Background Metastatic pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors associated with poor prognosis and limited therapeutic options. Recent advances in oncology-related immunotherapy, specifically targeting of the programmed death 1 (PD-1)/-ligand 1 (PD-L1) pathways, have uncovered new treatment potential for a variety of tumors. The expression of PD-L1 and PD-L2 was recently found to be present in 18% and 16% of PPGL, respectively, but only PD-L2 expression correlated with malignancy, hypoxia markers, and shorter survival. However, PD-L1 was suggested to be a malignant proliferation biomarker for PPGLs in another study. Given the promising outcomes of a clinical study in 9 cases of PPGL using pembrolizumab, a humanized IgG4 monoclonal antibody that targets the PD-1/PD-L1 pathway, we examined the PD-Ls expression in our representative PPGL cohort to explore if PD-Ls expression can predict malignancy and/or be a predictive marker for PD-Ls targeted therapy in PPGL.

Methods The Cancer Genome Atlas (TCGA) provided 173 patient samples to allow for observation of gene expression across four PPGL driver mutation groups (Cluster I: SDHB, VHL; Cluster II: NF1, RET) and NAM samples. Tumor RNA from the 48-patient cohort (sporadic; Cluster I: SDHB, VHL, EPAS1; Cluster II: RET, NF1) was evaluated to validate the results.

Results Expression of PD-L1, but not PD-L2, was elevated in our PPGL cohort, which aligns with TCGA analysis. Expression of PD-L1 was decreased in Cluster I PPGLs but not in Cluster II, suggesting that sporadic and Cluster II PPGLs could benefit from PD-1/PD-L1 targeted therapy more than Cluster I PPGL tumors. Within Cluster I, expression of PD-L1 was significantly lower in SDHB- and VHL-mutated tumors compared to sporadic tumors. Expression of PD-L2 did not differ between PPGL clusters. Metastatic PPGLs had significantly elevated Ki-67 levels, however PD-Ls expression was not affected by malignancy status.

Conclusions We conclude that PD-Ls expression in our cohort of PPGL tumors was not linked to malignancy, however, driver mutation analysis could be a selective marker for PD-Ls-targeted therapy.

REFERENCES

Ethics Approval The study protocol was approved by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Institutional Review Board (NIH Protocol 00-CH-0093).