Spatial Analysis of Tumor-Infiltrating Lymphocytes (TILs) Based on HER2 Expression Across Multiple Cancer Types

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Background Newer strategies of targeting HER2 such as novel HER2-targeted agents and combination with immune checkpoint inhibitors (ICIs) call for development of newer biomarkers based on deeper understanding of biology. To understand the immune microenvironment of HER2-expressing tumors, we performed spatial analysis of TIL in association with HER2 status, in the The Cancer Genome Atlas (TCGA) pan-carcinoma set.

Methods Hematoxylin and eosin (H&E)-stained slides, copy number alterations, and mRNA expression levels of HER2 for 7,322 patients across 22 cancer types and immunohistochemistry (IHC) results for 622 breast cancer patients were obtained from the TCGA data set. Spatial analysis of TIL distribution was done by an artificial intelligence-powered H&E analyzer, Lunit SCOPE IO. Intratumoral TIL (iTIL) and stromal TIL (sTIL) densities were defined as the number of TILs in each 1mm² grid of cancer area and stromal area. The HER2 amplified cancers were classified as per annotation of TCGA. Receiver operating characteristic (ROC) analysis was used to determine the optimal thresholds of mRNA expression showing maximal value of sensitivity and specificity, to discriminate HER2-expressed (≥ 1+) against HER2-negative (0) using IHC results. These thresholds were subsequently used in pan-cancer analysis, to define HER2-expressed vs. HER2-negative.

Results Overall, iTIL and sTIL densities of HER2 amplified cancers were lower than those of non-amplified cancers in the TCGA data set. Also, the iTIL and sTIL densities were mostly decreased in HER2-expressed cancers by the RNA-seq-based threshold. However, when breaking down into individual cancer types, TIL densities increased in endometrial cancer (UCEC) and ovarian cancer (OV). In UCEC (n = 148), iTIL density increased from 74.5±75.6 (mean±standard deviation) in HER2-negative to 167.17±322.30 in HER2-expressed and sTIL density increased from 649.2±517.2 to 875.2±1172.0, respectively. In OV (n = 70), although iTIL density was slightly increased from 50.5±53.6 to 52.9±63.5, sTIL density was notably increased from 243.6±215.6 to 540.9±563.9, respectively. Among the HER2-expressed cancers, the iTIL and sTIL levels were higher in those expressing PD-L1 or having high-tumor mutational burden (TMB). The differences were notable in urothelial carcinoma (TMB, PD-L1); breast cancer, cervical cancer, lung cancer, and thyroid cancer (PD-L1).

Conclusions HER2 amplification or expression was associated with lower immune infiltration in the pan-cancer cohort, consistent with previous data. Further investigation in individual tumor types may further identify possible responders for combination therapy with HER2-targeted agents and ICIs.

REFERENCE