P5-06-02: Comparison of lobular vs NST hormone receptor-positive metastatic breast cancer patients in early lines of treatment via comprehensive genomic profiling and whole-genome sequencing of circulating tumor DNA

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Background

Invasive lobular carcinoma (ILC) represents the most common special subtype of breast cancer, which demonstrates different clinical and histological features, particularly in the metastatic setting. As ILC is frequently hormone receptor-positive (HR+) and HER2-negative (HER2-), we compared circulating tumor DNA (ctDNA) profiles in patients with stage IV ILC to patients with stage IV HR+, HER2- BC with non-special type (NST).

Study workflow

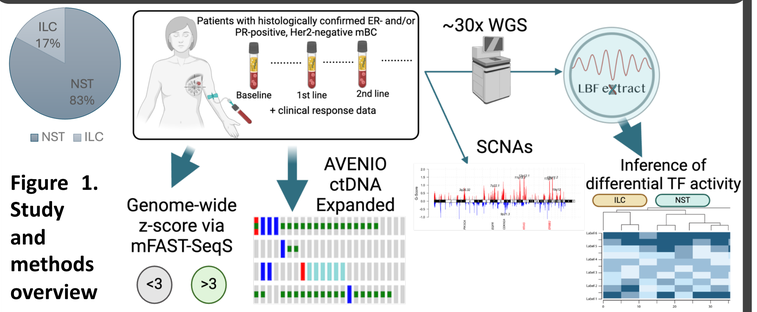

Figure 1. Study and methods overview

We obtained longitudinal ctDNA samples from 111 patients diagnosed with NST (n=91) or ILC (n=20) before initiating first or second-line endocrine-based therapy. Tumor content for each sample was estimated using mFAST-SeqS[1], an untargeted aneuploidy detection method which enables calculation of genome-wide z-scores that serve as a proxy for tumor fraction (TFx). The AVENIO ctDNA Expanded panel was used to assess variants in 77 genes. For select samples with suitably high TFx, 30x whole-genome sequencing (WGS) was performed to compare genome-wide somatic copy number alterations (SCNAs) and transcription factor (TF) activity between histological subtypes using the GISTIC2.0[2] and LBFextract[3] algorithms, respectively.

Results

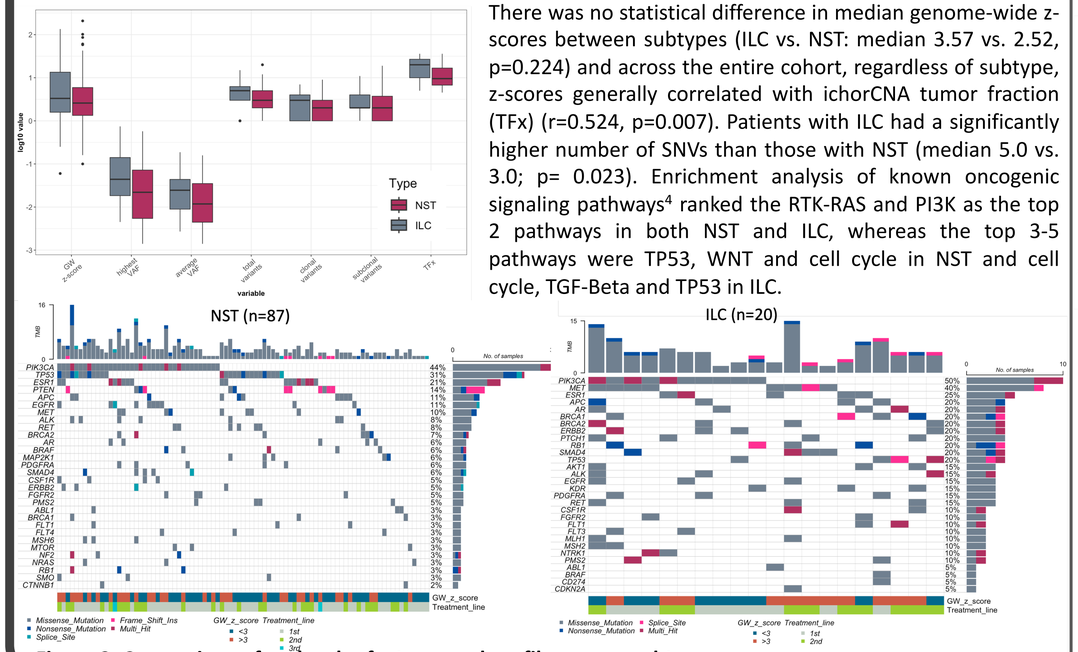

Figure 2. Comparison of molecular features and profiles across subtypes

There was no statistical difference in median genome-wide z-scores between subtypes (ILC vs. NST: median 3.57 vs. 2.52, p=0.224) and across the entire cohort, regardless of subtype, z-scores generally correlated with ichorCNA tumor fraction (TFx) (r=0.524, p=0.007). Patients with ILC had a significantly higher number of SNVs than those with NST (median 5.0 vs. 3.0; p= 0.023). Enrichment analysis of known oncogenic signaling pathways[4] ranked the RTK-RAS and PI3K as the top 2 pathways in both NST and ILC, whereas the top 3-5 pathways were TP53, WNT and cell cycle in NST and cell cycle, TGF-Beta and TP53 in ILC.

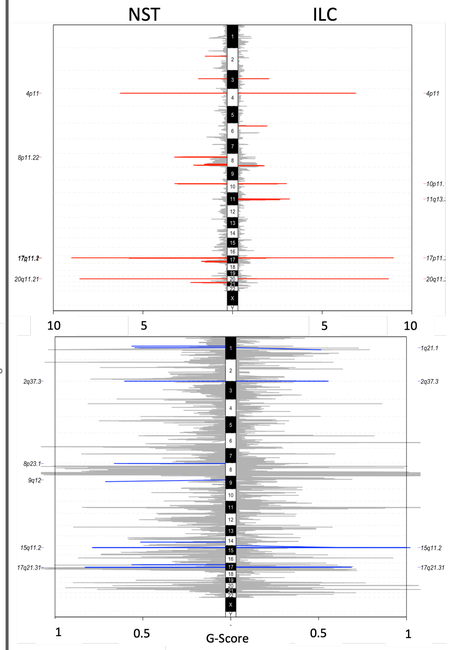

Figure 3. GISTIC2.0 analysis of recurrent SCNAs across subtypes

GISTIC2.0 revealed amplified regions of 11q13.3 (*CCND1, FGF19*), 11q14.1 (*CLNS1A, PAK1, AAMDC, RSF1*), 6p21.32, 6q21, 8p11.23, 6p11.2 and deleted regions of 1q21.1, 1p36.13, 12p13.31, 18q11.1 and 13q32.1 that were unique to ILC. The regions 8p11.22, 8q24.13, 8p12 and 13 additional regions and 9q12, 1p21.1, 1p11.2, 14q24.1, 14q32.33 21q11.2 were uniquely amplified and deleted in NST, respectively.

Conclusion

Based on our CGP and WGS approach for ctDNA analyses of hormone receptor positive mBC, we can elucidate distinct features of NST vs ILC in early lines of treatment, including the mutational profile, oncogenic pathways and distinct focal chromosomal aberrations, some of which are consistent with previous studies. By assessing TF activity through plasma DNA with LBFextract, the study could highlight the functional impact of these transcriptional drivers across these subtypes, despite minimal variations in other mutational or molecular features.

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References: [1]10.1373/clinchem.2014.234286; [2]10.1186/gb-2011-12-4-r41; [3]https://doi.org/10.1016/j.csbj.2024.08.007; [4]10.1016/j.cell.2018.03.035