Background Immune checkpoint inhibitors (ICIs) are well tolerated and clinically active against a wide variety of cancers. However, the risk of immune toxicity in patients with thymic epithelial tumors (TETs), especially thymomas, remains unacceptably high due to underlying defects in immune tolerance.\(^1\)\(^3\) Mechanisms of immune toxicity remain poorly understood and the mainstay of treatment is immunosuppression with systemic corticosteroids, which can potentially impact the anti-tumor activity of ICIs.

Methods To understand mechanisms of organ-specific immune toxicity, we evaluated blood and tissue samples from patients with TETs enrolled in an ongoing NIH IRB-approved clinical trial (NCT03076554; NCI protocol number: 17C0066) of avelumab, an anti-PD-L1 antibody who developed multi-organ immune-related adverse events (irAEs) following treatment. Participants received avelumab 10 mg/kg IV every two weeks until disease progression or development of intolerable AEs. Toxicity was assessed with CTCAE 5.0. Immune profiling was conducted using one or more of the following methods: evaluation of biopsies with routine hematoxylin and eosin staining and immunohistochemistry (IHC), peripheral blood immune cell subset analysis by flow cytometry, RNAscope for IL-6, IL-8 and TGF-ß1 mRNA expression, and spatial transcriptomics using the nanoscope Digital Spatial Profiler platform to investigate T-cells' transcriptional profiles at tumor and irAE sites.

Results Between April 2017 and February 2022, 32 participants were enrolled (median age: 55 years; 16 female; 16 thymomas). Five (16%) participants developed multiple irAEs during treatment. Objective anti-tumor responses were observed in 2 (40%) of 5 participants. Table 1 includes clinical characteristics and results of immune analyses. Histopathology and IHC were notable for a T-cell infiltrate and paucity of B cells across irAE sites. IL-6 and TGF-ß1 mRNA expression were variable in cases of upper gastrointestinal inflammation. Genes transcriptional profiles at tumor and irAE sites were enriched in 1811 genes in tumor and irAE samples (bone marrow) from subject 3 revealed distinct T-cell activation profiles in the bone marrow compared with tumor infiltrating T cells (figure 1).

Conclusions Organ-specific heterogeneity in mechanisms of ICI-related immune-mediated toxicity in individuals with TETs needs further evaluation. If confirmed, these findings highlight the need to tailor immunosuppressive treatments to specific irAEs and develop strategies for primary or secondary prophylaxis to decrease the risks associated with immunotherapy while maintaining clinical benefit in this population.

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Ethics Approval Samples used in this study were derived from an ongoing NIH IRB-approved clinical trial [NCT03076554; NCI protocol number: 17C0066]. Participants gave informed consent for participation in the clinical trial.