METAvivor Lay Summary

“Overcoming Treatment Resistance in Breast Cancer Brain Metastases”

April 10, 2024

Thanks to generous funding from METAvivor, we sought to identify predictors for the development of brain metastases, to compare primary breast tumors and brain metastases, and to understand the ways tumors become resistant to HER2-targeted treatments. We compared the genomic (gene-based) profiles in the tumors of nearly 2,500 patients with metastatic breast cancer, including 730 patients who eventually developed brain metastases, and 128 patients in whom we were able to profile a surgically removed brain metastasis. We also profiled the originally diagnosed primary breast tumor in over 500 patients with the goal of identifying risk factors that may increase the chance of developing brain metastases. Next, we compared the spatial and expression profile differences between primary tumors and brain metastases. Finally, we tracked changes in tumor mutations, as detected in blood and tumor tissue samples, in patients before and after exposure to HER2-targeted oral medications.

We confirmed that the HER2-positive triple-negative breast cancer subtypes were at higher risk of brain involvement. We found an increase in the number of copy-altered genes between primary tumors and brain metastases, reflecting an increase in gene instability as cancers metastasized. Within the brain metastasis samples, we found that the most commonly altered genes were *TP53* (68%), *PIK3CA* (25%), and *GATA3* (14%). *ERBB2* (43%) was the most commonly amplified gene, while *CDKN2A* and *PTEN* (12%), were most commonly deleted. We also identified several pathways (RTK-RAS and TP53) that were enriched in brain metastases. Finally, preliminary data suggest differences in the expression of immunity-related genes and hormone receptor pathway genes in brain metastases compared to primary tumors. In terms of HER2 resistance, we were able to identify known resistance mechanisms that appeared in about 40% of patients, but also identified potential new mechanisms of resistance in about 20% of patients. Overall, we hope that our findings will spur the development of new targeted therapies and treatment approaches to prevent and treat brain metastases.