### Thymic tumors and immune checkpoint inhibitors

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**Abstract:** Thymoma and thymic carcinoma, known as the most common features of thymic epithelial tumors (TETs), are thoracic malignancies displaying varied clinical features and prognosis. These neoplasms being frequently ineligible for surgical complete resection as a curative treatment because of extensive tumor spread, effectual nonsurgical treatments are needed; however, an optimal chemotherapeutic regimen has not been identified, although some regimens have been shown to be active. Immunotherapy is effective for other malignancies and may be promising as a therapeutic alternative for refractory TETs. Thus far, several studies have determined the expression of programmed death ligand 1 (PD-L1) and programmed death 1 (PD-1) in TETs, including its clinicopathological and prognostic significance. The results have been conflicting due to the different immunohistochemical antibodies employed and distinct cutoff values. However, many authors identified abundant PD-L1 expression in TETs, which is considered as an important predictive factor for therapeutic effect of PD-1 inhibitor for TETs has been reported as expected; however, concerns regarding immunological adverse events have been raised. To optimize these therapeutic agents for refractory TETs, additional studies which evaluate clinical availabilities of immunotherapeutic drugs and characterize their basic mechanisms of action against immunotherapeutic targets are both urgently required.

**Keywords:** Thymic tumor; thymic epithelial tumor (TET); tumor immunotherapy; programmed death ligand 1 (PD-L1); programmed death 1 (PD-1)

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#### Introduction

Thymic tumors are rare neoplasms originating from the thymus and distinctly exhibit generically indolent behaviors. Thymic epithelial tumors (TETs) represented by thymoma and thymic carcinoma are the most common features in this category (1). Complete surgical resection is the standard treatment for TETs (2-6); however, treatment is often challenging for clinicians because these tumors commonly invade adjacent structures or metastasize to distant organs. In these unresectable cases, multidisciplinary systemic chemotherapy or chemoradiotherapy is administered. The initial regimens include cisplatin/doxorubicin/

cyclophosphamide with or without prednisolone, cisplatin/ doxorubicin/vincristine/cyclophosphamide (ADOC), or cisplatin/etoposide for thymoma and carboplatin/paclitaxel or ADOC in thymic carcinoma (7,8). Nevertheless, the clinical efficacy of these agents is confirmed only by the results of some retrospective studies or phase II trials, and evidence from randomized controlled trial is lacking probably due to the rarity of the disease. Indeed, unsatisfied chemotherapeutic responses are often observed in clinical settings, particularly in the treatment of thymic carcinoma. Therefore, further improved treatment strategies based on solid oncogenic mechanisms are currently investigated.

Recent accumulating evidences on immune checkpoint

Study	Years	Histology	Clone for IHC	Number of cases with high PD-L1 expression	Evaluation (cutoff value)
Padda et al. (13)	2015	65 thymomas, 4 thymic carcinomas	15	68% (collectively)	Intensity (intermediate-strong staining)
Katsuya <i>et al.</i> (14)	2015	101 thymomas, 38 thymic carcinomas	E1L3N	23% of thymomas, 70% of thymic carcinomas	Quantitative, H-score (3, 1%)
Yokoyama <i>et al.</i> (15)	2016	82 thymomas	EPR1161 [2]	54%	Staining area (38%)
Yokoyama <i>et al.</i> (16)	2016	25 thymic carcinomas	EPR1161 [2]	80%	Quantitative, H-score (20, 7%)
Marchevsky <i>et al.</i> (17)	2017	38 thymomas, 8 thymic carcinomas	SP142	92% of thymomas, 50% of thymic carcinomas	Staining area (1%)
Weissferdt <i>et al.</i> (18)	2017	74 thymomas, 26 thymic carcinomas	E1L3N	64% of thymomas, 54% of thymic carcinomas	Number of cells (5%)
Arbour <i>et al.</i> (19)	2017	12 thymomas, 11 thymic carcinomas	E1L3N	92% of thymomas, 36% of thymic carcinomas	Staining area, M-score (25%)

 Table 1 Profiles of PD-L1 expression in thymic epithelial tumors

PD-L1, programmed death ligand 1; IHC, immunohistochemistry.

pathways enhanced the understanding of underlying mechanisms in tumor immunity. Programmed death ligand 1 (PD-L1) is a transmembrane glycoprotein expressed by antigen-presenting cells and modulates immune responses by binding to programmed death 1 (PD-1) receptor, a member of the B7 receptor family expressing on the surface of T cells (9,10). This sequence contributes inhibitory signals that mediate physiologic immune tolerance (11). Moreover, recent studies emphasized the role of PD-1/ PD-L1 pathway in facilitating tumor progression by inhibiting anti-tumor T cell responses to evade host immune surveillance mechanisms (12). Therefore, immune checkpoint inhibitors, which are novel therapeutic options for patients with malignant tumors, are effective against malignancies and have been widely used since their introduction. Several clinical trials showed the efficacy of anti-PD-1, anti-PD-L1, and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies, leading to their approval for clinical application in various malignant tumors by the U.S. Food and Drug Administration (FDA).

In TETs, some research identified the expression of immunotherapeutic targets in the tumor microenvironment, and other case reports also indicated novel antitumor responses from the agents targeting PD-1/PD-L1 pathway. Some phase I trials assessing the effectiveness of immune checkpoint inhibitors in solid malignant tumors included a small number of TETs and confirmed their effectiveness in each case. In addition, other phase II clinical trials on PD-1/PD-L1 pathway blockers for TETs are being currently performed. In this review article, we aimed to provide an overview on the current knowledge of immunotherapeutic targets focused on PD-L1 and PD-1 and discuss the potential for immune checkpoint blockade therapy in TETs.

#### **PD-L1** expression of neoplastic cells in TETs

Analyses of PD-L1 expression in TETs started in 2015 following the development of PD-L1 evaluation in various malignant tumors. However, only seven studies by far have examined PD-L1 expression in TETs, 4 of which are from the United States, while the other 3 are from Japan (*Table 1*). However, these studies included only a limited number of cases maybe since TETs are relatively rare malignant tumors and data are difficult to collect even in cancer centers.

Padda *et al.* first announced PD-L1 expression in 69 TETs evaluated via immunohistochemistry (IHC) using a clone of 15 (Sino Biological, Beijing, China) (13). They identified diffuse IHC staining in neoplastic cells in almost all PD-L1-positive cases with both cell membrane and cytoplasm. PD-L1 expression status was defined according to IHC staining intensity and the proportion was not considered. They concluded that 68% of the 69 TET cases showed high PD-L1 expression. Katsuya *et al.* reported that 23% of thymomas and 70% of thymic carcinomas have high PD-L1 expression by evaluating using H-score method with a cutoff value of 1%, which consider both staining proportion and intensity. They employed a clone of E1L3N (Cell Signaling Technology, Danvers, MA, USA),



Figure 1 Representative microphotographs of immunohistochemical detection of PD-L1 in type B1 thymoma (A,B) and thymic carcinoma (C,D). Hematoxylin and eosin staining (left column, original magnification, 200×) and PD-L1 immunostaining (right column, original magnification, 200×). Diffuse staining with weak/moderate and high intensity of PD-L1 is identified in type B1 thymoma (B) and thymic carcinoma (D), respectively.

which is a high reliable antibody (14). The authors reported that 54% of thymomas and 80% of thymic carcinomas overexpressed PD-L1 (15,16). PD-L1 was immunostained by using a clone of EPR1161 [2] (Abcam, Cambridge, UK), and evaluated considering staining area and H-score method, respectively. The optimal cutoff value was validated by using receiver operating characteristic curve and Youden's index. Meanwhile, Marchevsky et al. used a SP142 clone to investigate 38 thymomas and eight thymic carcinomas and found that 92% of thymomas and 50% of thymic carcinomas exhibit high-PD-L1 expression (17). They defined the cutoff value as 1% in each area. Weissferdt et al. surveyed 100 cases of TET (74 thymomas and 26 thymic carcinomas). PD-L1 was evaluated according to the number of tumor cells showing positive staining for E1L3N (18). The cutoff value was defined as the proportion of positive cells with 5% staining. They found that 64% of thymomas and 54% of thymic carcinomas have high PD-L1 expression. Arbour et al. recently studied 12 thymomas and 11 thymic carcinomas by using E1L3N clone and evaluated

PD-L1 expression according to staining area (M-score) (19). They considered the cutoff value as 25% in M-score and concluded that 92% of thymomas and 36% of thymic carcinomas revealed PD-L1 overexpression.

Although these studies evaluated the degree of PD-L1 expression of tumor cells via IHC using varied antibodies and cutoff values, a similar result has been obtained, indicating that neoplastic epithelial cells in TETs demonstrated relatively abundant PD-L1 expression (*Figure 1*). In other malignancies, PD-1- and PD-L1-based antibodies showed enhanced activity, particularly in PD-L1-positive tumors (20,21). Therefore, these results support the potential clinical efficacy of PD-1/PD-L1 blockade in TETs, although the practical application of such treatment modality is still under investigation in clinical trials.

# Clinicopathological and prognostic relevance of PD-L1 expression in TETs

Previous studies also showed some clinicopathological

Studies	Factors associated with high PD-L1 expression	Prognostic impact of high PD-L1 expression
Padda <i>et al.</i> (13)	Younger age, high stage, incomplete resection, aggressive histology	Worse OS (age- and sex-adjusted analysis)
Katsuya <i>et al.</i> (14)	Thymic carcinoma (rather than thymoma)	None
Yokoyama <i>et al.</i> (15)	Masaoka stage III/IV, WHO type B2/B3	Worse DFS
Yokoyama <i>et al.</i> (16)	None	Better OS
Marchevsky et al. (17)	Aggressive histology	-
Weissferdt et al. (18)	Neoadjuvant therapy in thymoma	None
Arbour <i>et al.</i> (19)	Thymoma (rather than thymic carcinoma)	Better OS

Table 2 Cliniconathological features and	d prognostic significance associated	with PD-L1 expression in t	hymic epithelial tumors
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PD-L1, programmed death ligand 1; WHO, World Health Organization; OS, overall survival; DFS, disease-free survival.

features related with high PD-L1 expression in TETs (*Table 2*). The seven studies mentioned earlier showed high PD-L1 expression associated with aggressive histology, such as in type B2/B3 thymoma or thymic carcinoma, although one study adversely identified significant association between high PD-L1 expression and the histology of thymoma rather than thymic carcinoma. Moreover, some studies found that high PD-L1 expression was significantly associated with advanced Masaoka-Koga stage. As such, PD-L1 is speculated to be particularly overexpressed in TETs with high malignant potential or in advanced unresectable cases that are considered sufficiently eligible for anti-PD-1/PD-L1 blockade therapy.

In terms of the prognostic impact of PD-L1 expression in TETs, the results slightly differ among the past studies. Katsuya et al. and Weissferdt et al. did not find any prognostic relevance of PD-L1 expression in TETs (14,18). By contrast, Padda et al. found that high PD-L1 expression in TETs was associated with poor overall survival (OS) in sex- and age-adjusted analysis (13). The authors also determined significant correlation between high PD-L1 expression and poor disease-free survival, but not in OS, after complete resection in thymoma (15). By contrast, significant association was found between high PD-L1 expression and better OS in thymic carcinoma patients (16). Similarly, Arbour et al. also noted that high-risk TET cases (type B2/B3 thymoma and thymic carcinoma) with high PD-L1 expression had significantly better OS by using Kaplan-Meier methods (19). These conflicting results may be due to the study design. For instance, the authors considered that thymomas and thymic carcinomas should be individually analyzed because these tumors demonstrate distinct clinical behaviors. Thymomas are widely known

to complicate autoimmune disorders represented by myasthenia gravis in approximately 25% of cases and pathologically involve immature T cells expressing terminal deoxynucleotidyl transferase (2). By contrast, thymic carcinomas are defined as tumors lacking immature T lymphocytes and never elicit autoimmune diseases (1). As such, the tumor microenvironment in thymoma and thymic carcinoma should be distinguished. In addition, thymic carcinoma also demonstrates significantly poor prognosis compared with thymoma (1). These factors should be considered when investigating the prognostic implications of PD-L1 expression in TETs, although it is often difficult owing to the rarity of the disease. Thus, the prognostic significance of PD-L1 expression in TETs should be determined only after analyzing thymoma and thymic carcinoma individually.

# **PD-1** expression of tumor infiltrating lymphocytes (TILs) in TETs

Four of the 7 aforementioned studies studying PD-L1 in TETs also assessed PD-1 expression of TILs in TETs. Katsuya *et al.* were the first to report PD-1 expression in TILs, but not in neoplastic cells in thymic carcinoma (14). Considering their cutoff value, 62% of thymic carcinoma was classified as high PD-1 expression; however, no prognostic relevance was detected. The authors examined 25 cases of thymic carcinomas and noted that PD-1 expression in TILs was not associated with PD-L1 expression, but increased PD-1-positive TILs indicated a poor prognosis. Meanwhile, Weissferdt *et al.* reported that PD-1-positive TILs were found in 23% of thymic carcinomas and 62% of thymomas according to their criteria. They also identified

a significant association between increased PD-1-positive TILs and high stage in thymic carcinoma; nevertheless, the prognostic impact was not determined. Arbour *et al.* reported a significant association between high PD-1 expression and high/moderate glucocorticoid-induced tumor necrosis factor receptor (GITR) expression in high-grade TETs. GITR is a modulator of regulatory T-cells and a costimulatory molecule that has the potential to activate

cytotoxic T-cells (22-25). Despite these studies, the prognostic significance of PD-1 expression in TETs remains unclear. Theoretically, PD-1 expression in thymic carcinoma may have poor prognostic relevance due to the negative regulatory effect of cytotoxic T cells through PD-1/PD-L1 pathway. However, some authors determined mutually exclusive staining between PD-L1 and PD-1 expression in TETs, suggesting that inactivation of the PD-1/PD-L1 pathway may compromise the effectiveness of blockade therapy in this pathway (14,17). This point should be further clarified in detail in future studies with additional measurements, such as double IHC.

# Immunotherapeutic agents currently approved for clinical administration in malignant tumors

Several kinds of anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies have been recently approved by the U.S. FDA for use in clinical settings (26). As of July 2017, the anti-PD-1 antibodies nivolumab and pembrolizumab are available, which are both fully humanized IgG4 monoclonal antibodies against PD-1 receptor. Nivolumab has been approved for patients with metastatic melanoma, nonsmall cell lung cancer, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, and classical Hodgkin lymphoma, while pembrolizumab has been approved for metastatic melanoma, non-small cell lung cancer, squamous cell carcinoma of the head and neck, urothelial carcinoma, classical Hodgkin lymphoma, and solid tumors with high microsatellite instability or mismatch repair deficiency. As anti-PD-L1 antibodies, atezolizumab, a humanized engineered monoclonal antibody of IgG1 isotype, is approved for clinical administration in patients with non-small cell lung cancer and urothelial carcinoma. Furthermore, anti-PD-L1 antibodies avelumab and durvalumab are also available. On the other hand, ipilimumab, a fully humanized anti-CTLA-4 monoclonal IgG1 antibody, is approved only for patients with malignant melanoma.

## Clinical availability of anti-PD-1/PD-L1 blockade therapy for TETs

Some authors published sufficient therapeutic effects of PD-1/PD-L1 inhibitors for TETs in individual case reports, contributing in the promotion of clinical trials for advanced TETs (27,28). Subsequently, some phase I clinical trials used PD-1/PD-L1 inhibitors for solid malignant tumors including TETs, and demonstrated acceptable clinical efficacy and safety of the drug despite the limited number of patients (29-31). However, severe systemic mucocutaneous toxicity requiring plasmapheresis caused by pembrolizumab in a patient with type B2 thymoma has been reported, suggesting the requirement of careful patient selection in using immunotherapeutic agents (27).

Some phase II trials evaluating the clinical availability of pembrolizumab for thymic carcinoma are currently in progress (32,33). Giaccone et al. investigated 23 thymic carcinoma patients with disease progression after at least one line of chemotherapy and without autoimmune disease or other malignancy and found a response rate of 24%; 1 patient achieved complete response, 4 achieved partial response, 9 achieved stable disease, and 7 had disease progression. The toxicity was reported to be well tolerated, and mild fatigue, fever, diarrhea, and rhinorrhea were the major side effects. However, serious autoimmune disorders developed in two patients; one patient experienced severe myositis and myocarditis that required pacemaker implantation and the other patient developed type I diabetes mellitus after treatment discontinuation. The other trials by Cho et al. targeted 33 TET patients (26 with thymic carcinomas and 7 with thymomas). The eligibility criteria included progression after platinum-based chemotherapy. Patients with active autoimmune disease that required systemic therapy within the past 1 year were excluded. The overall response rate was 24.2%; 8 patients had partial response, 17 had stable disease, and 8 had progressive disease. In this study, various  $\geq$  grade 3 immunological side effects were observed, including hepatitis, myocarditis, myasthenia gravis, thyroiditis, glomerulonephritis, colitis, and subcutaneous myoclonus.

These studies suggested that pembrolizumab can induce acceptable responses against TETs in clinical settings. However, future studies should be designed with extensive surveillance particularly focused on immunological adverse events. Remarkably, various autoimmune disorders of which the detailed pathogenesis remain uncertain are known to be complicated in thymoma, the most common of which is myasthenia gravis. These poorly understood autoimmune mechanisms may be associated with the development of severe immunological adverse events from PD-1/PD-L1 blockade. Although rare, a fatal case of myasthenia gravis caused by pembrolizumab has been reported (34). Therefore, attentive discussions by multidisciplinary experts are needed for the off-label use of PD-1/PD-L1 blockade agents for TETs.

### **Concluding remarks**

Given the poor response of TETs to chemotherapeutic agents, the clinical administration of immunotherapy is a promising therapeutic alternative for advanced TETs. However, further careful evaluation of the efficacy and safety of immunotherapy for TETs is required. To optimize these drugs for refractory TETs, additional studies which evaluate clinical availabilities of immunotherapeutic drugs and characterize their basic mechanisms of action against immunotherapeutic targets are both urgently required.

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### Footnote

*Conflicts of Interest*: The authors have no conflicts of interests to declare.

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