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REVIEW

Pulmonary Lymphoepithelioma-Like Carcinoma: A Mini-Review

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Abstract: Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare and distinct subtype of non-small-cell lung carcinoma associated with Epstein–Barr virus (EBV) infection. We systematically reviewed the recent research that expands our knowledge about PLELC, with main focus on its genetic profile, tumor-infiltrating environment, PD-L1 expression, circulating EBV-DNA, clinical utility of 18F-FDG PET/CT, and treatment strategy. A low frequency of typical driver mutations and widespread existence of copy number variations was detected in PLELC. Persistent EBV infection may trigger intense infiltration of lymphocytes, representing enhanced tumor immunity and possibly resulting in a better prognosis. Circulating EBV-DNA in the plasma of patients with PLELC may predict disease progression and response to therapy. PLELC is 18F-FDG avid, and 18F-FDG PET may help refine palliation strategies and subsequently improve the prognosis. Most of the reported patients present at early and resectable stage, and surgical resection with curative intent is the preferred approach. There is currently no consensus on the regimen of chemotherapy for patients with advanced stages. EGFR-targeted therapies seem to have no therapeutic effect, and the clinical impact of PD-1/PD-L1 therapy is uncertain but worthy of further research.

Keywords: pulmonary lymphoepithelioma-like carcinoma, genetic profile, EBV infection, PD-L1 expression, tumor inflammatory microenvironment, treatment strategy

Introduction

Pulmonary lymphoepithelioma-like carcinoma (PLELC) is a rare and distinct subtype of non-small-cell lung cancer (NSCLC) associated with Epstein–Barr virus (EBV) that is less reported and not well understood.[1] It accounts for ~0.7% of all NSCLC cases and usually affects young, nonsmoking, Asian populations[2] and clinical and radiographic manifestations are not pathognomonic.[1,3] The tumor has distinct pathologic features which are indistinguishable from those of undifferentiated nasopharyngeal carcinoma and is characterized by poorly differentiated tumor cells with large vesicular nuclei and prominent nucleoli showing syncytial growth patterns along with heavy lymphocytic infiltration.[4,5] It has also been reported that PLELC displays nonclassic morphology with little lymphocytic infiltration.[6] The tumor is typically positive for CK5/6, EMA, p63 and p40, suggesting squamous cell lineage.[7,8] The presence of EBV in the nuclei of tumor cells is essential for the diagnosis, which can be detected by in situ hybridization for EBV-encoded RNA (EBER). The majority of patients with PLELC are detected at early stage and may have better prognosis than other subtypes of NSCLC.[2,4]

This review is to summarize recent research that expands our knowledge about PLELC, with main focus on its genetic profile, tumor-infiltrating environment, PD-L1

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expression, circulating EBV-DNA, clinical utility of 18F-FDG PET/CT, and treatment strategy (see Table 1).

Genetic Profile of PLELC

Several driver mutations have been reported to cause NSCLC.[9] Owing to the rarity of PLELC, few previous studies existed investigating its genetic status and association with clinicopathologic characteristics.[8,10,11] Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) rearrangement have been the first well-characterized genetic alterations with corresponding targeted agents that have greatly changed the treatment paradigm of advanced NSCLC.[9] Other oncogenic drivers have emerged as novel molecular targets with potential therapeutic implications such as mutations in the gene Kirsten rat sarcoma viral oncogene homolog (KRAS), BRAF, and ROS1 and MET gene amplification.[12] An earlier study on the prevalence of EGFR mutations among different histological types of lung cancer demonstrated a low prevalence (1 of 11) of EGFR mutations in PLELC (see Table 2).[13] Chang et al showed p53 and EGFR mutations were uncommon in PLELCs.[8] In this study, p53 mutations were identified in only 3 of 46 cases (6.5%) and EGFR mutations were observed in 8 of 46 cases (17.4%) with a majority of exon 21 mutations but without L858R. Notably, EGFR mutations were more commonly found in patients with tumor size ≤3 cm.[8] Wang et al found that only 1 of 42 cases was observed to harbor EGFR L858R mutations.[14] Chang et al, in another study, found that the overall frequency of EGFR alterations was 12.1%.[15] Liang et al analyzed EGFR mutations in exons 18, 19, 20, and 21 in 11 patients with PLELC and found that all were wild type.[2] Yeh et al demonstrated that EGFR was wild type in all 18 patients in whose information was available.[6] Liu et al showed that none of the 32 patients with PLELC had EGFR mutations in exons 19 and 21.[10] Fang et al found that EGFR mutation rate was 1.8% (2 of 113).[16] Recently, Hong et al explored the landscape of PLELC and confirmed a low degree of typical driver mutations including EGFR, KRAS, and BRAF.[17] Although MET mutations were detected in two PLELC patients, none of them belong to the canonical MET exon 14 skipping mutations.[17] ALK gene rearrangement is rarely detected in PLELC as well.[6,14-16,18] It was absent in most studies. Only one patient of PLELC with EML4-ALK fusion gene was reported recently.[19] There were another two studies examining the prevalence of KRAS in PLELC, which failed to identify any KRAS mutated patients.[15,16] In addition, one of these studies

Table 1 Main Findings of the Study

	PLELC
Genetic profile	PLELC harbors a low frequency of typical driver mutations.
	A high prevalence of copy number variations exists in PLELC.
	Other molecular alterations may play a role (eg epigenetic regulation, MSI, and LOH).
Tumor microenvironment	Lymphocytes, which may be triggered by EBV infection, are intensely infiltrated.
	TAMs exist in a great amount, probably acting as a tumor-inhibitor.
PD-L1 expression	63.3–75.8% of PLELC harbors PD-L1 positivity and the proportion is higher than that in Lung AD.
	The prognostic significance of PD-L1 positivity remains inconsistent based on the literature.
Circulating EBV-DNA	Baseline plasma EBV-DNA may predict disease recurrence and progression.
PET/CT	PLELC may be FDG-avid and PET/CT may help refine disease stage in clinical practice.
Treatment strategy	The treatment of PLELC is the same as with other NSCLC. Surgical resection with/without adjuvant therapy is the preferred approach for early-stage PLELC.
	Multimodality treatment is suitable for advanced stage or metastatic PLELC.
	No consensus on the optimal regimen of chemotherapy exists.
	EGFR-targeted therapies are ineffective toward PLELC.
	Evidences on the clinical impact of immune-checkpoint inhibitors are limited and unconvincing.

Abbreviations: PLELC, pulmonary lymphoepithelioma-like carcinoma; AD, adenocarcinoma; MSI, microsatellite instability; LOH, loss of heterozygosity.

Table 2 Summary of Molecular Alterations in PLELC

References	Molecular Alterations	Methods	Prevalence
[13]	EGFR mutations (exons 18–21)	PCR	1 of 11
	KRAS mutations (exon 12, 13, and 61)		0 of 11
[8]	TP53 mutations (exons 5–8)	Nested PCR	3 of 46
	EGFR mutations (exons 18–21)		8 of 46
[14]	EGFR mutations (exons 18–21)	RT-PCR	1 of 42
	ALK rearrangements	FISH	0 of 42
[15]	EGFR mutations (exons 18–21)	PCR	8 of 66
	KRAS mutations (exon 2)		0 of 66
	BRAF mutations (exon 15)		0 of 66
[2]	EGFR mutations (exons 18–21)	Nested PCR	0 of 11
[6]	EGFR mutations	NA	0 of 18
	ALK rearrangements		0 of 11
[10]	EGFR mutations (exons 19/21)	RT-PCR	0 of 32
[16]	EGFR mutations	PCR	2 of 113
	KRAS mutations		0 of 113
	ALK rearrangements	FISH	0 of 113
[17]	EGFR mutations	WES	Rarely detected
	KRAS mutations		
	BRAF mutations		
	MET missense mutations		2 of 30
[18]	EML4-ALK fusion	PCR	0 of 11
[19]	EML4-ALK fusion	FISH	1 of 1
[21]	Trisomy/polysomy 11	FISH	6 of 8
[23]	MSI	PCR	2 of 7
	LOH		3 of 7

Abbreviations: MSI, microsatellite instability; LOH, loss of heterozygosity; WES, whole-exome sequencing.

revealed that no aberrations in BRAF and ROS1 in PLELC could be detected.[15] These results above suggested that typical driver mutations in other subtypes of NSCLC might not play an important role in the carcinogenesis of PLELC and EGFR-targeted therapy is not suitable for patients with advanced PLELC.

In addition to a low frequency of typical driver mutations, a high prevalence of copy number variations was noted in PLELC.[17,20] Xie et al showed that copy number variations were detected in 52% of the patients.[20] Interestingly, epigenetic regulation might participate in the process of carcinogenesis as reflected by Xie's finding that 78% of the patients had mutations in epigenetic regulators.[20] Moreover, the frequent overexpression of APOBEC family genes, which participated in innate immune response against virus infections, and frequent loss of type I IFN genes were seen in PLELC, reflecting the complex host-virus counteraction during the process of EBV-associated carcinogenesis.[17]

Chromosome 11 changes might be closely related to EBV-associated malignancies.[17] Chan et al compared the frequency of chromosome 11 copy number gains in three different types of EBV-associated malignancies and revealed that trisomy or polysomy 11 was detected in 6 of 8 PLELC.[21] Microsatellite instability (MSI) and loss of heterozygosity (LOH) represent molecular disorders acquired by the cell during neoplastic transformation and have been reported in several cancer types, including lung cancer.[22] Dacic et al found that MSI was detected in 2 of 7 PLELC cases and LOH was identified in 3 of 7 PLELC.[23] Relative higher frequency of LOH suggested inactivation of tumor suppresser gene in chromosome 5q23 might play a role in PLELC tumorigenesis.[23]

Tumor Inflammatory Microenvironment of PLELC

PLELC is a tumor with distinct morphologic features characterized by an undifferentiated malignant epithelial neoplasm with a markedly prominent lymphoid infiltrate.[24] Few studies explored the mechanism for lymphoid infiltration in the tumor stroma. Whether EBV triggered tumor-infiltrating lymphocytes (TILs) and the immunophenotype and antigen specificity of TILs in PLELC remain to be determined. Kobayashi et al found that tumor-infiltrating lymphocytes in EBV-positive PLELC were predominantly CD8+ and T cell intracytoplasmic antigen (TIA-1)+ cytotoxic T cells with closely linked with HLA-DR+ PLELC cells.[25] Chang et al reviewed the histopathology of 23 cases of PLELC and indicated that all of their cases showed prominent infiltration of CD8+ lymphocytes in the tumor cell nests and the surrounding stroma.[26] The antigen specificity of these CD8+ lymphocytes is not clear. The accumulation of these CD8+ lymphocytes with the cell-to-cell contact to tumor cells suggested that these CD8+ lymphocytes might be specific to tumor cell antigens coded either by EBV or EBV-induced cellular genes.[27] Kasai et al examined the immunophenotype of

TILs of two cases of EBV-positive PLELC and found the majority of TILs were cytotoxic T lymphocytes (CTL) in the resting state due to the findings of these TILs labeling with both CD8 and TIA-1 but not with granzyme-B.[28] They argued that local inhibition of EBV-specific CTL response such as T-cell anergy might be responsible for the lack of CTL activation at the tumor site.[29] TILs have been shown to be related to improved prognosis in certain types of cancer, including NSCLC.[30,31] Based on the current literature, we believe that persistent EBV infection in PLELC triggers intense infiltration of lymphocytes, whether activated or not, representing enhanced tumor immunity and possibly resulting in a better prognosis. Recently, Yeh et al quantitatively evaluated the tumor lymphocytic infiltration of 28 cases of PLELC via anti-CD45 staining.[6] Interestingly, lymphocytic infiltration pattern in PLELC constituted a wide and continuous spectrum. Larger tumor size, higher SUVmax, and shorter recurrence-free survival in CD45-low group compared to CD45-high group further supported the notion that high lymphocytic infiltration is associated with improved patient outcomes.[31,32]

In addition to lymphocytes, macrophages have also been detected in significant numbers in NSCLC, being likely to be important determinant of both prognosis and response to therapy.[33–35] Upon influence of various stimuli in the tumor microenvironment, tumor-associated macrophages (TAMs) interact with tumor cells to develop into a tumor-inhibitory or tumor-promoting phenotype.[33] The majority of TAMs are believed to be recruited from peripheral blood monocytes through a chemotactic gradient generated by tumor-derived chemotactic peptides.[36] Wong et al reveal that compared with conventional NSCLC, the TAMs infiltrate was more abundant and showed a closer proximity to the MCP-1-expressing tumor cells in PLELC.[37] Recruitment of TAMs mediated by MCP-1 from adjacent tumor cells of PLELC might promote tumor development through the elevation of survival and propagation of EBV. Furthermore, Wang et al showed significant expression of TAMs in PLELC and correlated with poor prognosis.[38] Moreover, elevated pretreatment monocyte-to-lymphocyte ratio (MLR) was shown to be associated with poor prognosis in patients of PLELC. It seems that TAMs act as a tumor-inhibitor in the tumor microenvironment of PLELC, but further investigations are warranted.

PD-L1 Expression in PLELC and Its Prognostic Value

Tumor immune evasion is an emerging hallmark of cancer.[39] One possible underlying mechanism might be that cancer co-opts inhibitory pathways such as the programmed cell death-1 (PD-1) pathway.[40] Lung cancer has been detected to express programmed cell death-1 ligand (PD-L1) on their cell surface, which is a known ligand of the PD-1 receptor on T cells.[41] This pathway causes T-cell exhaustion or apoptosis and subsequent immune escape.[42,43] Novel PD-1/PD-L1 monoclonal antibodies can block either of these two binding sites, thereby restoring function of exhausted T cells.[44] These immune-checkpoint inhibitors not only show preclinical activity in NSCLC, but have already entered clinical practice in advanced NSCLC either as monotherapy or in combination with chemotherapy, changing the therapeutic landscape of non-oncogene addicted patients.[45] Evidences revealed that 63.3–75.8% of the PLELC, which usually lacked common driver gene mutations like EGFR, showed PD-L1 positivity in tumor cells.[15,16,46,47] This proportion was higher than that in lung adenocarcinoma (13.5–53.6%) as shown in a meta-analysis by Zhang et al.[48] In view of the different EGFR mutation profiles reported in PLELC and lung adenocarcinoma, the association between frequent PD-L1 expression and EGFR wide-type status seemed plausible.[48] Given the finding that PLELC is strongly associated with EBV infection, PD-L1 induction dependent upon constitutive expression of the EBV-coded gene products, such as latent membrane protein-1 (LMP-1) is intuitive.[49,50] Moreover, Hong et al revealed the relationship between CD274 gene amplification and PD-L1 overexpression in PLELC, but how the underlying mechanism remained unknown.[17]

With respect to the prognostic significance of positive PD-L1 in tumor cells of PLELC, no consensus has been reached. Yu et al observed that PD-L1 (+) in tumor cells predicted longer DFS in patients with PLELC,[46] which was consistent with Jiang et al's results.[47] By contrary, Fang et al reported that PD-L1 high expression was associated with impaired DFS in resectable PLELC.[16] Moreover, no prognostic implication of PD-L1 frequent positivity in tumor cells of PLELC was reported in Chang et al's study.[15]

Association of EBV Infection and PLELC Occurrence and Prognostic Value of Circulating EBV DNA in PLELC

Because of the PLELC's close association with EBV infection, the 2015 World Health Organization classification requires the presence of EBV within the nuclei of the neoplastic cells in order to make its diagnosis.[24] The EBV is often detected in pulmonary LELC occurring in Asian patients,[2,3,6,8,10,14,51-54] but rarely detected or even undetected in other types of lung cancer such as adenocarcinoma, squamous cell carcinoma, and SCLC.[55,56] Negative expression of EBV in patients with PLELC from Western countries suggests EBV as not an indispensable factor for the development of PLELC.[56–59]

Previous studies have measured circulating EBV DNA in the plasma of patients with pulmonary LELC and suggested its role for monitoring response to therapy.[60,61] Xie et al demonstrated variation of plasma EBV DNA in two patients treated with chemotherapy and/or radiotherapy was consistent with their clinical course.[54] Xie et al performed a prospective multicenter study in Southern China investigating the association between baseline EBV DNA and OS and disease-free survival (DFS) in a total of 429 patients with pulmonary LELC and showed that baseline EBV DNA copy of at least 4000 copies/mL predicted disease recurrence and poorer survival among patients with early- or advanced-stage pulmonary LELC.[62] Through sequential blood draw, they found that plasma EBV DNA frequently preceded disease progression during posttherapy follow-up. Moreover, patients with persistently detectable plasma EBV DNA after radial resection had significantly worse OS and DFS than did those with EBV DNA after surgery.[62] Moreover, Lin et al reported that patients with high baseline EBV DNA exhibited significantly shorter PFS and OS than those with low baseline EBV DNA.[63] The above findings further supported an oncogenic role of EBV in Asian patients of pulmonary LELC.

Clinical Role of 18F-FDG PET/CT in PLELC

18F-FDG PET/CT is an anatomo-metabolic imaging modality that has recently been introduced to clinical practice and has been recommended by the National Comprehensive Cancer Network to use for routine staging of NSCLC.[64,65] The clinical utility of 18F-FDG PET/CT in PLELC remains unknown. Few case reports and retrospective studies described the 18F-FDG avidity of PLELC and found all cases were 18F-FDG avid with a wide range of reported maximum standardized uptake values (SUVmax) ranging from 1.7 to 34.5.[66–71] A small case series by Chan et al for the first time found that 18F-FDG PET/CT contributed to accurate evaluation of disease staging, treatment response as well as disease recurrence of PLELC.[71] Recently, Su et al identified that pretreatment 18F-FDG PET as independently associated with a better OS in patients with PLELC.[70] In their study, 18F-FDG PET led to an upstaging in 28.6% of patients with CT-defined stages III-IVa. Intuitively, 18F-FDG PET may help refine palliation strategies and subsequently improve the prognosis.[70]

Treatment Strategy of PLELC

No clinical practice guideline tailored for PLELC exists owing to its rarity. The treatment of PLELC is the same as with other NSCLC. Most of the reported patients present at early and resectable stage and surgical resection with curative intent is the preferred approach.[2] Surgery with adjuvant chemotherapy is recommended by some authors for the patients with stage IIIa for better prognosis.[2,72,73] PLELC is reported to be chemosensitive and radiosensitive and multimodality treatment including chemotherapy and/or radiotherapy may play important roles in advanced stage or metastatic PLELC.[74–76] More importantly, patients with locally advanced stage PLELC may benefit from a more aggressive multimodality approach.[70,73]

There is currently no consensus on the regimen of chemotherapy for patients with advanced PLELC.[1,63] Most of the previous reports on choice of chemotherapy regimen were based on small case series and retrospective studies.[1,73,77] 5-FU plus cisplatin or 5-FU-based chemotherapy was used in some patients before 2002. Platinum-based doublet chemotherapy was considered the standard regimen for NSCLC after 2002.[74] Xie et al reported two cases of advanced PLELC responding well to chemotherapy (paclitaxel plus carboplatin) and chemotherapy (docetaxel plus cisplatin) with radiotherapy, respectively.[54] Lin et al reported that 83.3% of the patients treated with palliative chemotherapy with docetaxel and cisplatin gained partial response (10 of 12 patients).[72] Liang et al demonstrated that PLELC was sensitive to paclitaxel-based or docetaxel-based regimen.[2] Qin et al explored the optimal regimen of chemotherapy for advanced stage PLELC and revealed that patients treated

Table 3 Case Reports of PLELC Treatment with Immune-Checkpoint Inhibitors

References	Age (years)	Sex	Smoking Status	Ethnicity	Stage[a]	First Treatment	Immunotherapy	Duration[b] (mts)	Outcomes	OS (mts)
[81]	56	M	Former smoker	Asian	IV	Surgery+chemo	4th Nivolumab	25	PR	62
	37	F	Never smoker	Asian	IIIA	Chemo+radio	3rd Nivolumab	27	PD	56
[80]	51	F	Former smoker	NM	IV	Chemo	2nd Nivolumab	7	DD	NM
[79]	76	F	Never smoker	Asian	IV	Chemo +cetuximab	3rd Atezolizumab	4	DD	28
[82]	56	F	Never smoker	Asian	IV	Chemo	2nd Nivolumab	5	PR	NM
[77]	37	F	Never smoker	Asian	IIIa+IV'	Surgery'+chemo'	2nd Nivolumab	NM	DD	48

Notes: [a]Stage at diagnosis/recurrence; [b] duration of immunotherapy; IIIa+IV', stage IIIa at diagnosis and stage IV at recurrence; surgery'+chemo', neoadjuvant chemotherapy and surgery at diagnosis, surgery and adjuvant chemotherapy at recurrence; 4th, fourth-line; 3rd, third line; 2nd, second-line.
Abbreviations: mts, months; OS, overall survival after diagnosis; chemo, chemotherapy; radio, radiotherapy; NM, not mentioned; PR, partial response; PD, progressive disease; DD, died of disease.

with paclitaxel plus platinum or gemcitabine plus platinum responded more favorably than that with pemetrexed plus platinum.[1] Hong et al demonstrated that gemcitabine plus platinum significantly improved objective response rate and progression-free survival compared to pemetrexed plus platinum as first-line treatment of metastatic PLELC.[17] Recently, Lin et al found that gemcitabine plus platinum achieved higher response rate and longer median PFS as compared to taxanes plus platinum or pemetrexed plus platinum.[63] Besides, Ho et al reported capecitabine monotherapy controlled disease progression in three of five patients with advanced or metastatic PLELC, suggesting the antitumor potential of capecitabine-containing chemotherapy regimen in PLELC.[78]

Cumulative toxicities induced by the long-term use of conventional chemotherapy propel the practitioners to choose other treatment approaches, such as EGFR-targeted therapy and immunotherapy.[76] Targeted therapies are believed to be not very useful due to the lack of actionable mutations.[8,10] Previous literature failed to demonstrate the obvious therapeutic effect of EGFR-targeted therapies towards PLELC.[1,2,8,10,14,74] Although high expression of PD-L1 in PLELC provides a rationale for implementation of PD-l/PD-L1 monoclonal antibodies, the clinical impact of these agents in PLELC has only been reported in limited case reports (see Table 3).[77,79-82] Among them, Kumar et al reported 2 cases of advanced stage PLELC progressed despite multiple lines of chemotherapy, but responded favorably to nivolumab, a PD-1 inhibitor.[81] Darasson et al demonstrated a case of a partial response and clinical improvement after pseudoprogression in a patient of PLELC treated with nivolumab after progression using 5 cycles of chemotherapy.[80] Narayanan et al presented a case of PLELC responding favorably to blockage with a PD-L1 antibody, atezolizumab.[79] Qiu et al described a case of PLELC responding well to nivolumab, manifesting as dramatic decline of tumor burden and serum tumor markers.[82] By contrast, Kim et al reported a case of chemotherapy-refractory PLELC showing rapid progression with second-line nivolumab.[77] Undoubtedly, a clinical trial testing PD-1/PD-L1 therapy was warranted before this line of treatment could be suggested as a new standard of care for advanced PLELC.

Conclusion

Pulmonary lymphoepithelioma-like carcinoma is a rare and distinct subtype of non-small-cell lung cancer (NSCLC) associated with Epstein–Barr virus (EBV) infection. EGFR mutation and ALK rearrangements are not commonly detected in PLELC. Persistent EBV infection may trigger intense infiltration of lymphocytes, representing enhanced tumor immunity and possibly resulting in a better prognosis. Circulating EBV-DNA in the plasma of patients with PLELC may predict disease progression and response to therapy. PLELC is 18F-FDG avid and 18F-FDG PET may help refine palliation strategies and subsequently improved the prognosis. Most of the reported patients present at early and resectable stage and surgical resection with curative intent is the preferred approach. There is currently no consensus on the regimen of chemotherapy. EGFR-targeted therapies seem to have no therapeutic effect and the clinical impact of PD-1/PD-L1 therapy is uncertain, but worthy of further research.

Abbreviations

PLELC, pulmonary lymphoepithelioma-like carcinoma; EBV, Epstein–Barr virus; NSCLC, non-small-cell lung cancer; EBER, EBV-encoded RNA; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; KRAS, Kirsten rat sarcoma viral oncogene homolog; MSI,

microsatellite instability; LOH, loss of heterozygosity; TILs, tumor-infiltrating lymphocytes; TIA-1, T cell intracytoplasmic antigen; CTL, cytotoxic T lymphocytes; TAMs, tumor-associated macrophages; MLR, monocyte-to-lymphocyte ratio; PD-1, programmed cell death-1; PD-L1, programmed cell death-1 ligand; LMP-1, latent membrane protein-1; DFS, disease-free survival.

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