

# Clinical Differences among the Aromatase Inhibitors<sup>1</sup>

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## Abstract

In the United States, three third-generation aromatase inhibitors are available commercially: anastrozole, letrozole, and exemestane. Anastrozole and letrozole are nonsteroidal agents, whereas exemestane is a steroid. The three agents differ in terms of structure and metabolic products and in the degree to which they suppress aromatase activity. The clinical significance of these differences is unclear. All three of the agents have been found to be equivalent or superior to megestrol acetate as a second-line therapy for metastatic breast cancer. In the first-line setting, large Phase III trials have demonstrated that anastrozole and letrozole are equivalent or superior to tamoxifen in women with metastatic disease. Multiple trials with widely varying study designs have been launched in the adjuvant setting comparing the aromatase inhibitors to tamoxifen. Early results from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial suggest a small but statistically significant improvement in disease-free survival for anastrozole compared with tamoxifen, but further follow-up is needed. This article explores the efficacy and tolerability of the aromatase inhibitors in both the metastatic and the adjuvant settings.

## Introduction

Hormonal therapies are an important part of treatment for both metastatic and early-stage breast cancer. The selective ER<sup>3</sup> antagonist (SERM) tamoxifen has been used in the treatment of metastatic breast cancer since the 1970s. By binding to ERs in tumor cells and preventing binding by endogenous estrogen, tamoxifen deprives breast cancer cells of the growth-stimulating effects of estrogen. In the metastatic setting, tamoxifen has been shown to result in tumor shrinkage and to delay disease progression (1). Tamoxifen is also used extensively in the adjuvant setting, where it has been shown to decrease breast cancer recurrence and increase survival in women with ER-positive and/or PR-positive tumors (2). This benefit has been shown to exist in all women with ER- and/or PR-positive tumors, regardless of nodal or menopausal status.

In recent years, drugs have been developed that deprive

breast cancer cells of estrogen through other mechanisms. The aromatase inhibitors prevent conversion of adrenal androgens into estrogens via the inhibition of the cytochrome P-450-dependent enzyme aromatase. This enzyme is responsible for the majority of estrogen production in postmenopausal women and in men.

Aminoglutethimide, the first aromatase inhibitor developed, was introduced in the late 1970s. The drug was shown to have efficacy in hormone receptor-positive breast cancer, but its use was limited by the concomitant suppression of cortisol and aldosterone production. In the mid-1990s, aromatase inhibitors with much greater specificity for the aromatase enzyme were developed, which produced no clinically relevant suppression of cortisol or aldosterone. These third-generation inhibitors include the steroidal drug exemestane and the nonsteroidal drugs letrozole, anastrozole, and vorozole. The steroidal inhibitor binds irreversibly to the aromatase enzyme, whereas the nonsteroidal inhibitors form covalent, reversible bonds. Despite this slight difference in the mechanism of action, both classes of drugs are very potent inhibitors of aromatase and have been shown to decrease estrogen levels to below the level of detection of most clinical assays (3–5).

## Second-Line Therapy for Metastatic Breast Cancer

The aromatase inhibitors initially gained FDA approval based on their efficacy as second-line therapy for metastatic breast cancer. Several randomized trials demonstrated that the third-generation aromatase inhibitors were equivalent or superior to megestrol acetate in this setting (6–11). The aromatase inhibitors were generally well tolerated and led to less weight gain than did megestrol.

Two large trials demonstrated the clinical equivalency of anastrozole and megestrol acetate in women who had failed first-line tamoxifen (6, 10). Buzdar *et al.* (9) published a combined analysis of these trials, in which 764 women were randomized to one of three arms: anastrozole 1 mg, anastrozole 10 mg, or megestrol acetate 40 mg 4 times daily. Overall, there were no significant differences in the efficacy endpoints across the study arms. Time to progression was ~21 weeks in all of the arms, and response rate was 10.3% in the anastrozole 1-mg arm, 8.9% in the anastrozole 10-mg arm, and 7.9% in the megestrol acetate arm. The estimated death hazard ratio was 0.80 (97.5% CI, 0.49–1.30) for anastrozole 1 mg *versus* megestrol and 0.71 (97.5% CI, 0.42–1.18) for anastrozole 10 mg *versus* megestrol. Although both study drugs were generally well tolerated with few patients withdrawing because of adverse effects, there was significantly more nausea in the anastrozole groups and significantly more weight gain in the megestrol group. More than 30% of women in the megestrol group had weight gain of  $\geq 5\%$ , and more than 10% had weight gain of  $\geq 10\%$ .

Letrozole was also shown to have similar efficacy to megestrol acetate in two large randomized studies. Domber-

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<sup>3</sup> The abbreviations used are: ER, estrogen receptor; PR, progesterone receptor; CI, confidence interval; DFS, disease-free survival.

nowsky *et al.* randomized 551 postmenopausal women who had failed tamoxifen or letrozole (0.5 mg or 2.5 mg) or megestrol acetate (160 mg; 7). The 0.5 mg dose of letrozole was found to be inferior to the 2.5 mg dose. Letrozole was found to produce significantly higher response rates than megestrol (24% for the 2.5 mg letrozole dose *versus* 16% for megestrol;  $P = 0.04$ ). There was no difference in time to progression between the groups (5.6 months for letrozole *versus* 5.1 months for megestrol). There was also no difference in the percentage of patients who derived clinical benefit (includes partial and complete responses as well as stable disease for  $\geq 24$  weeks). Clinical benefit was seen in 35% of patients treated with letrozole and 32% of patients treated with megestrol. Median duration of clinical benefit was significantly longer in the letrozole arm at 23.5 months *versus* 14.5 months in the megestrol arm ( $P = 0.001$ ). Megestrol was also significantly less tolerable, with 11% of patients discontinuing megestrol *versus* 3% discontinuing letrozole for adverse effects.

In another trial, Buzdar *et al.* compared two doses of letrozole to megestrol acetate as second-line therapy for postmenopausal women with metastatic breast cancer (11). In this trial, 602 women were randomized to letrozole (0.5 mg or 2.5 mg) or megestrol acetate (40 mg four times a day). In contrast to the trial of Dombrowsky *et al.*, letrozole did not display a dose-dependent antitumor effect in this trial. There was no significant difference among the groups in terms of response rate or duration of clinical benefit. Median time-to-disease progression was longer in the letrozole 0.5 mg arm (6 months) than in the letrozole 2.5 mg arm or the megestrol acetate arm (both 3 months). Patients treated with letrozole 0.5 mg had a significantly lower risk of disease progression than the patients treated with megestrol acetate (hazard ratio, 0.80;  $P = 0.044$ ). The difference in time to progression between the two letrozole arms did not reach statistical significance. There was no difference in survival among any of the groups.

Exemestane was also compared with megestrol as second-line therapy for metastatic breast cancer. Kaufman *et al.* (8) randomized 769 patients to 25 mg of exemestane *versus* 40 mg of megestrol four times daily. Response rates were similar between the two groups (15% in the exemestane arm *versus* 12.4% in the megestrol arm). Median time to progression was significantly longer in the exemestane arm (20 weeks *versus* 17 weeks). Median survival was also significantly longer in the exemestane arm (median survival not reached in the exemestane arm; 123 weeks in the megestrol arm). Again, adverse effects were greater in the megestrol arm, with weight gain of 17.1% in the megestrol group *versus* 7.6% in the exemestane group ( $P = 0.001$ ).

On the basis of these studies, the third-generation aromatase inhibitors were shown to be at least as effective as megestrol acetate. A meta-analysis pooled data from three of these large randomized trials comparing aromatase inhibitors to megestrol (12). This analysis demonstrated a survival advantage in favor of the aromatase inhibitors, with a relative risk of death of 0.79 (95% CI, 0.69–0.91). Given their efficacy and lack of significant side effects, the aromatase inhibitors have largely replaced megestrol as second-line hormonal therapy for metastatic breast cancer.

### First-Line Treatment for Metastatic Breast Cancer

Several large randomized trials have compared the third-generation aromatase inhibitors to tamoxifen for first-line treatment of metastatic breast cancer (13–16). Overall, these trials have demonstrated that the aromatase inhibitors have similar or slightly superior clinical efficacy as compared with tamoxifen. On the basis of these trials, both letrozole and anastrozole have gained FDA indications for first-line treatment of metastatic breast cancer.

Anastrozole has been compared with tamoxifen as first-line treatment for metastatic breast cancer in two large randomized trials and one smaller trial. The two large trials were carried out simultaneously in North America and in various centers throughout Europe and the rest of the world [the TARGET (Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability Study) trial], with the intention of combining data once the trials were completed (13, 14). Both trials randomized postmenopausal women with locally advanced or metastatic breast cancer to treatment with tamoxifen 20 mg every day or anastrozole 1 mg every day. Prior adjuvant therapy with tamoxifen was allowed, as long as the medication had been discontinued at least 12 months before study entry. All of the patients had ER- and/or PR-positive or unknown tumors. Primary outcomes included response rate, time-to-disease progression, and tolerability.

A total of 353 patients were enrolled in the North American trial and 668 patients in the TARGET trial. Patients in the tamoxifen and anastrozole groups were evenly matched in terms of demographic and disease characteristics, such as prior therapies and sites of metastatic disease. There were significantly more patients with ER/PR unknown tumors in the TARGET trial. In the North American trial, 89% of patients were known to be ER or PR positive, whereas in the TARGET trial, receptor status was known to be positive in only 45% of patients.

The trials were designed to show equivalency between tamoxifen and anastrozole for the major study endpoints. The North American trial raised the possibility that anastrozole may be superior to tamoxifen (13). There was no statically significant difference in response rate, with 21% of patients having a partial or complete response to anastrozole *versus* 17% to tamoxifen. However, treatment with anastrozole led to a significantly higher clinical benefit rate than did tamoxifen (59% *versus* 46%;  $P = 0.0098$  in post-hoc analysis). Median time to progression was also significantly longer in patients treated with anastrozole (11.1 months *versus* 5.6 months;  $P = 0.005$ ).

In contrast, the TARGET trial showed no statistically significant differences between the anastrozole and tamoxifen arms for any of the study endpoints (14). Response rates were 33% in both arms, clinical benefit rates were 56% in both arms, and median time-to-disease progression was 8.2 months in the anastrozole arms and 8.3 months in the tamoxifen arm. A small subgroup analysis of ER- and/or PR-positive patients showed significantly longer time-to-disease progression in the anastrozole arm (10.7 months *versus* 6.4 months;  $P = 0.022$ ).

Combined analysis of data from these two trials failed to show a significant difference between the two treatments (17). The response rate in the anastrozole arm was 29% *versus* 27.1% in the tamoxifen arm; clinical benefit rates were 57.1% for

anastrozole and 52% for tamoxifen ( $P = 0.11$ ); and time-to-disease progression was 8.5 months in the anastrozole arm versus 7 months in the tamoxifen arm ( $P = 0.103$ ). The trials were not mature enough at the time of publication to report survival data. Toxicity data displayed similar rates of hot flashes (~25%), nausea (~19%), and asthenia (~16%). Thromboembolic events (including venous thromboembolism, coronary ischemia, and ischemic cerebrovascular events) were significantly more common in the tamoxifen arm (6.5% versus 3.6% in the anastrozole arm;  $P = 0.043$ ). Overall, the combined analysis indicated that anastrozole appeared to be at least as efficacious and tolerable for first-line treatment of metastatic breast cancer. The North American data suggested that anastrozole might be superior to tamoxifen in patients known to have ER- or PR-positive disease.

One other small, nonblinded, randomized trial compared anastrozole to tamoxifen for first-line treatment of metastatic breast cancer. Milla-Santos *et al.* (15) randomized 238 patients with locally advanced or metastatic breast cancer to 1 mg of anastrozole versus 20 mg of tamoxifen. All of the patients were known to have ER- and/or PR-positive disease, and prior treatment with tamoxifen in the metastatic or adjuvant setting was not allowed. There was no significant difference in response rates: 34% in the anastrozole arm and 27% in the tamoxifen arm. Significantly more patients treated with anastrozole experienced clinical benefit (82% versus 55% with tamoxifen;  $P < 0.05$ ), and median time to progression was longer with anastrozole than with tamoxifen (12.3 months versus 5.3 months;  $P < 0.05$ ). At 35 months of follow-up, a greater proportion of patients treated with anastrozole were alive as compared with patients treated with tamoxifen (39 versus 8%; no  $P$  reported).

As a result of these trials, anastrozole gained an FDA indication for first-line treatment of metastatic breast cancer.

Letrozole has been demonstrated to have superior efficacy to tamoxifen as first-line treatment for metastatic breast cancer. Mouridsen *et al.* randomized 907 postmenopausal patients to 2.5 mg of letrozole or 20 mg of tamoxifen daily (16). All of the patients had locally advanced or metastatic breast cancer, and had ER- and/or PR-positive or unknown disease. The two arms were well balanced in terms of baseline characteristics, disease stage, and sites. Hormone receptor status was unknown in approximately one-third of the patients in each arm.

Patients treated with letrozole had a significantly longer time-to-disease progression than did patients treated with tamoxifen (41 weeks versus 26 weeks;  $P = 0.0001$ ). Response rates were also significantly higher in the letrozole arm (30 versus 20%;  $P = 0.0006$ ), as were rates of clinical benefit (49 versus 38%;  $P = 0.001$ ). Both of the medications were well tolerated, with only 7% of patients in each arm discontinuing the study medication because of toxicity. Thirty-eight % of patients treated with letrozole and 37% of patients treated with tamoxifen experienced an adverse event believed to be related to treatment. The most common side effects were hot flashes, nausea, and hair thinning. Incidence was similar in the two groups. Thromboembolic events were uncommon in this study but occurred slightly more often in the tamoxifen arm (2% in the tamoxifen arm versus 1% in the letrozole arm). On the basis of the results of this study, letrozole also gained an indication for use as first-line treatment for metastatic breast cancer.

A large, randomized trial is presently also underway comparing exemestane with tamoxifen as first-line therapy for metastatic breast cancer. Results from this trial are not yet available. Dirix *et al.* have reported in abstract form the results of a randomized Phase II trial comparing exemestane with tamoxifen as first-line therapy (18). A total of 122 patients were randomized to 25 mg of exemestane or 20 mg of tamoxifen daily. The group reported higher response and clinical benefit rates in the exemestane group, but statistical analysis was not included in the report.

### Aromatase Inhibitors in Early-Stage Breast Cancer

Many clinical trials are currently underway evaluating aromatase inhibitors in the adjuvant setting. These trials aim to demonstrate which hormonal therapy leads to the lowest rates of breast cancer recurrence and produces the most favorable side effect profile. Some of these trials directly compare the aromatase inhibitors and tamoxifen, whereas others look at sequential treatments using both tamoxifen and aromatase inhibitors.

One of the first adjuvant trials compared the standard 5 years of adjuvant tamoxifen to sequential treatment with tamoxifen followed by an aromatase inhibitor (19). Postmenopausal women who were free of disease after 3 years of adjuvant tamoxifen were randomized to 2 additional years of tamoxifen or to 2 years of aminoglutethimide at a dose of 250 mg a day. All of the patients were ER positive or unknown; 380 women were randomized. The trial was stopped early because of a high incidence of toxicity in the aminoglutethimide arm. At a median follow-up of 61 months, 114 events had occurred: 59 events occurred in the tamoxifen group, including 10 non-breast cancer deaths, and 55 events occurred in the aminoglutethimide group, including 2 non-breast cancer deaths. Most of the non-breast cancer deaths in the tamoxifen group were attributable to myocardial infarctions or other cardiovascular events. Forty-two patients in each arm developed metastatic disease. There were 19 breast cancer deaths in the tamoxifen arm and 10 in the aminoglutethimide arm. Overall, there was no difference in event-free survival between the two groups, but there was a statistically significant improvement in overall survival in the aminoglutethimide group ( $P = 0.005$ ) and a trend toward an improvement in breast cancer-specific survival in this group as well ( $P = 0.06$ ). However, treatment-related side effects were much more common in the aminoglutethimide group and led to discontinuation of the study medication in 14% of patients, as compared with 4% in the tamoxifen group.

At this time, only one trial comparing a third-generation aromatase inhibitor and tamoxifen in the adjuvant setting has been reported. The ATAC (Anastrozole or Tamoxifen Alone or in Combination) trial randomized 9366 postmenopausal women with invasive breast cancer to 5 years of adjuvant anastrozole, tamoxifen, or a combination of the two (20, 21). Women could be hormone-receptor positive or unknown. Primary endpoints were DFS and tolerability.

Baseline characteristics were well balanced across the three groups. The average age was 64, one-third of the patients had positive lymph nodes, and 64% had tumors less than 2 cm in size. Prior treatments were also similar between the groups: 48%

had undergone mastectomy, 62% had received radiation, and 21% had been treated with chemotherapy.

Median follow-up at the time of the interim analysis was 33.3 months. A total of 1079 events had occurred: 317 in the anastrozole arm, 379 in the tamoxifen arm, and 383 in the combination arm. There was a statistically significant improvement in DFS in the patients treated with anastrozole as compared with tamoxifen, with a hazard ratio of 0.83 (95% CI, 0.71–0.96). There was no difference in DFS between the combination arm and the tamoxifen arm. No survival analysis has been performed to date. The study also looked at the incidence of adverse events. Hot flashes, vaginal bleeding, endometrial cancer, stroke, and venous clotting were all more common in the tamoxifen arm, whereas musculoskeletal disorders, bone loss, and fractures were more common in the anastrozole arm. Toxicity in the combination arm was similar to that seen in the tamoxifen arm (21).

After the release of these data, ASCO (American Society of Clinical Oncologists) convened a multidisciplinary panel of experts to conduct a technology assessment on the role of aromatase inhibitors in the adjuvant setting (22). The group recommended that tamoxifen continue to be standard adjuvant therapy in early-stage breast cancer until additional data from this and other trials become available. In coming to this conclusion, the group cited concerns over the unknown effects of long-term treatment with aromatase inhibitors, especially on bone density. The group noted that the absolute difference in distant DFS was less than 1%, and there has been no difference reported in overall survival. Studies have shown that the full benefit of tamoxifen requires 5 years of treatment and that there is additional benefit even after tamoxifen is stopped. It is not clear whether the same profile will exist for anastrozole, thus raising further concern about the short follow-up in this study.

One other study that looked at the use of an aromatase inhibitor in early-stage breast cancer has been reported. Ellis *et al.* (23) have reported their experience comparing letrozole and tamoxifen in the neoadjuvant setting. The group randomized 324 postmenopausal patients who were not candidates for breast conservation to preoperative tamoxifen or letrozole (2.5 mg/day) for 4 months. Looking only at the hormone receptor-positive patients, clinical response rates were significantly higher in the letrozole arm (60 *versus* 41%;  $P = 0.004$ ). Patients treated with letrozole were also significantly more likely to be candidates for breast conservation after preoperative therapy, with 48% of these patients ultimately receiving a lumpectomy *versus* 36% of patients treated with tamoxifen ( $P = 0.036$ ).

The group also looked at response rates in patients whose tumors overexpressed HER2/neu and/or ErbB-1. Patients whose tumors overexpressed HER2/neu (14% of tumors) were significantly less likely to respond to tamoxifen as compared with patients whose tumors did not overexpress HER2/neu (17 *versus* 40%,  $P = 0.045$ ). However, HER2/neu overexpression did not appear to influence response to letrozole. Clinical responses to letrozole were seen in 69% of HER2-positive patients and 53% of HER2-negative patients. Similar results were seen in ErbB-1 positive tumors. Clinical response rates were higher in the letrozole arm than in the tamoxifen arm for all subgroups, but especially so in patients whose tumors overexpressed HER2/neu and/or ErbB-1 (88 *versus* 21%;  $P = 0.0004$ ). It should be noted,

however, that the group of patients with HER2/neu- and/or ErbB-1-positive tumors was quite small ( $n = 36$ ).

These studies suggest that the aromatase inhibitors may be useful in the treatment of early-stage breast cancer. The FDA has recently approved anastrozole for use in the adjuvant setting. However, before abandoning tamoxifen in the adjuvant setting, more data are needed proving the efficacy and documenting the side effects of long-term treatment with aromatase inhibitors.

### Differences among Aromatase Inhibitors

Although studies have demonstrated the superiority of the third-generation aromatase inhibitors to aminoglutethimide, a first-generation aromatase inhibitor (24), there are few published data comparing the third-generation aromatase inhibitors with each other. All three of these newer aromatase inhibitors reduce estrogen levels below detection levels of most clinical assays, although preclinical data do suggest some differences in degree of estrogen suppression and in selectivity for the aromatase enzyme. It is currently not known whether any of these pharmacological differences are clinically relevant.

Geisler *et al.* (3) recently published the results of a small double-blind, cross-over study looking at estrogen levels and aromatase activity in patients treated with letrozole and anastrozole. Twelve patients with ER-positive, metastatic breast cancer were treated with each of the two study medications for 6 weeks. Serum estrogen levels and total body aromatization were measured in each patient for both of the study drugs. The study found a significantly higher suppression of the aromatase enzyme with letrozole compared with anastrozole (>99.1 suppression *versus* 97.3% suppression;  $P = 0.0022$ ). Estrogen levels were also significantly lower during treatment with letrozole. Estrone levels were suppressed by 81% with anastrozole and 84.3% with letrozole ( $P = 0.019$ ); estrone sulfate levels were suppressed by 93.5% with anastrozole and by 98% with letrozole ( $P = 0.0037$ ). There was no significant difference in degree of estradiol suppression (84.9% for anastrozole and 87.8% for letrozole;  $P = 0.1088$ ).

Data suggest that anastrozole may be slightly more selective for the aromatase enzyme than is letrozole. Studies have shown no impact on cortisol or aldosterone levels in patients being treated with 3–10 mg/day anastrozole for up to 3 months (25, 26). In contrast, some studies have shown significant declines in cortisol and/or aldosterone levels in patients treated with 2.5 or 0.5 mg letrozole for 2–3 months. In one study, basal levels of aldosterone and cortisol did not significantly decrease after 3 months of treatment with letrozole, but peak values after Cortrosyn stimulation were significantly lower after 3 months of treatment (27). Another study showed a significant decrease in the plasma concentration of cortisol after 2 months of treatment with letrozole (28). However, cortisol and aldosterone levels did not fall below the lower limits of normal during the study period, and patients did not develop symptoms of adrenal insufficiency (29). These findings imply that letrozole may be less selective for the aromatase enzyme. It is not currently known whether this difference in selectivity will result in clinical effects with long-term usage.

Only one study has compared the clinical efficacy of third-generation aromatase inhibitors. Rose *et al.* (30) pre-

sented preliminary results from an open-label, randomized study comparing letrozole and anastrozole in second-line therapy for metastatic breast cancer. A total of 713 postmenopausal women were randomized; 48% had hormone receptor-positive disease; receptor status in the remainder was unknown. Baseline and disease characteristics were well matched between the groups. No difference was seen in the primary end point, time to progression. There was a significantly higher response rate in the letrozole arm (19.1 *versus* 12.3%;  $P = 0.014$ ) but no difference in rate of clinical benefit (27% for letrozole *versus* 23% for anastrozole;  $P = 0.218$ ). Both of the medications were well tolerated.

Several additional trials are under way comparing aromatase inhibitors in a variety of clinical settings. The ongoing adjuvant trials have several basic designs: some compare 5 years of adjuvant tamoxifen with an aromatase inhibitor; others look at the use of sequential therapy with tamoxifen and an aromatase inhibitor; and the last group studies tamoxifen followed by an aromatase inhibitor *versus* placebo. There are additional studies underway that directly compare two aromatase inhibitors in the metastatic setting, and a larger adjuvant trial is planned comparing anastrozole with exemestane. Data from these trials should be available within the next few years, and will help guide additional treatment recommendations for women with breast cancer.

## Conclusions

The aromatase inhibitors have proven to be very active drugs in the treatment of hormone receptor-positive breast cancer. They originally gained FDA approval on the basis of their efficacy as second-line therapy and their favorable side effect profiles. Recent studies have indicated that letrozole and anastrozole appear to be at least as effective as tamoxifen in first-line therapy and may prove to be superior in term of response rates and time-to-disease progression. Most studies have also indicated that aromatase inhibitors are less likely than tamoxifen to lead to serious adverse events, such as venous clotting, stroke, and endometrial cancer (16, 17). Incidence of hot flashes and nausea appear to be similar in patients treated with aromatase inhibitors and tamoxifen (17).

The role of aromatase inhibitors in early-stage breast cancer is not yet clear. Early results from one study suggest that anastrozole may be effective in preventing breast cancer recurrence. Further information is needed to determine whether or not aromatase inhibitors should be used in place of tamoxifen. Several studies are also evaluating the benefits of sequential administration of tamoxifen and an aromatase inhibitor.

Although several trials are in progress, there are currently few data comparing the clinical efficacy of the third-generation aromatase inhibitors. Some preclinical data suggest that there may be differences in the degree of estrogen suppression and in the selectivity of the drugs for the aromatase enzyme. Future trials must determine whether these differences are clinically important.

## Open Discussion

**Dr. Stephen Johnston:** Can we talk about what to do in the patients who fail on nonsteroidal aromatase inhibitors? In

the clinic that's the problem I'm facing now with the aromatase inhibitors becoming first line. In the United Kingdom, people are giving exemestane second line based on Per Lonning's data [J. Clin. Oncol., 18: 2234–2244, 2000], but some people are not wildly impressed by it. There's very little else out there. We don't know whether tamoxifen will work second-line. The models tell us that probably tamoxifen would not work but that fulvestrant or a tyrosine kinase inhibitor would work.

**Dr. Steven Come:** A patient who is progressing on an aromatase inhibitor is probably hypersensitive. The tumor is growing in a very low estrogen environment. I wonder whether that's different from the tumors that are primed with estradiol in these models. If so, fulvestrant might not work well after an aromatase inhibitor, particularly if there are dose issues and you are not able to effectively eliminate the receptor in a very hypersensitive situation.

**Dr. Johnston:** We've looked at it in long-term estrogen-deprived cells in the lab, and in that situation they're refractory to tamoxifen. They're refractory to estrogen. They go through a phase of being sensitive, but they're very sensitive to fulvestrant. If we're going to go from an aromatase inhibitor to fulvestrant, should we keep the aromatase inhibitor or withdraw it? Now, in the long-term estrogen-deprived cells, we continue the estrogen deprivation, and in those circumstances, they respond very well to fulvestrant. In fact, if we do begin to put estrogen back, the fulvestrant doesn't work quite as well. We would like to do a study in which we will randomize patients staying on the aromatase inhibitor or coming off. I think it's a key issue.

**Dr. Kent Osborne:** Dick Santen's data suggest that tumors can reset their thermostat. If you deprive them of estrogen for a long time they get supersensitive to it; then, when you give them back pharmacological estrogen, they undergo apoptosis. I think those data demand a trial of moderate or high-dose estrogen in patients coming off an aromatase inhibitor. For all of these different cross-overs, it's going to be important to try and figure out from molecular data which patients should get which treatment.

**Dr. Carlos Arteaga:** And a second biopsy is important.

**Dr. Come:** Last year we called for blocks on all trials. This year we ought to be thinking about repeat biopsies to look at as many markers as possible so that we can see what is changing over the course of therapy.

**Dr. Mitch Dowsett:** Potentially, the most exciting piece of technology will be getting the cells out of blood. I don't think anybody's really categorically demonstrated these are breast cancer cells and what their clonal relationship is with the primary. But if that was proven and if we came up with simple reliable techniques for separating those cells out, then that's going to potentially allow studies from one or two cells.

**Dr. Arteaga:** Your neoadjuvant studies have really taught me that one can get very good readouts within 2 weeks. And I was thinking just in the neoadjuvant setting, we can use some of these combinations and look for pharmacodynamic responses.

**Dr. Johnston:** It's a cleaner model to do direct comparisons because you're guaranteed to get samples on everybody. I've done quite a few studies trying to get biopsies on

metastatic disease. You often end up selecting patients who have a certain type of pattern of disease, the more slow-growing indolent pattern with superficial skin nodules. With the neoadjuvant model, you could get in a small number of patients some great data.

**Dr. Dowsett:** It doesn't teach us about resistance or acquisition of resistance.

**Dr. Johnston:** That's the problem; it doesn't teach us about resistance. The signaling pathways that we're talking about now in hormone-sensitive disease may not be up-regulated, and resistance may be an acquired phenomenon. So that will be the worry about relying on the presurgical model.

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