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Study suggests survival benefit for letrozole (Femara®) over tamoxifen and highlights the role of initial letrozole for postmenopausal women with early breast cancer

An article in the August 20, 2009 *New England Journal of Medicine* presented the results of a major clinical trial that involved 8,000 women with breast cancer. The trial studied the effectiveness of two drugs, the well-established anti-estrogen agent, tamoxifen, and the newer aromatase inhibitor, letrozole (Femara, manufactured by Novartis). The Breast International Group (BIG) 1-98 trial is uniquely designed to study two important questions for the treatment of postmenopausal women with early breast cancer who have the type of breast cancer that responds to endocrine treatments such as tamoxifen and letrozole (estrogen receptor positive or progesterone receptor positive). 1) Is a five year program of letrozole better than a five-year program of tamoxifen? and 2) Is a five-year program of letrozole better than a sequence that begins with tamoxifen for the first 2 years followed by letrozole for 3 years or better than a sequence that begins with letrozole for the first 2 years followed by tamoxifen for 3 years?

In 2005 this clinical trial showed that letrozole for 5 years was superior to tamoxifen for 5 years in preventing breast cancer recurrence, especially distant recurrence. This 2009 update shows a continued significant reduction (12%) in recurrences (including second malignancies and deaths prior to cancer event), and a suggestion of a reduction (13%) in deaths. The difference in outcomes between these two treatment programs is diluted because one quarter of the patients on the tamoxifen program “crossed over” and began to take letrozole after the early results were presented in 2005. The trend toward improved survival benefit has not been observed in other trials comparing 5 years of tamoxifen to other aromatase inhibitors.

Prof. Alan S. Coates, Scientific Committee Co-Chairman of the International Breast Cancer Study Group, which coordinated the trial, put the results in perspective, saying “The results of BIG 1-98 are of great importance for the majority of patients 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 seems the best—or the most promising—strategy to start with letrozole, but if necessary patients can switch to tamoxifen after two years without loss of efficacy. Together with optimal surgery, followed by chemotherapy and radiotherapy if needed, incorporation of letrozole early in the treatment plan is the best way to control the disease, especially for patients with a higher likelihood of recurrence, such as cancer that has spread to the lymph nodes near the breast. The trend for reduction in mortality with letrozole for 5 years compared with tamoxifen for 5 years reinforces our earlier results and confirms the need for careful long-term reporting of the patients’ health status even after treatment has been completed.”

Prof Beat Thürlimann, Head of the Breast Centre located at the Kantonsspital in St. Gallen Switzerland and the Study Chair of the BIG 1-98 trial commented: “This study makes it clear that the strategy of giving tamoxifen first, prior to starting an aromatase inhibitor, is no longer the best option. You should start with letrozole for at least two years and then you can consider switching if there is a compelling reason to switch.”



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Prof. Henning Mouridsen, Professor of Oncology at the Rigshospitalet in Copenhagen Denmark, chaired the writing committee and reflected on the results of the comparison of five years of letrozole with five years of tamoxifen, “The most important message is the consistent finding that letrozole improves disease-free survival, time to recurrence, and, with this update, overall survival.”

The BIG 1-98 trial compares:

- Tamoxifen for two years followed by letrozole for three years versus five years of letrozole
- Letrozole for two years followed by tamoxifen for three years versus five years of letrozole
- Five years of tamoxifen versus five years of letrozole

Methods and Results

BIG 1-98 is a multinational Phase III double-blind, randomized clinical trial conducted in 27 countries and involving more than 8,000 postmenopausal women with early breast cancer who have hormone receptor-positive tumors. The median time patients have been followed on the study is 6 years.

The primary trial conclusions are:

- Updated results of BIG 1-98 suggest superior overall survival with letrozole compared with tamoxifen
- Adjuvant endocrine therapy should start with letrozole especially for patients at higher risk for early recurrence
- Patients commenced on letrozole can be switched after 2 years to tamoxifen, if required
- Safety is consistent with known safety profiles of each agent
- Improved therapeutic approaches beyond five years are required to control late recurrence

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 tumor and surrounding tissue. Standard post-surgery therapy (early adjuvant) typically includes radiation (after breast-conserving surgery) and/or chemotherapy. Patients with hormone-sensitive tumors usually receive an endocrine agent for five years, either tamoxifen or letrozole (or other aromatase inhibitor).

BIG 1-98 is being conducted under the umbrella of the Breast International Group (BIG), coordinated and managed by the International Breast Cancer Study Group (IBCSG). The IBCSG is an active member of the BIG organization. Novartis, the producer and distributor of letrozole (Femara[®]), provided study drug and financial support.

About The International Breast Cancer Study Group

The International Breast Cancer Study Group (IBCSG) is a non-profit organization founded as the 'Ludwig Breast Cancer Study Group' in 1977, which is dedicated to innovative clinical research to improve the outcome for women with breast cancer. The IBCSG is headquartered in Bern, Switzerland as a non-profit foundation under Swiss law. The Statistical and Data Management Centers are in the United States (Boston, MA and



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Amherst, NY), and the central pathology review offices are in Milan, Italy and Glasgow, Scotland.

About the Breast International Group

The Breast International Group (BIG) is an international non-profit organization that serves as a network to coordinate participation in large breast cancer trials. BIG members are well-established clinical research institutions and cooperative groups based in Europe, Australia, New Zealand, South Africa, South America, and Canada, with affiliated centers around the world.

Additional information regarding BIG 1-98 and IBCSG can be found on the website www.ibcsq.org.

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