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CASE REPORT

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Large cell neuroendocrine carcinoma of the lung controlled for 4 years by a single administration of pembrolizumab: A case report

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Abstract

Large cell neuroendocrine carcinoma of the lung (LCNEC) is a rare and highly progressive tumor with a poor prognosis. Although immune checkpoint inhibitors have been approved for treatment of both small cell and non–small cell lung cancers, their role in the treatment of LCNEC is unclear. We describe a patient with postoperative recurrence of LCNEC who maintained complete remission for 4 years after a single administration of pembrolizumab. A 68-year-old Japanese man underwent thoracoscopic right lower lobectomy for LCNEC (pathological stage pT1bN0M0, stage IA2). Epidermal growth factor receptor and anaplastic lymphoma kinase were negative, and the programmed death ligand 1 expression rate in tumor cells was 5% (clone 22C3). Eight months later, the patient developed recurrence with mediastinal lymph node metastasis and pleural dissemination. Therefore, chemotherapy with cisplatin and etoposide was administered. However, relapse occurred 6 months later. Pembrolizumab was administered as second-line chemotherapy, which was discontinued after first dose because of interstitial pneumonia 1 month later. Thereafter, however, both the lymph node metastasis and pleural dissemination disappeared and did not relapse for 4 years. Pembrolizumab may be used as a treatment option for pulmonary LCNEC.

KEYWORDS

immune checkpoint inhibitor, immune-related adverse event, large cell neuroendocrine carcinoma of the lung

INTRODUCTION

Large cell neuroendocrine carcinoma of the lung (LCNEC) is a rare histologic subtype, accounting for ~3% of lung cancers.[1] Although LCNEC was originally classified as a variant of large cell carcinoma, the current World Health Organization classification groups this tumor as a neuroendocrine neoplasm along with typical carcinoid, atypical carcinoid, and small cell carcinoma.[2,3] LCNEC is generally reported to have a poor prognosis, and its treatment is challenging because the only definitive therapy is complete resection. Immune checkpoint inhibitors (ICIs) were recently approved for treatment of lung cancer and have reportedly had remarkable clinical effects in some patients with LCNEC.[4] We describe a patient with postoperative recurrence of LCNEC who achieved long-term survival without relapse after just one dose of pembrolizumab.

CASE REPORT

A 68-year-old Japanese man underwent thoracoscopic right lower lobectomy with systematic lymph node dissection for LCNEC (pathological stage pT1bN0M0, stage

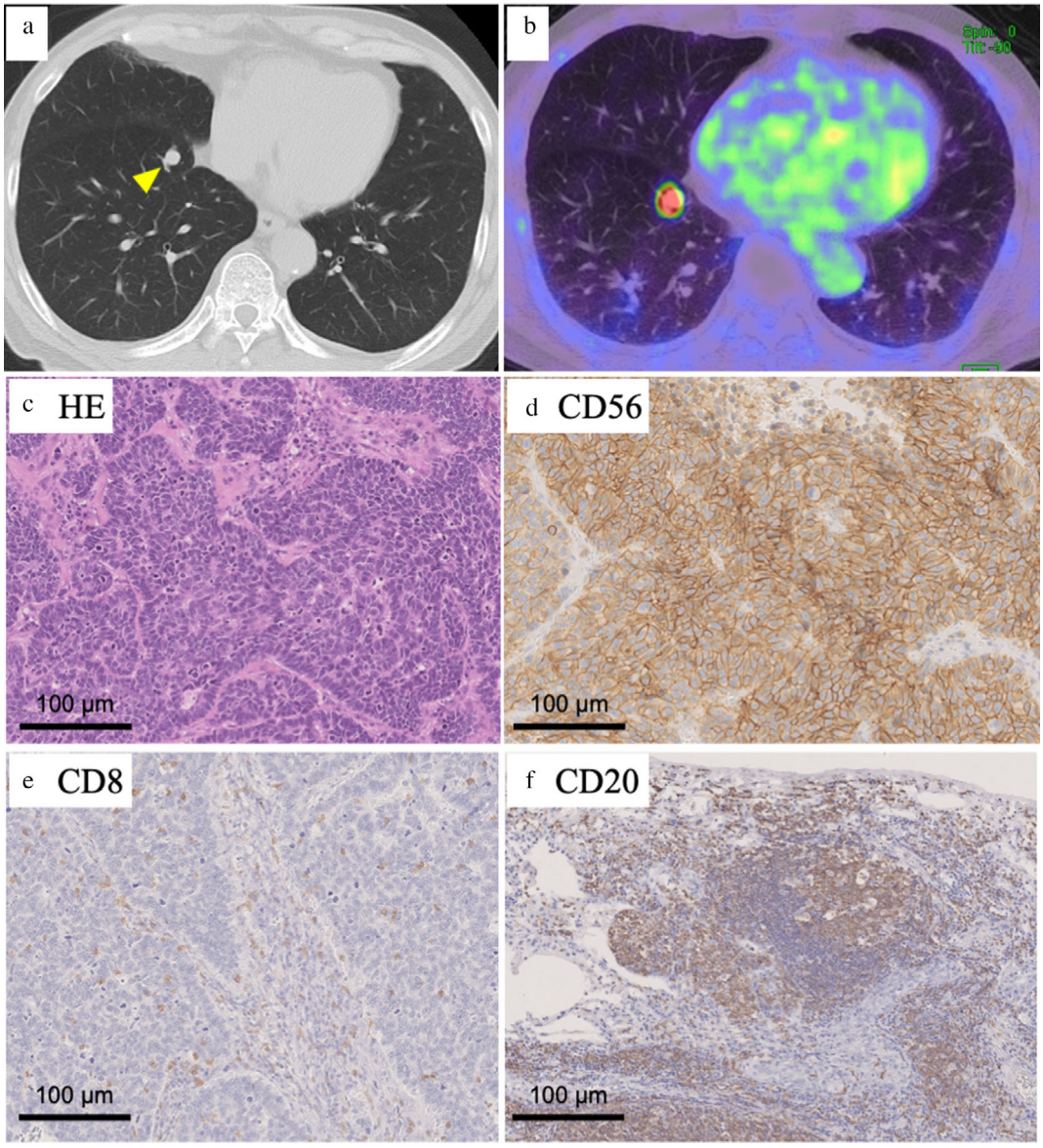

FIGURE 1 Radiological and pathological images at the time of the operation. (a) A smooth, round nodule was located in the right lower lobe. (b) The tumor had high fluorodeoxyglucose uptake on positron emission tomography–computed tomography. (c) On hematoxylin and eosin staining, the tumor cells had rich eosinophilic cytoplasm and prominent nucleoli, forming organoid nesting and rosette-like structures. (d) The tumor cells were stained for CD56. (e) The tumor area had high infiltration of CD8-positive cells. (f) A high number of CD20-positive tertiary lymphoid structures were present in the tumor area

IA2) (Figure 1(a)–(d)). Epidermal growth factor receptor mutation and rearrangements of anaplastic lymphoma kinase were negative, and the other driver oncogenes were not examined. The programmed death ligand 1 (PD-L1) expression rate in tumor cells (i.e., tumor proportion score) was 5% (clone 22C3). Eight months later, the patient developed recurrence with mediastinal lymph node metastasis and pleural dissemination (Figure 2(a),(b)). Endobronchial ultrasound-guided transbronchial needle aspiration of the subcarinal lymph node confirmed metastasis of LCNEC (Figure 2(c),(d)). Therefore, systemic chemotherapy with cisplatin and etoposide was administered, but relapse occurred 6 months later. Pembrolizumab was administered as second-line chemotherapy. Interstitial pneumonia occurred 1 month after administration of pembrolizumab (Figure 3(a),(b)). He was treated with oxygen therapy alone because his symptoms were mild (common terminology criteria for adverse events grade 2), and the ground-glass shadow disappeared (Figure 3(c),(d)). Notably, both the lymph node metastases and pleural dissemination thereafter disappeared and did not relapse for 4 years.

DISCUSSION

LCNEC is not only a rare histologic subtype accounting for only 3% of all lung cancers,[1] but it also has a poor prognosis; the median overall survival time of patients with advanced

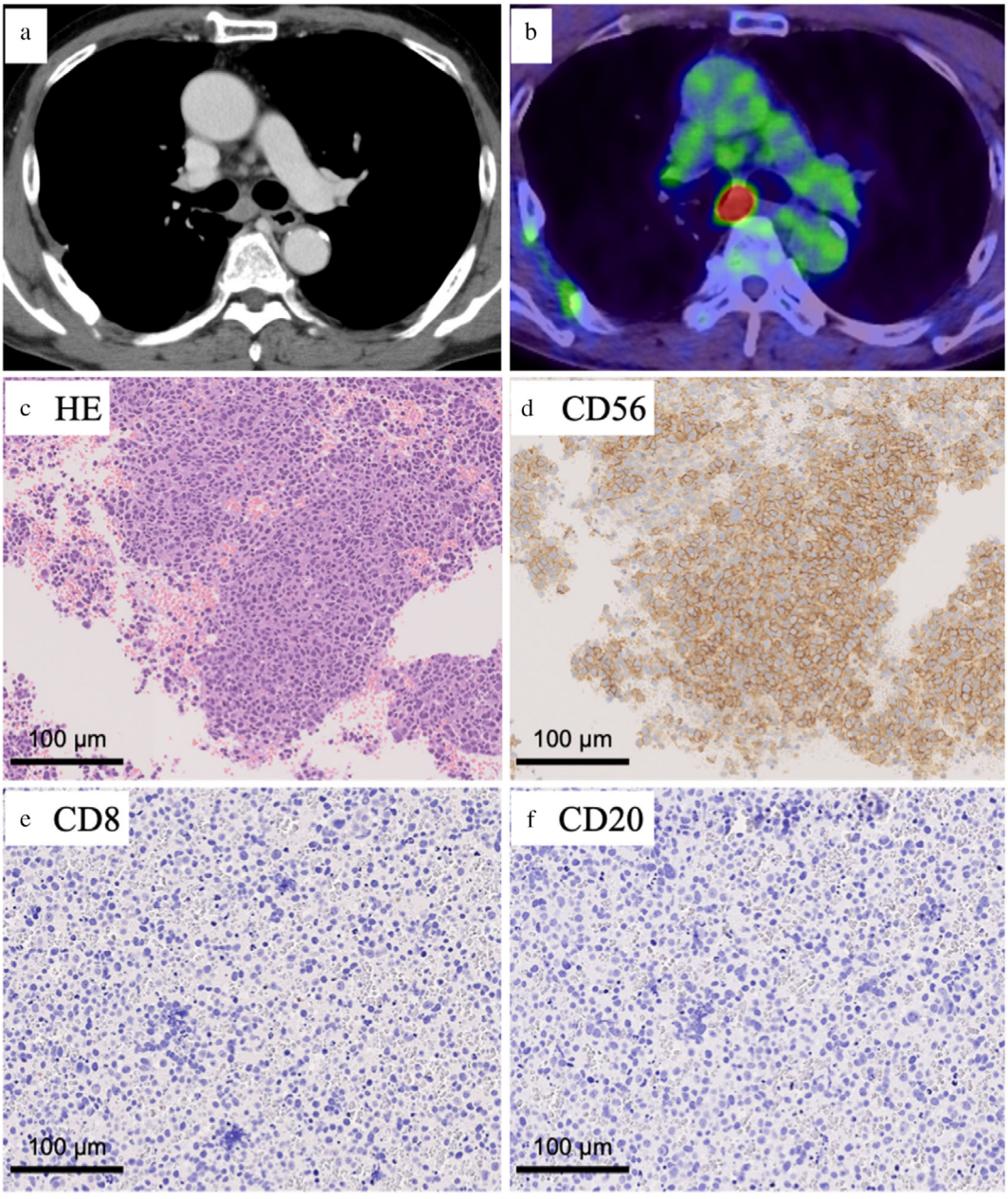

FIGURE 2 Radiological and pathological images at the time of recurrence. (a) A subcarinal lymph node was swollen on chest computed tomography. (b) The lymph node had high fluorodeoxyglucose uptake on positron emission tomography–computed tomography. (c) Endobronchial ultrasound-guided transbronchial needle aspiration of the lymph node revealed metastasis of large cell neuroendocrine carcinoma of the lung into the lymph node. (d) The metastatic lymph node was also stained for CD56. (e),(f) the metastatic lymph node had almost no CD8-positive tumor infiltrating lymphocytes, nor CD20-positive tertiary lymphoid structures

or recurrent LCNEC is 8 to 16 months.[1,5] The main reason for this poor survival is that complete surgical resection is the only effective therapy.[1] Treatment of advanced and recurrent LCNEC is similar to small cell lung cancer treatment. This is because both cancers have similar patient backgrounds, neuroendocrine features, and biological characteristics such as immunophenotypes and gene mutations.[6] Immunotherapy was recently shown to be effective for LCNEC and small cell lung cancer; however, survival is still far from satisfactory, as described above.[1] Nevertheless, some studies have shown that patients with LCNEC respond to ICIs, suggesting that immunotherapy might be effective for LCNEC.[7] In particular, complete remission (CR) of LCNEC to ICIs is extremely rare, with only three cases reported in the literature.[7] Agar et al.[5] reported no cases of CR among 17 patients with LCNEC who were treated with nivolumab. Our patient maintained CR for 4 years after a single administration of pembrolizumab; to the best of our knowledge, this is the first such case to be reported in the literature. Table 1 summarizes six patients with LCNEC who

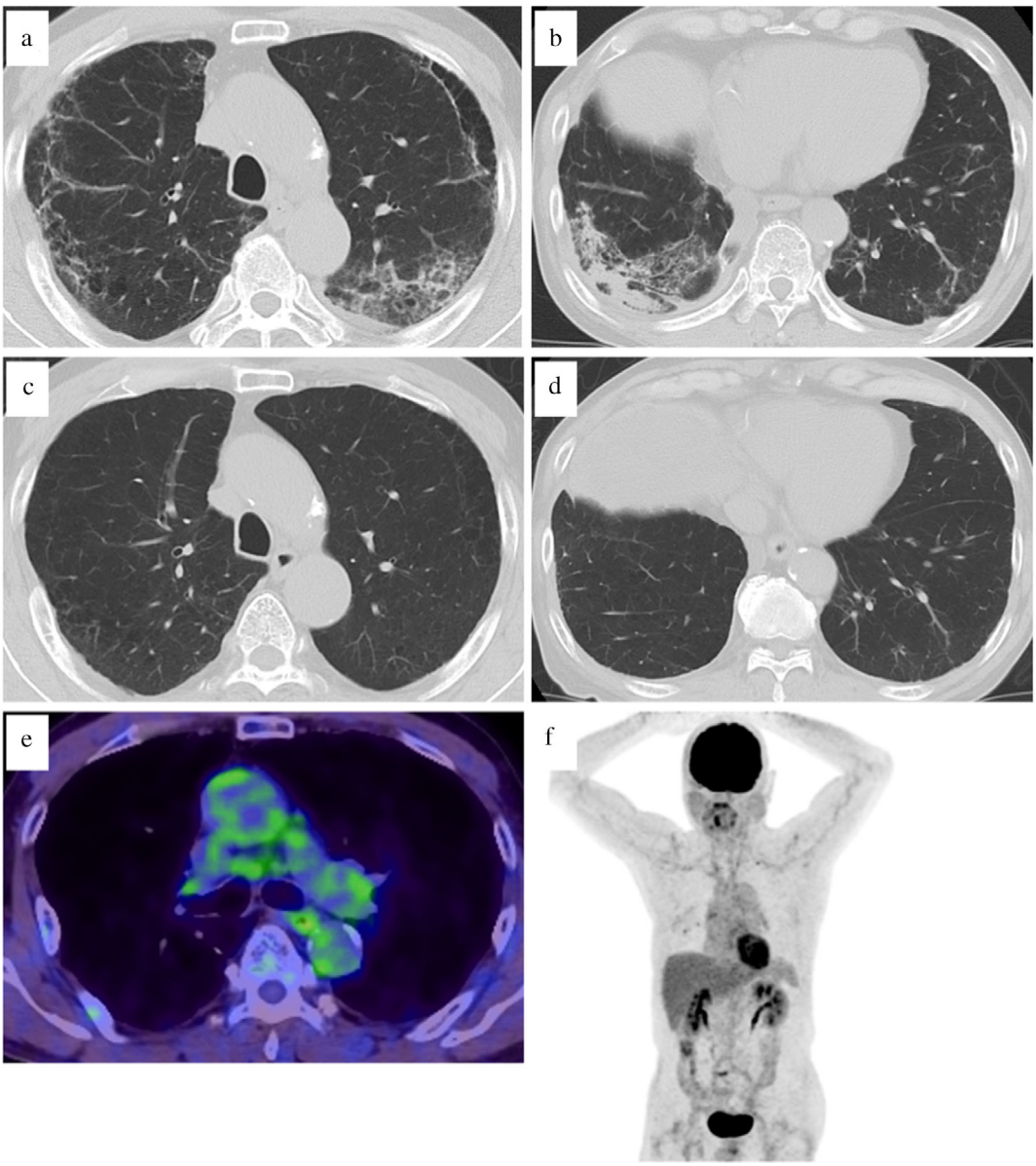

FIGURE 3 Radiological images after pembrolizumab therapy. (a),(b) Ground-glass shadows were observed in the bilateral lungs. (c),(d) The shadows disappeared 1 month later with oxygen therapy alone. (e),(f) both the lymph node metastases and the pleural dissemination also disappeared. No positive areas were observed on positron emission tomography 4 years after pembrolizumab therapy

were treated with ICIs or a combination of ICIs and cytotoxic agents in our institution. The patients' median age was 71 years and three of them (50%) were women. All patients, but one, (83%) were smokers. Half of the patients had PD-L1 expression of ≥50%, and two patients (33%) showed no PD-L1 expression. Four patients (66%) had a partial or complete response; except for the current patient, however, all patients relapsed and the median time to progression was 6.5 months. This illustrates the rarity of the current case. Two of these patients (33%), including the current patient, had both high CD8-positive tumor-infiltrating lymphocytes (TILs) and CD20-positive tertiary lymphoid structures (TLSs) in the tumor (Figure 1(e),(f)). We also stained CD8 and CD20 on metastatic lymph node of the current patient, whereas there were almost no CD8-positive TILs or CD20-positive TLSs in the lymph node (Figure 2(e),(f)). Although these tumor microenvironments possibly explain the remarkable response to pembrolizumab, there might be some differences in microenvironment between primary tumor and regional lymph node. Inamori et al.[8] suggested that the immunological status of tumors, nonmetastatic lymph nodes, and peripheral blood in colorectal cancer patients had several differences.

PD-L1 expression on tumor cells, TILs, TLSs, and the tumor mutation burden has been reported as possible predictive biomarkers for ICI efficacy. In fact, some tumors that respond to therapy show high lymphocyte infiltration.[4] PD-L1 is reportedly expressed in ∼10% to 20% of pulmonary

TABLE 1 Six patients with LCNEC who were treated with ICIs or a combination of ICIs and cytotoxic agents in our institution

Patient	Age	Sex	Diagnosis	Stage	Smoke (PY)	PD-L1: TPS (%)	$CD8^+$ TILs	$CD20^+$ TLSs	IO regimen	Chemo line	BCR	PD	TTP
Pt. 1	73	M	LCNEC	Rec	44	50	High	High	CBDCA + PTX + Bev + atezolizumab	1st	PR	Yes	13M
Pt. 2	74	F	LCNEC	Rec	0	<1	Low	Low	CBDCA + PTX + Bev + atezolizumab	1st	PR	Yes	12M
Pt. 3	70	F	Combined LCNEC	Rec	32	<1	Low	Low	CBDCA + nab-PTX + atezolizumab	2nd	PR	Yes	6M
Pt. 4	68	M	Combined LCNEC	Rec	44	55	Low	Low	CBDCA + pemetrexed + pembrolizumab	3rd	SD	Yes	4M
Pt. 5	71	F	Combined LCNEC	Rec	50	55	Low	Low	Pembrolizumab	3rd	PD	Yes	3M
Present	68	M	LCNEC	Rec	48	5	High	High	Pembrolizumab	2nd	CR	No	53M

Abbreviations: BCR, best clinical response; Bev, bevacizumab; CBDCA, carboplatin; CR, complete response; LCNEC, large cell neuroendocrine carcinoma; nab-PTX, nab-paclitaxel; PD, progressive disease; PR, partial response; PTX, paclitaxel; PY, pack-year; Rec, recurrence; SD, stable disease; TILs, tumor infiltrating lymphocytes; TLSs, tertiary lymphoid structures; TPS, tumor proportion score; TTP, time to progression.

LCNECs.[9] However, a recent study indicated that there may not be an accurate correlation between the PD-L1 expression level and effect of ICIs.[10] Among the reported patients with LCNEC who achieved CR by ICIs, many CD138-positive plasma cells were observed in their tumors.[4] Tumor-infiltrating plasma cells are regarded as a favorable prognostic factor in lung cancer.[11] In various cancer types, the presence of TLSs has been also associated with longer disease-free and overall survival in patients treated with ICIs.[12] The current patient also had many CD8-positive TILs and CD20-positive TLSs in his tumor. Therefore, the so-called immunological "inflammatory" features of his tumor may have contributed to his response to ICI therapy.

In conclusion, we experienced a rare case of pulmonary LCNEC that maintained CR for 4 years after one-time pembrolizumab monotherapy. ICIs are a promising treatment option for pulmonary LCNEC.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

INFORMED CONSENT

The patient agreed to publication of this case and provided written informed consent.

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REFERENCES

1. Fasano M, Della Corte CM, Papaccio F, Ciardiello F, Morgillo F. Pulmonary large-cell neuroendocrine carcinoma: from epidemiology to therapy. J Thorac Oncol. 2015;10(8):1133–41.
2. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, 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. 2015;10(9):1243–60.
3. Nicholson AG, Tsao MS, Beasley MB, Borczuk AC, Brambilla E, Cooper WA, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. J Thorac Oncol. 2022;17(3):362–87.
4. Kadota N, Hatakeyama N, Hino H, et al. Complete and durable response of pulmonary large-cell neuroendocrine carcinoma to pembrolizumab. Cancer Rep. 2022;5(8):e1589.
5. Agar C, Geier M, Léveiller G, Lamy R, Bizec JL, Tiercin M, et al. Brief report on the efficacy of Nivolumab in patients with previously treated advanced large-cell neuroendocrine cancer of the lung. JTO Clin Res Rep. 2021;2(4):100129.
6. Miyoshi T, Umemura S, Matsumura Y, Mimaki S, Tada S, Makinoshima H, et al. Genomic profiling of large-cell neuroendocrine carcinoma of the lung. Clin Cancer Res. 2017;23(3):757–65.
7. Oda R, Okuda K, Yamashita Y, Sakane T, Tatematsu T, Yokota K, et al. Long-term survivor of pulmonary combined large cell neuroendocrine carcinoma treated with nivolumab. Thorac Cancer. 2020;11(7):2036–9.

8. Inamori K, Togashi Y, Fukuoka S, et al. Importance of lymph node immune responses in MSI-H/dMMR colorectal cancer. *JCI*. Insight. 2021;6(9): e137365.
9. Kim HS, Lee JH, Nam SJ, Ock CY, Moon JW, Yoo CW, et al. Association of PD-L1 expression with tumor-infiltrating immune cells and mutation burden in high-grade neuroendocrine carcinoma of the lung. J Thorac Oncol. 2018;13(5):636–48.
10. Arfè A, Fell G, Alexander B, Awad MM, Rodig SJ, Trippa L, et al. Meta-analysis of PD-L1 expression as a predictor of survival after checkpoint blockade. JCO Precis Oncol. 2020;4:1196–206.
11. Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nat Med. 2015;21(8):938–45.
12. Germain C, Devi-Marulkar P, Knockaert S, Biton J, Kaplon H, Letaïef L, et al. Tertiary lymphoid structure-B cells narrow regulatory T cells impact in lung cancer patients. Front Immunol. 2021;12:626776.

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