Aromatase inhibitors versus tamoxifen in pre-menopausal women with ER+ early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7,030 women in four randomised trials

Background

- Tamoxifen reduces 15-year breast cancer mortality by one third in ER+ disease (EBCTCG Lancet 2011)

- Aromatase inhibitors (AIs) are even more effective than tamoxifen in post-menopausal women (EBCTCG Lancet 2015)

- AIs may benefit pre-menopausal women treated with ovarian suppression (OFS)
Methods

• Meta-analysis of individual patient data for 4 trials of pre-menopausal women with early stage breast cancer treated with OFS, randomised to AI or tamoxifen

• Primary outcomes were recurrence and cause specific mortality analysed by standard EBCTCG* methods

• 2p<0.05 for primary outcomes
• 2p<0.01 for subgroup analyses

*EBCTCG 1990
<table>
<thead>
<tr>
<th>Trial</th>
<th>Year started</th>
<th>Comparison</th>
<th>N</th>
<th>Median FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCSG 12</td>
<td>1999</td>
<td>Goserelin: (anastrozole vs tamoxifen) ± zoledronic acid x 3yrs</td>
<td>1694</td>
<td>8.0yrs</td>
</tr>
<tr>
<td>TEXT</td>
<td>2003</td>
<td>Triptorelin: (exemestane vs tamoxifen) x 5yrs</td>
<td>2635</td>
<td>9.1yrs</td>
</tr>
<tr>
<td>SOFT</td>
<td>2003</td>
<td>Triptorelin: (exemestane vs tamoxifen) x 5yrs</td>
<td>1998</td>
<td>7.9yrs</td>
</tr>
<tr>
<td>HOBOE</td>
<td>2004</td>
<td>Triptorelin: (letrozole vs tamoxifen) x 5yrs</td>
<td>703</td>
<td>5.3yrs</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>7030</td>
<td>8.0yrs</td>
</tr>
</tbody>
</table>
Chemotherapy by trial

- **ABCSG 12**: only neo-adjuvant allowed (5%)

- **TEXT**: optional, concurrently with OFS (60%)

- **SOFT**: before randomisation but patient had to remain pre-menopausal after completion (54%)

- **HOBOE**: before randomisation (63%)
Recurrence

7030 women
(40% N+)

RR 0.79 (0.69–0.90)
Logrank 2p = 0.0005
10–y gain 2.8% (CI 0.6 – 5.0)

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### Recurrence

**Preliminary findings presented at San Antonio Breast Cancer Symposium®, December 8th 2021**

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<table>
<thead>
<tr>
<th>Year code and study name</th>
<th>Treatment comparison</th>
<th>Events/Women</th>
<th>Al events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alised Al Tam</td>
<td>Logrank</td>
<td>Variance of O-E</td>
</tr>
<tr>
<td>99B1:2 Austrian BCSG XII</td>
<td>Gos:(Ana vs Tam)±Zol 3yr</td>
<td>114/855</td>
<td>103/839</td>
<td>2.9</td>
</tr>
<tr>
<td>03&lt; TEXT / IBCSG 25–02</td>
<td>Trip;(Exe vs Tam) 5yr</td>
<td>137/1324</td>
<td>195/1311</td>
<td>-35.9</td>
</tr>
<tr>
<td>03E SOFT / IBCSG 24–02</td>
<td>Trip;(Exe vs Tam) 5yr</td>
<td>115/999</td>
<td>139/999</td>
<td>-11.2</td>
</tr>
<tr>
<td>041.5 IT Naples HOBOE</td>
<td>Trip;(Let vs Tam) 5yr</td>
<td>38/350</td>
<td>47/353</td>
<td>-6.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>404/3528</td>
<td>484/3502</td>
<td>-51.0</td>
</tr>
</tbody>
</table>

- 99% or <-> 95% confidence intervals

**Heterogeneity between 4 trials: \( \chi^2 = 8.4; p = 0.04 \)**

**AI better**

**Tam better**

**Treatment effect 2p = 0.0005**

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Recurrence by follow up period

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/woman-years Allocated AI</th>
<th>Allocated Tam</th>
<th>Logrank Variance of O-E</th>
<th>Ratio of annual event rates</th>
<th>Ratio AI : Tam</th>
<th>Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>95/6836 (1.4% y)</td>
<td>108/6789 (1.6% y)</td>
<td>-7.7</td>
<td>0.85</td>
<td>0.85</td>
<td>(0.59–1.23)</td>
</tr>
<tr>
<td>2–4</td>
<td>142/9392 (1.5% y)</td>
<td>224/9122 (2.5% y)</td>
<td>-45.2</td>
<td>0.60</td>
<td>0.60</td>
<td>(0.46–0.79)</td>
</tr>
<tr>
<td>5–9</td>
<td>158/8975 (1.8% y)</td>
<td>150/8613 (1.7% y)</td>
<td>-1.2</td>
<td>0.74</td>
<td>0.74</td>
<td>(0.57–0.91)</td>
</tr>
<tr>
<td>10+</td>
<td>9/462 (1.9% y)</td>
<td>2/444 (0.5% y)</td>
<td>3.2</td>
<td>2.6</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>404/25665 (1.6% y)</strong></td>
<td><strong>484/24968 (1.9% y)</strong></td>
<td><strong>-51.0</strong></td>
<td><strong>0.788</strong></td>
<td><strong>0.788</strong></td>
<td><strong>(0.689–0.901)</strong></td>
</tr>
</tbody>
</table>

- 99% or ← 95% confidence intervals

Heterogeneity between 4 categories: $\chi^2_3 = 16.0; p = 0.001$

Treatment effect $2p = 0.0005$

Test for trend: $\chi^2_1 = 3.1; 2p = 0.08$

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**Distant recurrence**

**7030 women**

RR 0.83 (0.71–0.97)  
Logrank 2p = 0.02  
10–y gain 1.9% (CI 0.0 – 3.8)

**BC mortality**

**7030 women**

RR 1.01 (0.82–1.24)  
Logrank 2p = 0.94  
10–y gain 0.4% (CI –1.2 – 1.9)
Breast cancer mortality by follow up period

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women Allocated</th>
<th>Events/Tam Allocated</th>
<th>AI events Logrank Variance O-E</th>
<th>Ratio of annual event rates Ratio Al : Tam</th>
<th>Ratio (&amp; CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow up period, years (trend $\chi^2_1 = 3.4; 2p = 0.07$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>15/6900 (0.2%)</td>
<td>9/6876 (0.1%)</td>
<td>2.6</td>
<td>5.9</td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>85/9738 (0.9%)</td>
<td>69/9651 (0.7%)</td>
<td>7.1</td>
<td>37.5</td>
<td>1.21 (0.79 – 1.84)</td>
</tr>
<tr>
<td>5–9</td>
<td>81/9546 (0.8%)</td>
<td>98/9505 (1.0%)</td>
<td>-9.6</td>
<td>43.5</td>
<td>0.80 (0.54 – 1.19)</td>
</tr>
<tr>
<td>10+</td>
<td>4/513 (0.8%)</td>
<td>3/512 (0.6%)</td>
<td>0.6</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

- 99% confidence intervals

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Subgroup analyses by any recurrence

- 13 analyses investigating possible variability (so p<0.01 for significance)

- Proportional reduction in recurrence did not vary by age, BMI, tumour size, tumour grade, histological subtype, or presence/absence of chemotherapy
Recurrence by nodal status

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/Women Allocated</th>
<th>AI events Allocated</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AI</td>
<td>Tam</td>
<td>Ratio AI : Tam</td>
</tr>
<tr>
<td>N0</td>
<td>144/2132 (6.8%)</td>
<td>188/2999 (9.0%)</td>
<td>-27.3</td>
</tr>
<tr>
<td>N1–3</td>
<td>135/1014 (13.3%)</td>
<td>182/1049 (17.3%)</td>
<td>-25.9</td>
</tr>
<tr>
<td>N4+</td>
<td>124/379 (32.7%)</td>
<td>114/350 (32.6%)</td>
<td>1.7</td>
</tr>
<tr>
<td>N unknown</td>
<td>1/3 (33.3%)</td>
<td>0/4 (0.0%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Total</td>
<td>404/3528 (11.5%)</td>
<td>484/3502 (13.8%)</td>
<td>-51.0</td>
</tr>
</tbody>
</table>

2p = 0.0005

- Heterogeneity between 3 categories: $\chi^2 = 5.5; p = 0.06$
- Al better
- Tam better

Test for trend: $\chi^2 = 3.9; 2p = 0.05$

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Recurrence by nodal status*

**N0**

- RR 0.71 (0.57–0.89)
- Logrank 2p = 0.002
- 10-y gain 2.4% (CI -0.5 – 5.4)

**N1-3**

- RR 0.72 (0.58–0.91)
- Logrank 2p = 0.005
- 10-y gain 4.8% (CI -0.4 – 10.0)

*Smoothed from 5 years

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Bone fractures

Non-breast cancer death

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Conclusions

• Using AI rather than tamoxifen, in pre-menopausal women receiving OFS, reduces the risk of breast cancer recurrence by ~21%
• Reduction in distant recurrence (17%) but no effect on breast cancer mortality or overall survival – longer FU needed
• No increase in non-breast cancer deaths
• More fractures in women receiving AI
Acknowledgements

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)

Trialists who shared their data

7,030 women in 4 trials

The funding bodies