175 METASTATIC TRIPLE NEGATIVE BREAST CANCER HAS DISTINCT TUMOR IMMUNE LANDSCAPE

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Background Triple negative breast cancer (TNBC) is considered the most immunogenic breast cancer subtype due to higher levels of tumor infiltrating immune cells (TILS), elevated tumor mutational burden and PD-L1 expression, providing a rationale for immunotherapy. Here we aimed to investigate the differences in the immune microenvironment in TNBC vs. non-TNBC for primary and metastatic sites and their impact on survival.

Methods Comprehensive immune profiling, including PD-L1 IHC and the expression of 395 immune genes, was performed on 147 real-world FFPE breast cancer samples (32 primary, 115 metastatic). 37 samples were, by definition, triple negative for ER, PR, and HER2 overexpression. PD-L1 (CPS positive $\geq$1 and CPS positive $\geq$10) was determined using immunohistochemistry (SP142 and 22C3). mRNA expression signatures of tumor inflammation (TIGS, weak/moderate/strong) and cell proliferation (CP, poor/moderate/high) were determined by RNA-sequencing. Statistical comparisons of biomarkers between group were calculated using the Wilcoxon Rank-Sum test ($p<0.05$ for significance) and survival differences were quantified by Cox proportional hazards analysis.

Results Comparing TNBC and non-TNBC cases, TNBC cases were observed to have significantly higher TIGS [p=0.014] and PD-L1 expression [$p=4.4\times10^{-7}$]. Additionally, TNBC cases trended toward exhibiting greater cell proliferation [p=0.069]. These differences were found to be driven primarily by metastatic tumors, for which TNBC tumors showed significantly higher TIGS [p=0.015], cell proliferation [p=0.021], and PD-L1 expression [$p=2.9\times10^{-7}$] than non-TNBC tumors, while none of these significant associations were observed among primary tumors. For the entire cohort, PD-L1 positivity was significantly associated with worse survival for positivity thresholds of both 1% [HR=1.70, p=0.011] and 10% CPS [HR=1.54, p=0.042]. These trends were also found to be driven by metastatic tumors [1% threshold: HR=1.76, p=0.016; 10% threshold: HR=1.66, p=0.033]. Additionally, high cell proliferation status was significantly associated with worse survival [HR=1.83, p=0.03] regardless of TNBC status.

Conclusions Our comprehensive biomarker analyses showed that metastatic TNBC has a more inflamed tumor microenvironment and higher checkpoint target expression compared to non-TNBCs. Interestingly, we observed that although metastatic TNBC has a higher median PD-L1 CPS, tumors with lower PD-L1 expression had better overall survival. Further analysis of immune expression by site-specific metastases and correlation with immunotherapy outcomes is warranted to guide clinicians in selection of the ideal metastatic site to biopsy for therapeutic decision making. However, in a collective TNBC context, these data support the use of immunotherapy in metastatic TNBC.

Ethics Approval Ethics approval for this study was obtained from Roswell Park Comprehensive Cancer Center Institutional Review Board (Study# BDR 162622) and determined to be non-human subject research.

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