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Breast Cancer™ UPDATE

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

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POWERPOINT PRESENTATIONS:

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CME Certified

www.BreastCancerUpdate.com

Breast Cancer Update
A CME Audio Series and Activity

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 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 patients with HER2-positive breast cancer in the adjuvant, neoadjuvant 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 appropriate patients with metastatic disease about selection and sequencing of endocrine therapy and about the risks and benefits of combination versus single-agent chemotherapy.
- 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 7 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Chlebowski, Winer, Bear, Smith and Miller on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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Research To Practice designates this educational activity for a maximum of 4.25 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, 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. **www.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**. This monograph also contains clinical investigator PowerPoint presentations.

TABLE OF CONTENTS

For this issue of our series, we are pleased to pilot a new feature: Enhanced PowerPoint files with corresponding audio from research leader presentations conducted during our most recent CME meetings. These brief 10-minute educational talks are designed for individual and group use, including playback at community tumor board meetings. We would appreciate feedback on this new education strategy.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved by a peer review content validation process. The content of each activity is reviewed by both a member of the scientific staff and an external independent reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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Dr Chlebowski — Grants/Research Support: Amgen Inc, Pfizer Inc; Consultant and Other Financial/Material Support: AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Novartis Pharmaceuticals, Organon, Pfizer Inc, Sanofi-Aventis. **Dr Winer** — Speakers Bureau: Genentech BioOncology. **Dr Bear** — Honorarium and Speakers Bureau: Sanofi-Aventis. **Dr Smith** — No financial interests or affiliations to disclose. **Dr Miller** — Grants/Research Support: GlaxoSmithKline, Medarex Inc, Pfizer Inc, Roche Laboratories Inc, Sanofi-Aventis.

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UPCOMING EDUCATIONAL EVENTS

2005 American Society for Therapeutic Radiology and Oncology Annual Meeting
October 16-20, 2005
Denver, Colorado
Event website: **www.astro.org/annual_meeting**

European Cancer Conference
October 30-November 3, 2005
Paris, France
Event website: **www.fecs.be**

Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow
November 2-5, 2005
New York, New York
Event website: **www.mssm.edu/tcf**

28th Annual San Antonio Breast Cancer Symposium
December 8-11, 2005
San Antonio, Texas
Event website: **www.sabcs.org/Index.asp**

Miami Breast Cancer Conference
February 22-25, 2006
Miami Beach, Florida
Event website: **www.cancerconf.com**

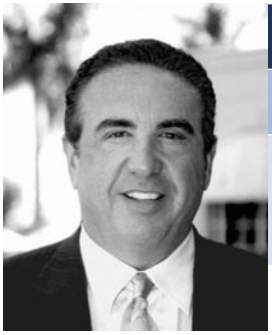
Fifth European Breast Cancer Conference
March 21-25, 2006
Nice, France
Event website: **www.fecs.be**

Join us for an upcoming live, interactive CME program.

Controversies in Systemic Therapy of Breast Cancer
October 29, 2005, 8:30AM - 3:30PM, The Westin Diplomat Resort & Spa, Hollywood, Florida

This program will focus on key management options for early and metastatic breast cancer and recent, relevant research results from the 2005 ASCO meeting.

For more information, log onto **www.BreastCancerUpdate.com/CMEmeetings** or email us at Meetings@ResearchToPractice.net. To register, call (800) 233-6153.



EDITOR'S NOTE

Neil Love, MD

Perspective from another world

Every person who has unexpectedly stepped off the edge of this planet into the bottomless pit of life-threatening illness knows that the view from down there is very different and that no amount of bargaining with whatever or whomever one believes in changes the reality that to survive, it is essential to be able to reach inside to find faith and courage.

Juliann Smith had already faced this frightful challenge as a college student when she was diagnosed with Hodgkin's disease. Fortunately, she was successfully treated with mantle irradiation, and her positive experience with a knowledgeable, kind and trustworthy medical oncologist led to a career shift from veterinary to human medicine. Two decades later, just like the physician who impacted her life when she was younger, Dr Smith was a very busy and well-respected medical oncologist in Southern California.

Dr Smith loved her practice and found it impossible to turn away patients. Her day started early and ended late, and she lived and breathed cancer medicine 24-7-52-365. Memories of the scary days of her youth when she was forced to peer anxiously into a linear accelerator had faded, but in 2000, at the age of 44, she once again plummeted into that dark hole, this time upon palpating an abnormality in her breast.

Some days later, Dr Smith — lying prone on a mammotomy procedure table — observed the face of her radiologist transform into a black cloud after inserting a needle into what was a gritty, highly suspicious mass. Within days, Juliann was confronting a node-positive, ER-positive, HER2-positive adenocarcinoma.

On the enclosed audio program, Dr Smith shares her story, her perspectives on decision-making in medical oncology and how this experience as a patient altered her approach as a physician. One might argue that in 2000, when she underwent therapy, the adjuvant systemic treatment path she chose (AC followed by TCH and an aromatase inhibitor) was not fully evidence-based.

The ATAC data had not yet been reported, and years later, there would still be questions about optimal endocrine therapy for patients in Dr Smith's situation (ER-positive, HER2-positive, node-positive disease in a premenopausal woman who ceases menstruation with chemotherapy). In terms of additional therapy to attack the other molecular target (HER2), in 2000, of course, the

spectacular results of the adjuvant trastuzumab trials were but a glimmer in our eyes. In the conversation below, Dr Smith explains why these decisions made sense to her then and now.

I don't quite know what to make of Dr Smith's perspective, but one must respect her viewpoint and understand that many other rational, balanced people feel the same way. Oncology research commentators are now spending a great deal of time pondering the clinical relevance of a number of new trial data sets. The issue of healthcare costs for these therapies is a topic of increasing interest. But for the moment, it is enough to just listen to a colleague tell her fascinating, gut-wrenching and all too familiar tale.

— Neil Love, MD
NLove@ResearchToPractice.net

DR LOVE: What was your reaction when you were diagnosed with breast cancer?

Juliann M Smith, MD
Eisenhower Lucy Curci Cancer Center
Rancho Mirage, California

DR SMITH: My entire world stopped. It was as if there was nothing else around me — as if everything just fell apart, and I knew that I had to do whatever I could to get rid of this cancer — whatever it took.

When I was having the breast biopsy and the radiologist did the first pass, she said, "This is definitely cancer." At that point, as I was lying on the table, the faces of women with breast cancer whom I had taken care of started going through my mind. And I started thinking of a series of women who had died at very young ages — in their thirties and forties — women I had basically taken through the disease.

I am still a believer in evidence-based medicine, and I try to have an evidence-based practice, but when it came to my own care, somehow that changed. While I wanted to do what was evidence based, I also was willing to go beyond that. I wanted to give myself whatever advantages I could, whatever made sense within the oncology literature.

I was very concerned about the HER2 positivity and wanted to address that, and trastuzumab really was the only way to truly get at that specific component of the malignant clone of cells. So I elected to go with trastuzumab and aggressive endocrine treatment and chemotherapy.

I ended up in the hospital three times. I was septic and actually had congestive heart failure at one point. But somehow, that was all okay, because I knew I was doing the maximum that I could, so that hopefully, I wouldn't have to face breast cancer again. I didn't care how sick I got, as long as I did everything that I could possibly do.

DR LOVE: I see you're receiving oxygen. What's that for?

DR SMITH: About two years after the chemotherapy, I developed very severe aortic and mitral valve disease and ended up having to have both valves replaced. And probably because of the mantle irradiation, I also developed premature artherosclerosis and had a 90 percent left main disease. So I got all that taken care of at one time. Surgery was complicated by sort of an unmasking of what has turned out to be very severe restrictive lung disease, which, presumably, is due to the mantle irradiation 20 years ago.

DR LOVE: Do you think the congestive heart failure during adjuvant therapy was related to the trastuzumab?

DR SMITH: I'm not sure that the doxorubicin was really out of my system when I received trastuzumab. I think that in my situation, it was a domino effect that included the doxorubicin, trastuzumab, bad valves, coronary disease and very severe restrictive lung disease.

DR LOVE: How has this experience changed your perspective on practicing oncology?

DR SMITH: It's changed it dramatically. It's now very difficult for me to give toxic chemotherapy to a patient, because I know what they're going to feel like. I have a great deal of empathy when I have to treat someone with, for example, TAC chemotherapy. I know the day-in and day-out sensation of being so incredibly fatigued that you can't get out of bed. I know what the anemia feels like, the nausea, the malaise. And it's very hard to know that I'm putting a woman through this, but I have to focus on the fact that we're hopefully getting rid of their breast cancer.

DR LOVE: How do you feel about the treatment decision you made for your breast cancer?

DR SMITH: I think it was the right decision. I'm very comfortable with it.

DR LOVE: What's your perspective on the way decisions are currently made in oncology in general?

DR SMITH: Most oncologists seem to be trying to practice evidence-based medicine, but it's such a complicated field that they are really all over the map in terms of treatment choices. I don't see much consistency from one oncologist to the next.

DR LOVE: How did you feel when you found out about the new data that's just come out on the use of adjuvant trastuzumab, showing that it works?

DR SMITH: I was very glad to see that. I feel that my beliefs were confirmed.

DR LOVE: How has this experience affected the way you communicate with patients?

DR SMITH: The most important thing is to give them a chance to talk about their concerns and fears. In the past, my style was basically to give patients a lot of information and say, "This is what we're going to do," and just kind of go through it all. Now I stand back and say, "This is what I would suggest, but what do you think?"

DR LOVE: Your case really brings up the whole issue of how much evidence you need in order to make a decision to embark upon a therapy. People talk about women with breast cancer wanting to receive chemotherapy for a one percent improvement in survival, but it's so hard to grasp. And you wonder whether or not the fear of recurrence is actually causing people to make illogical decisions.

DR SMITH: It may seem illogical to someone who doesn't have to live with cancer. But one percent is important to a breast cancer survivor. I think most cancer survivors would be willing to go through a significant amount of toxicity for a one percent benefit, especially younger patients. I don't know that this would necessarily apply to 75- and 80-year-old patients, but certainly people in their forties and fifties would definitely be willing to subject themselves to a lot of toxicity.

DR LOVE: Medical oncology practice has evolved to be very focused on the risk-benefit numbers, the Ravdin Adjuvant! Online model, et cetera. Many oncologists pulled back from the concept of "let's be as aggressive as possible even without trial data" because of the high-dose chemotherapy/stem cell debacle.

DR SMITH: My experience was that when you're diagnosed with cancer, the numbers don't matter and everything becomes 100 percent. It's you against the cancer. I'd be interested to take a survey of the women who went through high-dose chemotherapy with stem cell transplant and see if they have regrets. I suspect they probably don't.

I think that, as oncologists, we do have a responsibility to lead our patients through the quagmire of all the statistics and evidence-based medicine and try to be their guides. But when you're looking at it from the patient's perspective, you don't hear a lot of that. And I think all that really goes through their mind is, "Tell me what will cure me."

I would like to add another comment and that is how incredibly important my oncologist was to me, and how I really felt that my life was in his hands. I had complete and total faith in what he advised me to do. It's a remarkable gift our patients give us.

DR LOVE: What do you mean by that?

DR SMITH: Patients turn their lives over to us and put their faith in us and follow what we tell them to do. They almost elevate us to the level of God, because that's one of the ways of dealing with the intense fear that cancer brings. You have to believe that somebody is going to be able to walk this path with you and has the right answer and is certainly going to lead you to find the best answer that can be found.

I actually decided to go into oncology when I had Hodgkin's disease when I was 21. I was under the care of a wonderful oncologist, who actually is still practicing. He inspired me — he was just such a confident, intelligent person, and when he talked to me and we made eye contact, I just knew I was going to be okay. I could just tell from his manner. ■

INTERVIEW

Rowan T Chlebowski, MD, PhD

Dr Chlebowski is a Professor of Medicine at UCLA School of Medicine and Chief of Medical Oncology at Harbor-UCLA Medical Center in Torrance, California.

Tracks 1-16

Select Excerpts from the Interview*

Tracks 2-3

DR LOVE: Can you discuss the Women's Intervention Nutrition Study (WINS) that you presented at ASCO?

DR CHLEBOWSKI: The issue of dietary fat intake and breast cancer has been around for about 25 years. So to address this issue, we conducted a random-

* *Conducted on May 20, 2005*

ized clinical trial. We entered 2,437 women aged 48 to 79 from 37 clinical centers in the United States. They all received standard breast cancer management, including surgery, radiation therapy if indicated, tamoxifen for five years if estrogen receptor-positive and a defined chemotherapy if estrogen receptor-negative. The estrogen receptor-positive patients could also receive chemotherapy.

DR LOVE: What was the rationale for looking at nutrition and breast cancer recurrence?

DR CHLEBOWSKI: The whole issue probably began with the country-to-country differences in breast cancer incidence. Twenty-five years ago, the Japanese not only had fewer cancers but they had a much lower recurrence rate, and at that time, the difference in obesity between American and Japanese women wasn't that great.

There were a number of studies that looked at cohorts and suggested that dietary fat intake would affect recurrence. More recently, the attention in the observational studies has shifted away from dietary fat and more towards obesity and physical activity.

DR LOVE: When you look at those components — dietary fat, obesity and physical activity — what would be the mechanism of action as to why it would affect breast cancer recurrence?

DR CHLEBOWSKI: The prevailing thought was that obesity or dietary fat could be related to estrogen levels, and they can show that association. Of course, that would make it much less interesting if that were the only mechanism because now we have aromatase inhibitors.

One always had the consideration that it is more like the metabolic syndrome where you end up having obesity, insulin resistance associated with coronary heart disease, dementia, diabetes and the cancers — colon and breast cancer — at least in some of those studies. That kind of mechanism, metabolic syndrome, insulin regulatory pathways, had also been under consideration but not the primary focus.

DR LOVE: What were the endpoints of the study?

DR CHLEBOWSKI: Our primary study endpoint was relapse-free survival, which included all breast cancer recurrence sites, including contralateral breast cancers. We found that the dietary group had a longer relapse-free survival than the control population. 12.4 percent of the control group had a relapse compared to 9.8 in the diet group, which was a 2.6 percent absolute difference at five years or a 24 percent reduction in risk of recurrence.

DR LOVE: Do you think this is now something that should be brought up to women with breast cancer?

DR CHLEBOWSKI: We're not quite there yet in that we recognize the need for further follow-up, a peer-review publication and probably a confirmatory study. Having said that, the diet was associated with nutritional adequacy and

can be recommended for other health reasons and would also have no appreciable side effects.

The only issue that I could see is this guilt factor. For instance, the American Cancer Society has recommendations for dietary change after cancer diagnosis. They're all based on inference. Now we have a little signal that there might be a cancer benefit as well, but I don't think we would tell every patient that they have to do it. If somebody wanted to do something, you'd say, "Here's something that you could do. It may influence your breast cancer, but it also has other potential benefits."

Track 4

DR LOVE: Can you update us on the Women's Health Initiative (WHI) trials and summarize some of the most important findings that have come out in the last couple of years, particularly related to breast cancer?

DR CHLEBOWSKI: There are two key areas. First would be the WHI hormone trials, and the initial data reported was the comparison of estrogen plus progestin versus placebo in women who had a uterus (Rossouw 2002). Basically, the surprising finding was that coronary heart disease was increased by approximately 25 to 30 percent, as opposed to the prestudy estimates that anticipated it would be reduced with hormone use. Breast cancers were increased, as expected, but surprisingly, prognostic characteristics worsened. After one year of estrogen plus progestin use, abnormal mammograms increased by 74 percent.

These were some of the major findings. Basically, what happened with that was the FDA changed the labeling of estrogen plus progestin, and 33 million fewer prescriptions for menopausal hormone therapy were written in 2003 versus 2001.

Also, the trial of estrogen only versus placebo for otherwise healthy women who had a prior hysterectomy was stopped early. In that study, there was no effect on the global health index — the overall balance of risks and benefits (Anderson 2004). Actually, coronary heart disease didn't increase. Rather, there was approximately a nine percent decrease, but it was not statistically significant.

The other very interesting finding was that estrogen-only therapy ended up trending towards a decrease in breast cancers. There were approximately 24 percent fewer breast cancers on the estrogen-only arm. We're in the process of doing further analyses, and I believe this may well represent a real event. Short-term estrogen may well be associated with a reduction in breast cancer risk.

Track 5

DR LOVE: Can you summarize where we are in terms of the major randomized trials of aromatase inhibitors?

DR CHLEBOWSKI: We have 68 months' follow-up on the ATAC data, which means the majority of patients have completed their therapy and approximately a year of follow-up afterwards (Howell 2005). I see the toxicity data as being final, unless one proposes a new mechanism whereby returning estrogen back to the physiological levels causes different toxicities. The five-year toxicity data is very favorable for anastrozole compared to tamoxifen, because the three life-threatening toxicities — endometrial cancer, arterial and venous vascular events — were all significantly less with anastrozole.

DR LOVE: While endometrial cancer is certainly a disturbing event, I guess you could raise the question as to whether it is really life threatening.

DR CHLEBOWSKI: Endometrial cancer has a 15 percent mortality rate associated with it. When we look at the hip fractures, which are life threatening, the incidence was low and really not different at all between the patients on anastrozole versus tamoxifen. Tony Howell just reported on the cardiac deaths data, which were 49 versus 46 — really no difference at all after five years.

Track 13

DR LOVE: Putting aside toxicities, there has been a lot of discussion about whether the long-term — 10-, 15-, 20-year — relapse rate in some patients would be lower starting with tamoxifen for some period of time, followed by an aromatase inhibitor. What are your thoughts on that hypothesis?

DR CHLEBOWSKI: If you start with tamoxifen, after two and a half, three or five years, more patients will have relapsed than on an aromatase inhibitor (1.1). A substantial number of those patients will be irretrievable — they have incurable disease — and so you're banking on the fact that you'll be able to capture more patients later, but we don't have any data for that. That's just speculation.

While I believe sequencing therapy may be better, ultimately, I still don't see any reason not to start with the most effective therapy. An aromatase inhibitor followed by tamoxifen or a nonsteroidal aromatase inhibitor makes more sense to me. We have to wait to see the data from the BIG FEMTA trial, which includes an arm with letrozole as initial treatment followed by tamoxifen.

Track 16

DR LOVE: Can you discuss the issue of race, ethnicity and breast cancer subtypes?

DR CHLEBOWSKI: In the Women's Health Initiative, we have a large population, so we examined risk factors for breast cancer by ethnicity (Chlebowski 2005). We took 160,000 women, in whom we have a racial ethnic distribution, and tracked them as a prospective cohort. As expected, we found the age-adjusted breast cancer risk for African-Americans, Hispanics and Asian Pacific Islanders, compared to Caucasians, were all substantially less — 30 percent or so less (1.2), which is about the same as the SEER data.

We corrected for the Gail risk model, and their hazard ratios moved towards unity but were still different. We looked at approximately 22 risk factors, so we really have extensive risk-factor correction, and what we found was very interesting. We could almost completely explain the reduced risk of breast cancer in Hispanics and Asian Pacific Islanders. Their hazard ratios, with our risk factors in the final models, were 0.98 and 0.94.

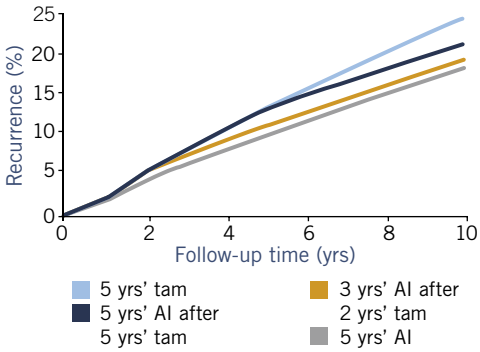
DR LOVE: What about the African-American population?

DR CHLEBOWSKI: Interestingly, for African-Americans, their hazard ratio compared to Caucasians was 0.75, which statistically was significantly lower. Even more interestingly, they had substantially lower risk for hormone receptor-positive cancers — about 50 percent of the Caucasians' risk.

The most interesting finding was our equivalent of triple-negative cancers — ER-negative, PR-negative and high grade. African-Americans have nearly

1.1

Time to Recurrence Deep Model* (5-Year Carry-Over)



* Assumes tamoxifen resistance may be preceded by phenotypic changes from PgR+ to PgR-, in micrometastases

SOURCE: Cuzick J, Howell A. Presentation. ASCO 2005. **Abstract 658.**

1.2

Hazard Ratio of Invasive Breast Cancer Incidence by Race/Ethnicity as Compared to Caucasians*

	Hazard ratio	*p*-value
Blacks	0.75	0.006
Hispanics	0.98	0.90
American Indians	0.89	0.78
Asian/Pacific Islanders	0.94	0.62

* Adjusted for covariates in Gail model plus education, BMI, physical activity, number of second-degree relatives with breast cancer, parity, hormone therapy (HT) use, prior contraceptive use, alcohol, smoking, dietary intake, HT x BMI interaction and mammography (as a time-dependent covariate)

SOURCE: Chlebowski RT et al. *J Natl Cancer Inst* 2005;97(6):439-48. **Abstract**

a fivefold-increased risk of having triple-negative cancers compared to Caucasians. In African-Americans, 31 percent of the cancers were triple negatives compared to 10 percent in Caucasians.

Other groups are looking at whether the triple negatives have genetic profiles similar to basaloid cancers, which are faster growing and more difficult to treat. We consider this kind of a unifying hypothesis in that, with these more common basaloid cancers, with the same mammographic screening or frequency, you're going to find higher-stage cancers, and with the same therapy that was given in the cooperative groups, they will have a worse outcome.

It's interesting that in several African-American populations, the triple negatives are close to 50 or 60 percent of the population, instead of a third. Studies are now underway looking at the genetic profiles of these mixed African-American populations compared to Caucasian populations. ■

SELECT PUBLICATIONS

Anderson GL et al. **Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial.** *JAMA* 2004;291(14):1701-12. **Abstract**

Chlebowski RT et al. **Ethnicity and breast cancer: Factors influencing differences in incidence and outcome.** *J Natl Cancer Inst* 2005;97(6):439-48. **Abstract**

Chlebowski RT et al. **Insulin, physical activity, and caloric intake in postmenopausal women: Breast cancer implications.** *J Clin Oncol* 2004;22(22):4507-13. **Abstract**

Grann V et al. **Regional and racial disparities in breast cancer-specific mortality.** *Soc Sci Med* 2005;[Epub ahead of print]. **Abstract**

Hebert JR et al. **Differences between estimated caloric requirements and self-reported caloric intake in the women's health initiative.** *Ann Epidemiol* 2003;13(9):629-37. **Abstract**

Howell A et al. **Results of the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. **Abstract**

Jakesz R et al; ABCSG and the GABG. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trail 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62. **Abstract**

Joslyn SA et al. **Racial and ethnic disparities in breast cancer rates by age: NAACCR Breast Cancer Project.** *Breast Cancer Res Treat* 2005;92(2):97-105. **Abstract**

Mouridsen HT, Robert NJ. **The role of aromatase inhibitors as adjuvant therapy for early breast cancer in postmenopausal women.** *Eur J Cancer* 2005;41(12):1678-89. **Abstract**

Rossouw JE et al. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial.** *JAMA* 2002;288(3):321-33. **Abstract**

Thürlimann B et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;**Abstract 511**.

Tsubura A et al. **Dietary factors modifying breast cancer risk and relation to time of intake.** *J Mammary Gland Biol Neoplasia* 2005;10(1):87-100. **Abstract**

INTERVIEW

Eric P Winer, MD

Dr Winer is the Director of the Breast Oncology Center at the Dana-Farber Cancer Institute and Associate Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-17

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Track 6	Bevacizumab in the second- and third-line settings
Track 7	Proposed ECOG pilot trial examining the role of adjuvant bevacizumab
Track 8	Combined analysis of NSABP-B-31/NCCTG-N9831 trials of adjuvant trastuzumab
Track 9	Cardiac toxicity induced by adjuvant trastuzumab
Track 10	Concurrent versus sequential administration of adjuvant trastuzumab and chemotherapy
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Select Excerpts from the Interview*

Tracks 3-4

DR LOVE: Cost and reimbursement issues aside, what are the clinical implications of the ECOG-E2100 bevacizumab data to clinical practice?

DR WINER: I believe the results of ECOG-E2100 are impressive enough that, in the absence of a contraindication to bevacizumab, I would now use it in a first-line setting, optimally in combination with paclitaxel as administrated in the study (Miller 2005a; [2.1, 2.2, 2.3]).

* *Conducted on June 25, 2005*

2.1

ECOG-E2100: Phase III Randomized Trial of Paclitaxel with or without Bevacizumab as First-Line Therapy in Patients with Locally Recurrent or Metastatic Breast Cancer

Protocol IDs: ECOG-2100, CTSU, NCT00028990, CAN-NCIC-E2100, NCCTG-E2100, NSABP-E2100
Accrual: 715 (Closed)

Eligibility
Locally recurrent or metastatic breast cancer
HER2-positive only if prior treatment with or contraindication to trastuzumab; no prior chemotherapy for metastatic disease
Adjuvant taxane allowed if disease-free interval >12 months; PS 0 or 1; no CNS metastases

R

- [Paclitaxel (90 mg/m^2 d1, 8 and 15) + bevacizumab (10 mg/kg d1 and 15)] q4wk
- Paclitaxel (90 mg/m^2 d1, 8 and 15) q4wk

SOURCES: Miller KD et al. Presentation. ASCO 2005a. No abstract available; NCI Physician Data Query, August 2005.

I doubt that the interaction is specific between paclitaxel and bevacizumab, although I'm well aware that when given with capecitabine in more advanced disease, bevacizumab seemed to be less active. I believe that's probably related to the setting rather than the drug.

DR LOVE: Of course, we have seen bevacizumab work with multiple different agents, particularly in colorectal cancer, and we've seen less activity in the second-line setting than the first-line setting in colorectal cancer.

DR WINER: I agree, and it's one of the reasons why I tend to think this is probably more the setting than the drug.

2.2

ECOG-E2100 Safety Results

	Paclitaxel + bevacizumab (n = 342)	Paclitaxel (n = 330)
Hypertension*		
Grade III	13%	0%
Grade IV	0.3%	0%
Thromboembolic		
Grade III	1.2%	0.3%
Grade IV	0%	0.9%
Bleeding		
Grade III	0.6%	0%
Grade IV	0.3%	0%
Proteinuria†		
Grade III	0.9%	0%
Grade IV	1.5%	0%
Neuropathy††		
Grade III	19.9%	13.6%
Grade IV	0.6%	0.6%

* $p < 0.0001$; † $p = 0.0004$; †† $p = 0.01$

SOURCE: Miller KD et al. Presentation. ASCO 2005a. No abstract available

DR LOVE: What about docetaxel versus paclitaxel, with bevacizumab?

DR WINER: I believe the two taxanes are more similar than they are different, but we have data with paclitaxel and, specifically, we have data with a weekly or almost weekly regimen. In the ECOG trial, paclitaxel was given three out of four weeks.

2.3

ECOG-E2100 Efficacy Results

	Paclitaxel + bevacizumab (n = 330)	Paclitaxel (n = 316)	*p*-value
Response rate	28.2%	14.2%	<0.0001
Progression-free survival	10.97 months	6.11 months	<0.001
Overall survival	Hazard ratio = 0.674 (CI 0.495-0.917)		0.01

"In conclusion, this is a positive study. The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and increases the objective response rate with minimal increases in toxicity. Longer follow-up will be required to confirm the impact on overall survival. Future studies in this area should begin to explore the role of bevacizumab in the adjuvant setting and continue to investigate methods to identify those patients who are most likely to benefit from VEGF-targeted therapies."

SOURCE: Miller KD et al. Presentation. ASCO 2005a. No abstract available

DR LOVE: What are your thoughts about nanoparticle albumin-bound (*nab*) paclitaxel with bevacizumab at this time and in the future?

DR WINER: At the moment, I wouldn't be in a rush to give it with bevacizumab. Once we have a little bit of data in terms of the safety of *nab* paclitaxel with bevacizumab, I believe it would be a reasonable substitution in a limited number of patients, such as a woman with a contraindication to paclitaxel based on hypersensitivity.

In the CALGB, we actually have planned a study comparing different schedules of *nab* paclitaxel and paclitaxel. In that study, bevacizumab will be combined with either paclitaxel or *nab* paclitaxel for those patients who don't have a contraindication to it.

DR LOVE: Are you currently using *nab* paclitaxel in your practice?

DR WINER: At our center, we elected to use it mostly, if not exclusively, in patients who have either had hypersensitivity reactions to paclitaxel that we thought were related to the cremophor or in patients who have trouble tolerating steroid premedication.

DR LOVE: Another issue with *nab* paclitaxel is the shorter infusion time. How much of a benefit is this?

DR WINER: The shorter infusion time potentially has two benefits. One is that it's better for patients to spend less time in the clinic. We don't want to take over people's lives. The second benefit is that, whether it's in an academic center or in practice, many medical oncologists and oncology nurses are struggling with infusion rooms that are bursting at the seams because of all of these new therapies, so minimizing the time a patient spends in the infusion room is ultimately quite important.

In addition, I believe avoiding steroid premedication is a big deal. Steroids are fine for some people the first or second time you take them, but after a while, the ongoing ups and downs of steroids can be a real problem.

Tracks 8-9

DR LOVE: Can you provide an overview of the adjuvant trastuzumab data presented at ASCO?

DR WINER: The adjuvant trastuzumab data were pretty impressive and very striking for all of us listening to the presentations (Romond 2005; Perez 2005b; Piccart-Gebhart 2005). I believe what made them that much more striking is that the benefits were seen so early on, although if one thinks about it, given the fact that events in patients with HER2-positive breast cancer tend to be seen early on, maybe that's not so surprising.

Essentially, there were results from one large study and another analysis of two studies that were combined. The two US studies, which were analyzed together, were the NSABP trial B-31 and the NCCTG Intergroup N9831 trial (Romond 2005; [2.4]). They analyzed the patients on the NSABP trial who were randomly assigned to AC followed by paclitaxel versus those who received AC followed by paclitaxel plus trastuzumab.

The NCCTG trial was more complicated and had a third arm in which patients received sequential trastuzumab. That arm was not included in the combined analysis, so essentially, the combined analysis compared AC followed by paclitaxel versus AC followed by paclitaxel with trastuzumab, followed by trastuzumab for a total of one year. The other trial was the HERA study (Piccart-Gebhart 2005; [2.5]), which was a more permissive study in that it allowed a range of different chemotherapy regimens, and women were simply randomized to trastuzumab or not at the completion of their chemotherapy.

DR LOVE: What did the data show?

DR WINER: The combined analysis showed a very impressive, highly statistically significant improvement in disease-free survival for women who received AC/paclitaxel plus trastuzumab, followed by trastuzumab, compared to those women who received no trastuzumab whatsoever. The reduction in the risk of recurrence was significant — in terms of the hazard ratio, there was a 40 to 50 percent reduction in the risk of disease recurrence. I'm purposely being a little vague about the actual number, because it could change a little over time. I don't think we should get hung up as to whether it's a 42 or 46 or 48 percent reduction — the reduction was significant.

Moreover, there was also the early suggestion of a survival benefit, and what's particularly noteworthy is that this wasn't a trial of trastuzumab early versus no trastuzumab. It was a trial of trastuzumab early versus almost certainly trastuzumab at the time of recurrence. I believe we have to presume that, if not all, almost all of the women who developed metastatic breast cancer received trastuzumab at that time.

2.4

2005 ASCO Adjuvant Trastuzumab Data — Adjuvant Chemotherapy with or without Trastuzumab: Combined Analysis of NSABP-B-31/NCCTG-N9831 Efficacy Data

Parameters	AC → paclitaxel (n = 1,679)	AC → paclitaxel + trastuzumab (n = 1,672)	Hazard ratio	*p*-value
Disease-free survival			0.48	$2p = 3 \times 10^{-12}$
Three-year disease-free survival	75%	87%		
Four-year disease-free survival	67%	85%		
Time to first distant recurrence			0.47	$2p = 8 \times 10^{-10}$
Three years from randomization	81%	90%		
Four years from randomization	74%	90%		
Overall survival			0.67	$2p = 0.015$
Three years from randomization	92%	94%		
Four years from randomization	87%	91%		

"Our conclusions for high-risk HER2-positive breast cancer: Trastuzumab, when given concurrently with paclitaxel following AC chemotherapy, reduces the risk of a first breast cancer event at three years by 52 percent. This benefit should change the standard of care. The relative risk reduction benefit was present and of similar magnitude in virtually all subsets of patients analyzed. There is not, however, statistical power to establish efficacy in the node-negative subset. The addition of trastuzumab reduced the probability of developing distant recurrence by 53 percent at three years and the hazard of developing distant metastases appears, thus far, to decrease over time. Early results at a median follow-up of two years show a statistically significant survival advantage, with a relative risk reduction of 33 percent."

SOURCE: Romond EH et al. Presentation. ASCO 2005. No abstract available

The follow-up is very short from these trials — a couple of years or less — and clearly, we need more follow-up. Whether this difference is maintained and to what extent this leads to a long-term survival benefit remains to be seen, although I think most people assume that there will be a significant survival benefit as we move forward.

DR LOVE: What about cardiac toxicity?

DR WINER: The downside with receiving trastuzumab, apart from the fact that it requires a year's worth of therapy, is the cardiac toxicity, which was defined as symptomatic congestive heart failure, so we're not talking about asymptomatic drops in ejection fractions. We're talking about real problems that we hope can improve over time, but about which we have relatively limited, if any, information about the long-term consequences. I generally tell patients that the risk of congestive heart failure is probably in the range of two to four percent, based on what we know so far, specifically in women who receive AC followed by paclitaxel with trastuzumab (2.6).

There was some suggestion that the cardiac toxicity may be less when trastuzumab is administered sequentially, as in the NCCTG trial where paclitaxel was given and then trastuzumab followed (Perez 2005b; [2.7]). Maybe that

2.5

2005 ASCO Adjuvant Trastuzumab Data — First Results of the HERA Trial: Trastuzumab for One Year versus Two Years versus Placebo After Chemotherapy for HER2-Positive Breast Cancer

Efficacy (One-year median follow-up)	Placebo (n = 1,693)	Trastuzumab for one year (n = 1,694)	Hazard ratio [95% CI]	*p*-value
Two-year disease-free survival	77.4%	85.8%	0.54 [0.43-0.67]	<0.0001
Relapse-free survival	78.6%	87.2%	0.50 [0.40-0.63]	<0.0001
Distant disease-free survival	81.8%	89.7%	0.51 [0.40-0.66]	<0.0001
Overall survival	95.0%	96.0%	0.76 [0.47-1.23]	<0.26

"In conclusion, at one-year median follow-up, trastuzumab given every three weeks for one year following adjuvant chemotherapy significantly prolongs disease-free survival and relapse-free survival for women with HER2-positive early breast cancer. Trastuzumab significantly reduces the risk of distant metastasis. Trastuzumab's clinical benefits are independent of patients' baseline characteristics and of type of adjuvant chemotherapy received. Trastuzumab therapy is associated with a low incidence of severe symptomatic congestive heart failure, but, clearly, longer follow-up is needed to better quantify this risk. All patients continue to be followed for long-term safety. Patients in the observation arm will be offered trastuzumab. Results regarding optimal trastuzumab duration, two years versus one year, should be available in 2008."

SOURCE: Piccart-Gebhart MJ on behalf of The Breast International Group (BIG), Non-BIG participating groups, Independent sites, F Hoffmann-La Roche Ltd. Presentation. ASCO 2005. No abstract available

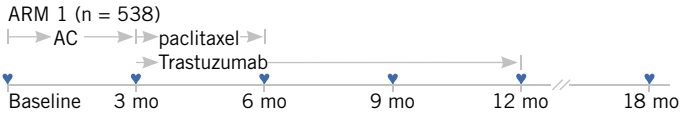
relates to a longer period of time from when the anthracycline is given to the beginning of trastuzumab. There was also the suggestion of less cardiac toxicity in the HERA trial, where chemotherapy and trastuzumab were not concurrent (Piccart-Gebhart 2005).

In the NSABP analysis, there was the suggestion that cardiac toxicity was more of a problem in older women, specifically in women who had borderline ejection fractions at baseline versus those who had better, stronger, higher ejection fractions. All of this needs to be sorted out.

DR LOVE: There were some cardiac safety data from the BCIRG trial presented by Dennis Slamon at ASCO. Can you talk about that?

DR WINER: In the BCIRG trial, in the group of women who received docetaxel, carboplatin and trastuzumab, the cardiac toxicity was substantially less than in women who received the anthracycline followed by docetaxel and trastuzumab. I think all of us are very hopeful that nonanthracycline-containing regimens will be the wave of the future, but we will just have to wait for the efficacy data. We need those data from the BCIRG trial, and I'm told that we will have those some time over the next several months — certainly at San Antonio, if not before.

2.6 2005 ASCO Adjuvant Trastuzumab Data — Assessment of Trastuzumab-Associated Cardiac Events: NSABP-B-31 Treatment and MUGA Schedule



Cardiac events (CE) 4.28%

Minus 0.78%

Cardiotoxicity uniquely attributable to trastuzumab (ARM 1 CE - ARM 2 CE)

= 3.5% CI, 1.6-5.3%

Protocol-defined acceptance of <4% congestive heart failure in anticipation of 25% reduction in death and reversible cardiac effects from trastuzumab; LVEF declines requiring cessation of trastuzumab were reversible in the vast majority of patients; therefore, trial accrual continued.

DERIVED FROM: Geyer CE Jr et al. Presentation. San Antonio Breast Cancer Symposium 2003;**Abstract 23**.

2.7 2005 ASCO Adjuvant Trastuzumab Data — Third Interim Cardiac Safety Analysis of N9831 Adjuvant Trastuzumab Trial

	Arm A [AC x 4 → T qwk]	Arm B [AC x 4 → T → H]	Arm C [AC x 4 → T + H → H]
Cardiovascular events, % (95% CI)*	0% (0.0-0.7%)	2.2% (1.1-3.8%)	3.3% (2.0-5.1%)

* Difference in incidence of cardiac events (CHF and cardiac deaths) between control arm (Arm A) and Arms B and C is <4%.

"Our cardiac monitoring plan included formal monthly review of left ventricular ejection fraction and clinical data, with the assistance of three cardiologists at Mayo and also, with the assistance of my colleague, Jim Ingle.

"Interim analyses were planned at 100, 300 and 500 patients per arm. These patients needed to have completed AC chemotherapy and had to be followed for at least six months after AC. So, that meant that these analyses were performed essentially with nine months of time from registration into the clinical study.

"So, what have we found so far? First, the difference in the incidence of cardiac events, defined as CHF and cardiac deaths, between the non-trastuzumab and trastuzumab arm is less than four percent…

"…as a brief summary, I can share with you that there have been zero events for the control arm, 2.2-percent events for the control versus sequential comparison, and 3.3-percent incidence for the control versus concurrent therapy with paclitaxel. Please note that the 95-percent confidence intervals for the analysis of control versus sequential and control versus concurrent overlap at this time."

SOURCE: Perez EA et al. Presentation. ASCO 2005;**Abstract 556**.

DR LOVE: What can we say about the effects of adjuvant trastuzumab in patients with node-negative tumors in terms of clinical practice at this point? How are you going to approach patients in your practice with HER2-positive, node-negative disease?

DR WINER: In the HERA study (Piccart-Gebhart 2005), they included patients with node-negative disease as long as their tumors were greater than a centimeter. A third of the patients participating were node-negative, but we don't know how many of the events occurred in those patients.

The NSABP trial had no patients with node-negative disease, and in the NCCTG study, patients with node-negative disease accounted for 14 percent of the total population but only six percent of the events (Romond 2005).

I think it's unlikely that the relative benefits of trastuzumab will be different in patients with node-negative versus node-positive disease. On the other hand, the absolute benefit will differ, because patients with node-negative disease, particularly with small tumors, have a lower risk of recurrence.

In my mind, it's reasonable to consider trastuzumab for patients who were eligible for the studies. The group of women that I'm a little more cautious about are those with relatively small, ER-positive, node-negative breast cancer. I realize that in the HERA study, a woman with a one- to two-centimeter, ER-positive, node-negative cancer could have been included, but I don't think we have a sense as to the benefit of trastuzumab in that patient.

I'm not entirely clear what that woman's risk of disease recurrence would be, particularly with modern hormonal therapy. I'm not saying that woman shouldn't receive trastuzumab, but I would say that we have to be a little more cautious when we're talking about the lower-risk patients, since they are at equal risk as the higher-risk patients to experience toxicities. ■

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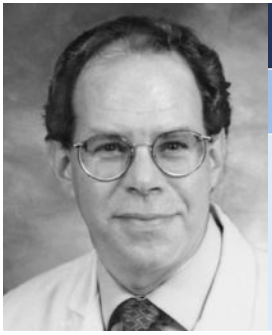


INTERVIEW

Harry D Bear, MD, PhD

Dr Bear is Chairman of the Division of Surgical Oncology, Professor of Surgery and Microbiology and Immunology and Walter Lawrence Jr Distinguished Professor in Oncology at Virginia Commonwealth University School of Medicine's Massey Cancer Center in Richmond, Virginia.

Tracks 1-13

Select Excerpts from the Interview*

Track 2

DR LOVE: Can you summarize the updated NSABP trial B-27 data?

DR BEAR: Although the numbers are low, the addition of docetaxel, preoperatively, in NSABP-B-27 doubled the pathologic complete response rate from 13 percent to 26 percent. In 2004, we presented the overall and disease-free survival data at San Antonio (Bear 2004).

The overall survival did not show any significant difference among the groups or between each of the docetaxel groups and AC alone. There was a trend towards improved disease-free survival with the addition of docetaxel, particularly when given preoperatively. When we examined relapse-free survival, which was similar to the definition of disease-free survival in the CALGB trial

* *Conducted on December 10, 2004*

9344 (Henderson 2003), we saw a significant improvement with the addition of preoperative docetaxel compared to AC alone.

The difference between the relapse-free survival result and the disease-free survival result was probably caused by a chance event, which was an increase in the number of second malignancies at other sites and in the contralateral breast in some of the patients who received docetaxel. Since that's included in disease-free survival, it sort of wipes out the beneficial effect. Most of the relapse-free survival benefit was caused by a reduction in local recurrences. We have not yet seen any difference in distant disease-free survival, which, in terms of patient survival, is probably the most important outcome.

DR LOVE: What's your interpretation of these data?

DR BEAR: I believe it relates to a number of factors, some of which are biological. The Skipper hypothesis is that metastatic clones of tumor cells behave differently from the primary tumor. We thought we had disproven that in the NSABP-B-18 trial (Fisher 1998), but it may be true in some patients, so that a patient who has a good response in the breast may not necessarily have a good response in the metastatic disease sites.

Probably the most important reason is a statistical issue.

One of the other major factors is that this group of patients, as compared to the CALGB-9344 (Henderson 2003) or NSABP-B-28 (Mamounas 2005) trials, is probably diluted by some better-risk patients. In those trials, all the patients had known positive nodes, whereas in B-27, the patients' nodal status is unknown and certainly included a number of ER-positive, node-negative patients whose benefit from any chemotherapy is probably fairly small.

If you look at the actual magnitude of the effect in terms of hazard ratios, it's really quite similar to CALGB-9344 or NSABP-B-28 with the addition of paclitaxel, so I think it's largely a sample size issue, as well as some potential biostatistical parameters that neutralized any effect on survival.

Track 7

DR LOVE: What's going on with NSABP-B-35, the trial in DCIS?

DR BEAR: That is a very interesting trial, and it's continuing to accrue very well. That study is examining what kind of an anti-estrogen should be given to patients with ER-positive DCIS. All the patients have been treated for DCIS with a lumpectomy and radiation therapy, and they are then randomly assigned to tamoxifen or anastrozole.

DR LOVE: What's been your experience in terms of tolerance of the aromatase inhibitors and anastrozole, as compared to tamoxifen?

DR BEAR: For the most part, they're very well tolerated. Patients seem to do quite well with anastrozole, and I think it's somewhat less of a problem with hot flashes and other side effects, compared to tamoxifen (3.1). However, aromatase inhibitors are certainly not trouble free.

DR LOVE: What's your take on the ATAC data (Howell 2005) and some of the other data that have been coming out in terms of switching aromatase inhibitors (Boccardo 2005; Coombes 2004; Goss 2003; Jakesz 2005a, b)?

DR BEAR: I believe it'll probably precipitate a fairly wholesale change in the primary treatment of ER-positive postmenopausal breast cancer patients. It clearly is the end of five years of tamoxifen as a standard treatment; I don't think we'll see that anymore.

3.1 **ATAC Trial 68-Month Analysis: Adverse Events***

	Anastrozole (%)	Tamoxifen (%)	Odds ratio† (anastrozole vs tamoxifen)	*p*-value
Drug-related AE	60.9	68.4	—	<0.0001
Drug-related SAE	4.7	9.0	—	<0.0001
AE leading to withdrawal	11.1	14.3	—	0.0002
Hot flashes	35.7	40.9	0.80	<0.0001
Vaginal bleeding	5.4	10.2	0.50	<0.0001
Vaginal discharge	3.5	13.2	0.24	<0.0001
Endometrial cancer	0.2	0.8	0.29	0.02
Hysterectomy	1.3	5.1	—	<0.0001
Ischemic cerebrovascular events	2.0	2.8	0.70	0.03
Venous thromboembolic events	2.8	4.5	0.61	0.0004
Joint symptoms/arthralgia	35.6	29.4	1.32	<0.0001
Fractures†	11.0	7.7	1.49	<0.0001

AE = adverse events; SAE = serious adverse events
Values <1 are in favor of anastrozole.
* Adverse events on treatment or within 14 days of discontinuation
† Fractures occurring before recurrence (includes patients no longer on treatment)

SOURCES: Howell A et al; ATAC Trialists' Group. *Lancet* 2005;365(9453):60–2. **Abstract**; Howell A, on behalf of the ATAC Trialists' Group. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 1**.

Track 8

DR LOVE: What's the status of the NSABP sentinel lymph node trial — B-32?

DR BEAR: Dr Julian presented the initial results from that trial at San Antonio in 2004, which consisted of the pathologic data and accuracy data for the half of the trial that received a sentinel node biopsy plus an axillary node dissection (Julian 2004). This was a trial of 5,600 patients randomly assigned to sentinel node biopsy with or without an axillary node dissection.

The false-negative rate in that trial was 9.5 percent, which some people thought was higher than expected, but it's right in line with other multicenter validation trials. There are individual institutional trials with much lower rates done by a few surgeons. Immunohistochemistry examination of the sentinel nodes was done as part of the trial, but it was done centrally, and it was blinded, so we don't know the results of those.

DR LOVE: What is the current role of sentinel node biopsy in the clinical setting?

DR BEAR: I think it probably should be the standard of care for most patients who don't have a specific contraindication to it. It has been in my practice since the completion of the trial. That's what I offer most patients with invasive breast cancer.

DR LOVE: Does the false-negative rate of 9.5 percent concern you?

DR BEAR: It doesn't really concern me. I feel pretty confident in the technique. We've been doing it a long time, and I've seen very few, if any, axillary recurrences that were unexpected, and that's probably the most significant thing that could happen. Obviously, the main answer to that question really is going to have to come from the long-term follow-up of the B-32 trial.

Track 9

DR LOVE: Can you discuss the development and validation of the Onco*type* DX assay?

DR BEAR: This is an exciting era in the management of breast cancer. Soonmyung Paik and the NSABP have developed Onco*type* DX, a genomic assay that reliably evaluates gene expression in paraffin-fixed tumor tissue. They obtained tumor tissue from a large number of the patients participating in the NSABP-B-14 trial and, using the assay, established a panel of 21 genes that were accurate at predicting the risk of recurrence among patients who were randomly assigned to either tamoxifen or placebo (Paik 2004a).

The panel of 21 genes as a predictor of recurrence — called the risk score — was validated in the NSABP-B-20 trial. In B-20, patients with node-negative, ER-positive disease were randomly assigned to tamoxifen alone or tamoxifen plus chemotherapy. In that group of patients, not only did the risk score estimate the risk of recurrence, it also significantly predicted whether or not patients would receive any benefit from adding chemotherapy to tamoxifen. Only the patients in the high-risk group — not the low- or intermediate-risk group — showed significant benefit from adding chemotherapy to tamoxifen (Paik 2004b).

A lot of unanswered questions remain, including patients with node-positive disease who are already at higher risk, a priori. Additionally, does this assay

apply to other types of patients? That is one of the things we're going to assess in the neoadjuvant setting in the NSABP-B-40 study.

DR LOVE: Are the patients in the NSABP-B-40 neoadjuvant trial going to be evaluated with a genomic assay?

DR BEAR: In the B-40 trial, core biopsies will be taken and retrieved for the purpose of gene expression analysis. We will be able to look at that panel of 21 genes as one of the ways to assess gene expression, which is a critical part of the study. ■

SELECT PUBLICATIONS

Bear HD et al. **A randomized trial comparing preoperative (preop) doxorubicin/cyclophosphamide (AC) to preop AC followed by preop docetaxel (T) and to preop AC followed by postoperative (postop) T in patients (pts) with operable carcinoma of the breast: Results of NSABP B-27.** San Antonio Breast Cancer Symposium 2004;**Abstract 26**.

Boccardo F et al. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole trial.** *J Clin Oncol* 2005;23(22):5138-47. **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**

Fisher B et al. **Effect of preoperative chemotherapy on the outcome of women with operable breast cancer.** *J Clin Oncol* 1998;16(8):2672-85. **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**

Henderson IC et al. **Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.** *J Clin Oncol* 2003;21(6):976-83. **Abstract**

Howell A et al. **Results of the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. **Abstract**

Jakesz R et al; ABCSG and the GABG. **Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a).** *Proc ASCO* 2005a;**Abstract 527**.

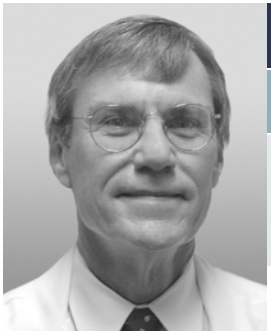
Jakesz R et al. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005b;366(9484):455-62. **Abstract**

Julian TB et al. **Preliminary technical results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer patients.** San Antonio Breast Cancer Symposium 2004;**Abstract 14**.

Mamounas EP et al. **Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28.** *J Clin Oncol* 2005;23(16):3686-96. **Abstract**

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004a;351:2817-26. **Abstract**

Paik S et al. **Expression of 21 genes in the recurrence score assay and prediction of clinical benefit from tamoxifen in NSABP study B-20.** Presentation. San Antonio Breast Cancer Symposium 2004b;**Abstract 24**.



PRESENTATION

Rowan T Chlebowski, MD, PhD

Dr Chlebowski is a Professor of Medicine at UCLA School of Medicine and Chief of Medical Oncology at Harbor-UCLA Medical Center in Torrance, California.

- **Update of the Women's Intervention Nutrition Study (WINS) trial**
- **Overview of Adjuvant Hormonal Therapy Trials: Comparing and Sequencing Tamoxifen with Aromatase Inhibitors***

Slide 1

I am going to talk a little about the WINS trial that was reported at ASCO in a plenary session. Women in this study were 48 to 79 years of age, mostly postmenopausal with early-stage breast cancer, Stage I to IIIA, and had received primary surgery, radiation therapy and conventional systemic therapy. Patients with receptor-positive tumors received tamoxifen, while those with receptor-negative tumors received chemotherapy — half anthracycline based and half nonanthracycline based. The women on tamoxifen could have elected to receive chemotherapy as well. The patients were randomized 60:40, with fewer to the dietary intervention group, so we would have more resources to allocate to the dietary intervention group or control.

1

WINS: Trial Design

Eligibility
- Women 48-79 yrs
- Early breast cancer
- Primary surgery +/- RTx
- Systemic therapy*
- Dietary fat intake ≥ 20% of calories

Recruitment 1994-2001, median follow-up 60 months

Randomization 60:40 within 365 days from 1° surgery n = 2437

R

- Dietary intervention (n = 975) to reduce fat intake maintaining nutritional adequacy
- Control (n = 1462)

* Tamoxifen required, chemoRx optional for ER+; chemoRx required for ER-.

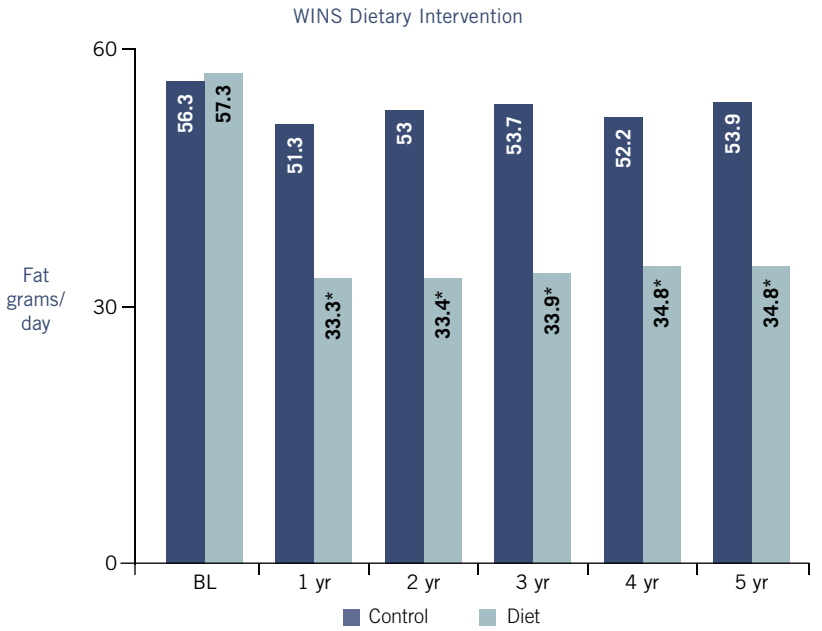
Strata = nodal status; systemic Rx; sentinel node

SOURCE: Chlebowski RT et al. Presentation. ASCO 2005;**Abstract 10**.

* *Presented at Research To Practice* Breast Cancer Update *CME Forum, Los Angeles, California, May 21, 2005. The enclosed graphics from the presentation are included in the PowerPoint files on CD 3. Please see page 1 for additional instructions.*

2

Fat Gram Intake by Group



- Diet group: Given fat gram goal by centrally trained, registered dieticians implementing a low-fat eating plan [1, 2]
- Eight biweekly individual sessions then every three month contact
- Monthly group sessions
- Self-monitoring of fat gram intake
- Control group: Women had dietician contacts every three months

* Significantly different by t-test from control and baseline, $p<0.0001$

[1] Chlebowski, Rose, Buzzard, et al *Breast Cancer Res Treat* 20:73-84, 1992
[2] Winters, Mitchell, Smiciklas-Wright, et al *J Am Diet Assoc* 104:551-9, 2004

SOURCE: Chlebowski RT et al. Presentation. ASCO 2005;**Abstract 10**.

Slide 2

Randomization took place about 220 days after initial surgery, so patients were entered after they completed their primary therapy, while they were receiving hormonal therapy. The dietary intervention was done at 37 centers around the United States.

The diet group was given a dietary fat gram goal by centrally trained, registered dieticians, implementing a predefined low-fat eating plan. The dieticians

were trained in behavioral intervention techniques. Patients received eight biweekly individual counseling sessions then one session every three months. There was no counseling towards weight reduction.

This was more of a switching trial than a weight-reduction trial. There were monthly group sessions, and patients self-monitored their fat intake. We captured information about their diet with telephone re-calls. The control group saw the dieticians every three months and talked about nutritional adequacy.

Fat gram intake for this group went from about 56 to 33 fat grams per day — about a 40 percent reduction in daily fat gram intake — which was sustained by most of the individuals.

There was a four-pound weight loss, which wasn't much but still was three standard deviations different. The weight loss at least signals that some dietary change had occurred.

3

WINS Relapse-Free Survival by Treatment Group

Groups	Diet (events/n)	Control (events/n)	HR (95% CI)	*p*-value*
All patients	96/975	181/1462	0.76 (0.60-0.98)	0.034
ER-positive	68/770	122/1189	0.85 (0.63-1.14)	0.277
ER-negative	28/205	59/273	0.58 (0.37-0.91)	0.018

* All *p*-values from adjusted Cox proportional hazards model. Consideration of disease-free survival as endpoint (adding other cancers and all deaths) including 389 events had similar outcome (adjusted Cox HR 0.81, 95% CI 0.65-0.99, p=0.042 favoring dietary intervention).

SOURCE: Chlebowski RT et al. Presentation. ASCO 2005. **Abstract 10**.

Slide 3

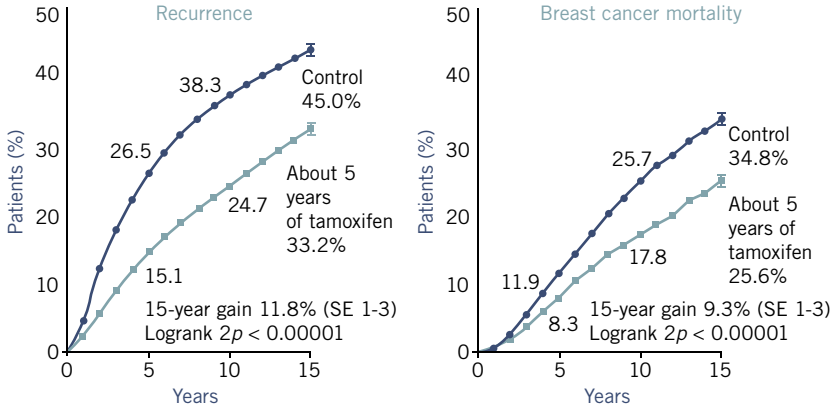
Here is our primary study endpoint of WINS relapse-free survival. This is an interim result, as the follow-up is continuing. As you can see, the hazard ratio was 0.76 with a *p*-value of 0.034 for Cox proportional hazard, and there was a three percent difference at five years.

We did a subgroup analysis by receptor status. The hazard ratio for relapse-free survival for patients with estrogen receptor-positive tumors was 0.85 and not significant. In the 478 patients with ER-negative disease, there was a hazard ratio of 0.58, with a 42 percent reduction in risk and eight percent absolute difference at five years. This is hypothesis generating but very intriguing to us, as the curves just break apart initially.

• Overview of Adjuvant Hormonal Therapy Trials: Comparing and Sequencing Tamoxifen with Aromatase Inhibitors

4

Early Stage Breast Cancer
Tamoxifen: About Five Years versus Not



ER-positive or Unknown

SOURCE: Reproduced from *The Lancet*, Vol 365, Early Breast Cancer Trialists' Collaborative Group. **Effects of chemotherapy and hormonal therapy for early breast cancer recurrence and 15-year survival: An overview of the randomised trials**, 1687-717, 2005, with permission from Elsevier. **Abstract**

Slide 4

These are data from the Early Breast Cancer Trialists' Collaborative Group, which is now published and available online. You can see that there was a 14 or 15 percent reduction in recurrence risk with tamoxifen. To the right, this is mortality risk going forward. That is why tamoxifen has been the standard therapy for all these years.

5

Tamoxifen

- Adjuvant efficacy well established
- Life-threatening side effects of tamoxifen
  - Endometrial cancer
  - Pulmonary emboli (venous vascular events)
  - Stroke (arterial vascular events)
- Side effect profile established after 20 years of trials, but it took 15 years of trials to identify a breast cancer benefit
- With large trials, side effect profile should be more easily established

Slide 5

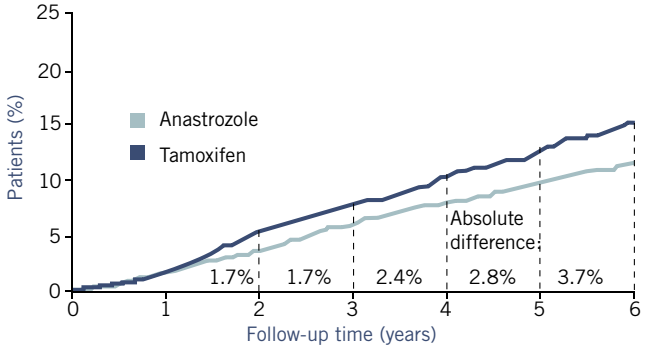
We also know that there are life-threatening toxicities for tamoxifen — endometrial cancer, pulmonary embolus, stroke. It took us 20 years to figure out that tamoxifen had an endometrial cancer risk. But we also should say that if we did 32 trials of tamoxifen versus nothing, it still took us 15 years to

figure out that tamoxifen worked. So I think that if a trial has 3,000 or 4,000 patients in each arm, we'll get to a toxicity issue sooner.

6

ATAC: Time to Recurrence Curves Shown for HR+ Patients

	A	T	HR	95% CI	*p*-value
HR+	282	370	0.74	(0.64-0.87)	0.0002
ITT	402	498	0.79	(0.70-0.90)	0.0005



At risk:							
Anastrozole	2618	2540	2448	2355	2268	2014	830
Tamoxifen	2598	2516	2398	2304	2189	1932	774

SOURCE: With permission from Howell A. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 1**.

Slide 6

You've seen this before; the only point I want to make about the ATAC data is that they're at 68 months. That means that almost a year of follow-up has occurred for people who have stopped their aromatase inhibitors.

So when we look at the toxicity of the ATAC trial, this is what it will be. There aren't any studies for more than five years of aromatase inhibitors. People say, "I'm worried about long-term use of aromatase inhibitors." Well, this should be the toxicity that you're going to see, because it's five years of toxicity.

Slide 7

These are the updated data on side effects. At the 68-month follow-up, half the patients have been off therapy for nearly a year, and we saw the expected reduction in all three life-threatening toxicities of endometrial cancer, stroke and venous thromboembolic disease. You can see all of them were significant.

7 **Anastrozole vs Tamoxifen in ATAC: Side Effects at 68-Month Follow-Up**

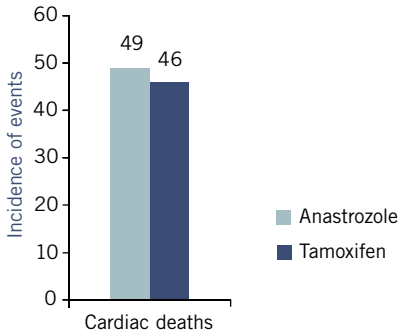
	A	T	*p*-value
Hot flashes	35.7	40.9	<0.0001
Vaginal bleeding	5.4	10.2	<0.0001
Vaginal discharge	3.5	13.2	<0.0001
Endometrial cancer	0.2	0.8	0.02
Ischemic cerebrovascular	2.0	2.8	0.03
Venous thromboembolic	2.8	4.5	0.0004
Joint symptoms	35.6	29.4	<0.0001
Fractures	11.0	7.7	<0.0001
Hysterectomy	1.3	5.1	<0.0001

SOURCES: Howell A. *Lancet* 2005;365(9453):60-2. **Abstract**; Howell A. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 1**.

Slide 8

There are 3,000 patients in each arm. Cardiac deaths were 49 versus 46 — so there wasn't much of a signal for myocardial infarction issues with anastrozole — at least with the data from the 68-month follow-up from the ATAC trial.

8 **Anastrozole vs Tamoxifen: Cardiac Death in ATAC**



SOURCE: Howell A. *Lancet* 2005;365(9466):1225-6. No abstract available

Slide 9

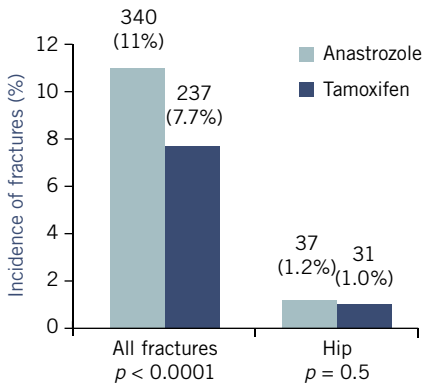
The other point I want to make is that many oncologists have a lot of concern regarding bones. I think it's going to be not only a preventable, treatable situation but also something that is likely to go away completely in the near future. There is no difference in hip fractures after 68 months with anastrozole and tamoxifen. You can see that hip fracture is one percent — a tenth of a percent per year. This is for a group of patients who had no prescreening when they entered the study and no ongoing protocol-defined follow-up for bone. These are high numbers. If you're going to actually do any screening, any treating, you're going to have lower numbers than that. The hip fractures are the ones that are associated with a survival detriment.

Slide 10

Here are the fracture rates from the update of the ATAC data presented by Tony Howell. You can see that at the five-and-a-half-year point, the fracture rates look like they're converging. For hormonal therapy, we know that when you stop estrogen/progestin or estrogen alone, bone loss is accelerated. It's two to three times the rate of loss in normal menopause. Will we get accelerated bone recovery when we add back the hormones? We'll know that soon from the bone density studies that are ongoing. There may not be long-term consequences of five years of aromatase inhibition.

9

Anastrozole vs Tamoxifen: Hip Fracture



Numbers refer to one or more fractures occurring at any time before recurrence (includes patients no longer receiving treatment)

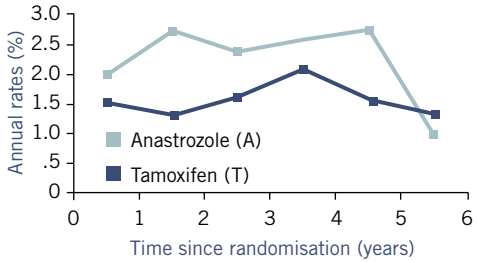
SOURCE: ATAC Trialists' Group. *Lancet* 2005;365:60-2. **Abstract**

Slide 11

The other issue is cognition. A few years ago, we thought that preclinical observational studies suggested that exogenous estrogens and lowering of progestins would be important in maintaining cognition. There were trials started in patients with dementia. The Women's Health Initiative studies that I've been involved with have totally changed that concept.

10

The Long-Term Fracture Risk with Anastrozole Is Predictable and Manageable



SOURCE: With permission from Howell A. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 1**.

In two randomized, placebo-controlled clinical trials, 16,000 otherwise healthy women received estrogen plus progestin therapy for five years, and the dementia was only two and a half years, but there was a 40 percent increase in stroke and doubling of dementia risk in a subset of patients 65 years of age or older who received estrogen/progestin versus placebo for just two and a half years. In the estrogen-alone trial, there was a 40 percent increase in stroke and a 50 percent increase in dementia. A preplanned combined analysis had

a statistically significant 76 percent increase in dementia. So the old idea is that exogenous estrogens maintain cognition. The new concept is that anything that causes arterial vascular events — like estrogen, estrogen plus progestin, maybe tamoxifen — will be likely to increase not only stroke but also decrease brain function and increase the risk of dementia. We don't know what aromatase inhibitors will do to cognition, but the testing has to be two tailed, because one could equally say that it might have favorable impacts on cognition.

Slide 12

The BIG 1-98 study is our only switching study. We probably won't get results from it for several years, and they may not be definitive. These are big studies, with 8,000 patients, but the switching parts — tamoxifen/letrozole, letrozole/tamoxifen — are half that size. There are 1,250 patients in each of those arms, numbers that would be small for switching.

Slide 13

Here are data similar to the ATAC data — 13.6 percent rate of relapse with tamoxifen versus 10.2 percent with letrozole — about the same difference after this relatively short period of follow-up.

11

Hormones, AI and Cognition

Preclinical and observational studies suggest exogenous estrogen (E) may support cognition in postmenopausal women

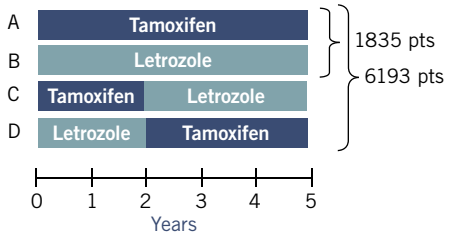
In two randomized, placebo-controlled clinical trials with 27,112 women, E plus progestin or E alone increased dementia and stroke risk

	Stroke	Dementia
E+P	1.41 (1.07-1.85)	2.05 (1.21-3.48)
E Alone	1.39 (0.10-1.77)	1.49 (0.83-2.66)
Combined Trials		1.76 (1.19-2.60)

SOURCES: Shumaker SA et al. *JAMA* 2004;291(24):2947-58. **Abstract**; Anderson GL et al. *JAMA* 2004;291(14):1701-12. **Abstract**; Shumaker SA et al. *JAMA* 2003;289(20):2651-62. **Abstract**; Rossouw JE et al. *JAMA* 2002;288(3):321-33. **Abstract**

12

BIG 1-98: Study Design



SOURCE: Thürlimann B for the BIG 1-98 Collaborative Group. Presentation. St Gallen Conference 2005. **Abstract**

13

BIG 1-98: Breast Cancer Events

	Breast Cancer Events		
Years from randomization	Tamoxifen	Letrozole	*p*-value
3	8.1%	6.2%	
5	13.6%	10.2%	0.0002

SOURCE: Thürlimann B for the BIG 1-98 Collaborative Group. Presentation. ASCO 2005;**Abstract 511**.

Slide 14

Here are the data for deaths, cardiac — 26 with letrozole versus 13 with tamoxifen. You didn't see anything at all like this in the MA17 trial, comparing letrozole versus placebo after tamoxifen — there was absolutely no signal of cardiac issue there.

It was alluded to that the population is different, but it actually isn't that different. It is 15 percent Eastern European. Almost all the rest, 85 percent, is Western European, but there is no US, and the UK is under-represented compared to the other trials.

The population is mostly Western European, so there was no great explanation for that difference.

14

BIG 1-98: Deaths without Recurrence (DWR)

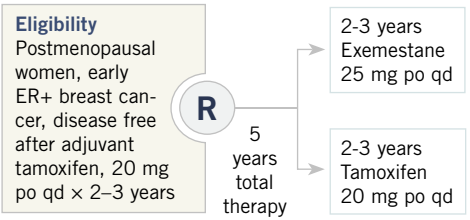
	Letrozole	Tamoxifen
Patients	4003	4007
Total deaths	166	192
Total DWR	55	38
– Cerebrovascular	7	1
– Thromboembolic	3	2
– Cardiac	26	13
– Other	19	22
	* $p = 0.08$	

* Overall *p*-value based on cumulative incidence

SOURCE: Thürlimann B for the BIG 1-98 Collaborative Group. Presentation. St Gallen Conference 2005. **Abstract**

15

IES Schema



SOURCE: Coombes RC et al. *N Engl J Med* 2004;350(11):1081-92. **Abstract**

Slide 15

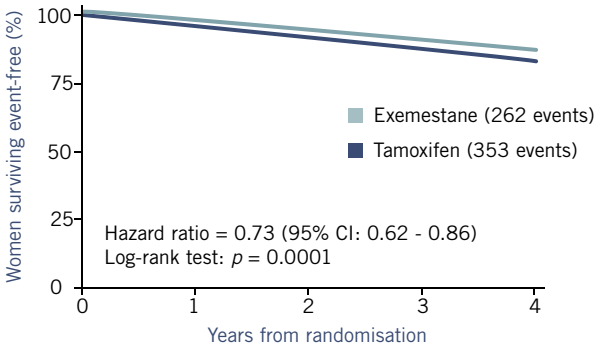
Now we'll go to the switching trials. This is the IES trial, which is exemestane versus tamoxifen after two to three years of tamoxifen.

Slide 16

You can see with this recent update that there was a 27 percent reduction in recurrence risk. And there was a trend towards a survival benefit, which we didn't see in the ATAC trial. We'll get into that later in terms of what that would mean when you're switching in the middle and randomizing in the middle versus randomizing at the start. So there was a 20 to 27 percent reduction in risk of recurrence and a trend toward survival — but there were more myocardial infarctions on exemestane.

16

IES: Disease-Free Survival



No. events/at risk					
Exemestane	0/2352	57/2233	65/2081	75/1413	41+24†/661
Tamoxifen	0/2372	82/2243	105/2062	96/1359	47+23†/650

† Events occurring more than 4 years after randomisation

SOURCE: With permission from Coombes RC. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 3**.

Slide 17

These were small numbers — 20 with exemestane versus eight with tamoxifen. Also, there were more vascular deaths — 15 versus seven. Is this a signal?

There is much interest in this area. As the bone health goes away, this surfaces— but you could say these are very small numbers, with these relatively small differences, when you're in trials involving thousands of patients.

17

Cardiovascular Effects in IES

- More myocardial infarctions on exemestane compared to tamoxifen
  - All patients (20 vs 8, $p = 0.023$)
  - On treatment (14 vs 7, $p = 0.126$)
- More vascular deaths on exemestane compared to tamoxifen
  - Vascular deaths (15 vs 7)

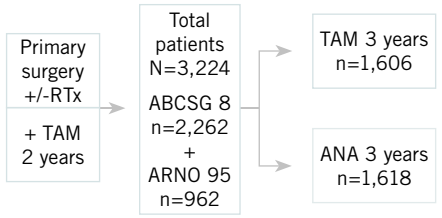
SOURCE: Coombes RC et al. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 3**.

Slide 18

The Austrian Breast Cancer Study Group 8 and ARNO combined trials with women on two years of tamoxifen. These were all postmenopausal women with early-stage breast cancer, almost all receptor-positive, who were randomly assigned to tamoxifen or anastrozole.

18

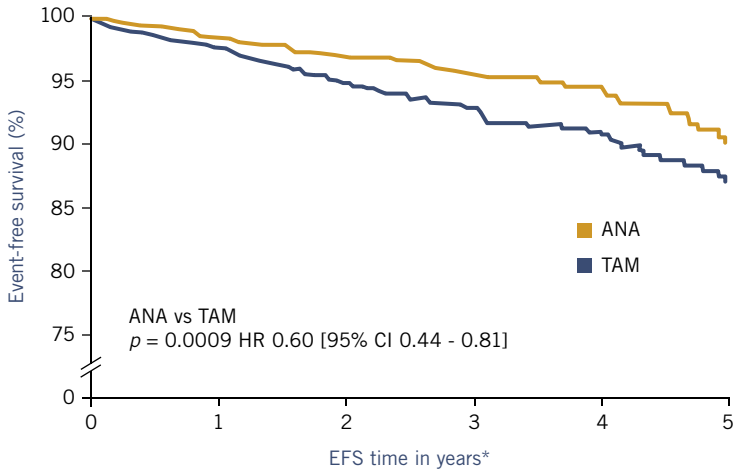
ABCSG 8/ARNO 95
Combined Analysis Trial Structure



SOURCE: Jakesz R et al. *Lancet* 2005;366(9484):455-62. **Abstract**

19

Event-Free Survival



At risk:

TAM	1606	1217	858	593	343	176
ANA	1618	1243	874	623	375	178

* Zero point = 2 years after surgery

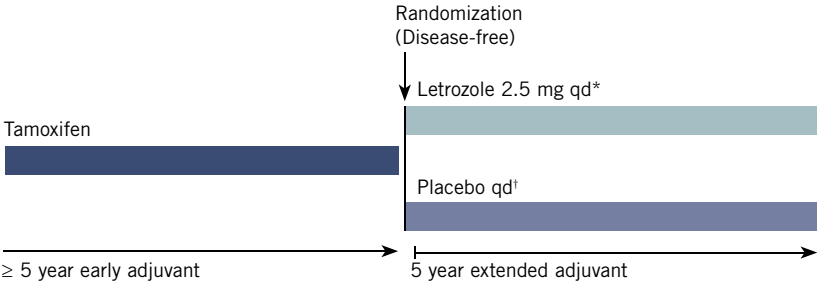
SOURCE: With permission from Jakesz R et al. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 2**.

Slide 19

With that switching in the middle, at four standard deviations, there was a 40 percent reduction in recurrence risk. This trial of switching in the middle also showed a trend towards a survival difference.

20

MA-17: Trial Design



Primary end point: DFS
Secondary end points: OS/safety/QOL
* n = 2575 (efficacy); 2154 (safety) in the letrozole arm.
† n = 2582 (efficacy); 2145 (safety) in the placebo arm.

SOURCE: Goss PE et al. *N Engl J Med* 2003;349(19):1793-802. **Abstract**

Slide 20

There was a 42 percent reduction in risk of recurrence in the MA17 trial, with switching at the end.

Slide 21

Look at the toxicity data. For cardiovascular events, it's six percent with letrozole versus six percent with placebo — no difference. Hypercholesterolemia: 16 percent versus 16 percent — no difference. What we have at the end is this interesting dichotomy between the BIG FEMTA trial with Western European patients, with randomization at first, and the MA17 trial with Western European, US and UK patients having no difference. That is an issue that has not been completely addressed.

21

MA-17: Incidence of Adverse Events (All Grades)

	Percent of patients		
	Letrozole	Placebo	*p*-value
Hot flashes	58	54	0.003
Arthritis/arthralgia	25	21	<0.0001
Muscle pain	15	12	0.04
Vaginal bleeding	6	8	0.005
Hyper cholesterolemia	16	16	0.79
Cardiovascular events	6	6	0.76
Osteoporosis	8	6	0.003
Discontinuations due to adverse events	5	4	0.02
Discontinuations for other reasons	4	5	0.1

90% of AEs Grade 1 or 2.

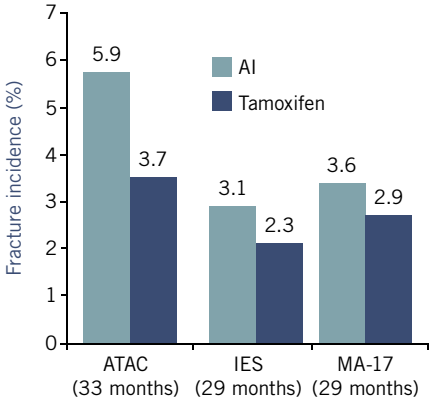
SOURCE: Goss PE et al. Presentation. ASCO 2004;**Abstract 847**.

Slide 22

I think the bone health issue is going away. At 33 months, you can see numerically more fractures on ATAC, IES and MA17, but for all these trials there was no prescreening or ongoing therapy for bones. One can calculate that 70 percent of these fractures occurred in women who had preexisting osteoporosis when they entered the trial. You should never get these numbers if you're doing screening and intervention.

22

Fractures in Aromatase Inhibitor Adjuvant Trials



AI = aromatase inhibitor; ATAC = Arimidex (anastrozole), Tamoxifen, Alone or in Combination; IES = Intergroup Exemestane Study; MA-17 = Extended Adjuvant Treatment with Letrozole Trial.

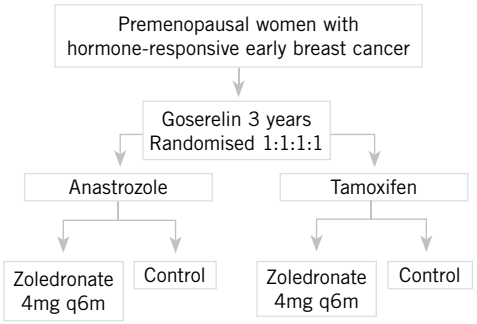
SOURCES: The ATAC Trialists' Group. *Lancet* 2002;359(9324):2131-9. **Abstract**; Coombes RC et al. *N Engl J Med* 2004;350(11):1081-92. **Abstract**; Goss PE et al. *N Engl J Med* 2003;349(19):1793-802. **Abstract**

Slide 23

Just to show you that bisphosphonates work — this is ABCSG 12. Interestingly, they take premenopausal women with receptor-positive disease, make them postmenopausal with goserelin acetate and then give them anastrozole versus tamoxifen. So these women are made postmenopausal very suddenly.

23

ABCSG* 12



* Austrian Breast Cancer Study Group

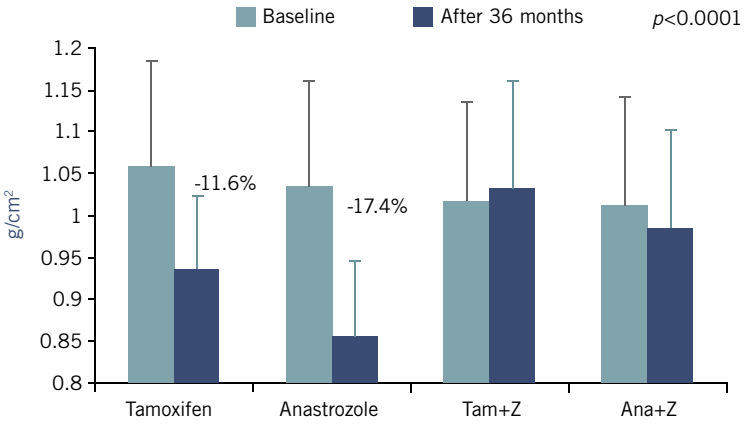
SOURCE: Gnant M et al. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 6**.

Slide 24

What happens when you give them either zoledronic acid or not? If you don't give them zoledronic acid, you can see that tamoxifen wasn't able to fully prevent this rapid loss of bone. There was more loss with anastrozole, which was completely abrogated by zoledronic acid. Four milligrams of zoledronic acid every six months completely abrogated bone loss. The Z-FAST trial had about the same results.

24

ABCSG-12 Trial: Lumbar Spine BMD



SOURCE: With permission from Gnant M et al. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 6**.

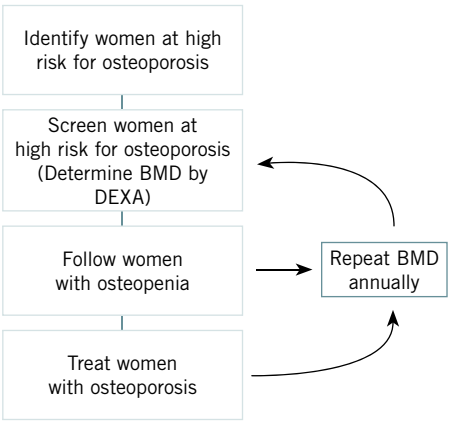
Slide 25

The ASCO bone health guideline, which I helped write, was published in 2003. We're in the process of updating it now, saying that every woman should obtain a bone mineral density reading; that we should follow or treat osteopenia as an option, treat women with osteoporosis and repeat bone mineral density tests annually.

We think that probably only about 20 percent of women then would need a bisphosphonate while on aromatase inhibitors, but we'll have to see if that's the case or not.

25

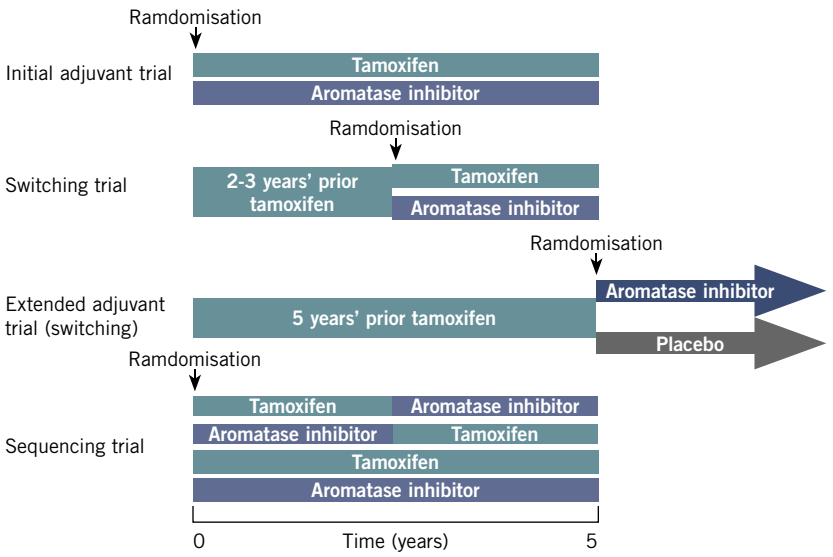
ASCO Bone Health Guideline Strategy for Osteoporosis/Fracture Prevention in Breast Cancer Patients



ASCO = American Society of Clinical Oncologists; BMD = bone mineral density; DEXA = dual energy X-ray absorptiometry.
Hillner, Ingle, Chlebowski et al. *J Clin Oncol* 2003;21:4042-4057.

26

Adjuvant Trial Designs



SOURCE: Cuzick J et al. Presentation. ASCO 2005;**Abstract 658**.

Slide 26

We're going to finish by looking at the difference in these study designs. With the ATAC and BIG FEMTA trials of tamoxifen versus aromatase inhibitors, note that the randomization is at the start. With the switching trials, randomization is after two or three years. That means the women who progressed in the first two years, who had life-threatening toxicity of any kind, who had a myocardial infarction or couldn't take the pills aren't here. So we don't know what the results would be if they randomized at the start. The only true sequencing trial we have is BIG FEMTA, and its results are two or three years away. You can see that the extended adjuvant trial is very much like a switching trial, because you're giving this and then the randomization occurs. Women who relapse on tamoxifen, et cetera, won't be around for the second randomization.

Slide 27

This effect has been alluded to in models. The problem that I have with the models in terms of trying to figure out what's going on is they all assume they know what's going to happen if you would have done the randomization at first versus the randomization in the middle. I don't think you can take those numbers in the middle and tack them onto a model, because you just don't

know what happened in the middle. The models are interesting, but not very informative.

Slide 28

In conclusion, these are the rationales for using AIs: Efficacy against early recurrence peaks, side effects defined in five years. If you're worried about the long-term effects of an aromatase inhibitor, I think we've seen them, unless you want to come up with a hypothesis of why, after estrogen comes back, you expect to see further side effects.

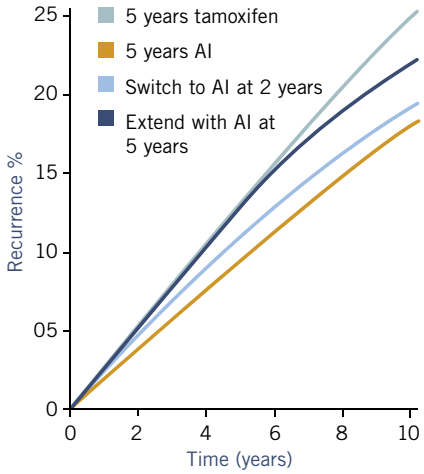
The side-effect profile is favorable versus tamoxifen for endometrial cancer, stroke and PE. Bone loss is preventable and treatable.

These are the rationales for using tamoxifen: Long experience with its use, concern over side effects with bone and coronary heart disease with aromatase inhibitors, no survival difference in these studies and cost associated with recurrence.

In the model analyses, all the models say they know what happens, and I don't think anybody does. Reasonable oncologists can disagree. ■

27

Cuzick's Model of AI/Tamoxifen Effect



Models (Cuzick or Burstein)

Both models involve assumptions that HR for AI after tamoxifen similar in sequencing and switching trials.

No data for this assumption at this time.

SOURCES: Cuzick J et al. Presentation. ASCO 2005;**Abstract 658**; Burstein H et al. Presentation. ASCO 2005;**Abstract 529**.

28

Conclusion

- Rationale for AI:
  - Efficacy against early recurrence peak
  - Side effects defined while on 5 years of AI (68 mos ATAC)
  - Side effect profile favorable vs tamoxifen (endometrial CA, stroke, PE)
  - Bone loss preventable/treatable (no hip Fx increase)
- Rationale for Tamoxifen:
  - Long experience with use
  - Concern over side effects (Bone, CHD?)
  - No survival difference
  - Cost
  - Model analyses

Reasonable oncologists can disagree

SELECT PUBLICATIONS

Anderson GL et al; Women's Health Initiative Steering Committee. **Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial.** *JAMA* 2004;291(14):1701-12. **Abstract**

Burstein HJ et al. **Optimizing endocrine therapy in postmenopausal women with early stage breast cancer: A decision analysis for biological subsets of tumors.** *Proc ASCO* 2005;**Abstract 529**.

Chlebowski RT et al. **Dietary fat reduction in postmenopausal women with primary breast cancer: Phase III Women's Intervention Nutrition Study (WINS).** *Proc ASCO* 2005;**Abstract 10**.

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**

Cuzick J, Howell A. **Optimal timing of the use of an aromatase inhibitor in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer.** *Proc ASCO* 2005;**Abstract 658**.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005;365(9472):1687-717. **Abstract**

Gnant M et al. **Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal breast cancer patients receiving adjuvant endocrine treatment with goserelin plus anastrozole versus goserelin plus tamoxifen — Bone density subprotocol results of a randomized multicenter trial (ABCSG-12).** San Antonio Breast Cancer Symposium 2004;**Abstract 6**.

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**

Howell A et al; ATAC Trialists' Group. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. **Abstract**

Jakesz R et al; ABCSG and the GABG. **Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: Combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial.** San Antonio Breast Cancer Symposium 2004;**Abstract 2**.

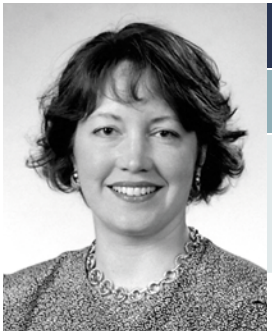
Jakesz R et al. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62. **Abstract**

Rossouw JE et al. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial.** *JAMA* 2002;288(3):321-33. **Abstract**

Shumaker SA et al; WHIMS Investigators. **Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial.** *JAMA* 2003;289(20):2651-62. **Abstract**

Shumaker SA et al. **Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study.** *JAMA* 2004;291(24):2947-58. **Abstract**

Thürlimann BJ et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;**Abstract 511**.



PRESENTATION

Kathy D Miller, MD

Dr Miller is the Sheila D Ward Scholar of Medicine and Associate Professor of Medicine in the Department of Hematology/Oncology at Indiana University School of Medicine in Indianapolis, Indiana.

- **For most patients with metastatic disease, is sequential single-agent chemotherapy more appropriate than combination chemotherapy?**
- **Is bevacizumab combined with paclitaxel or capecitabine generally the preferred first-line chemotherapy for patients with metastatic disease?***

On the question of the use of a sequential single agent over combination chemotherapy for most patients with metastatic disease, it will be no surprise to most of you that I would strongly agree.

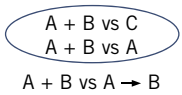
These are the reasons why I would agree that single-agent chemotherapy in a sequential fashion should be the preferred choice for the vast majority of our patients.

Slide 1

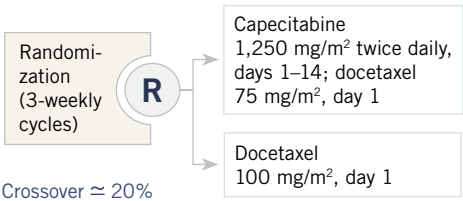
This question has been tackled in different ways. These three separate trial designs really don't ask the same question — they ask two different questions. These first two trial designs ask, Is a particular drug beneficial in breast cancer?

The third design, which includes a sequential strategy

1 Trial Designs



2 AB vs A: Docetaxel + Capecitabine (TX) vs Docetaxel (T)



Crossover ≃ 20%

Patients responding or with stable disease after six weeks of treatment continued until disease progression or unacceptable toxicity

SOURCE: O'Shaughnessy J et al. *J Clin Oncol* 2002;20(12):2812-23. Reproduced with permission from the American Society of Clinical Oncology. **Abstract**

* *Presented at Research To Practice* Breast Cancer Update *CME Forum, Los Angeles, California, May 21, 2005. The enclosed graphics from the presentation are included in the PowerPoint files on CD 3. Please see page 1 for additional instructions.*

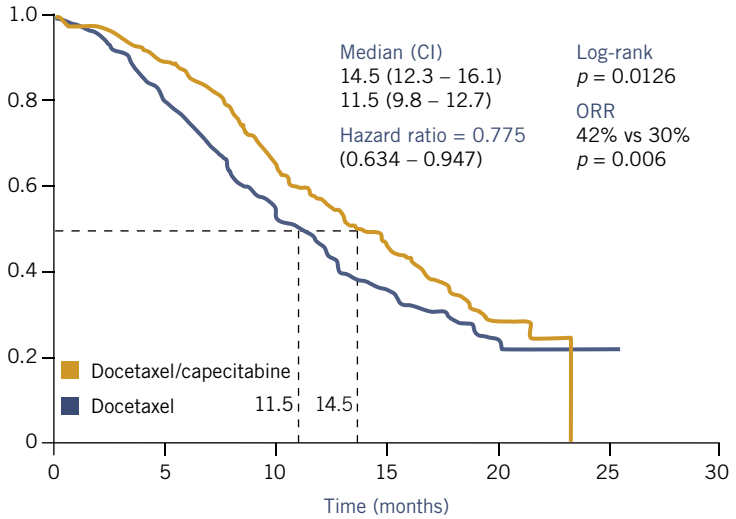
versus a combination strategy, asks how to best use drugs that we already know or assume are active.

Slide 2

This is a trial that is familiar to you — the docetaxel/capecitabine trial with the doses and schedules that you see here. Only about 20 percent of patients crossed over, so this is not a trial that asked, How do we best use capecitabine in our patients? It's a trial that asked, Is capecitabine beneficial?

3

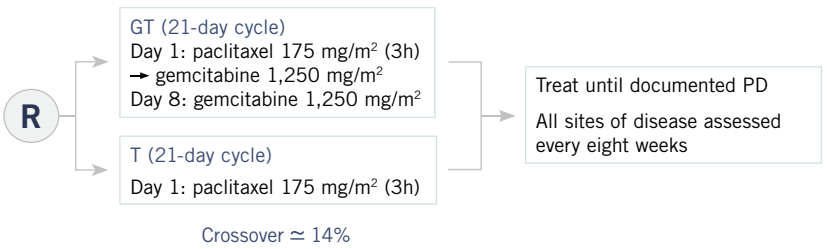
Overall Survival: Docetaxel + Capecitabine vs Docetaxel



SOURCE: O'Shaughnessy J et al. *J Clin Oncol* 2002;20(12):2812-23. Reproduced with permission from the American Society of Clinical Oncology. **Abstract**

4

AB vs A: Paclitaxel + Gemcitabine (GT) vs Paclitaxel (T)



Crossover ≃ 14%

Prior adjuvant anthracycline required

SOURCE: Albain K et al. Presentation. ASCO 2004;**Abstract 510**.

Slide 3

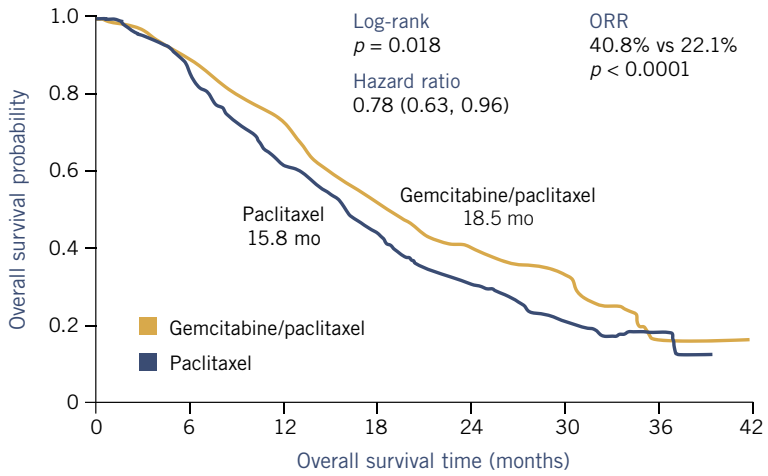
It clearly is. Those patients who received capecitabine had a much higher response rate, better time to progression and improvement in overall survival.

Slide 4

There's a similar trial design with gemcitabine with about 15 percent cross-over. The question is the same: Is gemcitabine beneficial in this disease? The question is not, How do we best use gemcitabine in our patients?

5

Interim Overall Survival: Paclitaxel + Gemcitabine vs Paclitaxel



SOURCE: With permission from Albain K et al. Presentation. ASCO 2004;**Abstract 510**.

Slide 5

The results were very similar with improvements in overall survival and response rates. In both of these trials, there was increased toxicity in the combination arm and no difference in overall survival. You could argue that the slight increase in response rates is discounted, in a quality-of-life sense, by the increase in toxicities.

Slide 6

There have been many other trials that have had similar designs. These trials go back to the 1970s, and there were only three that found improvement in overall survival. What is striking about all three of them is that they coincide with the introduction of a new therapy that we have all come to accept as one that is highly active and beneficial for at least some of our patients.

There are several trials that have looked at the strategy question rather than the drug question.

6

AB vs A or C

	RR	TTP	OS	
Heideman	=	=	=	
Norris	=	=	=	
Berruti	=	=	=	
Bishop	=	=	=	
French Epi/FEC	C	=	=	
Ejlertsen	=	C	=	
Nabholtz	=	S	S	Docetaxel
Sjostrom	S	S	=	
Bonneterre	S	S		
O'Shaughnessy	C	C	C	Capecitabine
Albain	C	C	C	Gemcitabine

7

AB → CD vs A → C: Sequential Combos vs Sequential Monos

N = 303	Epi → MMC		CEF → MMC/Vbn	
RR%	48	16	55	7
DOR (mo)	10.5		12 ($p = 0.07$)	
OS (mo)	16		18 ($p = 0.62$)	

Treatment-related toxicity and QOL assessment favored sequential single-agent therapy

SOURCE: Joensuu et al. *J Clin Oncol* 1998;16(12):3720-30. **Abstract**

Slide 7

This is a trial from our European colleagues that looked not only at single drugs but also whether sequential single agents versus sequential combinations — keeping the single agents in those combinations — are beneficial. There were no improvements in any of the endpoints with the combination therapy regimen, and treatment-related toxicity and quality of life certainly favored the single agents.

Slide 8

The largest trial and perhaps the one that has been the hallmark for this particular question is George Sledge's E1193 trial using doxorubicin and paclitaxel as either single agents or in combination, with a planned crossover to the other agent in patients randomized to the single-agent arms.

Slide 9

On this slide, I have tried to summarize all of the results that I think are important for this trial. As initial therapy, there were slightly greater response rates and about a two-month improvement in time to progression for the combination, but there was no difference in overall survival or quality of life. In the crossover results, response rates, time to progression and overall survival at the time of second-line therapy were also essentially equivalent. With these particular agents, we couldn't define a superior sequence.

8

AB vs A → B vs B → A
E1193: Combination vs Sequential

A 60 mg/m²

T 175 mg/m² over 24 hours

AT 50 mg/m² → 3 hours → 150 mg/m² over 24 hours

A (n = 245) → A (n = 128)

T (n = 242) → T (n = 129)

AT (n = 244)

SOURCE: Sledge G et al. *J Clin Oncol* 2003;21:588-92. **Abstract**

9

AB vs A → B vs B → A
E1193: Combination vs Sequential

	RR (%)	TTF (mo)	OS (mo)
A	36	6	19.1
T	34	6.3	22.5
AT	47*	8.2*	22.4
*p	A = 0.017 T = 0.006	A = 0.002 T = 0.057	

QOL using FACT-B — no significant difference

Crossover results

A → T	22	4.5	14.9
T → A	20	4.2	12.7

SOURCE: Sledge G et al. *J Clin Oncol* 2003;21:588-92. **Abstract**

Slide 10

There are several other trials, going back to the 1970s, which have used this particular trial design. The Baker trial actually included five chemotherapy agents, either given all together or in sequence. The results are markedly consistent. There was no difference in overall survival in any of these efforts.

10

AB vs A → B

	RR	TTP	OS
Baker	=	=	=
Smalley	C	C	=
Chlebowski	C	C	=
Joensuu	=	=	=
Sledge	C	C	=

Slide 11

We have to go back to what our therapy goals for metastatic disease are. This is what my patients tell me. This is not really what I say. My patients tell me they wish to live longer and better during that time, however long or short it might be.

Our clinical trials always tell us about response rates. They may tell us about duration of response or time to progression. Occasionally, they tell us about overall survival, though these time-to-event variables in uncontrolled trials are very hard to dissect and interpret.

And they often either don't assess quality of life, or our quality-of-life tools are fairly crude and only tell us about large differences.

We have fairly good data that tell us that those clinical trial results, other than overall survival, really don't translate very well into extending survival and improving or maintaining quality of life.

11

Goals of Therapy in MBC

Individual goals

- Extend survival
- Improve or maintain quality of life

Clinical trial outcomes

- Response rate
- Response duration
- TTP
- TTF
- Overall survival
- Quality of life

12

Chemotherapy for MBC

- Sequential single agents preferred for most patients
  - Variety of options – no single 'gold standard'
  - Limits toxicity
  - Supported by clinical trial data
- Combinations appropriate for rapidly progressive symptomatic disease
  - Reduction in symptoms outweighs potential toxicity
  - May not be candidate for subsequent therapy if continued progression

Slide 12

That is why, in my opinion, for most patients, the sequential single-agent approach is preferred — it gives us a variety of options.

From this year's ASCO, several other trials are looking at whether the order of those agents makes a difference. We have yet to identify any particular order that, overall, gives patients greater benefit than a different order. So there are many options that allow us to individualize both treatment options and the order of treatment for our patients, based on what our patients bring to us.

For those patients we all talk about but rarely see who have such symptomatic, rapidly progressive disease that you think — if they don't respond to the first treatment option, you're not going to get another chance in four, six or eight weeks — a combination is certainly appropriate. I just don't think that happens very often, certainly not in the first-line setting. Usually, when I see patients in that situation, they've already had much previous chemotherapy, so my options are already limited.

- **Is bevacizumab combined with paclitaxel or capecitabine generally the preferred first-line chemotherapy for patients with metastatic disease?**

Slide 13

E2100 is based on a different hypothesis. It really is not asking a chemotherapy question. It's based on our understanding that angiogenesis is important in breast cancer. There are many pro-angiogenic factors that are produced by breast cancer, but the vascular endothelial growth factor (VEGF) is one of the most common and potent ones.

13

E2100 — Rationale

- Tumor growth is dependent on angiogenesis
- Bevacizumab is a humanized monoclonal antibody directed against VEGF
  - Recognizes all VEGF-A isoforms
  - Active in patients with refractory MBC
    - 9% response rate as monotherapy
    - Increases ORR but not PFS in combination with capecitabine
- Greater activity expected in less heavily pretreated patients

SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

We do know that bevacizumab is an agent that has some activity in breast cancer but is not particularly great in refractory patients, with only about a nine percent response rate as monotherapy. This was a slight improvement in the response rate, but progression-free or overall survival did not improve in those patients.

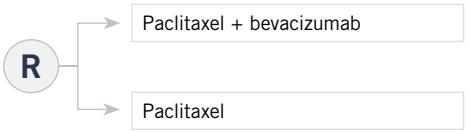
The hypothesis that E2100 was designed to test was based on the biology that using this sort of agent earlier in the course of the disease would give greater activity.

14

E2100 — Study Design

Stratify

- DFI ≤ 24 mo vs > 24 mo
- < 3 vs ≥ 3 metastatic sites
- Adjuvant chemotherapy yes vs no
- ER+ vs ER- vs ER unknown



SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

Slide 14

This trial randomized patients to paclitaxel with or without bevacizumab. A fairly common four-week treatment cycle was used, with a schedule of weekly paclitaxel for three weeks and then one week off. Patients were eligible if they had metastatic or locally recurrent disease that was not curable with any local therapy approach.

Slide 15

Essentially, this is a trial for patients with HER2-negative disease, because the trial schema does not include trastuzumab. Patients with HER2-positive disease were only allowed into this trial if they had received previous trastuzumab therapy. Note that patients couldn't have received previous chemotherapy for metastatic disease. We thought this could apply to someone who was in one of the adjuvant trastuzumab studies and progressed fairly soon after her trastuzumab therapy or someone who received trastuzumab monotherapy for metastatic disease and then wanted to enter this trial. In reality, there were only a handful of patients with HER2-positive disease, and they all came from South Africa, where trastuzumab is not available. Otherwise, patients had to be healthy and, significantly, patients with CNS metastases were excluded. We did require screening before entry.

15 E2100 — Key Eligibility Criteria

- Locally recurrent or metastatic breast cancer
  - HER2+ only if prior treatment with trastuzumab or contraindication
- No prior chemo regimens for MBC
  - Adjuvant taxane allowed if DFI > 12 months
- ECOG PS 0 or 1
- No CNS mets (head CT or MR required)
- No significant proteinuria (> 500 mg/24h)
- No therapeutic anticoagulation

SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

16 E2100 — Statistical Design

- Primary endpoint: progression-free survival
  - 85% power for a 33% improvement
    - 6 vs 8 months
  - One-sided Type I error ≃ 2.5%
  - Requires 650 eligible patients
- Final analysis after 546 PFS events
  - Interim analyses after 270 and 425 events
  - Asymmetric boundaries to stop early either for demonstrated benefit or for lack of benefit

SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

17 E2100 — Current Analysis

- Study activated Dec 21, 2001
- Closed March 24, 2004
  - 715 eligible patients
- First planned interim analysis
- Data cutoff February 9, 2005
- 355 events
  - Progression – 291
  - Death without documented progression – 64

SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

Slide 16

We had fairly modest goals for this trial. We were hoping to find an improvement in progression-free survival from six to eight months in the paclitaxel-alone arm. That would have required 650 patients. There were planned interim analyses that used very stringent O'Brien-Fleming boundaries to release the results early, either because there was a clear

benefit or a definite lack of benefit.

Slide 17

The results that we have now are from the first planned interim analysis. The trial accrued 715 eligible patients over about two and a half years. The data is now current through February 9th of this year and includes 355 events, most of which are progression. The 64 patients who were censored at death without progression had progressive disease in most of the situations — but there was not adequate imaging or documentation to meet RECIST criteria for disease progression.

Slide 18

Patients were well matched. They were the usual age for a breast cancer trial — in their mid-fifties, though there were patients enrolled who were in their mid-eighties.

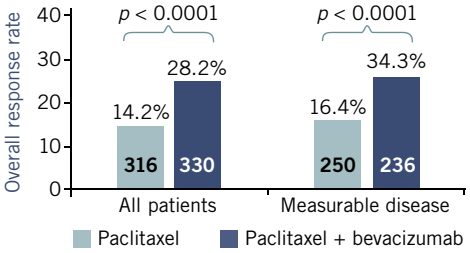
Two thirds of the patients in this trial had received adjuvant chemotherapy, which is much higher than previous metastatic trials. That tells us that how we treat these patients has shifted, so you can't easily compare results of first-line trials done today to results of first-line trials done 10 years ago.

18 E2100 — Patient Characteristics

	Paclitaxel (n = 350)	Paclitaxel + bevacizumab (n = 365)
Treated	346	365
Median age	55 (27-85)	56 (29-84)
DFI ≤ 24 months	41%	41%
≥ 3 sites	29%	28%
Adjuvant chemo	64%	65%
ER-positive	63%	64%

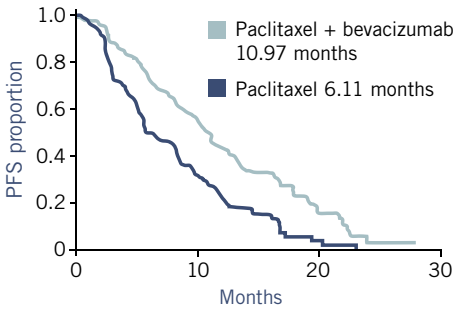
SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

19 Response



SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

20 E2100 — Progression-Free Survival

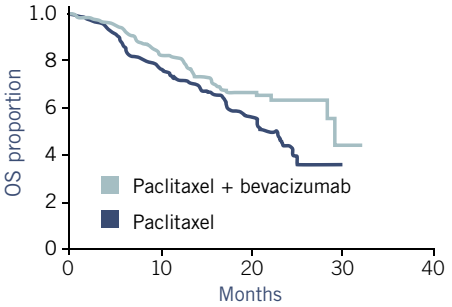


SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

The response data are the first encouraging bit of news, and this is my evidence that we can evaluate response in patients without measurable disease quite well.

21

E2100 — Overall Survival



Hazard ratio = 0.674 (0.495–0.917)

Log-rank test $p = 0.01$

SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

Slide 19

E2100 did not require measurable disease because progression-free survival was the primary endpoint. As the PI, I didn't care if you could tell me if the patient was responding, but I was fairly certain that good clinicians would know when their patients were progressing, and that was the endpoint we were interested in.

If you look at the subset of about three quarters of patients who had measurable disease, the estimates of response were very similar.

Slide 20

Progression-free survival was clearly improved by much greater than we had expected. Our estimates of a six-month progression-free survival for patients receiving paclitaxel alone was 6.1 months, with an improvement to 10.97 months or a 51 percent decrease in the risk of progression for patients receiving the combination.

22

E2100 — Bevacizumab Toxicity: NCI-CTC Grade III and IV

	Paclitaxel (n = 330)		Paclitaxel + bevacizumab (n = 342)	
	Percent			
	Grade III	Grade IV	Grade III	Grade IV
HTN*	0	0	13	0.3
Thromboembolic	0.3	0.9	1.2	0
Bleeding	0	0	0.6	0.3
Proteinuria†	0	0	0.9	1.5

NCI-CTC v3.0, worst per patient; * $p < 0.0001$; † $p = 0.0004$

SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

23

E2100 — Other Toxicities, NCI-CTC Grade III and IV

	Paclitaxel (n = 330)		Paclitaxel + bevacizumab (n = 342)	
	Percent			
	Grade III	Grade IV	Grade III	Grade IV
Neuropathy*	13.6	0.6	19.9	0.6
Fatigue	2.7	0	4.7	0.3
Neutropenia	0	3	0.9	4.4
↓ LVEF	0	0	0.3	0

NCI-CTC v3.0, worst per patient; * $p = 0.01$

SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

Slide 21

The overall survival data, I must caution you, are early, so I cannot tell you what the median survivals are. They're just now being reached, and that part of the curve is very unstable. What is not likely to change, however, is that there is a survival advantage in this trial, with about a 33 percent decrease in the risk of death in patients receiving the combination therapy.

24

Conclusions and Future Directions

- Addition of bevacizumab to paclitaxel
  - Significantly prolongs progression-free survival
  - Increases objective response rate
  - Longer follow-up required to assess impact on OS
- Further studies should
  - Explore the role of bevacizumab in the adjuvant setting
  - Develop methods to identify patients who are most likely to benefit from VEGF-targeted therapies

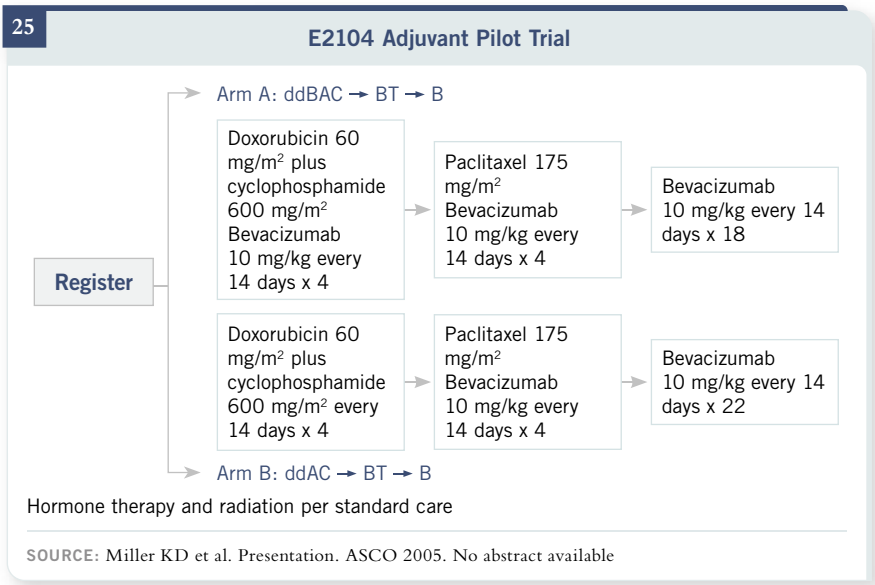
SOURCE: Miller KD et al. Presentation. ASCO 2005. No abstract available

Slide 22

Increase in toxicity was minimal. We've known about the bevacizumab-associated toxicities, and this is about what we expected. About 15 percent of patients developed hypertension and needed treatment, and there was a small proportion of patients with significant proteinuria without any other signs of renal dysfunction. In this relatively healthy breast cancer patient population, thromboembolic events and bleeding were not a problem, and they were not different in the two treatment groups.

Slide 23

There's only one important difference in the chemotherapy-associated toxicity, which is a slight increase in the risk of Grade III neuropathy. It could be that there's an interaction between the drugs that increases neuropathy. What's



more likely is, since paclitaxel-related neuropathy is both duration of treatment and dose related, patients were responding to therapy for a much longer time and were exposed to a greater duration of taxane therapy.

Slide 24

Overall, we were delighted to be able to finally say that the addition of bevacizumab in patients with newly diagnosed metastatic breast cancer — or at least newly requiring chemotherapy for their metastatic breast cancer — improves the progression-free survival and the objective response rate. It also appears to improve overall survival, though we'll need further follow-up to know the magnitude of improvement in overall survival.

We are continuing to look for ways to identify those patients who are most likely to benefit from this approach. These patients were not positively selected for any molecular feature because, at this point, we don't know how to select them.

Slide 25

We're also looking forward to exploring bevacizumab in the adjuvant setting and will very soon be activating an adjuvant pilot trial in the Eastern Cooperative Oncology Group. This trial will hopefully then be followed, in very quick succession, with a full adjuvant trial to try and look for improvements in disease-free and overall survival.

• Is bevacizumab combined with paclitaxel or capecitabine generally the preferred first-line chemotherapy for patients with metastatic disease?

I would agree with this second question as well. For most patients, weekly paclitaxel or capecitabine in combination with bevacizumab provides the most effective first-line chemotherapy. The trial I've just shown you, E2100, clearly finds significant improvements in all of those response parameters for incorporating bevacizumab with weekly paclitaxel.

It's important to think about the eligibility criteria and which of our patients with metastatic disease would not have been eligible for this trial. We don't yet know about the role of bevacizumab or the safety of bevacizumab in combination with trastuzumab regimens in patients who are HER2-positive. At this point, I would not add bevacizumab to those patients' treatment. We also excluded those patients who had received adjuvant taxane therapy and progressed within 12 months. I don't think it would be reasonable to re-treat those patients with paclitaxel, even in combination with bevacizumab. So for those patients who've recently had an adjuvant taxane and are progressing, we really don't have good data.

From our previous capecitabine trials, I can tell you that those patients who receive an anthracycline and taxane and progress within 12 months do miserably, and I suspect they would do miserably no matter what we did for them. If you are interested, it's reasonable to use bevacizumab in those patients, but we don't have randomized trial data to support that at this point.

Slide 26

We have safety and response data with bevacizumab in combination with capecitabine in exactly that patient population. Response rates increased slightly, but most of those extra responses were fairly short lived.

26 **Capecitabine + Bevacizumab**

	Cap (n = 230)	Cap + bev (n = 232)
ORR (Inv)	19.1%	30.2% ($p = 0.006$)
ORR (IRF)	9.1%	19.8% ($p = 0.001$)

SOURCE: Miller KD et al. *J Clin Oncol* 2005;23(4):792-9. **Abstract**

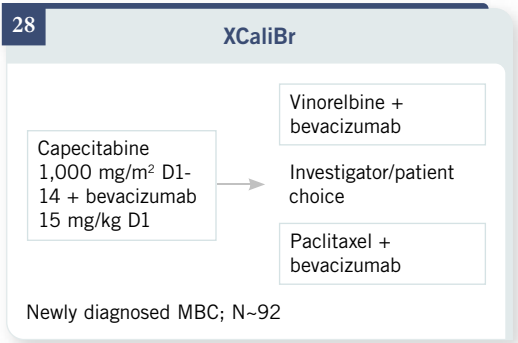
27 **Vinorelbine + Bevacizumab**

	Number of patients	Percent of patients
CR	1	2%
PR	16	29%
CR + PR	17	30%
SD	25	45%
PD	12	21%
Not evaluable	2	4%

SOURCE: Burstein H et al. San Antonio Breast Cancer Symposium 2002;Poster 446. **Abstract**

Slide 27

There are also safety and response data in patients who were pretreated with vinorelbine. Either one of those would be regimens for which at least there is some evidence, although more on safety than on efficacy.



Slide 28

Finally, there is another trial that will be starting very soon called XCaliBr. This trial will look at newly diagnosed patients, essentially the same group as in the E2100 trial — needing chemotherapy, but using capecitabine in combination with bevacizumab. This trial allows but does not require patients to continue bevacizumab after initial progression, either with vinorelbine or paclitaxel, at the patients' and investigators' choice.

This is a fairly small Phase II trial with only 92 patients, so it certainly will not be definitive. Randomization to continuing bevacizumab or not is not included. That is an open question we need to address quickly. But the trial will, at least, give us some comparative data on response rates and time-to-event variables, with a different chemotherapy regimen. That will be particularly helpful as the taxanes are used more and more in the adjuvant setting and as we hope to move to more oral therapies and therapies that don't include alopecia and some of those toxicities for our patients with metastatic disease. ■

SELECT PUBLICATIONS

Albain KS et al. **Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival.** *Proc ASCO* 2004;**Abstract 510**.

Burstein HJ et al. **Phase II trial of the anti-VEGF antibody bevacizumab in combination with vinorelbine for refractory advanced breast cancer.** San Antonio Breast Cancer Symposium 2002;Poster 446. **Abstract**

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. ASCO 2005. No abstract available

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005;23(4):792-9. **Abstract**

O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23. **Abstract**

Sledge GW et al. **Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An intergroup trial (E1193).** *J Clin Oncol* 2003;21(4):588-92. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The WHI trial in women who had a uterus, comparing estrogen plus progestin versus placebo, showed that coronary heart disease was significantly _____ with hormone use.**
   a. Increased
   b. Decreased
2. **The WHI trial in women who had a prior hysterectomy, comparing estrogen only versus placebo, showed no effect on the overall balance of risks and benefits.**
   a. True
   b. False
3. **The five-year toxicity data from the ATAC trial favors _____ because the life-threatening toxicities — endometrial cancer, arterial and venous vascular events — were all significantly less with this agent.**
   a. Tamoxifen
   b. Anastrozole
4. **In the WHI trials, the age-adjusted breast cancer risk for which of the following groups was substantially less as compared to Caucasians?**
   a. African-Americans
   b. Hispanics
   c. Asian Pacific Islanders
   d. All of the above
5. **The WHI trials showed that African-Americans have nearly a fivefold risk of ER-negative, PR-negative and high-grade breast cancer as compared to Caucasians.**
   a. True
   b. False
6. **In the ECOG-E2100 trial, the addition of bevacizumab to paclitaxel had which of the following effects?**
   a. Prolonged progression-free survival
   b. Increased objective response rate
   c. Significantly increased incidence of toxicities
   d. Both a and b
7. **The combined analysis of the NSABP-B-31 and NCCTG-N9831 adjuvant trastuzumab trials showed statistically significant improvement in disease-free survival for women who received AC/paclitaxel plus trastuzumab versus AC/paclitaxel with no trastuzumab.**
   a. True
   b. False
8. **In the HERA trial evaluating adjuvant trastuzumab, approximately _____ percent of patients had node-negative disease.**
   a. Zero percent
   b. Ten percent
   c. Thirty-three percent
   d. Fifty percent
9. **In the cardiac safety analysis of NCCTG-N9831, the difference in incidence of cardiac events between the nontrastuzumab and trastuzumab arms was less than four percent.**
   a. True
   b. False
10. **In NSABP trial B-27, the addition of preoperative docetaxel to AC failed to significantly increase the pathologic complete response rate.**
    a. True
    b. False
11. **In NSABP trial B-35, patients with ER-positive DCIS are treated with lumpectomy and radiation therapy then randomly assigned to receive:**
    a. Tamoxifen or anastrozole
    b. Tamoxifen or exemestane
    c. Tamoxifen or letrozole
    d. Five years of tamoxifen or two years of tamoxifen followed by three years of anastrozole
12. **The initial results of the NSABP-B-32 sentinel node trial revealed a false-negative rate of:**
    a. 2.5 percent
    b. 4.5 percent
    c. 9.5 percent
    d. 14.0 percent

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

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Breast Cancer Update — Issue 7, 2005

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor	N/A = Not applicable to this issue of *BCU*

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 adjuvant, neoadjuvant, 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 patients with HER2-positive breast cancer in the adjuvant, neoadjuvant 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 appropriate patients with metastatic disease about selection and sequencing of endocrine therapy and about the risks and benefits of combination versus single-agent chemotherapy. . . . . 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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
Rowan T Chlebowski, MD, PhD	5 4 3 2 1	5 4 3 2 1
Eric P Winer, MD	5 4 3 2 1	5 4 3 2 1
Harry D Bear, MD, PhD	5 4 3 2 1	5 4 3 2 1
Juliann M Smith, MD	5 4 3 2 1	5 4 3 2 1
Kathy D Miller, MD	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

EVALUATION FORM

Breast Cancer Update — Issue 7, 2005

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Will the information presented cause you to make any changes in your practice?

☐ Yes ☐ No

If yes, please describe any change(s) you plan to make in your practice as a result of this activity:

.....

What other topics would you like to see addressed in future educational programs?

.....

What other faculty would you like to hear interviewed in future educational programs?

.....

Additional comments about this activity:

.....

Degree:

☐ MD ☐ PharmD ☐ NP ☐ BS ☐ DO ☐ RN ☐ PA ☐ Other .....

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As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I am willing to participate in a follow-up survey.

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