A long and winding road: Decisions regarding ovarian function suppression and duration of endocrine therapy

Raquel Nunes, MD

• Previous trials were confounded by:
  - inclusion of women who became permanently postmenopausal from chemotherapy or who had an unknown or negative hormone-receptor status.
  - lack of a 5-year tamoxifen control group.

• In postmenopausal women, aromatase inhibitors improve outcome compared to tamoxifen

• The most effective endocrine treatment for premenopausal women was uncertain (added benefit of ovarian function suppression - OFS)
• The Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT) were launched in 2003 to determine:

– if adjuvant endocrine therapy with an aromatase inhibitor improve outcomes when compared to tamoxifen among premenopausal women treated with OFS (SOFT/TEXT)

– The added value of OFS in women taking tamoxifen (SOFT)

### SOFT and TEXT Designs

**SOFT (n=3066)**

- Premenopausal HR+
- ≤12 wks after surgery
- No planned chemo (57%)
- OR planned chemo ≤ 8 mos after chemo (43%)

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

**TEXT (n=2672)**

- Premenopausal HR+
- ≤12 wks after surgery
- No planned chemo (40%)
- OR planned chemo (60%)

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

**Regan M. JCO 2018**

- Median follow-up 8 years

- Median follow-up 9 years

**Primary analysis of combined data of TEXT and SOFT**

- Median follow up 68 months
- Primary endpoint was DFS
In TEXT and SOFT,

- Among premenopausal women with HR positive BC, adjuvant endocrine therapy with exemestane + OFS as compared with tamoxifen + OFS significantly improved DFS, BCFI and DRFI.

- Difference was higher among patients treated with chemotherapy.

• Among premenopausal women with HR positive BC, adjuvant endocrine therapy with exemestane + OFS as compared with tamoxifen + OFS significantly improved DFS, BCFI and DRFI.

• Difference was higher among patients treated with chemotherapy.
• Primary analysis of SOFT compared adjuvant tamoxifen with or without OFS after a follow up of 67 months

• Comparison of exemestane plus OFS with tamoxifen alone became a secondary objective

• Comparison of exemestane plus ovarian suppression with tamoxifen plus ovarian suppression was analyzed by means of a combined analysis with the TEXT data

No difference in the general population

Addition of OFS was beneficial in patients treated with chemotherapy
Benefit more marked in the very young population

- A total of 350 women were younger than 35
- Freedom from breast cancer:
  - Tamoxifen: 67.7%
  - Tamoxifen + OFS: 78.9%
  - Exemestane + OFS: 83.4%  △ 15.7%

In conclusion,

- The addition of ovarian suppression to adjuvant tamoxifen did not significantly improve disease-free survival in the general population.
- In the higher risk cohort of patients who remained premenopausal after chemotherapy, freedom from breast cancer,
  - Tamoxifen+OFS > tamoxifen 4.5%
  - Exemestane + OFS > tamoxifen 7.7%
- Benefit was higher in the very young population
Efficacy of OFS in SOFT-DFS

Benefit was higher in the group treated with chemotherapy

Freedom from distant recurrence in the patients treated with chemotherapy

In HER2 negative disease:
- Tamoxifen: 80.8%
- Tamoxifen + OS: 79.8%
- Exemestane + OS: 86.8%

Francis et al. NEJM 2018
Efficacy of OS in SOFT - Overall Survival

Benefit in the younger population (< 35 yo)

Exemestane or tamoxifen with ovarian suppression
Adverse events

<table>
<thead>
<tr>
<th>AE</th>
<th>Tamoxifen</th>
<th>Tamoxifen + OFS</th>
<th>Exemestane + OFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis/embolism</td>
<td>2.2</td>
<td>2.3</td>
<td>1.2</td>
</tr>
<tr>
<td>MSK</td>
<td>6.7</td>
<td>5.7</td>
<td>7.1</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>3.9</td>
<td>7.2</td>
<td>14.8</td>
</tr>
<tr>
<td>Vaginal dryness/dyspareunia</td>
<td>42/24</td>
<td>49/27</td>
<td>57/31</td>
</tr>
</tbody>
</table>

Update - results

- Adding OFS to tamoxifen significantly improved disease free and overall survival
- Exemestane + OFS further reduced recurrence, including distant recurrence

Individualizing the benefit

Analysis Approach

- 4919 (86%) of 5707 SOFT and TEXT patients with HER2-negative cancers
  - Excluded HER2+ by local or central lab, and/or absent IHC by central lab
- Endpoint: distant recurrence-free interval (DRFI)
  - From randomization until distant recurrence (proven or ambiguous or death officially reported)
  - 5 years freedom from distant recurrence, by Kaplan-Meier estimate
- Assessed magnitude of absolute improvement across a continuum of risk of recurrence
- Examined 4 cohorts of patients, defined by trial and chemotherapy use
Risk features were combined into a single value for each patient.

Characteristics by Cohort (HR+/HER2-)

<table>
<thead>
<tr>
<th>TEXT</th>
<th>SOFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Age 50-59</td>
<td>63%</td>
</tr>
<tr>
<td>60-69</td>
<td>30%</td>
</tr>
<tr>
<td>≥ 70</td>
<td>7%</td>
</tr>
<tr>
<td>Tumor Size &lt; 2 cm</td>
<td>30%</td>
</tr>
<tr>
<td>≥2 cm</td>
<td>70%</td>
</tr>
<tr>
<td>Grade 1</td>
<td>3%</td>
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<td>Grade 2</td>
<td>47%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>46%</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
</tr>
<tr>
<td>Black</td>
<td>30%</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
</tr>
</tbody>
</table>

No Chemotherapy

<table>
<thead>
<tr>
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<th>SOFT</th>
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</thead>
<tbody>
<tr>
<td>Age 50-59</td>
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<tr>
<td>Tumor Size &lt; 2 cm</td>
<td>15%</td>
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<tr>
<td>≥2 cm</td>
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<td>45%</td>
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<tr>
<td>Grade 3</td>
<td>52%</td>
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<tr>
<td>Race</td>
<td>White</td>
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<tr>
<td>Black</td>
<td>27%</td>
</tr>
<tr>
<td>Other</td>
<td>10%</td>
</tr>
</tbody>
</table>

Distant Recurrence-free Interval by Cohort (HR+/HER2-)

<table>
<thead>
<tr>
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<th>SOFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Absolute improvement at 6 yr, ENOSF x T-HFS: 2.5%</td>
<td>3.1%</td>
</tr>
<tr>
<td>No Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Absolute improvement at 6 yr, ENOSF x T-HFS: 2.3%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

STEPP of 8-yr Freedom from Distant Recurrence:

TEXT ChemoTherapy

In the cohort, for %:
- 64.9% 2-HFS
- 8.6% 2-HFS
- 40.3% 2-T-HFS
- 40.3% 2-T-HFS
- 40.3% 2-T-HFS
- 40.3% 2-T-HFS
Benefits more modest in the group not treated with chemotherapy

Conclusions

Among premenopausal women in SOFT & TEXT with HR+HER2-negative cancers, magnitude of absolute improvement in 8-yr freedom from distant recurrence varied widely according to risk of recurrence:

- Those at higher risk may experience 10-15% improvement with E+OFS vs T+OFS or T alone
- Improvement with E+OFS may be 4-5% for patients at intermediate risk, most of whom also received chemotherapy
- For those at low risk, potential benefit of escalating endocrine therapy from T-alone may be minimal, as >97% of these women were without distant recurrence at 8 years
ASCO recommendations

- For women at higher risk for cancer recurrence due to tumor stage (II, III) or biologic features, OFS in addition to adjuvant endocrine therapy was recommended
  - Women younger than 35
- Women with stage I disease for whom chemotherapy is not deemed necessary should not receive OFS
- 5 years of duration
- Monthly administration of GnRH is preferred

No specific data for measuring estradiol levels or monitoring the effectiveness of GnRH agonist therapy
- Monitoring of estradiol levels is not recommended
- Physicians should be alert to signals suggesting recovering of ovarian function

ASCO recommendations - AI vs Tamoxifen

- No survival advantage
- OFS can be administered with AI or Tam
- Inclination to offer an AI at some point in women treated with OS
- Favor OS and AI for higher risk and younger women
HR positive breast cancer has a significant risk of late recurrence

- Despite 5 years of adjuvant therapy, ER-positive tumors retain a substantial risk of late recurrence
- There are more recurrences after 5 years than in the first 5 years after diagnosis

Does extended adjuvant therapy after 5 years of ET improve clinically meaningful outcomes in postmenopausal women with HR positive early breast cancer?
Questions regarding duration

- Extended duration of tamoxifen
  - 5 vs 10 years
- Aromatase inhibitor following tamoxifen
- Extended duration of aromatase inhibitor

ECOG trial, continue tamoxifen vs stop
- Suggestion for benefit of tamoxifen continuation

Scottish trial, 5 years vs indefinite
- Indefinite duration was worse

NSABP B14, 5 vs 10 years
- Continued tamoxifen was worse

Tamoxifen after 5 years of tamoxifen

Adj Tamoxifen To Offer More (aTTOM)

Adj Tamoxifen Longer Ag Shorter (ATLAS)
ATLAS - extended duration of tamoxifen

In aTTOM, a similar 4% decrease in recurrence was seen. Increased risk of PE and EC.

AI after 5 years of tamoxifen

Extended AI after 5 years of therapy that included an AI
Optimal duration of dosing in years 5 to 10

<table>
<thead>
<tr>
<th>Duration</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 x 10</td>
<td>0.02 BB</td>
</tr>
<tr>
<td>7 x 10</td>
<td>1.001 49</td>
</tr>
</tbody>
</table>

- **DFS benefit**: Yes
- **OS benefit**: No
- **New BC benefit**: Yes

**Toxicity**

- In MA 17 R, QOL worse
- Intermittent AI therapy in SOLE was associated with significant less worsening in physical well-being, mood and sleep disturbances
- Bone related AEs more frequent, trend toward higher osteoporotic fractures (0.6% to 2.4%)
- Trend towards higher arterial thrombotic events
Putting it all together

• Relative benefits for extended ET appear most pronounced in women who switch from tamoxifen to an AI
• A substantial fraction of improvement in DFS from continuing AI was driven by prevention of CBC
• Low magnitude of benefit of treatment longer than 7 or 8 years

Survival benefits with extended therapy have been observed in women who received 10 vs 5 years of tamoxifen and 5 years of AI after 5 years of tamoxifen
• No survival benefit for extended AI therapy

Patients who received 5 years of tamoxifen—ASCO guidelines

• Patients who have had an initial 5 years of tamoxifen should have extended endocrine treatment with either tamoxifen or an AI
• Postmenopausal women should incorporate AI-based therapy during their course of adjuvant endocrine treatment, but the best time to start such therapy remains unclear
Patients who received an AI as part of their treatment during the initial 5 years - ASCO guidelines

- Extended AI should be considered in women with node negative disease and higher risk features
- Women with node positive disease should be offered an AI for a total of 10 years
- Women should not receive more than 10 years of total treatment
- As prevention of second breast cancers is a major benefit, this specific risk should inform the decision
- Side effects and absence of survival benefit should be taken into consideration

Burstein et al. in J Clin Oncol 2016

Extended Aromatase Inhibitor treatment following 5 or more years of endocrine therapy: a meta-analysis of 22,192 women in 11 randomised trials

Early Breast Cancer Trialists’ Collaborative Group

All authors declare no relevant conflict of interest

Gray et al. in SABCS 2018

Summary: effect of extended AI therapy after 5-10 yrs on recurrence differs by type of prior endocrine therapy
Recurrence by nodal status – all trials

Node-negative  N 1-3  N 4+ 1000 women 1001 women 1001 women

Graphs showing recurrence rates for node-negative, N 1-3, and N 4+ patients.

Note: The graphs are too small to read clearly in the provided image.