**Background**

- The addition of pertuzumab to neoadjuvant trastuzumab-based chemotherapy significantly improves pCR rates in HER2-positive breast cancer, but effects on long-term survival are modest.1 \(^2\)
- BluePrint (BP) is an 80-gene molecular subtyping test that classifies breast tumors as basal, luminal, or HER2 subtype. A small proportion of tumors exhibits two functionally activated BluePrint pathways and are referred as dual subtypes.2
- Results from an APHINITY sub-analysis suggest that pertuzumab benefit is largely restricted to patients with single-activated HER2-type tumors.3

**Methods**

- Stage II-III HER2 positive breast cancer treated with trastuzumab-based chemotherapy between January 2013 - January 2016
- Pertuzumab was available in hospitals participating in the TRAIL2 study (NCT01996267 - BOOG 2012-03)4
- Data was collected from the nationwide Netherlands Cancer Registry
- BluePrint molecular subtypes were successfully determined using pre-treatment biopsies for 822 patients of whom 404 received pertuzumab and 398 matched controls did not receive pertuzumab
- Pathological complete response (pCR) and overall survival (OS) were analyzed by treatment arm and BluePrint subtypes using logistic and Cox regression
- Kaplan-Meier curves are shown for illustration purposes

**Results**

- BluePrint read out: 81.4% HER2-type, 32.8% Luminal-type and 1.8% Basal-type
- BluePrint dual subtypes: 13% reclassified, mostly to luminal HER2 (10.6%)
- pCR is higher in patients treated with pertuzumab (40% vs. 66%). Absolute pCR rate and increase with pertuzumab were higher in single HER2 subtype (47% vs. 77%) than in the other BP subtypes combined (17% vs. 27%)
- Overall survival is higher in patients treated with pertuzumab (adjusted hazard ratio [aHR] 0.41, 95% CI 0.24 - 0.69). Increase in OS was higher in patients with single HER2 subtype (aHR 0.31, 95% CI 0.16 - 0.60) than in the other BP subtypes (aHR 0.64, 95% CI 0.24 - 1.73)
- However, tests for interaction between pertuzumab and BluePrint subtypes are not significant (data not shown)

**Baseline & treatment characteristics**

<table>
<thead>
<tr>
<th>Her2 subtype</th>
<th>No Pertuzumab (n=424)</th>
<th>Pertuzumab (n=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>50.6 (12.5)</td>
<td>49.3 (9.85)</td>
</tr>
<tr>
<td>HR-status negative</td>
<td>158</td>
<td>137.3</td>
</tr>
<tr>
<td>Clinical T-stage cT2</td>
<td>289</td>
<td>68.2%</td>
</tr>
<tr>
<td>Clinical N-stage cN0</td>
<td>123</td>
<td>31.1%</td>
</tr>
<tr>
<td>Chemotherapy no anthracyclines</td>
<td>158</td>
<td>37.3%</td>
</tr>
<tr>
<td>Surgical BCS</td>
<td>262</td>
<td>61.8%</td>
</tr>
<tr>
<td>Grade grade 1-2</td>
<td>158</td>
<td>37.3%</td>
</tr>
<tr>
<td>Grade grade 3</td>
<td>262</td>
<td>61.8%</td>
</tr>
</tbody>
</table>

**Kaplan-Meier curves**

**Survival curves for single HER2 subtype**

- HR: 0.60 (95% CI: 0.39 - 0.92)
- aHR: 0.64 (95% CI: 0.24 - 0.69)

**Survival curves for other BP subtypes**

- HR: 0.31 (95% CI: 0.16 - 0.56)
- aHR: 0.64 (95% CI: 0.24 - 1.73)

**Conclusion**

The benefit of adding pertuzumab to (neo)adjuvant trastuzumab-based chemotherapy is highest in patients with a molecularly defined single-activated HER2-subtype. In the other subtypes combined, pCR rates and survival are worse with less pronounced benefit of pertuzumab. Patients with single HER2 subtype identified by BluePrint could be optimal candidates for chemotherapy de-escalation.

**References**

2. Fasching, Breast Can Res 2013
3. Krop, SABCS 2020
4. Von Minckwitz NEJM 2017
5. Piccart, SABCS 2019
6. Kuilman, EBCC2020
7. Krop, SABCS, 2020
8. vd Voort, JAMA Oncol 2021

**Supporting Information**

- Table A: Baseline & treatment characteristics
- Figure 1: Kaplan-Meier curves for survival by HER2 subtype and BluePrint subtype
- Figure 2: pCR rates without and with pertuzumab across HER2 and BluePrint subtypes
- Figure 3: Survival rates with and without pertuzumab among HER2 and BluePrint subtypes

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