GeparX - GBG 88

Investigating Denosumab as an add-on to neoadjuvant chemotherapy in RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-paclitaxel schedules in a 2x2 factorial design

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-This is a joint study by GBG and AGO-B-
Disclosures

- Advisory/consultancy: AZ, MSD, Novartis, Pfizer, Roche
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Background

- Anticancer activity of RANK- ligand inhibition with denosumab is still under discussion \(^1,^2,^3\)

- The GeparSepto study demonstrated an increased pCR rate with weekly nab-paclitaxel but it remains still unclear which schedule should be preferred for nab-paclitaxel in terms of toxicity and efficacy \(^4,^5,^6,^7\)

- The GeparX study addresses both questions in a 2x2 factorial design

2x2 Study Design

N=780
- Early BC
- cT1c and high risk or cT2-cT4a-d

2x2

Stratification factors:
- sTILs
- Subtype
- EC schedule
- Denosumab (nab-paclitaxel randomization)

Treatment backbone:
- HER2+: trastuzumab (ABP 980) + pertuzumab q3w
- TNBC: carboplatin (AUC 2) q1w in addition to taxane

SURGERY + pCR Rate

12 wks nab-paclitaxel 125 mg/m² q1w
EC 90/600 mg/m² q2w/q3w
Denosumab 120 mg s.c. q4w 24 weeks

12 wks nab-paclitaxel 125 mg/m² q1w
EC 90/600 mg/m² q2w/q3w
Denosumab 120 mg s.c. q4w 24 weeks

12 wks nab-paclitaxel 125 mg/m² d1,8 q22
EC 90/600 mg/m² q2w/q3w
Denosumab 120 mg s.c. q4w 24 weeks

12 wks nab-paclitaxel 125 mg/m² d1,8 q22
EC 90/600 mg/m² q2w/q3w
Co-Primary Objectives and Endpoint

To compare the pCR (ypT0 ypN0) rate of:

- neoadjuvant treatment with or without denosumab in addition to neoadjuvant chemotherapy

and

- of nab-Paclitaxel 125mg/m² weekly with nab-Paclitaxel 125mg/m² day 1,8 q22
Main Inclusion Criteria

- Primary carcinoma of the breast
- Patients must be in the following stages of disease:
  - cT2 - cT4a-d or
  - cT1c and cN+ or
  - cT1c and pN_{SLN}+ or
  - cT1c and ER neg and PgR neg or
  - cT1c and Ki-67>20% or
  - cT1c and HER2-pos
- Central testing of ER, PgR, HER2 status, Ki-67
- No significant dental/oral disease
- No prior use of bisphosphonates or denosumab ≤ 1 year
Sample Size and Statistical Considerations

- Sample size (primary endpoint) planning assumed a pCR improvement
  - by denosumab from 35% to 46% (OR=1.58)
  - by different nab-paclitaxel schedules from 36% to 45% (OR=1.45)

- With 778 recruited patients, the $\chi^2$-test of pCR rates between the denosumab and no denosumab arms will have 92% power to the 2-sided significance level $\alpha=0.1$

- The $\chi^2$-test of pCR rates between the two nab-paclitaxel schedules will have 80% power to the 2-sided significance level $\alpha=0.1$

- Primary objectives will be tested according to the improved Bonferroni procedure: the smaller of the two p-values will be compared with $\alpha = 0.1$ and the larger p-value will be compared with $\alpha=0.2$ to keep the overall significance level of the study of $\alpha=0.2$
### Main Baseline Characteristics (N=780)

<table>
<thead>
<tr>
<th></th>
<th>With Denosumab N (%)*</th>
<th>Without Denosumab N (%)*</th>
<th>Nab-Pac weekly N (%)*</th>
<th>Nab-Pac d1,8 q22 N (%)*</th>
<th>Overall N (%) *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years), median (range)</strong></td>
<td>49.0 (23.0-78.0)</td>
<td>48.5 (22.0-80.0)</td>
<td>49.0 (23.0-78.0)</td>
<td>49.0 (22.0-80.0)</td>
<td>49.0 (22.0-80.0)</td>
</tr>
<tr>
<td><strong>Pre-/perimenopausal</strong></td>
<td>218 (55.9)</td>
<td>235 (60.3)</td>
<td>229 (58.7)</td>
<td>224 (57.4)</td>
<td>453 (58.1)</td>
</tr>
<tr>
<td><strong>cT1/cT2</strong></td>
<td>357 (92.5)</td>
<td>369 (95.6)</td>
<td>362 (94.3)</td>
<td>364 (93.8)</td>
<td>726 (94.0)</td>
</tr>
<tr>
<td><strong>cT3/T4</strong></td>
<td>29 (7.5)</td>
<td>17 (4.4)</td>
<td>22 (5.7)</td>
<td>24 (6.2)</td>
<td>46 (6.0)</td>
</tr>
<tr>
<td><strong>cN+</strong></td>
<td>155 (40.1)</td>
<td>154 (39.8)</td>
<td>152 (39.0)</td>
<td>157 (40.8)</td>
<td>309 (40.0)</td>
</tr>
<tr>
<td><strong>HER2-/HR+</strong></td>
<td>153 (39.2)</td>
<td>157 (40.3)</td>
<td>155 (39.7)</td>
<td>155 (39.7)</td>
<td>310 (39.7)</td>
</tr>
<tr>
<td><strong>TNBC</strong></td>
<td>160 (41.0)</td>
<td>157 (40.3)</td>
<td>159 (40.8)</td>
<td>158 (40.5)</td>
<td>317 (40.6)</td>
</tr>
<tr>
<td><strong>HER2+</strong></td>
<td>77 (19.7)</td>
<td>76 (19.5)</td>
<td>76 (19.5)</td>
<td>77 (19.7)</td>
<td>153 (19.6)</td>
</tr>
<tr>
<td><strong>Ki-67 &gt; 20%</strong></td>
<td>317 (81.3)</td>
<td>331 (84.9)</td>
<td>327 (83.8)</td>
<td>321 (82.3)</td>
<td>648 (83.1)</td>
</tr>
<tr>
<td><strong>sTILs &gt;50%</strong></td>
<td>31 (7.9)</td>
<td>31 (7.9)</td>
<td>31 (7.9)</td>
<td>31 (7.9)</td>
<td>62 (7.9)</td>
</tr>
<tr>
<td><strong>EC q2w</strong></td>
<td>206 (52.8)</td>
<td>208 (53.3)</td>
<td>207 (53.1)</td>
<td>207 (53.1)</td>
<td>414 (53.1)</td>
</tr>
</tbody>
</table>

* valid percent

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## Chemotherapy Discontinuations

<table>
<thead>
<tr>
<th></th>
<th>Denosumab N (%)</th>
<th>No Denosumab N (%)</th>
<th>Nab-Pac weekly N (%)</th>
<th>Nab-Pac d1,8 q22 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completed all treatments</strong></td>
<td>297 (78.2)</td>
<td>319 (82.2)</td>
<td>283 (72.9)</td>
<td>333 (87.6)</td>
</tr>
<tr>
<td><strong>Discontinued nab-paclitaxel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local progression</td>
<td>56 (14.7)</td>
<td>48 (12.4)</td>
<td>80 (20.6)</td>
<td>24 (6.3)</td>
</tr>
<tr>
<td>Distant relapse/ secondary malignancy</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.3)</td>
<td>-</td>
<td>-</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>42 (11.1)</td>
<td>40 (10.3)</td>
<td>68 (17.5)</td>
<td>14 (3.7)</td>
</tr>
<tr>
<td>Patient's / Investigator's decision</td>
<td>7 (1.8)</td>
<td>3 (0.8)</td>
<td>10 (2.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td><strong>Started EC</strong></td>
<td>350 (92.1)</td>
<td>371 (95.6)</td>
<td>359 (92.5)</td>
<td>362 (95.3)</td>
</tr>
<tr>
<td><strong>Discontinued EC</strong></td>
<td>24 (6.3)</td>
<td>25 (6.4)</td>
<td>27 (7.0)</td>
<td>22 (5.8)</td>
</tr>
<tr>
<td>Local progression</td>
<td>2 (0.5)</td>
<td>1 (0.3)</td>
<td>-</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Distant relapse/ secondary malignancy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Death</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Adverse event</td>
<td>14 (3.7)</td>
<td>13 (3.4)</td>
<td>21 (5.4)</td>
<td>6 (1.6)</td>
</tr>
<tr>
<td>Patient's / Investigator's decision</td>
<td>8 (2.1)</td>
<td>11 (2.9)</td>
<td>6 (1.6)</td>
<td>13 (3.4)</td>
</tr>
</tbody>
</table>
### Serious Adverse Events (SAEs)

<table>
<thead>
<tr>
<th></th>
<th>Denosumab N=380</th>
<th>No Denosumab N=388</th>
<th>Nab-Pac weekly N=388</th>
<th>Nab-Pac d1,8 q22 N=380</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No of SAEs</td>
<td>179</td>
<td>179</td>
<td>216</td>
<td>142</td>
</tr>
<tr>
<td>Pts with at least 1 SAE</td>
<td>109 (28.0%)</td>
<td>109 (28.0%)</td>
<td>123 (31.5%)</td>
<td>95 (24.4%)</td>
</tr>
</tbody>
</table>

**Selected SOCs**

<table>
<thead>
<tr>
<th>Category</th>
<th>Denosumab</th>
<th>No Denosumab</th>
<th>Nab-Pac weekly</th>
<th>Nab-Pac d1,8 q22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>24</td>
<td>32</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td>Blood/ lymphatic system disorders</td>
<td>53</td>
<td>53</td>
<td>57</td>
<td>49</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>12</td>
<td>19</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td>12</td>
<td>5</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>General disorders</td>
<td>48</td>
<td>38</td>
<td>25</td>
<td>13</td>
</tr>
</tbody>
</table>

- **Osteonecrosis of the jaw occurred in 2 cases with denosumab**
Results pCR Rate (ypT0 ypN0)

**Denosumab**

- Δ pCR -1.8%
- p = 0.582*

<table>
<thead>
<tr>
<th></th>
<th>With Denosumab (N=390)</th>
<th>Without Denosumab (N=390)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>41.0%</td>
<td>42.8%</td>
</tr>
</tbody>
</table>

**Nab-Paclitaxel Regime**

- Δ pCR 5.9%
- p = 0.062* (significance level α=0.1)

<table>
<thead>
<tr>
<th></th>
<th>Nab-Paclitaxel weekly (N=390)</th>
<th>Nab-Paclitaxel d1,8 q22 (N=390)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>44.9%</td>
<td>39.0%</td>
</tr>
</tbody>
</table>

- p-value stratified test; stratified by sTILs, Subtype, EC schedule and denosumab (only nab-paclitaxel regime)
Results pCR Rate in Subgroups for Nab-Paclitaxel Regimen

**TNBC (N=317)**

- **Δ pCR 10.4 %**
  - Nab-paclitaxel weekly N=159
  - Nab-paclitaxel d1+d8 q3w N=158
  - p=0.056*
  - Δ pCR 1.3 %

**HR+/HER2- (N=310)**

- **Δ pCR 1.3 %**
  - Nab-paclitaxel weekly N=155
  - Nab-paclitaxel d1+d8 q3w N=155
  - p=0.913*

**HER2+ (N=153)**

- **Δ pCR 6.0 %**
  - Nab-paclitaxel weekly N=76
  - Nab-paclitaxel d1+d8 q3w N=77
  - p=0.289*

- ∆ pCR 6.0%

- 57.9%

* p-value stratified test; stratified by sTILs, subtype, EC schedule and denosumab
Summary and Conclusion

- In the GeparX study the addition of denosumab to NACT did not increase the pCR rate in early BC (41% with denosumab vs 43% without denosumab; p=0.582)

- Nab-paclitaxel 125mg/m² weekly resulted in a significantly higher pCR rate than given d1,8 q22 (45% vs 39%; p=0.062)

- Nab-paclitaxel 125mg/m² weekly resulted in a higher rate of SAEs and a higher rate of treatment discontinuations mainly due to adverse events compared to nab-paclitaxel 125mg/m² d1,8 q22

- In TNBC optimized NACT with nab-paclitaxel 125mg/m² weekly plus carboplatin followed by EC achieves a pCR rate of at least 60%

- Further translational research (e.g. RANK expression) is ongoing
Acknowledgement

- All patients and their families
- All participating sites
- Slides are available on the webpage of GBG: www.gbg.de

Cooperating partners

Central Pathology:
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Wolfgang Schmidt
Peggy Wolkenstein
Britta Beyer

Financial and Drug Support

Cryostorage Biomaterial

Patient Self-Registry

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