Adjuvant endocrine therapy after SOFT and TEXT trials

Marco Colleoni, Milan (I)
Women diagnosed with hormone receptor–positive breast cancer who are pre- or perimenopausal should be offered adjuvant endocrine therapy with:

– Tamoxifen for an initial duration of 5 years

J Clin Oncol 2014;32: 2255-69
Optimal endocrine adjuvant treatment for pre-menopausal women in 2015

• Tamoxifen

• Tamoxifen and ovarian function suppression (OFS)

• Exemestane and OFS
Tamoxifen

About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease, by entry age

Lancet 2005; 365: 1687–1717
### Tamoxifen

**About 5 years of tamoxifen versus not in ER-positive (or ER-unk) disease, by entry age**

#### Recurrence/woman-years

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/woman-years</th>
<th>Tamoxifen events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated tamoxifen</td>
<td>Adjusted control</td>
<td>Logrank</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(a) Dose of tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg/day</td>
<td>841/30896 (2.7%/y)</td>
<td>119/27508 (4.4%/y)</td>
<td>−237.8</td>
</tr>
<tr>
<td>30–40 mg/day</td>
<td>571/16279 (3.6%/y)</td>
<td>74/13540 (5.5%/y)</td>
<td>−146.7</td>
</tr>
<tr>
<td><strong>(b) Presence or absence of cytotoxics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chem with Tam vs Chem alone</td>
<td>223/3926 (5.7%/y)</td>
<td>27/5297 (1.1%/y)</td>
<td>−54.5</td>
</tr>
<tr>
<td>Chem then Tam vs Chem alone</td>
<td>242/8254 (2.9%/y)</td>
<td>319/7662 (4.2%/y)</td>
<td>−48.6</td>
</tr>
<tr>
<td>Tam alone vs Nil (no adjuvant)</td>
<td>947/34795 (2.7%/y)</td>
<td>1352/30387 (4.4%/y)</td>
<td>−281.4</td>
</tr>
<tr>
<td><strong>(c) Entry age</strong> (trend $\chi^2 = 3.8; 2p = 0.05$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;40</td>
<td>113/2321 (3.5%/y)</td>
<td>17/52660 (0.7%/y)</td>
<td>−36.8</td>
</tr>
<tr>
<td>40–49</td>
<td>275/9461 (2.9%/y)</td>
<td>35/8776 (0.4%/y)</td>
<td>−49.0</td>
</tr>
<tr>
<td>50–59</td>
<td>452/14694 (3.1%/y)</td>
<td>57/13114 (4.4%/y)</td>
<td>−94.5</td>
</tr>
<tr>
<td>60–69</td>
<td>498/17399 (2.9%/y)</td>
<td>72/44546 (5.0%/y)</td>
<td>−163.0</td>
</tr>
<tr>
<td>≥70</td>
<td>70/2105 (3.3%/y)</td>
<td>10/1867 (2.7%/y)</td>
<td>−25.0</td>
</tr>
<tr>
<td>Age unknown</td>
<td>1412/46975 (3.0%/y)</td>
<td>419/40148 (4.7%/y)</td>
<td>−384.5</td>
</tr>
</tbody>
</table>

#### Breast cancer mortality/women

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths/women</th>
<th>Tamoxifen deaths</th>
<th>Ratio of annual death rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allocated tamoxifen</td>
<td>Adjusted control</td>
<td>Logrank</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(a) Dose of tamoxifen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 mg/day</td>
<td>561/3550 (21.9%)</td>
<td>77/3530 (15.8%)</td>
<td>−116.5</td>
</tr>
<tr>
<td>30–40 mg/day</td>
<td>475/1675 (27.3%)</td>
<td>574/1631 (35.2%)</td>
<td>−90.5</td>
</tr>
<tr>
<td><strong>(b) Presence or absence of cytotoxics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chem with Tam vs Chem alone</td>
<td>168/488 (34.4%)</td>
<td>212/462 (45.9%)</td>
<td>−41.7</td>
</tr>
<tr>
<td>Chem then Tam vs Chem alone</td>
<td>142/1204 (11.8%)</td>
<td>181/1176 (15.4%)</td>
<td>−21.3</td>
</tr>
<tr>
<td>Tam alone vs Nil (no adjuvant)</td>
<td>708/3533 (20.0%)</td>
<td>955/3523 (27.1%)</td>
<td>−144.0</td>
</tr>
<tr>
<td><strong>(c) Entry age</strong> (trend $\chi^2 = 0.4; 2p = 0.1$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;40</td>
<td>119/3938 (29.9%)</td>
<td>174/1177 (17.7%)</td>
<td>−21.9</td>
</tr>
<tr>
<td>40–49</td>
<td>173/1119 (15.5%)</td>
<td>219/1139 (19.2%)</td>
<td>−24.8</td>
</tr>
<tr>
<td>50–59</td>
<td>330/1591 (20.7%)</td>
<td>394/1535 (25.7%)</td>
<td>−45.2</td>
</tr>
<tr>
<td>60–69</td>
<td>379/1822 (20.8%)</td>
<td>527/1789 (29.5%)</td>
<td>−87.3</td>
</tr>
<tr>
<td>≥70</td>
<td>62/266 (23.3%)</td>
<td>89/286 (31.3%)</td>
<td>−13.6</td>
</tr>
<tr>
<td>Age unknown</td>
<td>1018/5225 (19.5%)</td>
<td>1348/5161 (26.1%)</td>
<td>−207.0</td>
</tr>
</tbody>
</table>

**Lancet 2005; 365: 1687–1717**

**Marco Colleoni - 11th Meet The Professor, Advanced International Breast Cancer Course - Padua, September 11th, 2015**
OFS

Overview: effects of ovarian ablation in the absence of chemotherapy

Recurrence-free survival

- Node-negative, age <50: Ovarian ablation
  - 84.0%
  - 80.3%
  - 75.4%
  - 73.5%
  - 66.5%

- Control
  - 82.5%
  - 66.5%
  - 51.8%
  - 44.1%
  - 37.4%
  - 30.5%
  - 24.0%

Difference:
- Node-negative, age <50: Ovarian ablation
  - 8.9 SD 4.2 events per 100 (logrank 2p = 0.01)

- Control
  - 13.4 SD 3.8 events per 100 (logrank 2p = 0.0002)

Overall survival

- Node-negative, age <50: Ovarian ablation
  - 88.7%
  - 88.6%
  - 82.6%
  - 76.6%
  - 78.7%

- Control
  - 88.6%
  - 82.6%
  - 78.7%
  - 76.6%
  - 70.9%

Difference:
- Node-negative, age <50: Ovarian ablation
  - 5.6 SD 4.0 deaths per 100 (logrank 2p = 0.01)

- Control
  - 12.5 SD 3.9 deaths per 100 (logrank 2p = 0.0007)

Lancet 1996; 348: 1189–96
OFS
LHRH analogue + Tamoxifen advanced disease

PFS

OS

OFS
IBCSG 13-93
Accrual: 1993-1999

Premenopausal, node-positive breast cancer

Randomize

\[ \text{ACx4} \rightarrow \text{CMFx3} \]
\[ \text{ACx4} \rightarrow \text{Gap} \rightarrow \text{CMFx3} \]
\[ \text{ACx4} \rightarrow \text{CMFx3} \rightarrow \text{Tam} \]
\[ \text{ACx4} \rightarrow \text{Gap} \rightarrow \text{CMFx3} \rightarrow \text{Tam} \]

\[ \text{n=1,246} \]

J Clin Oncol 2006; 24:1332-41
OFS
Trial 13-93: Tamoxifen Question
ER+ and ER-, Disease-Free Survival

ER+

ER-

J Clin Oncol 2006; 24:1332-41
OFS

IBCSG Trial 13-93:
Amenorrhea and Tamoxifen for ER+

Percent Alive and Disease-Free

Years from Randomization

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>5 Yr % (S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea</td>
<td>286</td>
<td>70</td>
<td>80 (2)</td>
</tr>
<tr>
<td>No Amenorrhea</td>
<td>46</td>
<td>17</td>
<td>65 (7)</td>
</tr>
</tbody>
</table>

Stratified Logrank p-value = 0.05

J Clin Oncol 2006; 24:1332-41
OFS
Overview: addition of LHRH agonist to tamoxifen

Lancet 2007; 369: 1711–23
ZIPP Trial
Side effects of OFS

J Clin Oncol 2003; 21: 1836-1844
ZIPP Trial
Side effects of OFS

The Goserelin group reported significantly higher problem levels in terms of:

- Vasomotor symptoms
- Vaginal dryness
- Changes in body Image
- Sleep Disturbances
- Sexual disfunctions

J Clin Oncol 2003; 21: 1836-1844
J Clin Oncol 2001; 19: 2788-2796
## OFS Panel Voting St Gallen 2013

### Endocrine Therapy: Establishing Standards for Premenopausal

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian function suppression (OFS) should be added to Tam:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In all patients?</td>
<td>14.9</td>
<td>80.9</td>
<td>4.2</td>
</tr>
<tr>
<td>In the young (e.g. &lt; 40 yr)?</td>
<td>40.9</td>
<td>50.0</td>
<td>9.1</td>
</tr>
<tr>
<td>AI + OFS is a valid option in all patients?</td>
<td>6.3</td>
<td>87.5</td>
<td>6.3</td>
</tr>
</tbody>
</table>
OFS

SOFT [IBCSG 24-02, BIG 2-02]

Premenopausal, ER and/or PgR ≥ 10%

Patients who remain premenopausal within 6 months after CT, or receive tamoxifen alone as adequate treatment

- Any CT
  - Tamoxifen x 5y
  - OFS + Tamoxifen x 5y
  - OFS + Exemestane x 5y

- No CT
  - OFS (ovarian function suppression) = triptorelin x 5 y, oophorectomy or ovarian RT

Final Accrual: 3066 patients
Adjuvant OFS in premenopausal breast cancer: primary analysis

NEJM 2015; 372: 436-446
Adjuvant OFS in premenopausal breast cancer: secondary objectives

NEJM 2015; 372: 436-446
After Prior Chemotherapy

T+OFS v T: Absolute improvement in 5-yr BCFI of 4.5%

NEJM 2015; 372: 436-446
All women < 35 years of age

94% received chemotherapy

NEJM 2015; 372: 436-446
## Selected Adverse Events

<table>
<thead>
<tr>
<th>CTCAE v3.0</th>
<th>T+OFS (N=1005)</th>
<th></th>
<th>T (N=1006)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hot flushes/flushes</td>
<td>93%</td>
<td>13%</td>
<td>80%</td>
<td>8%</td>
</tr>
<tr>
<td>Sweating</td>
<td>62%</td>
<td>--</td>
<td>48%</td>
<td>--</td>
</tr>
<tr>
<td>Libido decrease</td>
<td>47%</td>
<td>--</td>
<td>42%</td>
<td>--</td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>50%</td>
<td>--</td>
<td>42%</td>
<td>--</td>
</tr>
<tr>
<td>Depression</td>
<td>52%</td>
<td>4%</td>
<td>47%</td>
<td>4%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>57%</td>
<td>5%</td>
<td>46%</td>
<td>3%</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>75%</td>
<td>5%</td>
<td>69%</td>
<td>6%</td>
</tr>
<tr>
<td>Osteoporosis (% T&lt; -2.5)</td>
<td>20% (6%)</td>
<td>0.3%</td>
<td>12% (3%)</td>
<td>0.1%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23%</td>
<td>7%</td>
<td>17%</td>
<td>5%</td>
</tr>
<tr>
<td>Glucose intolerance (diabetes)*</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hyperglycaemia*</td>
<td>5%</td>
<td>1%</td>
<td>2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Any Gr 3- 4 targeted AE</td>
<td>--</td>
<td>31%</td>
<td>--</td>
<td>24%</td>
</tr>
</tbody>
</table>

*NEJM 2015; 372: 436-446*
### OFS Panel Voting St Gallen 2013

**Endocrine Therapy: Establishing Standards for Premenopausal**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Abstain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian function suppression (OFS) should be added to Tam:</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• In all patients?</td>
<td>14.9</td>
<td>80.9</td>
<td>4.2</td>
</tr>
<tr>
<td>• In the young (e.g. &lt; 40 yr)?</td>
<td>40.9</td>
<td>50.0</td>
<td>9.1</td>
</tr>
<tr>
<td>AI + OFS is a valid option in all patients?</td>
<td>6.3</td>
<td>87.5</td>
<td>6.3</td>
</tr>
</tbody>
</table>
Ais plus OFS
DFS for women who received adjuvant therapy by zoledronic acid versus no zoledronic acid and tamoxifen vs anastrozole (ABCSG-12)

Ais plus OFS
TEXT and SOFT
Tamoxifen vs. Exemestane
n=4,690

RANDOMIZE

RANDOMIZE

Tam+OFS

Tam+OFS

Exe+OFS

Exe+OFS
Ais plus OFS
TEXT and SOFT
Exemestane+OFS improved DFS

Difference 3.8% at 5 years

5.7 years median follow-up

NEJM 2014; 371:107-118
Ais plus OFS
TEXT and SOFT
Exemestane+OFS improved BCFI and DRFI

5.7 years median follow-up

NEJM 2014; 371:107-118
## 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>
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</td>
<td>39%</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>N=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>

NEJM 2014; 371:107-118
Exemestane+OFS, as compared with tamoxifen+OFS, significantly improves DFS, BCFI and DRFI.

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

New treatment option for premenopausal women with endocrine-responsive operated breast cancer.
### Endocrine Therapy: Panel voting question

#### Premenopausal: Selection factors

<table>
<thead>
<tr>
<th>Factors arguing for including ovarian function suppression (OFS) are:</th>
<th>Yes %</th>
<th>No %</th>
<th>Abstain %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;= 35 years?</td>
<td>81.0</td>
<td>19.0</td>
<td>0</td>
</tr>
<tr>
<td>Premenopausal oestrogen level after adjuvant chemotherapy?</td>
<td>73.7</td>
<td>26.3</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3?</td>
<td>55.9</td>
<td>38.2</td>
<td>5.9</td>
</tr>
<tr>
<td>Involvement of 4 or more nodes?</td>
<td>89.7</td>
<td>10.3</td>
<td>0</td>
</tr>
<tr>
<td>Adverse result of multi-gene test?</td>
<td>60.0</td>
<td>24.4</td>
<td>15.6</td>
</tr>
<tr>
<td>Factors arguing for use of OFS + AI rather than OFS + tamoxifen are:</td>
<td>Yes %</td>
<td>No %</td>
<td>Abstain %</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>-------</td>
<td>------</td>
<td>-----------</td>
</tr>
<tr>
<td>Age &lt;= 35 years?</td>
<td>59.4</td>
<td>37.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Premenopausal oestrogen level after adjuvant chemotherapy?</td>
<td>43.9</td>
<td>51.2</td>
<td>4.9</td>
</tr>
<tr>
<td>Grade 3?</td>
<td>57.1</td>
<td>35.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Involvement of 4 or more nodes?</td>
<td>92.5</td>
<td>5.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Adverse result of multi-gene test?</td>
<td>65.8</td>
<td>31.6</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT)

Lancet Oncol 2015; 16: 848-58
Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): hot flushes

Lancet Oncol 2015; 16: 848-58
Role for Risk in Predicting Benefit of Endocrine Therapy

- Explore risk as a factor for treatment selection in premenopausal populations in TEXT and SOFT
- Focus on treatment selection for women with HER2-negative disease
- Composite risk score for breast cancer-free interval (BCFI) calculated using Cox model including:
  - age, nodal status, tumor size and grade, ER, PgR, Ki-67
STEPP
Subpopulation Treatment Effect Pattern Plot

• Method to consider the predictive value of markers that are continuous
• Analyzes a series of overlapping subpopulations
• Allows investigation of absolute treatment effect at specific point in follow-up (e.g., 5-year DFS)
STEPP of 5-year BCFI according to Composite Risk Score: Overall HER2-negative

Median Composite Risk Score in Subpopulations

Crafted courtesy of M. Regan
STEPP of 5-year BCFI according to Composite Risk Score: TEXT No Chemo

Exemestane + OFS
Tamoxifen + OFS

Median Composite Risk Score in Subpopulations

5-year BCFI (%)

Courtesy of M. Regan
STEPP of 5-year BCFI according to Composite Risk Score: TEXT Chemo

Median Composite Risk Score in Subpopulations

Exemestane + OFS
Tamoxifen + OFS

5-year BCFI (%)

Median Composite Risk Score in Subpopulations

Exemestane + OFS
Tamoxifen + OFS

5-year BCFI (%)

Courtesy of M. Regan
STEPP of 5-year BCFI according to Composite Risk Score: SOFT No Chemo

Median Composite Risk Score in Subpopulations

- Exemestane + OFS
- Tamoxifen + OFS
- Tamoxifen

Courtesy of M. Regan
STEPP of 5-year BCFI according to Composite Risk Score: SOFT Prior Chemo

Median Composite Risk Score in Subpopulations (SOFT Prior Chemo)

- Exemestane + OFS
- Tamoxifen + OFS
- Tamoxifen

Median Composite Risk Score in Subpopulations (SOFT No Chemo)

- Exemestane + OFS
- Tamoxifen + OFS
- Tamoxifen

Courtesy of M. Regan
STEPP of 5-year BCFI according to Composite Risk Score: TEXT +/- Chemo

Median Composite Risk Score in Subpopulations

Exemestane + OFS
Tamoxifen + OFS
Tamoxifen

Courtesy of M. Regan
STEPP of 5-year BCFI according to Composite Risk Score: SOFT Prior Chemo

Median Composite Risk Score in Subpopulations

- Exemestane + OFS
- Tamoxifen + OFS
- Tamoxifen

0.16 0.51 1.00 1.50
0       
20     
40     
60     
80     
100    
E+OFS
T+OFS
T
5-year BCFI (%)

0 20 40 60 80 100
E+OFS
T+OFS
T

5-year BCFI (%)

Median Composite Risk Score in Subpopulations (SOFT No Chemo)

0.16 0.51 1.00 1.50
0       
20     
40     
60     
80     
100    
E+OFS
T+OFS
T

5-year BCFI (%)

Courtesy of M. Regan
Selection of Endocrine Therapy for Premenopausal Women

• Absolute improvement in 5-year BCFI with Exemestane+OFS, vs. Tam+OFS and vs. Tam alone, extends across most of the continuum of risk in the TEXT and SOFT HER2-negative population

• Exception was women with lowest risk scores had excellent outcomes with all endocrine therapies

• Role for Tam+OFS for women at high risk who do not tolerate an AI with OFS
aTTom Results

10 vs. 5 Years of Tamoxifen:
Recurrence by Treatment

580 vs. 672 recurrences
RR = 0.85 (95% CI, 0.76-0.95)
p = 0.003

An additional 143 vs.
216 recurrences since 2008

At Risk:
Continue 3,468 3,283 3,113 2,933 2,754 2,513 2,210 1,959 1,576 1,239 924 682 463 314 190 101
Stop 3,485 3,305 3,139 2,928 2,714 2,453 2,180 1,908 1,527 1,143 843 618 429 275 164 87

Abbreviations: RR, recurrence rate

ASCO, 2013
Recurrence (A) and breast cancer mortality (B) by treatment allocation for 6846 women with ER-positive disease

The Lancet 2013; 381: 805-816
Treatment duration
Adjuvant Endocrine Therapy for Women with Hormone Receptor-Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update

After 5 years, women should receive additional therapy based on menopausal status.

– If women are pre- or perimenopausal, or if menopausal status is unknown or cannot be determined, they should be offered continued tamoxifen for a total duration of 10 years

J Clin Oncol 2014; 32: 2255-69
St. Gallen 2015
Extended therapy (total 10 years)

Premenopausal:

• Should be considered for premenopausal patients initially node-positive or with other adverse pathology


• Long-term follow-up of TEXT and SOFT is critical to improve decision-making about extended treatment
Conclusion

• Pre-menopausal women with endocrine responsive breast cancer and their physicians must weigh the risks and benefits of all therapeutic options

• Tamoxifen alone, Tamoxifen plus OFS or Exemestane plus OFS can be considered as proper endocrine therapies in premenopausal patients

• Some patients do very well with tamoxifen alone (the only economically viable alternative in many circumstances)
Conclusion

- Exemestane plus OFS might be preferred in premenopausal patients at higher risk, where higher incidence of early recurrence is expected.
- Tamoxifen plus OFS is a reasonable option for premenopausal patients who presented some adverse risk factor to warrant adjuvant chemotherapy and who retained premenopausal estradiol.
- Magnitude of benefit from OFS larger in women under age 35.
Conclusion

• AE profiles for OFS, AIs, tamoxifen and their combination differ
• Women should be evaluated at baseline for risk factors, preferences, expectations, co-morbidities, and monitored during treatment
• Quality of life issues and health status, which might influence the acceptance and adherence to treatment, are key for proper selection of tailored adjuvant endocrine therapies