Randomized Comparison of Adjuvant Aromatase Inhibitor Exemestane plus Ovarian Function Suppression vs Tamoxifen plus Ovarian Function Suppression in Premenopausal Women with Hormone Receptor Positive Early Breast Cancer: Joint Analysis of IBCSG TEXT and SOFT

Olivia Pagani, MD
on behalf of the
TEXT and SOFT Investigators and
International Breast Cancer Study Group (IBCSG)
TEXT and SOFT

- Trials coordinated by IBCSG
- Collaboration of the Breast International Group (BIG) and North American Breast Cancer Group (NABCG)
- Financial support/drug supply: Pfizer, Ipsen, US NCI
Premenopausal Endocrine Therapy

• Optimal adjuvant endocrine therapy for premenopausal women with HR+ breast cancer is uncertain

• Tamoxifen for at least 5 years is a standard of care

• Ovarian function suppression (OFS) may be given in addition

• IBCSG designed TEXT and SOFT to determine optimal endocrine therapy in premenopausal women with HR+ breast cancer
Does adjuvant therapy with the aromatase inhibitor (AI) exemestane improve disease-free survival relative to tamoxifen in premenopausal women treated with OFS for HR+ breast cancer?
TEXT and SOFT Designs

Enrolled: Nov03-Apr11

- Premenopausal
- ≤12 wks after surgery
- Planned OFS
- No planned chemo
  OR planned chemo

- Premenopausal
- ≤12 wks after surgery
- No chemo
  OR

- Remain premenopausal
  ≤ 8 mos after chemo

RANDOMIZE

Tamoxifen+OFS x 5y
Exemestane+OFS x 5y

RANDOMIZE

Tamoxifen x 5y

Tamoxifen+OFS x 5y
Exemestane+OFS x 5y

Joint Analysis
(N=4690)

Tamoxifen+OFS x 5y
Exemestane+OFS x 5y

OFS=ovarian function suppression

Median follow-up 5.7 years

Suppression of Ovarian Function Trial (N=3066)

Enrolled: Nov03-Apr11

Median follow-up 5.7 years

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Eligibility

• Premenopausal women with HR+ (ER and/or PgR≥10%) invasive breast cancer confined to breast +/- axillary nodes

• Proper local-regional treatment with no residual disease

• Randomized within 12 weeks of surgery for all women in TEXT and women in SOFT who did not receive chemotherapy

• Women in SOFT who received prior (neo)adjuvant chemotherapy randomized ≤8 months of chemotherapy completion when premenopausal status demonstrated
  – These patients were permitted to receive oral endocrine therapy prior to randomization

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Treatments

Protocol treatment was for 5 years from randomization

• **Ovarian Function Suppression**
  
  **TEXT**
  
  • All women started with GnRH agonist triptorelin (IM q28d)
  • Triptorelin initiated concurrently with chemotherapy, if it was given
  • Bilateral oophorectomy or irradiation as alternatives to triptorelin after 6 months

**SOFT**

• Choice of OFS method

• **Oral endocrine therapy**
  
  • Exemestane 25 mg daily, or
  • Tamoxifen 20 mg daily
  • In TEXT started 6 to 8 weeks after initiation of OFS, or after chemotherapy if given

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Study Procedures

• Adjuvant trastuzumab allowed, if indicated
• Annual mammography and bone densitometry recommended
• Bisphosphonates not permitted unless T-score ≤ -1.5 or participating in a randomized adjuvant trial
• Targeted AEs and other grade 3-5 AEs (CTCAE v3.0)
• Quality-of-life self-assessment of global and symptom-specific indicators

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Endpoints

Primary
Disease-free survival (DFS)
– Invasive recurrence (local, regional, distant)
– Invasive contralateral breast cancer
– Second (non-breast) invasive malignancy
– Death without prior cancer event

Secondary
Breast cancer-free interval (BCFI)
– Invasive recurrence or contralateral breast cancer
Distant recurrence-free interval (DRFI)
– Distant recurrence
Overall survival (OS)
– Death from any cause

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Statistical Considerations

• DFS event rate much lower than anticipated (Regan et al., The Breast 2013)

• Protocols amended in 2011 (before efficacy data available):
  – For the E+OFS v. T+OFS comparison, a planned secondary joint analysis of TEXT & SOFT was promoted to become the primary analysis
  – With data cut-off in late-2013 (>5 years median follow-up), power 84% for HR=0.75 (2-sided $\alpha=0.05$) in the combined analysis
  – No interim analyses

• ITT analysis; stratified by trial, chemotherapy use, nodal status

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### Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No chemo TEXT (N=1053)</th>
<th>No chemo SOFT (N=943)</th>
<th>Chemo TEXT (N=1607)</th>
<th>Prior chemo SOFT (N=1087)</th>
<th>Overall (N=4690)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;40 yr</td>
<td>16%</td>
<td>9%</td>
<td>30%</td>
<td>49%</td>
<td>27%</td>
</tr>
<tr>
<td>LN +</td>
<td>21%</td>
<td>8%</td>
<td>66%</td>
<td>57%</td>
<td>42%</td>
</tr>
<tr>
<td>T-size &gt;2cm</td>
<td>19%</td>
<td>15%</td>
<td>53%</td>
<td>47%</td>
<td>36%</td>
</tr>
<tr>
<td>HER2 +</td>
<td>5%</td>
<td>3%</td>
<td>17%</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>Surgery to random. (median)</td>
<td>1.5 mo</td>
<td>1.8 mo</td>
<td>1.2 mo</td>
<td>8.0 mo</td>
<td>1.6 mo</td>
</tr>
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</table>
Exemestane+OFS Improved DFS

5.7 years median follow-up

Difference 3.8% at 5 years

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<table>
<thead>
<tr>
<th></th>
<th>No. Patients</th>
<th>HR (95% CI)</th>
<th>5-yr DFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E+OFS</td>
<td>T+OFS</td>
<td>E+OFS</td>
</tr>
<tr>
<td>All Patients</td>
<td>2346</td>
<td>2344</td>
<td>91.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chemotherapy, TEXT</td>
<td>526</td>
<td>527</td>
<td>96.1</td>
</tr>
<tr>
<td>No chemotherapy, SOFT</td>
<td>470</td>
<td>473</td>
<td>95.8</td>
</tr>
<tr>
<td>Chemotherapy, TEXT</td>
<td>806</td>
<td>801</td>
<td>89.8</td>
</tr>
<tr>
<td>Prior chemotherapy, SOFT</td>
<td>544</td>
<td>543</td>
<td>84.3</td>
</tr>
<tr>
<td>Lymph Node Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1362</td>
<td>1350</td>
<td>95.1</td>
</tr>
<tr>
<td>Positive</td>
<td>984</td>
<td>994</td>
<td>85.6</td>
</tr>
</tbody>
</table>
## Sites of First Failure

<table>
<thead>
<tr>
<th>Site of First Failure (DFS event)</th>
<th>E+OFS (N=2346)</th>
<th>T+OFS (N=2344)</th>
<th>Overall (N=4690)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All DFS events N (%)</td>
<td>216 (9.2)</td>
<td>298 (12.7)</td>
<td>514</td>
</tr>
<tr>
<td>Local</td>
<td>23 (1.0)</td>
<td>28 (1.2)</td>
<td>51</td>
</tr>
<tr>
<td>Contralateral breast</td>
<td>9 (0.4)</td>
<td>27 (1.2)</td>
<td>36</td>
</tr>
<tr>
<td>Regional ± above</td>
<td>9 (0.4)</td>
<td>30 (1.3)</td>
<td>39</td>
</tr>
<tr>
<td>Soft tissue / distant LN ± above</td>
<td>4 (0.2)</td>
<td>6 (0.3)</td>
<td>10</td>
</tr>
<tr>
<td>Bone ± above</td>
<td>54 (2.3)</td>
<td>65 (2.8)</td>
<td>119</td>
</tr>
<tr>
<td>Viscera ± above</td>
<td>75 (3.2)</td>
<td>105 (4.5)</td>
<td>180</td>
</tr>
<tr>
<td>Second (non-breast) malignancy</td>
<td>38 (1.6)</td>
<td>32 (1.4)</td>
<td>70</td>
</tr>
<tr>
<td>Death without prior cancer event</td>
<td>2 (0.1)</td>
<td>5 (0.2)</td>
<td>7</td>
</tr>
<tr>
<td>Death with recurrence suspected</td>
<td>2 (0.1)</td>
<td>--</td>
<td>2</td>
</tr>
</tbody>
</table>

60% of first failures involved distant sites
Exemestane+OFS Reduced Recurrence

- 4% absolute improvement in 5-yr freedom from breast cancer for exemestane+OFS
- No significant difference in overall survival

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Some women have excellent prognosis with highly-effective endocrine therapy alone. >97% breast cancer-free at 5 years when treated with exemestane+OFS.
Women Who Received Chemotherapy

Absolute improvement with exemestane+OFS

- 5-yr freedom from breast cancer: 5.5% in TEXT and 3.9% in SOFT
- 5-yr freedom from distant recurrence: 2.6% in TEXT and 3.4% in SOFT

66% N+; 53% T-size >2cm; 30% <40 years

57% N+; 47% T-size >2cm; 49% <40 years
### Selected Adverse Events

<table>
<thead>
<tr>
<th>CTCAE v3.0</th>
<th>Exemestane+OFS (N=2318)</th>
<th>Tamoxifen+OFS (N=2325)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Depression</td>
<td>50%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>89%</td>
<td>11%</td>
</tr>
<tr>
<td>Osteoporosis (% T&lt; -2.5)</td>
<td>39% (13%)</td>
<td>0.4%</td>
</tr>
<tr>
<td>Fracture</td>
<td>6.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Cardiac ischemia/infarction</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>1.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>CNS ischemia</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>CNS bleeding</td>
<td>0.6%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Hot flushes/flashes</td>
<td>92%</td>
<td>10%</td>
</tr>
<tr>
<td>Sweating</td>
<td>55%</td>
<td>--</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>52%</td>
<td>--</td>
</tr>
<tr>
<td>Libido decrease</td>
<td>45%</td>
<td>--</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>31%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>13%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
Adverse Events and QOL

• AE profiles comparable with postmenopausal women
• Incidence of targeted grade 3-4 AEs similar (31% and 29%)
• Early cessation of all assigned treatments more frequent with exemestane+OFS (16% vs. 11%)
• Patients self-report differential effects, but overall quality of life did not favor either treatment (*Abstract #557*)
Conclusions

- Exemestane+OFS, as compared with tamoxifen+OFS, significantly improves DFS, BCFI and DRFI and is a new treatment option for premenopausal women with HR+ early breast cancer.

- No significant difference in overall survival, conclusions premature at this early point in follow-up of HR+ breast cancer.

- Side effect profile of exemestane+OFS mirrors that seen with AIs in postmenopausal women.

- Some premenopausal women diagnosed with HR+ breast cancer have an excellent prognosis with highly-effective endocrine therapy alone.

- Long-term follow-up needed.
More from TEXT and SOFT

• Manuscript published online at *New England Journal of Medicine*

• Monday General Poster session:
  – Quality of life Board #21 (Abstract #557)
  – SOFT-EST estrogen suppression substudy Board #49 (Abstract #585)

• OFS question from SOFT (tamoxifen+OFS vs tamoxifen) end of 2014

Presented by: Olivia Pagani, MD
5,000+ women who participated in the trials

- Physicians, nurses, data and trial coordinators, and pathologists in 510 centers worldwide
- Pfizer and Ipsen for drug supply and financial support
- IBCSG Data Management Center, Coordinating Center, Central Pathology Office, Statistical Center
- STP Steering Committee, DSMC

IBCSG
ANZBCTG
SAKK
GOCCHI
CEEEOG
EORTC
GBG
ICORG
NCRI/ICR-CTSU
SOLTI

US NCI
Alliance (CALGB, ACOSOG, NCCTG)
SWOG
ECOG-ACRIN
NRG (NSABP, RTOG)
NCIC-CTG
NCI CTSU

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