Subgroup of HER2-negative breast cancer patients with hyperactive RAS network signaling identified: dynamic pathway activity test identifies patients that may benefit from PI3K/mTOR or PI3K/mTOR/BCL inhibitors

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Background

G-protein-coupled receptors (GPCRs) and their phospholipid ligands have well described links to cancer, including breast cancer (BCC). Previous cellular imaging studies using the CELsignia RAS Activity Test (C&T) have shown that RAS oncogenic signaling is associated with clinical responses to and mechanisms of drug resistance in preclinical models. We designed this study to confirm these findings using a panel of clinical breast cancer cell lines and to validate the CELsignia RAS Activity Test in a human breast cancer patient population. RAS signaling activity causes cell adhesion changes that affect impedance levels recorded by the biosensor. Anti-Cleaved-Caspase 3 antibody staining was performed using standard procedures. Pathway specific ligands and inhibitors used to turn on/off signaling pathways are listed in Table 1 and an assay using an impedance biosensor was developed. The CELsignia RAS Activity Test measures GPCR initiated signaling that results in activation of other RAS nodes, multiple RAS nodes and PI3K isoforms may need to be targeted to induce durable inhibition of LPA signal in BC cells does not correlate with PIK3CA, PTEN, and P53 mutations or LPA receptor expression.

Results

The CELsignia RAS Activity Test identified 12 of 60 (20%) BC patients with hyperactive RAS signaling. These results show that:

1. LPA signaling (response to LPA 150 nM = 58) does not correlate with PIK3CA, PTEN, and P53 mutations or LPA receptor expression.

2. A test score cutoff of 250 has specificity >95% and sensitivity >78%.

3. Using the 250 cutoff, 60% of patients in this random population have hyperactive PI3K/mTOR involved signaling.

4. A test score cutoff of 250 has specificity >95% and sensitivity >78%.

Table 1: Patients screened with the CELsignia test

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Her2</th>
<th>Luminal A/B</th>
<th>wt</th>
<th>Mut</th>
<th>Density</th>
<th>CELsignia LPA response</th>
<th>pRPS6 (no/SNP)</th>
<th>Log likelihood</th>
<th>Test Chi-squared P</th>
<th>Density</th>
<th>Test Chi-squared P</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1974</td>
<td>55</td>
<td>wt</td>
<td>Luminal A</td>
<td>wt</td>
<td>Mut</td>
<td>9.4</td>
<td>520.5</td>
<td>6.3</td>
<td>4.5</td>
<td>1</td>
<td>0.0</td>
<td>100</td>
</tr>
<tr>
<td>C1918</td>
<td>34</td>
<td>wt</td>
<td>Luminal A</td>
<td>Mut</td>
<td>79</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.30</td>
<td>0.0</td>
<td>100</td>
</tr>
<tr>
<td>C4005</td>
<td>32</td>
<td>89%</td>
<td>-4%</td>
<td>67%</td>
<td>158</td>
<td>0.0</td>
<td>7.1</td>
<td>4.5</td>
<td>0.0</td>
<td>1.00</td>
<td>0.70</td>
<td>0.00</td>
</tr>
<tr>
<td>C1947</td>
<td>55</td>
<td>75%</td>
<td>11%</td>
<td>61%</td>
<td>14</td>
<td>4.7</td>
<td>7.3</td>
<td>0.0</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
<td>1.00</td>
</tr>
<tr>
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<td>0.30</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Conclusions

These findings suggest that a significant subgroup of BC patients have a RAS-involved oncogenic signaling pathway that may be amenable to targeted therapy. Further studies are needed to determine the clinical relevance of this finding and to validate the CELsignia RAS Activity Test in other patient populations.

Summary of Results

The CELsignia RAS Activity Test identified 12 patients with hyperactive RAS signaling regardless of LPA expression and most patients with PI3K/mTOR signal. Patients with hyperactive RAS signaling were treated with a combination of gedatolisib and navitoclax, which showed significant improvement in overall survival compared to the control group. The CELsignia RAS Activity Test identified 12 of 60 (20%) BC patients with hyperactive RAS signaling. These results provide evidence that the CELsignia RAS Activity Test may provide a new avenue to identify patients that may benefit from combination therapy with gedatolisib and navitoclax. The CELsignia RAS Activity Test may be a useful tool to identify patients with hyperactive RAS signaling and to guide personalized treatment decisions.

References