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Breast Cancer® UPDATE

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

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INTERVIEWS

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TUMOR PANEL CASE DISCUSSION

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CME Certified

Breast Cancer Update
A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 5 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Chlebowski, Cuzick, Dickler, Giordano and Jahanzeb on the integration of emerging clinical research data into the management of breast cancer.

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UPCOMING EDUCATIONAL EVENTS

ACOSOG Annual Meeting
August 16-18, 2007
St Louis, Missouri
Website: **www.acosog.org**

The 2007 Breast Cancer Symposium
September 7-8, 2007
San Francisco, California
Website: **www.asco.org**

SWOG Fall Group Meeting
October 4-7, 2007
Huntington Beach, California
Website: **www.swog.org**

ECOG Fall Group Meeting
November 9-11, 2007
Fort Lauderdale, Florida
Website: **www.ecog.org**

30th Annual San Antonio Breast Cancer Symposium
December 13-16, 2007
San Antonio, Texas
Website: **www.sabcs.org**

RTOG Winter Meeting
January 17-20, 2008
San Diego, California
Website: **www.rtog.org**

INTERVIEW

Sharon Giordano, MD, MPH

Dr Giordano is Assistant Professor of Medicine in the Department of Breast Medical Oncology at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-20

Select Excerpts from the Interview

Track 1

DR LOVE: Can you discuss your 2006 ASCO presentation regarding the rates of congestive heart failure among older women with breast cancer (Giordano 2006a)?

DR GIORDANO: We examined the SEER–Medicare database, which is a large national database of people with cancer who are 65 years of age and older,

to determine how people were treated in the adjuvant setting. Then we compared the rates of heart failure at five and 10 years. Although the patients who received anthracyclines tended to be younger and healthier, they had higher rates of heart failure than patients who received other kinds of chemotherapy, such as CMF (Giordano 2006a; [1.1]).

We saw high rates of congestive heart failure, even among patients who were not treated with any chemotherapy and those treated with nonanthracycline-based chemotherapy (Giordano 2006a; [1.1]). They are based on Medicare coding, which is an important caveat to remember. We don't have ECHO results or physician examinations — we have billing codes from Medicare to indicate heart failure. However, studies have shown that this is a valid and accurate way to assess heart failure occurrence.

DR LOVE: How much of an additional risk of congestive heart failure do you think is introduced by an anthracycline?

DR GIORDANO: An increase in risk of about five to 10 percent is associated with receiving an adjuvant anthracycline, which is substantial.

DR LOVE: Most oncologists tell their patients that it is one percent.

DR GIORDANO: That one percent figure is based on clinical trials evaluating the short-term toxicities of the anthracyclines. Our numbers are based on five- and 10-year rates.

DR LOVE: Are you telling your patients that by using an anthracycline-containing regimen (ie, four cycles of AC), you're creating an excess risk of heart failure of five or 10 percent in the long run?

DR GIORDANO: Because these data are not from a randomized controlled trial, I cannot say it with that degree of certainty. I am telling them that we currently don't have an accurate way of estimating the risk.

1.1

Rates of Congestive Heart Failure in Women 66 to 70 Years of Age According to Adjuvant Chemotherapy Received for Breast Cancer: Analysis of the SEER-Medicare Database

	Five years	Ten years
Adjuvant anthracycline (n = 898)	19%	47%
Adjuvant nonanthracycline (n = 1,008)	14%	33%
No adjuvant chemotherapy (n = 6,939)	12%	28%

SOURCE: Giordano SH et al. *Proc ASCO* 2006a;**Abstract 521**.

Track 5

DR LOVE: What about trastuzumab and cardiac toxicity?

DR GIORDANO: Clearly trastuzumab increases the risk of cardiac toxicity.

Administering trastuzumab concurrently with chemotherapy seems to incur a higher risk than administering them sequentially, but you're balancing that against trastuzumab perhaps being more effective when administered concurrently than sequentially to chemotherapy.

It's frequently an issue that arises, especially for the patients with low-risk disease. For those patients — similar to using TC (docetaxel/cyclophosphamide) for patients with HER2-negative disease and a high risk of cardiac toxicity — I'll often use TCH (docetaxel/carboplatin/trastuzumab) for the patients with HER2-positive disease and a high risk of cardiac toxicity.

DR LOVE: What is your opinion of the data from BCIRG 006 with TCH (Slamon 2006)?

DR GIORDANO: The evidence appears stronger and stronger that TCH is equivalent to the anthracycline-based regimens (Slamon 2006; [1.2]). If I had a patient who was older or one with pre-existing heart disease for whom I was worried about cardiac toxicity, I would first use TCH.

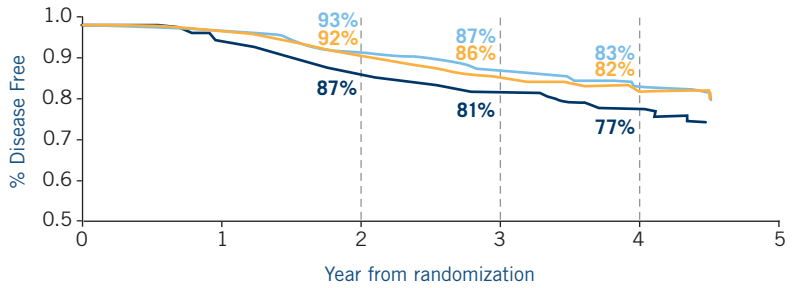
DR LOVE: What about patients with pre-existing hypertension or diabetes?

DR GIORDANO: Those factors might weigh into my decision, but neither one of them by itself would sway me one way or the other. Patients with a borderline ejection fraction of 50 or 55 percent who clinically appear to be well and perhaps don't have any cardiac risk factors and with whom you want to use chemotherapy also are great candidates for TCH.

1.2

Updated Analysis of Disease-Free Survival in BCIRG 006

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



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

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

Track 4

DR LOVE: What's your opinion about the use of adjuvant chemotherapy for patients with ER-positive tumors?

DR GIORDANO: Increasingly, data suggest that patients with ER-positive tumors benefit less from chemotherapy than patients with ER-negative tumors, but I'm not convinced at this point that they receive no benefit. Studies like TAILORx (1.3), in which we are stratifying patients with ER-positive disease by risk as determined with the Onco*type* DX assay, might help establish whether there is a subset of patients who don't need chemotherapy.

For patients who are borderline candidates for chemotherapy, if they have ER-positive disease, I'm less inclined to use chemotherapy. I believe, however, that patients who have high-risk disease, even if it's ER-positive, still clearly benefit.

DR LOVE: Are you enrolling patients on TAILORx, and how do you use the Onco*type* DX assay off protocol?

DR GIORDANO: We do participate in TAILORx, which runs the Onco*type* DX assay for the patient. If a patient's tumor is categorized as presenting intermediate risk, then she is randomly assigned to hormonal therapy with or without chemotherapy. If the patient's tumor is in the low-risk category, she receives hormonal therapy alone. If the patient's tumor is in the high-risk category, she receives chemotherapy and hormonal therapy.

I've used the Onco*type* DX assay off protocol — to help both myself and the patient make a decision as to whether to use chemotherapy — for patients who are borderline candidates for chemotherapy because they do not want chemotherapy or they have comorbidities or fairly low-risk tumors.

I can't say that I have a clear cutoff, but for patients with tumors larger than two centimeters, I'm inclined to use chemotherapy. I typically don't order the Onco*type* DX assay in that situation.

Tracks 8, 10

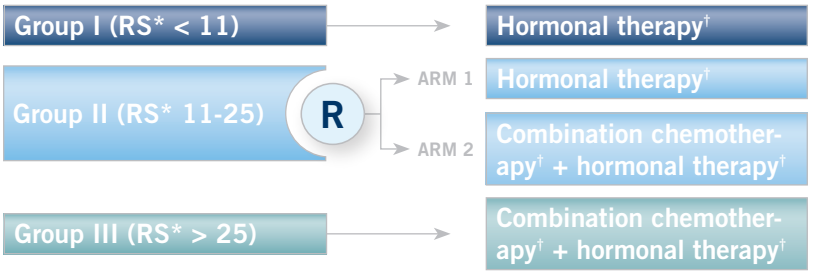
DR LOVE: What do we know about adjuvant endocrine therapy for men with breast cancer?

DR GIORDANO: Not enough. More than 90 percent of men with breast cancer have hormone receptor-positive disease (Giordano 2004). When I'm selecting adjuvant hormonal therapies, I almost exclusively use tamoxifen because we have strong data in the metastatic setting with male patients, and we have retrospective series showing a survival benefit for men treated with adjuvant tamoxifen (Goss 1999; Giordano 2005; Fentiman 2006). None of the data are at the level of a randomized trial, but at least we have solid data. The controversy comes in with the use of the aromatase inhibitors and whether they are going to be equally, less or more effective than tamoxifen. You can make arguments in any direction about how effective they might be. Most of the

1.3

TAILORx: A Phase III Randomized Trial of Adjuvant Combination Chemotherapy and Hormonal Therapy versus Adjuvant Hormonal Therapy Alone in Women with Previously Resected Axillary Node-Negative Breast Cancer with an Intermediate Score of the Onco*type* DX Assay

Target Accrual: 10,046 (Open)
Date Activated: April 7, 2006



* Onco*type* DX recurrence score
† Physician's choice for hormonal therapy and chemotherapy

Select Eligibility Criteria

- ER-positive and/or PR-positive breast cancer
- Negative axillary nodes
- Tissue from primary tumor available for Onco*type* DX assay
- 18-75 years of age
- HER2-negative
- Tumor size 1.1-5.0 centimeters (tumors 5 millimeters to 1.0 centimeter allowed if intermediate or poor nuclear and/or histologic grade or lymphovascular invasion)

Study Contact

Eastern Cooperative Oncology Group
Joseph Sparano, MD
Tel: 718-920-4826

SOURCES: PACCT-1 Protocol, August 23, 2006; **www.ecog.org**.

estrogen in men comes from peripheral aromatization, so it makes sense that if you could shut that down with aromatase inhibitors, it may be effective.

However, when anastrozole was first being developed, it was tested in healthy male volunteers. Those patients exhibited a decline in estrogen levels — although not as complete as the decline among women — but because of the feedback loop, they also experienced a doubling of their testosterone levels (Mauras 2000).

The bottom line is that we have a couple of case reports with responses to the aromatase inhibitors (Zabolotny 2005; Italiano 2004). We have a case series of five patients in which a few had stable disease but no responses were recorded (Giordano 2002). So few data are available on their efficacy that I'm reluctant to use them in the adjuvant setting.

DR LOVE: What about the LHRH agonists?

DR GIORDANO: Those agents are likely to be effective. I've had patients who responded nicely to LHRH agonists in the metastatic setting, and I've had some good responses with the combination of an LHRH agonist and an aromatase inhibitor. This makes sense because you're shutting back the negative feedback loop in addition to shutting off the aromatase.

We published a letter to the editor in the *Journal of Clinical Oncology* in which we reported two cases. One of them was interesting because the patient had failed leuprolide and an aromatase inhibitor as single agents but responded to the combination (Giordano 2006b).

DR LOVE: What about adjuvant chemotherapy in male breast cancer? Do we have any data?

DR GIORDANO: We have minimal data. One prospective study from the NCI treated about 30 men who had Stage II, node-positive breast cancer with CMF and then compared the outcomes to historical controls. This study indicated a better survival than expected compared to the historical controls (Bagley 1987; Walshe 2007).

We've retrospectively analyzed the MD Anderson experience (Giordano 2005). It appears that survival is a little better, but we have no data to guide us. I believe it's reasonable to expect that chemotherapy would be the same for male and female patients, and I use the same regimens.

Track 14

DR LOVE: I'm curious about your opinion of the data on bevacizumab with paclitaxel that came out a couple of years ago from ECOG-E2100 (Miller 2005). How are you approaching the management of metastatic disease, specifically the use of chemotherapy and bevacizumab?

DR GIORDANO: I'm discussing bevacizumab in combination with taxanes with patients up front in the first-line metastatic setting. I haven't been using it in the second-, third- or fourth-line setting. I know ECOG-E2100 included patients who had received adjuvant taxanes, but often taxanes aren't my first choice in the up-front metastatic setting because so many of my patients have already received them as adjuvant therapy. I usually start with capecitabine.

Track 17

DR LOVE: How do you approach the initiation of adjuvant endocrine therapy for the postmenopausal patient?

DR GIORDANO: I start up front with an aromatase inhibitor. My belief is that the data show it's a more effective medication. I recognize that we haven't directly compared starting with tamoxifen and switching to an aromatase inhibitor to starting with an aromatase inhibitor. However, the data we have show that the aromatase inhibitors are better, and I have a concern about the

patients who would relapse in the period when they're receiving tamoxifen who might not relapse if I had started with an aromatase inhibitor. So my preference is to start with an aromatase inhibitor.

DR LOVE: How do you approach the postmenopausal patient who has received five years of tamoxifen, particularly those women who may have been off therapy for one, two, three or four years?

DR GIORDANO: If they've been off tamoxifen for six months or a year, then I would probably start an aromatase inhibitor as extended adjuvant therapy. I don't feel we have enough data for starting an aromatase inhibitor two, three or four years after. This is a sort of "do no harm" principle because toxicity is associated with the aromatase inhibitors, especially bone loss, and we don't have high-quality evidence available for that group of patients.

Having said that, I wonder if a benefit might exist. When we've previously observed recurrence rates for ER-positive breast cancer, the hazard each year flattens out indefinitely. At 10 years, a person still does have a significant risk. ■

SELECT PUBLICATIONS

Bagley CS et al. **Adjuvant chemotherapy in males with cancer of the breast.** *Am J Clin Oncol* 1987;10(1):55-60. **Abstract**

Fentiman IS et al. **Male breast cancer.** *Lancet* 2006;367(9510):595-604. **Abstract**

Giordano SH et al. **Congestive heart failure (CHF) in older women treated with anthracycline (A) chemotherapy (C).** *Proc ASCO* 2006a;**Abstract 521**.

Giordano SH, Hortobagyi GN. **Leuprolide acetate plus aromatase inhibition for male breast cancer.** *J Clin Oncol* 2006b;24(21):e42-3. No abstract available

Giordano SH et al. **Adjuvant systemic therapy for male breast carcinoma.** *Cancer* 2005;104(11):2359-64. **Abstract**

Giordano SH et al. **Breast carcinoma in men: A population-based study.** *Cancer* 2004;101(1):51-7. **Abstract**

Giordano SH et al. **Efficacy of anastrozole in male breast cancer.** *Am J Clin Oncol* 2002;25(3):235-7. **Abstract**

Goss PE et al. **Male breast carcinoma: A review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955-1996.** *Cancer* 1999;85(3):629-39. **Abstract**

Italiano A et al. **Complete remission obtained with letrozole in a man with metastatic breast cancer.** *Rev Med Interne* 2004;25(4):323-4. No abstract available

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

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

Walshe JM et al. **A prospective study of adjuvant CMF in males with node positive breast cancer: 20-year follow-up.** *Breast Cancer Res Treat* 2007;103(2):177-83. **Abstract**

Zabolotny BP et al. **Successful use of letrozole in male breast cancer: A case report and review of hormonal therapy for male breast cancer.** *J Surg Oncol* 2005;90(1):26-30. **Abstract**

INTERVIEW

Rowan T Chlebowski, MD, PhD

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

Tracks 1-19

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you review the recent data on the decrease in breast cancer incidence in the United States?

DR CHLEBOWSKI: Over the last 20 years, the age-adjusted incidence of breast cancer had been increasing at about half a percent per year until the last few years.

Between 2002 and 2003, data from the NCI's SEER registries show approximately a seven percent reduction in the incidence (Ravdin 2007). Peter Ravdin, some other NCI investigators and I began examining the data to determine whether this was real and why it occurred.

We reviewed all of the SEER registries, which capture 26 percent of the cancer data in the United States, and all nine reported the same reduction. We examined the data for a month-to-month variation and found no fluctuation over the last 10 years.

In addition, we reviewed the data for 15 or 20 common types of cancer and found no change in any of them during this time period. When we examined subgroups, we found that almost all of the reduction occurred in patients with breast cancer in the ER-positive subgroup and among ages 50 to 69.

We examined the second-primary breast cancer cases to see if the statistics might be influenced by the use of tamoxifen and/or aromatase inhibitors, but those weren't decreased. Indeed, it appears the reduction is real and it's limited to postmenopausal women with ER-positive breast cancer.

DR LOVE: To what do you attribute the reduction?

DR CHLEBOWSKI: A few changes during this time frame could have accounted for this reduction, and one was the use of mammography. In early 2000 to 2001, the Cochrane Collaboration challenged the effectiveness of mammography, and major organizations examined whether this was truly an issue.

When the smoke cleared, they continued to support mammograms, but a decrease of one percent occurred in mammography use across the country between 2000 and 2003. The biggest decrease was among women ages 50 to 69 — a 3.2 percent decrease.

Another change that occurred during this time was a decline in the use of hormone replacement therapy (HRT; [2.1]). In early 2002, reports on the use of estrogen with progesterone suggested that there was not a chronic disease benefit. Rather, there was a chronic disease risk associated with HRT, and a tremendous reaction occurred in the population. In the WHI estrogen with progesterone trial, we started with 16,000 women, but in the end we had 9,000 women still randomly assigned to placebo or estrogen with progesterone. Overnight, we informed the women in a letter to stop their study pills.

The number of HRT prescriptions in the United States decreased from 60 million in 2000 and 2002 to 25 million in 2003.

Track 9

DR LOVE: Can you review the updated data from the WINS trial?

DR CHLEBOWSKI: This randomized, prospective clinical trial involved mainly postmenopausal women, ages 48 to 78 at entry, with early-stage, resected breast cancer. It was conducted at 39 institutions throughout the United States, and patients were randomly assigned to a dietary intervention targeting reduction of fat intake or not.

All the women received standard breast cancer management. If the patient had receptor-negative disease, adjuvant chemotherapy was required. For patients with receptor-positive disease, it was elective.

At ASCO 2005 I reported an interim efficacy analysis, which suggested an approximate 24 percent reduction in relapse-free survival, the primary study endpoint (Chlebowski 2006a). The hazard ratio for survival was 0.89, which was not significant.

At the San Antonio meeting in 2006, we presented a follow-up interim analysis (2.2). At that point, the relapse-free survival hazard ratio was 0.79, which was borderline, and the overall survival hazard ratio was 0.78, a 22 percent reduction in mortality, although not significant (Chlebowski 2006b).

In subgroup analysis, we saw statistically significant reductions in ER-negative, PR-negative cancer. In examining 362 such cases, we saw a 54 percent reduction in recurrence and a 66 percent reduction in mortality. This was an unplanned subgroup, but it is an interesting signal.

When we compare the WHI to the WINS data, we see a similar trend with a doubling or tripling of the effect, especially among patients with PR-negative disease.

We don't know whether any effect occurred in ER-positive tumors, because the hazard ratio for relapse-free survival in ER-positive, PR-positive breast cancer was 0.90. Although it's in the right direction, we need further follow-up.

2.1

Discontinuation in Menopausal Hormone Replacement Therapy as a Contributor to a Decline in Breast Cancer Incidence

"Discontinuation of hormone-replacement therapy could have caused a decreased incidence of breast cancer by direct hormonal effects on the growth of occult breast cancers, a change that would have been expected to affect predominantly estrogen-receptor-positive tumors.

If the decrease in breast-cancer incidence had been associated with discontinuation of hormone-replacement therapy, the rapidity of change suggested that clinically occult breast cancers stopped progressing or even regressed soon after discontinuation of the therapy.

The hypothesis that hormone withdrawal can rapidly influence the growth of breast cancer is supported by anecdotal reports of regression of breast cancer after discontinuation of hormone-replacement therapy..."

SOURCE: Ravdin PM et al. *N Engl J Med* 2007;356(16):1670-4. **Abstract**

2.2

Women's Intervention Nutrition Study Evaluating Dietary Fat Reduction and Breast Cancer Outcomes: Efficacy Data (N = 2,437)

Endpoint	Hazard ratio	95% CI	*p*-value
Relapse-free survival			
All patients	0.79	0.62-1.00	NR
ER-positive/PR-positive	0.90	0.64-1.25	0.60
ER-positive/PR-negative	0.78	0.39-1.57	0.33
ER-negative/PR-positive	0.67	0.21-2.14	0.69
ER-negative/PR-negative	0.46	0.26-0.80	0.005
Overall survival			
All patients	0.78	0.59-1.03	NR
ER-positive/PR-positive	0.88	0.61-1.28	0.59
ER-positive/PR-negative	0.69	0.31-1.54	0.27
ER-negative/PR-positive	1.02	0.26-3.97	0.98
ER-negative/PR-negative	0.34	0.16-0.70	0.003

NR = not reported
Hazard ratio < 1 favors dietary fat reduction.

SOURCE: Chlebowski RT et al. Presentation. San Antonio Breast Cancer Symposium 2006b;**Abstract 32**.

Track 13

DR LOVE: What are your thoughts on extended adjuvant endocrine therapy?

DR CHLEBOWSKI: It's true that hormone receptor–negative breast cancer recurs more frequently early and then less commonly after three or four years than hormone receptor–positive breast cancer, and then the recurrence tails continue for a long period. The concern about the hormone receptor–positive tail is legitimate, so I believe we are headed toward longer-duration hormonal therapy.

DR LOVE: How do you estimate a patient's residual risk of relapse when considering further therapy?

DR CHLEBOWSKI: It's difficult to calculate the patient's risk of recurrence because there are so many variables.

Data from a variety of trials tell us that about half of the recurrence risk and only a third of the risk of dying is in the first five years.

It comes back to the questions of what our threshold is for treatment side

effects to warrant an intervention and what is the toxicity of that intervention. In terms of aromatase inhibitors, and perhaps especially anastrozole, the toxicity profile seems to be settling so well that I am less concerned about administering a longer-duration therapy.

Track 14

DR LOVE: Can you review the available data on up-front aromatase inhibitors?

DR CHLEBOWSKI: The data we have in the front-line setting with anastrozole in the ATAC trial and letrozole in the BIG 1-98 trial are the easiest to compare (2.3).

The BIG 1-98 trial has four arms, but the 51-month update compares the letrozole to the tamoxifen monotherapy arms only, not the crossover arms. In this update, the hazard ratio for time to distant recurrence, which was 0.73 in the 26-month report, is now 0.81 (BIG 1-98 Collaborative Group 2005; Coates 2007). In the ATAC trial at 68 months, we see a hazard ratio of 0.84 (Howell 2005).

Track 15

DR LOVE: What did the BIG 1-98 data show with regard to letrozole and cardiovascular disease, and how does that compare to the other aromatase inhibitors?

DR CHLEBOWSKI: The BIG 1-98 trial had a higher rate of Grade III, IV and V events and deaths with letrozole versus tamoxifen. However, it's difficult to make cross-study comparisons of some of these endpoints. In BIG 1-98, they asked more specifically about some of the cardiac toxicities.

I believe letrozole brings the potential for a slight increase of coronary artery disease, but whether that's a substantial difference or related to the peculiarities of the BIG 1-98 trial is difficult to know.

A reasonable person could say that the MA17 data are more reliable estimates because it's placebo controlled, and I don't believe any effect has been seen.

DR LOVE: What about the incidence of strokes?

DR CHLEBOWSKI: Anastrozole is the only one of the three aromatase inhibitors that has shown a reduction in the rate of strokes in the clinical trials when compared to tamoxifen.

In the ATAC trial, the incidence of ischemic cerebrovascular events was two percent among patients on anastrozole and 2.8 percent among patients on tamoxifen, which was statistically significant (Howell 2005).

2.3

Update Data from BIG 1-98: Five Years of Aromatase Inhibitors Compared to Tamoxifen as Initial Adjuvant Therapy

	BIG 1-98[1] (N = 4,922)			ATAC[2] (N = 9,366)		
Endpoint	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Disease-free survival	0.82	0.71-0.95	0.007	0.83	0.73-0.94	0.005
Overall survival	0.91	0.75-1.11	0.35	0.97	NR	NR
Time to recurrence	0.78	0.65-0.92	0.004	0.74	0.64-0.87	0.0002
Time to distant recurrence	0.81	0.67-0.98	0.03	0.84	0.70-1.00	0.06

BIG 1-98 = letrozole versus tamoxifen monotherapy arms, 51-month follow-up, all cases are estrogen receptor-positive
ATAC = anastrozole versus tamoxifen, 68-month follow-up, hormone receptor-positive cases only
HR = hazard ratio for aromatase inhibitor (AI) versus tamoxifen (<1.0 favors AI)
NR = not reported

SOURCES: [1] Coates AS et al. *J Clin Oncol* 2007;25(5):486-92. **Abstract**; [2] Howell A, on behalf of the ATAC Trialists' Group. *Lancet* 2005;365(9453):60-2. **Abstract**

Tracks 16-18

DR LOVE: What about aromatase inhibitors and bone density?

DR CHLEBOWSKI: It's difficult for me to be particularly concerned about the risk of fractures with aromatase inhibitors.

Per Lonning conducted a trial in early-stage breast cancer, evaluating exemestane versus placebo for two years. At the one-year follow-up, the bone had returned to normal in the spine and was returning to normal in the hip, with no intervention (Lonning 2005; Geisler 2006). That gave us the first signal that this complication is self correcting, even if you do nothing.

The second signal was in the ATAC trial, which involved no pretreatment, no screening and no calcium/vitamin D or protocol-defined bisphosphonate therapy.

The 68-month data showed the hip fracture rate was similar among the patients who received anastrozole versus tamoxifen — 1.2 versus one percent, respectively (Coleman 2006).

DR LOVE: What about the bisphosphonates and recurrence?

DR CHLEBOWSKI: In the update from Z-FAST/ZO-FAST, which compares the use of bisphosphonates for patients on aromatase inhibitors up front to delayed therapy, we saw a signal that fewer breast cancer recurrences might occur among patients who receive this therapy, even in the delayed setting (Brufsky 2006a).

DR LOVE: What was your take on bone density data from the ATAC trial presented at ASCO in 2006 (Coleman 2006)?

DR CHLEBOWSKI: The ATAC data show approximately an eight percent difference in bone mineral density, which is statistically significant, but one has to remember just how much bone loss you need to drop a T-score — it's 10 to 12 percent. To go from normal to osteoporosis, it's 20 to 25 percent bone loss. They aren't big numbers.

However, none of the patients in the ATAC trial who had normal bone mineral density developed osteoporosis with five years of aromatase inhibitor therapy. When I examine the accumulated data, it seems unlikely that we would cause any hip fractures treating 50- and 60-year-olds with aromatase inhibitors for five years.

DR LOVE: What's your approach to monitoring bone density and using bisphosphonates for patients on aromatase inhibitors?

DR CHLEBOWSKI: I'm involved in the process of updating the ASCO bone health guidelines, and I believe it's clear now that almost no one needs annual bone mineral density testing. I expect the recommendation will be every two years. In addition, if the baseline test is normal and insurance issues exist, I believe you can wait longer.

As for prophylactic bisphosphonates, the question is, where do you draw the line? Some clinicians might choose to initiate bisphosphonates at a T-score of -1.5, based on Coleman's data, and that's probably reasonable (Coleman 2006). ■

SELECT PUBLICATIONS

Beral V et al. **Evidence from randomised trials on the long-term effects of hormone replacement therapy.** *Lancet* 2002;360(9337):942-4. **Abstract**

Black DM et al. **Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group.** *Lancet* 1996;348(9041):1535-41. **Abstract**

Braithwaite RS et al. **Meta-analysis of vascular and neoplastic events associated with tamoxifen.** *J Gen Intern Med* 2003;18(11):937-47. **Abstract**

Brufsky A et al. **An integrated analysis of zoledronic acid (ZA) for prevention of aromatase inhibitor associated bone loss (AIBL) in postmenopausal women (PMW) with early breast cancer (BCa) receiving adjuvant letrozole (LET).** San Antonio Breast Cancer Symposium 2006a;**Abstract 107**.

Brufsky A et al. **Management of cancer-treatment-induced bone loss in postmenopausal women undergoing adjuvant breast cancer therapy: A Z-FAST update.** *Semin Oncol* 2006b;33(2 Suppl 7):13-7. **Abstract**

Brufsky A et al. **Twenty-four month follow-up of the effect of zoledronic acid (ZA) on aromatase inhibitor associated bone loss (AIBL) in postmenopausal women (PMW) with early breast cancer (BCa) receiving adjuvant letrozole (LET).** San Antonio Breast Cancer Symposium 2006c;**Abstract 5060**.

Chlebowski RT et al. **Dietary fat reduction and breast cancer outcome: Interim efficacy results from the Women's Intervention Nutrition Study.** *J Natl Cancer Inst* 2006a;98(24):1767-76. **Abstract**

Chlebowski RT et al. **Mature analysis from the Women's Intervention Nutrition Study (WINS) evaluating dietary fat reduction and breast cancer outcome.** Presentation. San Antonio Breast Cancer Symposium 2006b;**Abstract 32**.

Chlebowski RT et al. **The Women's Health Initiative randomized trial of calcium plus vitamin D: Effects on breast cancer and arthralgias.** *Proc ASCO* 2006c;**Abstract LBA6**.

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**.

Coates AS et al. **Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: Update of study BIG 1-98.** *J Clin Oncol* 2007;25(5):486-92. **Abstract**

Coleman RE et al. **Effect of anastrozole on bone mineral density: 5-year results from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial.** *Proc ASCO* 2006;**Abstract 511**.

Cummings SR et al. **Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: Results from the Fracture Intervention Trial.** *JAMA* 1998;280(24):2077-82. **Abstract**

Geisler J et al. **Changes in bone and lipid metabolism in postmenopausal women with early breast cancer after terminating 2-year treatment with exemestane: A randomised, placebo controlled study.** *Eur J Cancer* 2006;42(17):2968-75. **Abstract**

Grimes DA, Lobo RA. **Perspectives on the Women's Health Initiative trial of hormone replacement therapy.** *Obstet Gynecol* 2002;100(6):1344-53. **Abstract**

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

Lonning PE et al. **Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer.** *J Clin Oncol* 2005;23(22):5126-37. **Abstract**

Low AK et al. **Hormone replacement therapy and coronary heart disease in women: A review of the evidence.** *Am J Med Sci* 2002;324(4):180-4. **Abstract**

Mauriac L et al. **Predictors of early relapse in postmenopausal women with hormone receptor-positive breast cancer in the BIG 1-98 trial.** *Ann Oncol* 2007;18(5):859-67. **Abstract**

Nabholtz JM, Gligorov J. **Cardiovascular safety profiles of aromatase inhibitors: A comparative review.** *Drug Saf* 2006;29(9):785-801. **Abstract**

Nelson HD et al. **Postmenopausal hormone replacement therapy: Scientific review.** *JAMA* 2002;288(7):872-81. **Abstract**

Pradhan AD et al. **Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: Prospective analysis from the Women's Health Initiative observational study.** *JAMA* 2002;288(8):980-7. **Abstract**

Prentice RL et al. **Low-fat dietary pattern and risk of invasive breast cancer: The Women's Health Initiative Randomized Controlled Dietary Modification Trial.** *JAMA* 2006;295(6):629-42. **Abstract**

Ravdin PM et al. **The decrease in breast-cancer incidence in 2003 in the United States.** *N Engl J Med* 2007;356(16):1670-4. **Abstract**

Thurlimann B et al; Breast International Group (BIG) 1-98 Collaborative Group. **A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer.** *N Engl J Med* 2005;353(26):2747-57. **Abstract**

Vakaet LA, Buyse M. **Comparative results of two adjuvant trials comparing 5 years of an aromatase inhibitor (AI) with five years of tamoxifen (TAM) in postmenopausal women with early breast cancer (EBC).** Poster. San Antonio Breast Cancer Symposium 2006;**Abstract 2084**.

Weiss LK et al. **Hormone replacement therapy regimens and breast cancer risk(1).** *Obstet Gynecol* 2002;100(6):1148-58. **Abstract**

Rowan T Chlebowski, MD, PhD, Maura N Dickler, MD and Mohammad Jahanzeb, MD

Tracks 1-25

Select Excerpts from the Discussion

Tracks 1-3

Case Discussion 1

A 60-year-old woman who underwent lumpectomy and radiation therapy for a 2.1-cm, intermediate-grade, ER-positive, PR-positive, HER2-negative infiltrating ductal carcinoma with two positive nodes.

She refused adjuvant chemotherapy and has completed five years of an aromatase inhibitor. Assessment of bone status reveals a T-score of -1.5. The patient is not receiving a bisphosphonate (From the practice of Dr Chlebowski)

SOURCE: Track 1.

DR LOVE: What are you generally doing for patients who complete five years of an adjuvant aromatase inhibitor (3.1)?

DR CHLEBOWSKI: At present, when I start patients on an aromatase inhibitor, I tell them about the lack of data, the potential safety concerns and my plan to prescribe the aromatase inhibitor for at least seven years.

I also say we might have more data on duration as time goes on. I do that up front because a fair number of patients who complete five years of therapy say, "I'm done with my cancer treatment."

Of course, this gets back to the issue of adherence with these longer regimens. I recently conducted a review evaluating tamoxifen adherence in three population-based studies (Chlebowski 2006).

It appears that 30 to 50 percent of women are stopping their tamoxifen treatment between the fourth and fifth year, and Dr Partridge presented a study demonstrating the same results with aromatase inhibitors (Partridge 2006; [3.2]).

Not many oncologists believe that up to half of the women aren't taking their medication in the fourth year. It's interesting to talk about longer duration of therapy if half of the women are taking a shorter duration volitionally.

DR LOVE: MJ, how do you approach the patient who has completed five years of adjuvant hormonal therapy?

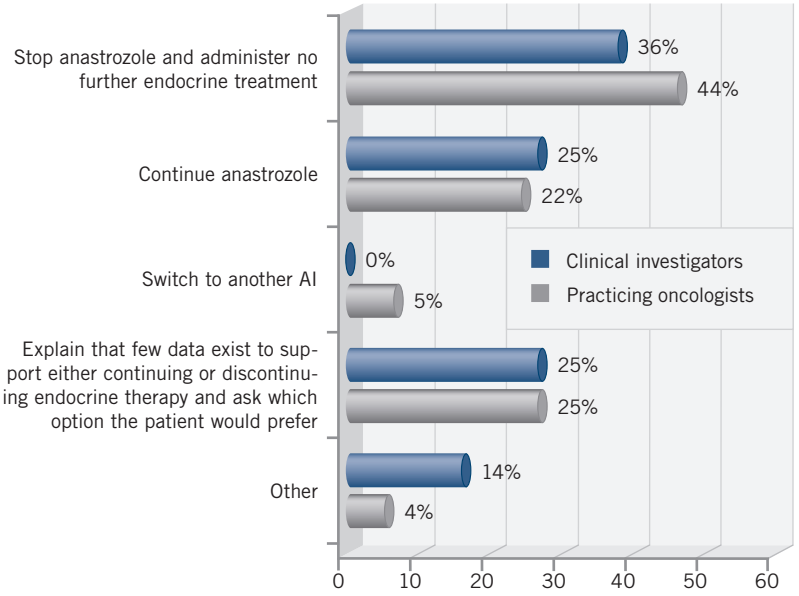
DR JAHANZEB: After five years of tamoxifen, it's easy. I fall back on the MA17 data and offer an aromatase inhibitor (Goss 2005).

After five years of an aromatase inhibitor, I'm left with telling the patient that the risk of relapse continues and something ought to be done, but I don't know what that something is.

If they are tolerating the aromatase inhibitor, are able to afford it and want to

3.1

A 61-year-old woman was treated five years ago at age 56 (postmenopausal) for an ER-positive, PR-positive, HER2-negative tumor with four positive nodes. She received chemotherapy/anastrozole for five years and has tolerated therapy without major difficulties. Which of the following would you recommend?



SOURCE: Love N; Research To Practice. *Patterns of Care in Medical Oncology* 2007;4(1). Available at: www.PatternsOfCare.com

continue taking it, like Rowan, I say, "Continue to take it." I'm not, however, telling them to take it two more years because I don't know the optimal duration. I'm hoping that within two years, more snippets of data will emerge, and then I'll update the recommendation.

Without much data but with some gut feeling, I am more emphatic about asking those patients with strongly ER-positive/PR-positive disease to continue taking it. With those who have weakly ER-positive disease, I'm not that particular about it.

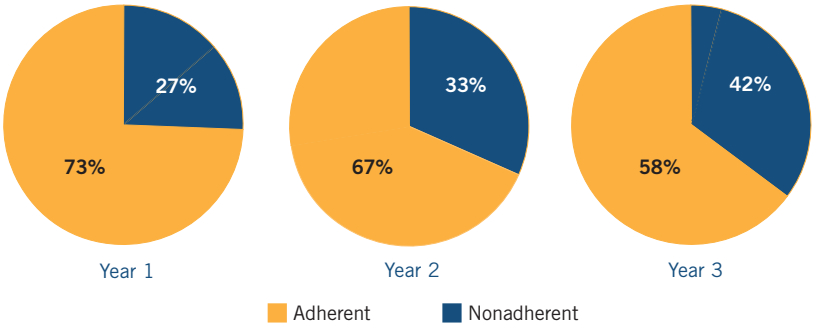
DR DICKLER: I often opt for continuing therapy, particularly for my patients at high risk.

If we know letrozole extends the benefits of five years of tamoxifen and the patient is at the five-year junction, I want to protect the patient during years five through possibly 10 after finishing five years of an aromatase inhibitor.

For this patient who had positive nodes, I would offer her continued aromatase inhibitor therapy, watch her bone density closely and take it on a year-

3.2

Mean Annual Adherence with Adjuvant Anastrozole: Analysis of Prescription Transactions Extracted from Insurance Claims Databases*



* Average of three databases

SOURCE: Adapted from Partridge AH et al. San Antonio Breast Cancer Symposium 2006;**Abstract 4044**.

by-year basis. I also wonder whether switching to tamoxifen would be the optimal strategy. I'm anxiously awaiting the results from BIG 1-98 in terms of the sequencing strategy. Switching after several years from one mechanism of action to another may be the best approach.

DR CHLEBOWSKI: Some people will recommend starting tamoxifen first so they can administer seven years of therapy. I don't find that attractive because we have the same lack of data for that strategy as we do for seven years of an aromatase inhibitor, and you're spotting people the first couple years of recurrences. You don't need to administer tamoxifen first to administer more than five years of aromatase inhibitor therapy, as I view the evidence.

Tracks 4-8

Case Discussion 2

A 64-year-old woman who underwent a modified radical mastectomy for a 2.5-cm, ER-positive, PR-positive, HER2-negative tumor. Ten out of 12 nodes were positive. She has an ejection fraction of 51 percent and a history of hypertension, diabetes, coronary artery disease, two CABGs and congestive heart failure (From the practice of Dr Jahanzeb)

SOURCE: Track 4.

DR LOVE: Maura, this is a difficult situation — 10 positive nodes and a history of congestive heart failure. What do you think you would have done?

DR DICKLER: It's a difficult case because she's not that old, but she has significant comorbidity from cardiovascular disease and breast cancer. These cases are a little easier when the patient is sitting in front of you because seeing what she looks like and getting her take on treatment is important.

The use of an anthracycline is not absolutely contraindicated in this setting, but this is a good case in which to consider the use of docetaxel and cyclophosphamide (TC). It's short therapy, and it's safer than AC. I would talk to her about dose-dense AC → T and also TC.

For patients who are particularly risk averse and for whom I want to use chemotherapy, I even still bring CMF into the mix. It is better tolerated in general, and I can probably get her through it. I would talk with her about each regimen and the potential benefits.

DR LOVE: Would you consider using an anthracycline for this patient?

DR DICKLER: She has an ejection fraction of 51 percent. You can follow her closely and obtain a MUGA scan after two cycles. It's her other comorbidities that worry me equally.

AC can be a tough regimen. We use steroids as antiemetics, and she's a diabetic, although with TC we do the same. That's why I'd bring CMF into the mix because it's less stressful and you don't need as many steroids in terms of the antiemetics.

I wouldn't rule out an anthracycline because 10 positive nodes pose a significant risk. This is a patient for whom I would conduct an evidence-of-disease evaluation.

I would do a CT scan and a bone scan because if I found any evidence of distant metastatic disease, I would offer her hormonal therapy. It would change her treatment significantly, and I could save her the morbidity of chemotherapy.

DR CHLEBOWSKI: I like the concept of TC, and we've been using it. I might use six instead of four cycles and tell her we have no data.

DR LOVE: What happened with this patient?

DR JAHANZEB: We talked to her about CMF, and we felt that most oncologists in the United States wouldn't consider it adequate therapy for this type of situation. We also talked about TC and the less-often-used regimen of CMF followed by docetaxel for three cycles.

We ultimately decided on TC, and without any data, we told her we believed four cycles were not enough and that maybe she should receive six cycles. She was treated with five cycles and had difficulty.

She received steroids, which made the diabetes management difficult with every cycle. She also developed progressive fatigue.

We told her, "We can't tell you whether there's a difference between five and six cycles. If this is how you feel, then let's call it a day and send you for radiation therapy," which is what we did.

DR LOVE: Are you observing that TC is better tolerated than AC?

DR CHLEBOWSKI: It's about the same — maybe a little better. I don't experience too much difficulty with it. Taxanes can be difficult for anybody, especially docetaxel in terms of taking it serially, but we've been pleased with our ability to deliver TC.

DR JAHANZEB: I find that single-agent docetaxel at 100 mg/m^2 is more difficult to tolerate than TC, which uses docetaxel at 75 mg/m^2.

DR DICKLER: I agree. I've had some good experiences with TC. I believe it's better tolerated, in general, than AC.

When I have a patient with higher-risk, node-negative disease, with whom I sometimes discuss AC → T but I don't feel as strongly, I say I have a middle-of-the-road regimen — TC — which is associated with less cardiac toxicity. Patients are comforted by that.

I don't use much AC for four cycles anymore. If TC offers an improved disease-free survival and none of the risk for congestive heart failure (Jones 2006; [3.3]), my bias is to use TC instead of AC.

3.3

Docetaxel and Cyclophosphamide (TC) versus Doxorubicin and Cyclophosphamide (AC) for Women with Early Breast Cancer (Median Follow-Up = 5.5 Years)

	TC (n = 506)	AC (n = 510)	Hazard ratio	*p*-value
Five-year disease-free survival	86%	80%	0.67	0.015
ER-negative/PR-negative	HR = 0.64 (95% CI: 0.38-1.04)			
ER-positive or PR-positive	HR = 0.71 (95% CI: 0.47-1.08)			
Node-positive	HR = 0.67 (95% CI: 0.45-0.98)			
Node-negative	HR = 0.73 (95% CI: 0.42-1.27)			
Five-year overall survival	90%	87%	0.76	0.13

Hazard ratios < 1 indicate values in favor of TC.

Toxicities (Grades III/IV)	TC	AC	*p*-value
Neutropenia	61%	55%	
Neutropenic fever	5%	2.5%	0.07
Nausea	2%	7%	<0.01
Vomiting	<1%	5%	<0.01

"We conclude that our study has established a new standard nonanthracycline regimen, TC, for the adjuvant treatment of early-stage breast cancer."

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

Tracks 9-13

Case Discussion 3

A 44-year-old woman of Ashkenazi Jewish descent whose mother had postmenopausal bilateral breast cancer. In 1998, the patient elected to undergo a bilateral mastectomy when she was diagnosed with DCIS. At that time, an incidental focus of ER-positive, PR-positive, HER2-negative, node-negative, invasive lobular carcinoma was found for which she did not receive any adjuvant therapy.

In June 2001, her tumor markers became elevated, and multiple lesions were discovered in her liver, the largest of which was 6.7 centimeters (From the practice of Dr Dickler)

SOURCE: Track 9.

DR CHLEBOWSKI: This patient has a whole range of treatment options, and this is one setting in which I'm almost reactive with the patient. In a clinical setting, you can go from the minimalist approach with tamoxifen to saying, "I'm going to use combination chemotherapy and try to get a higher response rate. Then maybe I'll switch to hormone therapy."

The tricky part with a younger patient is trying to explain the business at hand. It's important to figure out how this person views her life with this condition. Does she want to aggressively attack it? Some of us would feel strongly that we want to use chemotherapy to reduce the tumor burden and then do something else.

Or you can consider that the first regimen you start somebody off with — this is more my guiding principle — will be the one they will be on longest. In that case, you could either use tamoxifen or capecitabine as the initial therapy. I believe somebody at this age is likely to say, "I want to be as aggressive as possible." Then I go with a combination chemotherapy regimen, and we've been using capecitabine and docetaxel.

DR LOVE: MJ, how would you think this through?

DR JAHANZEB: I like to get a handle on the velocity of the disease, which is critical. Because of our biases, patients who are younger, have a larger tumor burden or have rapidly progressing disease tend to receive combination chemotherapy. Even if the disease is ER-positive or PR-positive, we start with chemotherapy, which is appropriate, if they have visceral crisis.

In this case, although the metastases are large, you know that she has not had her breasts for about four years. So it took at least four years for this to develop in her liver. That would tell me I could gamble on the side of being conservative and first try tamoxifen. My philosophy in metastatic disease is usually to do as little as possible for as long as possible.

So I would start with tamoxifen, keeping a close eye and evaluating her sooner rather than later for rapid progression. I wouldn't expect tamoxifen to work

before an average of four months, but this type of patient I would reevaluate within eight weeks to confirm that she's not rapidly progressing.

DR LOVE: Let's say she responds well to tamoxifen, and then her disease progresses. Then what?

DR JAHANZEB: At that time, I would use ovarian suppression with an aromatase inhibitor. Then, in the third-line setting, one could consider fulvestrant with ovarian suppression. I would like to maximize all the benefit from hormonal therapy and then switch to sequential single-agent chemotherapy. I like to start with nonalopecia-producing and less toxic single agents first, then go to the alopecia-producing or more toxic single agents and then to combination chemotherapy.

DR LOVE: What happened with this patient?

DR DICKLER: She obtained various opinions reflecting the options at hand. She opted to receive combination chemotherapy and was treated with doxorubicin and docetaxel for six cycles. She had a tremendous response initially.

After six cycles of chemotherapy, she received leuprolide and tamoxifen. She had a short-lived response to hormonal therapy, and within several weeks we diagnosed progression of disease in her liver.

DR LOVE: Rowan, if you saw this patient for a second opinion after she had a great response to chemotherapy and not much of a response to tamoxifen, what would you recommend?

DR CHLEBOWSKI: I don't believe we have many data indicating that how quickly somebody's disease progresses on hormone therapy determines whether she will respond to further hormone therapy. From the limited data from randomized trials, 30 to 40 percent of patients derive a clinical benefit from a second hormonal agent. Having said that, if she hasn't received capecitabine before, I would probably use that.

DR LOVE: What about capecitabine and bevacizumab?

DR CHLEBOWSKI: That combination is reasonable and could be considered.

DR JAHANZEB: Assuming we know she received docetaxel previously, I would be a little leery about using capecitabine/bevacizumab because that particular trial was negative. She received both an anthracycline and a taxane, and those patients did not seem to benefit in Kathy Miller's study of bevacizumab with capecitabine (Miller 2005). At the point of progression — knowing that she had received an anthracycline and a taxane — I would have tried capecitabine alone.

DR LOVE: Maura, what happened?

DR DICKLER: I presented this case because I have learned so much from this patient over many years. She was offered participation in that "negative" trial of capecitabine with or without bevacizumab. She was assigned to receive capecitabine and bevacizumab at the end of 2001.

It's now 2007, and she's still on that therapy. She had a partial response in terms of the scans, in that her liver never completely normalized, but recently she had a PET scan and no uptake was observed in the liver.

She has always had significant hand-foot syndrome and has undergone numerous dose reductions. About two years ago, she also developed significant hypertension and proteinuria that ranged from 1.0 to 3.5 grams. She has never had nephrotic syndrome but has had changes in her lipid profile.

The hypertension is managed with three medications — beta blockers, ACE inhibitors and calcium channel blockers. For the proteinuria, she has been closely followed by one of our nephrologists. We've managed it, at times, by arranging a break from the bevacizumab, which reduces the proteinuria relatively quickly. In a couple of weeks, we have been able to reduce the proteinuria to about one gram. Also, at times, we've reduced her dose of bevacizumab.

More recently, she's developed some chest heaviness that's been extensively worked up. Although we're unsure of the etiology, she believes it's the capecitabine. Because we have no definite evidence of disease and I believe she's deriving a lot of toxicity from the capecitabine, I recently offered her letrozole and stopped the capecitabine.

DR LOVE: What about the bevacizumab?

DR DICKLER: We are running a feasibility study of letrozole with bevacizumab, in which we've enrolled 43 patients. Although she's not part of that trial, it's proved safe, and we are in the late phases of designing a randomized trial in the CALGB evaluating endocrine therapy with or without bevacizumab, so I will probably continue the bevacizumab but closely watch her proteinuria.

Tracks 14-16

Case Discussion 4

A 52-year-old woman who underwent lumpectomy for a 2-cm, intermediate-grade, ER-positive, PR-positive, HER2-negative infiltrating ductal cancer with one positive node. She received six cycles of adjuvant TAC and completed two years of tamoxifen. Her menses had stopped six months prior to the initial diagnosis, and she has been amenorrheic for 30 months (From the practice of Dr Chlebowski)

SOURCE: Track 14.

DR LOVE: MJ, how would you have thought through the decision to switch this patient from tamoxifen to an aromatase inhibitor?

DR JAHANZEB: I would have obtained a hormone profile to assess her menopausal status. I've had patients who three years after chemotherapy have resumed their ovarian function, which scares me. So not only would I have obtained one, I would have repeated it six months later.

If she was menopausal, I would have discussed switching to an aromatase inhibitor, but I would try to talk her into staying on tamoxifen for five years and then taking an aromatase inhibitor for five years.

DR DICKLER: I feel similarly cautious about sequencing therapies for these patients too early because I have found that ovarian function can resume later than you expect. I suspect this woman is menopausal, but I would have checked estradiol levels frequently over time and then waited longer. However, you could probably sequence her therapies at this juncture.

Following TAC for six cycles, most patients become amenorrheic. I'd talk to her about it, but I wouldn't want to switch her too early to an aromatase inhibitor, which wouldn't be effective if she still had some residual ovarian function.

DR CHLEBOWSKI: I don't check hormone levels because I wouldn't consider switching her regardless of her hormone levels. If you obtain an estradiol level today, it will not tell you what will happen next week or the week after. For a patient who is sexually active, menstruating and taking an aromatase inhibitor, which is an egg stimulant, you run the risk of multiple pregnancies in addition to using ineffective therapy.

Many patients are probably being switched early, and the consequences are unclear. This is about the only group with which I'm enthusiastic about using tamoxifen for a while.

DR LOVE: What about ovarian suppression?

DR CHLEBOWSKI: Although Phase II trials are being conducted, and Bob Carlson is running one with about 50 patients (Carlson 2007), it's not clear how well or completely you're suppressing ovarian function with goserelin. I wouldn't be willing to use goserelin in the adjuvant setting with an aromatase inhibitor.

Tracks 17-20

Case Discussion 5

A 53-year-old, African American woman who underwent lumpectomy for a 4-cm, Grade III, ER-negative, PR-negative, HER2-negative, node-negative, infiltrating ductal carcinoma (From the practice of Dr Jahanzeb)

SOURCE: Track 17.

DR DICKLER: If this patient came to us, I would offer her participation in our pilot feasibility trial evaluating dose-dense AC → *nab* paclitaxel with bevacizumab. Otherwise, I would use dose-dense AC → T.

DR CHLEBOWSKI: We would probably administer six cycles of TAC.

DR LOVE: What did you end up doing for this patient?

DR JAHANZEB: We offered her participation in a study of metronomic

chemotherapy, which she declined. She clearly had high-risk disease, despite negative nodes. So we discussed our usual high-risk regimens — TAC, AC → docetaxel or dose-dense therapy — in that order, with de-emphasis on the dose-dense therapy because of our biases. She chose AC → docetaxel.

Tracks 22-24

Case Discussion 6

A 40-year-old premenopausal woman with symptomatic, ER-positive, PR-positive, HER2-positive inflammatory metastatic breast cancer. She is the mother of three young children, and her own mother died of breast cancer at 44 years of age (From the practice of Dr Dickler)

SOURCE: Track 22.

DR JAHANZEB: This is aggressive disease in a young patient, so I would like to be aggressive and use a combination regimen. Because she has HER2-positive disease, I would use trastuzumab in combination with chemotherapy. The next question is, will it be with single-agent or combination chemotherapy?

The only trial that demonstrated a benefit with triplet therapy was Nick Robert's study of paclitaxel/carboplatin/trastuzumab versus paclitaxel/trastuzumab. Although the trial wasn't powered and didn't show a survival benefit, it did show a benefit in time to progression (Robert 2006), which can also be important. I would be tempted to talk to her about that triplet therapy.

DR LOVE: MJ, what are your thoughts on docetaxel/carboplatin/trastuzumab (TCH) for this patient?

DR JAHANZEB: I would have talked to her about TCH. If we wanted to use just a single agent, which is my personal bias because of the results of our Phase II trial of vinorelbine/trastuzumab (Jahanzeb 2002), we would use vinorelbine to spare her the alopecia, the steroids and the neurotoxicity.

DR LOVE: What about the role of hormonal therapy?

DR JAHANZEB: Not concurrently. Once the disease is under control, for maintenance, then the question would have been, would you continue trastuzumab? Would you simply continue trastuzumab or add hormones at that time?

This patient is premenopausal, and we have no evidence supporting tamoxifen with trastuzumab. If she were postmenopausal after chemotherapy or we rendered her postmenopausal by ovarian ablation, we could consider the TAnDEM trial data showing that anastrozole with trastuzumab at least doubled the time to progression compared to anastrozole alone (Mackey 2006; [3.4]).

DR LOVE: How did you end up treating this patient?

DR DICKLER: She was offered participation in our Phase II clinical trial of *nab* paclitaxel, carboplatin and trastuzumab. She did extremely well with that

regimen. She had a partial response and complete normalization of the breast. The left axillary node shrank, and her pain was reduced.

She did have an unusual reaction to carboplatin, with intense pain during the infusion in her lower extremities and some flushing. It occurred several infusions into her treatment. Carboplatin was stopped and she continued on *nab* paclitaxel and trastuzumab until a maximal response was detected, followed by ovarian suppression and letrozole. ■

3.4

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

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

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

† Unplanned subgroup analysis

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

SELECT PUBLICATIONS

Carlson RW et al. **Goserelin plus anastrozole in the treatment of premenopausal hormone receptor positive, recurrent or metastatic breast cancer.** *Proc ASCO* 2007;**Abstract 1030**.

Chlebowski RT, Geller ML. **Adherence to endocrine therapy for breast cancer.** *Oncology* 2006;71(1-2):1-9. **Abstract**

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

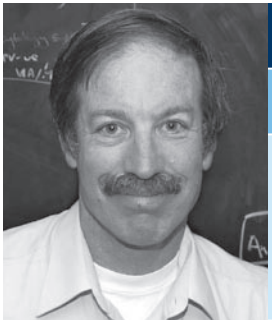
Jones SE et al. **Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer.** *J Clin Oncol* 2006;24(34):5381-7. **Abstract**

Mackey JR et al. **Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

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**

Partridge AH et al. **Adherence with adjuvant anastrozole therapy among women with early stage breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 4044**.

Robert N et al. **Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2006;24(18):2786-92. **Abstract**



INTERVIEW

Jack Cuzick, PhD

Dr Cuzick is John Snow Professor of Epidemiology at the Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Wolfson Institute of Preventive Medicine, Queen Mary's School of Medicine and Dentistry at the University of London in London, United Kingdom.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Could you review the meta-analysis you published regarding adjuvant LHRH agonists in premenopausal patients with hormone receptor-positive breast cancer (LHRH-Agonists Overview Group 2007)?

DR CUZICK: The LHRH agonists are a much-underused treatment. The trials have been around for some time but, individually, none of the trials has been convincing regarding what constitutes their best use. We managed to get all the individual patient data from virtually every trial in the world, and we

addressed two major questions: Are the LHRH agonists, when used alone, as effective as chemotherapy and second, if used in addition to chemotherapy, do they provide any additional benefit?

DR LOVE: The other question that oncologists have is how LHRH agonists compare to tamoxifen alone.

DR CUZICK: No direct comparisons to tamoxifen have been conducted, but some evidence emerged that LHRH agonists with tamoxifen added benefit compared to tamoxifen alone.

Unfortunately, no trials have addressed the most relevant question: If everybody receives tamoxifen, is adding an LHRH agonist the same as adding chemotherapy? This is unfortunate because it is a key question right now.

This overview was focused on chemical castration with LHRH agonists (4.1), and the trials were grouped into three classes. A few patients received an LHRH agonist versus nothing — only 338 patients. The effects were as predicted but not quite significant because of the small numbers. They demonstrated approximately a 30 percent reduction in recurrence and mortality.

4.1

Impact of Adjuvant LHRH Therapy on Recurrence and Death After Recurrence in Patients with Hormone Receptor-Positive Breast Cancer

		Percent change in hazard ratio (95% CI)			
	Number	Recurrence	*p*-value	Death after recurrence	*p*-value
No sys ± LHRH	338	-28.4	$p = 0.08$	-17.8	$p = 0.49$
No sys ± (LHRH + tam)	407	-58.4	$p < 0.0001$	-46.6	$p = 0.04$
Tam ± LHRH	1,013	-14.5	$p = 0.20$	-15.9	$p = 0.33$
Chemo ± LHRH	2,376	-11.7	$p = 0.07$	-12.9	$p = 0.11$
Chemo + tam ± LHRH	365	-15.9	$p = 0.37$	-32.6	$p = 0.14$
(Chemo + tam) ± LHRH*	2,741	-12.2	$p = 0.04$	-15.0	$p = 0.04$
Any sys ± LHRH†	3,754	-12.7	$p = 0.02$	-15.1	$p = 0.03$
Chemo ± (LHRH ± tam)	1,210	-26.7	$p = 0.001$	-24.4	$p = 0.01$
Chemo vs LHRH	3,184	3.9	$p = 0.52$	-6.7	$p = 0.40$
Chemo vs LHRH + tam	1,577	-10.1	$p = 0.25$	-11.1	$p = 0.37$

Sys = systemic therapy; LHRH = LHRH agonist; tam = tamoxifen; chemo = chemotherapy

* Combination of previous comparisons (chemo ± LHRH and chemo + tam ± LHRH)

† Combination of previous comparisons (tam ± LHRH, chemo ± LHRH and chemo + tam ± LHRH)

SOURCE: Cuzick J et al; LHRH-Agonists in Early Breast Cancer Overview Group. *Lancet* 2007;369(9574):1711-23. **Abstract**

The next group of trials directly evaluated an LHRH agonist versus chemotherapy. Most of the chemotherapy was CMF, but some anthracycline-based regimens were administered. Almost 4,000 patients were in that grouping, and the evidence suggested that they were essentially equally effective.

One of the limitations is that the chemotherapy was from an older era, but in fact, we could find no real difference between the anthracycline-based and the CMF-based chemotherapy. It does suggest that, certainly for women with estrogen receptor-positive, low-risk cancer, an LHRH agonist with tamoxifen is a reasonable option and chemotherapy isn't necessary for all those patients.

The third round of trials evaluated the addition of an LHRH agonist to chemotherapy, tamoxifen or both. The effects were modest — a 10 to 15 percent improvement in recurrence and mortality — and that was true whether it was added to tamoxifen, chemotherapy or both.

DR LOVE: In the studies of LHRH agonists in breast cancer, was the interval used for ovarian suppression one month or three months?

DR CUZICK: These were almost exclusively with monthly injections. A lot of interest is shown in that question because it would be much more convenient if it were three monthly.

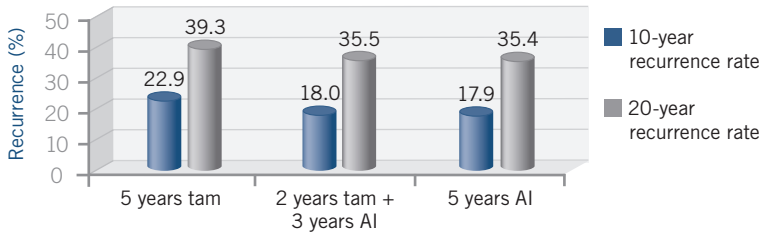
The data I've seen suggest that many, but not all, women can achieve ovarian suppression with three-monthly injections. The results are somewhat variable, and enough uncertainty exists that three-monthly injections are not typically recommended.

Track 6

DR LOVE: Controversy has existed for the last five or six years about the optimal sequence or the optimal endocrine therapy for postmenopausal women. Can you discuss the model you developed and where you believe this is heading (Cuzick 2007a; [4.2])?

4.2

Modeling Initial Use of Tamoxifen (Tam), Aromatase Inhibitor (AI) or Sequencing Strategies with Five Years of Treatment



SOURCE: Cuzick J et al. *Proc ASCO* 2007a;**Abstract 541**.

DR CUZICK: We've produced a model that evaluates and updates the data based on the most recent trial results. The model predicts that up-front treatment with an aromatase inhibitor will be the best strategy, in terms of both efficacy and toxicity.

The efficacy benefits of the up-front aromatase inhibitor over the switching strategy are modest, but I believe a lot of confusion has occurred, specifically about comparing the up-front treatments directly to the switching strategies, because the switching trials only evaluate patients that completed two years of treatment without side effects or a recurrence. It's a different population from the population receiving the up-front strategy.

Track 8

DR LOVE: In our Patterns of Care studies, we've seen a progressive shift since the 2001 publication of the ATAC data toward the use of up-front aromatase inhibitors.

That clearly is now the dominant initial strategy, at least in the United States, but a pocket of investigators still believe that tamoxifen should be considered up front for a couple of years for patients with node-negative disease. Do you agree or disagree with that?

DR CUZICK: I disagree. The only value of tamoxifen is for patients who do not tolerate the aromatase inhibitors. A subgroup of patients develop problematic arthralgias, but by and large the side effects of tamoxifen are worse than the side effects of the aromatase inhibitors.

The number of patients stopping treatment because of side effects was substantially and significantly higher with tamoxifen than with the aromatase inhibitors. We know problems are associated with tamoxifen, such as thromboembolic events and a range of gynecological problems, including endometrial cancer and a four times higher rate of hysterectomies (Duffy 2005, 2006).

So for patients with low-risk disease, the issues are more related to safety and tolerability than efficacy, and overall, the aromatase inhibitors are better. Clearly toxicities do occur, to the extent that some patients cannot tolerate these agents, and in those cases, tamoxifen is better than nothing.

For patients with higher-risk disease, the efficacy profile is most important. I can't, therefore, identify a group of patients for whom I wouldn't want to start with an aromatase inhibitor.

Track 15

DR LOVE: Can you review the IBIS-1 tamoxifen prevention trial data?

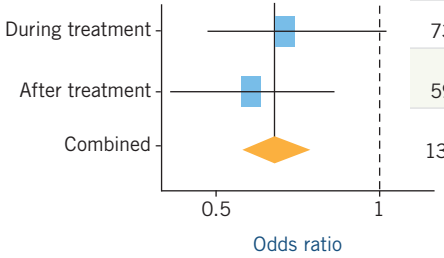
DR CUZICK: The IBIS-1 study began in 1994 and demonstrated essentially a 50 percent reduction in new ER-positive breast cancer, with no effect on ER-negative tumors (Cuzick 2002).

The European trials have kept themselves blinded. That study and the Royal Marsden study, which originally was the pilot study for IBIS-1, have been ongoing, and we recently updated the data with a median follow-up of eight years (Cuzick 2007b).

The results were exciting and as good as we could have ever hoped for. The benefit in the five years after stopping treatment was greater than the benefit during the five years of active treatment (4.3).

4.3

Long-Term Efficacy of Tamoxifen for Chemoprevention in IBIS-1: Incidence of Invasive ER-Positive Breast Cancer During and After Treatment (Median Follow-Up = 95.6 Months)



	Placebo	Tamoxifen	OR (95% CI)
During treatment	73	54	0.74 (0.51-1.07)
After treatment	59	33	0.56 (0.35-0.87)
Combined	132	87	0.66 (0.50-0.87)

SOURCES: Cuzick J et al. *J Natl Cancer Inst* 2007b;99(4):272-82. **Abstract**; Cuzick J et al. San Antonio Breast Cancer Symposium 2006;**Abstract 34**.

Track 17

DR LOVE: Can you provide an update on data related to quality of life in the ATAC study?

DR CUZICK: Not surprisingly, we see somewhat but not enormously higher rates of arthralgias with anastrozole.

The rate is 30 percent with tamoxifen and 36 percent with anastrozole (Buzdar 2006; [4.4]). So the effect is real, but it's a small effect compared to the fact that arthralgia is not uncommon in the early postmenopausal years anyway.

So to some extent, the aromatase inhibitors are being blamed for some arthralgias that they don't cause. They do increase the risk, but a lot of arthralgias will occur anyway.

We will learn more about that from the IBIS-2 study because we'll be comparing anastrozole to placebo, and there's no doubt that a fair amount of arthralgia is occurring in the placebo arm.

We have a nice paper that will be ready for San Antonio, in which we've analyzed the ATAC trial for the risk factors for arthralgia and its severity. There are risk factors for arthralgia that are stronger than treatment with an aromatase inhibitor.

4.4

Incidence of Arthralgias in Clinical Trials of Adjuvant Endocrine Therapy with Aromatase Inhibitors for Postmenopausal Women with Breast Cancer

Clinical trial	Median follow-up (years)	Drug	N	Definition of arthralgias	Incidence of arthralgias (%)	*p*-value
ATAC[1]	5.7	Anastrozole	3,092	Joint disorder	35.6	
		Tamoxifen	3,094		29.4	<0.0001
BIG 1-98[2]	4.25	Letrozole	2,448	Joint pain	20	
		Tamoxifen	2,447		13.5	<0.001
MA17[3]	2.5	Letrozole	2,572	Joint pain	25	
		Placebo	2,577		21	<0.001
NSABP-B-33[4]	2.5	Exemestane	799	Joint pain	1.0	
		Placebo	799		0.5	NR
IES[5]	4.6	Exemestane	2,320	Joint pain	18.6	
		Tamoxifen	2,338		11.8	<0.0001
ITA[6]	3.0	Anastrozole	223	Musculoskeletal	8.4	
		Tamoxifen	225	disorders	12.0	0.2
ABCSG	2.3	Anastrozole	1,120	Bone pain	19	
Trial 8[7]		Tamoxifen	1,117		16	0.05

SOURCES: [1] Howell A et al. *Lancet* 2005;365(9453):60-2. **Abstract**; [2] Coates AS et al. *J Clin Oncol* 2007;25(5):486-92. **Abstract**; [3] Goss PE et al. *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**; [4] Mamounas E et al. Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 49**; [5] Coombes R et al. *Lancet* 2007;369(9561):559-70. **Abstract**; [6] Boccardo F et al. *J Clin Oncol* 2005;23(22):5138-47. **Abstract**; [7] Jakesz R et al. *Lancet* 2005;366(9484):455-62. **Abstract**

Impact of Clinical Trial Reporting of Aromatase Inhibitor-Associated Arthralgias

"As part of toxicity analyses, all the major adjuvant trials of AIs have reported the incidence of musculoskeletal symptoms. However, none of the trials employed patient symptom questionnaires that focused specifically on musculoskeletal symptoms or asked directly about arthralgia.

The reported incidence of musculoskeletal symptoms reflects different definitions of symptoms, and is principally based on formal toxicity reporting, relying on patient self-report without corresponding rheumatological evaluation...

Consequently, the symptoms designated 'arthralgia' may differ widely among the trials, and the method of data capture strongly suggests that the reported trial incidence is substantially lower than the incidence seen in the clinic."

SOURCE: Burstein HJ. *Breast* 2007;16(3):223-34. **Abstract**

Track 10

DR LOVE: What are your thoughts about the duration of use of adjuvant aromatase inhibitors?

DR CUZICK: Duration of endocrine treatment is probably one of the key questions now, particularly whether we should treat beyond five years.

For the patient at average to higher risk, the question of five versus 10 years of treatment with an aromatase inhibitor is an important one.

DR LOVE: What do you think is going on when you see drops in recurrence rates when starting an aromatase inhibitor after five years of tamoxifen, maybe even with a delay of a few years after completing tamoxifen?

DR CUZICK: Breast cancer is striking in that the recurrence rate never drops below two percent per year, even out to 20 years. It's a disease with a long recurrence rate (4.5).

It's difficult to believe that those are all true recurrences. Many of those, to some extent, must be development of lesions that are not fully invasive at the time of diagnosis. So there's a mixture of prevention and treatment.

However, the data are impressive in indicating that longer treatment for many patients is likely to be beneficial. We've evaluated that in our modeling poster this year at ASCO and have also come to the conclusion that there are benefits to 10 years of treatment (Cuzick 2007a; [4.6]). ■

4.5

Late Risk of Relapse and Mortality Among Postmenopausal Women with Estrogen-Responsive Early Breast Cancer After Five Years of Tamoxifen

"…In a population-based setting, subgroups of women may be identified who are at variable levels of risk of relapse after 5 years of tamoxifen. Standard pathologic prognostic markers may be used to stratify patients at high, intermediate and low risk of breast cancer relapse and death.

Node-positive or T2 tumors are associated with a relatively high risk (>15%) of relapse or second breast cancer. Women with initially node-negative and grade 2 or 3 tumors are at intermediate risk of relapse of 10%.

A small subset of postmenopausal women can be identified who are at low (<5%) risk of relapse and may be adequately treated by 5 years of tamoxifen.

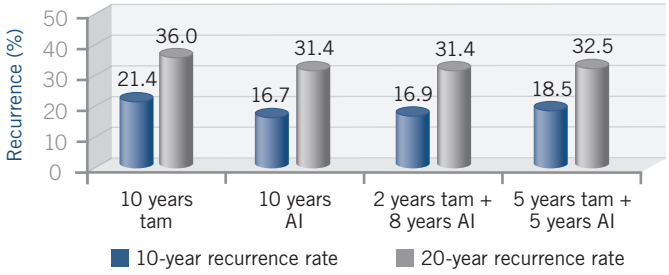
The subgroup analysis of node-negative patients should be approached cautiously due to the small number of patients and should be further investigated in other databases.

For women whose adjuvant therapy included an AI during the first 5 years after diagnosis, the risk of breast cancer as well as the role for further adjuvant hormonal therapy is not yet defined and will be determined by the results of randomized clinical trials and population-based studies."

SOURCE: Kennecke HF et al. *Ann Oncol* 2007;18(1):45-51. **Abstract**

4.6

Modeling the Effects of Up-Front Tamoxifen (Tam), Aromatase Inhibitor (AI) or Sequencing Strategies with 10 Years of Treatment



SOURCE: Cuzick J et al. *Proc ASCO* 2007a;**Abstract 541**.

SELECT PUBLICATIONS

Buzdar A et al. **Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: Long-term safety analysis of the ATAC trial.** *Lancet Oncol* 2006;7(8):633-43. **Abstract**

Coates AS et al. **Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: Update of study BIG 1-98.** *J Clin Oncol* 2007;25(5):486-92. **Abstract**

Coombes RC et al. **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 et al. **Optimal use of aromatase inhibitors for adjuvant treatment of hormone-sensitive early breast cancer: Up front or sequenced after tamoxifen?** *Proc ASCO* 2007a;**Abstract 541**.

Cuzick J et al. **Long-term results of tamoxifen prophylaxis for breast cancer — 96-month follow-up of the randomized IBIS-I trial.** *J Natl Cancer Inst* 2007b;99(4):272-82. **Abstract**

Cuzick J et al; LHRH-Agonists in Early Breast Cancer Overview Group. **Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: A meta-analysis of individual patient data from randomised adjuvant trials.** *Lancet* 2007;369(9574):1711-23. **Abstract**

Cuzick J et al. **First results from the International Breast Cancer Intervention Study (IBIS-I): A randomised prevention trial.** *Lancet* 2002;360(9336):817-24. **Abstract**

Duffy S et al. **Anastrozole is associated with a lower risk of endometrial abnormalities than tamoxifen: First report of the ATAC trial endometrial sub-protocol at 6 years follow-up.** San Antonio Breast Cancer Symposium 2006;**Abstract 4055**.

Duffy SR et al. **Gynecologic interventions during adjuvant therapy with anastrozole or tamoxifen: Results from the ATAC trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 2056**.

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA.17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

Howell A et al. **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**

Kennecke HF et al. **Late risk of relapse and mortality among postmenopausal women with estrogen responsive early breast cancer after 5 years of tamoxifen.** *Ann Oncol* 2007;18(1):45-51. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In a review of insurance claims databases, Dr Ann Partridge demonstrated that at three years, similar to the published tamoxifen data, approximately 40 percent of patients were nonadherent to adjuvant aromatase inhibitor therapy.**
   a. True
   b. False
2. **The primary comparison of the ECOG-E1199 trial demonstrated a disease-free survival difference between _____.**
   a. Paclitaxel and docetaxel
   b. Every three-week and weekly schedules
   c. Both a and b
   d. None of the above
3. **In the US Oncology adjuvant trial, the disease-free survival rate was significantly superior for AC (doxorubicin/cyclophosphamide) compared to TC (docetaxel/cyclophosphamide).**
   a. True
   b. False
4. **In the TAnDEM trial, postmenopausal patients with ER-positive and/or PR-positive, HER2-positive metastatic disease had a doubling in time to progression when trastuzumab was added to _____.**
   a. Tamoxifen
   b. Letrozole
   c. Anastrozole
   d. All of the above
5. **In a subgroup analysis from WINS, statistically significant reductions in relapse-free and overall survival were seen in patients with _____ breast cancer.**
   a. ER-positive, PR-positive
   b. ER-positive, PR-negative
   c. ER-negative, PR-positive
   d. ER-negative, PR-negative
6. **According to the SEER registries, between 2002 and 2003 the age-adjusted incidence of invasive breast cancer in the United States decreased by approximately _____ percent.**
   a. Two
   b. Five
   c. Seven
   d. 10
7. **In BIG 1-98, adjuvant letrozole resulted in a higher rate of Grade III to V cardiac events and cardiac deaths than tamoxifen.**
   a. True
   b. False
8. **With regard to bone health, the 68-month update of the ATAC trial demonstrated that _____.**
   a. Similar hip fracture rates emerged with anastrozole and tamoxifen
   b. No patient who began with normal bone density developed osteoporosis with five years of anastrozole treatment
   c. Both a and b
9. **In the meta-analysis by Dr Cuzick and colleagues, adjuvant LHRH agonists resulted in superior disease-free survival compared to tamoxifen among premenopausal patients with hormone receptor-positive disease.**
   a. True
   b. False
10. **Dr Cuzick and colleagues used published data to model the benefits of initial adjuvant treatment with aromatase inhibitors versus sequencing after tamoxifen and demonstrated that 10 years of up-front aromatase inhibitor therapy was superior to five years of tamoxifen followed by five years of an aromatase inhibitor.**
    a. True
    b. False

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

EVALUATION FORM

Breast Cancer Update — Issue 5, 2007

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 will be issued upon receipt of your completed Post-test and 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 switching to or sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of 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 appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data for biologic therapies and determine how these should be incorporated into the treatment algorithm for appropriate patients with metastatic disease. . 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions. . . . . 5 4 3 2 1 N/A

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
Jack Cuzick, PhD	5 4 3 2 1	5 4 3 2 1
Maura N Dickler, MD	5 4 3 2 1	5 4 3 2 1
Sharon Giordano, MD, MPH	5 4 3 2 1	5 4 3 2 1
Mohammad Jahanzeb, 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

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EVALUATION FORM

Breast Cancer Update — Issue 5, 2007

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.....

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

.....

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.....

Additional comments about this activity:

.....

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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:

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