



# Pembrolizumab in patients with thymic carcinoma: a cautionary tale

Jessica A. Hellyer, Sukhmani K. Padda, Heather A. Wakelee

Department of Medicine, Division of Oncology, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, California

*Correspondence to:* Heather A. Wakelee. Department of Medicine, Division of Oncology, Stanford Cancer Institute/Stanford University School of Medicine, Stanford, California. Email: hwakelee@stanford.edu.

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The development of novel treatment options for advanced-stage thymic neoplasms remains a challenge. The rarity of this disease has precluded the conduct of large randomized controlled trials and all current data stem from phase II clinical trials and retrospective cohort studies. Thymic carcinomas comprise a small subset of thymic epithelial neoplasms and despite the fact that they behave more aggressively and have a worse prognosis than thymomas, they are either analyzed in combination with thymomas or excluded from clinical trials altogether (1).

Current standard of care front line therapy for advanced thymic carcinoma is platinum-based chemotherapy (2). Carboplatin/paclitaxel is recommended by the National Comprehensive Cancer Network (NCCN) based on a phase II study which included 23 patients with thymic carcinoma and showed an objective response rate (ORR) of 21.7% (95% CI, 9.0–40.4), median progression-free survival (PFS) of 5 months (95% CI, 3.0–8.3), and median overall survival (OS) of 20 months (95% CI, 5.0–43.6) (3,4). A similar study conducted by the West Japan Oncology Group looked at carboplatin/paclitaxel in a cohort of patients with advanced thymic carcinoma and found an overall response rate of 36% (95% CI, 21–53%) and a median PFS of 7.5 (6.2–12.3) months (5). Other commonly used regimens include cisplatin/etoposide and cyclophosphamide/doxorubicin/cisplatin (CAP), which is the NCCN preferred regimen for advanced thymoma (2). A systematic review and pooled analysis of over 200 patients in 10 chemotherapy trials

showed that in patients with thymic carcinoma, the response rate to cisplatin-based chemotherapy was superior to carboplatin-based regimens (53.6% *vs.* 32.8%, respectively,  $P=0.00209$ ) (6). However, to date no one standard front line regimen exists.

Optimal treatment in the relapsed-refractory setting for advanced thymic carcinoma is poorly understood and data is limited. Although studies have identified several molecular abnormalities in thymic malignancies such as *EGFR*, *mTOR*, *TP53*, *HRAS*, *NRAS*, and *c-KIT*, there is limited data on the efficacy of targeting these mutations (7–10). Sunitinib, a multi-targeted tyrosine kinase inhibitor of VEGFR, KIT and PDGFR is an option for patients with thymic carcinoma based on an open-label phase II trial that included 25 patients with thymic carcinoma. At a follow-up of 17 months, 6 (26%) patients had a partial response and 15 (65%) had stable disease with median duration of response of 16.4 months. However, there was no association between *c-KIT* mutational status and response (11). Everolimus, a mTOR inhibitor designed to target the P13K/AKT/mTOR pathway, demonstrated efficacy in a phase II trial that included 19 thymic carcinoma patients and achieved a disease control rate of 78% and median PFS of 5.6 months (12). Although the sample size was small, there were no clear mutations identified that were associated with response to everolimus in this study. Despite increasing use of targeted therapy in thymic carcinoma, there is yet to be clear predictive biomarkers that enrich responses to these

treatments.

Over the last few years, the success of programmed death receptor ligand-1 (PD-L1) and programmed death receptor-1 (PD-1) immune checkpoint inhibitors (ICI) in other tumor types have led to numerous trials looking to expand the reach of these drugs. Up until recently, ICI had not been tested in patients with thymic epithelial neoplasms due to the concern for enhanced immune-related adverse events (irAE). Although autoimmune conditions, most commonly myasthenia gravis, are common in patients with thymoma, patients with thymic carcinoma rarely develop autoimmune disorders (13). The prevalence of autoimmune disorders in thymic epithelial neoplasms is not surprising since thymic tissue is responsible for T-cell maturation and is critical in maintaining immune homeostasis. PD-L1 expression by immunohistochemistry is a predictive biomarker for response to ICI therapy in select tumors such as non-small cell lung cancer (NSCLC) (14). We were one of the first institutions to report on PD-L1 expression in thymic epithelial neoplasms using a tissue microarray comprising 69 tumors, with all cases having some tumor expression of PD-L1 and the majority (68%) with intermediate-strong expression (15). This prevalent PD-L1 expression has been corroborated by several other groups including Weissferdt *et al.* in which 54% (14/26) of thymic carcinomas had high PD-L1 expression (16). One of the first experiences using pembrolizumab, a PD-1 ICI, in a patient with thymic carcinoma was published in 2016 showing a positive response and opened the door for several phase II trials (8,17).

In this study, Giaccone and colleagues sought to assess the efficacy of pembrolizumab in a single-arm, phase II study of 41 patients with advanced, previously treated thymic carcinoma conducted in the US. Importantly, patients were only eligible for this study if they had no history of autoimmune disease. Pembrolizumab was administered at 200 mg intravenously every 3 weeks for up to 2 years.

The cohort was primarily male (70%) and white (82%) with a median age of 57-year-old, and they were heavily pretreated with a median of two prior therapies (range, 1–6). Despite this being an advanced disease cohort with relatively extensive metastatic disease burden, 52% had received a previous thymectomy and 58% had prior chest radiation. At a median follow-up of 20 months, one patient had a complete response and eight had partial responses for an overall response rate of 22.5% (95% CI, 10.8–38.5). An additional 21 patients (53%) had stable disease for a disease

control rate of 73%. For those patients who achieved a complete or partial response, the median duration of response was 22.4 months (95% CI, 12.3–34.7). Median PFS was 4.2 months (95% CI, 2.9–10.3) and median OS was 24.9 months (95% CI, 15.5–not reached).

Correlative studies performed on archival tumor samples, even if exploratory, are critical in expanding our understanding of this rare tumor type. In a post-hoc analysis of 37 patients, those with high PD-L1 expression ( $\geq 50\%$ ) had a longer PFS compared with those with low (1–49%) or no (<1%) expression [median 24 months (95% CI, 5.8–42.3) *vs.* 2.9 months (95% CI, 1.7–4.1 months), respectively]. Gene expression profiling was performed in 33 samples to examine the T-cell-inflamed interferon- $\gamma$  expression profiles. Prior studies have shown a correlation between high expression of interferon- $\gamma$  and response to PD-1 blockade (18). Similar to prior trials, there was a significant correlation between interferon- $\gamma$  expression and tumor response ( $P=0.044$ ). Targeted exome sequencing was completed in 36 patients with the most common mutation occurring in *TP53* (36%). Those patients with *TP53* mutations were more likely to have low or absent PD-L1 expression ( $P=0.043$ ) and there was a trend toward shorter OS. These represent several potential immunotherapy biomarkers for thymic carcinomas that could be confirmed in future studies.

The most common grade 1–2 adverse events with pembrolizumab in patients with thymic carcinoma were fatigue (46%), hepatic enzyme elevation (25%), and diarrhea (10%). In addition, 6 (15%) patients developed one or more severe (grade 3–4) irAEs, with four requiring hospitalization and five receiving high-dose steroids. Two patients developed myocarditis/polymyositis requiring pacemaker placement, and one patient developed grade 4 myositis. There were four instances of hepatitis and one diagnosis of bullous pemphigoid. There was one case of new onset insulin-dependent type 1 diabetes mellitus and a case of myasthenia gravis requiring intravenous immunoglobulin (IVIG). The onset of these severe adverse events ranged from cycle 2 to 10 of pembrolizumab. There were no deaths related to adverse events. The 15% rate of grade 3 or higher irAEs in this study is substantially higher than that seen in other epithelial tumors such as NSCLC (19). This is somewhat surprising given patients with thymic carcinoma in contrast to patients with thymoma, rarely have autoimmune disorders and no patients with a history of autoimmune disorder were eligible for this study (20).

Similar to other thymic epithelial neoplasm studies,

limitations include small sample size, open-label design, and lack of a control population. In addition, although the association between depth of response and PD-L1 status is interesting, it bears noting that this analysis was done post-hoc and the study was not powered to detect this difference.

This study was the first prospective trial to demonstrate activity of PD-1 ICI pembrolizumab in patients with metastatic thymic carcinoma. The rate of response is in line with a similar trial conducted in Korea by Cho *et al.* (21) of pembrolizumab in 33 patients with thymic epithelial neoplasm, 26 with thymic carcinoma and 7 with thymoma. Five of 26 patients with thymic carcinoma had a partial response and an additional 14 had stable disease for an overall response rate of 19.2% (95% CI, 8.5–37.9) and a disease control rate of 73.1% (95% CI, 53.9–86.3). The median PFS was 6.1 months. Similar to the Giaccone *et al.*, this trial found 4 of 26 patients (15.4%) had a serious (grade 3–4) irAE, with the most common being hepatitis (7.7%), myasthenia gravis (7.7%; one of two patients had preexisting myasthenia gravis) and subacute myoclonus (3.8%). This led to treatment discontinuation in 3 out of the 4 patients. Time of onset varied from cycle 1 to 10 of pembrolizumab. Unlike the Giaccone *et al.* study, there were no cases of myositis or myocarditis reported in the thymic carcinoma population. All patients received steroids and 7 patients required additional immune modulation such as IVIG, infliximab, or cyclophosphamide. As would be expected, the severe irAE rate for thymomas was higher (71.4%; 5/7) in this study and further enrollment for this histotype was halted.

The response rate seen with pembrolizumab is in line with several other second line thymic carcinoma trials and retrospective cohort studies. For example, in a retrospective analysis of single agent pemetrexed in 10 patients with thymic carcinoma at our institution, one had a partial response and 5 had stable disease, the median PFS was 6.5 months, and the median OS was 12.7 months (22). A phase II study of capecitabine plus gemcitabine in 8 patients with advanced refractory thymic carcinoma demonstrated a response rate of 38% (partial response in 3 of 8 patients) and median PFS of 6 (95% CI, 3–10) months (23). Newer targeted agents such as sunitinib and everolimus in patients with thymic carcinoma have shown a response rate of 26% and 16.7%, respectively, and median PFS of 7.2 (95% CI, 3.4–15.2) months (11) and 5.6 (95% CI, 2.6–8.5) months (12), respectively.

While the response rate and median PFS of advanced thymic carcinoma to pembrolizumab is similar to that of

other second line agents, the high rates of grade 3–4 irAEs are alarming. This study by Giaccone *et al.* and that by Cho *et al.* demonstrate rates of severe irAEs of close to 15% which is significantly higher than that seen in other epithelial tumors (19). This difference is dramatically illustrated by examining the randomized phase III studies of PD-1/PD-L1 ICI in previously treated advanced NSCLC. In the KEYNOTE-010 trial of pembrolizumab *vs.* docetaxel, grade 3–5 adverse events of special interest due to their likely immune etiology occurred in approximately 5% of patients with the most common being pneumonitis (2%; led to death in 2 of 7 patients), colitis (1%) and skin reaction (1%) (24). Similarly, in the CheckMate-057 trial of nivolumab (PD-1 ICI) *vs.* docetaxel, severe (grade 3–5) treatment-related adverse events occurred in about 5% of patients with the most common being pneumonitis (1%), elevated hepatic enzymes (1%) and diarrhea (1%); death occurred in one patient from encephalitis (25). Finally, the OAK trial of atezolizumab (PD-L1 ICI) *vs.* docetaxel had similarly low rates of severe (grade 3–4) immune-mediated adverse events, with four patients with grade 3 pneumonitis (<1%) and two with grade 4 hepatitis (<1%) (26). Not only were the rates of severe irAEs low in these studies, but the relatively high frequency of unusual events, such as the myositis/myocarditis (3/41) seen in Giaccone *et al.* study, were not observed.

Given the high rate of irAEs in this study, work needs to be undertaken to help predict which patients with thymic carcinoma are at risk for developing these severe autoimmune toxicities. Although Giaccone *et al.* note an association between being female and Asian descent with a higher rate of irAEs, it is worth noting that the Cho *et al.* study, which was a single-center study conducted in Korea, found similar rates of autoimmune toxicity in their study population. Preliminary work from both studies show an association between high PD-L1 expression and response to pembrolizumab. Future work powered to look at the correlation between PD-L1 expression among other novel biomarkers such as the interferon- $\gamma$  gene expression signature in thymic carcinomas and response to ICI is needed to best select patients who would benefit from these agents. In addition, biomarkers need to be elected for study to understand which patients are at risk for these severe autoimmune toxicities.

In summary, pembrolizumab is an option for clinicians treating patients with advanced chemorefractory thymic carcinoma with no history of autoimmune disease as the rates of response are similar to other second-line

chemotherapeutic and targeted agents. However, great caution should be exercised in prescribing these agents, as both phase II studies of pembrolizumab in patients with thymic carcinoma have shown a significant increase in severe and unusual irAEs, far surpassing the rates seen in other epithelial tumors. More work is needed to better understand this observation to mitigate these autoimmune toxicities and to refine the patient selection process.

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### Footnote

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

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