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HIGH VISTA EXPRESSION ON TUMOR-INFILTRATING LYMPHOCYTES IS PROGNOSTIC OF POOR SURVIVAL IN PATIENTS WITH ENDOMETRIAL CANCER

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Background Immune checkpoint inhibitor therapy has become an effective treatment option for many types of cancers. By enhancing the function of anti-tumor T cells, inhibitors targeting PD1, PDL1, and CTLA4 have shown durable clinical results and increased patient survival. However, the response rate to these checkpoint blockades is generally limited to 30-40% of patients, with the majority failing to respond. This suggests the need to investigate other targets for immunotherapy. One promising candidate is V-domain Immunoglobulin Suppressor of T cell Activation (VISTA), an immune checkpoint protein expressed on several lymphocyte and myeloid lineages, including regulatory T cells, cytotoxic T cells, monocytes, and myeloid-derived suppressor cells. VISTA has been found to potently impair anti-tumor immunity by negatively regulating the activation and function of tumor-reactive T cells. Targeting VISTA has therefore been the focus of several preclinical and clinical studies, with current anti-VISTA antibodies in development as well as in clinical trial. Our study explores the association of VISTA expression on tumor-infiltrating lymphocytes (TILs) with patient outcomes in endometrial cancer.

Methods Pretreatment tissue samples were collected from 121 women diagnosed with endometrial cancer at University Hospitals Cleveland, Cleveland, Ohio, between 2006 and 2012. Tumor microarray (TMA) sections of 4 micron thickness were fixed for multiplex immunohistochemistry using clinically established protocols and stained with a panel of PanCK, CD3, FOXP3, VISTA, TIGIT, and DAPI. TMA measurements were quantified to determine patient subpopulations based on protein expression. Using these data, Kaplan-Meier curves were constructed to analyze overall survival and recurrence-free survival for different groups based on checkpoint protein expression levels in immune cell subsets. Follow-up time for survival outcomes was from 2006 to 2018.

Results We found that the high expression of VISTA on TILs correlates to worse overall survival as well as worse recurrence-free survival. In contrast, TIGIT expression on TILs is not a prognostic factor.

Conclusions Our data elucidate VISTA's importance as a prognostic immune marker for poorer outcomes in patients with endometrial cancer. These results also demonstrate the value of exploring VISTA as a potential immunotherapy target for improving survival.

Ethics Approval Our studies have been approved by the Ethics Committee of the Cleveland Clinic Foundation.

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