



Update from the 28th Annual San Antonio Breast Cancer Symposium

The San Antonio Breast Cancer Symposium is one of the most important breast cancer conferences. Approximately 7,000 physicians, oncologists, radiologists, epidemiologists, basic scientists, and breast cancer advocates from throughout the world arrive in San Antonio each year eager to hear the latest study results and learn about new trends in breast cancer research and treatment. The 2005 Symposium, which was held December 8-11, included 600 general presentations and poster presentations. Below is a summary of some of the research findings that are most significant to women recently diagnosed with breast cancer and those making treatment decisions.

Herceptin Update

Trastuzumab (brand name Herceptin) is a targeted breast cancer treatment for women with HER2-positive disease. About 30 percent of all women diagnosed with breast cancer have tumors that make more HER2 (human epithelial growth factor receptor-2, also sometimes referred to as HER-2 or Her-2/neu or erb-b2) than they should. Herceptin is a monoclonal antibody that targets this genetic malfunction. It slows tumor growth by putting out antibodies to the HER2 protein on breast cancer cells. Herceptin can fight tumors alone, but it works best when given along with or after chemotherapy.

Herceptin was approved in 1998 for women with advanced breast cancer. Soon thereafter, researchers began looking at whether it would be effective in women with early stage disease. Dennis Slamon, MD, director of Clinical/Translational Research at UCLA's Jonsson Cancer Center, presented data from the Breast Cancer International Research Group (BCIRG) 006 trial, one of the studies exploring the most effective way to use Herceptin in the adjuvant (after surgery) setting.

The trial enrolled 3,222 women from all over the world with early stage HER2-positive breast cancer between March 2001 and February 2004. Patients received one of three adjuvant treatment regimens:

- The standard therapy of doxorubicin (brand name Adriamycin) and cyclophosphamide (brand name Cytoxan) followed by docetaxel (brand name Taxotere) (ACT).
- An experimental regimen of Adriamycin and cyclophosphamide followed by Taxotere and one year of Herceptin (ACTH), with the Herceptin given at the same time as the Taxotere.
- An experimental regimen of Taxotere and carboplatin and one year of Herceptin (TCH), with all three drugs started at the same time.

The trial found that the two study arms that included Herceptin were better at reducing recurrence than was the standard chemotherapy regimen. Specifically, 147 of the women who received the standard treatment, ACT, died or relapsed compared with 77 who received ACTH and 98 who received TCH. This means that in the ACTH group the risk of recurrence was reduced by 51 percent while in the TCH group the risk was reduced by 39 percent.



The researchers decided to use the TCH combination after laboratory studies suggested that these drugs worked well when used together. This finding had been somewhat of a surprise, as carboplatin isn't one of the best breast cancer treatments. Previous studies have found that when Herceptin is given along with or after Adriamycin, an anthracycline commonly used to treat breast cancer, the risk of heart damage increases and the hope was that carboplatin would not have the same risk. The BCIRG study confirmed this finding. Of the 3,222 women in the study, 306 experienced a greater than 10 percent loss of heart function. Of those, 180 (17.3 percent) received Adriamycin followed by Herceptin (ACTH), while 91 (9 percent) received the standard ACT regimen and 82 (8 percent) received the experimental TCH treatment.

Topo II

About 35 percent of women with HER2-positive tumors also have extra copies of a gene called topoisomerase II alpha, or Topo II. The BCIRG study found that women who were both HER2-positive and Topo II-positive were less likely to have a recurrence than were women who were solely HER2-positive. The study also found that the women who were Topo II-positive were more likely to respond to Adriamycin than were women who didn't overexpress that gene. If other studies confirm that women whose tumors are Topo II-positive are more likely to respond to and benefit from Adriamycin, then this could be a way to determine which women should be offered Adriamycin and which could be offered another drug.

The FinHer Trial

Heikki Joensuu, MD, from Helsinki University Hospital, presented interim results from the FinHer trial. In this study, women with early stage HER2-positive breast cancer received either chemotherapy alone or chemotherapy and nine weeks of Herceptin. This is a novel use for Herceptin, as it is usually used for one year. All of the women received single-agent chemotherapy with docetaxel (brand name Taxotere) or vinorelbine (brand name Navelbine) followed by three courses of FEC (5-fluorouracil, epirubicin, and cyclophosphamide). The Herceptin was started at the same time as the FEC.

Dr. Joensuu reported that the women who had received Herceptin were significantly less likely to have their cancer recur, with 11 of 115 women experiencing a recurrence, compared with 26 of 116 women who did not receive Herceptin. The use of Herceptin in this fashion was not found to increase the risk of heart failure. These women will need to be followed longer in order for researchers to fully assess the benefit of nine weeks of Herceptin.

Susan says:

The BCIRG 006 study is the fourth large clinical trial to find that Herceptin reduces the risk of a cancer recurrence in women with HER2-positive early stage disease. (Read about past study findings [here](#).) The problem is that Herceptin, especially when used after Adriamycin, increases the possibility that heart damage will occur.

This is not a new concern. It is something that we have always had to take into account when giving Herceptin to women with HER2-positive metastatic disease. But it poses new problems now that we have a series of studies that indicate that Herceptin cuts the risk of recurrence in half when used as adjuvant treatment for women with early stage disease. We know that some women with early stage disease might not have their cancer recur, even if they didn't receive Herceptin. And the last thing we want to do is damage the heart of someone who really didn't need the treatment to begin with. The problem is that we aren't yet able to know which women will do okay without Herceptin and which will truly benefit from it.



This means we have to be very careful with how we give Herceptin. And this is why the findings about Topo II are so exciting. Knowing that women who are Topo II-positive respond well to Adriamycin means that this group of women is more likely to benefit from combining Herceptin and Adriamycin, which increases the benefit in the risk/benefit equation of ACTH. In turn, if a woman is not Topo II-positive, it may make sense for her to receive Taxotere and carboplatin, as this will decrease her risk of recurrence but with less risk of heart damage. A test that indicates if a woman's tumor is positive for both HER2 and Topo II is now being developed. This is another example of what the future of cancer treatment holds: targeting therapy based on the specific type of cancer a woman has.

The Finnish study was interesting because it showed that using Herceptin for nine weeks reduces the risk of recurrence. Because Herceptin is such an expensive drug—about \$40,000 for one year of treatment—the nine-week option may make the drug more accessible to more women and could change the way Herceptin is used in the adjuvant setting if the same results are seen after the women have been followed longer.

Presentation titles:

- Phase III Randomized Trial Comparing AC-T Followed by AC-TH with TCH in HER2-Positive Early Breast Cancer Patients: BCIRG 006 Study. Abstract 1.
- Topoisomerase II-alpha Gene Amplification as a Predictor of Responsiveness to Anthracycline-Containing Chemotherapy in the BCIRG 006 Trial of Herceptin in the Adjuvant Setting. Abstract 1045.
- Trastuzumab in Combination with Docetaxel or Vinorelbine as Adjuvant Treatment of Breast Cancer: The FinHer Trial. Abstract 2.

Tamoxifen and Aromatase Inhibitor Update

Switching from Tamoxifen to Anastrozole (Arimidex)

A series of studies has found that switching from tamoxifen to the aromatase inhibitor anastrozole (brand name Arimidex) after two to three years of treatment is more effective than five years of tamoxifen. Walter Jonat, PhD, from the University of Kiel, presented the results of a meta-analysis that combined data from three of these switching trials. A meta-analysis is a statistical technique that allows researchers to combine results from separate but related studies.

In all three trials women with hormone-sensitive (ER- and/or PR-positive) tumors who had been on tamoxifen for two or three years were randomized to either stay on tamoxifen or switch to anastrozole for the remainder of their five years of treatment. The meta-analysis found that the women who switched to anastrozole were less likely to have a recurrence than were those who stayed on tamoxifen.

Susan says:

The results of this meta-analysis are similar to what each of the three trials found on its own. This lends support to the idea of having women who are currently receiving tamoxifen switch to anastrozole or another aromatase inhibitor after two to three years of treatment.

We don't yet know if it's better to start on tamoxifen and then switch to an aromatase inhibitor, or to take an aromatase inhibitor for five years. And we still don't know everything we need to know about the side effects associated with anastrozole or other aromatase inhibitors. Still, it now looks like switching to an aromatase inhibitor halfway through five years of hormonal therapy is going to



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be a good option for many women. To learn more about choosing between tamoxifen and an aromatase inhibitor or switching from tamoxifen to an aromatase inhibitor, [click here](#).

Presentation title:

- Switching from Adjuvant Tamoxifen to Anastrozole in Postmenopausal Women with Hormone-Responsive Early Breast Cancer: A Meta-Analysis of the ARNO 95 Trial, ABCSG Trial 8, and the ITA Trial. Abstract 18.

DCIS

Radiation for Ductal Carcinoma In Situ (DCIS): 10-Year Follow-Up

Ductal carcinoma in situ (DCIS) is considered a pre-cancer because it is not able to spread to other parts of the body. However, if left untreated, about 30 percent of women with DCIS would go on to develop invasive breast cancer. Because we don't yet know how to tell which DCIS will become invasive and which won't, we treat all women who are found to have DCIS. The question is, what is the optimal treatment for this group of women?

In the 1980s, researchers with the European Organization for Research and Treatment of Cancer (EORTC) started a trial to assess whether surgery was sufficient treatment for DCIS or if radiation should be given after surgery.

The trial enrolled 1,010 women who were diagnosed with DCIS between 1986 and 1996. Half were randomly assigned to receive radiation after their surgery; the other half only had surgery. The women have now been followed for 10 years. The trial found that women who received radiation had an 85 percent chance of not having a recurrence while women who did not receive radiation had a 75 percent chance of not having a recurrence.

The risk of developing cancer in the opposite breast was similar in both groups.

Susan says:

Women with DCIS often question whether they need radiation, especially since what they have is a pre-cancer. Undoubtedly, there are many women with DCIS who receive radiation who probably would be fine without it. The problem is that we still don't have a good way of assessing who these women are. Until then, as this 10-year follow-up study indicates, it makes sense for women with DCIS to have radiation after their lumpectomy.

Presentation title:

- Radiotherapy in Breast-Conserving Treatment for Ductal Carcinoma In Situ (DCIS): Ten-Year Results of European Organization for Research and Treatment of Cancer (EORTC) Randomized Trial 10853. Abstract 7.

Update on Oncotype DX

Genetic Test Can Help Predict Which Women Are Most Likely to Have Local or Regional Recurrence

For the past three years, researchers from the National Surgical Adjuvant Breast and Bowel



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Project (NSABP) and Genomic Health, a company based in Northern California, have presented data about their Oncotype DX test at the San Antonio Symposium.

Last year, the group reported that the Oncotype DX test not only could predict which women with node-negative, estrogen receptor (ER)-positive breast cancer were most likely to have a distant recurrence (metastasis), but which women would benefit most from having chemotherapy instead of tamoxifen. This year, the group presented data indicating that the Oncotype DX test is a good predictor of which women treated with tamoxifen are most likely to have a local or regional recurrence.

Oncologists currently use a woman's age, tumor size, tumor grade, and estrogen receptor status to assess her risk for having her cancer recur. But it is still a "best guess" scenario. There's no perfect way of determining which women will have their tumors recur and thus who will benefit from chemotherapy and who doesn't really need it. As a result, many women receive chemotherapy who probably don't need it, while others who could benefit don't get it.

Genomic Health developed its genetic test, Oncotype DX, by analyzing tumor samples from nearly 700 women who had been involved in a 1980s NSABP study. The analysis identified 21 genes that appeared to be related to how likely a woman who was node-negative, ER-positive, and had been treated with tamoxifen was to have her cancer recur outside the breast (metastasize) within 10 years. The researchers then gauged the reliability of the test by testing tumor tissue stored from 668 women who had been enrolled in the NSABP B-14 trial from 1982 to 1988. The women's outcomes had been tracked by the NSABP, which allowed the researchers to compare the test's prediction with actual recurrences. They found that the 21-gene test was able to accurately divide women into three groups—low, medium, and high risk for recurrence.

The Oncotype DX test is already available for women with estrogen-sensitive tumors. The test can only be done at Genomic Health. All that requires, however, is having a woman's tumor sample, which is stored in the pathology department at her hospital, sent to Genomic Health. The test costs about \$3,500; some insurance plans may cover it.

If you have the test done, your result will be reported as a "recurrence score" from 0–100.

- A recurrence score less than 18 means a woman has a low risk of recurrence. For example, a woman with a recurrence score of 3 would have about a 4 percent chance of recurrence, while a woman with a score of 15 would have about a 9 percent chance of recurrence. It is this group of women who had a recurrence rate of about 5 percent whether they received tamoxifen alone or tamoxifen plus chemotherapy.
- A score between 18–30 signifies an intermediate risk of recurrence. For example, a woman with a recurrence score of 20 would have about a 12 percent chance of recurrence, while a woman with a score of 28 would have about an 18 percent risk of recurrence.
- A score of 31 or higher indicates a woman has a high risk of recurrence. For example, a woman with a recurrence score of 35 would have about a 22 percent risk for recurrence, while a woman with a score of 45 would have about a 30 percent risk for recurrence. It is this group of women who derived the most benefit from chemotherapy.



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Susan says:

Oncologists hope that one day they will be able to provide all women with breast cancer with individualized treatment that is determined by specific aspects of the breast tumor. Testing for HER2 status and hormone sensitivity have aided us in this process. The new genetic test, Oncotype DX, is another step in that direction. It can't predict what will happen to each individual woman, but it does provide increased information about which women are more likely to benefit from chemotherapy.

Only women whose tumors are node-negative and ER-positive can use the test. It has not been tested in and cannot give an accurate score in any other women. Still, this does represent about 50 percent of all women diagnosed with breast cancer.

The test has already begun having an impact on the choices women make. A poster presented by Ruth Oratz, MD, a clinical associate professor at New York University School of Medicine, described an evaluation of the experiences of four oncologists treating 68 early stage, estrogen receptor-positive women with breast cancer who had the Oncotype DX test. They found that the treatment that women and their oncologists initially decided upon changed for 14 of the 68 women in the study after their recurrence scores were reported. Specifically, seven women opted for hormone therapy alone instead of chemotherapy and hormone therapy after learning that they had a low recurrence score while seven decided to have chemotherapy and hormone therapy instead of just hormone therapy after learning they had a high recurrence score.

I think that if a woman has the test done and finds that she has a high chance for recurrence and will most likely benefit from chemotherapy, it will help make her decision to have chemotherapy easier. For those who have an intermediate score, it will still be a personal decision about whether to have chemotherapy in addition to hormonal therapy. And for the 50 percent of women with early stage breast cancer who have a low risk of recurrence and who appear to obtain the same benefit from tamoxifen as from tamoxifen and chemotherapy, the decision to forgo chemotherapy may be easier. But this, too, will still remain a very personal and individual choice.

Presentation titles:

- Association Between the 21-Gene Recurrence Score Assay and Risk of Locoregional Failure in Node-Negative, ER-Positive Breast Cancer: Results from NSABP B-14 and NSABP B-20. Abstract 29.
- Impact of Oncotype DX on Decision Making in Breast Cancer Clinical Practice. Abstract 2049.

New Findings

Advanced Breast Cancer

Gefitinib (Iressa) Studied in Advanced Breast Cancer

The Australian-New Zealand Breast Cancer Trials Group investigated whether the drug gefitinib (brand name Iressa) would be effective in women with estrogen receptor (ER)-negative and progesterone receptor (PR)-negative breast cancers or in women whose tumors are hormone-sensitive but have stopped responding to hormone therapy. Gefitinib is a tyrosine kinase inhibitor.

Tyrosine kinase is an enzyme involved with cell communication; it "talks" to the epidermal growth factor receptor (EGFR). Gefitinib blocks the EGFR, which is found on the surface of many types



of cancer cells. This prevents tyrosine kinase from sending the message the EGFR must hear to get the cell to grow and divide. Like Herceptin, gefitinib is a targeted therapy. This means it is able to attack cancer cells without wreaking havoc on normal cells, like chemotherapy does.

Gefitinib received accelerated FDA approval in May 2003 for treatment of non-small cell lung cancer after studies showed tumors responded well to the drug. However, data released in June 2005 indicated that people taking gefitinib did not live longer than those taking a placebo. This led the FDA to issue an alert that it was relabeling gefitinib and only permitting limited distribution of the drug for use in patients with non-small cell lung cancer.

After the FDA approval in 2003, researchers began testing gefitinib's effectiveness in other types of cancers. The Australian-New Zealand Breast Cancer Trials Group explored whether the drug would be effective in women with ER-negative breast cancers or in women whose tumors were ER-positive but no longer responding to tamoxifen or an aromatase inhibitor. Previous laboratory studies had suggested that these types of tumors were more likely to express EGFR and thus, theoretically, were more likely to respond to gefitinib.

The Trials Group enrolled 66 women with advanced breast cancer: 39 whose breast cancers had stopped responding to hormone therapy and 27 whose tumors were ER-negative and PR-negative. They found that after 28 weeks of treatment with a dose double that used to treat non-small cell lung cancer, no woman in either group had tumors that responded to the drug, even partially. This finding led the researchers to stop the trial early.

The authors noted that studies presented at the American Society of Clinical Oncology (ASCO) conference in 2003 suggested that advanced breast cancer responded to gefitinib, but that their study was not able to confirm this finding.

Susan says:

The story of gefitinib is an example of how data on new treatments that look promising do not always play out the way researchers or people with cancer hope. This is why it's important to read any news stories about "new cancer breakthroughs" with a critical eye. Drugs that fight cancer in the laboratory setting don't always do so in humans. And drugs that initially appear to be effective in slowing tumor growth all too often don't end up keeping people alive longer. We can't let our desire to find drugs that work allow us to get too far ahead of what the evidence shows. And we need to remember that lab findings and small studies must be confirmed by larger studies in humans before we know for sure how effective a drug will be.

Presentation title:

- Gefitinib Has a Low Clinical Benefit Rate in Advanced Breast Cancer Patients. Abstract 4080.

Young Women

Predicting Infertility After Treatment Ends

For many premenopausal women, facing a breast cancer diagnosis also involves confronting the possibility that chemotherapy can put a woman into early menopause, rendering her infertile. Studies have shown that the older a woman is, the more likely this is to occur. Scientists are now



looking for other ways to predict which women are most likely to become infertile after their cancer treatment ends.

Researchers from Duke University in Durham, North Carolina, presented a poster on the early results of a study that explored whether inhibin, a hormone produced by the ovary, could predict infertility after chemotherapy. The presence of inhibin correlates with cell activity, and previous studies have shown that levels of inhibin decrease as a woman approaches menopause.

The researchers measured levels of inhibin in premenopausal women with early stage breast cancer before they started chemotherapy, right after their treatment was completed, and six months later. They also analyzed the women's menstrual histories. A woman was considered as having had premature ovarian failure if six months after completing chemotherapy her period still had not returned.

Preliminary findings indicate that a woman's inhibin A level appears to correlate with whether her period will resume, with women whose periods do not return having lower inhibin levels prior to the start of chemotherapy (57.4 compared with 83.4). The authors note that if their future research supports this initial finding, testing for inhibin A levels could be a way to help premenopausal women decide whether they want to undergo fertility treatments prior to starting chemotherapy.

Susan says:

The older a premenopausal woman is, the less likely she is to have her periods return after chemotherapy ends. It is possible that testing for inhibin A may prove to be a better determinant than age of whether a woman's periods are likely to return. If so, this might help some women decide whether to undergo egg harvesting or in vitro fertilization (IVF) prior to the start of their cancer treatments. You can learn more about current options for cancer patients faced with infertility on the website www.fertilehope.org. The options for extending fertility are expanding. However, many of these options remain experimental, most are not covered by insurance, and all are very expensive. More resources and information about pregnancy after a breast cancer diagnosis can be found [here](#).

Presentation title:

- Inhibin A and B as Predictive Markers for Chemotherapy-Induced Premature Ovarian Failure Among Premenopausal Women with Early Stage Breast Cancer. Abstract 1027.

Statins May Lower the Risk of ER-Negative Breast Cancer

Statins are a class of drugs used to lower blood cholesterol and reduce the risk of heart attack and stroke. They are some of the top-selling drugs on the market today. Lab studies have found that the statins that are lipophilic, such as fluvastatin (brand name Lescol), simvastatin (brand name Zocor), lovastatin (brand names Mevacor and Altacor), and atorvastatin (brand name Lipitor), inhibit ER-negative breast cancer. No clinical trials have been conducted in women.

Anjali Kumar, MD, at the University of California, San Francisco, presented a retrospective cohort study that looked to see if there was a relationship between statin use and the development of ER-negative breast cancer. Dr. Kumar and his team looked at records from 2,141 women who had been diagnosed with breast cancer at Kaiser Permanente in California, a large HMO. They



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identified 303 women with breast cancer who had used a lipophilic statin for one or more years prior to being diagnosed with cancer. They found that only 2 percent of the women who took statins had tumors that were ER-negative, compared with 17 percent of women diagnosed with breast cancer who did not use statins or who had used them for less than one year.

Susan says:

This study adds to the data we have from laboratory studies that indicate that statins may reduce breast cancer risk. However, as we learned from hormone replacement therapy (HRT), we cannot know for sure that a drug can reduce risk until we perform a clinical trial where a group of women are randomized to take a drug or a placebo and then we follow them to see what happens.

Furthermore, study results published in January 2006, just a month after the San Antonio conference, indicate that this finding may not pan out. Because laboratory tests had suggested that statins might help ward off a range of cancers, including breast cancers, many researchers have been interested in statins, not just those studying breast cancer. To look more closely at statins and cancer, researchers conducted a meta-analysis of 26 statin studies involving 87,000 patients. A meta-analysis allows researchers to synthesize research results from similar studies. This meta-analysis found that no type of cancer was affected by statin use and that statins did not reduce the incidence of cancer or cancer deaths. So, while it's still possible that statins have a unique effect on ER-negative breast cancers, much more research will be done to confirm this finding or to provide any reason for women to take statins to try to reduce their risk of any type of cancer, including breast cancer.