

Breast Cancer Advisor

BY DR. SILVANA MARTINO

January 2014



Dear Readers,

It is the start of a new year and even as I get a bit older, I still experience great joy at this time. A feeling that there is a new beginning; a hope that this year will be better; new goals are set; things to learn; events to look forward to. I hope that 2014

brings you all the best, as well. I wish each of you much health and happiness.

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

CONTENTS

OUR NEW ADMINISTRATIVE DIRECTOR

NICK BELARDO 1

MEETING REVIEW

REPORT FROM THE 2013,
SAN ANTONIO BREAST
CANCER SYMPOSIUM. 2

OUR NEW ADMINISTRATIVE DIRECTOR-NICK BELARDO

It is with great pleasure that I introduce to you Mr. Nick Belardo, The Angeles Clinic Foundation's new Administrative Director. Nick assumed his position in September of 2013, and already has made many contributions to the Foundation. He majored in Broadcast Journalism at Kent State University in Kent, Ohio and has



continued next page

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.

NEW DIRECTOR continued

extensive experience in event planning and hospitality, which he plans to use while working for the Foundation in order to bring a unique style to all of its efforts. Nick is excited to use his new role to elevate the Foundation's already tremendous achievements.

As the Administrative Director, Nick will headline all Foundation events, fundraising efforts and communications regarding the Foundation. He is currently working on initiatives to spread greater cancer awareness to the community. Nick is very excited to join The Angeles Clinic Foundation and is eager to expand on the Foundation's established success and to ensure that its mission is met.

Nick welcomes your questions or comments. You can reach him by phone or e-mail.

Nick Belardo

2001 Santa Monica Blvd., Suite 560W

Santa Monica, CA 90404

Office 310.582.7909

Cell 310.251.3491

Fax 310.582.7996

nbelardo@theangelesclinic.org

MEETING REVIEW**REPORT FROM THE 2013, SAN ANTONIO BREAST CANCER SYMPOSIUM**

This is probably my favorite breast cancer meeting. I have been going to it for at least 30 years. I have seen it grow from a meeting of a few clinicians to a large international event that combines both clinical trial results and the latest in laboratory science in breast cancer. It is clearly one of the top places where

investigators hope to have the opportunity to present their data. It is a four-and-a-half day event with meetings from 7 am to around 11 pm. It is exhausting but well worth it. I have summarized the presentations, which from a clinical perspective, I personally considered most valuable. In addition to these clinical results, many other presentations were about the basic biology of cancer. These topics are not emphasized here, but I anticipate that they will bear fruit in the not too distant future.

Though this issue of the Breast Cancer Advisor looks different, I have not abandoned the prior format. There simply was a lot of material from the San Antonio Breast Cancer Symposium that I wanted to share with you.

1. The meeting began with a plea from Dr. Kent Osborne, who is one of the organizers of the Symposium that in adjuvant trials, long term follow-up is critical if we are to assess survival endpoints. This is particularly important for patients with hormone positive tumors, where approximately 50% of recurrences occur after five years from diagnosis. Long term follow-up should extend a minimum of 20 years for these patients.

2. The value of breast cancer screening using mammography was discussed by Dr. H. Gilbert Welch from the Dartmouth Institute for Health Policy and Clinical Practice in Thetford, VT. Simply stated, his conclusion was that though screening mammography clearly has had the result of identifying smaller disease, it has not reduced advanced disease nor resulted in a comparable reduction in deaths from breast cancer. Furthermore, he concluded that the reduction in the death rate from breast cancer that has been seen in the U.S. and other Western countries is primarily from improvements in therapy, especially systemic therapy, and minimally from screening mammography.

continued next page

YOUR SUPPORT

The **Breast Cancer Advisor** newsletter is funded by donors like you.

Help us keep the content pure, with no outside influence, by donating to The Angeles Clinic Foundation.

Make a donation directly online by clicking

[Donate Now](#)

or mail to: The Angeles Clinic Foundation, 2001 Santa Monica Blvd., #560W, Santa Monica CA, 90404

Your gift to The Angeles Clinic Foundation is fully tax deductible.

MEETING REVIEW continued

3. There are now several agents that target the HER2 receptor. Since no single drug causes a response in all tumors, it is important to ask whether two anti-HER2 drugs are better than one. Two studies were presented looking at the combination of Herceptin and lapatinib in the neoadjuvant (pre-operative) setting where one can measure the rate of complete pathological response (pCR). Both studies confirmed that patients who achieve a pCR do better than patients who do not. This is particularly true for tumors that are also hormone receptor negative versus hormone receptor positive. Both studies demonstrated that using both HER2 drugs together in addition to chemotherapy increases pCR rate. It was also apparent from both studies, that diarrhea was a dominant side effect with the combination. Approximately one-third of the patients could not complete the entire program due to side effects. Cardiac toxicity did not appear to be increased. I believe that the real question in HER2 positive tumors is whether pertuzumab or T-DM1 are not better anti-HER2 therapy rather than the addition of lapatinib.

4. Dr. Dennis Slamon from UCLA presented results of the BETH trial. This was a large adjuvant trial in node positive and high risk node negative patients who had HER2 positive disease. They were treated with adjuvant chemotherapy and randomized to receive Avastin or not. The results of this study were that Avastin did not add further benefit, but did add more toxicity. This is yet another negative study for this anti-angiogenesis drug.

5. One of the more interesting topics discussed was that of tumor infiltrating lymphocytes. It has generally been held that most tumors, including breast cancer, were not immunogenic. That is, there was little reaction from the immune system against tumors. It appears that this may have been incorrect. Many breast cancers, especially those that are HER2 positive and those that are triple negative (hormone and HER2 negative)

appear to have variable levels of lymphocytes surrounding them. The more lymphocytes are present, the better the prognosis. Several studies were presented that demonstrate that patients whose tumors have more lymphocytes surrounding them tend to respond better to anti-HER2 therapies and also to chemotherapy. It may be that these therapies work in part through the immune system.

6. While the value of screening mammography is being questioned, others are continuing to work on better ways to achieve an early diagnosis of breast cancer. One technique being evaluated is the use of MRI for the general population. Since MRI is costly and time consuming, a method that is both performed quickly and can be read quickly is being studied. In a group of 1,700 women all of whom had normal mammograms and normal ultrasound, this technique identified additional abnormalities in 11/1,000 women. Of these, 39% were DCIS, most of which were high grade. The invasive lesions that were identified were primarily node negative. This is not the first presentation that I have heard on this topic, but it is the first applied to a general risk population rather than to a high risk population.

7. Dr. Monica Morrow, a prominent breast surgeon from Memorial Sloan-Kettering Cancer Center in New York, discussed the topic of local control of breast cancer. She stated that all systemic therapies that reduce distant recurrence also decrease local recurrence. Consequently, we may not need to be as aggressive with local therapies such as surgery and radiation as we once thought. This concept is important in considering the size of tumor margins (the amount of benign tissue surrounding a cancer that is also surgically removed) and the number of lymph nodes that need to be removed. In general, she argued for less surgery.

8. Dr. Max Wicha from the University of Michigan

continued next page

PREVIOUS ISSUES

You can review all previous issues of the Breast Cancer Advisor on our website at:

www.theangelesclinicfoundation.org

click on the NEWSLETTER tab

MEETING REVIEW continued

Comprehensive Cancer Center in Ann Arbor, Michigan has been working on the concept of stem cells for many years and I consider him one of the pioneers in this field. He described the variability in the nature of tumor stem cells. He described that while the tumor is located within an organ, the stem cells in the tumor have epithelial qualities. However, when stem cells separate from a tumor and invade the blood stream and are circulating, they have mesenchymal properties. These changes have many biological consequences, including the possibility that the present essays designed to identify circulating tumors cells may be inadequate since they are designed to identify cells that have epithelial rather than mesenchymal features.

9. The added value of radiation therapy following lumpectomy in women age 65 and over was the topic of the PRIME 2 trial. This multi-center study enrolled 1,300 women with tumors of 3 cm or smaller, that were node negative and hormone positive. They were excluded if their tumor was grade 3 or had lymphovascular invasion. The women were randomized to lumpectomy plus whole breast radiation versus lumpectomy alone. All received hormonal therapy but not chemotherapy. Their results demonstrated that in this group of favorable tumors, the level of hormonal positivity was important. Those with lower estrogen receptor levels had a local recurrence rate of 11% versus only 3% for those with tumors that had a high level of estrogen receptor. The group randomized to receive whole breast radiation had a modest 3% difference in local recurrence compared to those randomized to surgery only. Survival was the same with or without radiation. Over 70% of deaths were from a cause other than breast cancer. This final point is very important to understand. The mean age for the women in this trial was 70. In this age category, one is dealing with women who have what is termed “competing causes of death”. That is to say, because of other illnesses that are common as a population gets older, breast

cancer may not be their cause of death-it will be something else.

10. For several decades, it has been standard practice to not remove the primary tumor in those who already had distant metastases. The logic being that the primary disease was only a portion of the overall disease burden, and since you could not remove all of the disease, removal of a small portion would have no beneficial effect. There actually are animal data that suggested that if you removed the primary in the face of metastatic disease, that the metastatic disease actually appeared to grow, suggesting that the presence of the primary maintained some degree of control over the distant metastases. This concept was challenged a few years ago when several retrospective, non-randomized studies suggested that the opposite was true. They demonstrated that women with metastatic disease who had their primary tumor surgically removed had a longer survival. Two randomized studies in stage four patients were presented, one from India and one from Turkey. The TATA study from India found that the survival was identical whether the primary was removed or not. The Turkish study found that the group who had their primary removed lived 4 months longer than the group that did not, but this difference was not statistically significant. Neither study had sufficient numbers to identify a subgroup of patients for whom this might be a particularly good approach. There are several larger studies ongoing, one in the U.S. and one in Japan, that will add more data to this issue, but, for now removal of the primary lesion in metastatic patients should not be a routine practice.

11. Results from the NSABP B-32 study were presented. This trial of nearly 4,000 women with sentinel lymph node negative disease, as determined by H&E staining (the typical way of looking at lymph nodes) who were randomized to either have an axillary lymph node dissection or not was updated. About 80% of patients had hormone positive disease, and about

continued next page

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.

MEETING REVIEW continued

80% had a lumpectomy and radiation. At 10 years of follow-up, there was no difference in disease free survival, overall survival, distant disease or local recurrence. They also looked at the sentinel nodes by more detailed immunohistochemistry (IHC) analysis and did note some minor difference in outcome, but it was not statistically significant. They concluded that lymph node dissection in patients with H&E negative sentinel nodes is not needed and that IHC testing of H&E negative sentinel nodes is similarly not necessary.

12. The first results of the IBIS-II study were presented. This was a multicenter, randomized trial of nearly 4,000 postmenopausal women who were at higher than average risk for developing a breast cancer, who were randomized to Arimidex (an aromatase inhibitor hormone) versus a placebo. The group has been observed for about five years. A 53% reduction in breast cancer development was reported. The reduction was only in hormone positive breast cancer. No difference in the development of hormone receptor negative breast cancer was noted. Interestingly, they also noted a decrease in skin cancer and colon cancer. A similar observation was made in a similar prevention study when the hormone Aromasin was used. No new or unusual side effects were encountered that were not already recognized as part of the pattern with these hormones. This level of breast cancer risk reduction is similar to what is generally seen with other anti-estrogen hormones. It does add another choice in the postmenopausal population. Please note that this was a comparison to a placebo, so we do not know how this drug compares to other agents used such as tamoxifen.

13. An interesting trial was presented by the U.S. Oncology Group. They reported on a phase II non-randomized trial of postmenopausal women with metastatic, hormone receptor positive, breast cancer that were treated either with the hormone Femara or Femara plus dasatinib a small-molecule kinase

inhibitor. Their main goal was to measure “clinical benefit rate” with each treatment. The trial defined this parameter as a combination of response rate and stable disease for six months. They did not find much difference in this measurement. However, what the trial did observe was that the group treated with the combination had about twice the rate of progression free survival as the group treated with the hormone only. Since this was not a randomized trial, we cannot be certain that this difference is real. Another study will need to be done to answer the question properly. Two prior studies adding dasatinib to other hormones in patients with more extensive prior therapy did not demonstrate a benefit, so we remain cautiously optimistic.

14. The issue of bisphosphonates such as Zometa and clodronate were discussed by several speakers. Long term data was presented based on the Oxford Overview Analysis. The conclusion reached was that this class of drugs when added to other therapies for the treatment of newly diagnosed breast cancer provided benefit only for women who are postmenopausal. There was a reduction in bone metastases and a 2-3% improvement in absolute survival. These benefits hold true in hormone positive and hormone negative patients, node positive and node negative disease and with or without chemotherapy. No specific drug or schedule appeared superior, so even doses used for osteoporosis can be used. No reduction in second primary breast cancers was noted, so suggestions made in some studies that these agents may have the ability to prevent primary breast cancer seems unlikely.

An additional European neoadjuvant study using bisphosphonates was presented. The NATAN study was in patients who received chemotherapy using an anthracyclines-taxane based program pre-operatively, but who did not achieve a pathological complete response (meaning that they had residual tumor), and who were randomized to receive Zometa for the next five years or not. The

continued next page

HOW TO RECEIVE FUTURE ISSUES

You may request future issues of this newsletter by e-mailing your request to:

smartino@theangelesclinicfoundation.org

MEETING REVIEW continued

results demonstrated no difference in disease free survival or overall survival. There was a suggestion that in women age 55 and over there might be some benefit. This again suggests that the bisphosphonates require a low estrogen state to provide any benefit.

15. The results of the CALGB 40603 study were presented by Dr. William Sikov. The primary goal of this neoadjuvant trial in triple negative breast cancer was to determine whether the addition of carboplatin, Avastin or both increased pathologic complete response rates when compared to weekly Taxol followed by dose dense chemotherapy. The results demonstrated that the addition of carboplatin either alone or with Avastin increased pCR rate by 10%. The addition of Avastin alone did not increase pCR rate significantly. Each agent added toxicity. There is a small but growing body of evidence that the addition of carboplatin in the treatment of triple negative breast cancer has some benefit. There is also a growing body of evidence that the addition of Avastin to the treatment of breast cancer is of minimal to no benefit.

16. The research team from the Gruppo Italiano Mammella presented the seven year results of an adjuvant study in node positive patients who were randomized to either epirubicin/Cytosan-Taxol with or without the addition of 5-fluouracil (5-FU). Both therapies were further randomized to be given either every three weeks or every two weeks known as the dose-dense fashion. They did not find any difference whether 5-FU was added or not. They did find that survival was better when therapy was given every two weeks rather than every three weeks, confirming prior studies that these drugs given in a dose-dense schedule are more effective. They further confirmed prior studies suggesting that dose-dense therapy is most efficacious in hormone negative breast cancer. Two patients in the dose dense therapy group

developed leukemia.

17. The ROSE/TRIO-012 study was reported. This study looked at the anti-angiogenesis, monoclonal antibody drug ramucirumab in HER2 negative patients with metastatic or locally advanced breast cancer. Randomization was to docetaxel plus placebo, or to docetaxel plus ramucirumab. Neither progression free survival nor overall survivals were different. So far, the use of anti-angiogenesis drugs in breast cancer has not been successful though this concept remains of great interest to many.

18. The results of SWOG S0500 were presented. This study in patients with metastatic disease was designed to test whether using the level of circulating tumor cells (CTCs) in a patient's blood could be used to assist in choosing chemotherapy. Circulating tumor cells are detectable in approximately 75% of people with metastatic breast cancer. In about half of these, the level is elevated. It is known that patients with lower values at baseline and those whose number of CTCs decrease with therapy have a better outcome. This report looked at patients who after one cycle of chemotherapy had their CTC counts still elevated suggesting that the one cycle of chemo that they had received had not reduced the count. At this point, the patients were randomized to either continue on the same therapy or switch to another therapy. The choice of therapy (which drugs to use) was left to their own physician and was not mandated by the protocol. The results of this study did not demonstrate any benefit to the switching strategy in either progression free survival or overall survival. This was a disappointment.

The next step is to not only count the number of CTCs but to actually study these cells to see if their mutations can be used to identify which drugs might be most effective for an individual patient.

VISIT OUR WEBSITE AT

www.theangelesclinicfoundation.org

or call us at (310) 582-7909