



# Emerging biomarkers for checkpoint inhibitors in thymic epithelial tumors

Dwight H. Owen, Gregory A. Otterson

Division of Medical Oncology, Department of Internal Medicine, Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

*Correspondence to:* Gregory A. Otterson. 320 W 10th Ave, B450B Starling Loving Hall, Columbus, OH 43210, USA. Email: greg.otterson@osumc.edu.

*Response to:* Sekine I, Aida Y, Suzuki H. Expression patterns and prognostic value of programmed death ligand-1 and programmed death 1 in thymoma and thymic carcinoma. *Mediastinum* 2018;2:54.

Guleria P, Jain D. PD-1/PD-L1 expression in thymic epithelial tumors: the predicament persists. *Mediastinum* 2018;2:60.

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Despite recent advances in the treatment of thymic epithelial tumors the only curative intervention remains surgical resection. Recent studies have evaluated novel treatments in patients with refractory TET including with targeted therapies and immune checkpoint inhibitors (1,2). Although several studies have evaluated the expression of immune markers such as programmed death-1 (PD-1) and its ligand PD-L1, there is no clear consensus on the role of these biomarkers in TET. We thank Dr.'s Guleria and Jain as well as Dr.'s Sekine, Aida, and Suzuki for their interest in our study evaluating PD-L1 and PD-1 expression in thymic epithelial tumors (TETs) (3). Both teams have raised many interesting issues which we believe are worthy of further discussion and may be used to help guide future research in these rare entities.

In their editorial, Dr.'s Guleria and Jain raise the important issue of the changes brought about by the 2015 WHO Classification when compared with the 2004 classification (4). Dr.'s Guleria and Jain note that some of the variation in association between stage and PD-L1 expression in many of these studies may be due in part to the changes in classification. We fully agree that this may be a confounding variable, especially given that many prior studies, ours included, utilized the 2004 classification (5-8), while other used the 2015 classification (9-12) or did not clearly specify the classification system used (13-16). Dr.'s Guleria and Jain also noted that there have recently been genetic changes discovered in TET including mutations in *GTF2I*. We fully agree that a further area of study would be the correlation between immune checkpoint

protein expression and mutations in *GTF2I* (17) as well as other mutations such as *TP53*, *KRAS* and *HRAS*, which were found to occur in TET in the recently published TCGA study of 117 TET samples (18). Another result of this study was the finding that thymomas have the lowest mutational burden among adult cancers, although the tumor mutational burden in thymic carcinoma samples was higher (18). The low rate of tumor mutation burden in thymoma may be another reason to exercise caution when exploring the role of immune checkpoint inhibitors in these patients given the high rate of immune-related adverse events (irAE) (19). However, the finding of association between aneuploidy and thymoma-associated myasthenia in the TCGA study raises the possibility of predicting irAE which may assist in patient selection for treatment with checkpoint inhibitors (18).

We fully agree with Dr.'s Guleria and Jain as well as with Dr.'s Sekine, Aida, and Suzuki regarding the issue of variability in terms of assays used in prior studies and the need for uniformity in evaluation of expression of immune markers. Sakane *et al.* recent published such a study, where 53 cases of thymic carcinoma were evaluated for PD-L1 expression comparing the 4 commonly used assays (SP142, SP263, 22C3, and 28-8) (10). They found that expression of PD-L1 in immune cells was highly discordant among the four assays, but a better association was seen when testing tumor cells. However, as pointed out by Sekine *et al.*, there was discordance of expression in 47.2% of cases. These findings may be due to differences in the assays as well as tumor heterogeneity, but regardless point to the limitations

of PD-L1 as a biomarker. Tumor mutational burden has been shown to be a predictive biomarker in metastatic non-small cell lung cancer (NSCLC) (20,21), and given the findings of the TCGA study should be investigated as a biomarker in patients with TET undergoing treatment with immune checkpoint inhibitors. However we believe caution must be used when translating findings from NSCLC to thymic malignancies. For instance, the often used cut-off of 50% for high expression of PD-L1 is primarily supported by the Keynote-024 study of first line therapy in metastatic NSCLC (22). It should be pointed out that nearly all specimens utilized in prior studies of PD-L1 expression in TET utilized samples from surgical resections, and that these findings may not be relevant for patients undergoing systemic therapy for unresectable disease. Finally, Sekine *et al.* rightly point out the role that multiplex immunohistochemistry may play in assessing expression of PD-L1 among immune and tumor cells.

We believe the best way forward to answer these and other as yet unidentified questions is for national and international registries, such as The International Thymic Malignancy Interest Group (23), to begin collecting these biological as well clinical data. Given the rarity of these tumors, this is likely the only viable method to reconcile the differences seen among our study and others.

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