



MEDIA RELEASE

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Letrozole reduces the risk of post-surgery recurrence of early breast cancer when compared with tamoxifen, study shows

An international clinical trial in which Australia is making a major contribution, has shown that in postmenopausal women with early breast cancer, the drug letrozole offers better post-surgery protection against breast cancer recurrence than does tamoxifen, the current standard of care.

First data from the trial, Breast International Group (BIG) 1-98, which involved the largest number of women from Australia recruited to an international breast cancer treatment trial, showed a significant improvement difference in disease-free survival in favour of letrozole.

The data was presented today at the Primary Therapy of Early Breast Cancer 9th International Conference in St.Gallen, Switzerland.

BIG 1-98 is the first clinical trial designed to test both a head-to-head comparison of letrozole with tamoxifen from the beginning of treatment, and a sequencing of both agents, during the first five years following breast cancer surgery.

The study involves postmenopausal women with early, hormone-sensitive breast cancer and is testing the following five year treatment plans:

- five years of tamoxifen alone versus five years of letrozole alone;
- the sequence of tamoxifen for two years followed by letrozole for three years;
- the sequence of letrozole for two years followed by tamoxifen for three years.

Professor John Forbes, University of Newcastle, BIG 1-98 Study Chair for the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) and a Member of the BIG 1-98 International Steering Committee said, "This is the only trial worldwide testing the value of continuous treatment versus the sequencing of tamoxifen and letrozole. These early positive results for the initial comparison of letrozole and tamoxifen tell us we are on track to answer questions about sequencing these treatments."

Professor Alan Coates, Chief Executive Officer of the Cancer Council Australia and Co-Chairman of the International Breast Cancer Study Group (IBCSG) Scientific Committee said, "BIG 1-98 represents a monumental international collaboration involving Australian researchers to extend the evidence base for adjuvant therapy of breast cancer. It adds to our knowledge of the advantages of the aromatase inhibitors in this role, and will assist women and their doctors in reaching appropriate treatment choices."

Methods and Results

BIG 1-98 is a multinational Phase III double-blind, randomized, multicentre trial that is being conducted in 27 countries and involves more than 8,000 postmenopausal women with early breast cancer who have hormone receptor-positive tumours.

The Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) conducted the BIG 1-98 study in 29 centres in Australia and New Zealand. More than 800 women in Australia and New Zealand, 10% of the worldwide total, were recruited to the study.

The primary goal of the study was to determine if letrozole could reduce the risk of a disease-free survival event (breast cancer recurrence, occurrence of a second primary cancer or death without recurrence having occurred) compared with tamoxifen. Many breast cancers depend on oestrogen for their growth. Letrozole is an aromatase inhibitor, a type of drug that blocks production of oestrogen in postmenopausal women. Tamoxifen works by blocking the effect of oestrogen at the tumour cell.

At a median follow-up of 26 months the study shows that, compared with tamoxifen, letrozole reduced the risk of such events by 19%. This means that about 1 in 5 of the early recurrences of breast cancer that might occur on tamoxifen is being prevented by letrozole. Among the 4003 patients in the letrozole group, 84.0% remained alive and disease-free at five years compared with 81.4% of the 4007 patients in the tamoxifen group. The reduction in rates of recurrence was seen for both local (breast) recurrences and distant recurrences. It is usually the distant recurrences that lead to increased breast cancer death rates, hence it is likely that letrozole will show a survival advantage with longer follow up.

There was also a difference in side effects reported, related to these different actions.

- Tamoxifen
 - more venous thrombosis and embolism (clots), a relatively rare but potentially serious effect.
 - vaginal bleeding more often, leading to more endometrial abnormalities (changes in the lining of the womb) and endometrial biopsies.
- Letrozole
 - more bone fractures
 - elevation of cholesterol, though this was usually mild.
 - heart attacks and strokes slightly more often, though these events were very rare with both treatments.

Overall, there were less deaths on letrozole than on tamoxifen.

Professor Richard Gelber of Harvard Medical School and Statistician for the trial said, "The first results of BIG 1-98 demonstrate clear superiority of letrozole compared with tamoxifen to reduce the risk of breast cancer recurrence (especially in distant metastatic sites) for postmenopausal women following surgery for breast cancer which contains hormone receptors in the tumor cells. The two drugs are well tolerated, but letrozole therapy compared with tamoxifen is associated with increased risks of bone fractures, hypercholesterolemia, and deaths without breast cancer recurrence due to cerebrovascular accident or cardiac causes. This finding, which is not associated with compromised overall survival, requires additional attention, because previous studies of the cardiovascular risk of the aromatase inhibitors have not focused properly on this aspect. Until additional information becomes available, aromatase inhibitors should be used with caution, especially in patients at elevated risk for cardiovascular disease."

Professor Forbes added, "Longer follow-up will clarify the side effect profile. We know for example that this class of drugs increases bone fracture rates compared to tamoxifen – an additional 2-3 fractures per 100 women compared to tamoxifen. We know that tamoxifen protects bone and this may contribute to the small difference seen in favour of tamoxifen. Other recent research data indicates that this effect is likely to be preventable, but we will continue to monitor all side effects carefully as we have done in similar trials."

Professor Forbes concluded, "We already knew that letrozole was effective if given after the five years of tamoxifen is completed. This new data tells us that letrozole is also a more active drug than tamoxifen when given from the beginning and this means that with longer follow up, the trial can answer the important questions about treatment sequencing.

"We are indebted to the women from Australia and worldwide who are taking part in the trial. Ultimately, with longer follow-up to also test the sequencing, the commitment of the women involved in the trial will lead to a better outcome for many thousands of other women worldwide."

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Notes to Editors

About the BIG 1-98 trial

BIG 1-98 is being conducted under the auspices of the Breast International Group (BIG) and coordinated and managed by the International Breast Cancer Study Group (IBCSG) in collaboration with Novartis, maker of letrozole (Femara®). The IBCSG is an active member of the BIG organization. In Australia and New Zealand the trial is being conducted by the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG), based at the University of Newcastle.

Early breast cancer is defined as cancer that is localized to breast tissue and/or nearby lymph nodes. Worldwide, about 800,000 women are diagnosed with early breast cancer every year. Primary therapy for early breast cancer usually involves surgery to remove the tumour and surrounding breast tissue. Standard post-surgery therapy (adjuvant therapy) typically includes radiation and/or chemotherapy, followed by treatment with five years of tamoxifen, previously the “gold standard of care” for postmenopausal women.

How letrozole works

Many breast cancers are stimulated to grow by the natural hormone oestrogen. Tamoxifen, the current standard treatment, works by blocking the effect of oestrogen on breast cancer cells. The new class of anti-cancer drugs called aromatase inhibitors work by reducing the production of oestrogen in postmenopausal women thus depriving cancer cells of the source of oestrogen. Letrozole is an aromatase inhibitor.

About the Australian New Zealand Breast Cancer Trials Group

The Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) is Australia's national breast cancer research group. It is dedicated entirely to breast cancer research through the conduct of multi-institution clinical trials. Working in collaboration with 300 researchers in more than 70 of the leading medical institutions in Australia and New Zealand, and with similar research groups in 15 countries internationally ensures Australia and New Zealand are at the forefront of breast cancer research progress and this delivers benefits to women immediately. Additional information can be found at www.anzbctg.org.

About the International Breast Cancer Study Group

The International Breast Cancer Study Group (IBCSG), created as the 'Ludwig Breast Cancer Study Group' in 1977, is dedicated to innovative clinical research designed to improve the outcome of women with breast cancer. Additional information regarding BIG 1-98 or IBCSG can be found at www.ibcsg.org.

About the Breast International Group

The Breast International Group (BIG) is an international non-profit organisation dedicated to coordinating large breast cancer trials among its members. The participants are well-established clinical research and cooperative groups based in Europe, Australia, New Zealand, South Africa and Canada, with affiliated centres around the world.

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