Homologous Recombination Deficiency (HRD) as a predictive biomarker of response to neoadjuvant platinum-based therapy in patients with triple-negative breast cancer (TNBC): A pooled analysis

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Background and Rationale
- Genetic instability and a high frequency of BRCA1 and BRCA2 germline mutations are commonly associated with triple-negative breast cancer (TNBC).- TNBC patients with homologous recombination (HR) deficient tumors have significantly higher pathologic complete response (pCR; ypT0/is) rates when treated with platinum-based chemotherapy regimens than TNBC patients whose tumors are HR non-deficient.

We performed a pooled analysis of clinical trials that included patients with TNBC treated with neoadjuvant platinum-based chemotherapy to better estimate the pCR rates amongst HR deficient tumors.

Study Design
A total of 267 patients with TNBC and known HR deficiency status from the following neoadjuvant clinical trials were available for analysis:
- NCT001486945 18 12 Cisplatin
- NCT005803333 32 12 Cisplatin with bevacizumab

The HRD score is the unweighted sum of LOH (number of LOH regions >15 Mb but less than the length of a whole chromosome) + LST (breakpoints between regions of imbalance >10Mb after filtering out regions <3 Mb) + TAI (regions of allelic imbalance that extend to the subtelomere but do not cross the centromere) + Filtered LOH (number of regions with >15 Mb LOH but ≤1-kB intervals between breakpoints). Filtered LOH is distinguished from LST by filtering out regions <3 Mb.

The HRD score for BRCA1 or BRCA2 mutations with higher HRD scores is more likely to achieve a pCR.

Results
- In this primary analysis, HR deficiency status was associated with an improved odds of pCR.
- Adjusted OR: 4.46; p<0.001

Table 1: Correlation of pCR and binary HRD score (<42 versus ≥42)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>HR Deficient</th>
<th>No HR Deficiency</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>Yes</td>
<td>0.31-1.08</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0.3-2.46</td>
<td></td>
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</table>

Table 2: Determinants of HRD Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1/2 mutation</td>
<td>Presence</td>
<td>4.64</td>
<td>2.30-9.37</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>Absence</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
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</tbody>
</table>

Conclusions
- In this pooled analysis of 6 phase II trials of platinum-based neoadjuvant chemotherapy, HR deficiency status was significantly associated with an improved odds of pCR among those with and without a BRCA1/2 mutation.
- Adjusted OR for pCR in HR deficient ≥4.46; p<0.001
- Overall, 67% of cases were HR deficient
- Associations between response and stage, age and planned duration of therapy were not significant
- HR deficiency was correlated with response
- The neoadjuvant chemotherapy regimens included heterogeneous (non-anthracycline/non-taxane, taxane-based or anthracycline/taxane-based) and the majority of patients received cytotoxic chemotherapies varied (1-3) as did the use of other investigational therapies (bevacizumab, iniparib, vorinostat).

References
2. Clinical Trials ID: NCT00616967 (TBCRC 008)
5. Gibbs EL, et al. JCO 2010
6. Clinical Trials ID: NCT005803333
8. Clinical Trials ID: NCT001486945
9. Clinical Trials ID: NCT005803333
10. Clinical Trials ID: NCT005803333
11. Clinical Trials ID: NCT005803333
12. Clinical Trials ID: NCT005803333
13. Clinical Trials ID: NCT005803333
14. Clinical Trials ID: NCT005803333
15. Clinical Trials ID: NCT005803333
16. Clinical Trials ID: NCT005803333

Figure 1. HR score by pCR status in BRCA1/2 mutation negative subset

- Patients lacking BRCA1 or BRCA2 mutations with higher HRD score are more likely to achieve a pCR
- p = 0.0005

Table 3: Determinants of HRD Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age</td>
<td>18-28 years</td>
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<td></td>
<td>29-39 years</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
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<tr>
<td></td>
<td>40-69 years</td>
<td>1.0</td>
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<tr>
<td></td>
<td>≥70 years</td>
<td>1.0</td>
<td>1.0</td>
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Table 4: Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td>Stage</td>
<td>I (ref)</td>
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<tr>
<td></td>
<td>II</td>
<td>0.39</td>
<td>0.15-1.02</td>
<td>0.118</td>
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<td></td>
<td>III</td>
<td>0.3</td>
<td>0.09-1.04</td>
<td>0.022</td>
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<tr>
<td></td>
<td>Total</td>
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