Update from the 29th Annual San Antonio Breast Cancer Symposium

The San Antonio Breast Cancer Symposium is one of the most important breast cancer conferences. Approximately 8,000 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 2006 Symposium, which was held December 14-17, included more than 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.

Breast Cancer Statistics Fall in 2003

The big headlines from the symposium were generated by researchers from the M. D. Anderson Cancer Center, the National Cancer Institute, and the Harbor/UCLA Medical Center who reported that there was a sudden dramatic (7%) decrease in breast cancer in the United States in 2003—14,000 less breast cancers in one year alone—and that this decrease appears to be largely due to the fact that millions of women stopped using HRT in 2002.

Why are the researchers so certain the decline is linked to women’s decreased use of HRT? In July 2002, the Women’s Health Initiative (WHI), a large randomized trial comparing HRT to a placebo, was stopped suddenly after an interim analysis found that HRT did more harm than good—including increasing breast cancer risk. Virtually overnight, women threw out their HRT and stopped refilling prescriptions. And as the data shows, as more women stopped taking HRT, more women stopped getting breast cancer. As far as we can tell, nothing else of the same magnitude occurred that could explain the decreased breast cancer rate. Further, the biggest drop in breast cancer incidence (12%) was in women between the ages of 50-60 who had tumors that were hormone sensitive (ER or PR positive)—the population of women taking HRT and the type of tumor that would be fueled by estrogen.

Some people heard this news and said: Given that cancer takes years to develop, it just doesn’t make sense that stopping HRT could reduce breast cancer rates so quickly. But based on what we know now about how cancer develops, this could indeed have occurred.

It’s true that breast cancer takes years to develop. But it’s not just the cancer cells but also the environment that they live in that affects how fast they develop. In the past, we blamed everything on the cancer cell, as if it were a criminal that functioned autonomously. But we now know that the local tissue around the cancer (stroma) that the cancer cells live in also plays a critical role in determining whether a cancer or even a precancer, like ductal carcinoma in situ (DCIS), will remain dormant or become invasive. Estrogen and progesterone are two of the major influences on the stroma. As soon as a woman starts taking HRT, her breasts will appear denser on a mammogram. And as we know from the WHI, breast cancer increases as well. This is because of the impact the hormones have on the stroma, making it more inviting and supportive to cancer cells. In essence, the stroma is providing a nurturing environment for the cells to function criminaly. Likewise, as soon as a woman starts to take tamoxifen to reduce her breast cancer risk, her breasts appear less dense on a mammogram. In this case, it’s because tamoxifen is keeping estrogen away from the stroma. In turn, the stroma is providing an environment that is, in essence, rehabilitating those criminal cancer cells.

Some experts have suggested that when women stopped taking HRT it just delayed breast cancer development and that we will see a rise in cancer statistics again. However, we know that when women take tamoxifen to reduce their breast cancer risk the benefit persists long after the
drug is stopped. So, it’s certainly biologically plausible that the effect of stopping HRT would not only be fast but that it will also persist, which would mean we would not see rates increase again. Time will tell. Even so, this is undoubtedly the final proof we need that taking hormonal therapy after menopause for the prevention of the diseases of aging makes no sense.

Inflammatory Breast Cancer Update
Massimo Cristofanilli, MD, of the M. D. Anderson Cancer Center, reported the findings from a Phase II multi-center international clinical trial exploring the benefit of a targeted therapy, called lapatinib, for women with newly diagnosed Inflammatory Breast Cancer (IBC). Only about two percent of women diagnosed with breast cancer have IBC, which has made it difficult to study. Until now, no therapies specific to IBC have been studied in multi-center trials.

Lapatinib blocks epidermal growth factor receptor 1 and 2. It is also a HER2neu tyrosine kinase inhibitor. This means it has the ability to block the activity of the HER2 protein as well as the EGFR receptor that the protein attaches to. Although lapatinib has been studied previously in trials in women with HER2-positive breast cancer, this trial marked the first time that it was being studied in women with IBC.

The trial enrolled 49 women with IBC. All of them had IBC that was HER2-positive and/or EGFR-positive. (EGFR stands for epidermal growth factor receptor.) Approximately 25 percent (12) of the women had metastatic disease. The women received two weeks of daily lapatinib alone, followed by three months of daily lapatinib and weekly chemotherapy with the drug paclitaxel. Thirty-five of the women completed the trial and then had surgery.

The researchers found that tumor size was reduced by half in 86 percent (30) out of the 35 women in the trial. Also, three of the first 21 patients that had surgery had a complete pathological response, meaning that there was no evidence of disease at the time of surgery. The study also found that women with IBC who were HER2-positive responded better than those who were EGFR-positive. As a result, future studies will probably focus only on women with IBC who are HER2-positive.

Lapatinib is manufactured by GlaxoSmithKline. The most common side effects of lapatinib were diarrhea and skin rash. If you have IBC and are interested in learning more about clinical trials testing lapatinib, you should contact the Inflammatory Breast Cancer Clinic and Research Program at M. D. Anderson. Call the Information Line at 1-800-392-1611, option 3.

Treating Women Over 70
Kevin Hughes, MD, of Massachusetts General Hospital, in Boston, presented further follow-up findings from a study comparing the benefits of radiation and tamoxifen to tamoxifen alone in women 70 or older with stage I breast cancer who had had a lumpectomy. This trial, which took place between July 1994 and February 1999, enrolled 636 women. After nearly eight years of follow-up, that the only statistically significant difference between the two groups was in the incidence of local recurrence: 1 percent (3) of the women who had had tamoxifen and radiation had a local recurrence compared with 7 percent (23) of the women who had had tamoxifen alone. Only two women in each group died of breast cancer. Many more died of other diseases—86 in the tamoxifen and radiation group and 82 in the tamoxifen alone group. Based on these findings the researchers concluded—and most oncologists would undoubtedly agree—that tamoxifen without radiation is a reasonable option for women 70 and older with stage I ER-positive breast cancer.
Aromatase Inhibitor Update

Research reports from two studies gave us a bit more information on aromatase inhibitors. One of these studies, the NSABP B-33 trial, looked at the benefit of using exemestane after five years of tamoxifen. All of the women enrolled in the study were postmenopausal and disease-free after five years of tamoxifen. All of the women in this trial were randomized to exemestane (brand name Aromasin) or a placebo for five years. However, in 2003, after another study reported a benefit from giving women letrozole (brand name Femara) after five years of tamoxifen, the women enrolled in the NSABP B-33 trial had to be told what drug they were taking so that those taking the placebo could choose to start taking exemestane, and those taking exemestane could choose to stop treatment. After learning which drug they were on, 560 of the 783 women taking exemestane chose to stay on the drug. Of the 779 women taking the placebo, 344 chose to start taking exemestane.

After following the women for 30 months, there was a borderline statistically significant improvement in disease-free survival in favor of the exemestane group (91% vs. 89%). However, there was no statistically significant difference in overall survival (there were 13 deaths among the women taking the placebo and 6 among the women taking exemestane). This means there was only about a 2 percent benefit from taking another drug for five years. This small benefit has to be weighed against side effects related to aromastase inhibitors, such as pain in the bones and joints and an increased risk for fracture (there were 28 fractures among the women taking exemestane versus 20 among the placebo group.) Bottom-line: women will need to discuss with their doctors their risk for recurrence and assess whether they think taking an aromatase inhibitor for five years after five years of tamoxifen is right for them.

The second trial discussed, called EFECT, is a Phase III trial comparing fulvestrant (brand name Faslodex) with exemestane (brand name Aromasin) as a second hormone treatment in postmenopausal women with metastatic disease who had not previously used a non-steroidal aromatase inhibitor. The study randomized 693 women to receive either fulvestrant or exemestane. At the most recent data analysis, about 82 percent of the women taking fulvestrant had had their disease progress compared with 87 percent of the women receiving exemestane. In other words, there was basically no difference between the two drugs. Bottom-line: There appears to be no difference between these estrogen blockers.

Treating Breast Cancer in Premenopausal Women

Two presentations provided information on research studies of interest to young women with early breast cancer. One presentation described a meta-analysis (a large analysis of the findings of a number of studies) of 13 of the randomized trials that have looked at the impact of LHRH agonists, like lupron and goserelin (brand name Zoladex). LHRH agonists are oral drugs that put premenopausal women into temporary menopause. There are two types of trials that have evaluated the benefit of using an LHRH agonist: those that evaluated the effectiveness of adding an LHRH agonist to chemotherapy and those that compared an LHRH agonist alone to chemotherapy. Some of the trials also included the use of tamoxifen in all patients or only in the LHRH group. The researchers combined the data from 13 different trials, allowing them to study a total of 6437 women with ER-positive tumors. They found that an LHRH agonist used with tamoxifen was more effective than chemotherapy and tamoxifen. However, adding the LHRH agonist did not reduce the risk of death. They also found that when an LHRH agonist was added to chemotherapy, it was more effective than chemotherapy alone. Further, the addition of an LHRH agonist (with or without tamoxifen) to chemotherapy significantly reduced recurrence. However, it did not significantly reduce the risk of death.

The bottom-line: For premenopausal ER-positive women, using an LHRH agonist was as
effective as chemotherapy in reducing the risk of recurrence or death. Although the researchers made it clear that these findings will need to be confirmed when all the trial data is available, this study suggests that the main way that chemotherapy works in premenopausal ER-positive breast cancer is by causing menopause to occur. We do not yet know if adding an aromatase inhibitor to an LHRH inhibitor is better; those studies are now being done.

The second presentation, which reviewed data from the ABCSG-05 study, which compared the chemotherapy regimen CMF to goserelin and tamoxifen, also supports the belief that inducing menopause is what is most effective in reducing recurrence. In this prospective trial, 1037 women with hormone-sensitive tumors were randomized to receive either 6 cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or 3 years of goserelin plus 5 years of tamoxifen. After following the women for ten years, they found that the women who received goserelin followed by tamoxifen had higher overall survival rates (82 percent) than the women who received chemotherapy (74.6 percent). When they looked more closely at the chemotherapy group, however, the investigators found that the women who were put into menopause by chemotherapy did as well as the women who had goserelin followed by tamoxifen, especially if they were HER2-negative and did not have low levels of hormone sensitivity. Based on these findings, the researchers concluded it may be advisable for premenopausal patients with hormone-sensitive tumors who are not put into menopause by chemotherapy to go onto an LHRH agonist.

Oncologists who believe in chemotherapy is will undoubtedly point out that most of the studies evaluated in this meta-analysis used the chemotherapy regimen CMF (cyclophosphamide, methotrexate, fluorouracil) and not with what we currently use AC (doxorubicin/cyclophosphamide) followed by T (paclitaxel). This may be true. However, the fact that the ABCSG-05 study showed there was a survival difference between the women in whom chemotherapy induced menopause and in those whom it did not, supports the belief that it is the inducement of menopause that matters most.

African American Women: Understanding Racial Differences
A series of posters presented data from new and ongoing studies on African American women and breast cancer. Researchers are trying to understand why postmenopausal African American women, although less likely to get breast cancer than white women, are more likely to die of the disease. They are also trying to gain insight into why premenopausal African American women are more likely to get breast cancer than white premenopausal women, and to have tumors that are “triple negative” —ER, PR and HER-2 negative—and thus harder to treat.

It has long been believed that the higher death rates were due to the fact that African American women were more likely to have their disease diagnosed later and to receive a lower quality of care. But as we have learned more about the different types of breast cancers, it has become apparent that differences in tumor biology appear to play a role as well.

One of these studies compared the experiences of African American and white women who were enrolled in two adjuvant Phase III trials run by the Southwest Oncology Group (SWOG). The objective of this study was to assess whether African American women were more likely than white women enrolled in these two trials to discontinue treatment, delay treatment, or receive lower chemotherapy doses, all of which could influence treatment outcomes. The investigators found that both groups of women received the same chemotherapy doses, but that African American women were more likely to experience treatment delays or to discontinue treatment. Further, after adjusting for these differences, they still found that African American women were more likely than white women to die of breast cancer. Based on this finding the researchers concluded that it is the type of tumors that African American women develop and the treatments
available for these tumors types that may, in part, be driving this survival difference.

This finding was supported by one of the poster presentations, which described a study investigating the prevalence of triple negative breast cancers among patients in a cancer center in Atlanta, GA. They found that 33.8 percent of the African American women had triple negative tumors compared with 13.6 percent of the non-African American women. Further, while triple negative tumors were much more prevalent among women under age 50, the prevalence differed by race, with 46.3 percent of the younger African American women having this type of tumor compared with 24.3 percent of the non-Black women. Further, 61.5 percent of the African-American women under age 40 had triple negative tumors. The research noted this high triple-negative rate was clearly connected to the higher death rates seen in African American women.

**Treating DCIS**

Researchers from the Eastern Cooperative Oncology Group (ECOG) and the North Central Cancer Treatment Group (NCCCTG) presented the most recent data from the E5194 trial, which is exploring whether there is a low-risk subset of women with DCIS who will do well with surgery alone and not have to have surgery and radiation. This trial enrolled women from 1997 to 2002. To be eligible for the trial, the women had to have low or intermediate grade DCIS that was less than 2.5 cm or high grade DCIS that was less than 1 cm.

The investigators found that at five years only 6.8 percent (39) of the 580 women with low or intermediate grade tumors had a recurrence. Half had a recurrence of DCIS; the other half was found to have invasive cancer. In addition, 3.5 percent (20) of the women developed a new DCIS or cancer in the opposite breast. Of the 102 women with high grade DCIS, 13.7 percent (14) had a recurrence, with 53 percent found to have a recurrence of DCIS and 47 percent found to have invasive cancer. In addition, 4.2 percent(4) of the women developed a new DCIS or cancer in the opposite breast.

This is believed by many to be an acceptably low risk of recurrence for women with low or intermediate grade DCIS, and that for this group of women surgery alone appears to be sufficient. However, based on this study, surgery alone is insufficient for women with high grade DCIS, even if the DCIS is small in size. The researchers intend to continue to follow these women, which will provide us with additional information about recurrence rates for surgery alone.

**Reducing Risk of Recurrence: Does Diet Play a Role?**

Dr. Rowan Chlebowski, MD, of Harbor-UCLA Medical Center, presented new data from the Women’s Intervention Nutrition Study (WINS), which is investigating whether a low-fat diet can reduce the risk of a cancer recurrence. The trial enrolled 2400 women. Half were taught how to maintain a low-fat diet in which 20 percent or less of the calories came from fat. The other half were not taught any low-fat eating skills. After following the women for nearly six years, the researchers found that there were 22 percent fewer deaths among the women on the low-fat diet, but this was not a statistically significant finding.

When the investigators looked more closely, though, they found that among the 362 women with ER or PR negative tumors, the diet did have a statistically significant impact. In fact, there were 66 percent fewer deaths among the women on the low-fat diet, which resulted in an 11 percent absolute survival difference.

Based on this finding, it makes sense to have women with tumors that are ER and PR negative meet with a dietitian or nutritionist to discuss how to decrease fat in their diet. Studies indicate that most women have diets in which about 35 percent of their calories come from fat. Reducing
this to 20 percent or less is not easy, but doing so may have a large benefit for women with ER or PR negative tumors.

And although the benefit did not reach statistically significance for women with hormone-sensitive tumors, future studies may find a low-fat diet benefits them as well. Further, reducing dietary fat and replacing these fats with fruits and vegetables and whole grains can help reduce risk of heart disease and other illnesses. So, women with hormone-sensitive tumors may certainly want to meet with a dietician or nutritionist and learn ways to reduce their fat intake as well.