SABCS 2019: An Update on Survivorship Research

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Froedtert & MCW
Off-Label Use Disclosure(s)

I do intend to discuss an off-label use of a product during this activity.

The following product will be discussed: Denosumab (neo-adjuvant) Oral paclitaxel
Financial Disclosure(s)

I currently have or have had the following relevant financial relations to disclose:

– Institutional contracted research support from:
  – VM Oncology
  – Context Therapeutics

The following slides are adapted from the presentations at the 2019 SABCS. Distribution is not permitted.
Abstracts to be Discussed

• Bone modifying agents in the neoadjuvant setting
• Novel oral paclitaxel- neuropathy
• Cardiotoxicity- update
• AIs, adherence
  - Adherence- text messaging
• Cancer Disparities
  - Neighborhood poverty-adherence
  - SES-Clinical trial participation/completion
  - Geriatric Oncology
• Women’s Health Initiative-Update
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

Jens-Uwe Blohmer, Theresa Link, Sherko Kümmel, Michael Untch, Marianne Just, Peter A. Fasching, Andreas Schneeweiss, Pauline Wimberger, Oliver Stötzer, Jens Huober, Marc Thill, Christian Jackisch, Kerstin Rhiem, Claus Hanusch, Carsten Denkert, Knut Engels, Valentina Nekljudova, Sibylle Loibl

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

- Anticancer activity of RANK- ligand inhibition with denosumab is still under discussion \(^1,2,3,4\)

- 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 \(^5,6,7,8\)

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

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2x2 Study Design

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

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

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

12 wks nab-paclitaxel 125 mg/m² d1,8 q22
EC 90/600 mg/m² q2w/q3w

SURGERY + pCR Rate
Co-Primary Objectives and Endpoint

To compare the pCR \((ypT0 \, ypN0)\) rate of:

- neoadjuvant treatment \textbf{with or without denosumab} in addition to neoadjuvant chemotherapy

and

- of \textbf{nab-Paclitaxel 125mg/m\(^2\) weekly} with \textbf{nab-Paclitaxel 125mg/m\(^2\) 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 pNslN+.dor
  - 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 ≤ 1year
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>Pre-/perimenopausal</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>cT1/cT2</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>cT3/T4</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>cN+</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>HER2-/HR+</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>TNBC</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>HER2+</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>Ki-67 &gt; 20%</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>sTILs &gt;50%</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>EC q2w</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
### 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>257 (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>5 (1.3)</td>
<td>4 (1.0)</td>
<td>1 (0.3)</td>
<td>8 (2.1)</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><strong>Adverse event</strong></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>Discontinued EC</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><strong>Adverse event</strong></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><strong>Total No of SAEs</strong></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>
<tr>
<td><strong>Selected SOCs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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

\[\Delta \text{pCR} -1.8\% \quad p=0.582^*\]

\[\Delta \text{pCR} 5.9\% \quad p=0.062^* \quad (\text{significance level } \alpha=0.1)\]

With Denosumab

\(N=390\)

Without Denosumab

\(N=390\)

41.0%

42.8%

Nab-Paclitaxel Regime

With Nab-Paclitaxel

\(N=390\)

44.9%

39.0%

\(\Delta \text{pCR} \quad \text{weekly} \)

\(\Delta \text{pCR} \quad \text{d1,8 q22} \)

Nab-Paclitaxel Regime

\(N=390\)

\(N=390\)

Results pCR Rate in Subgroups for Nab-Paclitaxel Regimen

TNBC \((N=317)\)

\[\Delta \text{pCR} 10.4\% \quad p=0.056^*\]

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

\[\Delta \text{pCR} 1.3\% \quad p=0.031^*\]

HER2+ \((N=153)\)

\[\Delta \text{pCR} 6.0\% \quad p=0.028^*\]

* p-value stratified test; stratified by sTILs, subtype, EC schedule and denosumab (only nab-paclitaxel regimen)
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
Critique

• **Strengths**
  • New concept
  • Active compound in lab models

• **Challenges**
  • Multiple comparisons
  • Confounding
    (carboplatin, HER2 based therapies)
Oral paclitaxel with encequidar (OPE): The first orally administered paclitaxel shown to be superior to IV paclitaxel on confirmed response and survival with less neuropathy: A Phase III clinical study in metastatic breast cancer


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Metastatic Breast Cancer and Paclitaxel

- Taxanes remain a foundation of breast cancer treatment¹
  - IV Paclitaxel FDA-approved schedule for mBC²,³: 175 mg/m² Q 3 weeks
  - IV Paclitaxel US clinical practice³: 80 mg/m² IV Q week (varies by site, Q 3-4 weeks)

- Benefits of an oral mode of administration include patient convenience, home treatment, lack of IV access, removal of the risk of infusion hypersensitivity reactions and the need for prophylactic corticosteroids⁴,⁵

- Paclitaxel is not orally absorbed because it is excreted by the P-glycoprotein (P-gp) pump⁶

- Encequidar (HM30181A) is a highly specific, potent inhibitor of P-gp and increases the absorption of oral paclitaxel⁷

- Oral paclitaxel and encequidar (OPE) is composed of 30 mg capsules of solubilized paclitaxel and a 15 mg tablet of encequidar

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Dose Justification for OPE

Phase I PK Study¹
(N=36)

- AUC was comparable¹; OPE 205 mg/m² QD x 3 versus IV paclitaxel 80 mg/m² x 1
- OPE peak concentration ~1/7 of IV paclitaxel

Phase II Study in Pre-treated mBC²
(N=26)

<table>
<thead>
<tr>
<th>Best Tumor Response</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Population (N=26)</td>
<td>0</td>
<td>42.3</td>
<td>46.2</td>
<td>11.5</td>
</tr>
</tbody>
</table>

¹Median=2 lines of therapy; ²Patient had a new lesion; ³≥90% is clinically meaningful.

³AUC, area under the curve; mBC, metastatic breast cancer; PK, pharmacokinetic; QD, once daily.

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San Antonio Breast Cancer Symposium®, December 10-14, 2019

Study Design

OPE:IV Paclitaxel, 2:1 randomization

Baseline

1-3

4-6

7-9

10-12

13-15

16-18

19

20,21

22

23,24

25+

Treatment Period (weeks)

Cycle 1

Cycle 2

Cycle 3

Cycle 4

Cycle 5

Cycle 6

Cycle 7

Cycle 8

Cycle 9+

Extension Period (weeks)

Primary Endpoint

Final Analysis

*360 Evaluable Patients
OPE (n=240)
IV Paclitaxel (n=120)
80% power, 15% difference in confirmed RR (P=0.045)

Primary Objectives
- Efficacy Endpoint (Prespecified mITT Population)
  Confirmed tumor response by week 19
  - 2 consecutive scans of PR/CR using RECIST v1.1
  - Blinded and adjudicated central independent review
  - Safety and Tolerability (Safety Population)

Secondary Objectives
- PFS
- OS

*If first response at week 19, then week 22 scan obtained; *Defined as last patient, last scan; *Computer-generated algorithm assigning overall response. CR, complete response; mITT, modified intent-to-treat; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RR, response rate.

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Patient Selection and Analysis Populations

**Key Inclusion Criteria**
- Histologically or cytologically confirmed breast cancer
- Measurable metastatic target lesion disease by RECIST v1.1
- ECOG PS of 0 or 1

**Key Exclusion Criteria**
- Central nervous system metastasis
- <1 year since previous taxane treatment (adjuvant/metastatic)

**Intent-to-treat Population (ITT, N=402)**
- All patients who were randomized
- OPE (n=265); IV Paclitaxel (n=137)

**Safety Population (N=399)**
- All patients who received ≥1 dose of OPE or IV Paclitaxel
- OPE (n=264); IV Paclitaxel (n=135)

**Prespecified mITT Population (N=360)**
- Baseline evaluable scan: patients with metastatic RECIST lesion on central review
- All patients who received at least 7 doses of OPE or one dose of IV Paclitaxel
- OPE (n=235); IV Paclitaxel (n=125)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

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Paclitaxel Dosing and Administration

**Oral Paclitaxel and Encequidar (OPE)**
- Encequidar: 15 mg tablet
- Oral paclitaxel: each capsule contains 30 mg solubilized paclitaxel

**Intravenous Paclitaxel**
- Administered as 175 mg/m² over a 3-hour infusion every 3 weeks (1 cycle)

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Baseline Patient Characteristics and Demographics: Prespecified mITT Population (N=360)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>OPE (n=235)</th>
<th>IV Paclitaxel (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (range)</td>
<td>57.2 (30-90)</td>
<td>55.7 (32-85)</td>
</tr>
<tr>
<td>Age category ≥65, %</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>ECGD status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS 0</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>PS 1</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>Hormone receptor status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR positive/HER2 negative</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>HR positive/HER2 positive</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Triple negative</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>HR and HER2 unknown</td>
<td>17</td>
<td>21</td>
</tr>
</tbody>
</table>

*Black, Caucasian, other; †in addition, approximately 5% for each HR positive/HER2 unknown and other; ‡Data unavailable or missing. HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

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### Prior Therapies and Metastatic Disease in Prespecified mITT Population

<table>
<thead>
<tr>
<th>Prior Therapy Exposure</th>
<th>OPE (n=235)</th>
<th>IV Paclitaxel (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>≥3</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Number of prior chemotherapies in metastatic setting, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior taxane exposure (any setting), %</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Prior anthraclycline exposure (any setting), %</td>
<td>56</td>
<td>55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastatic Disease</th>
<th>OPE (n=235)</th>
<th>IV Paclitaxel (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of metastatic sites, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>≥3</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Visceral metastases, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All(^a)</td>
<td>75</td>
<td>78</td>
</tr>
<tr>
<td>Liver</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Lung</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>Lymph node involvement, %</td>
<td>69</td>
<td>66</td>
</tr>
</tbody>
</table>

\(^a\) Liver, lung, pleura, heart, pancreas, adrenal, brain, bowel, ovaries, bladder; bone metastases, n (%): OPE, 1 (<1); IV paclitaxel, 0 (0).

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Primary Endpoint in Prespecified mITT Population (Final Analysis): OPE Increased Confirmed RR Compared to IV Paclitaxel

Confirmed Response Rate

Δ = 14.8%
P = 0.005

- OPE (n=235)
- IV Paclitaxel (n=125)

<table>
<thead>
<tr>
<th>Tumor Evaluations</th>
<th>OPE</th>
<th>IV Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable disease, %</td>
<td>23.8</td>
<td>39.2</td>
</tr>
<tr>
<td>Progressive disease, %</td>
<td>16.2</td>
<td>21.6</td>
</tr>
</tbody>
</table>

*ITT analysis of the primary endpoint is also significant.

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Ongoing Analysis PFS in Prespecified mITT\textsuperscript{a} Population

---

**PFS, mITT (N=360) | OPE (n=235) | IV paclitaxel (n=125)**

<table>
<thead>
<tr>
<th></th>
<th>PFS</th>
<th>OPE</th>
<th>IV paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median estimate, months</td>
<td>9.3</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Censored summary, %</td>
<td>58.3</td>
<td>48.0</td>
<td></td>
</tr>
<tr>
<td>Patients with event\textsuperscript{b}, %</td>
<td>41.7</td>
<td>52.0</td>
<td></td>
</tr>
<tr>
<td>Patients discontinued with no event\textsuperscript{b} (censored), %</td>
<td>40.4</td>
<td>36.8</td>
<td></td>
</tr>
<tr>
<td>Patients ongoing with no event\textsuperscript{b} (censored), %</td>
<td>17.9</td>
<td>11.2</td>
<td></td>
</tr>
</tbody>
</table>

---

\textsuperscript{a}In the ITT analysis, a nonsignificant numerical trend was seen for the median PFS favoring the OPE median.

\textsuperscript{b}Event is defined as radiological disease progression by central review or death collected in eDC within 90 days of the last tumor assessment. CI, confidence interval; HR, hazard ratio.

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Ongoing Analysis OS in Prespecified mITT Population

**Log-Rank Test** $P=0.0353$

**Numbers of Subjects at Risk**

<table>
<thead>
<tr>
<th></th>
<th>OPE</th>
<th>IV Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>235</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>229</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>218</td>
<td>99</td>
<td></td>
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<tr>
<td>218</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>190</td>
<td>65</td>
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</tr>
<tr>
<td>190</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>162</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>130</td>
<td>33</td>
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<tr>
<td>107</td>
<td>24</td>
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<tr>
<td>84</td>
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<tr>
<td>66</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>7</td>
<td></td>
</tr>
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<td>31</td>
<td>1</td>
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</tr>
<tr>
<td>23</td>
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<td>18</td>
<td>1</td>
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<td>7</td>
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<tr>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**OS, mITT (N=360)**

<table>
<thead>
<tr>
<th></th>
<th>OPE (n=235)</th>
<th>IV Paclitaxel (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median estimate, months</td>
<td>27.9</td>
<td>16.9</td>
</tr>
<tr>
<td>Censored summary, %</td>
<td>68.9</td>
<td>58.4</td>
</tr>
<tr>
<td>Patient deaths (events), %</td>
<td>31.1</td>
<td>41.6</td>
</tr>
<tr>
<td>Discontinued patients and survival status unknown (censored), %</td>
<td>17.9</td>
<td>18.4</td>
</tr>
<tr>
<td>Patients ongoing or being followed up (censored), %</td>
<td>51.1</td>
<td>40.0</td>
</tr>
</tbody>
</table>

**ITT results:**

- Median estimate (months), OPE (27.7), IV Paclitaxel (16.9); Log-rank test $P=0.114$
- HR=0.684 (95% CI: 0.475, 0.985)

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TEAEs (CTCAE Grade ≥2) With ≥10% Overall Incidence Rate:
Safety Population (N=399)

Data for hyperuricemia and hypertriglyceridemia are not presented; includes burning sensation, dysesthesia, hypoesthesia, hypesthesia, neuralgia, neuropathy peripheral, neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy; includes arthralgia, back pain, pain in extremity; Grade 5 anemia, n (%): OPE, 1 (0.4); IV paclitaxel, 0 (0); includes abdominal pain, upper abdominal pain, and abdominal pain upper.

CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

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Neuropathy\textsuperscript{a} TEAEs (CTCAE Grade $\geq 2$): Safety Population (N=399)

\begin{itemize}
\item Neuropathy TEAEs include burning sensation, dyesthesia, hypoesthesia, hypesthesia, neuralgia, neuropathy peripheral, neurotoxicity, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.
\end{itemize}

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Conclusions

- Oral paclitaxel and encequidar is the first oral taxane in a Phase III trial to demonstrate a significant improvement in confirmed overall response rate compared to IV paclitaxel
  - In the modified intent-to-treat population, centrally confirmed ORR increased from 25.6% with IV paclitaxel to 40.4% with OPE ($P=0.005$)
  - Response with OPE was durable with 33.7% of patients responding for >200 days
- Although PFS was similar, oral paclitaxel and encequidar was associated with improved overall survival in the modified intent-to-treat population
- Oral paclitaxel and encequidar was associated with a lower incidence of neuropathy and alopecia but a higher incidence of low-grade gastrointestinal adverse events compared to IV paclitaxel
- Oral paclitaxel and encequidar provides an important oral therapeutic option for patients with metastatic breast cancer, representing a meaningful improvement in the clinical profile of paclitaxel
Critique

• **Strengths**
  • New concept
  • Novel, and an oral agent
  • Less neurotoxic

• **Challenges**
  • Toxicities are not minimal
Interim analysis of the SAFE trial (NCT2236806): A Ph 3 RCT evaluating a cardiovascular disease prevention strategy using beta-blockers and/or ACE inhibitors in non-metastatic breast cancer patients treated with anthracyclines-Lorenzo Livi et al.

Results of the interim analysis of the SAFE trial.

**Eligibility**
- Patients on adjuvant therapy anthracyclines +/- trastuzumab.

**Primary endpoint**
- evaluation of reduction in both systolic and diastolic function
- early and late subclinical cardiotoxicity

**Imaging**
Echocardiography, pulsed tissue doppler, global linear strain (GLS), and 3D- LVEF.
### Methods

The SAFE trial is a 2x2 factorial design, Ph 3, RCT evaluating the impact of bisoprolol (B) (5 mg), ramipril (R) (5 mg), or both drugs as compared to placebo (P) on subclinical heart damage evaluated by speckle-tracking cardiac ultrasound.

<table>
<thead>
<tr>
<th>Intervention A</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention B</th>
<th>YES</th>
<th>A+B</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>NO</td>
<td>A</td>
<td>No Intervention</td>
</tr>
<tr>
<td>LVEF</td>
<td>3 months</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Placebo</td>
<td>-3.3%; p&lt;0.001</td>
<td>-5.2%; p&lt;0.001</td>
<td>-3.7%; p=0.004</td>
</tr>
<tr>
<td>Ramipril</td>
<td>-2.4%; p=0.001</td>
<td>-1.9%; p=0.010</td>
<td>-2.2%; p=0.045</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>No difference</td>
<td>-2.5% p=0.002</td>
<td>No difference</td>
</tr>
<tr>
<td>Bisoprolol+ Ramipril</td>
<td>No difference</td>
<td>-3.0%, p=0.002</td>
<td>No difference</td>
</tr>
<tr>
<td>GLS</td>
<td>3 months</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------</td>
<td>----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>placebo</td>
<td>5.7%; p&lt;0.001</td>
<td>7.8%; p&lt;0.001</td>
<td>7.1%; p&lt;0.001</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.7%; p=0.002</td>
<td>3.2%; p=0.014</td>
<td>No difference</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>No difference</td>
<td>2.7%; p=0.035</td>
<td>3.2%; p=0.008</td>
</tr>
<tr>
<td>Bisoprilol+ Ramipril</td>
<td>No difference</td>
<td>No difference</td>
<td>No difference</td>
</tr>
</tbody>
</table>

P5-14-24. Interim analysis of the SAFE trial
Both R+B and the R arms showed a withdraw rate of 7% with a dose reduction rates of 21% and 17%, respectively.

**Conclusion.**
- Following the stopping rules, the closure of the R arm is required and the study will continue with 3 arms.
- At the interim analysis, a cardiovascular disease prevention strategy using beta-blockers and/or ACE inhibitors significantly impacted on subclinical heart damage.
Critique

• **Strengths**
  - Not a new concept
  - Novel - with sub-clinical damage
  - Overall cardiotoxicity with anti-neoplastic agents is getting lower

• **Challenges**
  - Reason for Ramipril to cause a decline in LVEF at 12m?
  - Specify the comorbidities and the benefits
Drugs don’t work in people who don’t take them!

**Hormonal Therapy and Breast Cancer Treatment**

- Hormonal therapy is the most effective way to reduce recurrence in hormone sensitive breast cancers (EBCTG)
- AI’s standard of care for post menopausal women (ATAC)
- 10 years of therapy > 5 years (MA17r)
- AI + Ovarian Suppression > Tamoxifen for pre menopausal women (SOFT/TEXT)
- AI’s > Tam for DCIS (NSABP B35)
- AI’s effective for primary prevention (IBIS II)
Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer.
Why Are Treatments Not Started or Discontinued?

- COST
- Behavior
- Toxicity

Association Between Prescription Copayment Amount and Adherence

Hershman DL et al., JNCI, 2014
Poverty -PROs, Adherence-Sedhom R et al.

San Antonio Breast Cancer Symposium, December 10-14, 2019

Abstract PD10-07: patient reported outcomes and early discontinuation of endocrine therapy according to neighborhood poverty rate

- Prospective cohort of non-metastatic breast cancer (n=320)
- Serial collection of PROs re endocrine symptoms, sexuality, pain, fatigue, mood, and others
- Key question: could greater symptom burden be an explanation for lower adherence in low SES patients?

- Key findings:
  - Overall discontinuation rate for side effects 13-17% at 41 months
  - No baseline differences in PRO measures by neighborhood poverty group
  - Pain interference improved over time in mod/high NP groups, no change in low NP group
  - No difference in reported discontinuation by NP group after 41 months

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Results

• Mean age 61 years
• White 83%
• Black 10%
• Postmenopausal 65%
• Stages I-II breast ca 84%

• NP groups
  • Low 30%
  • Medium 40%
  • High 30%
• AI users 56% (more in low NP group)
• Tamoxifen 44%
Figure 1: Discontinuation by NP rate

Hazard Ratio
High vs. Low: 1.46 [0.7, 3.06], P = 0.32
Med vs Low: 1.22 [0.6, 2.51], P = 0.58

Cumulative Probability of Discontinuing Due to Side Effects/Intolerance

No. at Risk
Low  50  50  50  50  50  50  50  50  50
Med  129 129 129 129 129 129 129 129 129
High  58  58  58  58  58  58  58  58  58

Months From Enrollment
0  6  12  18  24  30  36  42  48
Persistent increase in the endocrine symptoms, and a slight decrease in physical symptoms are reported overtime.
Critique

San Antonio Breast Cancer Symposium, December 10-14, 2019

**Strengths**

- Use of validated instruments collected over time
- Rich clinical data complementary to claims-based studies
- Appropriate adjustment for multiple comparisons

**Challenges and Questions**

- Somewhat low representation of minority + young patients
- Low neighborhood poverty patients were older, less often Black, yet their discontinuation rates were no different – why?
- Is neighborhood poverty information (zip code level) a reflection of individual SES, other built environment factors, or neither?
- Health beliefs and tolerability of symptoms are missing pieces
RANDOMIZED TRIAL OF TEXT-MESSAGING TO REDUCE EARLY DISCONTINUATION OF ADJUVANT AROMATASE INHIBITOR THERAPY IN WOMEN WITH BREAST CANCER: SWOG S1105

Aromatase Inhibitor use > 30 days
Aromatase inhibitor use <24 months
Scheduled for 3 years of AI therapy
Presence of mobile phone

Text Messaging
Twice a Week for 36 Months
Weekday / Weekend - 8 AM

Usual Care

CLINIC VISITS EVERY 3 MONTHS +/- 21 days (PRO’s and Urine Collected)
Measures
Pill number (dispensed for 30 days vs. 90 days)
Medication cost
PROs (> median, lower than median) - pain (BPI)
FACT-ES (endocrine symptoms),
FACT-G (QOL)
TSQM - Treatment Satisfaction Questionnaire for Medicine,
and BMQ (Brief Medication Questionnaire)
Methodology: Adherence failure (multiple logistic regression)
Time to adherence failure (Cox-Regression)
Measuring non-adherence: Urine metabolite of AI
(<10 Units, or undetectable)
Results

• 5/2012-9/2013
• Participating sites= 40
• N=724
• Median age 60.9 years
• 64% of the AI users were on <12m prior to enrollment
Factors analyzed for non-adherence

<table>
<thead>
<tr>
<th>FACT-ES</th>
<th>OR= 1.64. 95% CI: 1.2- 2.22, p=0.02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Pain Inventory</td>
<td>OR= 1.68, 95% CI: 1.23-2.28, p=0.001</td>
</tr>
<tr>
<td>FACT G</td>
<td>OR= 1.70, 95% CI: 1.25-2.31, p=&lt;0.001</td>
</tr>
<tr>
<td>Satisfaction with medication (TSQM Global)</td>
<td>OR= 1.55, 95% CI: 1.1- 2.17, p=0.01</td>
</tr>
<tr>
<td>Beliefs about medication (BMQ)</td>
<td>OR= 1.51, 95% CI :1.01-1.42, p=0.04</td>
</tr>
<tr>
<td><strong>Time to adherence failure (TTAF)</strong></td>
<td></td>
</tr>
<tr>
<td>Lack of private insurance</td>
<td>HR=1.20, 95% CI: 1.01-1.41, p=0.04</td>
</tr>
<tr>
<td>30 day vs. 90 day supply</td>
<td>HR=1.20, 95%CI: 1.01-1.42, p=0.04</td>
</tr>
</tbody>
</table>
PRO Associations with 36 month adherence

Baseline QoL and endocrine symptoms associated with non-adherence...

As are less positive attitudes and beliefs about medication.
Critique
PD10-08 RCT of text  Hershman et al.

San Antonio Breast Cancer Symposium, December 10-14, 2019

**Strengths**
- Inclusion of measures of medication attitudes/beliefs
- Biologic assay to verify adherence
- Potential to identify high-risk patients before they are under-treated
- Person-level SES data

**Challenges and Questions**
- Results conflict with other studies finding that race (Black) does impact adherence – different adherence measures, different sample (trial participants), or different age distribution?
- No PRO subset had >75% patients adherent, reminding us of need to address “unexplained variation”
- How do we target baseline symptom burden, beliefs and attitudes?
PD 10-09 Impact of insurance, and SES on protocol completion and survival in clinical trials- Obeng Gyasi et al.

<table>
<thead>
<tr>
<th></th>
<th>E1199 N=4954</th>
<th>E5103 N=4836</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private insurance</td>
<td>83.8%</td>
<td>82%</td>
</tr>
<tr>
<td>SES index</td>
<td>53.8 (SES derived from zip using AHRQ SES index aggregated at county level)</td>
<td>54.1</td>
</tr>
<tr>
<td><strong>Patients with Government Insurance vs. private insurance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment completion</td>
<td><strong>OR [95% CI]</strong> 0.73 [0.57-0.94]</td>
<td>0.76 [0.64-0.91]</td>
</tr>
<tr>
<td>Association with death</td>
<td><strong>HR [95%CI]</strong> 1.44 [1.22-1.70]</td>
<td>1.29 [1.06- 1.58]</td>
</tr>
<tr>
<td></td>
<td>No association between SES index measure and treatment completion or OS.</td>
<td></td>
</tr>
</tbody>
</table>
Prior ECOG 1199 Analyses: Black/White and Subtype-Specific Differences in Outcome

<table>
<thead>
<tr>
<th>Source*</th>
<th>Adjustment Factors</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carolina Breast Cancer Study 1993-2006</td>
<td>Age, diagnosis year, stage</td>
<td>1.9 (1.3-2.9) for BCSS</td>
</tr>
<tr>
<td>5 marker (HR/HER2/HER1/CK5/6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>City of Hope 1994-98</td>
<td>Age, stage</td>
<td>1.9 (0.9-3.9) for BCSS</td>
</tr>
<tr>
<td>4 marker (HR+/HER2-/F53-)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 1199 trial participants (stage II-II/II)</td>
<td>Age, BMI, tumor size, nodes, surgery type, hormonal tx</td>
<td>1.6 (1.2-2.1) for DFS</td>
</tr>
<tr>
<td>chemo-treated) (HR+/HER2-)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*In all studies, outcomes for women with triple negative disease were similar between black and white patients

2 Ma H, Lu Y et al. BMC Cancer 2013 13:225
Critique

San Antonio Breast Cancer Symposium, December 10-14, 2019

**Strengths**
- RCT data used as a novel source of rich patient-level data for secondary analysis including detailed treatment records
- Use of a multi-factor measure of area SES (AHRQ score) validated and associated with differences in other health outcomes

**Challenges and Questions**
- Vast majority (~83%) of patients had private insurance
- Given the median age of 51, publicly insured patients may have been primarily Medicaid beneficiaries
- Lack of co-morbidity adjustment may bias OS analyses
- County level may not be sufficiently granular to related SES to patient experience
- How well do trial participants represent other residents of low-SES zip codes?
- In NCI-funded trials with a wealth of person-level data, why are we working backward from zip codes to understand SES?
PD 10-10 Geriatric Oncology - decreased relative dose intensity - dRDI, Sedrak M et al.

- Prospective
- Multicenter [16 sites]
- Age ≥ 65
- Breast ca (st I-III) ER+/HER2-
- Neo/adjuvant
- RDI = ratio of actual dose delivered to intended dose

- **Primary Outcome**
  - dRDI-defined as <85% (associated with poorer survival) (Bonadonna et al. NEJM, 1995)
  - Logistic regression
  - Others
  - CGA, socio-demographics
  - Dose delays, reductions
PD 10-10 Geriatric Oncology - dRDI

- N=323
- Med age 69 [65-86]
- HR+/HER2-=216
- TNBC=107
- TC=47%
- Anthracyclines =46%
- CMF=7%

- Mean RDI 90%
- 21% had dRDI<85%
- HR+/TNBC-same RDI
- Multivar. Regression
- CMF/Anthracyclines 28% rRDI (OR 3.34)
- Abn LFT 41% rRDI, OR 2.25
Most breast cancer patients ≥65 can tolerate full dose neo/adjuvant chemotherapy. Performance status, organ function, and chronologic age may be good tools to identify high risk patients.
What did we learn and what is next?

• Heterogeneity in patient symptom experiences on/attitudes toward ET over time is immense...“one size fits all” approaches may not ever work to improve ET delivery

• How we measure SES with relationship to treatment is important, and person-level + neighborhood-level data both play a role

• Public insurance status (Medicaid?) may predict adverse outcomes during clinical trials better than neighborhood-level SES measures

• Most breast cancer patients over 65 can tolerate full dose (neo) adjuvant chemotherapy, and performance status, organ function and chronologic age may be good tools to identify high-risk patients
MY PROfile: A web-based tool to assess patient PROs in women with metastatic breast cancer (P6-12-09)-Mougalian SS et al.

- Address both physical symptoms and non-physical symptoms
- Conducted at Yale, and Affiliated Cancer Center
- Participants were requested to respond to validated surveys
- Physical, non-physical, emotional well-being, spiritual, religious concerns
- Alcohol, and drug use
- Patients were followed for six months
- Participants can complete these surveys as frequently as they wish [but at least once prior to the provider visit]
Results

Participants=28

- Reported symptoms
- Physical symptoms - 68%
- Emotional well-being - 50%
- Both physical and non-physical
- Non-physical symptoms = 32%
- Impact of treatment on diet/activity 21%
- Impact on walking/housework 18%
- Family health 11%
- Alcohol and drugs n=1
MY PROfile- (P6-12-09)

Fatigue = 57%
Pain 54%
Nausea 30%
Constipation 22%
Diarrhea 22%
Worry 36%
MY PROfile- (P6-12-09)

Fears 30%
Nervous 30%
Appearance 25%
Treatment decisions 26%
13 of 28 used My PROfile at least 3 times during follow up.

Conclusion:
Tools to collect should include additional domains that affect of QOL.
Use of cancer survivorship patient engagement toolkit (CaS-PET) in breast cancer patients—Rosenblatt et al. University of Maryland.

- Feasibility study evaluating the impact of a toolkit
- Univ of Maryland faculty developed
  Cancer Survivorship Patient Engagement Toolkit (Cas-PET)
- Included:
  survivorship care plans, education on health topics, discussion boards, patient portal-based discussion
- Methods: 30 cancer survivors
- Within 6 months of completion of active treatment
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Results</th>
<th>N-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age</td>
<td></td>
<td>57.2 +/- 13 years</td>
</tr>
<tr>
<td>Racial Breakdown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>African American</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Type of Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Hormone Therapy</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Stage of Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCIS</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>STAGE 1-3 Invasive</td>
<td></td>
<td>13</td>
</tr>
</tbody>
</table>
## Change in Values pre and post Cas-PET

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Test Statistic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to treatment</td>
<td>25.2</td>
<td>23.2</td>
<td>T=2.767</td>
<td>0.019</td>
</tr>
<tr>
<td>Fruit and veg consumption</td>
<td>9.7</td>
<td>12.4</td>
<td>T=2.311</td>
<td>0.039</td>
</tr>
<tr>
<td>Physical activity (total MET)</td>
<td>5.1</td>
<td>6.7</td>
<td>T=1.995</td>
<td>0.069</td>
</tr>
<tr>
<td>Global distress scale</td>
<td>0.9</td>
<td>0.9</td>
<td>T=0.189</td>
<td>0.853</td>
</tr>
<tr>
<td>Fear of recurrence</td>
<td>15.0</td>
<td>16.4</td>
<td>T=0.806</td>
<td>0.435</td>
</tr>
</tbody>
</table>
Menopausal Hormone Therapy and Breast Cancer: Long Term Findings from the Women’s Health Initiative Randomized Clinical Trials


The Lundquist Institute for Biomedical Innovation at Harbor-UCLA

Women’s Health Initiative Investigators

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The Women’s Health Initiative (WHI)

WHI is a multi-component study designed to address determinants of major chronic disease in women

Clinical Trials = 68,132

- DM
  - 48,835
- HT
  - 27,347
- CaD
  - 36,282

Observational Study = 93,676

Total cohort = 161,808

Includes 4 clinical trials (2 Hormone Therapy, Dietary Modification, Calcium Plus Vitamin D), n=68,132 and an Observational Study, n=93,676

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WHI Hormone Therapy (HT) Randomized Trials

Postmenopausal women with prior hysterectomy
N= 10,739

Postmenopausal women with no prior hysterectomy
N= 16,608

Eligibility
- Age 50-79
- No prior breast cancer
- Mammogram not suggestive

Primary monitoring outcomes:
- Coronary heart disease for benefit
- Invasive breast cancer for harm

CEE (Conjugated equine estrogen) 0.625 mg/d
Placebo

CEE 0.625 mg/d + medroxyprogesterone acetate (MPA) 2.5 mg/d
Placebo


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Methods

- Randomized, placebo-controlled double-blind design implemented at 40 US clinical centers entering postmenopausal women from 1993-1998
- Annual mammography protocol-mandated
- Breast cancers were verified by central medical record and pathology report review
- Deaths were verified by central death certificate and medical record review enhanced by 9 serial National Death Index (NDI) queries which capture 98% of US deaths¹

# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CEE-alone</th>
<th>Placebo</th>
<th>CEE plus MPA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>30.9</td>
<td>30.8</td>
<td>33.4</td>
<td>33.1</td>
</tr>
<tr>
<td>60-69</td>
<td>44.9</td>
<td>45.4</td>
<td>45.3</td>
<td>45.1</td>
</tr>
<tr>
<td>70-79</td>
<td>24.2</td>
<td>23.8</td>
<td>21.3</td>
<td>21.8</td>
</tr>
<tr>
<td>≥ College degree</td>
<td>23.2</td>
<td>24.6</td>
<td>34.4</td>
<td>35.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>21.0</td>
<td>20.3</td>
<td>30.4</td>
<td>30.8</td>
</tr>
<tr>
<td>25-29</td>
<td>34.0</td>
<td>35.5</td>
<td>35.3</td>
<td>35.2</td>
</tr>
<tr>
<td>≥30</td>
<td>45.0</td>
<td>44.2</td>
<td>34.2</td>
<td>34.0</td>
</tr>
<tr>
<td>Gail 5 year risk ≥ 1.75</td>
<td>29.4</td>
<td>29.3</td>
<td>33.4</td>
<td>33.1</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used</td>
<td>52.2</td>
<td>51.0</td>
<td>73.8</td>
<td>74.4</td>
</tr>
<tr>
<td>Past user</td>
<td>35.2</td>
<td>35.9</td>
<td>19.7</td>
<td>19.6</td>
</tr>
<tr>
<td>Current user</td>
<td>12.6</td>
<td>13.1</td>
<td>6.5</td>
<td>6.1</td>
</tr>
</tbody>
</table>
Hormone Therapy and Breast Cancer Incidence in WHI HT Randomized Trials

CEE+MPA and CEE alone have opposite effects on breast cancer incidence

Breast Cancer Subgroups (CEE+ MPA Trial)

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Hormone Therapy and Breast Cancer Characteristics

<table>
<thead>
<tr>
<th>Breast cancer events</th>
<th># of events (Annualized %)</th>
<th>CEE-alone</th>
<th>Placebo</th>
<th>HR(95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CEE-alone</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+PR+</td>
<td>146(0.19)</td>
<td>176(0.23)</td>
<td>0.83</td>
<td>(0.66, 1.04)</td>
<td>0.06</td>
</tr>
<tr>
<td>ER+PR−</td>
<td>23(0.030)</td>
<td>48(0.063)</td>
<td>0.45</td>
<td>(0.27, 0.75)</td>
<td></td>
</tr>
<tr>
<td>ER−PR−</td>
<td>39(0.052)</td>
<td>36(0.047)</td>
<td>0.97</td>
<td>(0.61, 1.55)</td>
<td></td>
</tr>
</tbody>
</table>

ER+, PR-, breast cancers have unfavorable prognosis


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# Hormone Therapy and Breast Cancer Mortality

<table>
<thead>
<tr>
<th></th>
<th>Deaths from Breast Cancer HR (95% CI)</th>
<th>P-Value</th>
<th>Deaths After Breast Cancer HR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CEE plus MPA</strong></td>
<td>1.45 (0.98-2015)</td>
<td>0.06</td>
<td>1.29 (1.02-1.63)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>CEE-Alone</strong></td>
<td>0.56 (0.34-0.92)</td>
<td>0.02</td>
<td>0.75 (0.56-1.01)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

1. Follow-up began at randomization and includes death directly attributed to breast cancer.
2. Follow-up began at randomization and includes all deaths after breast cancer.

CEE plus MPA increased deaths after breast cancer
CEE-Alone decreased deaths from breast cancer

---

## Conclusions

- Use of CEE-alone and CEE plus MPA have opposite effects on breast cancer.
- CEE-alone significantly decreases breast cancer incidence and deaths from breast cancer, which persist over decades after discontinuing use.
- CEE plus MPA significantly increases breast cancer incidence and associated mortality, which persist over a decade after discontinuing use.
- These findings, in conjunction with other hormone therapy effects on clinical outcomes, should inform clinical decision making.

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Thank you