

Pulmonary Lymphoepithelioma-Like Carcinoma Treated with Immunotherapy or Chemotherapy: A Single Institute Experience

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Background: Lymphoepithelioma-like carcinoma (LELC) is a rare malignant tumor of the lung. It is related to EB virus infection. Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) are rarely found in this disease, while high level programmed cell death ligand 1 (PD-L1) expression is observed. Here a series of patients with advanced LELC treated with immunotherapy were summarized.

Methods: This retrospective, observational study was conducted in patients who were pathologically confirmed, metastatic or recurrent LELC patients. Patients were prescribed with either chemotherapy or immunotherapy, according to treating physicians' discretion.

Results: A total of 27 patients were included in our study, 10 with immunotherapy (ICI group) and 17 with chemotherapy (Chemo group). The objective response rates (ORR) of the two groups were 80.0% and 70.5% ($p=0.678$), and disease control rates (DCR) were 100% and 88.2% ($p=0.516$). However, the response depth was better in the ICI group. Although the cohort of patients in the ICI group was in a disadvantageous state (both up-front and salvage), the progression-free survival (PFS) was much longer (15.0 and 7.9 m, $p=0.005$). The 1-year PFS rate in the ICI group was also much higher (40% and 5.9%, $p=0.047$).

Conclusion: This study implicated the high efficiency of ICI therapy in this disease.

Keywords: lymphoepithelioma-like carcinoma, ICIs, PD-L1, immunotherapy

Introduction

Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare malignant tumor of the lung. It belongs to the category of non-small cell lung cancer (NSCLC) with an incidence of $\leq 0.7\%$ of all NSCLC.¹⁻⁴ According to the World Health Organization Classification of Tumors of the Lung (2015), LELC was classified into "other and unclassified carcinomas". Morphological features are similar to those of undifferentiated nasopharyngeal carcinoma.^{5,6} Typically, poorly differentiated tumor cells and a large number of lymphocyte infiltration can be observed.^{7,8} LELC may be related to EB virus infection, and has a higher incidence in Southeast Asia, such as Guangdong, Hongkong, Taiwan, and Singapore, than in Europe and the US.^{9,10} Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), the most sensitive driver genes to targeted therapy in NSCLC, are rarely found in this disease.¹¹⁻¹³ Recent studies showed a higher proportion of programmed cell death ligand 1 (PD-L1) positivity tumor cells in LELC than adenocarcinoma and squamous cell carcinoma.^{8,11,13} No standard-of-care for this disease is established, but the current therapy often contains multimodality treatments, such as radio-

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chemo-therapy.^{14–16} Hereto, immunotherapy has been suggested in anecdotal case reports,^{17–22} and apparently more cases are needed to confirm its efficacy. Here we summarized our experience of patients with advanced LELC treated with immunotherapy.

Patients and Methods

Patients

This retrospective, observational study was conducted in our hospital. This study was approved by the Ethics Committee on Biomedical Research (No. 669). All admitted lung cancer patients were screened through the Hospital Information System from January 2012 to June 2020. Enrolled patients were pathologically confirmed, metastatic or recurrent LELC patients. PD-L1 expression was centrally stained and assessed with antibody 22C3.

Treatment

Patients were prescribed chemotherapy or immunotherapy. Immunotherapy drugs included pembrolizumab (Merck & Co., Inc., Whitehouse Station, NJ, USA), or sintilimab (Innovent, China), or nivolumab (Bristol-Myers Squibb, New York, NY, USA). The chemotherapy regimen consisted of either platinum-based doublet chemotherapy, or albumin paclitaxel or pemetrexed monotherapy. The tumor responses were assessed the RECIST 1.1 and adverse events were graded on CTC AE 4.0. Tumors were assessed every 2 months radiographically, including computed tomography of the chest and upper abdomen, magnetic resonance imaging of the head, and bone scintigraphy. Tumor response was evaluated as complete response (CR), partial response (PR), stable disease (SD), or progression disease (PD), according to RECIST 1.1. The PFS was defined as the duration from the initiation of the therapy to the date of disease progression, intolerable side effects, or death from any cause.

Statistics

Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). The quantitatives were compared using chi-square test and Fischer's exact test according to Cochran's rule. The Kaplan–Meier curves were used to compare survival. All P-values were based on a two-tailed hypothesis, and statistical significance was assumed if $p < 0.05$.

Results

Clinical Characteristics

A total of 27 patients were included. Ten and 17 patients received immunotherapy (either alone or in combination with other therapies, ICI group) or chemotherapy (Chemo group), respectively (Figure 1, Table 1). Of notice, immunotherapy was administered either as up-front or salvage therapy (1st-line $n=4$, ≥ 2 nd-line $n=6$), while chemotherapy was used in the 1st-line therapy. The median age was 57.2 and 55.2 years in each group. Some patients received surgery before (3/10 in ICI group, 3/16 in Chemo group). Extrapulmonary metastases were common (80% in ICI group, 53% in Chemo group). In the ICI group, PD-L1 expression was assessed in 9 patients. In the whole cohort, no EGFR or ALK aberration was detected in any patients, and FGFR3 gene amplification was found in only 1 case (ICIs group).

Treatment

In the ICI group, 3 drugs were prescribed, including pembrolizumab ($n=3$), nivolumab ($n=3$), and sintilimab ($n=4$). These ICIs were either combined with chemotherapy ($n=3$) or small molecular antiangiogenic agents ($n=3$), or as a single agent ($n=4$). The median cycle of administration was 7.5 (range: 2–25).

Efficacy

The objective response rates (ORR) of the two groups were 80.0% (8/10) and 70.5% (12/17), respectively, with no significant difference ($p=0.678$). The disease control rates (DCR) were also similar (100% and 88.2%, $p=0.516$). The response depth was better in the ICI group.

The median follow-up time was 22.4 months (range 3.5–60.9 months). A longer PFS was achieved in the ICI group than the Chemo group (15.0 and 7.9 m, $p=0.005$, Figure 2). The 1-year PFS rate in the ICI group was also much higher (40% and 5.9%, $p=0.047$). During treatment course, 4 patients had disease progression in ICI group, compared to 13 in Chemo group. Till the time of preparation of this manuscript (Aug 2020), persistent PR ($n=5$ and 3) and SD ($n=1$ and 1) were maintained in ICI and Chemo groups. Distant metastases including intra- and extra-pulmonary in ICI (2/10 and 1/10) were comparable to those in Chemo group (4/17 and 5/17, $p=0.42$).

Toxicities of Immunotherapy

Two patients developed grade 1 hypothyroidism. After thyroxine replacement, both gradually recovered without

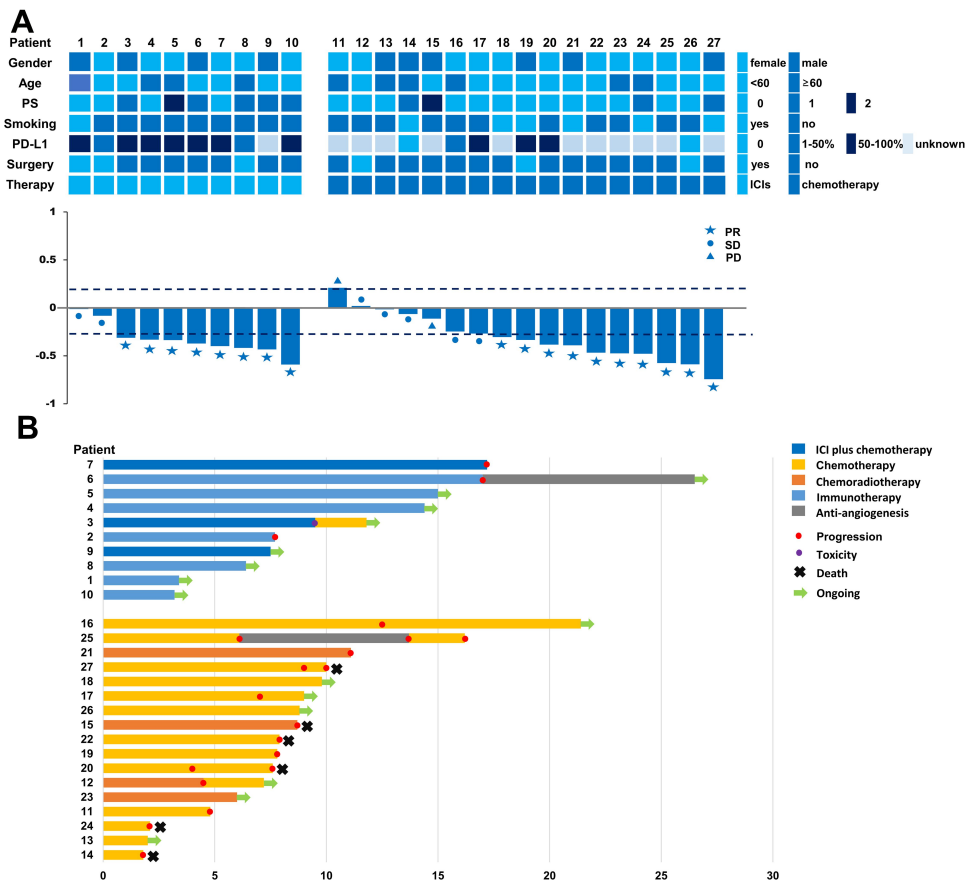


Figure 1 Tumor response of each patient receiving ICI or chemotherapy (A). Time course of treatment in each patient (B).

delay in therapy. One patient achieved a PFS of 3.7 mon, and another was maintained in PR for 6.4 mon. One patient had severe (grade 4) immune-related multi-organ failure (below).

Patients Report

Patient 4 was a 63-year-old female. She was admitted because of gradual onset of productive cough, and intermittent hemoptysis, accompanied by a slight fever (≤ 38.5 oC) without any obvious causes. A comprehensive workshop consisting of enhanced chest CT, PET-CT, and MRI of the brain, showed a mass in the left lung lower lobe with hilar mediastinal lymph node enlargement, left main bronchus and lower lobe bronchus invasion, and the lesions of right humerus and pleural. Bronchoscopy and pathology revealed poorly differentiated NSCLC in the lower left main bronchus, Immunohistochemistry (IHC) staining demonstrated PCK (+), p63 (+), CK5/6 (+), TTF-1 (-), EBER1/2-ISH (+), PDL1 (+,70%), ALK-V (-) and ros-1 (-). She was diagnosed as LELC in the left lung with metastases

to the mediastinal and hilar lymph nodes, pleura and right humerus (cT4N2M1c, stage IVb). No EGFR or ALK aberrations were detected in the next generation sequencing of her tumor.

She was prescribed with 2 cycles of pemetrexed plus pembrolizumab (2mg/kg) combination therapy. But an enlargement of the tumor in the left lung was shown in the following CT scan. Radiotherapy at the dose of 6gy/3f was given concurrently with pembrolizumab as salvage therapy, and pembrolizumab was used regularly as maintenance therapy. After the 3 cycles of pembrolizumab, the size of the tumor and the lesions of the lymph node became smaller (Figure 3). After 1 year of therapy, the patient sustained remission without further complaints (sustained PR).

Patient 3 was a 55-year-old never smoking male. He came to our hospital and complained of unrelenting cough for 2 months with occasional hemoptysis. Enhanced CT of the chest showed an irregular mass in the middle lobe of the right lung, and multiple enlarged lymph nodes in the mediastinum and right hilum. He

Table 1 The Demographic Feature of Enrolled Patients

Patient	Gender	Age	PS	Smoking	PD-L1	Surgery	TNM	Stage	Line	Therapy
1	M	68	0	yes	80%	yes	rT0N0M1c	IVB	2nd	Sintilimab
2	F	56	0	no	30%	yes	rT1bN0M1b	IVB	2nd	Pembrolizumab
3	M	55	1	no	90%	no	T4N2M1c	IVB	1st	Pembrolizumab+ Nab-paclitaxel+ carboplatin
4	F	63	0	no	70%	no	T4N2M1b	IVB	1st	Pembrolizumab
5	F	70	2	no	90%	no	T4N3M1a	IVA	4th	Nivolumab+ Anlotinib
6	M	46	1	no	60%	no	T3N3M1c	IVB	5th	Nivolumab+ Apatinib
7	F	56	0	no	80%	no	T4N2M1b	IVB	2nd	Nivolumab+ Docetaxel
8	F	61	1	no	40%	yes	rT3N2M1c	IVB	2nd	Sintilimab+ Anlotinib
9	F	54	1	no	unknown	no	T1N3M1c	IVB	1st	Sintilimab+ Nab-paclitaxel+ Carboplatin
10	M	43	0	no	80%	no	T3N3M0	IIIC	1st	Sintilimab
11	F	76	0	no	unknown	no	T4N2M1c	IVB	1st	Nab-paclitaxel
12	F	58	0	no	unknown	yes	rT0N3M1a	IVA	1st	Nedaplatin+ Fluorouracil+ RT
13	M	77	0	no	unknown	no	T3N2M0	IIIB	1st	Pemetrexed
14	M	63	1	yes	0	no	T4N1M1a	IVA	1st	Pemetrexed+ Cisplatin
15	M	52	2	no	unknown	no	T4N3M1b	IVB	1st	Gemcitabine+ Cisplatin+ RT
16	F	60	0	no	20%	no	T2bN2M1b	IVB	1st	Paclitaxel+ Cisplatin
17	F	52	0	no	50%	no	T2N3M1b	IVB	1st	Gemcitabine+ Cisplatin
18	F	50	0	yes	unknown	no	T4N3M1a	IVA	1st	Nab-paclitaxel+ Cisplatin
19	M	32	0	yes	65%	yes	rT2N0M1a	IVA	1st	Gemcitabine+ Cisplatin
20	F	55	0	no	85%	no	T4N2M1a	IVA	1st	paclitaxel+ Carboplatin
21	M	47	0	yes	unknown	no	T4N3M0	IIIC	1st	Fluorouracil+ Cisplatin+ Bevacizumab+ RT
22	F	49	0	no	unknown	no	T4N1M1c	IVB	1st	paclitaxel liposome +Cisplatin
23	F	63	0	no	unknown	no	T4N2M1c	IVB	1st	Paclitaxel+ Cisplatin+ Endostar+ RT
24	F	62	1	yes	unknown	no	T4N3M1b	IVB	1st	Paclitaxel+ Cisplatin
25	F	52	0	no	unknown	no	T4N3M1b	IVB	1st	Docetaxel+ Nedaplatin
26	F	48	0	no	0	yes	rT4N2M1a	IVA	1st	Pemetrexed+ Cisplatin+ Endostar+ Anlotinib
27	M	44	1	yes	unknown	no	T4N3M1b	IVB	1st	Gemcitabine+ Cisplatin

Abbreviations: F, female; M, male.

received Endobronchial Ultra-sound guided Transbronchial Needle Aspiration (EBUS-TBNA) of 4R lymph node. According to pathology and imaging, he was diagnosed LELC of the right lung, with right

hilar and bilateral mediastinal lymph nodes, liver metastasis (cT4N3M1c, stage IVb).

His tumor had high PD-L1 expression (90%). Two cycles of pembrolizumab (200mg) combined with

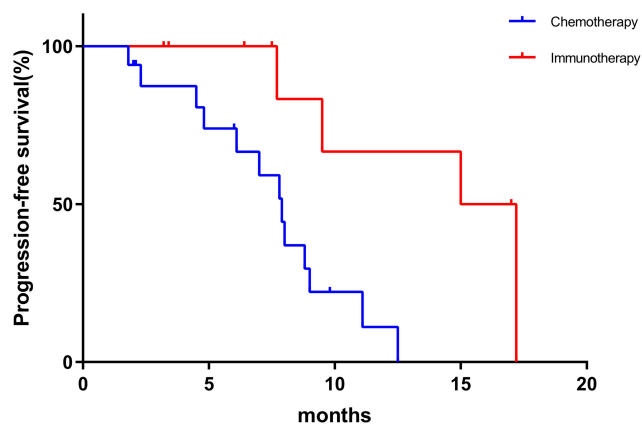


Figure 2 PFS in Chemo group was inferior to that in ICI group.

chemotherapy (albumin-bound paclitaxel 460mg, carboplatin 650mg every 3 weeks) were prescribed and his tumor achieved PR.

However, before the initiation of cycle 3, he had a significant up-rise of transaminase, myocardial enzymogram, and other biochemical components (Figure 4). Left ventricular systolic function was normal (EF 72%) in echocardiography, and no obvious abnormality was shown on cardiac MRI. He was diagnosed as

immune-related multi-organ damage, including myocarditis, myositis, and acute liver injury. After intense methylprednisolone (2mg/kg) therapy, all these biochemical parameters gradually resolved. Unfortunately, he developed severe bacterial and fungal pneumonia. During this period, no anti-tumor treatment was given, which contributed to his slightly enlarged tumor.

Discussion

There was no consensus on the treatment of advanced LELC. Although fluorouracil was suggested before the year of 2000,¹⁴ the regimen gradually switched to paclitaxel/gemcitabine plus cisplatin.^{15,23} Targeted therapy revolutionizes the standard-of-care for those with NSCLC harboring sensitive gene mutations, while both EGFR and ALK mutations were hardly found in LELC.^{11–13} Interestingly, several lines of evidence support the role of immunotherapy for treatment of this disease.

EBV

Almost all patients of LELC had positive staining for EBER in fluorescence in situ hybridization. High

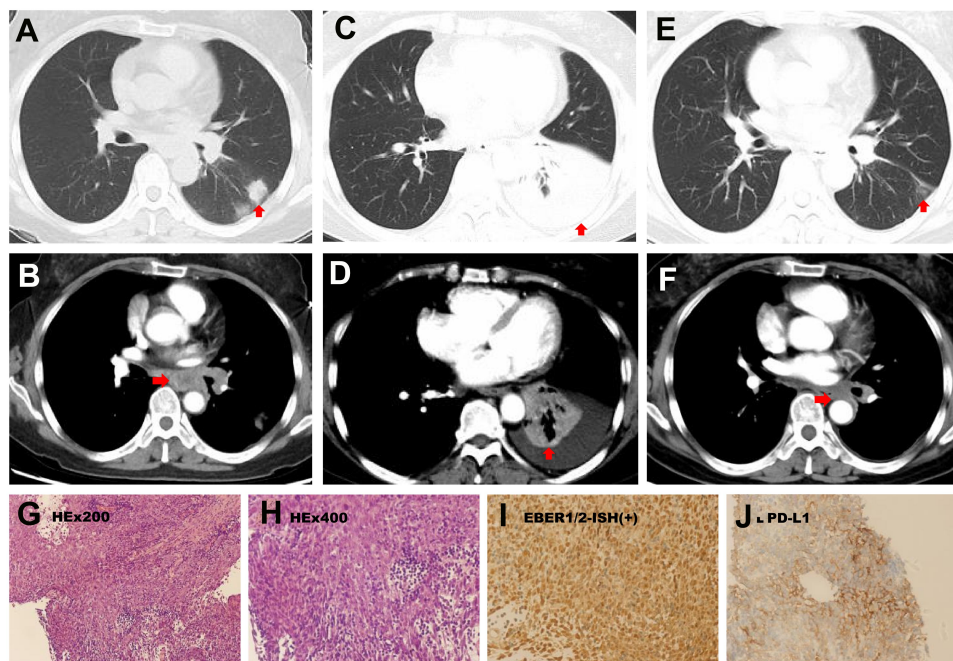


Figure 3 The patient had a mass in his left lung lower lobe and enlarged mediastinal lymph nodes at base line (A and B). After 2 cycles of chemotherapy and immunotherapy, her mass increased in size, accompanying with appearance of pleural effusion (C and D). When radiotherapy and immunotherapy were given, shrunken tumor and lymph nodes were observed (E and F). Carcinoma cells in the background of infiltrating lymphocytes (G and H). In Situ Hybridization showed positive Epstein-Barr Virus-encoded RNA (I). Programmed Cell Death Ligand 1 staining by immunohistochemistry (J). Red arrow in Figure 3 (A–F) represent the tumor.

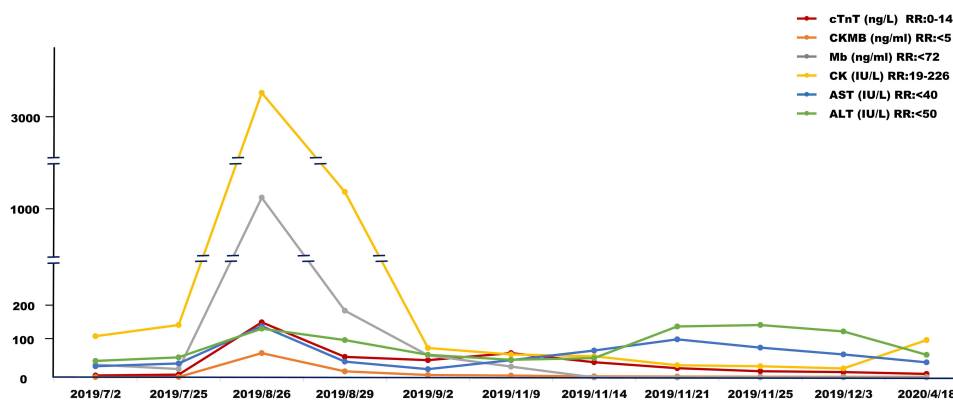


Figure 4 The dynamic change of cTnT, CKMB, Mb, CK, AST and ALT during treatment.

baseline EBV-DNA concentration in the serum is an independent poor prognostic marker in LELC patients.^{24,25} And it was suggested that EBV infection might be a biomarker of favorable outcomes in immunotherapy. Kim showed that PD-L1 expression in patients with EBV-positive non-Hodgkin's lymphoma was significantly higher than EBV-negative (56% vs 11%, $p < 0.001$), and 7 EBV-positive patients achieved survival benefits after pembrolizumab treatment.²⁶ Kang et al proved hepatocellular carcinomas with EBV-positive tumor-infiltrating lymphocytes had a better outcome.²⁷

Tumor Microenvironment

EBV-related LELC has a unique tumor microenvironment. Tumor antigens, either by EBV or EBV induced-cell products, recruit tumor infiltrating lymphocytes (TILs) inside the tumor stroma.⁷ In one report, in 84.7% of patients the staining of TILs accounted for $\geq 50\%$.⁸ There had been reports TILs, either in an activated or suppressed status, contributed to a better outcome in immunotherapy with LELC.²⁸

PD-L1 Expression

Studies showed a high level of PD-L1 expression in this tumor. Chang evaluated 66 patients of LELC and the PD-L1 expression positivity (defined as $> 5\%$) was 75.8%.²⁹ Similar PD-L1 expression ($> 5\%$) rate of 65.7% was reported by Yu ($n=67$).³⁰ In another study, a high level of PD-L1 expression ($\geq 50\%$) was reported in 61% (36/59) of patients.⁸ High PD-L1 expression is generally associated with good response to PD-1/PD-L1 inhibition. All these

data implicated LELC might be a good candidate for ICI therapy.

Previously, 7 reports observed the efficacy of ICI in advanced LELC. Six of them were case reports (Table 2), and the final one consisted of 2 patients.¹⁷⁻²² Kim firstly reported a LELC patient whose PD-L1 and EBER were both positive had the tumor controlled for only 1 month after nivolumab therapy.¹⁸ All the other papers reported a good prognosis after ICI treatment.

Compared with the aforementioned anecdotal case series, our study consisted of a relatively large number of patients ($n=10$). Also, we compared the efficacy of ICI therapy with that of traditional chemotherapy. Although the cohort of patients in ICI group was in a disadvantageous state (both up-front and salvage), the response depth was better and the PFS was much longer. Our results strongly supported ICI in these patients.

The current study had its limitation. It was based on a retrospective cohort from a single institute, and contained a limited number of patients. This was due to the scarcity of LELC, and also only recent advent of ICI in clinic. However, compared with previous case reports, our study presented a series of patients and the data might be more convincing. Secondly, ICI and Chemo group were unbalanced. Although more patients in the ICI group were in the late lines of therapy, they still had a better efficacy than those in the Chemo group. This might further support the efficacy of ICI in this group of patients.

In summary, our study provided a series of patients of LELC successfully treated with ICI. This study implicated the high efficiency of ICI therapy in this disease, especially for those with high PD-L1 expression. Prospective

Table 2 Summary of Seven Reports Observed the Efficacy of ICI in Advanced LELC

Source	Age (y)	Gender	Smoking	Ethnicity	Stage	Gene	PD-LI	EBV	Line	Therapy	PFS (m)	Response	OS (m)	Death
Qiu et al	56	F	never	Asian	IVA	no	80%	+	2nd	Nivolumab	NR	PR	NR	NR
Kim et al	37	F	never	Asian	IVB	no	+	+	2nd	Nivolumab	I	PD	36	Yes
Kumar et al	56	M	Yes	Asian	IVB	no	NR	+	4th	Nivolumab	25	PR	62	No
	37	F	never	Asian	NR	NR	5%	+	3rd	Nivolumab	27	SD	56	No
Darrason et al	51	F	Yes	NR	IVB	no	-	+	2nd	Nivolumab	7	SD	28	Yes
Narayanan et al	76	F	never	Asian	IVA	no	50%	+	3rd	Atezolizumab	4	PR	28	Yes
Tang et al	50	F	NR	Asian	IVB	no	10%	+	2nd,3rd	Nivolumab; Nivolumab+ nedaplatin+ paclitaxel	5,5	PR, PR	16	No
Xie et al	56	F	never	Asian	IIB	NR	30%	NR	1st	Nivolumab+ gemcitabine	I	SD	NR	NR
	49	F	never	Asian	IIIB	NR	60%	NR	1st	Nivolumab+ anlotinib+ gemcitabine	NR	SD	NR	Yes
	48	M	NR	Asian	IVA	NR	15%	NR	3rd	camrelizumab+ apatinib	NR	SD	NR	Yes

Abbreviations: LELC, lymphoepithelioma-like carcinoma; F, female; M, male; OS, overall survival; NR, not reported; PR, partial response; PD, progressive disease; SD, stable disease; Y, yes; N, no.

randomized studies are warranted to confirm this conclusion.

Disclosure

The authors report no conflicts of interest in this work.

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