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Prognostic Significance of Tumor-Associated Macrophages in Pancreatic Neuroendocrine Tumors

predictors of biologic behavior of the tumor.

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BACKGROUND: Neuroendocrine tumors (NETs) are a highly heterogeneous group of malignancies with variable clinical course. Checkpoint inhibitors have shown modest antitumor activity, but rational immunotherapy strategies have been hampered by a lack of understanding of the NET immune milieu.

METHODS: Resection specimens from 55 patients with metastatic pancreatic NETs were evaluated. Characterization of the tumor microenvironment (i.e. tumor-associated lymphocytes [TILs] and tumor-associated macrophages [TAMs]) was performed using immunohistochemistry for CD4 (helper T cells), CD8 (cytotoxic T cells), FoxP3 (regulatory T cells), and CD68 (macrophages). Areas of highest density inside the tumor were quantitated using the Aperio Image Toolbox image analysis tool (Aperio© ImageScope Version 12.3.3.7031). The Kaplan-Meier method was used to estimate survival, and the log-rank test was performed for comparisons between groups. Cox regression was used to evaluate the relationship between each cell type and survival with consideration of the confounding effect from other factors.

RESULTS: Whereas TILs were not associated with overall survival (OS), TAMs, identified by CD68 staining, were strongly associated with OS. Patients with lower TAM infiltration had a 10-year OS of 66 % (95%CI 39-83), while those

with higher TAM infiltration had a 10-year OS of 26% (95% CI 6-53%), and this difference was statistically significant (p=0.026).

CONCLUSION: TAMs were significantly correlated with inferior survival in pancreatic NETs. TAM depletion may therefore present an appealing and rational target for immunotherapeutic approaches in NETs.