Extending Duration of Adjuvant Tamoxifen Treatment to 10 Years
Reduced Risk for Late Breast Cancer Recurrence, Improved Survival

- Greatest additional benefit was seen in the second decade after diagnosis.
- Findings are directly relevant to women taking tamoxifen.
- Women on other ER-positive breast cancer endocrine treatments may benefit.

SAN ANTONIO — Ten years of adjuvant treatment with tamoxifen provided women with estrogen receptor-positive breast cancer greater protection against late recurrence and death from breast cancer compared with the current standard of five years of tamoxifen, according to the international ATLAS (Adjuvant Tamoxifen — Longer Against Shorter) study.

“Five years of adjuvant tamoxifen is already an excellent treatment that substantially reduces the 15-year risk for recurrence and death from estrogen receptor (ER)-positive breast cancer, but ATLAS now shows that 10 years of tamoxifen is even more effective,” said Christina Davies, M.D., a coordinator in the Clinical Trial Service Unit at the University of Oxford in the United Kingdom.

She presented the results at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium, held here Dec. 4-8. The results were simultaneously published in the Lancet.

“The main additional benefit from continuing tamoxifen treatment is to reduce breast cancer mortality during the second decade after diagnosis,” Davies said. “We already knew that five years of tamoxifen reduces breast cancer mortality in this late period by almost a third in comparison with no tamoxifen. We now know that 10 years of tamoxifen is even better, approximately halving breast cancer mortality during the second decade after diagnosis.”

Researchers enrolled 6,846 women with ER-positive breast cancer between 1996 and 2005. Half had node-positive disease. All the women had been using tamoxifen for five
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years, and the researchers randomly assigned them to continue treatment for another five years or to stop immediately.

After about eight years of follow-up, the researchers observed 1,328 breast cancer recurrences and 728 deaths after recurrence. The treatment allocation had little effect on either recurrence rates or death rates during the period five to nine years after diagnosis. However, during the second decade following diagnosis, the women who continued tamoxifen treatment had a 25 percent lower recurrence rate and a 29 percent lower breast cancer mortality rate compared with women who stopped after five years.

Risk for death from breast cancer five to 14 years after diagnosis was 12.2 percent among those who continued use versus 15 percent among those who stopped — an absolute gain of 2.8 percent. The researchers observed the greatest benefit during 10 to 14 years after diagnosis.

Davies noted that continuing tamoxifen use can increase side effects, with endometrial cancer being the most life-threatening. Because endometrial cancer is generally curable, the cumulative risk for death between five and 14 years after diagnosis was 0.4 percent versus 0.2 percent. Because this risk is heavily outweighed by the reduction in breast cancer deaths, overall mortality was significantly reduced by longer treatment. In premenopausal women, for whom tamoxifen is often the endocrine treatment of choice, there was no apparent excess of endometrial cancer.

“Many women with ER-positive breast cancer take tamoxifen, or some other adjuvant endocrine treatment, but the current recommendation is to stop after five years,” said Davies. “ATLAS showed that protection against breast cancer recurrence and death is greater with 10 years than with five years of tamoxifen use. Women and their doctors should be aware of this evidence when deciding how long to continue tamoxifen, or any other endocrine treatment.”

The study was funded by Cancer Research U.K., the U.K. Medical Research Council, AstraZeneca, the United States Army and the European Union.

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The mission of the 2012 CTRC-AACR San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR) and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR’s scientific prestige in basic, translational and clinical cancer research to expedite the delivery of the latest scientific
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advances to the clinic. For more information about the symposium, please visit www.sabcs.org.

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Title: ATLAS. 10 v 5 years of adjuvant tamoxifen (TAM) in ER+ disease: Effects on outcome in the first and in the second decade after diagnosis

Christina Davies1, Hongchao Pan1, Jon Godwin2, Richard Gray1, Richard Peto1 and on Behalf of ATLAS Collaborators Worldwide1. 1Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), University of Oxford, Oxford, United Kingdom and 2Institutes for Applied Health and Society & Social Justice Research, Glasgow Caledonian University, Glasgow, United Kingdom.

Body: Background: In ER+ early breast cancer, 5 years of tamoxifen greatly reduces recurrence throughout the first decade (years 0-9) with little further gain later, and reduces breast cancer mortality (BCM) substantially throughout years 0-14 (EBCTCG, Lancet 2011; 378: 771-84 – see Table). It is not known how 10 years TAM compares with the current standard of just 5 years TAM.

Methods: In 1996-2005 the international ATLAS trial randomized 6846 women with ER+ disease who had had ~5 years of adjuvant TAM to continue another 5 years (to year 10) or stop at year 5 (control). Annual follow-ups recorded compliance, hospital admissions, breast cancer recurrence (including new contralateral), any other new primary cancer and cause of death.

Results: Compliance was ~80%, as after 2 years 84% of those allocated continue and 4% of those allocated stop were still taking endocrine treatment (>99% TAM). With mean 7.1 woman-years follow-up (30,000 w-y in years 5-9, 16,000 in years 10-14, 2000 later), 1328 recurrences were reported (900 in years 5-9, 379 in years 10-14). Recurrence was significantly lower with10 than 5 years TAM (Table: logrank 2p=0.002, rate ratio (RR)=0.90 se 0.06 in years 5-9 and 0.75 se 0.08 in years 10+). So were both BCM (2p=0.01, RR=0.97 se 0.10 in years 5-9 and 0.71 se 0.09 in years 10+) and all-cause mortality (2p=0.01, with no increase in non-BCM). Proportional risk reductions were homogeneous by country, age and stage. Kaplan-Meier risks in years 5-14 (K-M)were: recurrence 21.4 vs 25.1%, BCM 12.2 vs 15.0%. Uterine cancer K-Ms in those randomized at age 50+ were: incidence 2.6 vs 1.6% (2p=0.08), mortality 0.2 vs 0.2%. In pre-menopausal women (where AIs are not an alternative to TAM) there was no apparent excess of uterine cancer.
**Discussion:** Compared with just 5 years TAM, continuing TAM to year 10 safely protects further against recurrence and, particularly during the second decade, BCM. Combining results from ATLAS and the EBCTCG meta-analyses of 5 years TAM vs none (both had ~80% compliance), in a hypothetical trial of 10 vs 0 years TAM with ~80% compliance, 15-year BCM would be reduced by at least one-third. Hence, full compliance with 10 years TAM would yield even greater benefit (Table). Further follow-up of ATLAS will assess more reliably the apparently substantial mortality reduction in the second decade after diagnosis.

<table>
<thead>
<tr>
<th>Time from diagnosis</th>
<th>EBCTCG 5v0 TAM: ~80% comply</th>
<th>ATLAS 10v5 TAM: ~80% comply</th>
<th>Product of trial RRs: effect of 10v0 TAM if ~80% comply</th>
<th>RR for effect of 10v0 TAM if all comply**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4y</td>
<td>0.53 [0.48-0.57]e</td>
<td>1</td>
<td>0.53 [0.48-0.57]e</td>
<td>0.41</td>
</tr>
<tr>
<td>5-9y</td>
<td>0.68 [0.60-0.78]e</td>
<td>0.90 [0.75-1.02]</td>
<td>0.61 [0.51-0.73]e</td>
<td>0.52</td>
</tr>
<tr>
<td>10+</td>
<td>0.94 [0.79-1.12]</td>
<td>0.75 [0.62-0.90]</td>
<td>0.70 [0.54-0.91]</td>
<td>0.63</td>
</tr>
<tr>
<td>BCM</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0-4y</td>
<td>0.71 [0.62-0.80]e</td>
<td>1</td>
<td>0.71 [0.62-0.81]e</td>
<td>0.64</td>
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<tr>
<td>5-9y</td>
<td>0.66 [0.58-0.75]e</td>
<td>0.97 [0.79-1.18]</td>
<td>0.64 [0.50-0.82]</td>
<td>0.55</td>
</tr>
<tr>
<td>10+</td>
<td>0.73 [0.62-0.88]e</td>
<td>0.74 [0.62-0.88]</td>
<td>0.62 [0.40-0.88]</td>
<td>0.40</td>
</tr>
</tbody>
</table>

**Estimated gain if all comply=1.25x gain if ~80% comply.**  
*2p<0.01, §2p=0.001, ‡2p=0.0001, c2p<0.00001