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**Media Release**

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## **New clinical trial results show better outcomes for post-menopausal women with early breast cancer**

A successful new treatment approach for early breast cancer, using tamoxifen therapy first and then switching to the aromatase-inhibitor drug exemestane in sequence, instead of the standard continuous tamoxifen, was reported today in *The New England Journal of Medicine*.

The paper concluded that switching to exemestane therapy for 2-3 years after the initial 2-3 years of tamoxifen results in a significant improvement in both disease-free survival and a significant reduction of new breast cancers in the opposite breast, when compared with the standard five years of continuous tamoxifen treatment.

The trial was an international double-blind study involving 4,742 post-menopausal women who had previously been diagnosed with hormone sensitive (ER+) early breast cancer, and who had remained free of breast cancer for 2-3 years; 2,380 women were randomised to continue on tamoxifen to complete a total of five years, and 2,362 to switch to exemestane to complete their five years of treatment.

The trial, the Intergroup Exemestane Study (IES), was conducted internationally by the International Collaborative Cancer Group, Imperial College London, in collaboration with 10 other international breast cancer trials groups and was led by Professor R C Coombes, Chair of the International Steering Committee. The Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) conducted the trial in Australia and New Zealand.

After a median of 30.6 months of follow-up, the primary end-point for the trial, disease-free survival, showed a statistically significant advantage for the patients who switched to exemestane (166 new breast cancers or deaths) compared with the women who remained on tamoxifen (266 new breast cancer events or deaths). This represents a 32% reduction in risk and a 4.7% absolute disease-free survival benefit at three years post randomisation ( $P < 0.001$ ). There were 93 deaths in the exemestane group and 106 in the continuous tamoxifen group, however this difference was not statistically significant at this analysis. There were nine new breast cancers diagnosed in the opposite breast in the exemestane group and 20 in the continuous tamoxifen group ( $P < 0.038$ ).

Professor John Forbes, Coordinator of the ANZ BCTG, from The University of Newcastle, said it is a very important result for women. "Taken with other recent results from large trials, showing that the aromatase inhibitors anastrozole and letrozole can also improve on the results obtained with five years of tamoxifen alone, it is clear that these drugs can lead to better outcomes for women with early breast cancer. Ongoing trials conducted by the ANZ BCTG and others will further define the optimal use of these important drugs."

“When women were switched to exemestane they had a better outcome in terms of breast cancer events compared with remaining on tamoxifen. We do not know if it might have been better to start with the exemestane from the time of diagnosis, as these women were already at least two years after diagnosis and free of disease when they entered this trial. The sequence might be important rather than just the exemestane, and this is being tested in another of our trials,” Professor Forbes said.

Side effects were different for the treatment groups. Exemestane was associated with arthralgia (joint pain) (5.4%) and diarrhoea (4.3%), but less vaginal bleeding (4.0% versus 5.6%), gynaecological symptoms (5.8% versus 9.0%) and thromboses (1.0% versus 2.0%). There were five patients diagnosed with endometrial cancer on exemestane and 11 on tamoxifen. There were more fractures reported on exemestane but the difference was not significant.

Professor Alan Coates, ANZ BCTG representative on the International Steering Committee, said he was very pleased to see the positive results. “The early improvement in disease-free survival and in prevention of new cancers in the opposite breast is most encouraging, but further follow-up is required to determine the ultimate value of this treatment approach for overall survival. There were 54 breast cancer deaths on exemestane and 67 on continuous tamoxifen, an encouraging result for overall survival so far, but the difference is not yet statistically significant and we must await further follow-up for final survival results. We also need longer follow-up to clarify the risk–benefit profile,” Professor Coates said.

Centres in Australia and New Zealand taking part in the trial were: NSW - Newcastle Mater Hospital, Royal Prince Alfred Hospital, Liverpool Cancer Centre, Dubbo Base Hospital; Victoria - Box Hill Hospital, Bendigo Hospital, Maroondah Hospital; South Australia - Royal Adelaide Hospital; New Zealand - Waikato Hospital, Auckland Hospital.

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**For interviews with Professor John Forbes or Professor Alan Coates, please contact:**

**Jenny Sly, Breast Cancer Institute of Australia  
Ph: (02) 4925 3022, Mobile: 0407 919 767**

**Health editors: Please see following page for additional notes.**

## Additional notes for health editors:

- Breast cancer cells that contain oestrogen receptors (ER) are dependent on the circulating hormone, oestrogen, for their continued growth. The oestrogen can be withdrawn from the cancer cells either by blocking this ER or by reducing the level of circulating oestrogen. In pre-menopausal women the main source of oestrogen is the ovary, and oestrogen can be withdrawn by removal of the ovaries.
- Tamoxifen works by blocking the ER, but with long term use some cancer cells may overcome the tamoxifen effect and become resistant.
- In post-menopausal women oestrogen is produced outside of the ovaries. The aromatase inhibitors, such as exemestane, work by blocking the production of oestrogen in fatty tissues, normal breast tissue and breast cancers, thus depriving the cancer cells of oestrogen. The newer aromatase inhibitors such as exemestane are very potent and specific for blockade of oestrogen production.
- Prior to the trials of the aromatase inhibitors, the standard for treating postmenopausal women with ER+ early breast cancer has been five years of treatment with tamoxifen after initial treatment with surgery and radiotherapy. On average, five years of post-operative treatment with tamoxifen reduces the risk of breast cancer recurrence by 47% and death by 26% compared with surgery and radiotherapy alone.
- Two other aromatase inhibitors have recently been shown to improve outcomes compared with five years of continuous tamoxifen treatment alone in the same population of women. These were used in a different way.

In the ATAC trial, five continuous years of the aromatase inhibitor anastrozole (Arimidex), compared with the standard treatment of five years of tamoxifen, was shown to produce a statistically significant improvement in disease-free survival and contralateral breast cancer rates, when both drugs were used **from the time of diagnosis**. (*The Lancet 2002, 359:2131-9*)

In the MA-17 trial, the aromatase inhibitor letrozole (Femara) was shown to improve outcomes when it was used for around two additional years **after the five years of tamoxifen had been completed**. In this trial, women had already reached five years of follow-up and were all free of breast cancer. (*The New England Journal of Medicine 2003:349:19*)

- Women who are post-menopausal with hormone-sensitive breast cancer, and who may benefit from these new treatments, comprise more than 40% of all breast cancers diagnosed in Australia. It is estimated that currently more than 1 million women worldwide are taking a planned five years of tamoxifen for treating early breast cancer. Approximately 20,000 women in Australia are taking tamoxifen in this setting. The results of this new trial are potentially important for these women and have important implications for the ANZ BCTG national clinical trials research program and future clinical trials.
- The aromatase-inhibitor drugs are available for use in Australia. They are available on the PBS for treating advanced breast cancer, but are not yet available for treating early breast cancer as in these trials.

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**ANZ Breast Cancer Trials Group Limited**  
**Operations Office**  
**Department of Surgical Oncology**  
**University of Newcastle**  
**Locked Bag 7**  
**Hunter Region Mail Centre NSW 2310**  
**AUSTRALIA**

**Ph: (02) 4925 3022**  
**Fax: (02) 4925 3068**  
**Email: j.sly@bcia.org.au**  
**ABN 64 051 369 496**  
**CFN 10881**  
**ATO N0939**