A Randomized Phase III Trial Comparing Nanoparticle-Based (nab) Paclitaxel With Solvent-Based Paclitaxel as Part of Neoadjuvant Chemotherapy for Patients With Early Breast Cancer
GBG 69 - GeparSepto

Abstract S2-07


A joint study of the AGO Breast and the German Breast Group (GBG)
Initial Study Design

- **N = 1200**
- **Arm A**
- **Arm B**

*Centrally confirmed:
- Subtypes HER 2/ HR
- Ki 67
- SPARC

**Paclitaxel**
- 80 mg/m² weekly

**nab-Paclitaxel**
- 150 mg/m² weekly

**Epirubicin 90 mg/m²**

**Cyclophosphamide 600 mg/m²**

**If HER2 positive:**
- Trastuzumab 8 mg/kg (loading dose) followed by 6 mg/kg
- Pertuzumab (absolute dose per application) 840 mg (loading dose) followed by 420 mg

If HR positive:
- Tamoxifen, Aromatase inhibitors according to AGO Guidelines

Final Study Design
(After 400 Patients Recruited)

Core biopsy* (before study entry)

N = 60
(HER2 positive)

Core biopsy* (after anti-HER2 treatment / before study entry)

N = 1200

Arm A

Arm B

*Centrally confirmed:
- Subtypes HER 2/ HR
- Ki67
- SPARC

12 weeks

12 weeks

Core biopsy optional

If HER2 positive:
- Trastuzumab 8 mg/kg (loading dose) followed by 6 mg/kg
- Pertuzumab (absolute dose per application) 840 mg (loading dose) followed by 420 mg

Core biopsy

Paclitaxel 80 mg/ m² weekly

nab-Paclitaxel 125 mg/ m² weekly

Epirubicin 90 mg/m²

Cyclophosphamide 600 mg/m²

Endpoints

Primary endpoint:
- pCR (ypT0 ypN0)
  - No invasive or *in situ* disease in breast or lymph nodes

Secondary endpoints:
- Other pCR definitions:
  - No invasive disease in breast or lymph nodes
  - No invasive disease in breast

- Toxicity and compliance

- pCR rates by SPARC (Secreted protein acidic and rich in cysteine protein expression, NCL-O-NECTIN; 1: 100;Novocastra)

### Selected Hematological Toxicities

<table>
<thead>
<tr>
<th>Adverse events (AE)</th>
<th>Grade</th>
<th>Paclitaxel N (%) N = 598</th>
<th>Nab-paclitaxel N (%) N = 606</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Any</td>
<td>526 (88.3)</td>
<td>560 (92.4)</td>
<td>.019</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>6 (1.0)</td>
<td>15 (2.5)</td>
<td>.076</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Any</td>
<td>485 (81.5)</td>
<td>528 (87.3)</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>368 (61.8)</td>
<td>366 (60.5)</td>
<td>.636</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
<td>25 (4.2)</td>
<td>28 (4.6)</td>
<td>.779</td>
</tr>
</tbody>
</table>

## Non-Hematological Toxicities

<table>
<thead>
<tr>
<th>AE</th>
<th>Grade</th>
<th>Paclitaxel N (%) N = 598</th>
<th>Nab-paclitaxel N (%) N = 606</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Any</td>
<td>465 (77.8)</td>
<td>502 (82.8)</td>
<td>.030</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>28 (4.7)</td>
<td>36 (5.9)</td>
<td>.369</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Any</td>
<td>264 (44.1)</td>
<td>310 (51.2)</td>
<td>.015</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>17 (2.8)</td>
<td>20 (3.3)</td>
<td>.739</td>
</tr>
<tr>
<td>Rash</td>
<td>Any</td>
<td>138 (23.1)</td>
<td>201 (33.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>4 (0.7)</td>
<td>7 (1.2)</td>
<td>.547</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>Any</td>
<td>105 (17.6)</td>
<td>168 (27.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>6 (1.0)</td>
<td>14 (2.3)</td>
<td>.112</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy*</td>
<td>Any</td>
<td>390 (65.2)</td>
<td>511 (84.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>16 (2.7)</td>
<td>62 (10.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Any</td>
<td>145 (24.2)</td>
<td>189 (31.2)</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>0 (0.0)</td>
<td>3 (0.5)</td>
<td>.249</td>
</tr>
</tbody>
</table>

* Nab-paclitaxel 125mg/m² - grade 3-4 peripheral sensory neuropathy: 6 (5.5%)

Primary Endpoint (pCR: ypT0 ypN0)

# pCR in Stratified Subgroups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Subgroup</th>
<th>pCR (%)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPARC</td>
<td>SPARC negative</td>
<td>28.8 vs 37.7</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>SPARC positive</td>
<td>29.8 vs 48.3</td>
<td>.074</td>
</tr>
<tr>
<td>Ki67</td>
<td>Ki67≤20%</td>
<td>19.6 vs 26.1</td>
<td>.137</td>
</tr>
<tr>
<td></td>
<td>Ki67&gt;20%</td>
<td>33.1 vs 44.0</td>
<td>.001</td>
</tr>
<tr>
<td>Biological</td>
<td>HER2-, HR+</td>
<td>12.0 vs 16.0</td>
<td>.183</td>
</tr>
<tr>
<td>subtype</td>
<td>HER2-, HR-</td>
<td>25.7 vs 48.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>HER2+, HR+</td>
<td>50.0 vs 56.4</td>
<td>.275</td>
</tr>
<tr>
<td></td>
<td>HER2+, HR-</td>
<td>66.7 vs 74.6</td>
<td>.371</td>
</tr>
<tr>
<td>HER2</td>
<td>HER2-</td>
<td>17.7 vs 27.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>HER2+</td>
<td>54.1 vs 61.8</td>
<td>.120</td>
</tr>
<tr>
<td>HR status</td>
<td>HR-</td>
<td>36.1 vs 56.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>HR+</td>
<td>25.6 vs 29.9</td>
<td>.169</td>
</tr>
</tbody>
</table>

Secondary Endpoints

pCR Rates According to Other Definitions

Conclusion

• Primary study endpoint was reached: Nab-paclitaxel increased significantly the pCR rate compared to paclitaxel (odds ratio [OR] 1.53; \( P < .001 \))

• This effect was seen in all subgroups, especially in patients with triple-negative tumors (OR 2.69)

• Nab-paclitaxel 150mg/m² weekly was associated with a higher rate of sensory neuropathy than paclitaxel

• Long term follow-up is needed to validate if the increase in pCR rate translates into a better disease-free survival and overall survival

Mutational Analysis of CALGB 40601 (Alliance), a Neoadjuvant Phase III Trial of Weekly Paclitaxel (T) and Trastuzumab (H) With or Without Lapatinib (L) for HER2-Positive Breast Cancer

Abstract S3-06


On behalf of the Alliance for Clinical Trials in Oncology
Specific Aims

- Evaluate the mutational landscape of 181 HER2-positive pretreatment tumors from the CALGB 40601 trial
- Correlate mutations in 9 genes with pCR to chemotherapy plus HER2 targeting
  - Focus primarily on three genes
    - TP53
    - PIK3CA
    - HER2

CALGB 40601 (Alliance), A Neoadjuvant Phase III Trial of Weekly Paclitaxel (wT) and Trastuzumab (H) With or Without Lapatinib (L) for HER2-Positive Breast Cancer

Clinical stage II-III HER2+

- wT+H+L x 16 weeks
- wT+H x 16 weeks
- wT+L x 16 weeks

Research tissue

Surgery

Recommended: Dose-dense AC → H x 34 weeks

Primary Endpoint: ASCO 2013

- In-breast pCR to dual therapy (THL) versus single (TH)
  - 56% versus 45% ($P = .12$)

pCR by Intrinsic Subtype (All Arms, n = 265)

Other subtypes:
- 3 Claudin-low (0% pCR)
- 14 basel-like (35% pCR)
- Excluded “normal” (n = 6)

Percentage

<table>
<thead>
<tr>
<th>Subtype</th>
<th>HER2-Enriched (n = 82)</th>
<th>Luminal A (n = 80)</th>
<th>Luminal B (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>70%</td>
<td>34% 36%</td>
<td></td>
</tr>
<tr>
<td>THL</td>
<td>80%</td>
<td>37% 40%</td>
<td></td>
</tr>
<tr>
<td>TH</td>
<td>71%</td>
<td>38% 41%</td>
<td></td>
</tr>
<tr>
<td>TL</td>
<td>52%</td>
<td>9% 22%</td>
<td></td>
</tr>
</tbody>
</table>

• Exome subset pCR Rate = 45% (51% THL, 47% TH, 34% TL)
• Consistent with overall study population


Selected Mutated Genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>% Mutated</th>
<th># Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>56%</td>
<td>102</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>20%</td>
<td>36</td>
</tr>
<tr>
<td>MALAT1</td>
<td>9%</td>
<td>17</td>
</tr>
<tr>
<td>GATA3</td>
<td>4%</td>
<td>7</td>
</tr>
<tr>
<td>ERBB2</td>
<td>4%</td>
<td>7</td>
</tr>
<tr>
<td>TRPS1</td>
<td>2%</td>
<td>4</td>
</tr>
<tr>
<td>MAP3K1</td>
<td>2%</td>
<td>3</td>
</tr>
<tr>
<td>AKT1</td>
<td>1%</td>
<td>2</td>
</tr>
<tr>
<td>MAP2K4</td>
<td>1%</td>
<td>1</td>
</tr>
</tbody>
</table>


• TP53 mutation gene expression signature (Troester, et al) previously show to be correlated with pCR (Carey, et al) was also highly correlated with the TP53 exome-based mutation calls (P<.001)
PIK3CA Mutations

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Wildtype</th>
<th>Mutant</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal-like</td>
<td>8</td>
<td>1</td>
<td>11%</td>
</tr>
<tr>
<td>Claudin-low</td>
<td>2</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>HER2-E</td>
<td>43</td>
<td>14</td>
<td>25%</td>
</tr>
<tr>
<td>Luminal A</td>
<td>51</td>
<td>4</td>
<td>7%</td>
</tr>
<tr>
<td>Luminal B</td>
<td>35</td>
<td>16</td>
<td>31%</td>
</tr>
<tr>
<td>Normal-like</td>
<td>3</td>
<td>1</td>
<td>25%</td>
</tr>
</tbody>
</table>

93% of mutations were in exons 9 and 20

PIK3CA mutation **not** correlated with pCR

2/8 HER2 mutations were detected at variant allele frequencies (VAF) greater than 10%.

HER2/ERBB2 Mutations

- HER2-E with V777L
  - THL Arm
  - Preclinically predicted sensitive to lapatinib
  - Achieved pCR

- Luminal A with L755S
  - TL Arm
  - Preclinically predicted resistant to Lapatinib
  - No pCR


Conclusions

• TP53 was the most frequently mutated gene (56% overall)
  – TP53 mutations were associated with increased pCR
  – TP53 mutations were correlated with a higher overall somatic mutation rate

• Mutations in PIK3CA and the lower frequency mutations in GATA3, MALAT1, ERBB2, TRPS1, MAP3K1, AKT1, MAP2K4 were not associated with pCR

• Activating HER2 mutations were uncommon but V777L and L755S behaved as predicted from preclinical studies

• Studies to simultaneously use genomic signatures, somatic mutations, and clinical variables for pCR predictions are underway

Neoadjuvant Chemotherapy With or Without Bevacizumab or Everolimus: Survival Analysis of the HER2-Negative Cohort of the GeparQuinto Study (GBG 44)

Abstract P3-11-01

Background

• The GeparQuinto study showed that adding bevacizumab (Bev) to 24 weeks of anthracycline-taxane-based chemotherapy increases pathologic complete response (pCR, breast and axilla) rates from 14.9% to 18.4% ($P = .04$) and in TNBC patients from 27.9% to 39.3% ($P = .003$)¹

• No difference in pCR rate was observed with everolimus (Eve) and paclitaxel in patients who had no early response to neoadjuvant chemotherapy²


Objectives

- Secondary objectives of GeparQuinto were:
  - DFS
  - OS

Materials and Methods

• Patients with HER2-negative tumors were randomized to neoadjuvant treatment
  – 4x epirubicin/cyclophosphamide (EC; E 90 mg/m\(^2\), C 600 mg/m\(^2\) q3w) followed by
  – 4x Docetaxel (T; 100 mg/m\(^2\) q3w)
  – ± Bevacizumab (15 mg/kg q3w) before surgery

• Patients not clinically responding to EC ± Bev were randomized to weekly paclitaxel (80 mg/m\(^2\)) ± everolimus (5 mg/day)

• Patients with hormone receptor-positive tumors received endocrine treatment after surgery; no Bev or Eve were given post surgery

Overall, 3-year DFS was 80.8% and 3-year OS was 89.7%. Outcome was not different for patients receiving bevacizumab compared to patients receiving chemotherapy alone overall and in subgroups.

Survival analysis according to pCR showed that patients with a pCR had a worse DFS if they received bevacizumab as part of their neoadjuvant therapy ($P = .062$). OS was not different.

Conclusions

• The use of 24 weeks of neoadjuvant bevacizumab containing therapy did not improve DFS and OS

• Patients achieving pCR had a trend for worse DFS if treated with bevacizumab compared to patients treated without bevacizumab

S0800 – Nab-Paclitaxel, Doxorubicin, Cyclophosphamide, and Pegfilgrastim With or Without Bevacizumab in Treating Women With Inflammatory or Locally Advanced Breast Cancer (NCI CDR0000636131)

Abstract P3-11-16

Background

- Locally advanced breast cancer (LABC), either inflammatory (IBC) or noninflammatory, remains a challenge despite progress in multimodality treatment.

- Standard anthracycline-taxane neoadjuvant combination chemotherapy for HER2-negative IBC and LABC generally yields poor pathologic complete response rates (pCR rate approx 10%) and long term survival rates less than 40%.

- S0800 sought to compare bevacizumab in combination with weekly nab-paclitaxel followed by dose-dense doxorubicin and cyclophosphamide (AC) to nab-paclitaxel and AC alone as neoadjuvant treatment for patients with HER2 negative IBC and LABC.


Background

- The rationale for using bevacizumab in S0800 is based on the proposed role of angiogenesis in improving flow and oxygenation and enhancing the delivery of chemotherapy agents (vascular pruning hypothesis)\(^5\), and the proapoptotic effect with certain classes of chemotherapeutic agents, particularly taxanes\(^1,5\)

- S0800 used nab-paclitaxel as the taxane backbone based on several potential advantages in locally advanced vascular tumors\(^2-7\)


Methods

- Prospective randomized phase II SWOG trial in women with HER2-negative in inflammatory or locally advanced breast cancer IBC (AJCC stages IIB, IIIA, IIIB, or IIIC).
- Randomization to either:
  - Arm 1: (n = 100)
    - Bevacizumab 10 mg/kg IV D1 q2w x 12 weeks +
    - nab-paclitaxel 100 mg/m² IV D1 every week for 12 weeks
    - Followed by AC every 14 days X 6 + pegfilgrastim (n = 100)
  - Arm 2: (n = 50)
    - nab-paclitaxel followed by AC + pegfilgrastim
  - Arm 3: (n = 50)
    - AC + pegfilgrastim followed by nab-paclitaxel
- Randomization stratified by HR status and disease (IBC/not IBC)
- Primary endpoint: pCR, defined as no evidence of invasive tumor at the primary tumor site and axillary lymph nodes in the surgical specimen

pCR Rates by Randomized Treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>No bevacizumab</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>HR-negative</td>
<td>28</td>
<td>59</td>
</tr>
<tr>
<td>HR-positive</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>IBC</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>LABC</td>
<td>22</td>
<td>37</td>
</tr>
</tbody>
</table>

Overall Survival by Randomized Treatment

Overall Survival Months Since Randomization

No bevacizumab (n = 122, 13 deaths)
Bevacizumab (n = 96, 8 deaths)
Stratified log-rank $P = .59$

Number at risk
No bevacizumab 112 110 71 24 2
Bevacizumab 96 92 61 12 2

# Grade 3/4 Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Nab-PAC+BEV→AC+PEG-G n = 92</th>
<th>Nab-PAC+BEV with AC+PEG-G arms n = 108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade 3-4</td>
<td>62 (67%)</td>
<td>70 (65%)</td>
</tr>
<tr>
<td>ARDS</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Enterocolitis infectious</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hematologic events (including, anemia, febrile neutropenia)</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Pain</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Conclusions

• Compared with combination anthracycline-taxane neoadjuvant chemotherapy, the Bev/Nab-paclitaxel/AC regimen significantly improved pCR rate overall, especially for triple-negative breast cancer (TNBC) patients

• The observed pCR rate in ER-negative disease (59%) suggests that the addition of bevacizumab to this chemotherapy backbone may improve outcome in this subset and justifies further testing of such an approach

• Similar findings were noted with the addition of bevacizumab in GeparQuinto and CALGB40602 in women with TNBC

• Grade 3 and 4 toxicities were common but did not differ by treatment arm

• This regimen using the weekly nab-paclitaxel backbone could be a good choice for TNBC/IBC neoadjuvant treatment

TBCRC023: A Randomized Multicenter Phase II Neoadjuvant Trial of Lapatinib, Trastuzumab, With or Without Endocrine Therapy for 12 Weeks vs 24 Weeks in Patients With HER2 Overexpressing Breast Cancer

Abstract S6-02

Targeting HER2 Pathway


Stage II/III HER2+ breast cancer

Lapatinib + trastuzumab (Plus estrogen deprivation if ER+)
12 weeks

Surgery

N = 64
Median tumor Size = 6 cm

<table>
<thead>
<tr>
<th></th>
<th>Path CR (ypT_{0-is})</th>
<th>Residual CA≤ 1cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>17 (27%)</td>
<td>14 (22%)</td>
</tr>
<tr>
<td>ER+</td>
<td>8 (21%)</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>ER-</td>
<td>9 (36%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>


Hypothesis

- In HER2-positive breast cancer, longer treatment with anti-HER2 therapy and endocrine therapy, if tumors are also ER-positive, will result in higher pCR rate.

1:2 randomization

Lapatinib + trastuzumab (Plus estrogen deprivation if ER+)cc

HER2+ breast cancer

Week 1

Biopsy

Week 1

Biopsy

Week 24

Biopsy

Week 1

Biopsy

Week 12

Biopsy

Week 12
Study Endpoints

• **Primary endpoint**
  – Pathologic complete response (pCR) in the breast (ypT₀-is ypNₓ)

• **Secondary endpoints**
  – Safety and tolerability
  – Time to first recurrence
  – Overall survival
## Toxicity

<table>
<thead>
<tr>
<th>Grade 3 toxicity</th>
<th>12 week N (%)</th>
<th>24 week N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated LFT</td>
<td>-</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>-</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (3%)</td>
<td>-</td>
</tr>
<tr>
<td>Renal calculi (SAE)</td>
<td>1 (3%)</td>
<td>-</td>
</tr>
</tbody>
</table>

No grade 4 toxicity

### Pathologic Response

<table>
<thead>
<tr>
<th>Path CR (ypT$_{0\text{-is}}$)</th>
<th>12 weeks (n = 33)</th>
<th>24 weeks (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4 (12%)</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>ER-positive</td>
<td>2 (9%)</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>ER-negative</td>
<td>2 (20%)</td>
<td>4 (18%)</td>
</tr>
</tbody>
</table>

Pathologic Response

Conclusions

• TBCRC023 did not meet its primary endpoint of increasing pCR to 45%. This was mainly due to lower than expected pCR in both arms.

• However, the study demonstrated a twofold numeric increase in pCR in the 24 weeks arm over the 12 week arm. That increase was more than threefold in the ER-positive subgroup.

• This is the first trial to show that longer treatment with dual anti-HER2 therapy in combination with endocrine therapy, and without chemotherapy, leads to a meaningful increase in pCR rate in ER-positive and HER2-positive breast cancer.