Dear Readers,

The big event that occurred since the last issue was the American Society of Clinical Oncology meeting in Chicago. Results on several interesting compounds were presented. Perhaps the most promising information was not about any specific drug but rather a conceptual change in how we think of cancer and how we study drugs. I have reviewed this concept under the title of "What is Personalized Medicine?"

Dr. Silvana Martino

The Angeles Clinic FOUNDATION

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Breast Cancer Advisor

BY DR. SILVANA MARTINO • June 2012

WHAT'S INSIDE

BIOLOGY BASICS

In this issue I want to discuss lobular carcinoma in situ (LCIS). This entity was first described in 1919 as a noninvasive overgrowth of the lobular portions of the milk-making breast gland. It was given the name of lobular carcinoma in situ in 1941, when it was thought to be a precursor of invasive lobular cancer. The treatment of LCIS was a mastectomy. With further observation, it was appreciated that subsequent invasive cancers occurred bilaterally and that the invasive cancers were both ductal and lobular. The more modern understanding of this lesion is that LCIS itself in not a cancer. Rather, it is a marker of increased risk for invasive breast cancer and not a direct precursor. There is not complete agreement on this understanding. There are still physicians who view LCIS as a precursor of invasive lobular carcinoma. When compared to the general population, women with LCIS have an 8 to 10 fold higher incidence of breast cancer. In series where women with LCIS have been observed for a long time, the incidence of true cancer was found to be 10-15% in the first 10 years, about 25% in 20 years, and 35% by 35 years. Please note that most women with LCIS will not develop true breast cancer.

Lobular carcinoma in situ rarely presents with clinical findings such as a palpable mass. Most of the time, LCIS is found incidentally on a biopsy done for

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another reason. When it is found on a core biopsy, the general strategy is to perform a larger surgical biopsy so that one can be certain that there is not a more advanced lesion nearby. If pure LCIS is found on a surgical biopsy, one does not routinely re-excise. If LCIS is found along with a more advanced lesion, treatment is based on the features of the more advanced lesion.

The treatment of pure LCIS is varied and influenced by the doctor's opinion, patient preference and whether there is a familial or genetic background of breast cancer. Three basic options are considered: (1) lifelong surveillance with the goal of detecting any subsequent malignancy at an early stage; (2) bilateral mastectomy; and (3) chemoprevention using the hormonal drugs tamoxifen which can be used for both pre or postmenopausal women, or raloxifene (Evista) for postmenopausal women. The aromatase inhibitor hormones are not yet approved for this indication. Removal of the ovaries in premenopausal women is also a reasonable option for risk reduction though I know of no study that has used it as a single therapy for LCIS. Of these options, bilateral mastectomy provides the greatest risk reduction. Even so, none of the options provided complete prevention, and one still remains with some degree of risk.

Finally, as is true with all versions of breast cancer, not all LCIS lesions are identical. A more detailed understanding of its variations will lead to a better definition of personal risk and more tailored treatment recommendations.

WHAT'S NEW

1. FDA Approval of pertuzumab

On June 8, 2012, the U.S. Food and Drug Administration approved pertuzumab for use in metastatic breast cancer. It will be marketed by Genentech under the trade name of PERJETA. It is available for patients with HER2- positive metastatic breast cancer who have not received either prior chemotherapy or prior other HER2 directed therapy (such as Herceptin or Tykerb) for their metastatic disease. It is part of a three drug combination along with Herceptin and Taxotere.

The basis for the approval is a study of 808 patients with HER2- positive breast cancer who were treated with Taxotere and Herceptin. They were randomized (like the flip of a coin) to receive either Pertuzumab or placebo. They were then observed to see when their disease progressed. Only eleven percent of them had received Herceptin at the time of their original diagnosis.

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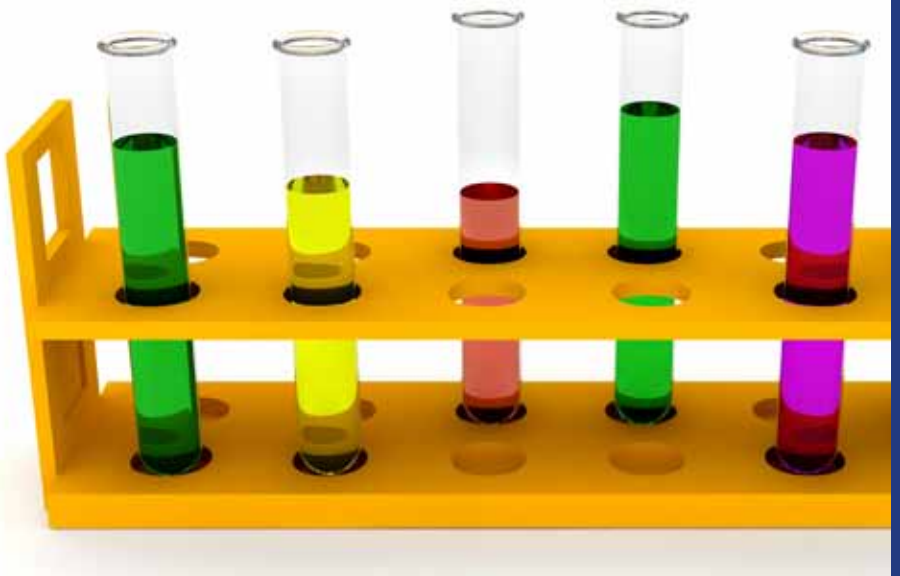

BIOGRAPHY

Dr. Silvana Martino

is the Director of Breast Cancer Research and Education at The Angeles Clinic Foundation. 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

The results demonstrate that the group who received pertuzumab had a longer period of disease stability (6 additional months) than the group that received placebo. At this time, it is not clear whether there may also be a difference in survival. The drug does not appear to add further risk for heart damage than is already seen with Herceptin alone.

This approval has been expected and is welcomed. There are now several studies that have demonstrated the value of combining Herceptin and pertuzumab in various patient groups having HER2-positive breast cancer. We anticipate that this combination will also be approved for early breast cancer as well.

The one caution that I will make is, that though these results are good, the patients studied were a bit unusual compared to typical American patients. Only 11% had received prior Herceptin at the time of their original breast cancer diagnosis, and only about half had chemo at their original diagnosis. Also, only one half of those with hormone positive disease had received prior hormonal therapy. This is not a common picture among those treated in the U.S., where I would expect that most would have had these therapies. Because of this, I would expect their recurrent breast cancer to be more resistant and somewhat less likely to respond. Never the less, I feel that pertuzumab is a valuable drug and clearly a step forward.

2. T-DM1

I first discussed this new treatment in the December 2011 newsletter. T-DM1 is a combination of Herceptin and a chemotherapy drug called emtansine. Both drugs are linked together and travel in the body together. At the recent ASCO meeting, Dr. Kimberly L. Blackwell from Duke University, presented results of the EMILIA study in HER2-positive metastatic breast cancer where T-DM1 was compared to treatment with the combination of Xeloda and Tykerb. The study included nearly 1,000 women all of whom had received prior treatment with Herceptin and a taxane. Patients were treated until disease progression or unacceptable toxicity occurred.

"It also appears that survival may be better with T-DM1, but the difference was not enough to be certain. The other important finding is that T-DM1 had fewer side effects."

The data demonstrate that T-DM1 resulted in a longer time to progression than the standard two drug combination of Xeloda and Tykerb. It also appears that survival may be better with T-DM1, but the difference was not enough to be certain. The other important finding is that T-DM1 had fewer side effects. This has been noted in other studies. It may be that since Herceptin can identify and target certain cancer cells, and since the chemotherapy drug is bound to Herceptin, that perhaps less chemotherapy is delivered to normal cells which do not have the HER 2 protein, thus reducing certain toxicities. This may turn out to be a valuable mechanism by which to deliver other chemotherapy drugs as well.

T-DM1 is still considered experimental, so it is not available for common use. Enough evidence of its value is mounting that we anticipate that it will be approved by the FDA.

A REQUEST

I recently spoke to one of my patients who suggested a new feature for the Breast Cancer Advisor. She informed me that she and other subscribers would like to read about other survivors particularly those who have done well and are many years from their original diagnosis. What have they done to stay well? Do they have insight to give to others? In what way have they found this experience to be positive? As I reflected on her request, I found that I liked the idea. The fact is that there are thousands of breast cancer survivors that either have never had a recurrence or that have done well even with metastatic disease. What can they teach others?

I am happy to hear from those of you in these happy circumstances. Please send me your story and I will periodically select some for inclusion in this newsletter. Even if you think you don't write well, give it a try. Be assured that your name will not be included in anything I print.

QUESTIONS & ANSWERS

Q. (Q) Dr. Martino, I was treated for breast cancer 16 years ago and have not had a recurrence. I have not seen my oncologist for several years because I did not feel a need as I have been doing well. During my recent visit, my oncologist told me that he wants me to do genetic testing since I was in my thirties when I was diagnosed. Why do I need to do this now? I feel fine and my mammogram was normal.

A. (A) There may be several reasons why your oncologist has suggested that you be tested for BRCA 1 and 2. Should you carry these genes, it will help your oncologist estimate the risk that you may develop a second breast cancer and also your risk of developing ovarian cancer. He may wish to discuss with you methods to reduce these risks. In addition, knowing if you carry either of these genes is important to other family members. If you have these genes, then other members of your family may also have inherited them. Their risk of breast and ovarian cancer is related to whether they may have inherited these genes as well. Though the BRCA1 and 2 genes are most predictive of breast and ovarian cancer, they also can predict for other malignancies such as prostate, pancreas, stomach, and thyroid. Since you were under age 40 when you were diagnosed with breast cancer you fall into a category where one should at least consider this type of testing. My advice is that you follow your doctor's recommendation.

E-mail your questions to:
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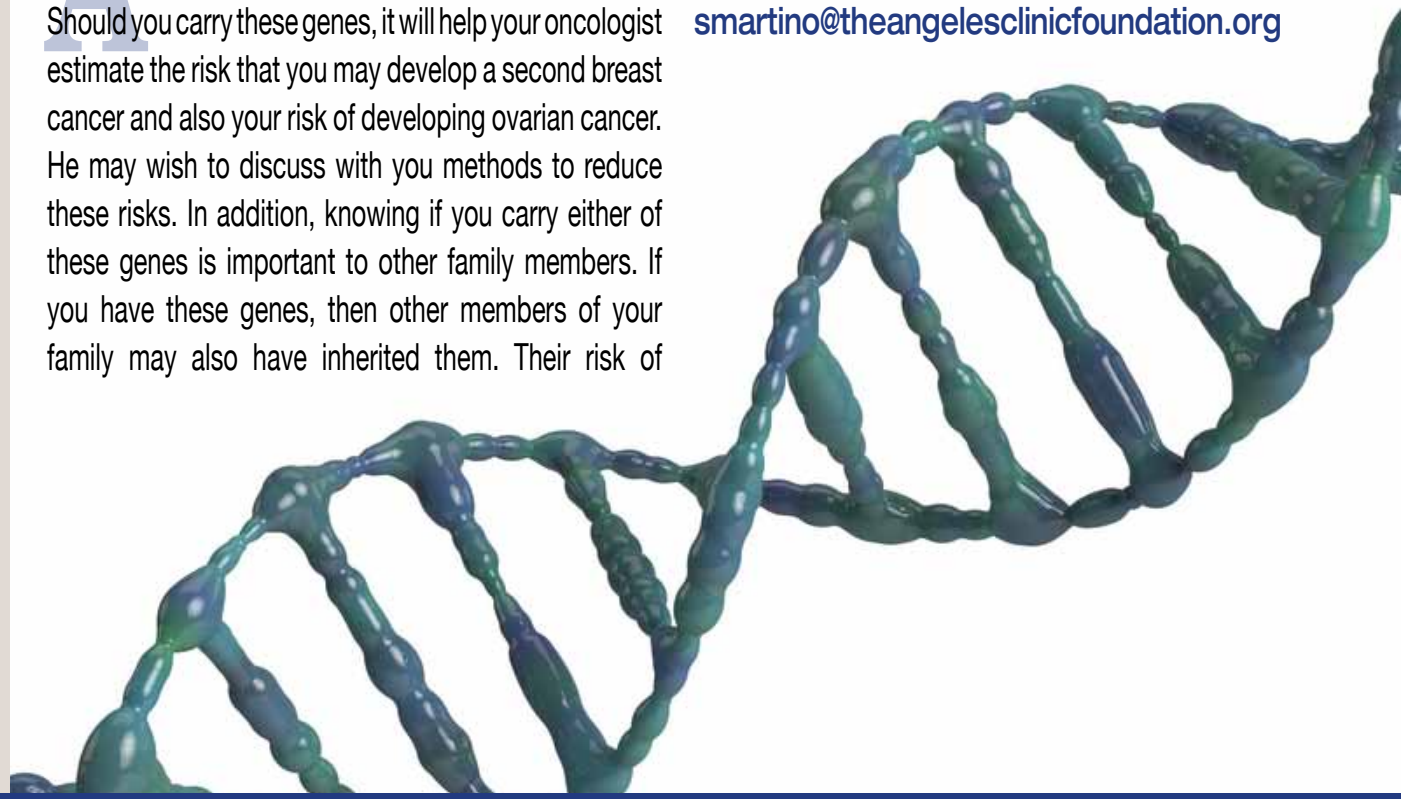

PERSONALIZED MEDICINE

What Is "Personalized Medicine"?

To introduce this concept, it is best to first review how new chemotherapy drugs are presently studied. Animal studies are generally conducted first and provide information on effectiveness and toxicity. From these data, selected drugs are then available for human testing. The first question to be answered (Phase 1) is what dose can humans tolerate and what is the accompanying toxicity. One begins at low doses extrapolated from animal studies, and increases the dose while observing patients for levels of toxicity. Eventually, a dose is reached at which the toxicity is too high and not acceptable. At that point, the highest dose with a tolerable level of toxicity is chosen to be studied further.

The second question that is answered (Phase 2) is whether the chosen dose is able to reduce the volume of tumor in patients with various cancers. One needs to answer this question for each tumor; breast cancer, lung cancer, colon cancer, etc. That a drug works against one cancer does not mean it will work against another form of cancer. From this phase, one then knows that a drug may work in colon cancer but not prostate cancer.

The third question is to further study the drug in a tumor where it has shown activity by comparing it to an existing drug already in use against that tumor (Phase 3). The goal is to determine if the new drug is better than existing therapy already in use. If the drug is superior to existing standard treatment, the results are then discussed with the FDA who must approve it before it is available for common use. This entire process takes years and is very costly.

The biggest drawback of this process however, is that the approval of a new drug is based on the assumption that all cancers of a common origin (breast cancers as an example) are the same and should be treated in the same manner. The final expression of this approach is the development of "treatment guidelines" which basically confine all doctors to treat patients with a common diagnosis in the same manner. These constraints are reinforced by insurance companies who choose to only pay for care when a patient receives therapy that is part of such guidelines. This would be great if in fact tumors with the same name all behaved the same. The fact is that they do not. Tumors may look the same, but their biological behavior varies considerably. This is why it is difficult to predict how an individual tumor will respond to treatment and what the prognosis for an individual is.

> ***"These constraints are reinforced by insurance companies who choose to only pay for care when a patient receives therapy that is part of such guidelines."***

Within the field of breast cancer, we have had some appreciation of the variable nature of tumors for some time. This is the basis of separating tumors into hormone positive versus negative and HER2 positive or negative. Making these distinctions allowed us to look for therapies other than chemotherapy; and therapies that were more effective because they targeted cells with specific characteristics.

The concept of personalized medicine is clearly a different paradigm. It is based on the recognition that tumors are different from person to person. That the primary lesion may be different from a recurrence; and that tumors

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change over time and with various treatments. These differences must be identified and exploited in making treatment decisions. Therapeutic decisions should not be confined to the characteristics of the original tumor. Better decisions are made if a tumor recurrence is biopsied, studied to identify its peculiar characteristics and therapy chosen based on these findings. Thus far it does appear that results are better when this approach is followed. What is not clear is how much better this will turn out to be and whether we will cure more people by using this process.

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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.

Upcoming Foundation Events

For more information, please call us at (310) 582-7909

Genetics of Breast Cancer

Presented by Dr. Melani Shaum
July 8, 2012 • 1:45 PM
University Synagogue
11960 Sunset Boulevard
Los Angeles, CA

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