CASE STUDY

Biomarkers for adjuvant therapy predict benefit in early stage triple negative breast cancer

Background and Objective

The Finland Capecitabine trial (FinXX) was a phase III trial which randomized early stage breast cancer patients to receive docetaxel with (TX+CEX) or without capecitabine (T+CEF) followed by anthracycline-based adjuvant chemotherapy.

A subset analysis revealed that patients with triple negative breast cancer (TNBC) had a 47% improvement in relapse-free survival (RFS) with an addition of capecitabine.

Building on the results of the FinXX trial, this study, executed by E. Aubrey Thompson, Ph.D., Torsten Neilsen, M.D., Ph.D., and their collaborators aims to identify potential predictive biomarkers for RFS in patients who may derive more benefit from adjuvant capecitabine. The study was a collaboration between the Mayo Clinic, University of British Columbia, Uppsala University Hospital, Helsinki University Hospital, and NanoString.

Materials, Methods and Initial Results

A total of 111 tumor tissue samples were collected from TNBC patients in the FinXX trial: 57 treated with T+CEF and 54 treated with TX+CEX. There were no significant imbalances in clinical and pathological characteristics across the patient samples.

Samples were run using the nCounter® Breast Cancer 360™ Gene Expression Panel with a custom 30 gene spike-in related to capecitabine activation and fluorouracil absorption, distribution, metabolism and/or elimination (ADME).

Four key immune markers and signatures (cytotoxic cells, endothelial cells, mast cells, and PDL2) were significantly associated with improved RFS in patients treated with capecitabine, suggesting that the sensitivity of TNBC to adjuvant capecitabine may be explained by interactions with the immune system. Moreover, genes related to enzymes involved in capecitabine activation, such as TYMP, were significantly associated with the benefit of capecitabine.

However, gene expression data alone was not able to address the morphological heterogeneity in TNBC. Given the complexity of the immune landscape in these tumors, correlating gene expression findings with spatial morphology is invaluable.

GeoMx® Digital Spatial Profiling

From the FinXX trial, 44 TNBC patients, 22 recurrent patients, and 22 non-recurrent patients were selected for GeoMx Digital Spatial Profiling (DSP): 12 Regions of Interest (ROIs) were selected from each sample, including 4 tumor-enriched areas, 2 CD45-enriched stromal areas, 2 CD45-enriched adjacent tumor areas, 2 CD68-enriched stromal areas, and 2 CD68-enriched adjacent tumor areas.

Initial results were presented at the San Antonio Breast Cancer Symposium in December 2019 and are summarized here. Overexpression of IDO1 in all segments as well as in both tumor and stroma segments was associated with improved outcomes, similar to the global gene expression analysis.

"The NanoString cancer panels, in general, and the Breast Cancer 360 Panel, in particular, in combination with the outstanding analytical tools developed by NanoString, provide straightforward, informatically-rich tools for characterization of the functional genomic landscape of breast cancer."

—E. Aubrey Thompson, PhD

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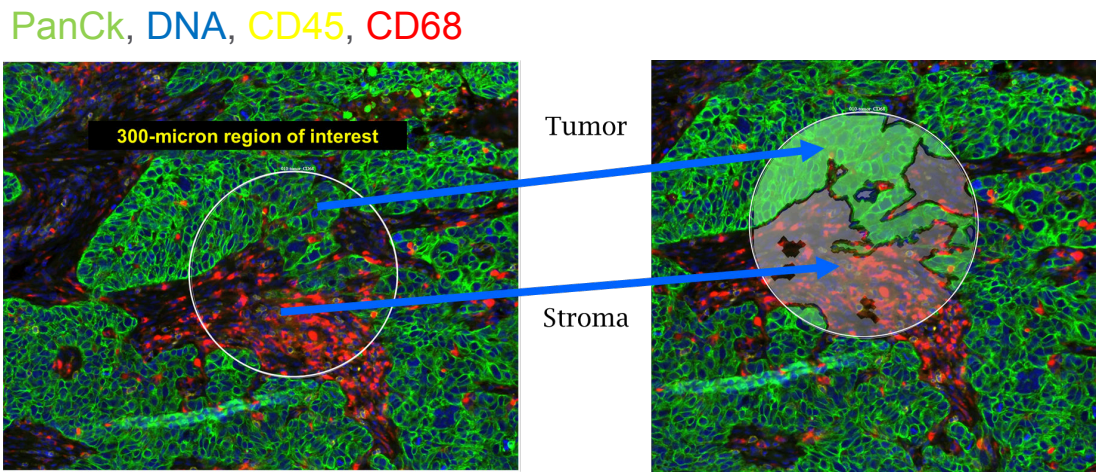

Figure 1: Regions of Interest (ROIs) and segmentation as visualized with GeoMx DSP

When analyzing tumor vs. stromal compartments separately, preliminary data suggested that high expression of intratumoral CD56, but not stromal CD56, is associated with an improved outcome. This observation was not seen when CD56 was evaluated with bulk gene expression analysis using the PanCancer IO 360™ Panel or when this protein was characterized in the whole segment with DSP. A similar observation was noted with intratumoral HLA-DR expression.

Similar observations were seen with conventional T cell markers, including CD3, CD4, and CD8, with high expression levels of these proteins in tumor segments associated with improved outcome. This was not observed when evaluating all segments combined and stromal-only segments. Moreover, using Kaplan-Meier survival analysis, only high expression of CD8 in the CD45-enriched tumor was associated with improved outcome (p=0.015).

This case study highlights the potential critical roles of tumor-infiltrating NK cells and antigen presentation via MHC Class II in patients with early stage TNBC and the importance of analyzing tumor vs. stromal compartments to gain new insight into immune features associated with therapeutic outcome. Spatial analysis of protein expression gives additional biological context and adds a new dimension to biomarker discovery for immunooncology.

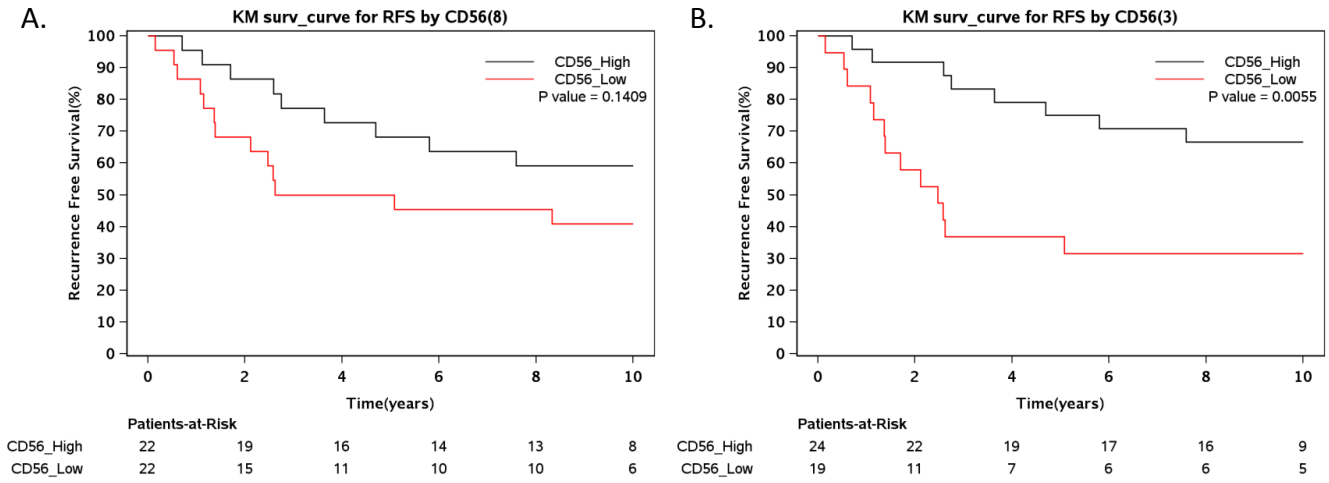

Figure 2: Kaplan-Meier survival curve showing recurrence-free survival (RFS) in patients with high vs. low CD56 protein expression in: A) all segments combined or B) tumor segments.

References:

Asleh K et al., Predictive biomarkers for adjuvant capecitabine benefit in early stage triple negative breast cancer in the FinXX clinical trial. Clin Cancer Res. 2020 Jan 31

Chumsri S et al., Digital Spatial Mapping of the Immune Landscape of Triple Negative Breast Cancer Reveals Novel Features of Immune-Tumor Cell Interaction. 2019 San Antonio Breast Cancer Symposium Poster# PD5-06

To learn more about GeoMx DSP at NanoString, visit nanostring.com/geomx

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