

# Letrozole Stems Breast Ca Return After Tamoxifen

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Use of the aromatase inhibitor letrozole was linked to a significant 63% reduction in disease recurrence in women with early-stage breast cancer who completed 5 years of tamoxifen therapy 1 to 7 years earlier, results of a phase III study suggest.

"It appears that most cancers remain estrogen dependent for long periods in follow-up and that their clinical courses can be improved by the judicious use of aromatase inhibitors, even very late in follow-up," study investigators reported online in the *Journal of Clinical Oncology*.

Until now providers, regulatory agencies, and health care funders have restricted the use of letrozole to women

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who were within 3 months of discontinuing tamoxifen, because the evidence supported its use only in these cases.

But many, if not most, breast cancer survivors have been off tamoxifen for more than 3 months. They have never been

offered letrozole even though they might benefit from it, wrote Dr. Paul E. Goss of Massachusetts General Hospital Cancer Center, Boston, and his associates in the National Cancer Institute of Canada Clinical Trials Group MA.17 study.

Ideally, the question would be settled by a randomized clinical trial. Such a study is under consideration, but even if it proves feasible, the results will not be available for years. In the meantime, assessing outcomes in a subgroup of women in the NCIC MA.17 trial "provides a unique opportunity to determine whether a later intervention with the aromatase inhibitor" is beneficial. These findings "provide the only available information that can be used to inform the decision these women and their physicians face," Dr. Goss and his associates said.

In the MA.17 trial, more than 5,000 postmenopausal women within 3 months of completing approximately 5 years of adjuvant tamoxifen therapy were randomly assigned to receive letrozole or placebo and were to be followed for another 5 years. But an interim analysis after a median of 2.4 years showed a distinct advantage with letrozole, so the trial was unblinded and the placebo group was offered letrozole for the remaining 2.6 years of the trial.

A total of 1,579 women switched to letrozole, and 804 elected no further treatment after unblinding. Of those who switched to letrozole, 31 (2%) developed recurrences, compared with 39 (5%) who did not take letrozole. The drug was associated with an adjusted hazard ratio of 0.37, corresponding to a 63% drop in disease recurrence (*J. Clin. Oncol.* 2008;26

[doi:10.1200/jco.2007.11.6798]).

Distant metastases occurred in 1% of women who switched to letrozole, compared with 2.4% of those who didn't take letrozole; a significant 61% reduction in the risk of developing distant metastases was reported. Similarly, mortality was lower with letrozole than without it (1.3% vs. 4.5%).

Interpreting these results is complicated by the fact that these study subjects self-selected for letrozole therapy or no

further therapy. The patients who chose letrozole were at greater risk of recurrence because of tumor characteristics, however.

"The fact that women who would have been expected to have a higher rate of recurrence actually did better on letrozole strongly suggests that letrozole was responsible for the reduced frequency of breast cancer events in these patients," Dr. Goss and his associates said.

Women who took letrozole were at in-

creased risk of developing fractures or osteoporosis, known adverse effects of long-term exposure to letrozole. It is possible, however, that these complications could be prevented with bisphosphonates, vitamin D, and calcium replacement therapy, they added.

In addition to the National Cancer Institute of Canada's funding, this study was supported by the Pharmacia Corp, a Pfizer company, and Novartis Pharmaceuticals Canada Inc. ■

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1. Centers for Disease Control and Prevention (CDC). Preventing tetanus, diphtheria, and pertussis among adults: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP) and recommendation of ACIP, supported by the Healthcare Infection Control Practices Advisory Committee (HICPAC), for use of Tdap among health-care personnel. *MMWR*. 2006;55(RR-17):21-22. 2. CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines: recommendations of the ACIP. *MMWR*. 2006;55(RR-3):22.

<sup>a</sup>Advisory Committee on Immunization Practices. <sup>b</sup>Tetanus, diphtheria, and acellular pertussis. <sup>c</sup>19-64 years of age. <sup>d</sup>11-18 years of age.

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