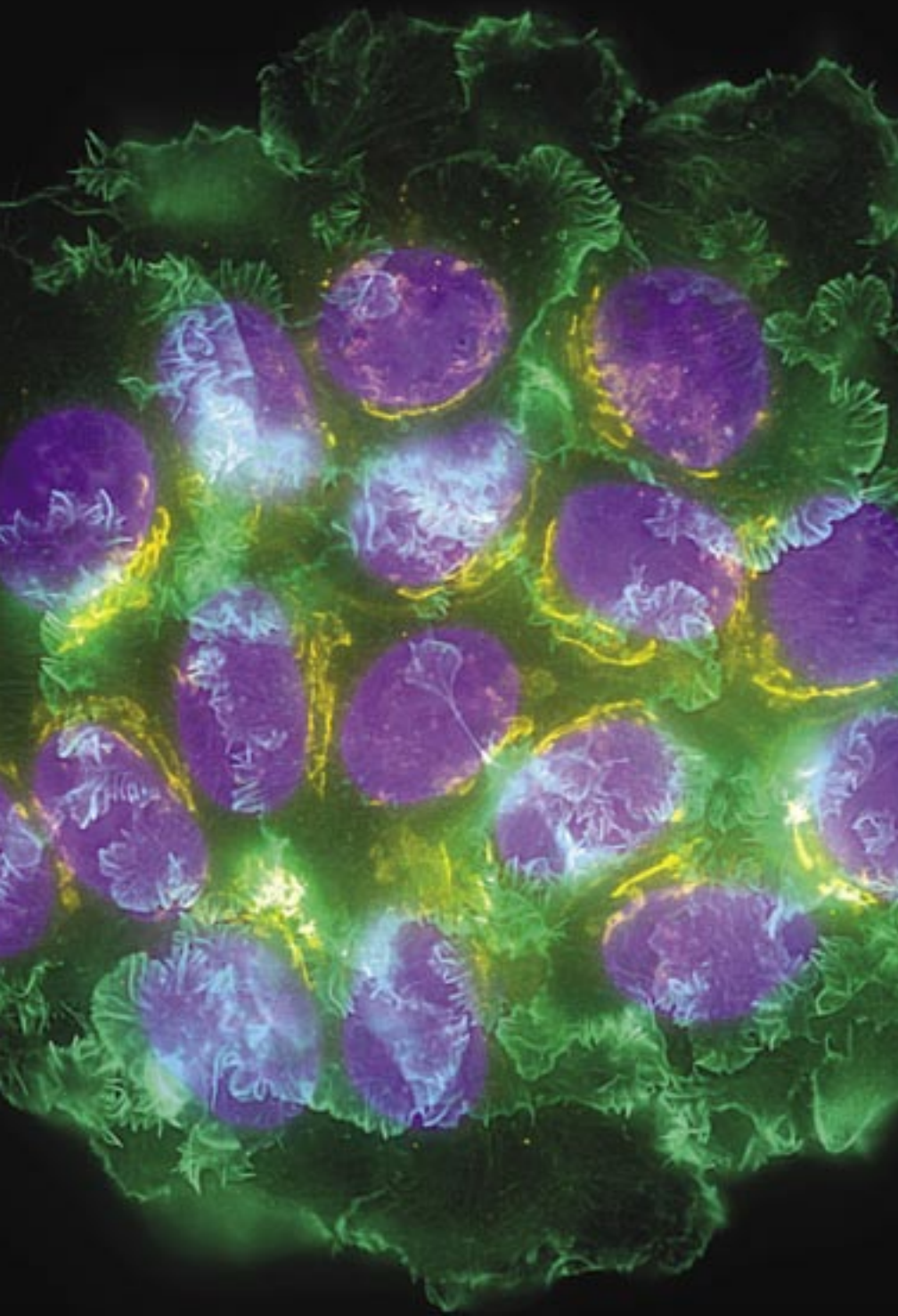
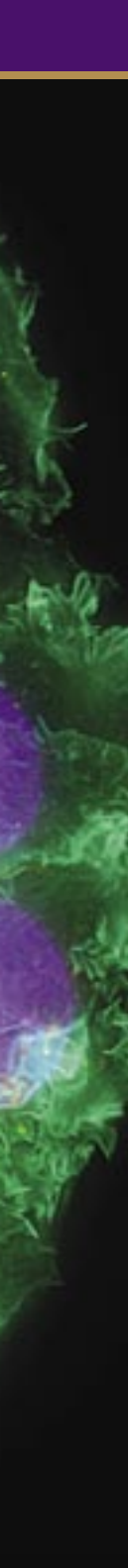


BREAST CANCER



A vertical strip on the left side of the page shows a microscopic image of breast cancer cells. The cells are stained in shades of green and purple, appearing as irregular, textured shapes against a dark background.

New treatments for breast cancer can make a major difference in the life of a woman with the disease: longer survival, free of cancer.

Breast Cancer

A Report on the Latest Research and Treatments from ASCO—the American Society of Clinical Oncology

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If you would like more information on these topics and other news from ASCO's 2006 Annual Meeting, visit www.OncologyReport.com

Breast Cancer Prevention

RALOXIFENE (EVISTA) AND TAMOXIFEN (NOLVADEX) FOR PREVENTING BREAST CANCER IN WOMEN AT HIGH RISK

To prevent breast cancer, a drug called raloxifene (Evista) appears to be just as effective as tamoxifen (Nolvadex and others), another medication commonly used to prevent the disease. Raloxifene, regularly used to fight bone loss in women, appears to cause fewer serious side effects. These results come from the Study of Tamoxifen and Raloxifene (STAR), one of the largest breast cancer prevention studies ever conducted, in which raloxifene was compared with tamoxifen. Tamoxifen has been approved by the U.S. Food and Drug Administration (FDA) to lower breast cancer risk among women at high risk for the disease and to reduce the risk of breast cancer recurrence.



Both drugs work by blocking **estrogen receptors**—tiny sites on cells that work like doorways, allowing the female hormone estrogen to enter the cells and promote their growth. The drugs block the **receptors** the way a guard might block a doorway. This prevents estrogen from getting inside and fueling tumor growth.

Conducted in medical centers across the United States and Canada, STAR involved nearly 20,000 postmenopausal women at high risk for breast cancer. The researchers compared women who took raloxifene daily for five years with women who took tamoxifen instead for the same length of time.

After four years, both drugs were equally effective in preventing **invasive breast cancer** by about 50 percent. Invasive breast cancer is cancer that has spread outside of the milk ducts, where it originated, into the fatty tissues of the breast and into other parts of the body.

Even though the drugs are similar in this way, there are a number of pros and cons that women with breast cancer and their doctors must weigh, bearing in mind that tamoxifen has been studied longer than raloxifene, so more is known about it. Here are some of the things to think about:

STAR Results: Raloxifene versus Tamoxifen

	Raloxifene	Tamoxifen
Ability to prevent <i>invasive</i> breast cancer	Equivalent to tamoxifen (167 of 9,745 women in STAR developed the disease)	Equivalent to raloxifene (163 of 9,726 women in STAR developed the disease)
Ability to prevent <i>non-invasive</i> breast cancer	Not as effective as tamoxifen (81 of 9,745 women in STAR developed the disease)	More effective than raloxifene (57 of 9,726 women in STAR developed the disease)
Risk of uterine cancer	36% lower risk than tamoxifen	Risk is higher, but still low overall
Known serious side effects	Blood clots, but 29% fewer than in women on tamoxifen	Uterine cancer, blood clots, strokes, and cataracts
Incidence of strokes in STAR	Equivalent to tamoxifen (51 of 9,745 women)	Equivalent to raloxifene (53 of 9,726 women)
Incidence of bone fractures in STAR	Equivalent to tamoxifen (96 of 9,745 women)	Equivalent to raloxifene (104 of 9,726 women)

What's New, What's Important

- Raloxifene (Evista), a drug commonly used to fight bone loss in women, appears to be just as effective at preventing invasive breast cancer as tamoxifen (Nolvadex and others), another medication commonly used to prevent breast cancer. Both treatments have pros and cons.
- Women who take anastrozole (Arimidex) to reduce their risk of breast cancer recurrence lose bone at a faster rate than normal over time.
- Trastuzumab (Herceptin) can be combined safely with radiation to prevent recurrence of certain types of breast cancer, but women receiving this combination should be checked regularly by their doctors to help prevent any heart problems.

Preventing Recurrence of Early Stage Breast Cancer

ANASTROZOLE (ARIMIDEX) FOR BONE LOSS IN POSTMENOPAUSAL WOMEN

After a woman has been treated for early-stage breast cancer, doctors commonly prescribe tamoxifen for five years to keep the disease from coming back. Tamoxifen helps prevent the recurrence of breast cancers that are **estrogen receptor-positive**—tumors that are sensitive to the growth-promoting effects of estrogen.

But researchers are looking at another class of drugs, called **aromatase inhibitors**, as an alternative to tamoxifen. These drugs work by blocking the production of estrogen. Estrogen is produced by the ovaries and other tissues of the body, using a substance called aromatase. Although aromatase inhibitors do not block the production of estrogen by the ovaries, they can block other tissues from making this hormone. That's why aromatase inhibitors are used mostly in women who have

reached menopause, when the ovaries are no longer producing estrogen.

An aromatase inhibitor called anastrozole (Arimidex) is being compared with tamoxifen in a large study called the Arimidex, Tamoxifen, Alone or in Combination (ATAC) clinical trial. For more than five years, ATAC researchers have been



tracking nearly 10,000 postmenopausal women who have been taking the drugs, separately or together, to prevent a recurrence of breast cancer.

Previous findings from the ATAC clinical trial have shown that anastrozole is more effective than tamoxifen at preventing breast cancer recurrence. But

unlike with tamoxifen, taking anastrozole can lead to bone loss. Tamoxifen is known to protect against bone thinning.

To judge the impact of anastrozole on bone, ATAC researchers compared the bone health of a small group of ATAC participants. They compared the bones of the lower back and hip bones of 81 women who had taken anastrozole for five years with those of 86 women who had been on tamoxifen for the same length of time. What they found was that bone loss was significantly greater among women who had taken anastrozole. Specifically, the women in the anastrozole group had lost more than 6 percent of the bone in their spine and more than 7 percent in their hips.

In contrast, the women who had been taking tamoxifen gained bone mass—almost 3 percent in their spines and nearly 1 percent in their hips. Normally, postmenopausal women lose

about 2 percent to 3 percent of their bone over the course of 5 years.

The researchers noted that none of the women in the anastrozole group developed **osteoporosis** if they began the study with normal strong bones. Osteoporosis is a bone-thinning disease that can lead to serious fractures.

The findings suggest that women who take anastrozole should have their bone health checked every one to two years.

They should also ask their doctors about other strategies for protecting their bones, such as taking calcium and vitamin D supplements.

The women in the ATAC clinical trial are still being followed to see what effects the drugs have on the participants after their treatment is finished.

SAFETY OF TRASTUZUMAB (HERCEPTIN) AND RADIATION FOR PREVENTING BREAST CANCER RECURRENCE

In 2005, important findings from a pair of studies sponsored by the National Cancer Institute showed that, when combined with chemotherapy, trastuzumab (Herceptin) prevents recurrence of early-stage **HER2-positive breast cancer**. HER2 is a gene that makes a substance, also called HER2, that controls cell division. If a breast cancer cell has too much HER2—that is, if it's HER2 positive—it tends to grow more rapidly.

Of the women treated with the trastuzumab/chemotherapy combination, 3 percent to 4 percent experienced serious heart problems—a side effect seen in other research with trastuzumab.

After chemotherapy, some women undergo radiation



treatments to ensure that any stray cancer cells are destroyed. Trastuzumab may increase the effectiveness of radiation on breast cancer cells, but it can also damage the heart. So a team of researchers with the North Central Cancer Treatment Group decided to see whether combining trastuzumab with radiation might reduce the recurrence of HER2-positive breast cancer and/or increase the incidence of heart problems.

The study involved more than 1,200 women treated with radiation and trastuzumab or trastuzumab alone after undergoing surgery for early-stage breast cancer. About a year-and-a-half later, about 2 percent to 3 percent of the women in both groups had experienced heart problems. In terms of side effects, the only significant difference between the groups was that a greater percentage of women treated with both radiation and trastuzumab developed low white blood cell counts, which can increase the risk of infection. No data were available about the effect on recurrence rates.

Given the findings, the researchers concluded that combining radiation and trastuzumab is a safe practice. However, *all women* treated with trastuzumab should have regular blood pressure checks and physical exams to help prevent any heart problems.

Treatment of Early-Stage Breast Cancer

GENES AND EFFECTIVENESS OF ANTHRACYCLINES

Dutch researchers have identified a gene abnormality that appears to be associated with the effectiveness of **anthracyclines** in women with breast cancer. Anthracyclines are a class of drugs that are highly effective at preventing the recurrence of breast cancer.

The researchers analyzed samples of tumors taken from nearly 800 women with breast cancer. The women were treated

What's New, What's Important

- A certain gene abnormality appears to be associated with the effectiveness of anthracycline drugs—a specific form of chemotherapy—in women with breast cancer.
- A type of breast tumor (EGFR-positive) more often found in black women and young women tends to resist treatment with chemotherapy and hormones.
- The drug gefitinib (Iressa) stalls growth of breast tumors that are fueled by the hormone estrogen and may also be effective for tumors that are weakly influenced by progesterone.
- Combining the drugs capecitabine (Xeloda) and paclitaxel (Taxol and others) is just as effective in treating advanced breast cancer as the more conventional treatment approach of combining paclitaxel with an anthracycline drug.
- Adding the drug carboplatin (Paraplatin and others) to docetaxel (Taxotere) and trastuzumab (Herceptin) does not increase the effectiveness of docetaxel and trastuzumab in women with advanced breast cancer.
- The combination of capecitabine and an experimental drug called lapatinib (Tykerb) slowed the growth of advanced breast tumors that had begun growing despite treatment with trastuzumab.

with nine cycles of a combination of either cyclophosphamide (Cytoxan, Neosar, and others), methotrexate, and fluorouracil (5-FU)—together called CMF—or cyclophosphamide, 5-FU, and the anthracycline epirubicin (Ellence)—together called CEF.

They found that women with an abnormal number of copies of a gene called topoisomerase II (TOP2A) benefitted more from treatment with the anthracycline-containing combination than with the CMF drug combination. Specifically, those with TOP2A abnormalities survived about 50 percent longer, overall, when treated with CEF than with CMF. In contrast, women with normal amounts of TOP2A did not gain any benefits from treatment with the anthracycline, compared with CMF.

In addition, the researchers found that nearly 80 percent of the TOP2A abnormalities occurred in tumors that were also HER2-positive. Previous research suggests that anthracyclines are particularly effective at stopping the growth of HER2-positive tumors.

The findings suggest that a breast cancer tumor's TOP2A profile may serve as a guide for identifying women who may benefit most from anthracycline-containing treatments.

Epidermal Growth Factor Receptors (EGFRs) and Breast Cancer

Some breast tumors are known to have excess numbers of **epidermal growth factor receptors (EGFRs)**. These substances lie on the surface of the breast cancer cells and take in messages ordering the cells to grow and divide. Although many normal cells contain EGFRs, some kinds of cancer cells have abnormally high amounts of them. In other words, the tumors **overexpress** EGFR. The more receptors on a cell, the more signals the cell receives to grow and multiply. Tumors that overexpress EGFR are called EGFR-positive. Researchers are trying to use knowledge of a breast tumor's EGFR content to learn how the cancer might respond to treatment.

EGFR AND RESPONSE TO HORMONE TREATMENT AND CHEMOTHERAPY

Scientists at the Baylor College of Medicine in Houston measured the EGFR content of breast tumor samples taken from more than 2,500 women. They compared the EGFR measurements with each woman's characteristics, such as age, and the tumor's features, such as size.

They found that EGFR-positive tumors were more common among black women and women younger than 50 years of age. What's more, the EGFR-positive tumors tended to be larger and to spread into the **lymph nodes**. The lymph nodes

are a linked system of small bean-shaped structures throughout the body that help filter out and destroy bacteria and other substances. Breast cancer cells can spread to other parts of the body via the lymph system.

The researchers also found that EGFR-positive tumors were more likely to also be HER2 positive, and thus tended to be more aggressive and recur more often.

In addition, the study showed that chemotherapy and hormone treatments given after breast cancer surgery to prevent the cancer from returning were less likely

to slow cancer growth and prolong the lives of women with EGFR-positive tumors than those of women whose tumors did not overexpress EGFR. In contrast, among women who received chemotherapy but not hormone treatment following surgery, EGFR status was not associated with the rate at which their breast tumors grew.



GEFITINIB (IRESSA) AND BREAST CANCER

Researchers may have identified a certain type of breast tumor that is sensitive to treatment with gefitinib (Iressa). Belonging to a class of drugs called **targeted treatments**, gefitinib works by blocking EGFR. Targeted treatments zero in on cell mechanisms that supply blood to tumors and promote their growth and division. And, rather than killing both healthy and unhealthy cells, as chemotherapy does, targeted treatments attack cancer where it begins, with relatively few side effects.

In a small study of women who took the drug for at least

two weeks before having surgery to remove a breast tumor, researchers in the Breast Cancer International Research Group analyzed tumor samples obtained before and after the surgery. They looked at more than 18,000 genes in the samples to see how tumors that stopped growing after treatment with gefitinib compared with tumors that kept growing.

They found that gefitinib stalled cancer growth in tumors with certain qualities that affected their sensitivity to the female hormones estrogen and progesterone. For one, they were estrogen receptor-positive. For another, they were **progesterone receptor-negative** (or weakly progesterone receptor-positive), meaning that their cancer cells didn't allow progesterone to enter and didn't rely on this hormone to grow.

The researchers estimate that about 10 percent to 25 percent of women with breast cancer may have estrogen-receptor positive, progesterone receptor-negative tumors. For these women, drugs like gefitinib, which put the brakes on EGFRs, may be effective treatments.

Advanced Breast Cancer

TREATMENT OF ADVANCED BREAST CANCER WITH ANTHRACYCLINES

Women with early-stage breast cancer are often treated with chemotherapy containing anthracyclines. This class of drugs has also been shown to be highly effective against **metastatic** breast cancer—that is, breast cancer that has spread to other parts of the body. The difficulty is that if a woman with advanced breast cancer has already been given an anthracycline early in her treatment, treating her again with an anthracycline may be unsafe. Doctors are concerned about the cumulative effects of anthracyclines on the heart.

The findings from a German clinical trial offer a possible solution to the problem. The study involved nearly 350 women with advanced breast cancer, divided into two groups.

One group received the anthracycline drug epirubicin in combination with another drug called paclitaxel (Taxol and others). The other group was treated with paclitaxel and capecitabine (Xeloda), which is not an anthracycline.

Overall, both chemotherapy combinations were almost equally effective. In about half of the women in both groups, the cancer disappeared, shrank, or stopped growing for about a year, overall. However, the women in the group that received capecitabine suffered fewer serious side effects from the chemotherapy than the women treated with epirubicin. According to the researchers, these encouraging results indicate that capecitabine-paclitaxel treatment is an effective option for women with advanced breast cancer who have already been treated with an anthracycline.

CHEMOTHERAPY AND TRASTUZUMAB FOR ADVANCED BREAST CANCER

Carboplatin (Paraplatin and others) and docetaxel (Taxotere), both forms of chemotherapy, and the targeted treatment called trastuzumab have all been shown separately to help slow the growth of advanced breast cancer. A group of scientists speculated that if the three drugs were taken together, they might boost each other's effectiveness.



To put the theory to the test, the Breast Cancer International Research Group evaluated the combination in a large international study. The clinical trial involved 263 women with HER2-positive breast tumors. Prior to entering the study, none of the participants had been treated for advanced breast cancer.

The women were divided into two groups. One received docetaxel and trastuzumab, and the other received docetaxel and trastuzumab along with carboplatin.



The researchers found no significant differences in the effectiveness of the different drug treatments. More than 70 percent of the women in both groups responded to the drugs, with their tumors disappearing, shrinking, or stabilizing (neither shrinking nor growing). Overall, these responses lasted for 10 to 11 months in both groups. And, women treated with both drug combinations were surviving

for more than three years after treatment, overall. The women in both groups experienced a similar frequency and severity of side effects, although the types of effects that occurred varied somewhat between the groups.

The findings suggest that adding carboplatin to docetaxel and trastuzumab does not increase the effectiveness of the latter two drugs.

LAPATINIB (TYKERB) AND CAPECITABINE (XELODA): AN OPTION WHEN TRASTUZUMAB STOPS WORKING

Although trastuzumab can shrink or slow the growth of some advanced breast tumors that produce large amounts of HER2, it eventually stops working. But a recent study has shown that the combination of chemotherapy and a new targeted treatment called lapatinib (Tykerb) helps control these tumors.

The international study involved more than 300 women with advanced breast cancer that continued growing despite treatment with anthracycline drugs, other chemotherapy,

and trastuzumab. The women were split into two groups. One group received capecitabine, which comes in a pill. The other group was given capecitabine along with lapatinib. Also available in pill form, lapatinib blocks the workings of both HER2 and EGFR.

Researchers took a preliminary look at how long tumors took to begin growing or spreading after treatment—a measurement called **time to progression**. They found that in women given both drugs, time to progression was almost twice as long (37 weeks, overall) as in women who took capecitabine alone (20 weeks). The early findings were so striking that the researchers decided to halt the clinical trial and give the women who had been taking capecitabine alone the option to also take lapatinib.

The researchers also monitored the women for brain **metastases**—tumors that had spread from the breast into the brain. HER2-positive breast cancer raises the risk for brain tumors. They found that only 4 women treated with lapatinib and capecitabine developed brain metastases, compared with 11 given capecitabine alone. Equally encouraging, the women who took lapatinib did not experience any more severe side effects, overall, than those who did not take the drug. Research on lapatinib is ongoing.

ESTROGEN BLOCKADES: ATAMESTANE, TOREMIFENE (FARESTON), AND LETROZOLE (FEMARA) FOR ADVANCED BREAST CANCER

Breast tumors that are estrogen-receptor positive or progesterone-receptor positive are often treated with drugs designed to block the production, or effects, of estrogen, which can fuel growth of the tumors. Researchers at 60 medical centers in four countries decided to see whether combining a drug that blocks estrogen production with one that blocks the hormone's effects—making an “estrogen blockade”—is more effective than either one alone against advanced breast cancer.

What's New, What's Important

- Researchers are trying to determine whether combining a drug that blocks estrogen production with one that blocks the hormone's effects—in essence, producing an “estrogen blockade”—is more effective than either drug alone against advanced breast tumors that are fueled by estrogen.
- Adding the drug docetaxel (Taxotere) to the standard chemotherapy given to women after surgery to remove breast cancer may prolong the time some of these women will live, free of cancer.
- After surgery, women given five different chemotherapies—an anthracycline, docetaxel, and a combination of drugs called CMF—in sequence survived longer without having a cancer relapse than women given the same drugs at one time.
- Chemotherapy administered continuously—almost daily—was more effective at eliminating breast cancer than the same drugs given every few weeks in women who had not yet had surgery to remove breast cancer.
- An experimental drug called denosumab holds promise as a treatment for women whose breast cancer has spread into the bones.

The study involved more than 850 women with estrogen receptor- and/or progesterone receptor-positive advanced breast cancer, divided into two groups. One group was treated with an experimental drug called atamestane, which blocks estrogen production, and toremifene (Fareston), a drug that blocks the effects of estrogen. The other group was treated only with letrozole (Femara), which prevents estrogen formation.

With treatment, 30 percent of the women in the two-drug “estrogen blockade” group responded to the drugs, with tumors that shrank or stopped growing. In contrast, 36 percent of women treated with letrozole alone had a response. In both groups, the cancer began spreading or growing again after

about 11 months, overall—the longest time-to-progression ever seen in a clinical trial that used hormone therapy as the first treatment for advanced breast cancer.

Other clinical trials looking at the use of estrogen blockades in women with advanced breast cancer are currently under way.

Chemotherapy Before and After Surgery for Breast Cancer

After surgical removal of a breast tumor, women are often treated with chemotherapy to reduce the risk that the cancer will come back. Sometimes women are also treated medically before surgery, to try to shrink the tumor and get rid of as much of the cancer as possible. Researchers are continually looking at different combinations of drugs and different ways of administering them to see which are most effective for these women.

DOCETAXEL (TAXOTERE) AND BREAST CANCER

Italian researchers conducted a clinical trial involving nearly 1,000 women with early-stage breast cancer that had spread into the lymph nodes. All of the women had undergone surgery to remove the cancer.

The women were split into two groups. One was treated with the drug epirubicin and the chemotherapy combination cyclophosphamide, methotrexate, and 5FU (together called CMF). The drugs were administered in a sequence: four cycles of epirubicin followed by four cycles of CMF.

The other group received the same treatment as well as the drug docetaxel. Docetaxel was administered after the last cycle of epirubicin and before the first cycle of CMF was given.

Five years later, 67 percent of the women in the epirubicin/CMF group had survived, free of cancer, compared with 74 percent of the patients who were also treated with docetaxel.

Researchers deemed this difference “borderline significant.” There was no significant difference in the risk of death between the two groups of women.

But although the findings were not highly significant from a statistical standpoint, for many women in the study the addition of docetaxel gave them an extra year, free of cancer.

In a related study, the Irish Oncology Group also looked at the impact of adding docetaxel to CMF and the anthracycline drug doxorubicin (Adriamycin and others). The study involved about 2,800 women with breast cancer that had spread into the lymph nodes. The women were split into three groups.

- Group 1 received doxorubicin plus CMF.
- Group 2 received chemotherapy in this sequence: three cycles of doxorubicin, followed by three cycles of docetaxel, followed by three cycles of CMF.
- Group 3 received four cycles of doxorubicin and docetaxel, while also receiving three cycles of CMF.

Group 2 fared the best, ending up with the best chance of surviving without experiencing a cancer relapse, for 5 years after treatment. The findings make sense, given that receiving the drugs one after the other allows patients to receive higher doses of each drug than they would be able to tolerate if they got them all at once. Researchers are still observing the women who participated in this study to see how the treatments affect their lifespan.

CONTINUOUS VERSUS INTERMITTENT CHEMOTHERAPY FOR ADVANCED BREAST CANCER

Researchers with the Southwest Oncology Group compared the effects of administering a standard chemotherapy combination every few weeks with delivering the same drugs almost daily. They looked at more than 250 women with breast tumors that were large and/or had spread into the lymph nodes

and surrounding tissue. None of the women had undergone surgery for the cancer prior to enrolling in the study.

The participants were divided into two groups. One group received doxorubicin and cyclophosphamide once every 3 weeks for 15 weeks. The other group received the same drugs



on an almost continuous basis—doxorubicin weekly and cyclophosphamide daily for 6 days a week—also for 15 weeks. In addition, they received a blood-cell growth factor to stimulate the production of white blood cells, which often become depleted as a result of cyclophosphamide chemotherapy.

After the 15 weeks of chemotherapy ended, both groups of women also received

paclitaxel. This drug was administered weekly for an additional 12 weeks.

Tumors disappeared in more than 30 percent of the women who were treated continuously. In contrast, the cancer was eliminated in only about 20 percent of the women who received treatment once every three weeks. Continuous chemotherapy was particularly effective in women with estrogen receptor-negative tumors; in more than 40 percent of these women, cancer disappeared with treatment.

These findings underscore the importance of considering how chemotherapy is administered to women with breast cancer. Given the effectiveness of continuous dosing observed in this clinical trial, the same group of researchers is looking at the impact of continuous dosing in women who have already undergone surgery for breast cancer.

On the Horizon: Denosumab and Bone Health in Women with Metastatic Breast Cancer

An experimental drug holds promise as a treatment for women whose breast cancer has spread into the bone. Called denosumab, the new medication belongs to a class of drugs known as **monoclonal antibodies**. These drugs target

specific receptors on the surface of cancer cells, sparing normal, healthy cells.

Denosumab targets **RANK ligand (RANK-L)**, a natural substance that stimulates the growth, function, and survival of cells that break down bone.

Several types of cancer

cells contain RANK-L. When cancer has spread to the bone, RANK-L can overwhelm the body and lead to significant bone loss. The bones can become severely weakened and susceptible to fractures (breakage).

Denosumab was tested in a study involving more than 250 women with breast cancer that had spread to at least one area of bone. The women were treated with either injections of denosumab under the skin or a **bisphosphonate**, which was given **intravenously** (through a vein). By helping prevent the loss of calcium from bone, bisphosphonates strengthen the structure of the bone, reduce bone pain, and lower the risk of fractures. They are often used to curb bone loss after menopause and in people with cancer that has spread into the bones.

Nearly 75 percent of the women treated with denosumab



showed a significant decrease in the level of NTx (short for “N-telopeptide of type I collagen”) in their urine. NTx is a measure of bone activity that increases in people with bone cancer. In contrast, about 50 percent of those given bisphosphonates had comparable NTx reductions. More than a year after treatment, 9 percent of the women given denosumab had experienced fractures, compared with 16 percent of the women treated with bisphosphonates. The frequency and intensity of side effects experienced among women in both groups were similar. Research with this promising new drug is ongoing.