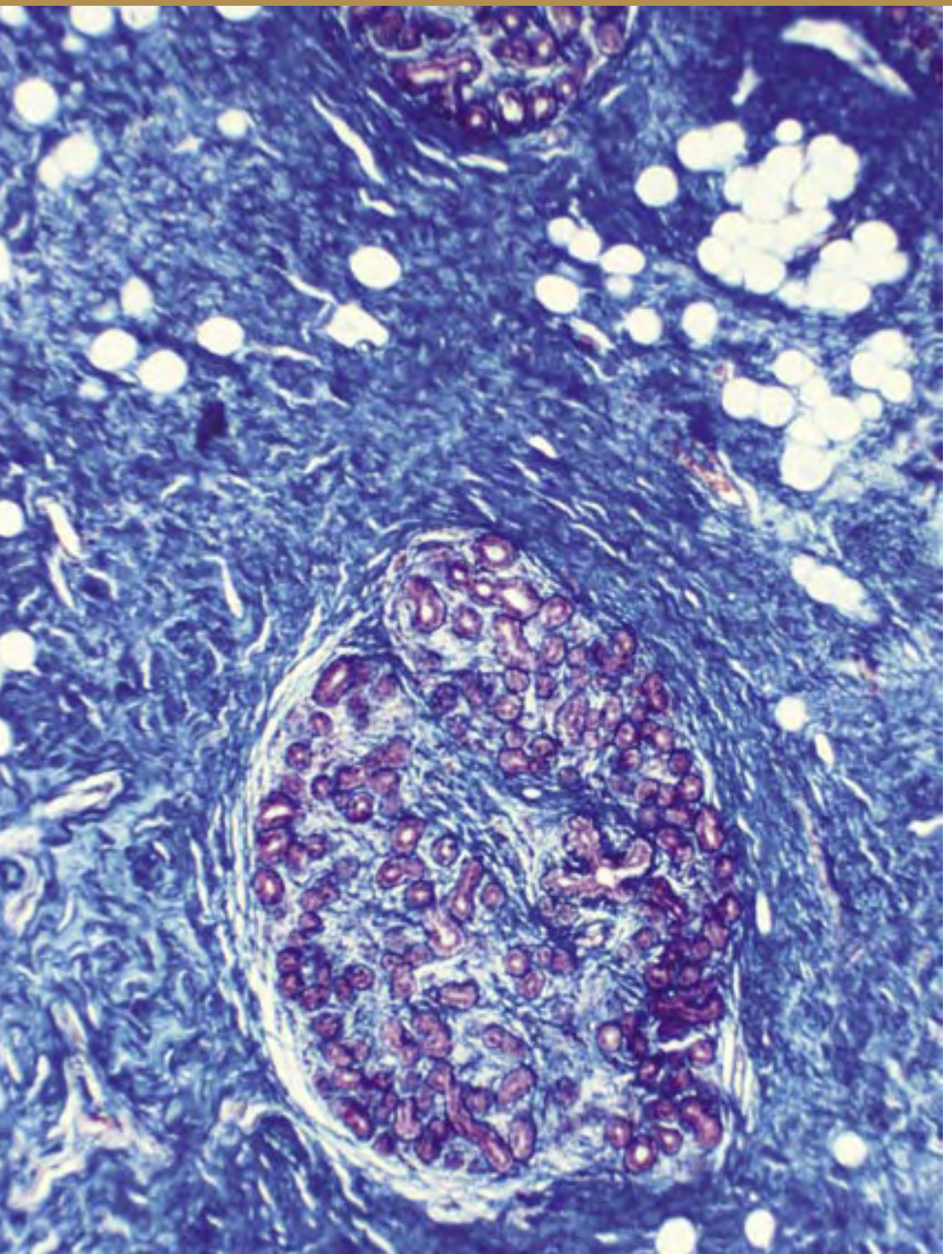

◀ Breast tissue

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A Report From the American Society of Clinical Oncology 2007 Annual Meeting

Breast Cancer

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Each year, breast cancer is diagnosed in more than 180,000 women in the United States. However, the outlook for patients continues to improve. Death rates from breast cancer are still declining, with larger decreases seen in women younger than 50. These decreases are believed to be the result of earlier detection through screening and increased awareness, as well as improved treatments such as those reported in this chapter.

Although doctors don't know exactly what causes breast cancer, certain risk factors are linked to the disease. But having a risk factor, or even several, doesn't mean that a person will get breast cancer. In fact, most women who do get breast cancer don't have any risk factors.

Many people wonder about environmental factors. Although a lot of research has been done, at this time there is no clear link between breast cancer and pollutants such as pesticides. There is also virtually no evidence to support the idea, popular on the Internet, that underarm antiperspirants or underwire bras can cause breast cancer.

Breast Cancer Diagnosis

MAGNETIC RESONANCE IMAGING SEEMS MORE ACCURATE THAN MAMMOGRAPHY FOR CERTAIN TUMORS

One reason more women are surviving breast cancer is early detection. Perhaps the most well-known screening method for breast cancer is mammography, the use of X-ray images of the breast that can find tumors in their earliest, most treatable **stages**. Researchers are now studying new approaches to breast imaging in the hope of detecting even more breast tumors before they progress to **invasive breast cancer**. This type of breast cancer has spread outside the milk ducts, where it originated, into fatty tissues of the breast or other parts of the body.

One encouraging diagnostic method is **magnetic resonance imaging (MRI)**, a test that uses radio waves to make computer images of tissues and structures inside the body. Mammography and MRI were compared in an ongoing German study of nearly 6,000 women. All of the women had both tests performed on both breasts. More than half of the women were having the MRI to check an irregular result on an earlier mammogram.

Researchers found that MRI appeared to be more accurate than mammography in diagnosing breast cancer confined to the milk ducts, a less serious, non-invasive cancer. Mammography diagnosed breast cancer in about 100 women, whereas MRI diagnosed breast cancer in about 150 women. About 50 percent of these early breast tumors could be seen on both

What's New, What's Important

- Magnetic resonance imaging (MRI) seems to be more accurate than mammography at diagnosing certain high-grade breast cancers and may be used more often in the future for early detection.
- Total mastectomy and breast-conserving surgery are equally effective in prolonging the lives of women with ductal carcinoma in situ of the breast, a precancerous tumor that could spread to other parts of the body.
- Lower doses of radiation given less frequently seem to be as effective as standard doses given more often in preventing cancer recurrence in women treated for early breast cancer. Lower doses of radiation cause fewer side effects.
- A diagnostic tool called the Onco*type* DX, which rates a woman's chance of her breast cancer recurring based on whether she has certain genes, may help doctors more confidently select the right treatment for the right person.

mammograms and MRI scans. But nearly 80 percent of the tumors found by MRI and missed by mammography were considered high grade—that is, more serious disease.

Early diagnosis of these high-grade tumors can help prevent aggressive invasive breast cancer. So MRI may become another tool doctors can use to diagnose breast cancer early, when treatment has a better chance of success.

Early-Stage Breast Cancer

MASTECTOMY VERSUS BREAST-CONSERVING SURGERY FOR EARLY BREAST CANCER

Ductal carcinoma in situ (DCIS) of the breast is a cancer in the milk duct that has not broken through into surrounding tissue. The rate of DCIS of the breast is increasing in the United States by half a percent a year, according to researchers from Sligo General Hospital in Ireland.

Current treatment options for DCIS of the breast are total mastectomy (removal of a breast) or breast-conserving surgery (lumpectomy, or limited removal of tissue containing the tumor) with radiation. Both approaches can include tamoxifen (Nolvadex and others). The findings of a large clinical trial of more than 50,000 women with DCIS show that both treatments are equally effective in prolonging the lives of these women.

Researchers from Ireland studied the records of more than 27,000 women treated with total mastectomy and more than 25,000 women treated with breast-conserving surgery and radiation from 1988 to 2003. Five years after treatment, more than 95 percent of women in both groups remained alive. Ten years after treatment, more than 90 percent of women in both groups remained alive.

Given the choice, most women with this type of cancer would likely opt for breast-conserving treatment.

REDUCED RADIATION FOR EARLY BREAST CANCER: JUST AS EFFECTIVE, WITH FEWER SIDE EFFECTS

Most women diagnosed with early invasive breast cancer receive some type of breast-conserving surgery to treat the cancer. Radiation after surgery is an accepted approach to preventing the cancer from returning. However, many women experience serious side effects as a result of the radiation, including thickened, inflamed skin (fibrosis) and swelling (edema). So researchers wondered whether lower doses of radiation given less often—which might cause fewer side effects—would be as effective as standard doses of radiation.

At 35 centers throughout the United Kingdom, researchers conducted clinical trials known as START: Standardization of Breast Radiotherapy. Almost 4,500 women who had had surgery for their cancer were separated into Trial A and Trial B. Patients in Trial A were treated for five weeks with either a standard dose of radiation in 25 treatments five days a week or one of two lower doses of radiation in 13 treatments on

alternating days. Patients in Trial B were treated for three weeks with either the same standard dose of radiation as in Trial A or one lower dose of radiation in 15 treatments.

After five years for Trial A and six years for Trial B, researchers found that women who received the lowest doses in both trials had milder side effects on healthy breast tissue than did those who received the standard dose. In terms of cancer recurrence, the women treated with the less frequent, lower doses of radiation had results that were just as good as those for women treated more often and with higher doses of radiation.

The researchers are excited about these results and suggest that the studies continue so we can learn more about long-term results.

Personalizing the Treatment of Breast Cancer

PREDICTING RECURRENCE OF BREAST CANCER WITH ONCO*TYPE* DX

Choosing the right treatment for a woman with breast cancer depends upon knowing whether she has **hormone receptor-positive** or **hormone receptor-negative tumors**. Although hormone receptor-positive breast cancer can spread to other parts of the body, it tends to grow more slowly than hormone receptor-negative cancer. Hormone receptor-positive breast tumors respond to hormone treatments such as tamoxifen (Nolvadex).

If doctors could predict which women would be more likely to experience a recurrence of their breast cancer and which ones would benefit most from chemotherapy and/or hormonal treatment, they could more effectively help patients select the best treatment. According to recent studies, there may be such a predictive test. Called the Onco*type* DX Recurrence Score (RS), this diagnostic tool rates a woman's chance of her breast cancer recurring based on whether she has certain genes.

In a large clinical trial conducted by the Eastern Cooperative Oncology Group, researchers evaluated more than 750 women with early breast cancer who had been treated with standard chemotherapy. For this analysis, researchers focused on the 465 patients who had hormone receptor-positive tumors. In this group, almost 200 women had a low RS, about 140 had an intermediate RS, and 125 had a high RS.

The RS was found to be a good predictor of recurrence in women with hormone receptor-positive cancer. The risk of cancer recurrence was much higher for those with an intermediate or high RS than for those with a low RS. Regardless of whether the cancer had spread to the **lymph nodes**, patients who had a low RS lived longer without the cancer returning than patients with a higher RS.

Researchers believe that these predictive results could affect the choice of treatment for these women.

In fact, a study conducted at Loyola University in Chicago showed that information learned from this test actually did change the decision making of some doctors treating women with early breast cancer.

This study included almost 90 women with **estrogen receptor-positive breast cancer** that had not spread to the lymph nodes. Their tumors were sensitive to the growth-producing effects of estrogen, and they were treated by 17 cancer doctors from four different practices. Knowing a woman's RS changed the treatment recommendations of more than 30 percent of the doctors and almost 30 percent of the

patients. The most common adjustment was to switch women with a low RS from a plan for chemotherapy plus hormone treatment to just hormone treatment.

Researchers concluded that having the information obtained from the Onco*type* DX RS helped doctors tailor treatment of breast cancer to a woman's unique genetic characteristics. Such results may also affect how doctors select for clinical trials women with breast cancer that has spread to the lymph nodes.

Advanced Breast Cancer

TRASTUZUMAB (HERCEPTIN) AND HEART SAFETY

Trastuzumab (Herceptin) has been a major advance in the treatment of both early- and late-stage breast cancers. It seems to work best with a type of cancer called **human epidermal growth factor receptor 2 (HER2)-positive breast cancer**.

However, trastuzumab also seems to be linked to an increase in side effects to the heart such as congestive heart failure (CHF). This is a condition in which the heart is working, but not as efficiently as it should.

So several groups of researchers have studied the use of trastuzumab to learn whether such heart problems progress over time. For example, nearly 1,800 women with HER2-positive breast cancer that had spread to the lymph nodes took part in a clinical trial as part of the National Surgical Adjuvant Breast and Bowel Project. Almost half of the women were treated first with doxorubicin (Adriamycin and others) and cyclophosphamide (Cytoxan, Neosar, and others) and then with a year of paclitaxel (Taxol). The other half received doxorubicin and cyclophosphamide as well, but then received trastuzumab along with the paclitaxel for a year.

After five years, CHF occurred in 4 percent of the women who received trastuzumab compared with 1 percent of the women who did not. The risk of CHF did not seem to increase over time in the women who received the combination chemotherapy that contained trastuzumab. Also, the risk essentially stopped when treatment with trastuzumab was discontinued. More studies are needed to be certain that there is no long-term damage to the heart.

What's New, What's Important

- Side effects to the heart associated with the use of trastuzumab (Herceptin) for breast cancer do not appear to increase over time. The risk stops when the drug is discontinued. Women treated with trastuzumab should be monitored for heart side effects, especially if they are at risk for congestive heart failure.
- Trastuzumab (Herceptin) may prove to be effective in shrinking tumors in women with HER2-negative metastatic breast cancer who also have multiple copies of chromosome 17.
- Letrozole (Femara) is more effective than tamoxifen in treating postmenopausal women with estrogen receptor-positive breast cancer.

TRASTUZUMAB IN HER2-NEGATIVE BREAST CANCER

As previously mentioned, trastuzumab seems to be most effective in treating HER2-positive breast cancer. However, clinical trials suggest that women with HER2-negative breast cancer whose tumor cells have extra copies of chromosome 17 may also benefit from trastuzumab. (The HER2 gene is located on chromosome 17.)

A clinical trial of the Cancer and Leukemia Group B (CALGB) treated a group of women with HER2-negative **metastatic** breast cancer who had multiple copies of chromosome 17 and were also FISH negative. (FISH refers to a type of HER2 test.) Twelve of the women received paclitaxel, and 19 received both paclitaxel and trastuzumab. The women who were treated with

the trastuzumab combination experienced significant decrease in the size of their tumor compared with the women who were treated with just paclitaxel—more than 60 percent decrease versus about 25 percent decrease.

CALGB researchers stressed that these are early results in a small number of patients. Before doctors can recommend this treatment approach for these select women with HER2-negative breast cancer, researchers need to conduct further clinical trials.

LETROZOLE (FEMARA) VERSUS TAMOXIFEN (NOLVADEX) FOR ADVANCED BREAST CANCER

Breast tumors that are estrogen receptor-positive are often treated with drugs designed to block the production, or effects, of estrogen, which can fuel the growth of these tumors. One of the newer estrogen-blocking drugs, called letrozole (Femara), has been tested in perhaps the largest review of this type of drug ever conducted. According to this clinical trial, letrozole is more effective than standard treatment in reducing the risk of estrogen receptor-positive breast cancer returning.

The clinical trial, which was performed by the International Breast Cancer Study Group, included more than 3,500 postmenopausal women who received letrozole or tamoxifen (Nolvadex and others) continuously for five years. Most women in the study (nearly 90 percent) had either estrogen receptor-positive or **progesterone receptor-positive** tumors.

Overall, women who were treated with letrozole experienced a nearly 30 percent reduction in the risk of their breast cancer returning. This benefit was seen in patients regardless of whether their tumors were progesterone receptor-positive or progesterone receptor-negative.

Because older people are underrepresented in clinical trials, researchers wanted to see whether these positive effects of letrozole also extended to older women with breast cancer. A separate analysis of information from the clinical trial focused on nearly 5,000 women treated with either letrozole or tamoxifen. The women were divided into three categories. The first group contained postmenopausal women below age 65, the second group contained women age 65 to 74, and the third group contained women age 75 or older.

Again, letrozole reduced the risk of breast cancer returning more than tamoxifen did. These benefits were seen consistently across all three age groups. Perhaps as important was the fact that these older women did not experience more side effects or more difficulty completing treatment than younger postmenopausal women.

Researchers concluded that letrozole is a better treatment than tamoxifen for postmenopausal women with estrogen receptor-positive breast cancer regardless of progesterone status and age.

CAPECITABINE (XELODA) PLUS BEVACIZUMAB (AVASTIN) FOR METASTATIC BREAST CANCER

Capecitabine (Xeloda) plus bevacizumab (Avastin) is another drug combination being studied for the treatment of metastatic breast cancer. Joining these two drugs seems to prolong the time until tumors grow in women who are receiving their first treatment for metastatic breast cancer.

More than 100 women took part in a clinical trial of this combination at Indiana University Cancer Center in Indianapolis and Northwestern University in Chicago. The time from the start of treatment until the disease grew was almost

six months. The time stretched to nearly nine months for about 60 women in the study who had estrogen receptor-positive tumors. In about six percent of women treated, the cancer disappeared. It shrank significantly in more than 30 percent of patients treated. Again, these responses were even better in those with estrogen receptor-positive cancer.

This drug combination warrants further study. Researchers are particularly interested in studying this approach in women who have estrogen receptor-positive tumors because it appeared to be much more effective in this group than in those with estrogen receptor-negative tumors.

IXABEPILONE AND CAPECITABINE FOR METASTATIC BREAST CANCER

For some women with metastatic breast cancer, the chemotherapies they receive lose their effectiveness over time. That's because metastatic breast cancer can become resistant to treatment. However, a new combination treatment may offer another option.

A compound called ixabepilone—which belongs to a new class of drugs known as epothilones—has been used in combination with capecitabine (Xeloda). At an international clinical trial led by researchers at Weill Cornell Medical College in New York City, these medications were given to more than 750 women with drug-resistant metastatic breast cancer. Ixabepilone is designed to interfere with the growth of cancer cells. This drug appeals to doctors because tumors are not likely to resist it.

More women treated with ixabepilone plus capecitabine lived longer without their cancer growing than women treated with capecitabine alone (almost six months versus approximately four months). The tumor either disappeared or significantly shrank in 35 percent of women who received both ixabepilone and capecitabine, compared with about 10 percent in women who received just capecitabine. Ixabepilone, which is also being studied in other types of cancer, is currently being reviewed

What's New, What's Important

- The combination of capecitabine (Xeloda) and bevacizumab (Avastin) seems to be an effective first-time treatment for women with metastatic breast cancer, particularly those with estrogen receptor-positive tumors.
- In combination with capecitabine (Xeloda), the new drug ixabepilone seems to reduce the risk of metastatic breast tumors growing in women whose cancer became resistant to previous treatment.
- The combination of lapatinib (Tykerb) and paclitaxel (Taxol) may slow or stop the growth of tumors in women with HER2-positive advanced breast cancer.
- The targeted treatment lapatinib (Tykerb) may become an option for reducing brain tumors in women with HER2-positive breast cancer that has spread to the brain after treatment with trastuzumab (Herceptin).

by the U.S. Food and Drug Administration and may become available later this year. In further clinical trials, researchers expect to compare ixabepilone with older drugs used to treat both metastatic and early breast cancer.

LAPATINIB (TYKERB) AND PACLITAXEL (TAXOL) FOR ADVANCED BREAST CANCER

A newer targeted medication called lapatinib (Tykerb) has shown promise as a treatment for some women with advanced breast cancer. Lapatinib interferes with HER2. Some treatments actually work better in women whose tumors are HER2 positive, and lapatinib appears to be one of them.

In an international clinical trial, researchers in more than 20 countries studied 580 women with metastatic breast cancer, dividing the group roughly in half. One group of women was given lapatinib plus paclitaxel (Taxol), a drug that has been used for many years to treat various cancers. The other group

was given paclitaxel plus a **placebo** (an inactive substance).

For women with HER2-negative advanced breast cancer (and for those whose cancer was not tested for HER2), neither treatment showed an advantage in terms of prolonging life or lengthening the time until tumors begin to grow after treatment.

But for women with HER2-positive advanced breast cancer, the lapatinib–paclitaxel combination did a significantly better job of slowing or stopping the growth of cancer than did paclitaxel plus placebo (60 percent versus about 35 percent). However, more patients treated with lapatinib did experience an increase in diarrhea and rash.

These encouraging results in women with HER2-positive breast cancer will have to be confirmed by studies that are now under way.

LAPATINIB FOR BRAIN METASTASES

For women with advanced-stage HER2-positive breast cancer who are treated with trastuzumab (Herceptin), the cancer can spread to the brain. Between 30 and 40 percent of these women experience this **metastasis**. Because there are no currently approved treatments for these patients, researchers have turned to the new **targeted treatment** called lapatinib. This medication has been shown to help control advanced breast tumors when used in combination with chemotherapy.

More than 200 women with HER2-positive breast cancer and brain **metastases** were studied in an international clinical trial. These patients had already received treatment with trastuzumab and radiation to the head. All women in the study received lapatinib twice a day in an oral pill.

Early results are available for about the first 100 women treated. Nearly 20 percent of these women had at least a 20 percent reduction in brain tumors. About 7 percent had at least a 50 percent reduction in brain tumors, with no cancer spreading outside the brain and no increase in nervous system symptoms. The final results of this study, which are eagerly awaited, will be based on the entire group of more than 200 women.

RACIAL DIFFERENCES IN THE TREATMENT OF ADVANCED BREAST CANCER

Huge strides have been made in the treatment of advanced breast cancer, but two studies suggest that not all women are benefiting from these improvements.

Researchers from the M. D. Anderson Cancer Center in Houston, Texas, studied the records of more than 15,000 women with advanced breast cancer newly diagnosed between 1988 and 2003. This information came from the National Cancer Institute's program known as SEER (Surveillance, Epidemiology, and End Results). When white women were compared with black women, there was a gap in overall survival after diagnosis that widened over time. From 1988 to 1993, white women lived an average of 20 months, compared with 17 months for black women. From 1994 to 1998, white women lived an average of 22 months, compared with 16 months for black women. From 1999 to 2003, white women lived an average of 27 months, compared with 17 months for black women.

In the second study from Emory University in Atlanta, Georgia, almost 100 women (96 percent black) were treated for advanced invasive breast cancer. This type of breast cancer has spread outside the milk ducts into the fatty tissues of the breast or other parts of the body. The benefits of

chemotherapy and radiation for advanced breast cancers are well known, but about 20 percent of these women refused chemotherapy, and about 35 percent of them refused radiation treatment.

Even though the information available in this SEER program is limited, these striking differences between the treatment of advanced breast cancer in white and black women certainly warrant further study. It is important for all women to take advantage of the treatment options available for advanced breast cancer.

On the Horizon

ERIBULIN MESYLATE (E7389) FOR ADVANCED BREAST CANCER

For women with advanced breast cancer that does not respond, or no longer responds, to standard treatments, there are a limited number of options. So researchers are constantly testing drugs and/or combinations of drugs to find effective alternatives. Preliminary findings suggest that a new drug called eribulin mesylate (E7389) might be a good prospect.

A natural product made from sea sponges, E7389 has been tested in clinical trials at several centers across the United States. In one clinical trial, E7389 was given to more than 100 women with advanced breast cancer who had received an average of four previous chemotherapy treatments. To be eligible for the study, the cancer had to have grown within six months of the last chemotherapy treatment.

What's New, What's Important

- Although there have been major strides against advanced breast cancer, two studies suggest a difference in how black women and white women are benefiting. This has led researchers to urge all women with advanced breast cancer to take advantage of the treatments now available.
- A new drug called eribulin mesylate (E7389) may be a promising alternative for women whose advanced breast cancer does not respond, or no longer responds, to treatment with other chemotherapies.
- Everolimus and pertuzumab are two new drugs that appear promising in treating women with recurrent or metastatic breast cancer.
- Combining axitinib with docetaxel (Taxotere) may be more effective in treating women with metastatic breast cancer than using docetaxel alone.

There was a significant decrease (of at least 50 percent) in the size of the tumor in about 12 percent of the women treated with E7389. This number increased to 17 percent when patients were included whose cancer neither grew nor shrank. The average time from the start of the treatment until the cancer grew was nearly 80 days. About 60 percent of the women experienced neutropenia, a low white blood cell count that can increase the risk of infection. It was the most common side effect of this 21-day treatment.

More needs to be learned about this promising treatment for advanced breast cancer.

EVEROLIMUS AND PERTUZUMAB FOR METASTATIC BREAST CANCER

Everolimus and pertuzumab, two new drugs, appear promising for the treatment of recurrent or metastatic breast cancer.

Researchers from the British Columbia Cancer Agency in

Canada tested two different doses of everolimus—10 mg daily and 70 mg weekly—in nearly 50 women with recurrent or metastatic breast cancer. The medication was given as a pill by mouth. The higher dose given weekly produced no responses, so this approach was discontinued. However, in the group that received the daily dose of everolimus, the tumor shrank in two women, so more women are being added to this group. Because inflammation of the lungs was a common side effect with the daily dose, patients receiving everolimus need careful X-ray monitoring. The final results of this trial should show whether future studies with everolimus are justified.

In another international clinical trial, conducted in Europe and Canada, researchers studied the combination of the new drug pertuzumab and trastuzumab, a similar drug. These two drugs complement each other, and seem to have an improved effectiveness when used together.

The researchers focused on more than 40 women who had HER2-positive metastatic breast cancer that grew after previous treatment with trastuzumab and chemotherapy. According to early findings of the women evaluated, 20 percent had a significant decrease (of at least 50 percent) in the size of the tumor. The cancer neither grew nor shrank in half of them. The most common side effect was diarrhea, which occurred in about 70 percent of treated women. No heart complications, which can be a concern with trastuzumab, were noted. Researchers are recruiting more women for the second stage of this ongoing clinical trial.

AXITINIB PLUS DOCETAXEL (TAXOTERE) FOR METASTATIC BREAST CANCER

A new drug may offer hope to women with metastatic breast cancer, which has spread to other parts of the body. Called axitinib, the new medication belongs to a class of drugs that blocks vascular endothelial growth factor (VEGF)—a substance that plays a critical role in the growth of blood vessels that feed cancer tumors. This drug is being studied in many other types of cancer too, including thyroid, lung, and kidney cancers.

Researchers from the University of California, San Francisco, tested axitinib in more than 150 women. More than half of these women had received chemotherapy after surgery at least one year before joining the study.

Patients were divided into two groups. Group 1 was treated with axitinib in combination with docetaxel (Taxotere), a drug commonly used to treat metastatic breast cancer. Group 2 was treated with docetaxel alone.

The group that received axitinib had a higher rate of decrease in tumor size than the group that did not (approximately 40 percent versus 20 percent). Also, the time it took for the tumors to begin growing or spreading after treatment was longer in women who were treated with axitinib than in those who were not. Axitinib seemed to work better in patients who had already received chemotherapy after surgery than in those who had not. This finding leads researchers to believe that the combination of axitinib and docetaxel may best be used to help reverse resistance to chemotherapy in these women whose tumors came back.

Please note: *Although the treatments discussed in this chapter are showing promise, most are still in clinical trials—some in earlier phases of research—and may not be available yet to the general public. Your doctor can help guide you as to which new medications could be right for you and whether you are eligible to take part in the clinical trials of these new treatments.*