Abstract SESS-1812: Correlation of Mutational Changes in Circulating Tumor DNA with Clinical Outcomes in HER2 Positive Metastatic Breast Cancer

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Background

- The presence of certain genetic mutations can be correlated with a poor response to HER2 directed therapies.
- Circulating tumor DNA (ctDNA) is a noninvasive tool to assess genomic alterations in progressive metastatic breast cancer (MBC).
- Understanding mutational changes in patients' ctDNA at disease progression can aid prognostication and identify potentially targetable mutations associated with resistance to specific therapies in HER2 positive MBC.

Methods

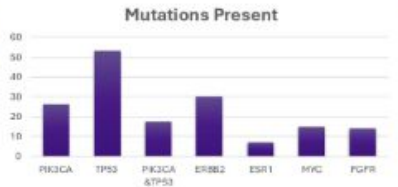
Inclusion Criteria
- Patients with HER2 positive breast cancer either at diagnosis on pathology or by ctDNA were included in the analysis.

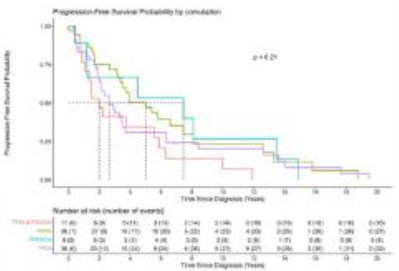
IRB
- Patients were prospectively enrolled from 2016-2024 under an IRB approved clinical trial (NU16B06) at Northwestern University

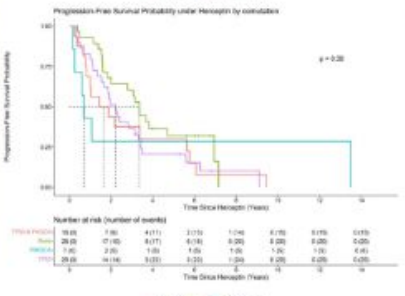
ctDNA
- Plasma ctDNA was analyzed by Guardant 360 and tissue NGS was performed using commercially available tests such as FoundationOne® or TempusX.
- All mutations (e.g. PIK3CA, ERBB2, ESR1, TP53, MYC, and FGFR) were identified via ctDNA/tissue NGS.

Analysis
- Additional clinical, pathologic, treatment, and response data was retrospectively collected as well for subgroup analysis.
- Statistical analyses were completed via a multivariate regression model.

Table 1: Patient Characteristics	N = 120
Race	
Asian	5 (4.3%)
African American	19 (16%)
Unknown	16 (14%)
White	76 (66%)
Age at Diagnosis	49 (41, 57)
Staging at Diagnosis M	
Not Metastatic	88 (76%)
Metastatic	28 (24%)
IBC	43 (37%)
ER Status at Primary Biopsy	
Positive	75 (65%)
Negative	41 (35%)
PR status at Primary Biopsy	
Positive	53 (46%)
Negative	63 (54%)
HER2 status at primary biopsy	
Positive	85 (73%)
Negative	31 (27%)
Treatment	
Chemotherapy	108 (96%)
Endocrine	73 (65%)
Anti-HER2	97 (86%)
Immunotherapy	10 (8.8%)
Mortality	
Alive	68 (59%)
Deceased	48 (41%)







Results

- 120 patients met inclusion criteria for the analysis. 74% percent of patients were HER2 positive at initial diagnosis while 26% developed HER2 positivity at time of metastatic spread.
- NGS and ctDNA findings showed PIK3CA mutation in 26% of patients, ERBB2 in 30%, ESR1 in 8%, TP53 in 53%, MYC in 15%, FGFR in 15% of patients.
- Mortality rate of the cohort was 41%.
- There were 86% of patients who received HER2 directed therapies.
- The median progression free survival (PFS) was 3.5 months (95% CI 2.6, 5.3).
- Patients with PIK3CA mutations (p=0.028) and TP53 mutations (p=0.042) had a worse 10-year survival rate than those without.
- Patients with PIK3CA and TP53 co-mutations had a worse 10-year survival rate (p=0.21) than those with neither mutation or having either PIK3CA or TP53 alone.
- Patients with TP53 and PIK3CA co-mutations had worse PFS HR 1.90 (1.02-3.55, p=0.044).
- Patients with TP53 and PIK3CA co-mutations also had worse PFS when being treated with Trastuzumab (HR 0.07, p=0.003) compared to patients with other mutational changes.
- Patients with PIK3CA and TP53 co-mutations were more likely to have evidence of progression to visceral metastatic disease on Trastuzumab, OR 0.16 (0.02-0.70, p=0.028).

Conclusion

- Molecular alterations identified in ctDNA at progression of disease in HER2 positive MBC can aid in understanding genomic evolution and drift as well as pathways to treatment resistance.
- This analysis of ctDNA in HER2+ MBC indicates that patients with TP53 and PIK3CA co-mutations are shown to have poorer 10-year survival rates, shorter PFS, worse response to Trastuzumab, and overall evidence of more aggressive cancers progressing into visceral metastatic disease.
- Understanding how the presence of these mutations correlate with resistance to specific therapies can guide individualized treatment decisions on which line of therapies will be most effective for patients with progressive HER2 positive MBC.