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Breast Cancer® UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

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SPECIAL FEATURE

Bone complications of breast cancer treatment; Osteonecrosis of the jaw

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STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, *Breast Cancer Update* uses one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Counsel appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations.
- Evaluate the emerging data for biologic therapies and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease.
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 2 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Holmes, Mamounas, Seidman, Lipton and Marx on the integration of emerging clinical research data into the management of breast cancer.

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HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs, review the monograph and complete the Post-test and Evaluation Form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **BreastCancerUpdate.com** includes an easy-to-use, interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **blue underlined text**.

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UPCOMING EDUCATIONAL EVENTS

American Association for Cancer Research Annual Meeting
April 14-18, 2007
Los Angeles, California
Event website: **www.aacr.org**

NCCTG Semi-Annual Meeting
April 16-19, 2007
Rochester, Minnesota
Event website: **http://ncctg.mayo.edu**

NSABP Semi-Annual Meeting
April 27-30, 2007
Jacksonville, Florida
Event website: **www.nsabp.org**

SWOG Semi-Annual Meeting
May 2-6, 2007
Chicago, Illinois
Event website: **www.swog.org**

ASCO 2007 Annual Meeting
June 1-5, 2007
Chicago, Illinois
Event website: **www.asco.org**

ECOG Semi-Annual Meeting
June 8-10, 2007
Washington, DC
Event website: **www.ecog.org**

CALGB Semi-Annual Meeting
June 21-24, 2007
Baltimore, Maryland
Event website: **www.calgb.org**

ASCO 2007 Breast Cancer Symposium
September 7-8, 2007
San Francisco, California
Event website: **www.asco.org**

EDITOR'S NOTE

Neil Love, MD

Oncolicious

The unique power of audio was recently reinforced when I picked up my teenage daughters from the airport for winter break. Hopping into the car, they commandeered the sound system and in an instant, a song I had never heard before was emerging from within.

Listen up ya'll, cuz this is it.
The beat that I'm bangin' is de-li-cious.
I'm Fergalicious.

Strangely enough, I was captivated by the hypnotic sound and, just like thousands of other Fergie fans, still can't seem to get the tune out of my head. When I finally realized I was hooked, I wasn't all that surprised. Through my unpredictable career as producer of our unique oncology-focused record label, I have come to learn that some "acts" just have a certain magic that pulls us in and won't let go. This program includes interviews with three new talents making their *Breast Cancer Update* debuts, Dr Robert Marx and Dr Allan Lipton, AKA "The Bone Brothers," and the oncofireball Dr Frankie Holmes. Within the first 30 seconds of each of these chats, I knew we had stumbled onto "stars."

Dr Marx is the first DDS I have interviewed, and from the moment he opened his mouth, I was riveted. A self-described "bone scientist," Dr Marx is chief of maxillofacial surgery a few miles away at my faculty alma mater, the University of Miami. Several years ago, this astute clinician began to observe an unusual syndrome characterized by open lesions in the mouth that were exposing mandibular bone.



From left to right: Dr Robert Marx, Dr Allan Lipton and Dr Frankie Holmes

Perplexed by the increasing number of such cases, Dr Marx and his dental colleague Dr Salvatore Ruggiero from the Long Island Jewish Medical Center began the medical detective work needed to uncover the common thread. They soon realized that all of these cases were cancer patients receiving intravenous bisphosphonates for metastatic disease to the bone. Dr Marx named this new entity *osteonecrosis of the jaw*, or ONJ, and published the first case series in 2003. When he arrived at our offices for the interview, this highly articulate and thoughtful investigator plopped down an impressive new paperback that he had just authored on ONJ (Figure 1). The book is filled with amazing photographs and artwork, which clarify what we currently understand about this strange clinical syndrome.

The practice implications of Dr Marx's comments are straightforward yet mind-boggling to contemplate. The most critical point is that dentists and, more specifically, oral surgeons must now be quickly integrated into the oncology treatment paradigm, specifically for any patient beginning intravenous bisphosphonate therapy. How this will occur in an expeditious manner is another question, but a good place to start might be to invite interested oral surgeons to participate in tumor board meetings and to obtain their thoughts about recommended protocols and indications for dental referrals.

Another brilliant *BCU* neophyte featured on this issue is Dr Allan Lipton, who further discusses the enormous clinical impact of bone and breast cancer. According to Allan, an estimated 400,000 patients in the United States are diagnosed annually with bone metastases resulting from a variety of different primary tumors. The vast majority of these individuals are of course receiving intravenous bisphosphonates, which the "bone people" now clearly believe are behind the rare, or maybe not so rare, ONJ syndrome.

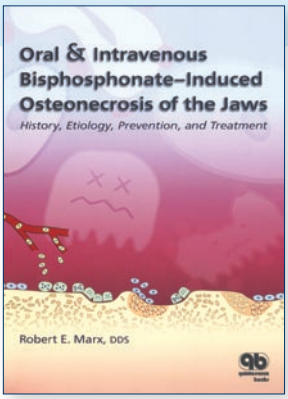
The final "new" soloist featured on this program is Dr Frankie Holmes, whose passion for her work and vast knowledge base follow in the footsteps of other US Oncology breast cancer investigators who have worked with us on many of our programs, including Drs Joyce O'Shaughnessy, Stephen Jones, Nicholas Robert and Joanne Blum.

1

Oral & Intravenous Bisphosphonate-Induced Osteonecrosis of the Jaws: History, Etiology, Prevention, and Treatment (Quintessence Books, 150 pages)

Robert E Marx, DDS
Chicago, 2007

http://www.quintpub.com/



For some time now, I have been trying to interview the profoundly busy Dr Holmes to provide our listeners with full access to the energetic clinician who regularly offers provocative questions and comments during the Q and As for breast cancer sessions in large scientific meetings. As expected, her interview did not disappoint.

Dr Holmes showed up at our temporary recording studio in San Antonio wearing a bright, multicolored outfit with a matching tote bag that was overflowing with papers and posters. Behind her cheerful attire was one of the most serious scientific minds I have encountered in a long while. During the time we chatted, Dr H flitted from topic to topic like a hummingbird, and her comments were punctuated by highly entertaining sound bytes that came forth in rapid staccato. Her analogy of pregnancy and chemotherapy-induced GI toxicity came complete with the type of demonstrative gagging sounds that told me she truly understands what her patients go through.

She then drew the analogy of Rapunzel in the tower and the lonely tumor cell seeking angiogenesis, and in the next sentence...well, you listen:

> *When I think about fine needle aspirations, I think about those last days in Vietnam — the pictures that we saw of those refugees clinging to the ruts of the helicopters that went off. It was just jam packed, and when you think about an FNA, that needle goes in there with tremendous suction. It sucks up cells, and you get a lot higher yield of tumor cells than you do of stroma.*

Prior to the days of the web, portable electronics and megatelecommunication, attending physicians who had a unique talent to teach clinical medicine in a captivating manner would influence only a few house staff members on rounds. Today, not only can Fergie become a household name in a few weeks, but we can also "discover" great teachers and motivators like the three new stars and two veterans (Drs Andrew Seidman and Terry Mamounas) on this action-packed issue.

It's delicious ■

— Neil Love, MD
NLove@ResearchToPractice.com
February 28, 2007

SELECT PUBLICATIONS

Lipton A. **Biochemical bone markers in breast cancer.** *Cancer Treat Rev* 2006;32(Suppl 1):20-2. **Abstract**

Marx RE. **Oral & intravenous bisphosphonate-induced osteonecrosis of the jaws: History, etiology, prevention, and treatment.** Quintessence Publishing Co Inc, 2007. No abstract available

Marx RE et al. **Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment.** *J Oral Maxillofac Surg* 2005;63(11):1567-75. **Abstract**

Marx RE. **Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic.** *J Oral Maxillofac Surg* 2003;61(9):1115-7. No abstract available

INTERVIEW

Frankie Ann Holmes, MD

Dr Holmes is Co-Director of Breast Oncology Research at Texas Oncology and US Oncology Breast Cancer Research in Houston, Texas.

Tracks 1-20

Track 1 Introduction

Track 2 US Oncology trial 02-103: Feasibility of core needle biopsies in clinical trials to correlate gene signatures with pathologic complete response

Track 3 Potential problems with tumor acquisition and analysis

Track 4 Neoadjuvant chemotherapy and lapatinib, trastuzumab or the combination for patients with HER2-positive disease

Track 5 Degree of HER2 amplification and dose response to trastuzumab

Track 6 Use of anthracycline-containing chemotherapy and trastuzumab in the treatment of HER2-positive disease

Track 7 Patients' response to requests for multiple biopsies

Track 8 NSABP-B-40: Neoadjuvant docetaxel, alone or with capecitabine or gemcitabine with or without bevacizumab

Track 9 Second interim report of the BCIRG 006 adjuvant trastuzumab trial

Track 10 BCIRG 006: Updated results of topoisomerase II as a predictive factor

Track 11 BCIRG 006 second interim analysis: Efficacy of AC → TH versus TCH

Track 12 US Oncology adjuvant trial comparing AC to docetaxel/cyclophosphamide (TC)

Track 13 Use of adjuvant chemotherapy in clinical practice

Track 14 Tolerability of adjuvant AC compared to TC

Track 15 US Oncology clinical trials for patients with HER2-negative or HER2-positive disease

Track 16 Management of cardiac health in patients with breast cancer

Track 17 Dose-dense nanoparticle albumin-bound (*nab*) paclitaxel and bevacizumab

Track 18 Mechanism of action of *nab* paclitaxel

Track 19 Potential advantages of *nab* versus standard paclitaxel

Track 20 Epigenetics and breast cancer

Select Excerpts from the Interview

Track 2

DR LOVE: Would you discuss the data you presented at San Antonio evaluating the feasibility of core needle breast biopsies for gene assays in community practice?

DR HOLMES: We just completed a neoadjuvant study of FEC followed by docetaxel and capecitabine (Holmes 2006). The key to this effort was that we were able to obtain tissue from core biopsies, which was a big step for us because we have community-based practices.

We submitted the core biopsy tissue for in vitro chemosensitivity testing to Dr Lajos Pusztai at MD Anderson to perform microarray assays and look for signatures denoting responsiveness. The primary objective was to correlate the patient's pathologic complete response with these molecular signatures.

We shipped 195 tissue samples to MD Anderson, but because tumors are comprised of tumor cells and stroma, we had approximately a 65 percent recovery of good tissue that could be evaluated. We had our learning curves, but we were able to prove that we could do this in the community.

Our next trial will be a neoadjuvant study conducted in patients with HER2-positive disease, and again, the key will be to continue to develop this approach toward personalized medicine.

The first two weeks of this study will be a run-in period during which we will administer trastuzumab, lapatinib or trastuzumab with lapatinib. We'll obtain a biopsy as a baseline, and at the end of two weeks we will rebiopsy to evaluate what changes have occurred.

Then, the patients will be treated with FEC-75 followed by weekly paclitaxel. During the entire time, they will receive the anti-HER2 agent(s) to which they were randomly assigned up front. Then they'll undergo surgery.

The endpoint will be pathologic complete response, and we hope to integrate that with tissue biomarkers. For the patients who do not achieve a pathologic complete remission, we would like to obtain a third, optional biopsy to see what's different about the tumor and to perhaps use that as a springboard for other therapy.

Tracks 9-11

DR LOVE: What's your take on the new data set presented at San Antonio on the BCIRG 006 trial (Slamon 2006)?

DR HOLMES: The idea behind the BCIRG 006 trial was to evaluate patients with centrally determined FISH-positive disease to establish whether up-front treatment with trastuzumab reduced relapse rate.

The second strategy was based on the understanding of the mechanisms of synergy and whether a nonanthracycline-containing regimen could be evaluated, particularly because of the known cardiotoxicity of trastuzumab. Would it be possible to incorporate trastuzumab earlier without having to wait until the completion of the anthracycline?

The three arms in the study were AC followed by docetaxel (AC → T), which was a standard in the community, AC followed by docetaxel/trastuzumab

(AC → TH) and trastuzumab/carboplatin/docetaxel (TCH).

The great thing about this trial is that it continues to provide new answers and new questions, and now we find that the TCH and AC → TH arms are equally effective (1.1).

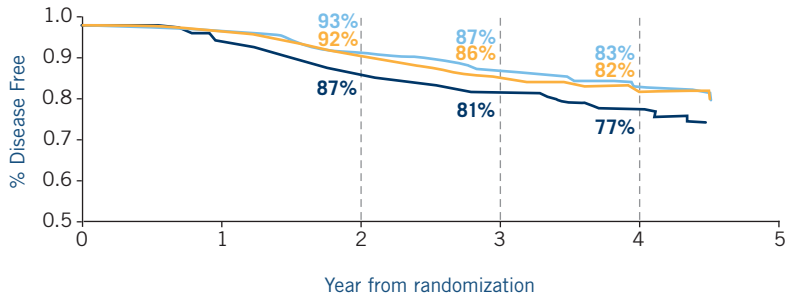
DR LOVE: What about the evaluation of TOPO II status? Is that helpful in selecting therapy for patients with HER2-positive disease (1.2)?

DR HOLMES: It is still an unanswered question. Some would say that if the disease is TOPO II-amplified, then perhaps the patient should receive an anthracycline. Others would argue that you can avoid the cardiotoxicity, because you do not have to administer the anthracycline, and you can choose a much more user-friendly trastuzumab regimen.

I believe that many more of us will probably use the TCH regimen if we're worried about cardiac toxicity.

1.1 **Updated Analysis of Disease-Free Survival in BCIRG 006**

	Patients	Events			
■	1073	192	AC → T		
■	1074	128	AC → TH	HR (AC → TH vs AC → T) = 0.61 [0.48;0.76]	P < 0.0001
■	1075	142	TCH	HR (TCH vs AC → T) = 0.67 [0.54;0.83]	P = 0.0003



AC = doxorubicin/cyclophosphamide; T = docetaxel; H = trastuzumab; TCH = docetaxel/carboplatin/trastuzumab

SOURCE: Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**. With permission from CIRG, **www.bcirg.org**.

Tracks 12-14

DR LOVE: Can you discuss the AC versus TC study reported by Steve Jones and your group, US Oncology (Jones 2005, 2006)?

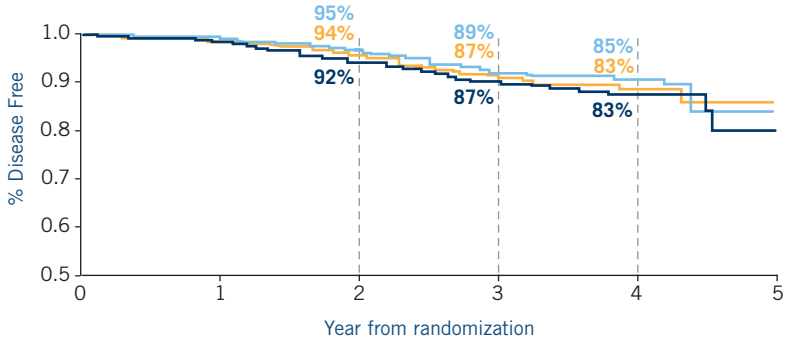
DR HOLMES: This was a straightforward, simple idea embraced by the community, many of whom have concerns about the anthracyclines. We have

1.2

Second Interim Analysis: Disease-Free Survival According to TOPO II Amplification During BCIRG 006 in Patients with HER2-Positive Early Breast Cancer

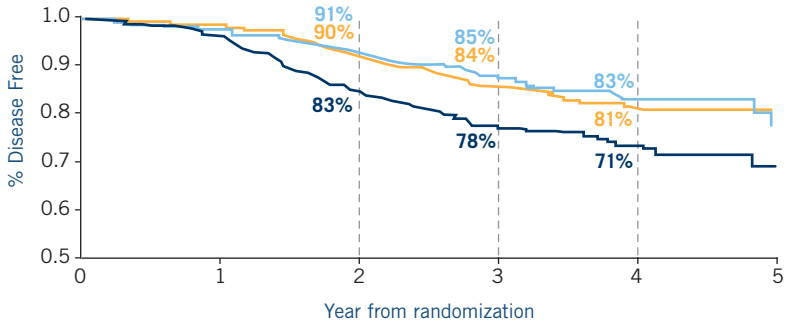
TOPO II amplified

Patients	Events	
328	42 AC → T	
357	35 AC → TH	P = 0.336
359	42 TCH	P = 0.648



TOPO II nonamplified

Patients	Events	
643	146 AC → T	
643	87 AC → TH	P < 0.001
618	92 TCH	P < 0.001



AC = doxorubicin/cyclophosphamide; T = docetaxel; H = trastuzumab; TCH = docetaxel/carboplatin/trastuzumab

SOURCE: Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**. With permission from CIRG, **www.bcirg.org**.

now seen not only a better outcome in the total population with TC but also benefits in every subset (1.3), although these were not preplanned analyses.

Of course, right now one question that comes immediately to mind is, what is the HER2 status of those patients? That analysis is ongoing. However, at the time that this trial was being conducted, HER2 status was not a routine parameter that we evaluated.

DR LOVE: Some people have said, "This is only one study." How do you evaluate the efficacy data?

DR HOLMES: It is one study, and it was a small study by modern adjuvant standards. However, it's not inconsistent with the data in the literature, which suggest that docetaxel is superior to the anthracyclines in head-to-head studies conducted in the metastatic setting. I don't have any problems with this study because it is reasonably sized, and the dose intensity was maintained.

I've started to incorporate the TC regimen much more frequently in my practice, especially in situations in which I have concerns about chemotherapy tolerance. However, at this time, I have not given up on the standard AC/taxane regimen for my patients with node-positive disease.

DR LOVE: What's your personal experience with the tolerability of TC versus AC?

DR HOLMES: AC is now recognized as a highly emetogenic regimen, and patients experience delayed nausea and vomiting. I was once on a panel that was discussing emesis, and somebody said, "Oh, that's just AC." Well, AC is associated with a lot of delayed nausea and vomiting.

You find a lot of hidden toxicity if you step into the shoes of a patient. It can be incapacitating. With TC, you don't have that burden of emesis and nausea.

1.3

Disease-Free Survival in Major Subgroups of Patients from a Phase III Trial of Doxorubicin/Cyclophosphamide (AC) versus Docetaxel/Cyclophosphamide (TC) as Adjuvant Therapy for Operable Breast Cancer

Group	N	Hazard ratio	95% CI
All patients	TC = 506; AC = 510	0.67	0.50 to 0.94*
Age < 50 years	TC = 210; AC = 214	0.64	0.38 to 1.04
Age ≥ 50 years	TC = 296; AC = 296	0.73	0.48 to 1.10
ER-/PR-	TC = 137; AC = 157	0.64	0.38 to 1.04
ER+/PR+	TC = 369; AC = 383	0.71	0.47 to 1.08
Node-negative	TC = 239; AC = 248	0.73	0.42 to 1.27
Node-positive	TC = 267; AC = 262	0.67	0.45 to 0.98*

* $p < 0.05$; HR < 1 favors TC

SOURCE: Jones SE et al. *J Clin Oncol* 2006;24(34):5381-7. **Abstract**

Tracks 17-18

DR LOVE: Let's talk about the US Oncology trials evaluating *nab* paclitaxel. It has been stated that neurotoxicity resolves more quickly with *nab* paclitaxel than with paclitaxel. Is that the case?

DR HOLMES: Yes. In our dose-dense trial, in which we were administering *nab* paclitaxel at 260 mg/m^2 every two weeks, I had two patients who experienced neurotoxicity, but we saw the deep tendon reflexes return quickly.

The other aspect of *nab* paclitaxel that's so terrific is the mechanism of action (1.4). Many tumor cells have a substance on them that you might think of like flypaper — SPARC, which stands for Secreted Protein Acidic and Rich in Cysteine.

SPARC has an affinity for albumin, which has the "payload" of drug inside. When this albumin-bound drug attaches to the tumor, the payload is delivered. There you have a particularly targeted therapy.

So number one, you have a targeted therapy, and number two, you don't have the Cremophor®, which is the source of the reactions with paclitaxel, for which we use dexamethasone, and which resulted in the use of long infusion times. Number three, although the Cremophor allowed us to basically dissolve pine bark and deliver it as a soluble substance, this would also accumulate in the bone marrow and in the nerves, causing prolonged retention of the drug in a place where it's not wanted. With *nab* paclitaxel, the drug is preferentially diverted to the target.

1.4

Proposed Mechanism of Drug Delivery for *Nab* Paclitaxel

"*Nab*-Paclitaxel utilises the natural properties of albumin to reversibly bind paclitaxel, transport it across the endothelial cell and concentrate it in areas of tumour.

The proposed mechanism of drug delivery involves, in part, glycoprotein 60-mediated endothelial cell transcytosis of paclitaxel-bound albumin and accumulation in the area of tumour by albumin binding to SPARC (secreted protein, acidic and rich in cysteine).

Clinical studies have shown that *nab*-paclitaxel is significantly more effective than paclitaxel formulated as Cremophor EL (CrEL, Taxol, CrEL-paclitaxel), with almost double the response rate, increased time to disease progression and increased survival in second-line patients."

SOURCE: Gradishar WJ. *Expert Opin Pharmacother* 2006;7(8):1041-53. **Abstract**

Tracks 18-19

DR LOVE: How are you approaching the use of *nab* paclitaxel in your practice for patients with metastatic disease?

DR HOLMES: I administer *nab* paclitaxel in preference to paclitaxel, period.

DR LOVE: How much of an advantage is it to be able to avoid premedication and to have shorter infusion times?

DR HOLMES: It's a huge advantage. Patients have a life. They have kids. They have day care. At its best, getting through the clinic is difficult. I have emergencies, so I'm backed up. There are all kinds of built-in delays.

We all think we know what it is to go through therapy from the patient's standpoint, but it's hard to remember all the delays, all the problems: "Oh gosh, counts aren't up today. You have to come back later."

To begin with, these people have a life, and their time is valuable. In addition, not having to take the dexamethasone is a huge benefit. How many people are hyperactive? They can't sleep that first night. They have to take the steroids and then take lorazepam or something else to relax them.

Finally, we all know that patients gain weight on adjuvant chemotherapy. Apparently, they do not eat more, and their energy intake isn't increased, but their energy expenditure is decreased. Add this anabolic agent on top of that, and we know that some women are sensitized to this.

Then there's that minority of patients who develop acne from the dexamethasone. Really, less is more, and avoiding premedication is a tremendous advantage. ■

SELECT PUBLICATIONS

Gradishar WJ. **Albumin-bound paclitaxel: A next-generation taxane.** *Expert Opin Pharmacother* 2006;7(8):1041-53. **Abstract**

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

Harries M et al. **Nanoparticle albumin-bound paclitaxel for metastatic breast cancer.** *J Clin Oncol* 2005;23(31):7768-71. No abstract available

Holmes FA et al. **Feasibility of testing core needle breast biopsies *ex vivo* in the ChemoFx® assay: Substudy results from US oncology trial 02-103.** San Antonio Breast Cancer Symposium 2006;**Abstract 5100**.

Jones SE et al. **Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer.** *J Clin Oncol* 2006;24(34):5381-7. **Abstract**

Jones SE et al. **Final analysis: TC (docetaxel/cyclophosphamide, 4 cycles) has a superior disease-free survival compared to standard AC (doxorubicin/cyclophosphamide) in 1016 women with early stage breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 40**.

Robert N et al. **Pilot study of dose dense doxorubicin + cyclophosphamide followed by ABI-007 in patients with early stage breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 2073**.

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin, and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

INTERVIEW

Eleftherios P Mamounas, MD, MPH

Dr Mamounas is Associate Professor of Surgery at the Northeastern Ohio Universities College of Medicine and Medical Director at Aultman Cancer Center in Canton, Ohio.

Tracks 1-13

Track 1 Introduction

Track 2 NSABP-B-33: Adjuvant exemestane in postmenopausal women completing at least five years of tamoxifen

Track 3 NSABP-B-33: Side effects and tolerability of extended adjuvant exemestane

Track 4 Annualized rate of cancer recurrence among patients with hormone receptor-positive disease

Track 5 Interchangeability of the aromatase inhibitors

Track 6 NSABP-B-42: Duration of adjuvant aromatase inhibitors after five years of hormonal therapy

Track 7 NSABP-B-34: Adjuvant clodronate in patients receiving systemic chemotherapy and/or tamoxifen or no therapy

Track 8 NSABP-B-40: Neoadjuvant docetaxel, alone or with capecitabine or gemcitabine with or without bevacizumab

Track 9 NSABP-B-40 correlative science studies

Track 10 Neoadjuvant clinical trial of bevacizumab with doxorubicin and docetaxel

Track 11 Proposed NSABP neoadjuvant trial of AC → paclitaxel with lapatinib, trastuzumab or the combination followed by adjuvant trastuzumab

Track 12 Role of anthracyclines in the treatment of patients with HER2-positive disease

Track 13 NSABP-B-37: Adjuvant chemotherapy for surgically resected locoregional relapse

Select Excerpts from the Interview

Track 2

DR LOVE: Can you describe the objective of the NSABP-B-33 study and what you reported at San Antonio (Mamounas 2006)?

DR MAMOUNAS: The B-33 trial was structured similarly to the NCIC-MA17 study (Goss 2003). Patients with ER-positive or PR-positive, Stage I or II breast cancer who received tamoxifen for five years were randomly assigned to five years of exemestane or placebo (Mamounas 2006; [2.1]).

The projected sample size of the study was 3,000 patients. In October 2003, as the study was accruing, the results of the NCIC-MA17 trial indicating benefit with letrozole in that setting after five years of tamoxifen were disclosed. For ethical reasons, we stopped accruing and unblinded the trial, with the idea of offering exemestane to patients on placebo and allowing patients on exemestane to continue the drug if they chose. We did that in October of 2003, and at the time we had 1,598 patients.

Approximately half of the patients on placebo chose to receive exemestane, but it is unclear what happened to the other half of those patients. We didn't collect that information, but it would be a mixture of alternatives: They may not have received any more therapy because they felt they were a long time from their diagnosis, or they may have received letrozole. Seventy-two percent of the patients who were on exemestane continued receiving exemestane. But the other 28 percent may not have received anything or may have received letrozole.

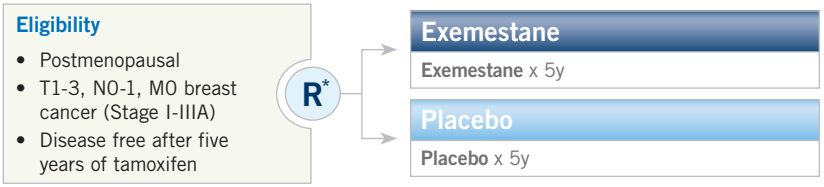
Like any other trial, the accrual started slowly and then ramped up. By the time we stopped, we were enrolling a lot of patients, but those patients did not contribute much to the overall data set. However, the fact that half of the patients were on exemestane and the other half were on placebo up to the point of unblinding apparently had an effect (2.2). On evaluation of the primary endpoint, a 32 percent reduction was evident in disease-free survival events. A 56 percent reduction was evident in relapse-free survival events, and this was statistically significant.

The median follow-up at that point was 30 months. Some reduction did occur in distant recurrence — about 31 percent — but this was not statistically significant. As in other studies, no survival difference appeared at this point, but very few deaths occurred: 16 in the exemestane group and 13 in the placebo group.

2.1

NSABP-B-33: Phase III Study Comparing Exemestane to Placebo After Five Years of Tamoxifen Therapy

Protocol ID: NSABP-B-33
Accrual: 1,598 (Closed)



* Trial unblinded in October 2003 after a median follow-up of 30 months

SOURCE: Mamounas E et al. Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 49**.

Interestingly, when we evaluated the subset analysis to see where the benefit was coming from, it was as we expected. Patients with node-positive disease at diagnosis, who had larger tumors, who had received prior chemotherapy or who were younger than age 60 — essentially the patients with more aggressive disease or disease with which you would expect events — were those who benefited the most from exemestane.

2.2 **NSABP-B-33: Outcomes After 30-Month Median Follow-Up**

Outcome	Exemestane (n = 783)	Placebo (n = 779)	RR	*p*-value
Disease-free survival	91%	89%	0.68	0.07
Relapse-free survival	96%	94%	0.44	0.004
Overall survival	16 deaths	13 deaths	1.2	0.63

SOURCE: Mamounas E et al. San Antonio Breast Cancer Symposium 2006;**Abstract 49**.

Track 6

DR LOVE: Can you discuss the NSABP-B-42 trial, which addresses treatment options after five years of adjuvant aromatase inhibitor therapy?

DR MAMOUNAS: We realized that soon a large number of patients will be reaching approximately five years of aromatase inhibitor therapy — or five years of sequential therapy during which tamoxifen was administered for two to three years and the aromatase inhibitor was administered for the remaining two to three years.

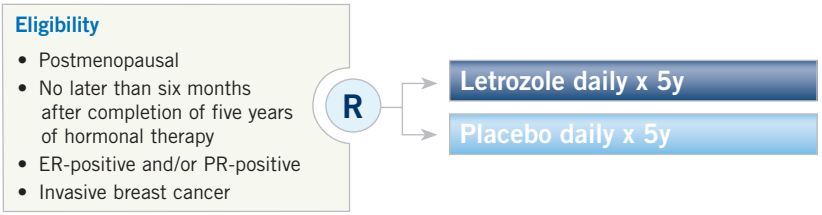
The B-42 trial is attempting to address the issue of duration for aromatase inhibitors after five years (2.3). It is similar to the B-14 trial, in which we administered five years of tamoxifen and then randomly assigned patients to an additional five years or not (Fisher 1996).

It's by no means obvious that 10 years of an aromatase inhibitor will be better than five years. We believed that would be the case for tamoxifen, and we were wrong. When we unblinded the B-14 study, we found that the placebo group was a little superior to the tamoxifen group — almost statistically significant for disease-free survival. Whether this is applicable to aromatase inhibitors remains to be seen.

Jim Ingle presented data from the MA17 trial showing that if you receive letrozole for longer periods of time it's better than if you receive it for shorter periods, but that was up to about four years (Ingle 2006). We don't have any information on what will happen after five years with an aromatase inhibitor. We have to consider the risk-to-benefit ratio. It may be a little better, but at what price? How much osteoporosis and other side effects will we see in the long term?

2.3

NSABP-B-42: A Phase III Trial to Determine Improvement in Disease-Free Survival with Adjuvant Letrozole Following Completion of Five Years of Hormonal Therapy with Either an Aromatase Inhibitor (AI) or Tamoxifen Followed by an AI



Primary Endpoint

- Disease-free survival

Secondary Endpoints

- Survival, recurrence-free interval, distant recurrence-free interval, osteoporotic fracture rate, arterial thrombosis

Target Accrual: 3,840 over 5.25 years

Current Accrual: 37 (2/13/07)

Date Activated: August 14, 2006

Study Contact

National Surgical Adjuvant Breast and Bowel Project
Eleftherios P Mamounas, MD, MPH
Protocol Chair

SOURCES: NSABP-B-42 Protocol, July 2006; **www.nsabp.pitt.edu**.

Track 8

DR LOVE: Can you discuss the design and rationale of the NSABP-B-40 study?

DR MAMOUNAS: As this trial was being developed, we were aware of the ECOG-E2100 data with bevacizumab in the metastatic setting (Miller 2005). We decided that B-40 would be a perfect setting in which to evaluate bevacizumab as neoadjuvant therapy.

We wanted to administer bevacizumab with a taxane and AC-based regimen, but we had the issue of not wanting to administer bevacizumab right before surgery, given some of the wound-healing problems we have seen in previous trials.

As the trial currently stands, we start with either docetaxel → AC or docetaxel/capecitabine → AC or docetaxel/gemcitabine → AC. We administer bevacizumab with all four cycles of the docetaxel-based regimen and with two cycles of the AC and then allow a gap of six or eight weeks before the patient goes to surgery (2.4).

After surgery, those patients randomly assigned to bevacizumab will continue on bevacizumab for a total of one year. This is to be on the same page as the future ECOG adjuvant trials, wherein one of the arms will receive at least one year of bevacizumab. The primary endpoint is pathologic complete response.

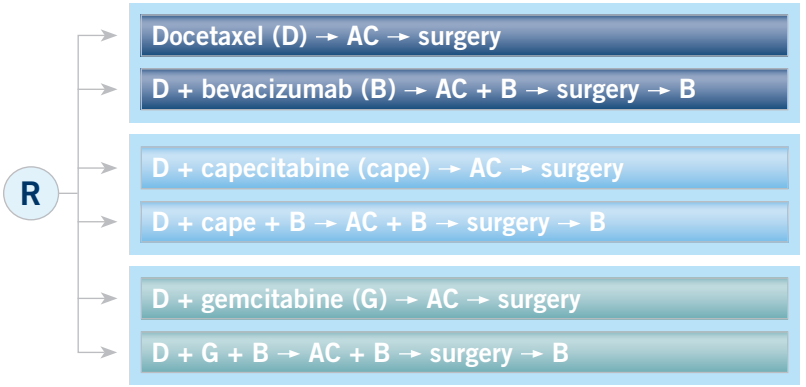
DR LOVE: This study is only for patients with HER2-negative tumors?

DR MAMOUNAS: Yes. As you know, we have now essentially separated the treatment of those patients. In fact, we'll be undertaking another trial in the neoadjuvant setting for patients with HER2-positive disease.

2.4

Phase III Randomized Trial of Six Neoadjuvant Regimens for Patients with Palpable and Operable HER2-Negative Breast Cancer

Protocol ID: NSABP-B-40
Target Accrual: 1,200
Eligibility: Tumor ≥ 2 cm; HER2-negative breast cancer



SOURCE: NSABP Group Meeting, April 2006.

Track 12

DR LOVE: What are your thoughts about the updated data from BCIRG trial 006 presented at the San Antonio meeting?

DR MAMOUNAS: A big question has been the role of anthracyclines in the treatment of HER2-positive breast cancer. Obviously, that became even more controversial with the updated BCIRG 006 data indicating that the TCH regimen performs essentially as well as AC → TH (Slamon 2006).

DR LOVE: Do these findings change your thoughts about the appropriate therapy for patients with node-positive, HER2-positive disease?

DR MAMOUNAS: No, I believe the standard of therapy at this point is the FDA-approved approach of administering an anthracycline followed by a taxane — particularly paclitaxel — and trastuzumab, for a year. Obviously, with the new data from BCIRG 006 (Slamon 2006), we'll have to see what the role of TCH is in this population of patients. That will evolve in the next few months.

DR LOVE: In what kinds of situations would it be appropriate right now to use adjuvant TCH or some other type of nonanthracycline regimen with trastuzumab?

DR MAMOUNAS: You can use it in pretty much all patients with HER2-positive disease because it's clearly a regimen with minimal cardiotoxicity. Some depression in left ventricular ejection fraction (LVEF) occurred, but that recovered after the discontinuation of trastuzumab. If you want to be more selective, that would be a good regimen for any patient for whom cardiac function is a concern. ■

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Baum M et al; The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses.** *Cancer* 2003;98(9):1802-10. **Abstract**

Baum M et al; ATAC Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359(9324):2131-9. **Abstract**

Buzdar AU et al. **Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

Coombes RC et al; Intergroup Exemestane Study. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. **Abstract**

Cristofanilli M et al. **A phase II combination study of lapatinib and paclitaxel as a neoadjuvant therapy in patients with newly diagnosed inflammatory breast cancer (IBC).** San Antonio Breast Cancer Symposium 2006;**Abstract 1**.

Fisher B et al. **Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors.** *J Natl Cancer Inst* 1996;88(21):1529-42. **Abstract**

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802. **Abstract**

Ingle JN et al. **Duration of letrozole treatment and outcomes in the placebo-controlled NCIC CTG MA.17 extended adjuvant therapy trial.** *Breast Cancer Res Treat* 2006;99(3):295-300. **Abstract**

Mamounas E et al. **Benefit from exemestane (EXE) as extended adjuvant therapy after 5 years of tamoxifen (TAM): Intent-to-treat analysis of NSABP B-33.** San Antonio Breast Cancer Symposium 2006;**Abstract 49**.

Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial coordinated by the Eastern Cooperative Oncology Group (E2100).** San Antonio Breast Cancer Symposium 2005;**Abstract 3**.

Slamon D et al. **BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Wedam SB et al. **Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer.** *J Clin Oncol* 2006;24(5):769-77. **Abstract**

INTERVIEW

Andrew D Seidman, MD

Dr Seidman is Attending Physician of Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-18

Track 1 Introduction

Track 2 Phase II trial of weekly versus every two-week versus every three-week *nab* paclitaxel in combination with bevacizumab as first-line therapy

Track 3 Reversibility of neurotoxicity associated with *nab* paclitaxel

Track 4 Potential advantages in the administration of *nab* versus standard paclitaxel

Track 5 Data required to incorporate novel agents into clinical practice

Track 6 Incorporation of bevacizumab into clinical practice

Track 7 Rationale for the use of bevacizumab in the adjuvant setting

Track 8 TAnDEM trial: Trastuzumab with anastrozole in hormone-dependent, HER2-positive metastatic breast cancer

Track 9 Cardiac safety with dose-dense AC followed by paclitaxel/trastuzumab

Track 10 Use of dose-dense AC without paclitaxel

Track 11 US Oncology adjuvant trial comparing AC to docetaxel with cyclophosphamide

Track 12 Perspective on anthracycline- and trastuzumab-associated cardiotoxicity

Track 13 Decreased incidence of breast cancer in the United States

Track 14 EFECT: Fulvestrant versus exemestane following nonsteroidal aromatase inhibitor therapy in advanced breast cancer

Track 15 NSABP-B-33: Extended adjuvant exemestane after five years of tamoxifen

Track 16 Impact of aromatase inhibitor-associated arthralgias

Track 17 Duration of adjuvant hormonal therapy

Track 18 Treatment after completion of upfront adjuvant aromatase inhibitor therapy

Select Excerpts from the Interview

Track 2

DR LOVE: Can you describe Memorial's Phase II trial of *nab* paclitaxel combined with bevacizumab and the rationale behind its design?

DR SEIDMAN: It's a randomized trial of weekly versus every two-week versus every three-week *nab* paclitaxel with concurrent bevacizumab as first-line therapy for metastatic breast cancer.

Following ECOG-E2100, and given the benefits of *nab* paclitaxel compared to paclitaxel (Miller 2005a; Gradishar 2005), we decided to evaluate in a randomized Phase II fashion the package insert dose of 260 mg/m^2 of *nab* paclitaxel on a schedule of every three weeks versus the same dose on a dose-dense schedule of every two weeks with G-CSF versus a dose of 130 mg/m^2 administered weekly, without interruption, in the CALGB-9840 manner (Seidman 2004). All the patients in this trial receive bevacizumab, and the target accrual is 225 patients, or 75 patients per arm.

We've completed our first interim safety analysis and, with approximately 20 patients per arm, so far no signal in any arm has indicated that we should stop accrual because of excessive toxicity.

Track 4

DR LOVE: What's your take on the use of *nab* paclitaxel in clinical practice?

DR SEIDMAN: The trial that led to the FDA approval of *nab* paclitaxel convinced me that this agent, at 260 mg/m^2, certainly is not less effective than Cremophor-based paclitaxel at 175 mg/m^2 (Gradishar 2005).

I find not having to administer premedications or corticosteroids, being able to infuse the drug over half an hour instead of three hours and not worrying about potential allergic reactions, which are occasionally life threatening, makes it a "no-brainer" in terms of which taxane I use.

Steroids are a double-edged sword in the sense that often, along with the prescription for steroids, I have to write a prescription for zolpidem because the patient can't sleep well at night. Also, with weekly taxanes and weekly steroids, I do see steroid myopathy and occasionally diabetics who have trouble controlling their blood sugars. What I hear most that limits the use of *nab* paclitaxel is the pharmacoeconomics of the drug, and I don't have a great response to that.

Track 6

DR LOVE: How do you incorporate bevacizumab into the management of breast cancer outside of a clinical trial?

DR SEIDMAN: Currently, I generally follow the ECOG-E2100 paradigm (Miller 2005a). For patients who are not participating in our AC/*nab* paclitaxel/bevacizumab pilot trial but for whom taxanes are appropriate, I use paclitaxel and bevacizumab. Occasionally, I will have patients who have received an adjuvant taxane within the past year and have relapsed, and my inclination at that point is to use capecitabine and bevacizumab, based on Kathy Miller's reported Phase III trial (Miller 2005b). Those are probably the two most common scenarios.

DR LOVE: Many people don't use the combination of capecitabine and bevacizumab because they consider the ECOG trial negative (Miller 2005b). How do you respond to that?

DR SEIDMAN: Despite the doubling of the response rate, it does concern me that the trial did not show a significant increase in the time to progression. Certainly a difference is evident between that population and that of the E2100 trial with regard to the extent of prior therapy.

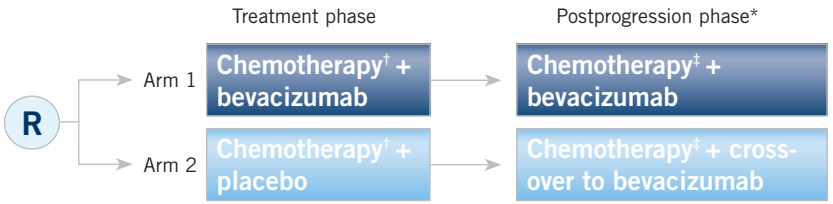
I don't see any reason to suspect that the addition of bevacizumab to one particular cytotoxic agent in breast cancer versus another will make a big difference in terms of efficacy. The RIBBON 1 trial, which allows a repertoire of commonly used chemotherapy regimens in the first-line setting, should inform us whether we need to worry about which agent we combine with bevacizumab (3.1).

DR LOVE: What do you think of George Sledge's XCaliBr study, which evaluated capecitabine/bevacizumab in the first-line setting?

DR SEIDMAN: That was a Phase II trial, and it's hard to know what to make of the data because it had no control arm. The nice thing about this trial is that the efficacy at a lower dose of capecitabine was similar to what Miller previously reported. In the XCaliBr trial (3.2) they used 1,000 mg/m^2 twice daily, whereas in the Phase III trial they used 1,250 mg/m^2 twice daily.

3.1

RIBBON 1 (AVF3694g): A Multicenter, Phase III, Randomized, Placebo-Controlled Trial Evaluating the Safety and Efficacy of Bevacizumab in Combination with Chemotherapy Regimens in Subjects with Previously Untreated Metastatic Breast Cancer



Bevacizumab = 15 mg/kg q3wk (or 10 mg/kg q2wk during postprogression phase)

* Optional, per investigator's discretion

† Anthracycline-based combination chemotherapy, q3wk taxane (docetaxel or *nab* paclitaxel) or capecitabine, as determined by the investigator before randomization

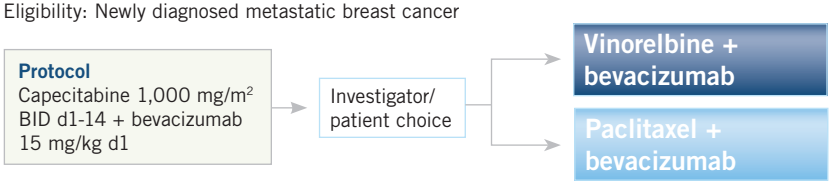
‡ Chemotherapy per investigator's discretion

SOURCES: NCI Physician Data Query, February 2007.
Genentech BioOncology, Protocol Schema, October 2006.
www.cancer.gov.

3.2

Phase II Study of Capecitabine/Bevacizumab Followed by Bevacizumab Continuation with Chemotherapy After Disease Progression

Protocol ID: XCaliBr
Accrual: 103 (Closed)
Eligibility: Newly diagnosed metastatic breast cancer



Efficacy Data from Clinical Trials Combining Bevacizumab and Capecitabine in Patients with Metastatic Breast Cancer

	XCaliBr[1] (n = 103)	AVF2119g[2] (n = 232) Investigator	AVF2119g[2] (n = 232) IRF
Objective response rate (95% CI)	34% (24.9-44.0)	30.2% (24.3-36.1)	19.8% (14.7-25.0)
Median duration of overall response (95% CI)	6.2 months (3.0-7.7)	NR —	5.0 months NR

[1] XCaliBr = Phase II trial of first-line capecitabine, 1,000 mg/m^2 BID with bevacizumab. Median duration of follow-up was 6.1 months. At the time of analysis, 44 patients were still in the first phase and 21 patients were in the second phase.

[2] AVF2119g = Phase III trial of first-line capecitabine, 1,250 mg/m^2 BID, with or without bevacizumab in patients previously treated for metastatic breast cancer. Data shown for patients who received capecitabine and bevacizumab.

IRF = independent review facility

CI = confidence interval

NR = not reported

SOURCES: [1] Miller K et al. Poster. San Antonio Breast Cancer Symposium 2006;**Abstract 2068**.
[2] Miller KD et al. *J Clin Oncol* 2005b;23(4):792-9. **Abstract**

Track 7

DR LOVE: Bevacizumab is now being studied in the adjuvant setting. What are your thoughts on those trials?

DR SEIDMAN: First, the theoretical consideration is that with a smaller volume of cancer, angiogenesis seems to be driven more by VEGF than other growth factors, whereas with a larger tumor volume, a greater list of growth factors seems to come into play. Thus we have every reason to hope and believe that perturbing VEGF receptor activation will have a big impact in the adjuvant setting.

DR LOVE: Your colleague Maura Dickler has reported data from a pilot trial

combining bevacizumab with hormonal therapy. Where do you think that is headed?

DR SEIDMAN: In the pilot trial, letrozole was administered with bevacizumab, and the data certainly showed the feasibility of combining an aromatase inhibitor with bevacizumab (Traina 2006). Given that cross talk occurs between estrogen signaling and VEGF signaling, there's certainly hope that intervening earlier with anti-angiogenic therapy, before the patient gets to the point of needing chemotherapy, might be beneficial.

Track 8

DR LOVE: What do you think about the data from the TAnDEM trial, evaluating anastrozole with trastuzumab in the metastatic setting?

DR SEIDMAN: I first glimpsed those data after they were initially presented in Istanbul at ESMO in September (Kaufman 2006). I was struck that the median time to progression in the anastrozole-alone arm was 2.4 months, whereas when combined with trastuzumab, the time to progression doubled to 4.8 months (Mackey 2006; [3.3]). Granted, this was ER-positive, HER2-positive disease, but that duration of response to anastrozole alone doesn't fit with what I see clinically. I have many patients in my own practice who have ER-positive, HER2-positive disease who do fine in the absence of trastuzumab.

The more important question is, if you use the combination of an aromatase inhibitor and trastuzumab early on for a patient with hormone-sensitive, metastatic breast cancer, what will be the implication of having already played your trastuzumab card when that patient ultimately develops hormone-refractory disease? We know that adding trastuzumab to chemotherapy, either paclitaxel or docetaxel, provides a survival advantage, so I'm not ready to change my practice based on the TAnDEM data.

Having said that, there are patients who come to me who are on antiestrogen therapy and trastuzumab, but usually their clinical story has some strange, unique aspect that makes me feel it's an appropriate thing to do.

One example in which applying the TAnDEM data would make sense would be for the occasional patient who's received adjuvant tamoxifen but not an aromatase inhibitor and then develops metastatic disease and is treated with chemotherapy and trastuzumab. Most of us are in the habit of stopping the chemotherapy at a certain point and just continuing trastuzumab, but in this case the patient has not received an aromatase inhibitor.

For me it would be a no-brainer at that point to use the chemotherapy and trastuzumab to maximum response, or to the point at which toxicity begins to accumulate, and then discontinue the chemotherapy and add the aromatase inhibitor.

Also, there are those patients who present with metastatic disease who have never received adjuvant therapy, yet you feel you should first treat them with

chemotherapy and trastuzumab, even if they have ER-positive disease. This would be another example in which, perhaps, after administering the chemotherapy and trastuzumab, you should put the chemotherapy aside and use the aromatase inhibitor out back instead of up front.

3.3

TAnDEM: Randomized Trial Comparing Anastrozole with or without Trastuzumab for Patients with HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer (N = 208*)

Parameter	Anastrozole	Anastrozole + trastuzumab	*p*-value
Median progression-free survival	2.4 months (95% CI 2.0-4.6)	4.8 months (95% CI 3.7-7.0)	0.0016
Partial response rate	6.8%	20.3%	0.018
Clinical benefit rate	27.9%	42.7%	0.026
Overall survival	23.9 months (95% CI 18.2-37.4)	28.5 months (95% CI 22.8-42.4)	0.325
Overall survival for patients without liver metastasis†	32.1 months (95% CI 22.0-38.6)	41.9 months (95% CI 30.3-52.8)	0.0399

* One patient did not receive the study drug and was excluded from analysis.

† Unplanned subgroup analysis

SOURCE: Mackey JR et al. San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

Track 14

DR LOVE: Would you discuss Bill Gradishar's presentation of the EFECT trial and your thoughts on those data?

DR SEIDMAN: The EFECT trial randomly assigned patients with metastatic breast cancer whose disease had progressed despite treatment with a nonsteroidal aromatase inhibitor to the steroidal aromatase inhibitor exemestane or to fulvestrant. Many of us have been using both of these approaches somewhat indiscriminately, perhaps influenced more by patient preference, such as for a monthly injection over taking a pill.

The EFECT findings afford us flexibility in our treatment options. I believe most clinicians will be influenced by patient preferences when choosing between an oral medication or a monthly injection. For many patients who are coming in monthly for a bisphosphonate, for example, an injection doesn't demand much more of them in terms of the frequency of office visits.

This trial also employed a loading schedule for fulvestrant, which is what I tend to use in my own practice. When using fulvestrant, one should probably follow the design of this trial, starting with the 500-mg loading dose followed by a subsequent dose of 250 milligrams two weeks later and then 250 milligrams monthly. ■

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Dang C et al. **Mature cardiac safety results of dose-dense (DD) doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) with trastuzumab (H) in HER2/neu overexpressed/amplified breast cancer (BCA).** San Antonio Breast Cancer Symposium 2006;**Abstract 2101**.

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

Harries M et al. **Nanoparticle albumin-bound paclitaxel for metastatic breast cancer.** *J Clin Oncol* 2005;23(31):7768-71. No abstract available

Ibrahim NK et al. **Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer.** *J Clin Oncol* 2005;23(25):6019-26. **Abstract**

Kaufman B et al. **Progression-free survival with anastrozole/trastuzumab in postmenopausal women with HER2-positive hormone-dependent metastatic breast cancer.** Presentation. Annual Congress of the European Society for Medical Oncology 2006;**Abstract LBA2**.

Link JS et al. **Bevacizumab (Avastin) and albumin bound paclitaxel (Abraxane) treatment in metastatic breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 1095**.

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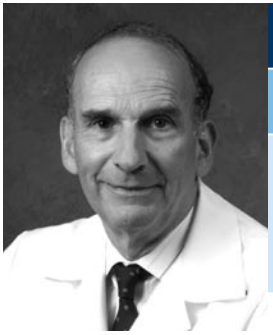

INTERVIEW

Allan Lipton, MD

Dr Lipton is Professor of Medicine and Oncology in the Division of Hematology/Oncology at the Pennsylvania State University's MS Hershey Medical Center in Hershey, Pennsylvania.

Tracks 1-16

Track 1 Introduction
Track 2 Historical development of the bisphosphonates
Track 3 Skeletal-related events in cancer
Track 4 Development of newer, more potent bisphosphonates
Track 5 Impact of bisphosphonates on the management of metastatic bone disease
Track 6 Tolerability and side effects of bisphosphonates
Track 7 Potential mechanisms for the development of osteonecrosis of the jaw (ONJ)
Track 8 Clinical presentation and management of ONJ
Track 9 Overview of adjuvant bisphosphonate data and ongoing trials
Track 10 Denosumab, an antibody against the RANK ligand, for the treatment and prevention of bone metastases
Track 11 Side effects and toxicity of denosumab
Track 12 Future development of denosumab
Track 13 Development of novel agents for the prevention and treatment of bone metastases
Track 14 Importance of understanding bone biology in medical oncology
Track 15 Bone loss associated with adjuvant aromatase inhibitor therapy
Track 16 Monitoring bone health and selecting adjuvant aromatase inhibitor therapy versus tamoxifen

Select Excerpts from the Interview

Track 3

DR LOVE: Can you bring us up to date on the new developments in cancer and bone?

DR LIPTON: In terms of background and incidence, this year in the United States 400,000 patients will be newly diagnosed with bone metastases. Most of those will have breast or prostate cancer.

Three quarters of the patients who develop metastatic disease from breast or prostate cancer will have skeletal involvement. One third of the patients with

lung cancer and approximately one third of the patients with kidney cancer who develop metastases will have skeletal involvement.

We also know from the placebo arms of the pamidronate and zoledronic acid trials that each patient who develops bone metastases will experience about one skeletal-related event (SRE) — defined as a bone fracture or the need for radiation or surgery to the bone — every three or four months without the use of a bisphosphonate. Skeletal involvement and SREs are terribly common in this patient population.

Track 5

DR LOVE: Do we know how bisphosphonates have affected the clinical course of metastatic cancer?

DR LIPTON: These drugs have dramatically changed the face of metastatic bone disease. In years gone by, it was not infrequent for patients to suffer toward the end of their illness from hypercalcemia of malignancy.

We used to teach fellows and residents that 10 to 20 percent of patients with metastatic bone involvement would develop hypercalcemia, usually within three months of their demise. Now it's pretty rare for a patient to develop hypercalcemia, and it's extremely rare to see a patient in the hospital with hypercalcemia of malignancy.

Similarly, in the past it was not uncommon for a patient to be in the hospital with a pathologic fracture. We know that the rate of fracture has been significantly decreased by somewhere between 30 and 50 percent with the widespread use of the bisphosphonates. I believe we've dramatically changed the course of metastatic bone disease for patients, the complications thereof, the attendant costs, their performance status and their quality of life.

Track 6

DR LOVE: What do we know about the side effects and complications associated with the bisphosphonates?

DR LIPTON: They're generally well tolerated compared to many chemotherapeutic agents we routinely use. The major side effects seen with the bisphosphonates can be categorized in two groups.

The first group includes the acute phase reactions. Within 24 or 48 hours of administering an intravenous bisphosphonate, perhaps one third to one half of the patients will experience an increase in body temperature. This low-grade fever is usually self limiting and treated with acetaminophen.

A number of patients will experience exacerbation of bone pain. They'll have arthralgias and increasing pain that is treated with narcotics. These symptoms usually diminish over 24 to 48 hours and are associated with the first dose of the bisphosphonate. With subsequent doses, you don't see this as frequently.

Other long-term side effects are more serious. All bisphosphonates administered at a high enough dose over a shorter period of infusion will cause renal toxicity. They will cause glomerular or tubular damage, depending on which bisphosphonate is used. You need to monitor renal function every month before the bisphosphonate is administered.

Another complication, which has received a lot of press recently, is osteonecrosis of the jaw (ONJ). It was not previously recognized with oral bisphosphonates administered for metastatic breast cancer, although it does occur at a low rate with the oral bisphosphonates used for the treatment of osteoporosis.

ONJ was not recognized in the 3,000-patient Phase III studies of zoledronic acid or in the pamidronate database. It was recognized in 2003 by two oral surgeons — Bob Marx in Miami and Salvatore Ruggiero at Long Island Jewish Hospital. They both reported an influx of patients with ONJ in their oral surgery practices (Marx 2003; Ruggiero 2004).

Our knowledge about ONJ comes from two large retrospective studies. Cathy Van Poznak conducted the first one at Memorial Sloan-Kettering. Of approximately 900 patients treated with an intravenous bisphosphonate, she found an incidence of ONJ of 0.6 percent. The median duration of bisphosphonate therapy was about 52 months (Van Poznak 2004).

Dr Hoff at MD Anderson conducted a retrospective review of data from over 4,000 patients who received an intravenous bisphosphonate. The overall incidence of ONJ was 0.8 percent. It was about one percent for the patients with breast cancer, and it seemed to be slightly higher among the patients with multiple myeloma (Hoff 2006).

The outlier in terms of incidence of ONJ is from Professor Dimopoulis, who reported in the Greek experience an incidence of ONJ of around seven percent (Bamias 2005). In this country, the incidence is probably around one percent. It's a phenomenon that is probably associated with bisphosphonate usage and appears to be more common the longer the drug is used.

Track 9

DR LOVE: Where are we headed in the field of bone metastases?

DR LIPTON: The treatment of bone metastases is in its relative infancy and has been somewhat ignored, but I believe we're headed into an exciting era. One study by Ingo Diel and another by Trevor Powles and Sandy Paterson suggest that adjuvant clodronate in addition to the usual adjuvant therapies can prevent bone metastases and may prolong survival (Diel 1998; Powles 2006). One negative study by Tiina Saarto using adjuvant clodronate showed the opposite — a higher rate of metastasis (Saarto 2004) — but imbalances existed in that study.

Adjuvant clodronate is being evaluated in NSABP-B-34. We're waiting for events to occur to see if this large trial can confirm the two smaller studies by Diel and Powles. We hope that NSABP-B-34 will be reported in 2008.

An Intergroup adjuvant study that will enroll 6,000 patients, being run by Julie Gralow, is comparing oral clodronate, oral ibandronate and intravenous zoledronic acid. It will be a comparison of two oral bisphosphonates and an intravenous bisphosphonate for the prevention of bone metastases (4.1). That study probably won't be reported until 2010 or 2011. ■

4.1

SWOG-S0307: A Phase III Randomized Study of Adjuvant Zoledronate versus Clodronate versus Ibandronate for Women with Resected Primary Stage I-III Adenocarcinoma of the Breast

Select Eligibility Criteria

- Stage I-III breast cancer
- Creatinine ≤ 2 times upper limit of normal
- Creatinine clearance ≥ 30 mL/min
- Lumpectomy or mastectomy within the past 12 weeks
- No metastases
- No coenrollment on protocols that measure bone density as an endpoint
- No concurrent bisphosphonates
- Standard adjuvant therapy

Endpoints

- Disease-free survival, overall survival, first disease recurrence, adverse events, parathyroid hormone-related protein status, N-telopeptide levels

Target Accrual: 6,000 within 4 years

Current Accrual: 283 (1/26/07)

Date Activated: July 15, 2005

Study Contacts

Southwest Oncology Group
Julie Gralow, MD, Study Coordinator
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North Central Cancer Treatment Group
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Eastern Cooperative Oncology Group
Carla Falkson, MD, Study Coordinator

National Surgical Adjuvant Breast and Bowel Project
Alexander Paterson, MD, Study Coordinator

Cancer and Leukemia Group B
Elizabeth Dees, MD, Study Coordinator

NCIC Clinical Trials Group
Mark Clemons, MD, Study Coordinator

SOURCES: SWOG Protocol S0307, June 12, 2006; **www.swog.org**.

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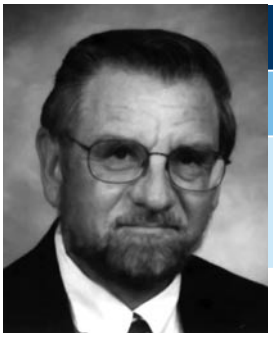


INTERVIEW

Robert E Marx, DDS

Dr Marx is Professor of Surgery and Chief in the Division of Oral and Maxillofacial Surgery at the University of Miami Miller School of Medicine in Miami, Florida.

Tracks 1-13

Track 1 Introduction

Track 2 History of identification of bisphosphonate-associated osteonecrosis of the jaw (ONJ)

Track 3 Pathophysiology of bisphosphonate-associated ONJ

Track 4 Clinical presentation of ONJ and treatment of associated infections

Track 5 Differential diagnosis of ONJ

Track 6 Clinical course of ONJ

Track 7 Incidence of bisphosphonate-induced ONJ

Track 8 Determining risks and benefits of bisphosphonates for patients with metastatic breast cancer

Track 9 Prophylactic dental care in patients considered for bisphosphonate therapy

Track 10 Duration of bisphosphonate therapy

Track 11 Bisphosphonate dose accumulation and the risk of developing ONJ

Track 12 Dental implants and bisphosphonate therapy

Track 13 Collaboration between medical oncologists, dentists and oral and maxillofacial surgeons in patient care

Select Excerpts from the Interview

Track 2

DR LOVE: Can you talk about the history of bisphosphonate-related osteonecrosis of the jaw (ONJ)?

DR MARX: We began to notice, in late 1999 and early 2000, a number of people who had exposed mandibular and maxillary bone and then developed secondary infections. We also noticed a peculiarity in that if we performed surgical debridement, after which we would expect healing and the bone to be covered, it didn't happen. In fact, it made the situation worse.

We accumulated a critical number of patients and then assessed retrospectively what those individuals had in common, which was that they were receiving pamidronate or zoledronic acid. It dawned on us that the problem was related to the use of bisphosphonates.

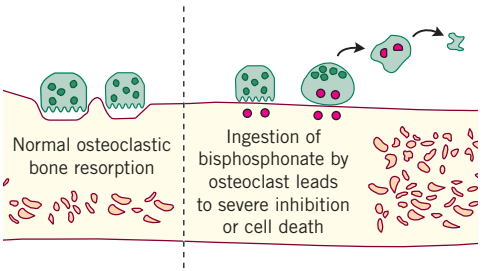
Initially, they were all patients with either metastatic breast cancer or multiple myeloma. We published a medical alert in the *Journal of Oral and Maxillofacial Surgery* in September 2003 (Marx 2003). About five to six months later, my colleague from New York, Dr Salvatore Ruggiero, published 63 additional cases (Ruggiero 2004). That seemed to spur Novartis to convene a panel of experts. We had several meetings and generated a position paper (Ruggiero 2006).

Track 3

DR LOVE: What do we know about the pathophysiology of ONJ?

DR MARX: The pathophysiology is directly related to dose and time of exposure to the bisphosphonate. The intravenous bisphosphonates, zoledronic acid and pamidronate, are absorbed directly into the mineral matrix of the bone, and they inhibit the enzyme farnesyl synthase, which is required by the osteoclasts for basic survival. It all has to do with osteoclast downregulation and apoptosis (5.1).

5.1 **Mechanism of Bisphosphonate-Associated Osteonecrosis of the Jaw (ONJ)**



Osteoclasts that resorb bone containing a bisphosphonate ingest the bisphosphonate, which causes cell death (apoptosis).

SOURCE: With permission. Marx RE. **Oral & intravenous bisphosphonate-induced osteonecrosis of the jaws: History, etiology, prevention, and treatment.** Chicago: Quintessence Publishing Co Inc, 2007. p 13.

What is unique about the mandible and maxilla is the presence of teeth or the wearing of dentures. Studies have shown that the bone in tooth-bearing areas of the jaw remodels 10 times faster than any other adult bone.

Therefore, vulnerability of the bone around the teeth is 10 times greater. Then you add the ubiquity of dental disease, like decay and periodontal disease, and you add increased inflammation and turnover.

If you use zoledronic acid or pamidronate, which affect the osteoclasts that are involved with bone turnover, the bone cannot turn over. Osteocytes live for 150 to 180 days. They die of a terminal lifespan, and they're not renewed or replaced. When the osteoclast resorbs bone, we know it releases insulin-like growth factors 1 and 2 and bone morphogenetic protein. This, in turn, stimulates and causes a differentiation of stem cells into osteoblasts and reforms the bone.

DR LOVE: What happens to the mucosa that covers the jawbone?

DR MARX: The overlying mucosa or gum tissue has blood supply that is dependent on the underlying bone. So when the bone dies off, the overlying mucosa essentially undergoes a necrosis too, and the bone becomes exposed. The most common place for ONJ to occur is the lower jaw in the molar area. That has to do with bite-force characteristics. When you bite down on food or during the swallowing process, you put pressure on your teeth. The greatest pressure is on the lower jaw in the molar area.

This is what makes the jaw vulnerable to anything that affects the osteoclasts, including intravenous and oral bisphosphonates. The bone has to adjust to this bite pressure, so it resorbs and renews itself on a more rapid basis to accommodate the forces of the chewing and swallowing cycles.

Approximately 30 percent of the cases occur spontaneously in people who do not have an underlying dental pathogenesis. On the other side of that coin are the people who have inflammation from dental decay, abscessed teeth or periodontal disease, which increase the rate of bone turnover. Therefore, you have a higher percentage of people developing bone exposures who have those underlying dental problems.

Track 4

DR LOVE: What are the typical clinical presentations?

DR MARX: The most common presentation is exposed bone. Most definitions include the presence of exposed bone in the oral cavity that fails to heal over eight weeks and is not associated with local radiation therapy (5.2, 5.3). The onset is asymptomatic in about one third of the patients. Because the exposed bone is necrotic, it's deenervated and not necessarily painful. Two thirds experience pain because of secondary infection.

Fortunately, we've been able to control the pain in 90 percent of individuals with relatively simple antibiotics. The bacteria associated with this are almost always anaerobes, which are sensitive to penicillin. The best therapy is penicillin VK 500 mg four times a day, which can be taken in the long term without toxicity. For patients not allergic to penicillin, it is the drug of choice.

5.2 Definition of Bisphosphonate-Related Osteonecrosis of the Jaw

Patients may be considered to have bisphosphonate-related ONJ if ***all*** of the following three characteristics are present:

1. Current or previous treatment with a bisphosphonate
2. Exposed bone in the maxillofacial region that has persisted for more than eight weeks
3. No history of radiation therapy to the jaws

SOURCE: American Association of Oral and Maxillofacial Surgeons. **Position paper on bisphosphonate-related osteonecrosis of the jaws.** Available at **www.aaoms.org/docs/position_papers/osteonecrosis.pdf**. Accessed January 3, 2007.

The pain, if you're taking penicillin regularly, is subdued within a week. It's a quick response.

Very few patients don't respond. If they don't respond to penicillin by itself, our backup is to combine it with metronidazole. For short periods, we double the antibiotic therapy. For the patient with a penicillin allergy, out of empirical trial and error, we have found levofloxacin to be the best alternative to penicillin.

5.3

Clinical Presentation of Bisphosphonate-Related Osteonecrosis of the Jaw

"ONJ may remain asymptomatic for many weeks or months and is usually identified by its unique clinical presentation of exposed bone in the oral cavity. These lesions typically become symptomatic when sites become secondarily infected or if there is trauma to adjacent and/or opposing healthy soft tissues from irregular surfaces of the exposed bone.

Signs and symptoms of ONJ include localized pain, soft-tissue swelling and inflammation, loosening of previously stable teeth, drainage, and exposed bone. These symptoms most commonly occur at the site of previous tooth extraction or other dental surgical interventions, but may occur spontaneously. Some patients may present with atypical complaints such as 'numbness,' the feeling of a 'heavy jaw,' and various dysesthesias."

SOURCE: Ruggiero SL et al. *J Oncol Prac* 2006;2(1):7-14. Available at **http://jop.stateaffiliates-asco.org/JanuaryIssue/7.pdf**. Accessed January 5, 2007.

Track 6

DR LOVE: What's the typical clinical course of ONJ?

DR MARX: It usually takes about eight to 12 doses of zoledronic acid to reach the risk range. With pamidronate it's a little bit slower — about 10 to 14 doses are required before people develop exposed bone.

As it is pertinent to the oral surgeon, an invasive dental procedure that has a risk of not healing and of developing exposed bone can parlay itself into losing, literally, half of the jaw. When people develop exposed bone, they tend to be confused about it.

We educate patients by telling them that it's likely to be permanent and that discontinuing the drug will not necessarily resolve it. The good news is that the exposed bone, by itself, is not painful, and we can control their pain with simple antibiotics and an antiseptic mouthwash called Peridex® (chlorhexidine gluconate).

Most people respond to that. They live with exposed bone, and they function normally. The risk for fracture is low, simply because the jaw has an overbuilding of strength. Unless part of it is surgically removed, it is not at much of a risk for fracture.

DR LOVE: How large are these lesions?

DR MARX: Some involve either the whole jaw or half the jaw. Some of them are large — seven, eight or 10 centimeters.

DR LOVE: Over a period of a few years, how often would a patient require antibiotics?

DR MARX: Some patients require ongoing antibiotic therapy. That's one of the values of penicillin therapy, which can be used continuously with few secondary problems. Some patients can be treated intermittently. We have them take the antibiotic when they have exacerbations of pain. It squelches the pain, and then they go on for a pain-free period and only restart the antibiotic should the pain return.

Tracks 7-9

DR LOVE: For patients who receive more than eight or 12 courses of a bisphosphonate, what's the incidence of ONJ?

DR MARX: The incidence is unknown. We have studies that report as little as 0.8 percent to as much as a 12 percent incidence. I believe the reality is probably somewhere in between, about a six to eight percent incidence, which is not based on any hard data.

The good news here is that it's controllable. Ninety percent of our patients — and we've recorded 143 patients so far — are living with exposed bone, eating relatively normally, pain free and functioning as they did prior to the bone exposure.

DR LOVE: I've heard oncologists say, "I'm not going to use a bisphosphonate if the patient has just one or two bone metastases" because of their concern about ONJ. Does that make sense to you?

DR MARX: I don't believe it makes sense. The message for the medical oncologists is — and I say this to the patients: "The bisphosphonates have been beneficial for you. Prior to the bisphosphonates, patients with your diagnosis suffered fractures, bone resorption, hypercalcemia, and a number of other complications that often led to severe disability and even death. These drugs have been good for patients like you.

With some education of medical oncologists and dentists, we can prevent most of this. If patients do develop it, we may not be able to cure it, but we can manage it. You can lead a normal life and still reap the benefits from this drug."

DR LOVE: Are there any preventive measures?

DR MARX: The message I want to impart to the oncologists is, when you identify patients with metastatic disease who require a bisphosphonate, refer them right away to a dentist who is familiar with ONJ. They should probably start with an oral and maxillofacial surgeon who can direct the care and a dentist who is familiar with this entity.

The medical oncologist should, if possible, defer the bisphosphonate for about two months (5.4), which is physiologically feasible according to cancer kinetics. The dentist needs to begin one fundamental task: Take care of the mouth to avoid future dental extractions or dental implants. They need to get the mouth in optimum health.

I tell the dentist or oral surgeon, "Give everybody a thorough examination. Take out any teeth that are abscessed, not restorable or have failing root canals. Do all of the invasive work while the bone is capable of healing through a remodeling process. Then begin preventive dentistry. Crowns, bridges, dentures and fillings are feasible anytime during bisphosphonate exposure because they are not invasive."

DR LOVE: What about performing this type of work while patients are on chemotherapy?

DR MARX: That is not too much of a problem, but chemotherapy does affect healing. The mouth is gifted with a blood supply and an immune response that generally handle that well.

DR LOVE: Are these recommendations your individual thoughts, or do they represent the oral surgery community in general?

DR MARX: They represent the oral surgery community in general. My parent organization, the American Association of Oral and Maxillofacial Surgeons, has published a position paper that includes most of this (AAOMS 2006; [5.4]). Eight other specialties of dentistry have their own position papers that mimic what I've said.

5.4

Treatment Strategies for Patients About to Start Intravenous Bisphosphonate Therapy

"The treatment objective for this group of patients is to minimize the risk of developing BRONJ [bisphosphonate-related osteonecrosis of the jaw]. Although a small percentage of patients receiving bisphosphonates develop osteonecrosis of the jaw spontaneously, the majority of affected patients experience this complication following dentoalveolar surgery.

Therefore *if systemic conditions permit*, initiation of bisphosphonate therapy should be delayed until dental health is optimized. This decision must be made in conjunction with the treating physician and dentist and other specialists involved in the care of the patient.

Non-restorable teeth and those with a poor prognosis should be extracted. Other necessary elective dentoalveolar surgery should also be completed at this time. Based on experience with osteoradionecrosis, it appears advisable that bisphosphonate therapy should be delayed, *if systemic conditions permit*, until the extraction site has mucosalized (14-21 days) or until there is adequate osseous healing. Dental prophylaxis, caries control and conservative restorative dentistry are critical to maintaining functionally sound teeth. This level of care must be continued indefinitely."

SOURCE: American Association of Oral and Maxillofacial Surgeons. **Position paper on bisphosphonate-related osteonecrosis of the jaws.** Available at **www.aaoms.org/docs/position_papers/osteonecrosis.pdf**. Accessed January 3, 2007.

Tracks 10-11

DR LOVE: What is the impact on the risk of ONJ of changing the dosing interval of the intravenous bisphosphonates to six months?

DR MARX: That is unstudied. What we have is an extrapolation from the oral bisphosphonates. We don't see individuals develop problems with alendronate until they're on it for three years. This is proof that the bisphosphonates cause the problem, not chemotherapy, because we have 35 cases due to oral bisphosphonates alone — 32 with alendronate, three with risedronate and none with ibandronate.

We found that you don't have a risk for osteonecrosis of the jaw until you've been on an oral bisphosphonate for three years, and most cases occur with five years or more of therapy. So it's related to dose accumulation.

The big difference between intravenous and oral bisphosphonates is that if you undergo a six-month drug holiday from alendronate, the bone heals or lends itself to a minor, office-based surgical debridement, indicating that the osteoclasts are able to repopulate. Stopping an intravenous bisphosphonate (zoledronic acid or pamidronate) — and this is another message to the medical oncologists — does not benefit oral exposed bone to any great degree. So if the benefits are still there for the cancer patient, don't hesitate to continue the medication.

DR LOVE: If a patient with metastatic bone disease develops ONJ, you're saying to continue the bisphosphonate?

DR MARX: If the medical oncologist feels that it's still benefiting the patient from a cancer perspective, yes, continue on. We can manage the oral exposed bone. You can't manage the runaway cancer. So if it's still benefiting the cancer, go ahead and continue the medication. There's no absolute reason to stop it. ■

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Ruggiero SL et al. **Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases.** *J Oral Maxillofac Surg* 2004;62(5):527-34. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the second interim analysis of BCIRG 006, no statistically significant difference appeared in disease-free survival between AC → TH and TCH in the overall population or in the population with amplification of TOPO II.**
   a. True
   b. False
2. **In the US Oncology adjuvant trial, docetaxel/cyclophosphamide (TC) and AC were equivalent with regard to disease-free survival.**
   a. True
   b. False
3. **In the US Oncology adjuvant trial, patients receiving AC experienced significantly more nausea and vomiting than those receiving TC.**
   a. True
   b. False
4. **The TAnDEM trial failed to demonstrate an advantage in progression-free survival when trastuzumab was added to anastrozole for patients with ER-positive, HER2-positive metastatic disease.**
   a. True
   b. False
5. **In NSABP-B-33, exemestane caused a statistically significant improvement in which of the following outcomes compared to placebo after five years of tamoxifen?**
   a. Relapse-free survival
   b. Overall survival
   c. Both a and b
6. **Patients may be considered to have bisphosphonate-related osteonecrosis of the jaw if the following characteristics are present:**
   a. Current or previous treatment with a bisphosphonate
   b. Exposed bone in the maxillofacial region that has persisted for more than eight weeks
   c. No history of radiation therapy to the jaws
   d. All of the above
7. **NSABP-B-42 will evaluate _____.**
   a. The optimal duration of aromatase inhibitor therapy
   b. The optimal dose of aromatase inhibitor therapy
   c. Long-term side effects of aromatase inhibitor therapy
   d. All of the above
   e. Only a and c
8. **In the first interim safety analysis of the Phase II trial comparing bevacizumab combined with *nab* paclitaxel weekly versus every two weeks versus every three weeks, no safety signal appeared for excessive toxicity in any arm of the study.**
   a. True
   b. False
9. **In the pilot study of dose-dense AC/paclitaxel with trastuzumab, _____ patient(s) out of 70 experienced significant, protocol-defined declines in LVEF.**
   a. One
   b. Four
   c. Seven
10. **Which of the following bisphosphonates is being evaluated as adjuvant therapy in NSABP-B-34?**
    a. Zoledronic acid
    b. Ibandronate
    c. Clodronate
    d. All of the above
11. **Which of the following bisphosphonates is being evaluated in the Intergroup adjuvant trial (SWOG-S0307)?**
    a. Zoledronic acid
    b. Ibandronate
    c. Clodronate
    d. All of the above
12. **The secondary pain associated with bisphosphonate-related osteonecrosis of the jaw is most commonly due to _____.**
    a. Bacterial infection
    b. Nerve damage
    c. Bone fracture
    d. All of the above

Post-test answer key: 1a, 2b, 3a, 4b, 5a, 6d, 7e, 8a, 9a, 10c, 11d, 12a

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Breast Cancer Update — Issue 2, 2007

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GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *BCU* address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the neoadjuvant, adjuvant, metastatic and preventive settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data for biologic therapies and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease. . 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions. . . . . 5 4 3 2 1 N/A

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Faculty	Knowledge of subject matter	Effectiveness as an educator
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Eleftherios P Mamounas, MD, MPH	5 4 3 2 1	5 4 3 2 1
Andrew D Seidman, MD	5 4 3 2 1	5 4 3 2 1
Allan Lipton, MD	5 4 3 2 1	5 4 3 2 1
Robert E Marx, DDS	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 N/A
Related to my practice needs. . . . . 5 4 3 2 1 N/A
Will influence how I practice. . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
Overall quality of material. . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence. . . . . 5 4 3 2 1 N/A

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BCU207

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U P D A T E

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