Editorial

PD-1/PD-L1 expression in thymic epithelial tumors: the predicament persists

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This editorial is based on the article titled "Expression patterns, prognostic value, and intratumoral heterogeneity of PD-L1 and PD-1 in thymoma and thymic carcinoma" recently published in *Journal of Thoracic Oncology*, where thymic epithelial tumors (TET) have shown increased expression of immune checkpoint inhibitors: programmed death 1 (PD-1) and its ligand PD-L1 (1).

The concept of immunotherapy has stormed the medical world with researchers seeking its possible benefits in different malignancies. Immune-evasion by T-cell checkpoint dysregulation has been the prime target of many clinical trials with drugs against PD-1 and PD-L1 leading the pack. The role of anti-PD-1/PD-L1 has been validated in many solid tumors with anti-PD-1 drugs pembrolizumab (Keytruda, Merck, Kenilworth, NJ, USA) and nivolumab (Opdivo, Bristol-Myers Squibb, New York, NY, USA) being approved by Food and Drug Administration (FDA) for melanoma and non-small cell lung carcinoma (NSCLC) and recently anti-PD-L1 atezolizumab (Tecentriq, Genentech/Roche, South San Francisco, CA, USA) for NSCLC and urothelial carcinoma (2). Thymus being an organ of the immune system, the benefits of immunotherapy seems lucrative in TET and studies are emerging attempting a clinicopathological correlation with use of such agents. However, due to TET not being a common neoplasm, large number of cases are not easily available for comparative studies. This fact may be acting as a confounding factor leading to discrepancies in the outcomes of various researchers.

The latest 2015 World Health Organization (WHO) classification of tumours of the lung, pleura, thymus and heart, has brought about conceptual changes and have redefined histologic criteria for subtyping thymomas (3). The application of these criteria while evaluation of histology slides has led to many thymomas being reclassified into a different subtype. The authors (1) have used the older WHO 2004 classification for subtyping their subset of TETs. In addition, the latest WHO classification describes a molecular basis to the development of these tumors with the discovery of the highly recurrent point mutation in the *GTF2I* oncogene. This mutation has been described in types A and AB and rarely in type B thymomas (4). Therefore, we believe that the grouping of TETs in this study should have been accordingly while correlating PD-L1 status with thymoma subtypes. The above described factors could have been the confounding factors leading to a finding contrary to previous studies (5-9). Also, only three cases of thymic carcinoma were included in the study, based on which the inference of a 100% positivity of PD-L1 in this subgroup may not be truly justified. Previous studies with larger number of thymic carcinomas in their cohort have shown thymomas to outnumber thymic carcinomas in PD-L1 expression pattern (7,8,10,11). As far as correlation of PD-L1 expression with stage of thymoma is concerned, the results have been controversial with no definite consensus yet. The results have varied from no correlation (5,12) to association of high PD-L1 expression with higher stages (6,9,13). Owen *et al.* also have not found any association of PD-L1 expression with the stage of thymoma (1).

A major dilemma faced by researchers studying PD-

L1 immunohistochemistry (IHC) has been the choice of the antibody clone which would affect the interpretation of results. Various trials have been instituted to compare and correlate the different clones available, among which the Blueprint PD-L1 IHC Assay Comparison Project has elaborated extensively on these clones (5,14,15). Owen *et al.* (1) in their study have chosen the 22C3 clone which has been designated the companion diagnostic assay for pembrolizumab (14,15). More than 90% concordance has been seen between 22C3 clone which stains on a Dako Immunostainer and the SP263 clone which requires Ventana Bench Mark platforms. The multicentre comparison carried out by Marchetti *et al.* have suggested use of SP263 clone as an alternative to 22C3 especially in centres which do not have the Dako system (15). The recommended scoring system of PD-L1 staining using the 22C3 clone is described as the tumor proportion score (TPS) in NSCLC, wherein the percentage of viable tumor cells with at least partial membrane staining as compared to total number of viable tumor cells is determined. Tumors showing at least 50% positivity are considered for first line and 1–49% positivity for second line chemotherapy in NSCLC (16). The authors (1) had used a semiquantitative scoring system where the PD-L1 expression was scored on a scale of 0–5 which has also been used by other researchers previously (17-19). The clone of PD-L1 being used in the study (1) has received FDA approval in NSCLC; it may be scored similarly in TETs. In that case TPSs may possibly be different. The authors (1) have also expressed similar concern and have recommended the validation of TPS in tumors other than NSCLC.

PD-1 expression in TETs has not been studied extensively with only few studies highlighting its expression. PD-1 has been found to be expressed in tumor infiltrating lymphocytes (TILs) rather than the epithelial cells (11,12). Its expression in the epithelial cells also has been noticed (20). The authors (1) have also demonstrated PD-1 IHC in thymomas, however, the detailed description of its expression pattern has not been elucidated. PD-1 positivity in thymomas has also encountered discrepant results where some authors have found no difference in its expression pattern among non-neoplastic thymus, thymomas or thymic carcinomas (8,12) whereas others have used it only in thymic carcinomas showing 65–70% positivity (11). Owen *et al.* (1) on the contrary, have found significant association of high/moderate PD-1 expression with low grade thymomas.

The hypothesis of intra-tumoral heterogeneity has been demonstrated in many solid malignancies and has helped explain the variations in IHC expression of many antibodies. PD-1/PD-L1 expression is also fraught with this concept as benefits of anti-PD-1/PD-L1 therapy are also seen in many NSCLC patients which have negative PD-L1 expression on IHC. Two studies by a similar group of authors tried demonstrating heterogeneity of PD-L1 expression on NSCLC specimens, where they have used different PD-L1 (E1L3N and SP142) clones in one study (21) and the same clone in sections from different areas of the tumor in the other study (22). The study using different clones has not shown concordance between the two clones which could be attributed to the difference in staining techniques as well as result interpretation. The other study which used the same clone (SP142) in sections from different areas of the tumor, concluded that the heterogeneity of PD-L1 expression was representative within as well as between blocks. Similar result was seen by a study conducted by us where tissue microarrays (TMA) were prepared using three cores from the same block, thus representing approximately 80–90% of the tumor area. We found no variation in PD-L1 staining pattern within the cores (5). Owen *et al.* (1) have found variation in PD-1 as well as PD-L1 staining in two of their three cases evaluated. PD-1 expression is seen in the TILs mostly in the stroma between the tumor nests and not within the tumor islands. This might be the cause of the variations in PD-1 score while evaluating PD-1 IHC on tumor sections. PD-L1 is expressed in the thymic epithelial cells predominantly. The figures depicting PD-L1 IHC have variable number of epithelial cells in the sections shown; thereby leading to a variable score. However, since a low cut-off of 1% positive tumor cells by 22C3 assay is required for commencing immunotherapy, the relevance of the size of tissue available for evaluation or the percentage of positive cells beyond 1% reduces further. Nevertheless, studies on a larger cohort of TETs is recommended to conclusively prove/refute this concept of tumoral heterogeneity.

Studies elaborating on the prognostic role of PD-1/PD-L1 expression in thymomas have also shown inconsistent results, mostly due to small sample sizes attributed to the uncommonness of this mediastinal neoplasm (5,6,12). The small sample size of the study by Owen *et al.* (1) also could not demonstrate any significant correlation with survival characteristics.

In summary, Owen *et al.* within the limitation of a small sample size, have attempted characterisation of immune check point inhibitor expression pattern in TETs, to establish potential candidates for availing benefits of immunotherapy. Their study highlights the importance of

use of validated methods for assessing IHC. In addition, they have also introduced the proposition of tumoral heterogeneity in thymomas raising queries which need further deliberation.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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