

Critics Question Price of Success in Halted Clinical Trial of Aromatase Inhibitor Letrozole

In October, results from a clinical trial showed that the aromatase inhibitor letrozole (Femara) reduced breast cancer recurrence after 5 years of tamoxifen therapy in postmenopausal women. The results were hailed as a boon for the breast cancer community; results from the trial, which was halted early, suggest that breast cancer survivors now have another option to continue to keep breast cancer at bay.

But some experts, including leading breast cancer patient advocates and some investigators, are saying that unblinding the study leaves patients in a quandary because too many questions have been left unanswered. They argue that clinical trial design that has disease-free survival—instead of overall survival—as an end point should be reconsidered.

In August, when an independent data and safety monitoring committee took the first interim look at outcomes in the 5,187-patient trial, they found results so unexpectedly strong that they concluded that the study must be unblinded so that all women on the trial could be offered letrozole.

“These results being so positive so soon came as a surprise to us all,” said Jeffrey Abrams, M.D., associate chief of the Clinical Investigations Branch of the National Cancer Institute. “When we planned these trials we did not think that letrozole would have such a major effect, or at least such a major effect so early.”

The committee found that 132 women taking a placebo had a recurrence of breast cancer, compared with 75 women on letrozole, with estimated 4-year disease-free survival rates of 87% and 93%, respectively, in the two groups—a statistically significant difference. Overall, letrozole reduced the risk of cancer recurrence by 43%. Although there were twice as many breast cancer

deaths in the placebo group (17) as in the letrozole group (9), the difference was not statistically significant. The trial’s results were published October 9 in the online edition of the *New England Journal of Medicine*.

Many researchers hailed the finding and the decision to halt the trial, saying it could potentially benefit the 200,000-plus women a year in the United States and Europe who finish tamoxifen treatment. The trial’s lead investigator in the United States, Mayo Clinic medical oncologist James Ingle, M.D., said that all women who have completed tamoxifen treatment should now discuss with their doctors the option of taking letrozole.

Because letrozole was approved in 2001 for first-line treatment in postmenopausal women with locally advanced or metastatic breast cancer, it can now be prescribed off-label for adjuvant prevention, even as its manufacturer, Novartis Pharma AG, seeks federal approval for use of the drug in a new indication.

Nationwide media reports called letrozole a breakthrough therapy in the fight against breast cancer recurrence. Soon after the study was published, another phase III, 3,000-patient placebo-controlled trial of an aromatase inhibitor, the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial of exemestane following tamoxifen, was shut down so participants could be given letrozole. But some patient advocates do not see such a great success.

Too Many Questions

The group most vocal against halting the study is the nation’s largest breast cancer advocacy group, the National Breast Cancer Coalition (NBCC), which quickly posted a rebuttal of sorts to the findings on its Web site

(www.natbcc.org). Their opinion was echoed within days in an October 12 editorial in the *New York Times*, which questioned whether scientists were engaging in “ethical overkill” by halting the study midstream.

The NBCC’s position is that patients were followed for much too short of a



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time—an average of just 2.4 years—and that the way recurrence was measured was not meaningful because local and metastatic recurrences of breast cancer

were considered together with new primary cancers in the contralateral breast—cancers that have different risk profiles and treatment options.

“The issue to us is long-term survival—is this drug really going to save lives?” asked NBCC president Fran Visco. “What are the long-term effects, and how do you balance those against what the benefits are? We really don’t know because it was stopped so early.”

To Susan Love, M.D., the unanswered question of long-term side effects will make it difficult for women to decide whether they should use letrozole and for how long. Love, president and medical director of the Susan Love, M.D., Breast Cancer Foundation, said that many women using the drug will experience an adverse effect on quality of life, while few will benefit. The results “weren’t strong enough” to suggest widespread use of the drug, especially since aromatase inhibitors like Arimidex (anastrozole) have already been shown to cause musculoskeletal problems, said

Love. "I know that is pooh-pooed by researchers, but patients really complain about aches and pains and arthritis, and that is a big quality-of-life deterrent," she said.

Citing the study's higher frequency of hot flashes, arthritis, and osteoporosis in women treated with letrozole in the study—a difference that was insignificant, but trended upward—Love said "it may well turn out, but we will never know, that 5 years of letrozole is worse than placebo."

The difference in recurrence is "so small, one event per 100 women per year," that a decision by the data and safety monitoring committee to extend the trial for another year would have been very reasonable and defensible, said Harold Burstein, M.D., Ph.D., a Dana-Farber Cancer Institute researcher who wrote an editorial that accompanied the study results.

The follow-up to the trial was "exceptionally short," he said. Less than



Barbara Brenner

1% of the women received 4 years of treatment, and none of the women to date have received the planned 5 years of letrozole therapy. At least another

year of data collection "would have answered some, if not all, these kinds of issues, and provided more toxicity and efficacy data," Burstein said. As it stands now, "we have a new set of problems, such as what is the duration of therapy, and who are the patients who are really most likely to benefit?"

Ending the trial based on a statistical interim analysis was ethical, he added, because that is the way the trial was designed. "But the real issue is do we really believe that the end point chosen, in this case disease-free survival, around which the vast majority of clinical trials in oncology are built, is really the end point we wish to seek?" Burstein asked.

"It has taken us 30 years to understand what [we now] know about tamoxifen, and now, with stopping a study on letrozole after only 2 1/2 years, when are we ever going to know about letrozole?" asked Barbara Brenner, executive director of Breast Cancer Action. Women struggling to figure out whether they should use the drug "are being used as guinea pigs, and my heart goes out to them," she said.

Defending Beneficial Findings

The criticism has seemed to surprise as well as frustrate researchers involved in the trial, which achieved what they call a "practice changing" result. "This is an event that unfortunately doesn't occur often, where your benefits far exceed what you expected," said the Mayo Clinic's Ingle. "We have an unequivocal answer that letrozole decreases risk of recurrence. In retrospect, I don't know how we would have designed it any differently, and I would not have."

He added that the attention paid to overall survival as a primary end point is misplaced. "All adjuvant studies of endocrine therapy supported by the NCI always have disease-free survival as a first end point," Ingle said. "If this study was wrong, then the portfolio of those other studies was wrong, and I don't think that is the case."

NCI's Abrams further explained the end point design: "Disease-free survival was chosen because we have a lot of [information] about tamoxifen, and the fact that disease-free survival correlated very closely with survival," he said. "So once we have that evidence, it becomes unethical not to share that information with patients."

The researcher who conceived of the trial and chaired it, Paul Goss, M.D., of the Princess Margaret Hospital in Toronto, said that, other than the NSABP, "there wasn't a single Western world breast cancer collaborative study group that wasn't involved directly in the design of this trial and the decision to use these end points and the statistical calculations."

And he said that the U.S. Food and Drug Administration "accepts disease-

free survival as a regulatory end point



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because they don't want people to do a death study for an agent that is relatively innocuous." Furthermore, disease-free survival, "particularly in terms of internal

metastasis, translates into inevitably fatal breast cancer," he said.

"You could not do an indefinite placebo-controlled trial with death as your end point and long-term toxicity as your end point ... in a first venture into a novel therapy. It is not possible," Goss maintained.

He emphasized that the study was never designed to test the duration of therapy, or even to be conducted for a 5-year period, and that incremental research questions, such as side effects, will continue to be studied. "No patient is going to go out and take 15 years of therapy all at once today. They are going to be advised to begin therapy and stay tuned," he said. "Our assumption was that we wanted to find a therapy that affords patients at least the same benefit that tamoxifen afforded patients when it was first given against a placebo."

Goss believes the study is invaluable because it shows that hormone-dependent breast cancer can still be sensitive to an anti-estrogen, even after tamoxifen's effect has reached a plateau. "There was a worry these cells were all resistant to antagonizing with estrogen, and that we weren't going to get any further mileage from that concept," Goss said. "This opens the door to say that estrogen is [the] conductor of the breast cancer orchestra and that we have not by any means exploited handcuffing the band leader. Continuing to take maximum advantage of the hormonal dependency of breast cancer over a very long period of time will likely offer a lot of benefit to patients."

—Renee Twombly