Great strides have been made in the diagnosis and treatment of early-stage breast cancer, thanks to advances in molecular medicine, interdisciplinary treatment, and rapid electronic communication. Hormonal therapy, the first and most successful targeted therapy for breast cancer, has saved many thousands of lives. Moreover, screening and adjuvant (postoperative) therapy have increased survival among women with breast cancer. The improvement in survival can be attributed to both adjuvant tamoxifen therapy and adjuvant chemotherapy and has been found in all subgroups of patients regardless of the presence or absence of tumor cells in draining lymph nodes, including women who are premenopausal, those who are postmenopausal, those with estrogen-receptor–negative tumors, and those with estrogen-receptor–positive tumors. Experts are now in the process of classifying breast cancer, which actually consists of a heterogeneous group of cancers, into multiple categories. It is essential to define each subgroup precisely and to delineate distinct characteristics and targets that will lead to tailored therapies that are better than the ones we have now.

In this issue of the Journal, the Breast International Group (BIG) 1-98 Collaborative Group reports on a randomized comparison of letrozole, an aromatase inhibitor, with tamoxifen as adjuvant therapy for postmenopausal women with early-stage breast cancer. Their findings validate the results of previous studies showing that aromatase inhibitors were more efficacious than tamoxifen in such women. The BIG 1-98 Collaborative Group found a reduction in the incidence of relapse of 3.4 percentage points at five years in the letrozole group, as compared with the tamoxifen group, after a median follow-up of 25.8 months. The incidence of both distant recurrence and contralateral breast cancers was reduced. The benefit was greatest in patients who had also received chemotherapy, who did not receive radiotherapy, and who had positive nodes. Longer follow-up is important to define the benefit of letrozole in patients with node-negative disease. There was no significant difference in survival between the two groups, but at this point, fewer deaths have occurred among women assigned to letrozole.

Five other large trials have also evaluated aromatase inhibitors. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, with a median follow-up of 68 months, found that, as compared with tamoxifen, adjuvant treatment with anastrozole reduced the recurrence rate by 3.7 percentage points in patients with hormone-receptor–positive tumors. The MA.17 trial, in which women first received tamoxifen for five years and then were randomly assigned to receive placebo or letrozole, found that letrozole improved disease-free survival by 4.6 percentage points, after a median follow-up of 30 months, with a survival difference in the node-positive group only. The Intergroup Exemestane Study (IES), with a median follow-up of 30.6 months, compared 2 to 3 years of tamoxifen followed by 2 to 3 years of exemestane with 5 years of tamoxifen therapy and found that the former regimen increased disease-free survival by 4.7 percentage points. The Italian Anastrozole Trial (ITA), with a median follow-up of 36 months, compared 2 to 3 years of tamoxifen followed by 2 to 3 years of anastrozole with 5 years of tamoxifen and found that sequential treatment re-
duced recurrent-free survival by 5.8 percentage points. Finally, a combined analysis of data from two prospective, multicenter, randomized trials (the Austrian Breast and Colorectal Cancer Study Group trial 8 plus the Arimidex–Nolvadex study) compared women who received two years of tamoxifen followed by three years of anastrozole with women who were given tamoxifen for five years. After a median follow-up of 28 months, sequential therapy was associated with an event-free survival rate that was 3.1 percentage points higher than the rate associated with tamoxifen alone. These five studies varied with respect to the number of women with hormone-receptor–positive tumors, node-negative tumors, and node-positive tumors and the definition of outcomes. It is clear, however, that these trials, with close to 30,000 participants, consistently demonstrate that treatment with an aromatase inhibitor alone or after tamoxifen treatment is beneficial. The questions that remain are the optimal duration of treatment with an aromatase inhibitor, whether tamoxifen or an aromatase inhibitor should be given first, whether sequential treatment is optimal, which aromatase inhibitor is best, and whether an aromatase inhibitor is beneficial for premenopausal women after ovarian ablation. The decrease in contralateral cancers among women treated with an aromatase inhibitor has important implications for chemoprevention. Ongoing trials should answer each of these questions.

One of the most exciting aspects of the findings of these evaluations of aromatase inhibitors is that an animal model predicted the results. In tumor cells and peripheral tissues in postmenopausal women, estrogen is synthesized by aromatase from androstenedione and testosterone. A mouse model was developed to simulate the hormonal milieu in postmenopausal women and used to investigate the ability of aromatase inhibitors and tamoxifen to hinder the growth of breast-cancer cells. This model predicted a superior clinical outcome with aromatase inhibitors. The same model also predicts that the administration of letrozole alone will be more effective than the sequential administration of tamoxifen and letrozole. Future analyses of the continued follow-up of the BIG 1-98 study, which includes a group randomly assigned to receive letrozole before tamoxifen therapy and a group assigned to receive letrozole after tamoxifen therapy, will answer this important question.

A hypothesis developed from the ATAC study is that estrogen-receptor–positive, progesterone-receptor–negative tumors are more susceptible to anastrozole than tumors that have both types of hormone receptors. Although this hypothesis was not supported by the findings of the BIG 1-98 study, because of the relatively short follow-up and multiple subgroup analyses in the study, the idea also cannot be ruled out. Data that support a differential benefit in patients with progesterone-receptor–negative tumors include the finding that patients with such tumors are likely to have HER-1–positive or HER-2–positive breast cancer, positive nodes, tumors with high rates of proliferation and aneuploidy, and lower median levels of estrogen receptors. All these features are typical of an aggressive tumor. Another area of fertile research is the crosstalk between growth factor signaling pathways and the estrogen receptor. This crosstalk may result in tamoxifen resistance by potentiating agonist properties of tamoxifen.

It is clear that unlike tamoxifen, aromatase inhibitors are not associated with an increased risk of thromboembolism or uterine cancer. The incidence of fractures and arthralgias is, however, increased among women taking these inhibitors. Both complications are the result of estrogen deficiency, and they require a thorough evaluation with the aim of limiting these adverse effects. In the BIG 1-98 study, the incidence of serious cardiac events was significantly higher among women given letrozole than among those given tamoxifen. An increase in cardiovascular events among patients receiving an aromatase inhibitor has also been suggested in the IES and ATAC studies. This finding may be due to a cardioprotective effect of tamoxifen, but whatever the mechanism, the potential for adverse cardiovascular events needs close and careful evaluation.

We have seen a substantial increase in the number of patients with small, node-negative tumors over the past several years. In the future, molecular characterization of individual tumors will assist in determining the metastatic potential of the tumor and its sensitivity to various agents. It is our responsibility as physicians to determine the appropriate adjuvant treatment for patients,
but the choices are increasingly complex. Fortunately, we have the results of large, prospective, well-designed, and well-executed clinical trials, such as BIG 1-98, to facilitate our recommendations. We await longer follow-up from all the studies to enable us to offer patients sound advice regarding the benefits and long-term risks of aromatase inhibitors. Meanwhile, all the evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes and who are at a substantial risk for recurrent disease.

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Trial Registration Report Card

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One measure of medical progress is new treatments. The discovery of a novel therapy takes time and money, but more important, it requires the mutual effort of groups that, while they share the common goal of improved treatment, often have fundamentally competing interests. These interests intersect at the clinical trial. Patients who are looking for more effective and safer treatment agree to take part in a clinical trial in the hope that they will benefit from such treatment or that others with similar conditions will benefit later. The company developing the new therapy shares the hope that the trial will be successful, because it wants to market the tested therapy exclusively and profitably for as long as possible before its competitors can launch a similar therapy into the marketplace. These goals, though overlapping, are inevitably in conflict and will generate tension. Such tension has been thrown into sharp relief over the past 15 months by the push for clinical trial registration.

The academic establishment and patients have argued that when patients, motivated by altruism, participate (or even consider participating) in a clinical trial, they are entitled to understand fully all the options available to them in the various trials that are currently recruiting subjects. In addition, their participation in a clinical trial should result in generalizable knowledge that will be available to future patients and investigators to improve patient care. This can happen only when appropriate details of the clinical trial are made available to the public in a timely fashion. The Internet and public registries have made this possible.

Some in industry have argued that to open