Randomized comparison of adjuvant tamoxifen plus ovarian function suppression versus tamoxifen in premenopausal women with hormone-receptor-positive (HR+) early breast cancer: The SOFT trial

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for SOFT Investigators,
International Breast Cancer Study Group,
Breast International Group,
and North American Breast Cancer Group
SOFT

• Trial coordinated by

• Collaboration of

• Financial support/drug supply: Pfizer, Ipsen, US NCI
Premenopausal HR+ Early Breast Cancer

- Adjuvant tamoxifen for ≥ 5 years is recommended
- The value of ovarian function suppression or ablation (OFS) for women who receive tamoxifen (T) is uncertain
- Women who develop chemotherapy-induced ovarian suppression (amenorrhea) have a reduced risk of relapse
- Likelihood of chemotherapy-induced amenorrhea correlated with older age; less likely in women < 35 years age

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Outcomes from Premenopausal Adjuvant Chemotherapy Trials with no Hormonal Rx

Goldhirsch A et al. JNCI Monogr 2001;30:44-51

Hazard Ratio of Relapse

- ER-, <35
- ER+, <35
- ER-, 35+
- ER+, 35+

Hazard Ratio of Relapse

0.5 1 1.5 2
Questions in Premenopausal Hormone-Receptor Positive Early Breast Cancer

- What is the value of adding OFS to adjuvant tamoxifen in premenopausal women?
- What is role of adjuvant therapy with the aromatase inhibitor (AI) exemestane + OFS in premenopausal women?
**SOFT: SUPPRESSION of OVARIAN FUNCTION TRIAL**

*Premenopausal ER+ve and/or PR+ve Breast Cancer*

3047 Patients Randomized in ITT, Dec 2003 - Jan 2011

**Two Patient Cohorts (stratified)**

- **No Chemotherapy** (47%)
  - Premenopausal, within 12 weeks of surgery
  - (Median time since surgery = **1.8 months**)

- **Prior Chemotherapy** (53%)
  - Premenopausal* after completing chemotherapy;
  - Randomization within 8 months of completion
  - (Median time since surgery = **8.0 months**)

→ **Tamoxifen x 5y** (n=1018)
→ **Tamoxifen+OFS x 5y** (n=1015)
→ **Exemestane+OFS x 5y** (n=1014)

**OFS=ovarian function suppression**
(GnRH triptorelin, oophorectomy or irradiation)

*According to locally-determined E₂ level in premenopausal range*
Protocol 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 ca
Distant recurrence-free interval (DRFI)
Overall survival
Statistical Considerations

• ITT analysis, stratified by chemo (yes/no), nodal status (-/+)

• Original plan for three pair-wise comparisons to detect HR=0.75 with analysis after 783 DFS events ($\alpha=0.0167$)

• Enrolled patients older, lower risk, better DFS than anticipated

• Protocol amendment 2011 (before efficacy data)
Statistical Considerations
Post-Amendment

• Primary analysis: T+OFS vs T
• After median follow-up of at least 5 years
• Anticipated 186 DFS events, power 80% for HR=0.665 comparing T+OFS vs T (two sided $\alpha=0.05$)
• Analysis according to use of prior chemotherapy (no/yes) was prospectively planned
• E+OFS vs T became secondary objective

(E+OFS vs T+OFS by combined analysis with TEXT Pagani et al, NEJM 2014)
## Primary Analysis: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No chemo 47% (n=949)</th>
<th>Prior Chemo 53% (n=1084)</th>
<th>Overall (n=2033)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>46 y</td>
<td>40 y</td>
<td>43 y</td>
</tr>
<tr>
<td>Lymph Node +ve</td>
<td>9%</td>
<td>57%</td>
<td>35%</td>
</tr>
<tr>
<td>Tumor &gt; 2 cm</td>
<td>14%</td>
<td>47%</td>
<td>32%</td>
</tr>
<tr>
<td>Grade 1</td>
<td>41%</td>
<td>14%</td>
<td>27%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>7%</td>
<td>35%</td>
<td>22%</td>
</tr>
<tr>
<td>HER2+ve</td>
<td>4%</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>Median time since surgery</td>
<td>1.8 mo</td>
<td>8.0 mo</td>
<td>3.2 mo</td>
</tr>
</tbody>
</table>
Primary Analysis: Disease-free Survival

5.6 years median follow-up

Primary analysis in overall population not significant \( (p=0.10) \)
Multivariable Cox model \( \text{HR}=0.78 \) \( (95\% \text{ CI } 0.62\text{-}0.98) \) \( p=0.03 \)
Secondary Objectives

T+OFS v T: 19% relative reduction in BC recurrence, p=0.09
E+OFS v T: 36% relative reduction in BC recurrence, 5y BCFI >90%
Events in Primary Analysis and by Chemotherapy Stratum
5.6 years median follow-up

<table>
<thead>
<tr>
<th>Primary Analysis T+OFS vs T (n=2033)</th>
<th>No chemo (n=949)</th>
<th>Prior Chemo (n=1084)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS event</td>
<td>299</td>
<td>70</td>
</tr>
<tr>
<td>BCFI event</td>
<td>260</td>
<td>47</td>
</tr>
<tr>
<td>DRFI event</td>
<td>185</td>
<td>13</td>
</tr>
<tr>
<td>2\textsuperscript{nd} non-breast ca as DFS event</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>Deaths</td>
<td>106 (5%)</td>
<td>10</td>
</tr>
</tbody>
</table>
Premenopausal No Chemotherapy

Cohort selected for low risk clinicopathologic features
90% ≥ age 40yr, 91% node negative, 85% tumor ≤ 2cm, 41% grade 1
Premenopausal after Prior Chemotherapy

**Prior Chemotherapy Breast Cancer-Free Interval**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts</th>
<th>Events</th>
<th>5-yr %</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>542</td>
<td>116</td>
<td>78.0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>T+OFS</td>
<td>542</td>
<td>97</td>
<td>82.5</td>
<td>0.78</td>
<td>0.60-1.02</td>
</tr>
<tr>
<td>E+OFS</td>
<td>544</td>
<td>80</td>
<td>85.7</td>
<td>0.65</td>
<td>0.49-0.87</td>
</tr>
</tbody>
</table>

**Prior Chemotherapy Distant Recurrence-Free Interval**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Pts</th>
<th>Events</th>
<th>5-yr %</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>542</td>
<td>90</td>
<td>83.6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>T+OFS</td>
<td>542</td>
<td>82</td>
<td>84.8</td>
<td>0.87</td>
<td>0.64-1.17</td>
</tr>
<tr>
<td>E+OFS</td>
<td>544</td>
<td>67</td>
<td>87.8</td>
<td>0.72</td>
<td>0.52-0.98</td>
</tr>
</tbody>
</table>

T+OFS v T: Absolute improvement in 5-yr BCFI of 4.5%
E+OFS v T: Absolute improvement in 5-yr BCFI of 7.7% and 5-yr DRFI of 4.2%
All women < 35 years of age

350 patients (11.5%) under age 35
94% received chemotherapy in this age group
Treatment Continuation

- 26% pts continuing some or all protocol-assigned treatment
- Overall 19% ceased tamoxifen early (+/- other Rx started)
- OFS entirely by GnRH agonist triptorelin for 81% patients
- Adherence with OFS
  - 91% at 1 year
  - 85% at 2 years
  - 78% at 4 years
## Selected Adverse Events

<table>
<thead>
<tr>
<th>CTCAE v3.0</th>
<th>T+OFS (N=1005)</th>
<th>T (N=1006)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hot flushes/flashes</td>
<td>93%</td>
<td>13%</td>
</tr>
<tr>
<td>Sweating</td>
<td>62%</td>
<td>--</td>
</tr>
<tr>
<td>Libido decrease</td>
<td>47%</td>
<td>--</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>50%</td>
<td>--</td>
</tr>
<tr>
<td>Depression</td>
<td>52%</td>
<td>4%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>57%</td>
<td>5%</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>75%</td>
<td>5%</td>
</tr>
<tr>
<td>Osteoporosis (% T&lt; -2.5)</td>
<td>20% (6%)</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23%</td>
<td>7%</td>
</tr>
<tr>
<td>Glucose intolerance (diabetes)*</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Hyperglycaemia*</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Any Gr 3- 4 targeted AE</td>
<td>--</td>
<td>31%</td>
</tr>
</tbody>
</table>

*Added during trial conduct, may be under-reported
SOFT: Conclusions

• The overall premenopausal population did not benefit from the addition of OFS -- some do very well with tamoxifen alone.

• For women at sufficient risk of recurrence to warrant adjuvant chemotherapy and who retained premenopausal estradiol, addition of OFS to tamoxifen reduced recurrence.

• OFS enables treatment with an aromatase inhibitor which further reduced recurrence in the higher-risk cohort.

• Addition of OFS increases menopausal symptoms, depression, hypertension, diabetes and osteoporosis.
SOFT: Conclusions

• Benefit from OFS is most striking in women under age 35.

• Long-term follow-up in SOFT is crucial to assess overall survival and late toxicities -- future analyses planned.

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

• Translational studies are vital (e.g. multigene assays to further tailor recommendations). SOFT is the largest trial ever conducted in young women and patients consented to prospective tissue collection. We appreciate further efforts at sites where block provision is not standard.
3,000+ women who participated in SOFT

- Physicians, nurses, data and trial coordinators, and pathologists in 426 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
CEEOG
EORTC
GBG
ICORG
NCRI/ICR-CTSU
SOLTI

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