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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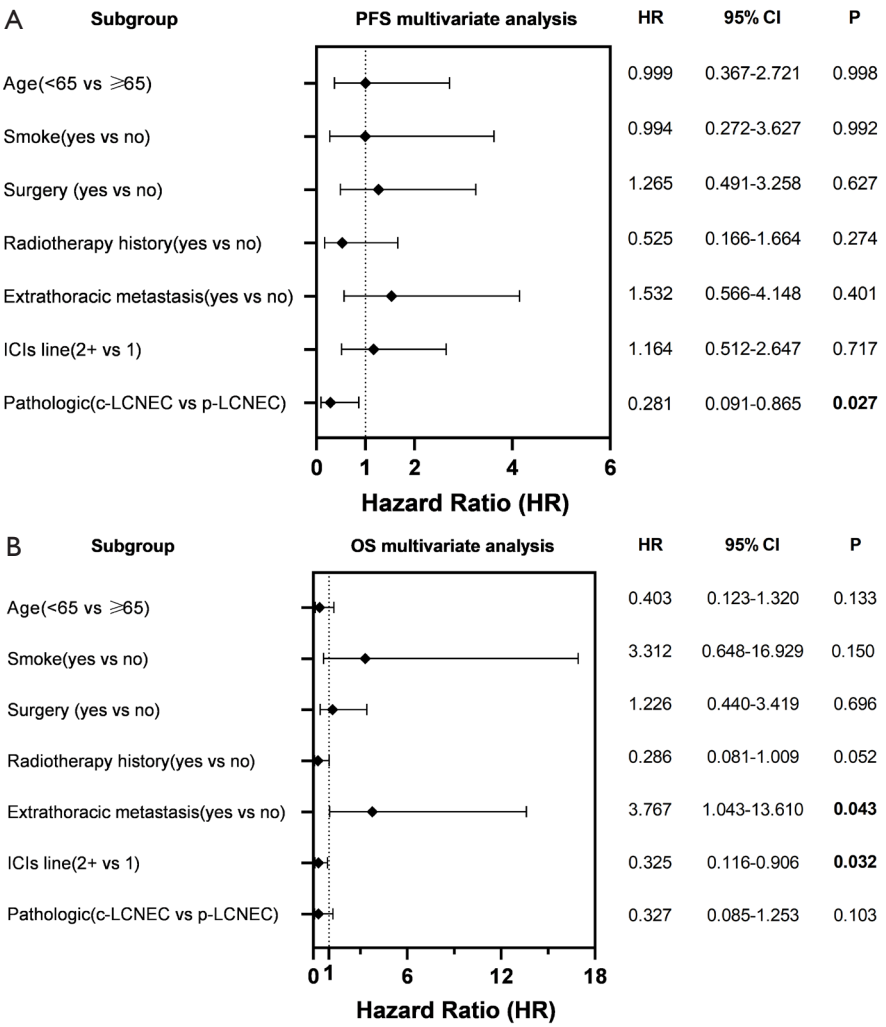

Figure S1 Forest plots for Cox regression multivariate analysis of ICIs treated L-LCNEC patients. (A) Forest plot illustrating Cox regression analysis results for variables associated with PFS. Pathological type is an independent prognostic factor for PFS (HR: 0.281, 95% CI: 0.091–0.865, P=0.027). (B) 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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