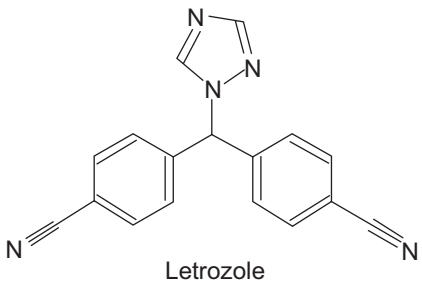
Femara Protects Against Breast Cancer Recurrence One to Seven Years After Completing Tamoxifen Therapy

Women may reduce the risk of their breast cancer returning by starting treatment with letrozole (Femara) anywhere from one to seven years after finishing tamoxifen therapy, according to a new analysis of the results from the landmark MA-17 trial, an international, double-blinded, randomized, multi-center Phase III trial to evaluate the effectiveness of letrozole versus placebo in breast cancer survivors who had completed five years of tamoxifen treatment.

The aromatase inhibitor letrozole (Femara) helps protect against the return of breast cancer even when treatment starts one to seven years after completing tamoxifen therapy. This new data comes from the results of a study involving women originally in the placebo arm of an international trial of letrozole.

The landmark MA-17 trial was an international, double-blinded, randomized, multi-center Phase III trial to evaluate the effectiveness of letrozole versus placebo in breast cancer survivors who had completed five years of tamoxifen treatment. An exploratory analysis of post-unblinding results from the MA-17 trial, led by the National Cancer Institute of Canada Clinical Trials Group, evaluated a subset of women in the original placebo group when the study was unblinded.

The analysis shows that women who started letrozole several years after completing the recommended five years of tamoxifen reduced their risk of breast cancer coming back by 63% compared to those who did not start letrozole. In addition, the risk of cancer spreading to other areas of the body was reduced by 61% and the chance that a new tumor would be found in the unaffected breast dropped by 82%. The median period before starting letrozole was 31 months, reported a group of researchers led by Paul E. Goss, director of Breast Cancer Research at Massachusetts General Hospital Cancer Center in Boston, in an early release article on March 10, 2008, in the *Journal of Clinical Oncology*.



Letrozole

"The important message for women is that it may never be too late for many breast cancer survivors to do more to protect themselves against the ongoing risk of disease recurrence," said Goss, who was the lead investigator of the MA-17 trial. "These data reinforce the need for women diagnosed with breast cancer to go back to their doctors and continue to discuss ways to reduce their risk of recurrence."

Letrozole is one of a class of drugs called aromatase inhibitors that suppress the production of estrogen, which stimulates the growth of breast tumors expressing the estrogen receptor. The most widely used estrogen-blocking drug is tamoxifen, but the benefits of tamoxifen treatment drop significantly after five years, while the drugs' side effects continue.

More than 50% of breast cancer recurrences and deaths occur five or more years after completing tamoxifen treatment. Letrozole is the only drug in the aromatase inhibitor class with data showing its potential to reduce the risk of breast cancer returning even when started several years after initial treatment with tamoxifen. Letrozole is currently approved for breast cancer treatment immediately after surgery or within three months of completing five years of tamoxifen treatment.

"While tamoxifen has been a very important and effective part of breast cancer treatment, more than half of all recurrences and two-thirds of breast cancer deaths still occur after five years of tamoxifen therapy," said Goss, who is also professor of medicine at Harvard Medical School. "Our study suggests that women who finished tamoxifen even several years ago may benefit from taking letrozole to further reduce their risk."

The MA-17 trial was unblinded in 2003, one year earlier than planned, after the first planned interim analysis showed a marked benefit for letrozole in reducing the risk of breast cancer recurrence. At that time, women in the placebo arm were offered the chance to start treatment with letrozole or to continue without additional treatment. The final analysis of MA-17 data, published in the September 7, 2005 *Journal of the National Cancer Institute*, confirmed that women taking letrozole had significantly better disease-free survival than those taking a placebo.

The new analysis published in the *Journal of Clinical Oncology* evaluated the subset of 2,383 women who were in the placebo group when the MA-17 trial was unblinded. Of these women, 1,579 chose to switch to letrozole, while 804 chose not to start letrozole. Almost three years after the MA-17 trial was halted and letrozole offered, those who began letrozole therapy had only a 2% risk of tumor recurrence, compared with almost 5% in those choosing no treatment. The risk of death from breast cancer during that period was cut in half in those receiving letrozole.

The safety analysis was consistent with many other letrozole trials in various treatment settings, reinforcing that letrozole is well tolerated. The primary increased side effect among women who received letrozole was bone fractures

and osteoporosis, compared with those on placebo (5.2% versus 3.1%). Doctors generally recommend that women have their bone health assessed before starting aromatase inhibitor therapy.

Research shows that letrozole offers protection against recurrence throughout several phases of breast cancer treatment in women with hormone-sensitive early breast cancer.

"It appears that estrogen-sensitive tumors remain hormone dependent and that patients' survival can be improved with careful use of aromatase inhibitors, even many years after completing tamoxifen treatment," said Goss. "These results can be put into practice right away to improve the outlook for women treated for receptor-positive breast cancer."

The research team notes that this study is limited by the fact that participants choose whether to take the drug themselves and were not randomly assigned. While a randomized clinical trial would more conclusively determine the benefit of letrozole treatment for those who have been off tamoxifen for several months or years – or even those who never took the drug – the results of this study can help guide physicians and patients in deciding whether letrozole therapy would be appropriate.

"Every patient who has previously taken tamoxifen should discuss these new results with her oncologist. The risk that hormone-dependent breast cancer will recur continues indefinitely, and our results imply that aromatase inhibition is effective whenever initiated," said Goss.

A separate intent-to-treat analysis of unblinded results from the MA-17 trial, published in the March 2008 *Annals of Oncology*, supports the significant benefit of initiating letrozole within three months of completing five years of tamoxifen. If women do not have the opportunity to begin letrozole treatment within three months of completing tamoxifen, the exploratory analysis published in the *Journal of Clinical Oncology* indicates they may still benefit from starting letrozole up to several years later.

The intent-to-treat analysis published in the *Annals of Oncology* evaluated the outcomes for women assigned to letrozole and placebo in the original trial study arms. Researchers led by Hyman Muss, professor of medicine at the University of Vermont, found that at a median follow-up of 64 months, letrozole significantly reduced the risk of breast cancer recurrence by 32% versus placebo. Letrozole maintained its significant benefit over placebo, even though more than 60% of women in the placebo group started letrozole when the study was unblinded. Results from this analysis affirm the safety and efficacy of letrozole as extended adjuvant therapy, that is, following the completion of five years of tamoxifen.

The results also show that the reduced risk of breast cancer recurrence persisted among all age groups, including women over 70, who are sometimes given less aggressive therapy due to concerns over side effects and magnitude of benefit. There were no differences in the side effects of letrozole or quality of life between the different age groups.

In an editorial in the same March 10 issue of the *Journal of Clinical Oncology*, Nancy U. Lin and Eric P. Winer, both of the Dana-Farber Cancer Institute, wrote that the new analysis of the MA-17 trial and other studies, taken in context with the other adjuvant endocrine trials reported in the last five to seven years, "strongly argue for a paradigm shift in the clinical research focus and management of patients with estrogen receptor-positive breast cancer." They suggest the "need to identify predictors of late recurrence and treatment approaches that will change the low, but unrelenting, risk of recurrence seen in patients with estrogen receptor-positive breast cancer. Perhaps most importantly, we need to recognize the heterogeneity of both breast cancer and patients with breast cancer, in order to develop individualized treatment strategies that lead to the greatest benefit while minimizing risk." ❑

Biopsy Techniques have made PSA Test Less Predictive

Prostate specific antigen (PSA) levels typically have correlated with prostate biopsy results in the detection of prostate cancer, but the correlation no longer exists for men with a normal prostate exam, according to a new study published in the March 10, 2008 online edition of Cancer. *The study suggests that improved biopsy techniques make PSA less useful in prostate cancer screening.*

PSA tests have been used an important diagnostic tool for prostate cancer, however, much of the data used to make this conclusion were generated in the early to mid 1990s, when prostate biopsies were performed differently than they are today. Since that time, there has been an increase in the number of prostate biopsies performed and an increasing number of biopsy samples taken from each patient.

Douglas Scherr, Michael Schwartz, and colleagues at the New York Presbyterian Hospital of the Weill Medical College of Cornell University, in New York, NY, set out to assess whether changes in prostate biopsy practice might have changed the predictive value of PSA tests.

The researchers performed a retrospective analysis of all prostate biopsies performed at their institution between 1993 and 2005, finding 1,607 that satisfied their inclusion and exclusion criteria. They divided the patients into three groups based on when they received their biopsies: 1993-1997, 1998-2001, and 2002-2005. They examined each group for the number of biopsies