## MEDIA RELEASE 12 DECEMBER 2008

### Study involving Australian women suggests survival benefit for letrozole over tamoxifen and highlights the role of initial letrozole for postmenopausal women with early breast cancer

An international clinical trial in which the Australian New Zealand Breast Cancer Trials Group (ANZ BCTG) is making a major contribution, has established 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.

Follow-up data from the trial, Breast International Group (BIG) 1-98 / International Breast Cancer Study Group (IBCSG) 18-98, which involved the largest number of women from Australia recruited to an international breast cancer treatment trial, was presented today at the 31st San Antonio Breast Cancer Symposium in San Antonio, Texas USA.

BIG 1-98 is being conducted in Australia by the ANZ BCTG. It is the first clinical trial designed to test both a head-to-head comparison of letrozole or tamoxifen alone from the beginning of treatment and the 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.

In 2005, first results from BIG 1-98 showed that letrozole for five years was superior to tamoxifen for five years in preventing breast cancer recurrence, especially distant recurrence. With this 2008 update there is a significant reduction in recurrences (including second malignancies and deaths prior to a cancer event). The 5-year event rates were: letrozole 509/2463, (14.4%), tamoxifen, 565/2459, (17.4%). The Hazard Ratio (HR) for events and 95% confidence intervals (CI) were: HR 0.88, CI 0.78-0.99, P=0.03. There was also a reduction in deaths of 13% (5-year rates: letrozole 303/2463, 8.2%, tamoxifen 343/2459, 9.1%, HR 0.87, CI 0.75-1.02, P=0.08).

The new data also suggests that, together with optimal surgery followed by chemotherapy and radiotherapy if needed, commencement of letrozole early in the treatment plan was the best way to remain free of cancer. This is especially true for patients with a higher likelihood of early recurrence, such as women who were found to have lymph nodes involved at the time of initial surgery.

Professor Alan Coates, Co-Chairman of the IBCSG Scientific Committee and lead investigator for the trial said, “The results of BIG 1-98 are of great importance to the majority of women with breast cancer. We already knew from our earlier results that letrozole alone is more effective than tamoxifen alone, but we did not know if giving both of the agents in a sequence (of letrozole followed by tamoxifen or tamoxifen followed by letrozole) would show superior results. We found that it appears to be better to start treatment with letrozole and continue for five years, but if necessary patients can switch to tamoxifen after two years without loss of efficacy.”

…/2

Professor John Forbes, University of Newcastle, Study Chair of BIG 1-98 for the ANZ BCTG and a Member of the BIG 1-98 International Steering Committee said, “This is an important trial. It is the only trial worldwide testing the value of continuous treatment with an aromatase inhibitor versus the sequencing of tamoxifen and letrozole. This new data, suggesting a reduction in mortality with letrozole for five years compared with tamoxifen for five years is likely to be real, and not simply the play of chance, as letrozole reduced the risk of distant recurrence by 15% (5-year rates letrozole 257/2463, 7.6%, tamoxifen 298/2459, 9.9%, HR 0.85, 95% CI 0.72-1.0, P=0.05) and it is these recurrences which are associated with reduced survival. This new data reinforces our earlier results and confirms the importance of careful long-term follow-up after treatment has been completed to obtain this new data.”

**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.

The ANZ BCTG conducted the BIG 1-98 study in 29 centres in Australia and New Zealand and recruited 804 women, 10% of the worldwide total.

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.

The primary conclusions of BIG 1-98 are:

- Updated results suggest superior overall survival with letrozole compared with tamoxifen;
- Adjuvant endocrine therapy should start with letrozole rather than tamoxifen, especially for patients at higher risk for early recurrence;
- Patients commenced on letrozole can be switched after two years to tamoxifen, if required;
- Improved therapeutic approaches beyond five years are required to control late recurrence.

Professor Forbes said, “BIG 1-98 is an impressive international collaboration involving Australian researchers to extend the evidence base for adjuvant therapy of breast cancer. The trial shows clearly that this population of women had a better outcome if their treatment commenced with letrozole rather than with tamoxifen. 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.”

Professor Forbes concluded, “We are indebted to the women from Australia and worldwide who are taking part in the trial. The commitment of these women involved in the trial will lead to a better outcome for many thousands of other women worldwide.”

**- ends -**

**For further information on this media release and to arrange interviews with ANZ BCTG researchers, please contact:**

**Jenny Leggett**
**Public Relations Manager**
**Breast Cancer Institute of Australia**
**Ph: (02) 4925 3022, Mobile: 0407 919 767**

**…/3**

**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). The IBCSG is an active member of the BIG organisation. 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 localised 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. A 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 80 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 the 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 membership. These include well-established clinical research and cooperative groups based in Europe, Australia, New Zealand, South Africa and Canada, with affiliated centres around the world. Additional information about the BIG can be found at www.breastinternationalgroup.org.

**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.leggett@bcia.org.au**