 (71.4)	18 (66.7)
No	2 (28.6)	9 (33.3)
Line of ICIs treatment, n (%)		
First	3 (42.9)	12 (44.4)
Second or more	4 (57.1)	15 (55.6)
ICIs regimens, n (%)		
Monotherapy	1 (14.3)	1 (3.7)
Combination treatment	6 (85.7)	26 (96.3)
PD-L1 status, n (%)		
Positive	1 (14.3)	4 (14.8)
Negative	1 (14.3)	3 (11.1)
NA	5 (71.4)	20 (74.1)
Best response, n		
Partial response	1	9
Stable disease	6	12
Progressive disease	0	6

LCNEC, large-cell neuroendocrine carcinoma; n, number; ICIs, immune checkpoint inhibitors; ECOG PS, Eastern Cooperative Oncology Group Performance Status; TNM, tumor, node, metastasis; AC, adenocarcinoma; SCC, Squamous cell carcinoma; PD-L1, programmed cell death 1 ligand 1; NA, not available.

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Table S2 Summary of previous studies

Author	Study design	Patients received ICIs (n)	Description	Results
Vrontis *et al.* (24)	Retrospective	8	8 LCNEC patients received platinum doublet plus atezolizumab as first-line treatment	ORR, 75% mPFS, 6.85 months Median response duration: 5.5 months
Naganuma *et al.* (25)	Retrospective	11	11 LCNEC patients received ICIs monotherapy	ORR, 9.1%; DCR, 36.4% mPFS, 2.7 months; mOS, 4.6 months 9 patients had irAEs 1 patient had serious irAEs
Shirasawa *et al.* (26)	Retrospective	13	13 LCNEC patients received ICIs 57 LCNEC patients did not receive ICIs	ICIs group: ORR, 39% mPFS, 4.2 months; mOS, 25.2 months Without ICIs group: mOS, 10.9 months (P=0.02)
Sherman *et al.* (27)	Retrospective	23	Group A1: LCNEC patients treated with ICIs (n=23) Group A1*: LCNEC patients treated with ICIs as a monotherapy (n=21) Group A2: LCNEC patients not treated with ICIs (n=14)	A1 group: mOS, 14.5 months A1* group: ORR, 33% mPFS, 4.2 months; mOS, 11.8 months A2 group: mOS, 10.3 months
Dudnik *et al.* (28)	Retrospective	41	41 LCNEC patients received ICIs 84 LCNEC patients did not receive ICIs	ICIs group: mOS, 12.4 months Without ICIs group: mOS, 6.0 months

*, monotherapy. ICIs, immune checkpoint inhibitors; LCNEC, large-cell neuroendocrine carcinoma; ORR, objective response rate; mPFS, median progression-free-survival; DCR, disease control rate; mOS, median Overall survival; irAEs, immune-related adverse events.

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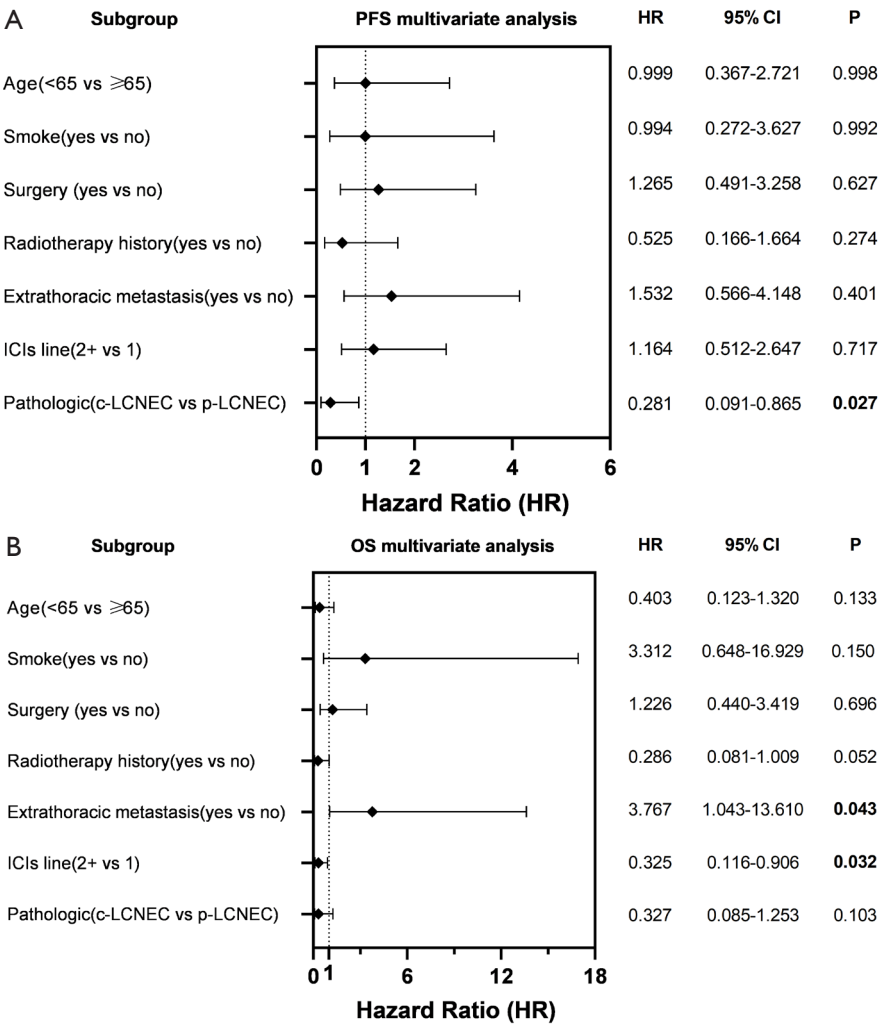

Figure S1 Forest plots for Cox regression multivariate analysis of ICIs treated L-LCNEC patients. (A) Forest plot illustrating Cox regression analysis results for variables associated with PFS. Pathological type is an independent prognostic factor for PFS (HR: 0.281, 95% CI: 0.091–0.865, P=0.027). (B) Forest plot illustrating Cox regression analysis results for variables associated with OS. Extrathoracic metastasis and ICIs line are independent prognostic factors for OS (HR: 3.767, 95% CI: 1.043–13.610, P=0.043; HR: 0.325, 95% CI: 0.116–0.906, P=0.032). PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ICIs, immune checkpoint inhibitors; c-LCNEC, combined large-cell neuroendocrine carcinoma; p-LCNEC, pure large-cell neuroendocrine carcinoma; OS, overall survival.

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