Background

Despite improvements in the treatment of HER2-positive breast cancer, high proportion of patients develops resistance to HER2-targeted agents. A number of mechanisms of resistance have been proposed, including:

- Mutations in PIK3CA
- Inactivation of anti-HER2 molecular targets
- Low levels of HER2 expression

Disease recurrence is a subset of HER2-positive patients suggests that approaches are needed to accurately assess HER2 status and/or clarify potential resistance markers to identify patients who may benefit from alternative treatments. Here, we report a comprehensive panomics approach that integrates whole genome sequencing (WGS), RNA sequencing (RNAseq); and quantitative proteomics to determine associations between tumor molecular profiles and prognosis among patients with HER2-positive breast cancer.

Patients and Methods

Patients were enrolled in the SUCCESS A, SUCCESS B and PRAEGNANT studies. SUCCESS A and SUCCESS B include high-risk breast cancer patients after primary surgery. All patients had received a standard chemotherapy and adjuvant trastuzumab for 12 months. Patients in SUCCESS B had received standard chemotherapy and adjuvant trastuzumab for a total of 24 months. PRAEGNANT is a registry of metastatic breast cancer patients. All patients selected for this study received a standard adjuvant chemotherapy, including anthracyclines and taxanes. Trastuzumab was given to all patients for a total of 12 months. Patients enrolled for this study had a median age of 50 years, 80% were postmenopausal and 67% of the patients were hormone receptor-positive.

Genomic Analysis

Matched tumor-normal samples (FFPE tumors and whole blood) underwent WGS; RNAseq performed on these archival tissues was successful in > 40% of cases. DNA copy number was assessed using whole genome hybridization CASA and RNA expression was assessed using both RNAseq (compute log2TPM and DNA (Copies) (see Figure 8).

Transcriptomic Analysis

Proteomics analysis was performed using a quantitative, multiplexed, selected reaction monitoring approach allowing the identification of a panel of 52 proteins.

Patient Disposition

<table>
<thead>
<tr>
<th>HER2+ Positive Patients</th>
<th>SUCCESS A</th>
<th>SUCCESS B</th>
<th>PRAEGNANT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Selected</td>
<td>43</td>
<td>24</td>
<td>16</td>
</tr>
</tbody>
</table>

Results

**HER2 Measurements and Response After Therapy**

**Percentage of Responders by Quintile of TLE3**

**Patient With Pathogenic, Nonsynonymous, Dinucleotide Mutation in BRCA1**

**Proteins Associated With Response Status**

**Associations between HER2 Protein, DNA, and RNA**

Conclusions

- In this small, exploratory study of patients treated with chemotherapy and trastuzumab, there appeared to be enrichment for higher response rates in patients with HER2 amplifications.
- Compared with HER2-positive breast cancer patients in TCGA, the rates of TP53 and PIK3CA mutations are different (48% for TP53 vs. 35%; TP53=3.079, potentially due to enrichment of patients with metastatic disease.
- A number of genome-wide strategies for predictive nucleotide substitutions identified in sporadic, drug-resistant BRCA2 variants as a potential driver of disease due to the loss of a function of chromosome 13 and a wild-type BRCA2 copy. 

**References**


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