

# Breast Cancer Advisor

BY DR. SILVANA MARTINO

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Dear Readers,

The 2014 American Society of Clinical Oncology (ASCO) meeting has just concluded. It will take a while for all of us to digest the results from all of the international studies that were presented.

I have reviewed some of the breast cancer related information in this issue, and I will bring you other important findings in the next several issues. It was an exciting meeting.

Best regards,  
Dr. Silvana Martino

## BIOGRAPHY

### Dr. Silvana Martino

is the Director of Breast Cancer Research and Education at The Angeles Clinic Foundation in Santa Monica, California. She is board certified in internal medicine and medical oncology. Dr. Martino has specialized in the treatment and research of breast cancer for over three decades. She is a nationally recognized leader in the field of breast cancer. Her body of work has included research in breast cancer prevention, treatments for early breast cancer and metastatic disease. Dr. Martino has conducted and coordinated large national and international studies which have resulted in changing the standard of care worldwide.

DR. MARTINO'S  
CURRICULUM VITAE

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## BIOLOGY BASICS

In this issue, I will discuss how drugs are developed and approved for clinical use. Though I will concentrate on drugs that are used to treat cancer, the same general process applies to drugs that are developed for other diseases.

Drugs originate from multiple sources. Some are from natural sources such as plants, bacteria or are found in the sea; others are chemically designed in a laboratory. Considerable cost is required to develop a new drug; consequently, most products are developed by large pharmaceutical companies who are either the original owners of a new drug or who purchase a new drug from a smaller company. The ultimate goal is to bring a drug to market for the treatment of a specific disease; however, much has to happen before this can be accomplished. Each drug must go through multiple "phases" in its development.

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# The Angeles Clinic FOUNDATION

*The Angeles Clinic Foundation is a nonprofit organization whose purpose is to sponsor and support programs, services, education, advocacy, and research related to cancer. Our goal is to make a difference in all aspects of the lives of people touched by cancer. Your support is important in the fight against cancer and the journey towards a cure.*

**BIOLOGY BASICS** continued

Before human clinical trials are considered, pharmaceutical companies conduct extensive **pre-clinical** testing done in test tubes and on cell cultures (in vitro testing) as well as in various animals (in vivo testing) in order to obtain a preliminary idea about how the drug behaves, what activity it may have, and its potential toxicities. If the results from this pre-clinical phase are not satisfactory, the drug is unlikely to be developed further.

If a drug is successful in the pre-clinical phase, it may then be taken to **phase 0**. This phase is sometimes referred to as human micro-dosing studies, and is designed to achieve a quick impression of whether a new drug behaves in humans in a manner similar to what was seen in pre-clinical studies. A small group of healthy volunteers may be given a low dose to see how they metabolize the drug. It is not the intent at this point to figure out what the benefits of the drug might be. The pharmacological information obtained may help a company decide among several drugs that may be in consideration for further development.

**Phase I** trials are the beginning of human testing for most new drugs. Based on the nature of the drug and its final intended purpose, this phase may involve healthy volunteers. In cancer drugs, this is rarely the case. The volunteers in this setting are cancer patients who usually have metastatic disease and who either have been on multiple other agents or who have a type of cancer for which there is no known effective therapy. This phase is designed primarily to identify a tolerable dose of the drug. This is done by treating a small group of patients starting at a low dose while closely observing them for side effects and measuring various parameters that reflect how the body handles a specific dose. If the starting dose is well tolerated, a

new group of patients is treated at a higher dose, while again closely monitoring them for toxicity. The dose is increased within each successive group of patients until side effects are observed that are not acceptable. This final dose is then judged to be too high. A modified dose is then chosen as the dose to be studied further. Often, different schedules of a drug are investigated, such as a once-per-week dose or an every-three-week dose. The purpose of phase I trials is to identify a dose(s) and schedule(s) to study further.

The next goal is to determine whether the dose chosen from phase I demonstrates any beneficial biological activity (**phase II**). It is at this point in oncology that one must answer the question of whether this drug and dose have the ability to shrink tumors. The question must be answered for each tumor type of interest. For example, one needs to study groups of patients with breast cancer, colon cancer, lung cancer, etc., in order to find out which cancers, if any, are affected since, if a drug works for one type of cancer, it does not automatically mean that it will work for other types.

From phase I and phase II trials, one has identified the optimal dose and tumor categories for which a drug has an effect. Toxicity data are gathered during both phases. Now, a drug moves to **phase III** studies where its effect is compared to therapy that is already commonly used for a specific tumor type. The question at this point is whether the new therapy is better than previous therapy and, therefore, should be made available to the general public. Phase III trials require randomization (like the flip of a coin) between two or more therapies. These studies are large, complex and expensive to perform. If a new drug demonstrates superiority over existing therapy, the collective data from all phases can then be brought to the FDA for approval. If FDA

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## BIOLOGY BASICS continued

approval is granted, the drug is then available for general use for patients with a particular tumor. It is at this point that insurance companies will begin to provide coverage for its use.

The final phase of drug development consists of post-marketing surveillance trials or **phase IV**. These trials are designed to gain insight into additional, rare, and long term side effects. These are also trials where special populations such as pregnant women or patients with kidney disease are studied. The drug may also be studied in combination with other drugs. Observations about interference with other medications that a patient may be taking are also part of this final phase.

As should be apparent, the steps that a drug must go through before it is approved for general use are multiple. Many feel that this takes too long and that ways must be found to shorten the process. I generally agree with this opinion, but we must recognize that if we shorten this process or try to skip any steps, we may miss side effects that are rare and side effects that may accumulate over time. We may sacrifice safety.

## WHAT'S NEW

### OBESITY INCREASES MORTALITY FROM BREAST CANCER IN PREMENOPAUSAL WOMEN

In several previous issues I have described the activities of an international research group known as the Early Breast Cancer Trialists' Collaborative Group of which I am a member. In brief, this group obtains direct data on patients participating in most of the randomized trials conducted worldwide in early breast cancer. Analysis of these data are periodically updated and published. The process is known as a meta-analysis. At our last meeting at Oxford University in Oxford, U.K., the group decided to look at the issue of weight and body mass index (BMI), and its

possible influence in patients with a known diagnosis of breast cancer. Data was available on 80,000 individual patients from 70 early breast cancer trials including information on weight, BMI, hormonal receptor status (ER/PR), menopausal status, tumor size, lymph node involvement, treatment, tumor recurrence and cause of death.

The results of this analysis demonstrated that overall, obese women (BMI, 30kg/m<sup>2</sup> or greater) when compared to women of normal weight (BMI, 20-15) had a higher 10-year mortality rate from breast cancer. When these data were further subdivided, it was found that the difference was statistically significant only in premenopausal women with hormone receptor positive breast cancer. There was a minimal difference in postmenopausal women with hormone positive disease. No effect was found in pre- or postmenopausal women with hormone receptor negative breast cancer.

The importance of these data is that they are based on a very large number of patients from around the world. They are inconsistent with some smaller studies that have suggested that obesity was probably more of an issue in postmenopausal women rather than premenopausal women. Note that the parameter measured was specifically mortality from breast cancer. It is likely that if one looked at other medical conditions such as cardiovascular disease, we probably would find that obesity is a poor prognostic factor for women of all ages.

These findings also need to be distinguished from the effect of obesity on the initial development of breast cancer. In this regard, most of the data available suggest that obesity increases the risk of developing breast cancer most notably in postmenopausal women rather than those who are premenopausal. The mechanisms by which fat increases the incidence of breast cancer is not entirely clear at this point,

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**WHAT'S NEW continued**

but it is believed that its role in increasing chronic inflammation and the increased production of local estrogen as occurs in the breast, are key factors.

In summary, these recent data add to our knowledge that increased weight and the accompanying increase in BMI should be avoided. Their negative effect is not restricted to the cancer process but to our overall health.

Reference: Data presented at American Society of Clinical Oncology meeting (ASCO), June, 2014.

**A NEW TREATMENT OPTION FOR PREMENOPAUSAL WOMEN WITH HORMONE RECEPTOR POSITIVE BREAST CANCER**

Most breast cancers, even in premenopausal women are hormone receptor positive. For the past several decades, tamoxifen administered for a total of five years has been standard therapy for premenopausal women with hormone receptor positive breast cancer. Recent data from two large trials comparing five versus ten years of tamoxifen changed practice worldwide. Ten years has become the new standard. Prior studies have also demonstrated that inactivating ovarian function can be beneficial in premenopausal women with hormone-positive breast cancer. From several studies, we learned that using the aromatase inhibitor hormones such as Aromasin, Arimidex and Femara are superior to tamoxifen for women who are postmenopausal. Would this class of drugs prove to be superior in premenopausal women if we first made them postmenopausal?

Two clinical trials were organized to address two very important questions in premenopausal women with hormone-positive, early breast cancer. The TEXT and the SOFT trials brought together several large cooperative breast cancer research groups from around the world. Two questions were addressed:

(1) is suppressing ovarian function coupled with giving tamoxifen for five years better than tamoxifen alone for five years, and (2) once ovarian function is suppressed, is it better to give five years of tamoxifen or five years of Aromasin to this group of patients?

Ideally, since tamoxifen alone has been the standard therapy adopted by most oncologists, question one should be answered first, resolving the issue of whether suppressing ovarian function is better than not doing it. With that question resolved, it then would be logical to have an answer to the second question comparing the administration of tamoxifen versus an aromatase inhibitor. However, it is the second question that is being answered first and the results presented at the 2014 ASCO meeting and simultaneously published in the New England Journal of Medicine. I am pleased to be one of the authors to this work.

The TEXT and SOFT trials are each randomized clinical trials that enrolled 2,672 and 3,066 premenopausal women with hormone receptor positive, early breast cancer, respectively, between November 2003 and April 2011. Over 500 medical institutions from 27 countries participated. Combining both trials, 4,690 women were randomized to five years of adjuvant treatment with either Aromasin plus ovarian function suppression (OFS) or with tamoxifen plus ovarian function suppression. Suppressing ovarian function could be accomplished in several ways; the use of LHRH agonist injections, surgical removal of both ovaries or by radiation to both ovaries. Since the trials had a similar design, the data have been combined. The SOFT trial also included a third treatment group where tamoxifen was given alone. This group will be compared to the tamoxifen plus ovarian function suppression group, and results will be presented at the December 2014 San Antonio Breast Cancer Symposium.

With 5 years of observation, the results demonstrate that 92.8% of women who were treated with Aromasin plus OFS remained free from breast cancer recurrence versus 88.8% of the women

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**DISCLOSURE**

The information contained in this newsletter is for educational purposes only. It is not designed to diagnose or provide treatment recommendations. Please consult your own physicians for all decisions about your care.

**WHAT'S NEW continued**

treated with tamoxifen and OFS. It should be noted that overall, both groups did well. The 4% absolute difference between the two groups is highly statistically significant. Survival data is not yet available from these studies.

The side effects reported by women in these two studies were typical of the side effects that have been previously recognized with these agents. No new side effects were observed. Quality of life measurements as reported by patients during the five year period demonstrate little difference between the two treatments.

So what does all of this mean? Do we now have a new standard treatment for premenopausal women with hormone receptor positive breast cancer? Should all premenopausal women with hormone-positive, early breast cancer have their ovarian function suppressed and be placed on Aromasin or some other aromatase inhibitor? Or, should we wait for December 2014 when the data addressing the more basic question of whether ovarian suppression is necessary at all will be presented? Does the fact that we now advise tamoxifen for ten years and not five, as was done in these trials affect the conclusion? What will be the long term consequences of suppressing ovarian function plus an aromatase inhibitor on bone density? Should we be adding an anti-bone resorbing agent to the treatment for these young women? As often happens in clinical research, one answer leads to other questions. The human body is complex and its systems are interrelated. Yet, it is within this complexity that we must move forward.

**NEW SURGICAL MARGIN GUIDELINES**

Although breast conserving surgical therapy (lumpectomy) has been performed for more than thirty years, controversy still exists as to how much normal tissue surrounding a tumor a surgeon should remove to reduce local recurrence and

maximize cosmetic results. Some have argued that one normal cell is an adequate margin; while others have advocated one or more centimeter margins as optimal. What has always been clear is that the more tissue that is removed, the less favorable are the cosmetic results that can be expected.

Recently, the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) convened a consensus panel to address the question of margin size. To reach a consensus, the panel conducted a meta-analysis that included 26,162 patients in 33 studies published between 1965 and 2013. None of these studies were direct, randomized comparisons of different margin sizes; nor did the panel have access to direct patient records. Their primary source of information consisted of published reports of patients treated with different margin widths. A commonly used technique at time of resection is for the surgeon to place a colored ink at the edges of the resected tissue. The ink is apparent to the pathologist and serves as a way to identify the edge of a resected specimen. It is the pathologist who, by viewing tissues sections under the microscope, determines the size of the surgical margins. A margin described by the pathologist as "no ink on tumor cells," meaning no cancerous cells touching the edge of the lumpectomy specimen, is the minimum margin size felt to represent a clear margin and a margin size used by many surgeons.

Following deliberations, the primary conclusion reached by this panel of experts is that, though positive margins must be cleared, there is no evidence to support the need for a margin larger than "no ink on tumor cells." Further, they concluded that this practice can be applied to ductal and lobular carcinoma, all age groups, triple negative breast cancers, HER2 positive breast cancers, with or without treatment with systemic therapy, and for ductal carcinoma in situ. These results have been widely published, including in the *Annals of Surgical Oncology*, the

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**WHAT'S NEW continued**

International Journal of Radiation Oncology Biology Physics, and the Journal of Clinical Oncology. It is my expectation that they will become standard practice.

**QUESTIONS & ANSWERS**

(Q) Dr. Martino, I have an early breast cancer and I am receiving four cycles of chemotherapy. For a few days after each treatment I don't feel like eating. My family insists that I must eat to keep up my strength. All this does for me is upset my stomach further. Is it necessary that I eat during those days even if I don't feel like it?

(A) It is common for someone receiving chemo to not feel like eating for a few days. If nausea is your issue, your oncologist can prescribe medications that will help. Even so, you still may not want much food in your stomach. It is also very common for families to focus on your intake while you are undergoing treatment. I think you know that they mean well. It can at times turn into a battle.

I think the issue is how long this loss of appetite goes on for you and whether you are losing weight because of it. Most of us can easily limit our food intake for a few days every few weeks without consequence. Sometimes eating multiple meals per day is easier to accomplish rather than three larger meals. I have also found that for some people there is a time of day when food is more tolerable. If so, eating more during that period may be useful. I have generally encouraged my own patients to concentrate more on liquids rather than solid food during this period. Dehydration is more important and should be avoided.

(Q) Dr. Martino, I have read that one can look for tumor cells in the blood and that this can predict prognosis from breast cancer. How can I have this done?

(A) Thus far, the concept of measuring tumor cells in blood (circulating tumor cells) is primarily applied to patients who have metastatic disease though, at times, one can find such cells even in patients with early breast cancer. These circulating tumor cells are presumed to represent cells that are traveling throughout the body and are part of the metastatic process. Several studies have demonstrated that the number of cells that are counted in a tube of blood have a relationship to one's prognosis. Very low numbers correlate with a longer survival.

The more common use that is made of this measurement is to give one a clue as to whether a therapy is probably working or not. Ideally, one should take a measurement before starting a new therapy, and then repeat the measurement about 4 weeks after the first treatment. A marked reduction in number of circulating tumor cells suggests that the therapy is probably going to work well. Tumor markers, another type of blood test, can provide similar information in some patients. Though these types of measurements can be helpful in making treatment decisions, they work best when used in combination with other clues to help decide if a therapy should be abandoned. In my experience, I have found that some patients focus intently on such measurements and forget that they should be viewed as only part of the information used to make important treatment decisions. In my own practice, I like to use circulating tumor cell measurements in patients who primarily have bone metastases, when it is difficult for x-rays and scans to demonstrate if a response is occurring.

A more recent use of these circulating tumor cells is to use them for the purpose of performing genetic analysis to help decide what mutations a tumor has and which drugs might be most effective.

These tests are easy to do, but not always easy to interpret. Your oncologist can arrange for your blood to be sent to commercial labs that do this type of analysis.

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