PIK3CA mutations predict resistance to trastuzumab/pertuzumab and nab-paclitaxel in primary HER2-positive breast cancer – massive parallel sequencing analysis of 293 pretherapeutic core biopsies of the GepaSepto study

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Background

• Massive parallel sequencing (NGS) is a promising tool to investigate key molecular events in cancer.
• Genetic alterations, such as PIK3CA mutations, are important for response to therapy in HER2+ breast cancer (BC).
• PIK3CA mutations were shown to predict lower pathological complete response (pCR) to double blockade with trastuzumab/ lapatinib in HER2+ primary BC.

We investigated genomic alterations in 364 pretherapeutic core biopsies from two prospective clinical trials with or without anti-HER2 therapy.

Materials and Methods

• In GepaSepto (G7), patients with HER2+ BC received trastuzumab and pertuzumab in addition to nab-paclitaxel or solvent-based paclitaxel as part of neoadjuvant therapy. Significantly higher pCR rates were observed in patients receiving nab-paclitaxel. Patients with HER2+ BC in GepaTrio (G3) received no anti-HER2 treatment in addition to neoadjuvant therapy.

• 417 formalin-fixed paraffin embedded (FFPE) core biopsies taken before therapy from HER2+ tumors of G3 and G7 were analyzed by deep targeted massive parallel sequencing.

• PIK3CA mutations were evaluated with a minimum coverage of 500 and a mean coverage of 6520 (exon 9) and 6346 (exon 20) per amplicon.

• Only non-synonymous mutations in the coding region that were called at variant allele frequency >10% and only cases with a tumor cell content of ≥20% were included.

The primary aim was to assess the predictive value of somatic PIK3CA mutations for pCR (ypT0 ypN0).

Secondary aims were to assess the predictive value of somatic PIK3CA mutations for pCR in subgroups of taxane and hormone receptor (HR) status.

Results

Table 1: Baseline patient and tumor characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>Tumor characteristics</th>
<th>No anti-HER2 treatment (G3; N=293)</th>
<th>dual HER2 treatment (G3; N=71)</th>
<th>Blockade (G7; N=293)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range), years</td>
<td>57 (32-78)</td>
<td>60 (22-78)</td>
<td>59 (22-78)</td>
<td>cT4-3</td>
</tr>
<tr>
<td>cN</td>
<td>45 (64.3)</td>
<td>131 (45.6)</td>
<td>48 (67.6)</td>
<td>203 (68.6)</td>
</tr>
<tr>
<td>ER and/or PgR positive</td>
<td>48 (67.6)</td>
<td>204 (69.0)</td>
<td>38 (53.6)</td>
<td>158 (53.9)</td>
</tr>
<tr>
<td>LBPC, TILs &gt;50%</td>
<td>17 (23.9)</td>
<td>49 (16.8)</td>
<td>110 (37.0)</td>
<td>168 (55.3)</td>
</tr>
</tbody>
</table>

Figure 1: Mutation frequencies overall and by HR status

Figure 2: pCR rates according to PIK3CA mutation without (G3) or with (G7) anti-HER2 therapy

Analysis by NGS was successful in 364/417 tumors (87%), 293 from G7 and 71 from G3 (Table 1). A total of 652 non-synonymous mutated genes were detected. Mutation frequencies of PIK3CA and other genes analysed in the same panel are displayed in Figure 1.

In the double anti-HER2 treated group, the pCR rate was significantly lower in the PIK3CA mut vs wt group, overall and in the HR+ cohort (Figure 3). In the nab-paclitaxel cohort, pCR rates were significantly lower in the PIK3CA mut vs wt group, whereas in the paclitaxel cohort, no significant difference was observed between the PIK3CA mut and wt group (Figure 3). The respective interaction could be demonstrated in univariate (p=0.039) as well as multivariable regression analysis (p=0.010) after adjusting for known baseline factors.

In the nab-paclitaxel treated group, significant differences between PIK3CA mut and wt could be observed in both the HR- and HR+ treated cohort (Figure 4).

Conclusions

Targeted NGS on FFPE core biopsies reliably identified the most common genomic alterations in HER2+ BC. PIK3CA mutation in HER2+ BC predicts resistance to anti-HER2 therapy. In addition, PIK3CA mutations were found to predict response to nab-paclitaxel in G7. The results show that mutational alterations are relevant for response in HER2+ BC.

References


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