

Letrozole Is First Hormonal Therapy To Significantly Reduce Spread Of Early Breast Cancer To Other Parts Of The Body After Standard Tamoxifen Treatment In Postmenopausal Women

- ***Landmark MA-17 trial demonstrated significant 40% reduction in the risk of distant breast cancer recurrence post-tamoxifen (extended adjuvant)***
- ***Letrozole also reduced mortality by 39% vs. placebo in postmenopausal women with early breast cancer that had spread to the lymph nodes at the time of diagnosis***

Basel, Switzerland, 8 June 2004 – New data from the landmark MA-17 study demonstrated a significant 40% reduction in the rate of distant breast cancer recurrences, or *metastases*, with extended adjuvant (post-tamoxifen) letrozole in postmenopausal women with early breast cancer. These data were presented today during the “Best of Oncology” session at the annual meeting of the American Society of Clinical Oncology (ASCO) in New Orleans. Distant metastases are a well-established risk factor for breast cancer death.

At the median 2.5 year follow-up, a survival advantage has now become apparent in those women whose cancer had already spread to lymph nodes at the time of diagnosis (node-positive). In this group of trial participants, which comprised approximately 50% of all patients in MA-17, deaths were reduced by a significant 39% vs. placebo. Patients with node-positive breast cancer are more likely to develop distant metastases and, therefore, may be at greater risk of dying from the disease. These results from the MA-17 trial indicated that letrozole first hormonal therapy to demonstrate a survival advantage in any population in the extended adjuvant setting. Across the entire study population, survival differences did not reach statistical significance in this analysis.

The term *extended adjuvant* describes the period following standard adjuvant treatment with tamoxifen. Even years after breast cancer diagnosis and primary treatment the ongoing risk of breast cancer recurrence and mortality remains significant for all patients. Extended adjuvant treatment with letrozole is the first therapy to effectively address this ongoing risk.

“Overall, the results of MA-17 may provide a new option for postmenopausal women completing standard adjuvant treatment with tamoxifen,” said Paul Goss, MD, PhD, director of Breast Cancer Prevention and Research, Princess Margaret Hospital, Toronto, Canada. “Treatment with letrozole resulted in a marked reduction in the risk of recurrent breast cancer and the occurrence of new breast cancer. Most importantly, treatment with letrozole also reduced distant metastases, which are very often fatal.”

Coordinated by the National Cancer Institute of Canada Clinical Trials Group at Queens University in Kingston, Ontario, the MA-17 study evaluated extended adjuvant treatment with Letrozole vs. placebo in nearly 5,200 postmenopausal women with

early breast cancer. The results showed that letrozole significantly lowered the risk of metastases overall by 40%. At the median 2.5 year follow-up, overall survival was unchanged in node-negative patients, but reductions in local recurrences, new primary tumors, and distant recurrences were consistent with those seen in node-positive patients. The data also showed that extended adjuvant treatment with letrozole reduced mortality by 39% in women with node-positive disease (P=0.035). Across all patients, 18% fewer deaths occurred with letrozole, a difference that, at the median 2.5 year follow-up, had not reached statistical significance.

In addition, an improvement in disease-free survival (reduced risk of disease recurrence in the breast, chest wall, lymph nodes or metastatic sites), the primary endpoint of the study, was achieved across all patients in the letrozole group. The data showed that taking letrozole after standard adjuvant therapy with tamoxifen cut a woman's risk of recurrence nearly in half as compared with placebo (42% reduced risk of recurrence; including metastases, contralateral breast cancer and recurrence within or near the original site; P=0.00003).

Safety Data

The MA-17 study also included pre-planned sub-studies that assessed the effect of letrozole on bone mineral density and lipid metabolism. There was no significant difference between treatment groups in bone fractures. The authors noted more newly diagnosed cases of osteoporosis in women taking letrozole vs. placebo (6.9% vs. 5.5%; P=0.04). The rate of clinical fractures, however, was not statistically higher for letrozole than for placebo (5.9% vs. 5.5%).

Neither the core MA-17 protocol nor the lipid sub-study showed significant differences between the letrozole and placebo groups in terms of cardiovascular events or lipid profiles. While the HDL:LDL cholesterol ratio decreased after the first six months of therapy, the decrease was similar in both groups.

Study Design

MA-17 is a Phase III, international, double-blind, randomized, multi-center trial. Last fall, data from an interim checkpoint from the core MA-17 trial prompted an Independent Data Safety Monitoring Committee and the investigators to unblind the study early so patients taking placebo could be offered the opportunity to switch to letrozole, regardless of their treatment-free interval since completion of tamoxifen therapy. All patients are still being followed under an amended protocol. The interim results from MA-17 received an expedited review from the *New England Journal of Medicine* and were published in the online edition in October 2003.

About Letrozole

Letrozole, an aromatase inhibitor, is an oral once-a-day first-line treatment for postmenopausal women with hormone receptor positive or hormone receptor unknown locally advanced or metastatic breast cancer. It is also approved for the treatment of advanced breast cancer in postmenopausal women with disease progression following antiestrogen therapy, and as neo-adjuvant (pre-operative) therapy. Letrozole is currently available in more than 80 countries worldwide. Not all indications are available in every country. Global filings for use of letrozole in the extended adjuvant setting were submitted in April 2004.

Letrozole Contraindications and Adverse Events

In the interim MA-17 analysis, the most common adverse events were hot flashes, sweating, edema, hypercholesterolemia, headache, arthralgia, myalgia, fatigue,

constipation and dizziness, in greater than 10% of patients in either arm of the study. Of these, hot flashes, arthralgia, and myalgia were more common in those receiving letrozole than placebo ($P < 0.05$). Vaginal bleeding was more common in those taking placebo ($P = 0.01$).

Letrozole is contraindicated in patients with known hypersensitivity to letrozole or any of its excipients. Letrozole is generally well tolerated. In a first-line registration trial versus the antiestrogen tamoxifen, the most commonly reported adverse events for letrozole were bone pain (22% vs. 21%), hot flashes (19% vs. 16%), back pain (18% vs. 19%), nausea (17% vs. 17%), dyspnea or labored breathing (18% vs. 17%), arthralgia (16% vs. 15%), fatigue (13% vs. 13%), coughing (13% vs. 13%), constipation (10% vs. 11%), chest pain (6% vs. 6%) and headache (8% vs. 6%). Letrozole may cause fetal harm when administered to pregnant women. There is no clinical experience to date on the use of letrozole in combination with other anticancer agents. The incidence of peripheral thromboembolic events, cardiovascular events, and cerebrovascular events was 3-4% in each treatment arm.

The foregoing release contains forward-looking statements that can be identified by terminology such as "reduced spread," "become apparent," "survival advantage," "deaths were reduced," "more likely," "may be," "improve overall survival," "lowered the risk," "improvement," "could be," "were submitted," "may offer," or similar expressions, or by express or implied discussions regarding potential new indications for letrozole or potential future sales of letrozole, or regarding the long-term impact of a patient's use of letrozole. Such forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause actual results with letrozole to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that letrozole will be approved for any additional indications in any market. Nor can there be any guarantee regarding potential future sales of letrozole. Neither can there be any guarantee regarding the long-term impact of a patient's use of letrozole. In particular, management's expectations regarding commercialization of letrozole could be affected by, among other things, additional analysis of letrozole clinical data; new clinical data; unexpected clinical trial results; unexpected regulatory actions or delays or government regulation generally; the company's ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; increased government pricing pressures; and other risks and factors referred to in the Company's current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected.

Additional Information

Additional information regarding letrozole or Novartis Oncology can be found at www.femara.com or www.novartisoncology.com. Additional media information can be found at www.novartisoncologyvpo.com.

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