PD9-03: Comprehensive genomic profiling and clinically targetable mutations of metastatic invasive lobular (ILC) and no special type (NST) breast cancer

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Background

Next generation sequencing (NGS) of circulating tumor DNA (ctDNA) provides non-invasive and real-time information on tumor biology including resistance mechanisms, which is especially important given the increasing availability of targeted treatment options for patients with metastatic breast cancer (mBC).

This study aims to understand the real-world use of ctDNA-based assays by reviewing testing patterns, genomic findings, and potential treatment impact with a **focus on differences by histology: invasive lobular (ILC) versus no special type (NST) breast carcinomas.**

Methods

- From January 2016 – March 2025, **1,378 mBC** patients had Guardant360 (Guardant Health) liquid biopsy testing obtained at the University of Pittsburgh Medical Center (UPMC) Hillman Cancer Center and its community locations. A total of **1,797 tests** were sent for NGS sequencing.
- Demographic and clinical data was obtained via the UPMC Hillman Cancer Center Tumor Registry and the electronic medical record. Clinical and genomic data were paired for analysis.
- Clinically relevant alterations were defined as those in *PIK3CA, ESR1, ERBB2, BRCA1, BRCA2, RB1* and *CDH1*.
- Variants of uncertain significance (VUS) were excluded in full cohort. Variants of clonal hematopoiesis (CHiP) were excluded in the newest generation assay.
- Among the patients with serial (≥2) ctDNA tests (n=292), breast cancer subtype and characteristics were documented and analyzed together with genomic data.
- 361 patients had ctDNA testing with the newest generation assay which includes tumor mutation burden (TMB) and tumor fraction.

Table 1: Demographics	NST n = 1037 (75.3%)	ILC n = 178 (12.9%)	Mixed n = 69 (5.0%)	Other n = 94 (6.8%)	Total n = 1378
Age range (median)	25-98 (64)	45-103 (70)	35-88 (68)	39-92 (69)	25-103 (65)
Sex					
Male	16 (1.5%)	0	0	2 (2.1%)	18 (1.3%)
Female	1021 (98.5%)	178 (100%)	69 (100%)	92 (97.8%)	1360 (98.7%)
Race/Ethnicity					
White	920 (88.7%)	162 (91.0%)	65 (94.2%)	85 (90.4%)	1232 (89.4%)
Black or African American	75 (7.2%)	10 (5.6%)	4 (5.8%)	6 (6.4%)	95 (6.9%)
Hispanic or Latino	5 (0.5%)	2 (1.1%)	0	0	7 (0.5%)
Asian	7 (0.7%)	0	0	0	7 (0.5%)
Other	12 (1.2%)	1 (0.6%)	0	2 (2.1%)	15 (1.0%)
Unknown	18 (1.7%)	3 (1.7%)	0	1 (1.1%)	22 (1.6%)
Serial ctDNA assays (median)	2-6 (2)	2-5 (2)	2-7 (2)	2-4 (2)	2-7 (2)

Results

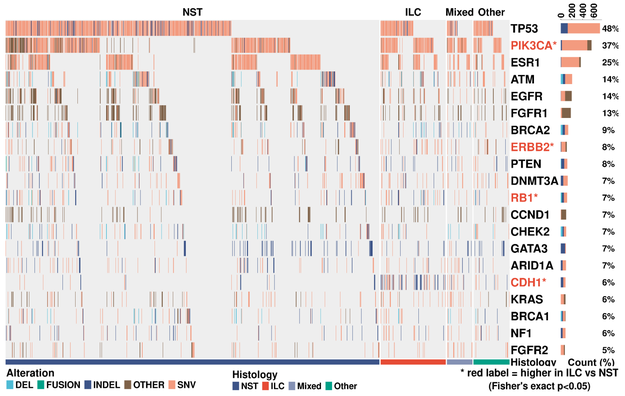


Figure 1: Oncoplot of genomic alterations by histologic subtype in full cohort. Red label highlight genes with higher mutation frequency in ILC as compared to NST: *PIK3CA, ERBB2, RB1* and *CDH1*.

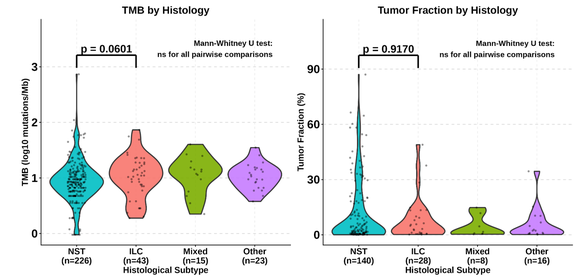
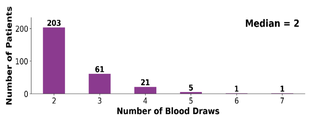


Figure 2: TMB (mut/Mb) and tumor fraction (%) by histologic subtype in a subset of patients with the latest ctDNA assay. Higher TMB seen in ILC with trend towards significance compared to NST.



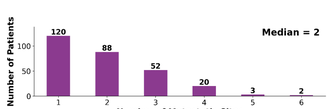


Figure 3: Number of ctDNA tests and sites of metastatic disease among patients with serial assays. (n=292)

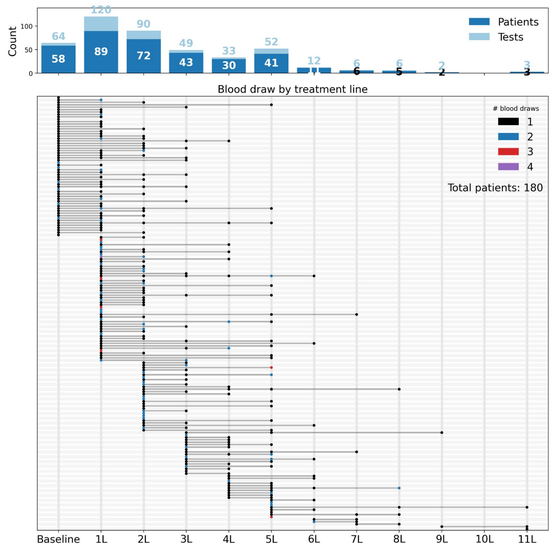


Figure 4: Timing of ctDNA testing by treatment line in a subset of patients with complete treatment data and serial testing time available (n=180). Most tests are conducted in 1st line. (1L)

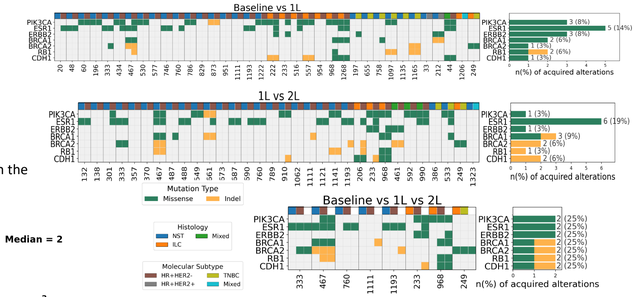


Figure 5: Clinically relevant alterations among a subset of patients with paired serial ctDNA testing and complete treatment data available. Mutations are compared before and after baseline, 1st line and 2nd line. *ESR1* appeared as the most prevalent acquired gene alteration.

Clinical Vignettes

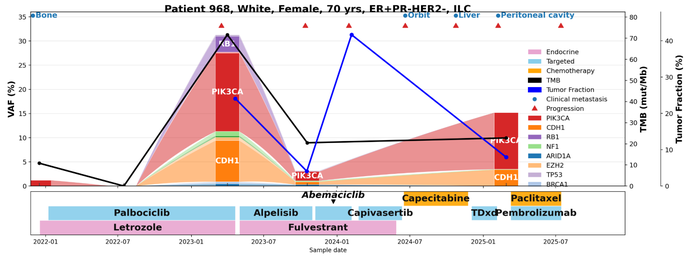


Figure 6: 70-year-old woman with metastatic ER+/PR-/HER2 ILC. Variant allele frequency and tumor fraction of alterations over time with annotated clinical details. Variant allele inclusion threshold: 0.1%. Tumor fraction measured by ichorCNA algorithm with shallow whole genome sequencing data.

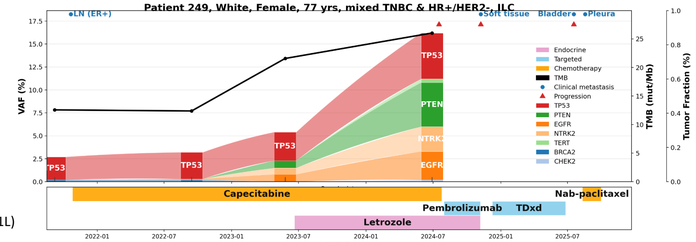


Figure 7: 77-year-old woman with metastatic mixed TNBC and HR+/HER2- ILC. Variant allele frequency and tumor fraction of alterations over time with annotated clinical details. Variant allele threshold: 0.1%.

Conclusions

- Among a large cohort of patients with mBC, 93.5% had detectable alterations including 59.4% with clinically relevant mutations on NGS-based ctDNA analysis. Serial ctDNA testing was performed in 21.2% of patients with a median of 2 ctDNA tests.
- The most frequent actionable alterations were in *PIK3CA* and *ESR1. ESR1* appeared as the most prevalent acquired alteration during treatment lines.
- *PIK3CA, ERBB2, RB1* and *CDH1* mutations were more common in ILC.
- Liquid biopsy testing results correlate well with metastatic ILC tumor response, providing potential guidance to early regimen change in metastatic ILC, whose progression is challenging to monitor with conventional methods.

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