Aromatase Inhibitors as Adjuvant Therapy

In the 68-month follow-up of the ATAC trial, adjuvant anastrozole continued to significantly prolong disease-free survival and time to recurrence and reduce distant metastases and contralateral breast cancers compared to tamoxifen. Data presented at the 2003 and 2004 San Antonio Breast Cancer Symposia demonstrated a greater advantage associated with adjuvant anastrozole in women with ER-positive, PR-negative tumors as compared to ER/PR-positive tumors. BIG FEMTA, a second trial comparing an aromatase inhibitor to tamoxifen, has now also demonstrated with less than three years of follow-up a significant improvement in disease-free survival, time to recurrence and time to distant metastases with adjuvant letrozole. An ongoing clinical trial will now compare the efficacy of two aromatase inhibitors — anastrozole and exemestane — as adjuvant therapy in women with hormone receptor-positive breast cancer.

ATAC TRIAL 68-MONTH ANALYSIS: EFFICACY ENDPOINTS AND TIMES TO RECURRENCE

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td>0.87 (0.77-0.99)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to recurrence</td>
<td>0.88 (0.79-0.98)</td>
<td>0.002</td>
</tr>
<tr>
<td>Overall survival</td>
<td>0.85 (0.75-0.95)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time to breast cancer death</td>
<td>0.94 (0.71-1.25)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**SELECT PUBLICATIONS**

- Buzdar AU, Hortobagyi GN. Analysis of the role of an aromatase inhibitor in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer. Lancet. 2001;358:1459-1466

**RECRUITMENT RATES IN THE ATAC TRIAL, ACCORDING TO ESTROGEN AND PROGESTERONE RECEPTOR STATUS**

<table>
<thead>
<tr>
<th>Recipient status</th>
<th>N</th>
<th>Anastrozole</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td>3,254</td>
<td>2,253</td>
</tr>
<tr>
<td>HR-positive patients</td>
<td>1,737</td>
<td>1,080</td>
<td>0.70</td>
</tr>
<tr>
<td>HR-negative patients</td>
<td>1,517</td>
<td>1,173</td>
<td>0.70</td>
</tr>
</tbody>
</table>

**68-MONTH FOLLOW-UP OF THE ATAC TRIAL**

The simplest interpretation of the ATAC data is that anastrozole prevents one in four of the relapses we see in patients on tamoxifen. That translates into highly significant improvements in disease-free survival, recurrence-free survival and distant disease-free survival. In the hazard ratio analysis plot from the ATAC trial, we’re seeing two peaks with tamoxifen. The first peak is lowered with tamoxifen, but a peak still occurs. In the anastrozole arm, the initial peak is lost and the second peak is flatter. I believe this is the most profoundly important observation in this trial, not only to help make therapeutic decisions but also to give a fascinatinng biological insight. The strongest argument for starting adjuvant endocrine therapy with an aromatase inhibitor is that aromatase almost abolishes that first peak. If you wait two to three years, as some of the trials are reporting, the effects are wonderful, but meanwhile, you’ve lost those patients who will relapse and ultimately die in those trials.

- Michael Baum, MD, DPhil. Breast Cancer Update 2005 (1)

**BIG FEMTA/BIG-1-98: LETROZOLE VERSUS TAMOXIFEN AS ADJUVANT ENDOCRINE THERAPY**

**ENDPOINTS AND TIMES TO RECURRENCE**

- **Event-free survival**: 0.87 (0.77-0.99) p = 0.002
- **Overall survival**: 0.85 (0.75-0.95) p = 0.001
- **Time to breast cancer death**: 0.94 (0.71-1.25) p = 0.64

**ADJUVANT EXEMESTANE VERSUS ANASTROZOLE IN POSTMENOPAUSAL WOMEN**

**Target Accrual: 5,800 (Open)**

**Protocol IDs:** NOVARTIS-2026703019, NCT00066573, CAN-NCIC-MA27, NU-99022, EU-99022, IBCSG-18-98, NCT00004205, IBSCG-1-98

**Protocol Chair:** James N Ingle, MD, Ph: 507-284-8432, Email: ingle.james@mayo.edu

**TRIAL LEAD ORGANIZATIONS:**

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  - **Protocol Chair:** John Saffle, MS, Ph: 713-798-2357, Email: john.saffle@md Anderson.edu

- **LETROZOLE VERSUS TAMOXIFEN**
  - **Target Accrual: 5,800 (Open)**
  - **Protocol Chair:** James N Ingle, MD, Ph: 507-284-8432, Email: ingle.james@mayo.edu

- **LETROZOLE VERSUS TAMOXIFEN**
  - **Target Accrual: 8,028 (Closed)**

**SELECT PUBLICATIONS**


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