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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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MIAMI BREAST CANCER CONFERENCE TUMOR PANEL DISCUSSION ON ADJUVANT SYSTEMIC THERAPY

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CME Certified

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STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the 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.
- 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 3 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Fox, Gradishar, Robertson, Borgen, O'Shaughnessy, Ravdin, Sainsbury, Shak and Sledge on the integration of emerging clinical research data into the management of breast cancer.

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UPCOMING EDUCATIONAL EVENTS

2006 Mission Conference of the Susan G Komen Breast Cancer Foundation: Many Faces, One Voice
June 11-13, 2006
Washington, DC
Event website: **komen.org**

23rd International Conference: Advances in the Application of Monoclonal Antibodies in Clinical Oncology
June 26-28, 2006
Mykonos, Greece
Event website: **immunology.org/meetings/mt54_05.htm**

UICC World Cancer Congress 2006
July 8-12, 2006
Washington, DC
Event website: **worldcancerconferences.com**

31st ESMO Congress
September 29-October 3, 2006
Istanbul, Turkey
Event website: **esmo.org**

NSABP Fall Meeting
October 13-16, 2006
Baltimore, Maryland
Event website: **nsabp.pitt.edu**

EDITOR'S NOTE

Neil Love, MD

ER-positive, tamoxifen-nonresponsive breast cancer is a bad disease

Professor John Robertson

Immediately after my first interview with Professor John Robertson in a dusty New York meeting room some years ago, I took a long walk in Central Park to ponder the man's words.

Underneath John's Beatle-esque haircut is a brain that spews megahypothesis after megahypothesis about breast cancer research from A to Z. My latest conversation with Professor Robertson is included in this program, and I have spent the last five days reading and rereading a 2001 paper* by his Nottingham group that he discusses during the interview.

As with many of the articles in Mark Lippman's *Breast Cancer Research and Treatment* (see an upcoming issue for an interview with Dr Lippman), this paper is loaded with fascinating but very complicated data points. Truth be told, I don't fully understand John's interpretation of this study, but it makes intuitive sense, which is always dangerous. John's bottom line favors starting an agent with greater antitumor activity (an aromatase inhibitor) rather than one with a longer safety track record (tamoxifen).

Like Soon Paik's mining of NSABP trials B-14 and B-20 to document the benefit of the Onco*type* DX™ assay, the Nottingham paper focuses on patients treated some time ago — in this case during the pre-adjuvant endocrine therapy days, when we could measure ER more accurately than we do today but did not offer hormone therapy until relapse.

Of great interest were the disease-free survival (DFS) curves of patients with ER-positive tumors that did not respond to tamoxifen when treated for metastatic disease.

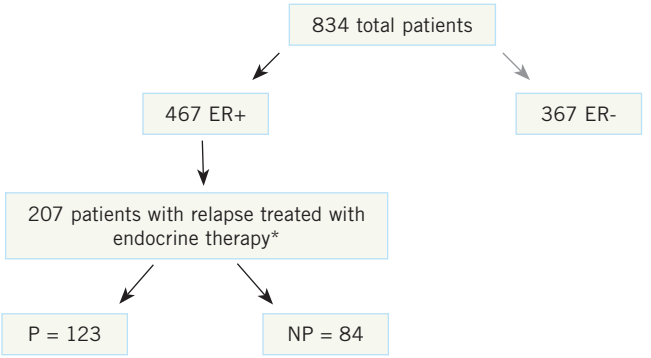
* Cheung KL, Nicholson RI, Blamey RW, Robertson JFR. **Selection of primary breast cancer patients for adjuvant endocrine therapy — Is oestrogen receptor alone adequate?** *Breast Cancer Res Treat* 2001;65(2):155-62. **Abstract**

These patients — with a median DFS of 21 months — relapsed much earlier than those who were endocrine responsive (Figures 1, 2). The patients also had significantly shorter survivals.

This pattern of early relapse and rapid downhill course is reminiscent of HER2-positive disease, and it is quite possible that many of these patients actually had HER2-positive tumors, although that information is not available.

1

Nottingham Breast Cancer Series (Patients Initially Treated from 1973 to 1983)



* 72% of patients received tamoxifen

P = progression at six months; NP = nonprogression at six months

SOURCE: Cheung KL et al. *Breast Cancer Res Treat* 2001;65(2):155-62. **Abstract**

2

Nottingham Breast Cancer Series — Patients with ER-Positive Tumors with Relapse — Progression (P)* versus Nonprogression (NP)† with Endocrine Therapy (n = 207)

	P	NP
Median disease-free survival (months)	21	41
	$p < 0.0001$	
Median postrelapse survival (months)	20	66
	$p < 0.0001$	
Median overall survival (months)	41	117
	$p < 0.0001$	

* Progression at six months on endocrine therapy of recurrent disease

† Tumor response or stable disease at six months

SOURCE: Cheung KL et al. *Breast Cancer Res Treat* 2001;65(2):155-62. **Abstract**

It is fascinating that the findings from this relatively obscure paper have numerous critical research and practice implications:

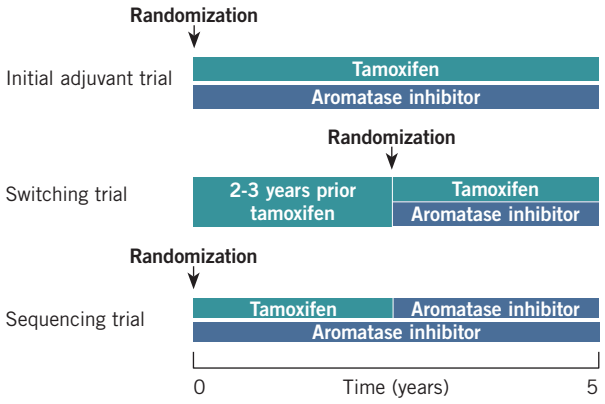
1. Clinical trials of sequencing endocrine therapies and trials of switching endocrine therapies focus on very different groups of patients (Figure 3).

A sequencing study randomly assigns patients up front to either five years of an AI or two or three years of tamoxifen followed by an AI, whereas a switching trial randomly assigns patients who have completed two to three years of tamoxifen to either continue tamoxifen or switch to an AI.

Presumably, if one waits two to three years to start an AI, the response rate is likely to be higher because many patients with unfavorable, "endocrine unresponsive" tumors will have relapsed before that time. The major randomized prospective sequencing trial (BIG 1-98) has not yet reported data on this question, but the Nottingham study suggests that hypothetical models making indirect comparison between trials such as ATAC and the switching trials are flawed because these studies focus on different patient populations.

3

Adjuvant Trial Designs

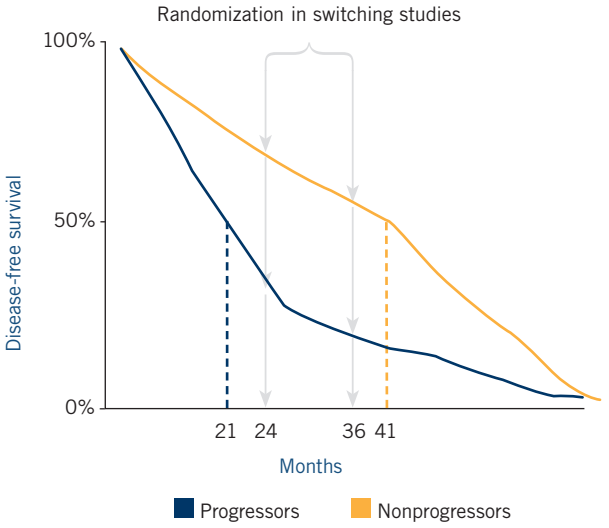


2. If one wishes to avoid relapse by using an AI instead of tamoxifen, the AI should be started early (Figure 4).

The Nottingham data set demonstrates that in patients with ER-positive tumors who later progressed on endocrine therapy, half of the relapses occurred within 21 months. The hazard curves for recurrence in ATAC (Figure 5) clearly demonstrate a significant difference during the first two years, suggesting that anastrozole may be effective in treating some of these tamoxifen-nonresponsive tumors. I look forward to asking oncologists, including the "TECHIES" on the ASCO AI technology assessment panel, what they think about the Nottingham data set and John's astute interpretation of it. I am particularly interested in learning whether they believe it is possible to select postmenopausal patients who should start treatment with tamoxifen rather than an aromatase inhibitor.

4

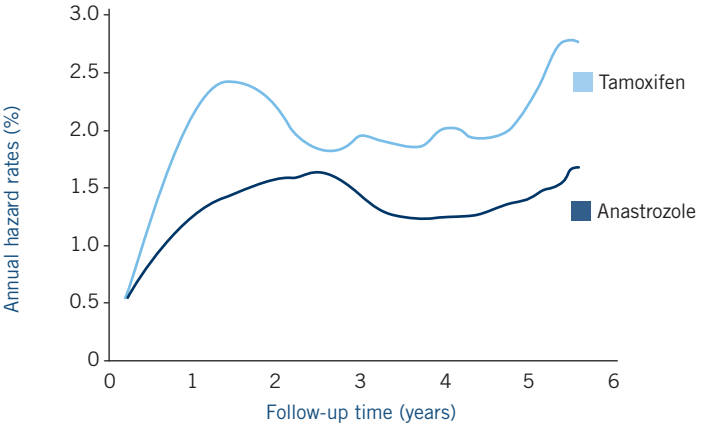
Disease-Free Survival in Progressors versus Nonprogressors on Endocrine Therapy for Recurrent Disease: Implications to Evaluating Switching and Sequencing Strategies



SOURCE: Derived from Cheung KL et al. *Breast Cancer Res Treat* 2001;65(2):155-62. **Abstract**

5

ATAC Trial: Smoothed Hazard Rates for Recurrence: HR-Positive Patients



SOURCE: With permission. Howell A, on behalf of the ATAC Trialists' Group. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 1**.

A small yet vocal minority of investigators believes that patients with lower-risk, node-negative, receptor-positive tumors are candidates for a sequencing strategy of two to three years of tamoxifen followed by an AI. A major part of the rationale for this line of thinking is the long-term safety data we have for tamoxifen versus the AIs. However, when one focuses on antitumor effect, following John's logic, those few node-negative patients who do relapse are more likely to do so in the first two years of therapy and will not be salvaged by a delayed AI approach.

In the next few weeks, our CME group will send out the edited proceedings of a Think Tank roundtable that we hosted recently in Miami with 12 renowned breast cancer investigators. The group was lively, to say the least, and when we discussed optimal long-term endocrine therapy for postmenopausal women with ER-positive tumors, I thought we would need to borrow Jerry Springer's bodyguards to separate the combatants.

John sat quietly through the verbal melee, and when his turn came, he quoted the 2001 Nottingham paper, and when he described the short DFS of the tamoxifen-unresponsive patients, you could see the cranial light bulbs go on around the table. Cliff Hudis interjected, "This looks like ER-negative disease." Exactly, except in this case, there may actually be an endocrine therapy (AIs) to help many of these patients. ■

— Neil Love, MD
NLove@ResearchToPractice.net

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INTERVIEW

Kevin R Fox, MD

Dr Fox is Director of the Rena Rowan Breast Center and Associate Professor of Medicine at the University of Pennsylvania Cancer Center in Philadelphia, Pennsylvania.

Tracks 1-19

Select Excerpts from the Interview

Track 5

DR LOVE: Can you talk about what we know about ovarian function and resumption of menses in premenopausal women after chemotherapy?

DR FOX: A great deal of data have been collected through NSABP trial B-30

and a project that was initiated by the late Dr Jeanne Petrek, which examined the natural history of loss of menstrual function during breast cancer treatment.

In this first large-scale evaluation of the effect of taxane-based chemotherapy on menstrual function, it was observed that the likelihood of becoming amenorrheic was age related, which you would expect with any chemotherapy regimen.

In a nonrandomized setting, in terms of amenorrhea, those patients who received taxanes fared a little worse than those who had not received taxanes (Petrek 2005).

These data also demonstrated that if a premenopausal woman is treated with chemotherapy and becomes amenorrheic, it is inappropriate to assume that she will remain in a state of real menopause. Based on the natural history data, it appears to take two years to establish with some certainty that a woman will remain in a state of menopause.

If a 45-year-old woman — five years from the mean age of menopause — receives chemotherapy and becomes amenorrheic, I do not believe we can be assured that her ovaries will remain in a state of menopause until we've followed her for two years.

Track 7

DR LOVE: How do you present the option of chemotherapy to premenopausal women who may be willing to accept an increased risk of relapse to maintain fertility?

DR FOX: The friendliest regimen with respect to not inducing permanent amenorrhea appears to be four cycles of AC (Petrek 2006). This regimen has been around long enough that we have accumulated experience, and in aggregate, AC produces less amenorrhea than CMF. Based on ASCO presentations, evidence suggests that the addition of a taxane may increase the amenorrhea rates more than AC alone.

Track 13

DR LOVE: Can you provide an update of clinical research on adjuvant hormonal therapy for premenopausal patients?

DR FOX: The most significant challenge in developing new therapeutic strategies for premenopausal women with hormone receptor-positive breast cancers is the issue of ovarian suppression.

We are participating in one of the two largest clinical trials (1.1) addressing this issue: the SOFT trial, which randomly assigns premenopausal women with receptor-positive cancers to receive tamoxifen alone, ovarian suppression for five years with tamoxifen or ovarian suppression for five years with exemestane.

1.1 **Trials of Adjuvant Endocrine Therapy with Ovarian Suppression**

Study	N	Eligibility	Randomization
IBCSG-24-02 (SOFT trial)	3,000 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	T x 5y OFS + T x 5y OFS + E x 5y
IBCSG-25-02 (TEXT trial)	1,845 (Open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Triptorelin ± chemotherapy + T x 5y Triptorelin ± chemotherapy + E x 5y

T = tamoxifen; OFS = ovarian function suppression with triptorelin, surgical oophorectomy or ovarian irradiation; E = exemestane

SOURCES: ibcsg.org; NCI Physician Data Query, April 2006.

Track 15

DR LOVE: What are your thoughts about the clinical trials of aromatase inhibitors for postmenopausal patients and their current implications for clinical practice?

DR FOX: At the moment, you have to evaluate the data based on where the patient is in her course of treatment.

The ATAC trial addresses one scenario, which is treatment of the newly diagnosed postmenopausal patient with estrogen receptor-positive breast cancer, and this trial provides irrefutable evidence that anastrozole is superior to tamoxifen with respect to reducing the risk of recurrence. The available data suggest that five years of an aromatase inhibitor is the best therapy for the newly diagnosed patient (Howell 2005).

The second scenario is that in which the patient is in the middle of a course of therapy. The International Exemestane Study and the trials of anastrozole, which were similarly constructed (Coombes 2005; Boccardo 2005; Jakesz 2005), were designed to enroll patients at the midpoint of a course of tamoxifen therapy and measure outcomes from the point of changing treatment.

Patients were randomly assigned to continue tamoxifen or to switch to an aromatase inhibitor for the balance of the five-year period.

For the patient in the middle of a course of tamoxifen therapy or the premenopausal woman who's become amenorrheic from chemotherapy and has been on tamoxifen and amenorrheic for two years, it is appropriate to switch to an aromatase inhibitor.

A third situation is that in which the patient has completed five years of tamoxifen. The only trial addressing this is MA17, which demonstrates that letrozole produces a small but measurable reduction in the risk of recurrence and an indication of a survival benefit in women with node-positive disease (Goss 2005).

Track 16

DR LOVE: Do you measure FSH, LH and estradiol levels in a premenopausal woman who becomes amenorrheic on chemotherapy before administering an aromatase inhibitor?

DR FOX: If our patients report two years of amenorrhea and we are considering switching them to an aromatase inhibitor, we always try to corroborate that information with an estradiol and an FSH level, recognizing the occasional shortcomings of either of those measurements.

In my own practice, I require that a patient have nonmeasurable levels of estrogen and an elevated FSH in the postmenopausal range before prescribing an aromatase inhibitor. ■

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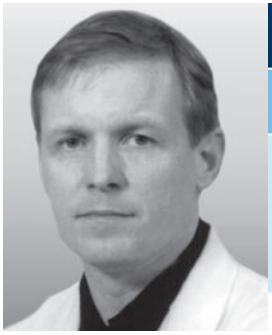


INTERVIEW

William J Gradishar, MD

Dr Gradishar is Director of Breast Medical Oncology and Associate Professor of Medicine at the Robert H Lurie Comprehensive Cancer Center at Northwestern University Feinberg School of Medicine in Chicago, Illinois.

Tracks 1-19

Select Excerpts from the Interview

Tracks 2, 4

DR LOVE: What is the current status of nanoparticle albumin-bound (*nab*) paclitaxel in the treatment of metastatic breast cancer, and how does it compare with paclitaxel in terms of neurotoxicity and efficacy?

DR GRADISHAR: In the last year, the use of *nab* paclitaxel has increased

significantly, and as clinicians gain more experience with it, they get a better understanding of when it's used most effectively.

When *nab* paclitaxel was developed, an underlying notion was that if you eliminated the solvents, all the neuropathy would disappear.

It has been demonstrated that Cremophor® is significantly related to the development of peripheral neurotoxicity that is long-lived and potentially not completely reversible once it develops in patients.

In the pivotal trial, an every three-week schedule of *nab* paclitaxel at 260 mg/m^2 was compared to the standard dose of paclitaxel at 175 mg/m^2. Interestingly, the rate of Grade III neuropathy with *nab* paclitaxel was in the range of 10 percent compared to two percent for the patients who received paclitaxel (Gradishar 2005).

However, what appears to be consistent with *nab* paclitaxel in both the every three-week and weekly schedules is that the neuropathy seems to be different than that seen with paclitaxel.

With *nab* paclitaxel it appears to be more short-lived, with the majority of patients being able to resume therapy within three weeks.

In terms of efficacy, approximately 40 percent of the patients had not received prior therapy for metastatic disease, and in that group of patients, the response rate for *nab* paclitaxel was far superior to the response rate among patients treated with paclitaxel (Gradishar 2005; [2.1]).

A CALGB trial will be evaluating weekly and every three-week schedules of *nab* paclitaxel versus paclitaxel in the metastatic disease setting, but we don't have any data from that trial yet.

2.1

Pivotal Phase III Trial of *Nab* Paclitaxel versus Paclitaxel: Efficacy Data

Parameter	*Nab* paclitaxel[1] (n = 229)	Paclitaxel[2] (n = 225)	*p*-value
Complete and partial response			
All patients	33%	19%	0.001
First-line therapy	42%	27%	0.029
Second-line or greater therapy	27%	13%	0.006
Median time to tumor progression	23.0 weeks	16.9 weeks	0.006
Median survival			
All patients	65.0 weeks	55.7 weeks	0.374
Second-line or greater therapy	56.4 weeks	46.7 weeks	0.024

[1] *Nab* paclitaxel 260 mg/m^2 every three weeks without premedication

[2] Paclitaxel 175 mg/m^2 every three weeks with premedication

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2005;23(31):7794-803. **Abstract**

Track 6

DR LOVE: In your opinion, what is the optimal first-line taxane in the metastatic setting?

DR GRADISHAR: The data are still more abundant with both paclitaxel and docetaxel than with *nab* paclitaxel, so for basing a decision on the length of experience, those agents have been around for a longer time.

However, I see no reason to believe that *nab* paclitaxel will prove inferior to those drugs with more data. I believe *nab* paclitaxel will compare favorably, if not prove to be superior.

When you examine clinical trials that have evaluated docetaxel or paclitaxel in similar patient populations with metastatic disease, the indirect evidence shows the activity of *nab* paclitaxel to be comparable to docetaxel.

These agents may have similar antitumor effects, so one should consider other factors, including toxicities, patient convenience and cost.

DR LOVE: If we determine that *nab* paclitaxel has the same antitumor effect as docetaxel and paclitaxel, do you believe the advantages of this agent, in terms of lack of premedication and shorter infusion time, make it the preferred agent?

DR GRADISHAR: That's an important question. When you think of busy office practices, the throughput of patients and the convenience to patients are important. An upside to *nab* paclitaxel clearly is the shorter infusion time and the lack of need for premedication.

As for the higher acquisition cost of *nab* paclitaxel, economic analyses suggest that some of the downstream expenses related to administering paclitaxel or docetaxel — specifically the costs of premedications and antibiotics or growth factors to manage the neutropenias or cytopenias — result in a net savings with the use of *nab* paclitaxel.

Although we need more information, I believe we shouldn't necessarily be put off by the up-front cost; we should take into account the whole package of managing the patient's treatment.

2.2

Nanoparticle versus Standard Paclitaxel

"Compared with three-weekly polyoxyethylated castor oil-based paclitaxel, ABI-007 would seem to have several advantages. First, efficacy with respect to response and time to progression seems superior. Second, and arguably most importantly, this is a taxane that can be given three-weekly, in 30 minutes, and without premedication. For patients with a contraindication to steroids, this is a major advantage. In addition, the lower incidence of myelosuppression favors ABI-007, and although sensory neuropathy was more common, this was reversible and relatively short lived for the majority of patients."

SOURCE: Harries M et al. *J Clin Oncol* 2005;23(31):7768-71. No abstract available

Track 9

DR LOVE: Would you summarize the clinical trial findings with bevacizumab in metastatic breast cancer?

DR GRADISHAR: One of the early trials suggested that combining bevacizumab with capecitabine, at least in patients who were heavily pretreated, did not bring much in the way of additional benefit compared to administering capecitabine alone (Miller 2005b).

That was disappointing and in contrast to what has been seen in other disease sites, particularly colorectal cancer, for which bevacizumab is widely used. Rather than abandoning the agent in breast cancer, another trial was initiated comparing paclitaxel with or without bevacizumab. The data clearly showed a benefit that favored the combination (Miller 2005a; [2.3]).

DR LOVE: Can you discuss the related XCaliBr study you are chairing with George Sledge?

DR GRADISHAR: Rather than assuming there was no reason to pursue bevacizumab with a 5-FU–like drug, the XCaliBr trial was designed to evaluate the combination of bevacizumab and capecitabine as first-line treatment for metastatic breast cancer (2.5). In this trial, the patients must have HER2-negative, measurable disease.

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

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

2.4

ECOG-E2100: Paclitaxel with or without Bevacizumab as First-Line Therapy

"The addition of bevacizumab to paclitaxel significantly prolongs progression-free survival and increases the objective response rate with minimal increases in toxicity. 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. The next step in this process will activate soon in a trial known as E2104. This adjuvant pilot trial will investigate the safety and feasibility of incorporating bevacizumab into standard adjuvant chemotherapy, using the dose-dense anthracycline followed by paclitaxel regimen, as used in the previous CALGB-9741 trial."

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

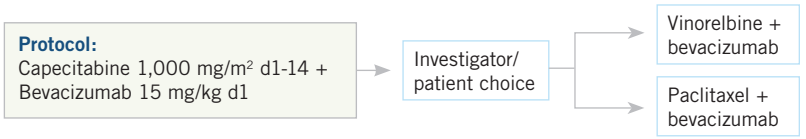
The trial has almost reached its accrual goal, which is around 100 patients, so we anticipate it will be closed soon. This study will examine the issue of continuing bevacizumab on disease progression and will try to determine if there's any differential effect between bevacizumab with vinorelbine or paclitaxel as second-line therapy.

2.5

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

Protocol ID: XCaliBr
Target Accrual: 92 (Open)

Eligibility: Newly diagnosed metastatic breast cancer



SOURCE: Presentation. Research To Practice *Breast Cancer Update* CME Forum, Los Angeles, California, 2005.

Track 15

DR LOVE: Our Patterns of Care studies indicate that clinical investigators use capecitabine much earlier in the treatment algorithm than physicians in community practice, and as I recall, you are among the investigators who use single-agent capecitabine pretty early in metastatic disease.

Has that approach changed with the bevacizumab data?

DR GRADISHAR: I still believe that capecitabine is a good up-front agent to use in metastatic disease for many patients, and that hasn't changed with the bevacizumab data.

However, the data that emerge from the XCaliBr study (2.5) may provide justification for using capecitabine with bevacizumab, assuming the data are positive and comparable to what we saw in the E2100 study (Miller 2005a).

DR LOVE: What type of patient do you consider an ideal candidate for front-line, single-agent capecitabine in the metastatic setting?

DR GRADISHAR: Capecitabine is comparable to our most active chemotherapy drugs, but I don't view any drug as the best agent in a particular situation. I would use capecitabine for patients with minimal visceral disease such as small liver metastases, but docetaxel or *nab* paclitaxel would be fine as well.

It's a judgment call that you make with each patient depending on her preferences. ■

SELECT PUBLICATIONS

Gradishar W et al. **Cost-effectiveness of nanoparticle albumin-bound paclitaxel versus docetaxel in the treatment of metastatic breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 5044**.

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

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

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

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 2005a;**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* 2005b;23(4):792-9. **Abstract**

Moreno-Aspitia A, Perez EA. **Nanoparticle albumin-bound paclitaxel (ABI-007): A newer taxane alternative in breast cancer.** *Future Oncol* 2005;1(6):755-62. **Abstract**

Nyman DW et al. **A phase I trial of ABI-007, nanoparticle paclitaxel, administered to patients with advanced non-hematologic malignancies.** *Proc ASCO* 2004;**Abstract 2027**.

Nyman DW et al. **Phase I and pharmacokinetics trial of ABI-007, a novel nanoparticle formulation of paclitaxel in patients with advanced nonhematologic malignancies.** *J Clin Oncol* 2005;23(31):7785-93. **Abstract**

O'Shaughnessy JA et al. **Weekly nanoparticle albumin paclitaxel (Abraxane) results in long term disease control in patients with taxane-refractory metastatic breast cancer.** San Antonio Breast Cancer Symposium 2004;**Abstract 1070**.

Perez EA et al. **Two concurrent phase II trials of paclitaxel/carboplatin/trastuzumab (weekly or every-3-week schedule) as first-line therapy in women with HER2-overexpressing metastatic breast cancer: NCCTG study 983252.** *Clin Breast Cancer* 2005;6(5):425-32. **Abstract**

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

Seidman AD et al. **CALGB 9840: Phase III study of weekly (W) paclitaxel (P) via 1-hour (h) infusion versus standard (S) 3h infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC.** *Proc ASCO* 2004;**Abstract 512**.

Sparano JA et al. **Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199.** San Antonio Breast Cancer Symposium 2005;**Abstract 48**.

Stinchcombe TE et al. **Preliminary results of phase I trial of carboplatin (CP) in combination with ABI-007 administered weekly or every 3 weeks in patients (pts) with solid tumors.** San Antonio Breast Cancer Symposium 2005;**Abstract 1092**.

Young O et al. **Randomized pre-operative study of 750 mg of fulvestrant and 20 mg tamoxifen in premenopausal women with estrogen receptor-positive breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 5084**.

INTERVIEW

Professor John F R Robertson, MB, ChB, BSc, MD

Dr Robertson is Professor of Surgery and Head of the Academic Division of Breast Surgery at the University of Nottingham City Hospital in Nottingham, United Kingdom.

Tracks 1-10

Select Excerpts from the Interview

Track 2

DR LOVE: In your opinion, should some postmenopausal patients be started on adjuvant tamoxifen up front and then switched to an aromatase inhibitor, or should postmenopausal women generally be started on an adjuvant aromatase inhibitor?

DR ROBERTSON: Until now, we regarded five years of tamoxifen as the gold standard for postmenopausal patients with ER-positive disease. Now we have data comparing five years of an aromatase inhibitor to tamoxifen. Two studies indicate that the aromatase inhibitors are clearly more effective and have different side-effect profiles (Howell 2005; Thürlimann 2005).

We currently have no data on sequencing studies, by which I mean trials that start tamoxifen up front and change to an aromatase inhibitor after two to three years, which is different from the switching trials. Sequencing trials are evaluating the concept of starting all patients on tamoxifen and switching

them over to an aromatase inhibitor at two to three years.

The switching trials involved taking a group of people who had reached two to three years — among whom there'd been a number of recurrences — and switching over the people who were still disease free. So the sequencing and the switching strategies are entirely different.

DR LOVE: It sounds as though you may be splitting fine hairs, but this is an important concept.

DR ROBERTSON: I believe so, in that we know that in the adjuvant setting, the peak of recurrences occurs after approximately two years among patients with either ER-positive or ER-negative disease.

It's likely that a disproportionate number of patients with ER-positive, hormone-resistant disease experience recurrence during the first two years, so afterwards a more hormone-sensitive group remains. Therefore, if a new drug is more efficacious, the hazard ratio for risk reduction will be larger in that population than in the initial population treated up front.

We conducted an interesting study in which we took approximately 1,000 patients who underwent surgery and radiation therapy but received no systemic therapy. Approximately 400 of those patients experienced recurrence.

For those who experienced recurrence, what happened with their metastatic disease informed us whether they were hormone sensitive. So we had four groups of patients: ER-positive, hormone sensitive; ER-positive, hormone insensitive; ER-negative, hormone sensitive (a small group of patients) and ER-negative, hormone insensitive.

In a replotting of the disease-free survival curves for the 400 patients with hormone sensitivity data, the curves for patients with ER-positive and ER-negative disease overlap.

However, the ER-positive, hormone-insensitive group experienced recurrences earlier than the ER-positive, hormone-responsive group, although they had not received prior hormonal therapy (Figure 2, page 4).

This indicates that those populations — although we call them ER-positive — have another factor that makes their disease recur more quickly. That's why they don't respond as well to hormonal therapy.

That's the point I'm making about the difference between using a sequencing policy up front and a switch policy at two to three years. In the switch strategy, a greater portion of the ER-positive, hormone-insensitive patients has been omitted. That is why a higher hazard ratio exists in the data from the switch studies.

For patients who are going to experience recurrence in the first couple of years, starting with an aromatase inhibitor instead of tamoxifen will reduce the risk of recurrence substantially.

Tracks 5, 7

DR LOVE: Would you discuss the trials comparing fulvestrant and aromatase inhibitors in the metastatic setting?

DR ROBERTSON: The SoFEA trial compares exemestane to fulvestrant following another aromatase inhibitor (3.1). The EFECT study is also testing the question of exemestane versus fulvestrant following another aromatase inhibitor. That study has finished recruiting and is now in the follow-up phase, so the results should be reported in the foreseeable future.

DR LOVE: What do you expect the SoFEA trial to demonstrate?

DR ROBERTSON: I hope we see an improvement by combining the two treatments, though I suspect we may have answers to that question before the SoFEA trial results are reported, in that metastatic studies often take a bit longer to run. A couple of ongoing studies are also combining therapies, and they may report sooner.

The SWOG-S0226 trial is comparing fulvestrant with anastrozole to anastrozole alone, so we may see whether the combination is better than a single-agent aromatase inhibitor, and that will be an interesting result.

We're conducting a presurgical study in the United Kingdom evaluating fulvestrant versus anastrozole versus the combination. This trial will extend the previous presurgical study we performed with 50 mg, 125 mg and 250 mg of fulvestrant (Robertson 2001).

This time we're using fulvestrant at 500 mg and anastrozole. We're attempting to determine whether we can elicit a greater effect by increasing the dose and

3.1

Phase III Trial of Fulvestrant with or without Concomitant Anastrozole versus Exemestane Following Progression on Nonsteroidal Aromatase Inhibitors

Protocol ID: ISRCTN44195747, SoFEA, NCT00253422
Target Accrual: 750

Eligibility
Postmenopausal women with ER- and/or PR-positive metastatic breast cancer that has progressed during endocrine therapy with a nonsteroidal aromatase inhibitor

R

- Fulvestrant + placebo
- Fulvestrant + anastrozole
- Exemestane

Study Contact:
Stephen Johnston, MD, Protocol Chair
Tel: 44-20-7808-2745
Institute of Cancer Research-UK

SOURCES: National Cancer Research Network Trials Portfolio. Available at http://controlled-trials.com/isrctn/trial/%7c/o/44195747.html April 15, 2006; NCI Physician Data Query, May 2006.

determining how that compares when we both increase the dose and decrease the estradiol level.

Track 9

DR LOVE: Would you discuss the data Mike Dixon presented at the 2005 San Antonio Breast Cancer Symposium evaluating higher doses of fulvestrant in premenopausal women?

DR ROBERTSON: Mike's study followed from one that we conducted two or three years ago, in which we administered 250 mg of fulvestrant to premenopausal women.

We did not see any effect on ER, PR or Ki-67 — the proliferation marker — when fulvestrant was administered two to three weeks before surgery (Robertson 2004).

So in our study we saw decreases in ER, PR and Ki-67 in postmenopausal patients, but we didn't see the same effects in the premenopausal patients at a dose of 250 mg.

Mike Dixon treated premenopausal patients with a dose of 750 mg of fulvestrant, and his data indicated similar effects on ER, PR and Ki-67 in premenopausal women with 750 mg (Young 2005) as we had seen in postmenopausal women with 250 mg (Robertson 2001). ■

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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**

Cheung KL et al. **Selection of primary breast cancer patients for adjuvant endocrine therapy — Is oestrogen receptor alone adequate?** *Breast Cancer Res Treat* 2001;65(2):155-62. **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**

Robertson JFR et al. **Effects of fulvestrant in premenopausal women with oestrogen receptor-positive primary breast cancer.** *Eur J Cancer Suppl* 2004;2(3):73;Abstract 59.

Robertson JF et al. **Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5, (10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer.** *Cancer Res* 2001;61(18):6739-46. **Abstract**

Saphner T et al. **Annual hazard rates of recurrence for breast cancer after primary therapy.** *J Clin Oncol* 1996;14(10):2738-46. **Abstract**

Thürlimann 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**

Young O et al. **Randomized pre-operative study of 750 mg of fulvestrant and 20 mg tamoxifen in premenopausal women with estrogen receptor-positive breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 5084**.

INTERVIEW

Patrick I Borgen, MD

Dr Borgen is Professor of Surgery at Weill Medical College of Cornell University and Chief of the Breast Service Department of Surgery at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-10

Select Excerpts from the Interview

Track 5

DR LOVE: How are you treating patients with DCIS in terms of endocrine therapy?

DR BORGEN: We have viewed tamoxifen as a highly appropriate option for treating a patient with ER-positive DCIS since the NSABP-B-24 trial (Fisher 1999).

However, when we consider risks, benefits and quality-of-life issues, it's common for our New York patients to demur, so we probably have one of the lowest percentages of patients with ER-positive DCIS on tamoxifen in the country. The same can be seen in our prevention setting, in which we've not been successful in getting patients to take tamoxifen.

DR LOVE: What are the concerns about tamoxifen in these settings?

DR BORGEN: The two most obvious concerns are endometrial cancer and gynecological events. Even when we provide the raw numbers on how infrequent those events are, because we are talking about minimal, if any, impact

on long-term survivorship and moderate impact on local control, it simply is not an attractive option.

DR LOVE: For a postmenopausal patient with DCIS who is interested in endocrine therapy but finds tamoxifen intolerable because of side effects, do you offer an aromatase inhibitor?

DR BORGEN: We'd like more information about DCIS and aromatase inhibitors, but since the initial publication of the ATAC data (Baum 2002), aromatase inhibitors have become our endocrine therapy of choice for postmenopausal patients with ER-positive, invasive cancers.

That literally happened overnight, like gangbusters, and so a "bleed over" to postmenopausal patients with DCIS is natural.

Track 6

DR LOVE: If clinical research data demonstrate a superior antitumor effect and a better toxicity profile with aromatase inhibitors versus tamoxifen, how do you think these agents will be accepted in the prevention and adjuvant settings?

DR BORGEN: In my clinical practice, it's clear that the aromatase inhibitors are vastly better tolerated than tamoxifen in postmenopausal patients. Our surgeons are beginning to give first-line endocrine therapy without a mandatory consult from medical oncology. This was a policy change at Memorial a few years ago. Our oncologists were overwhelmed by the volume of invasive carcinomas, so the surgeons took a front-line role. We perform bone density tests before we start our patients on aromatase inhibitors, and treating these patients has been satisfying.

DR LOVE: Surgeons, particularly breast cancer surgeons, used to prescribe tamoxifen routinely. It is interesting that, when the data began to favor the aromatase inhibitors, I saw surgeons hesitate in terms of treating patients with these agents. Do you find that is changing and surgeons are now using aromatase inhibitors?

DR BORGEN: Tamoxifen has a 40-year head start, and surgeons are sometimes slow to change, but it's definitely changing. We've treated a growing number of older patients with larger, ER-positive tumors with neoadjuvant aromatase inhibitors and seen some striking results.

We can downsize and downstage tumors for the majority of these patients, which leads to a far smaller surgical procedure, and in some cases the tumors go away completely, and we are left with following a patient closely. I believe the aromatase inhibitors belong in a breast surgeon's practice and armamentarium.

DR LOVE: Have you used neoadjuvant aromatase inhibitors in your practice or in a clinical trial setting?

DR BORGEN: Both. We were impressed by the initial work that Mike Dixon published from the United Kingdom (Dixon 1999, 2000, 2001; [4.1]). We conducted a small in-house study and corroborated his findings exactly, both in terms of tumor response rates and patient acceptance.

DR LOVE: Have you used neoadjuvant aromatase inhibitors to downsize tumors to convert a mastectomy to a lumpectomy?

DR BORGEN: Absolutely. Certainly in the older patient population we have done that. I would qualify that by saying it's not so much to convert a mastectomy to a lumpectomy as it is to downstage the disease.

4.1 **Aromatase Inhibitors versus Tamoxifen in the Neoadjuvant Setting**

Conclusion: "Neoadjuvant endocrine therapy does appear to be effective. Reductions in tumour volume using primary endocrine therapy in ER and/or PgR positive tumours are similar to those reported with neoadjuvant chemotherapy. In contrast, toxicity is much lower with neoadjuvant endocrine therapy and it is extremely well tolerated, with very few patients having to discontinue therapy because of side effects... .

The patients who are most likely to respond to neoadjuvant endocrine therapy are those who have higher levels of ER (ALLRED score 6 and above). Response rates to neoadjuvant therapy in postmenopausal women have been shown to be higher when using aromatase inhibitors than with tamoxifen. This may partly be due to the fact that aromatase inhibitors are effective in both erbB2 positive and negative cancers while tamoxifen is less effective in erbB2 positive tumours and that the aromatase inhibitors produce responses in tumours with lower levels of ER whereas tamoxifen does not."

SOURCE: Dixon JM et al. *J Steroid Biochem Mol Biol* 2003;86(3-5):295-9. **Abstract**

Track 9

DR LOVE: What is your opinion of the Onco*type* DX assay (4.2), and how do you see it beeing used clinically?

DR BORGEN: We're excited about the possibility of a truly genomic approach to the disease. We use the Onco*type* DX assay in borderline cases in which a low recurrence score would preclude cytotoxic chemotherapy. For the patient who has a larger tumor, a higher-grade tumor or other mitigating factors, we're not using Onco*type* DX as a sole factor in precluding chemotherapy, but in those borderline cases it's been enormously helpful.

DR LOVE: Medicare is now paying for the Onco*type* DX assay. Do you think that is tied to the fact that it appears to be cost effective?

DR BORGEN: That's correct. If we eliminated chemotherapy for one third of small, node-negative breast cancers — and the estimates could be higher than one third — then this would look like the best money ever spent on a medical test. ■

4.2

Practical Impact of the Oncotype DX Assay: Two Patients from Dr Borgen's Practice

A 59-year-old postmenopausal woman with a 9-mm, ER-positive, HER2-negative, node-negative breast cancer. No lympho-vascular invasion (LVI).

Oncotype DX assay: 6

Rx: Aromatase inhibitor; no chemotherapy

A 57-year-old postmenopausal woman with a 0.9-cm, ER-positive, HER2-negative, node-negative breast cancer. Questionable LVI. The patient was very fearful of chemo-therapy, having seen a neighbor go through this treatment.

Oncotype DX assay: 85

Rx: Aromatase inhibitor; dose-dense AC → T chemotherapy

Risk group	Recurrence score
Low	<18
Intermediate	18-30
High	>31

SOURCE: Paik S et al. *N Engl J Med* 2004;351(27):2817-26. **Abstract**

SELECT PUBLICATIONS

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

Clarke M et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005;366(9503):2087-106. **Abstract**

Dixon JM et al. **Neoadjuvant tamoxifen and aromatase inhibitors: Comparisons and clinical outcomes.** *J Steroid Biochem Mol Biol* 2003;86(3-5):295-9. **Abstract**

Dixon JM et al. **Letrozole as primary medical therapy for locally advanced and large operable breast cancer.** *Breast Cancer Res Treat* 2001;66(3):191-9. **Abstract**

Dixon JM et al. **The effects of neoadjuvant anastrozole (Arimidex) on tumor volume in postmenopausal women with breast cancer: A randomized, double-blind, single-center study.** *Clin Cancer Res* 2000;6(6):2229-35. **Abstract**

Dixon JM et al. **Lessons from the use of aromatase inhibitors in the neoadjuvant setting.** *Endocr Relat Cancer* 1999;6(2):227-30. **Abstract**

Fisher B et al. **Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B-24 randomised controlled trial.** *Lancet* 1999;353(9169):1993-2000. **Abstract**

Hughes KS et al; Eastern Cooperative Oncology Group. **Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer.** *N Engl J Med* 2004;351(10):971-7. **Abstract**

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. **Abstract**

Vogel VG et al. **National Surgical Adjuvant Breast and Bowel Project update: Prevention trials and endocrine therapy of ductal carcinoma in situ.** *Clin Cancer Res* 2003:9(1 Pt 2):495-501. **Abstract**

Highlights from a Miami Breast Cancer Conference Tumor Panel Discussion on Adjuvant Systemic Therapy

Note from the Editor: At this year's Miami Breast Cancer Conference during a case-based tumor panel discussion, faculty discussed recent clinical research findings involving

- Adjuvant trastuzumab for patients with HER2-positive disease
- Adjuvant endocrine therapy for patients with ER- and/or PR-positive disease
- Selection and schedule of adjuvant chemotherapy

Dr Sledge discusses exciting new data on adjuvant trastuzumab.

Dr Sainsbury reviews recent findings from a number of trials evaluating aromatase inhibitors in the neoadjuvant, adjuvant and postadjuvant settings.

Dr Ravdin compares adjuvant trials evaluating anthracycline/taxane combinations.

Panel above: Drs Richard Sainsbury, George Sledge, Peter Ravdin, Steven Shak and Joyce O'Shaughnessy discuss the practice implications of rapidly emerging clinical research in adjuvant systemic therapy of early breast cancer.

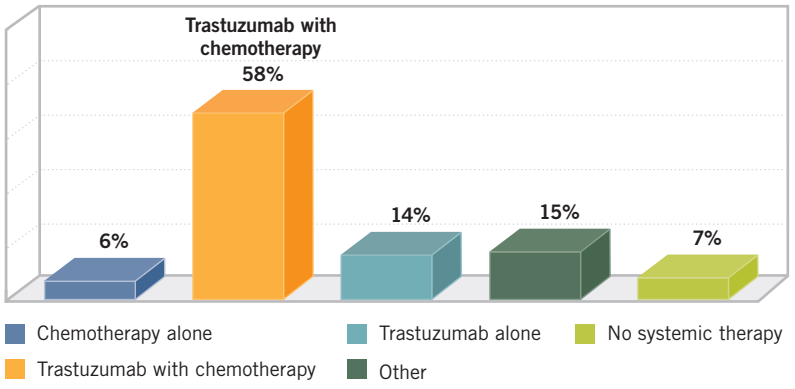
Adjuvant Trastuzumab for Patients with HER2-Positive Disease

Tracks 1-11

Track 1	Introduction
Track 2	Overview of adjuvant trastuzumab trial results
Track 3	Efficacy of adjuvant trastuzumab
Track 4	Adjuvant trastuzumab and cardiac safety
Track 5	Adjuvant dose-dense AC → T with trastuzumab
Track 6	Coamplification of HER2 and topoisomerase II and benefit from anthracycline-based chemotherapy
Track 7	Utility of the Onco*type* DX assay in patients with HER2-positive disease
Track 8	Use of adjuvant trastuzumab monotherapy
Track 9	Delayed adjuvant trastuzumab
Track 10	Incorporating adjuvant trastuzumab data into the Adjuvant! Online program
Track 11	Impact of tumor size and nodal status on the use of adjuvant trastuzumab

5.1

Miami Breast Cancer Conference Poll Question: The Patient Is a 55-Year-Old Woman in Good Health with a 0.8-Centimeter, ER/PR-Positive, HER2-Positive, Grade II IDC and Negative Lymph Nodes. The Recurrence Score Is 85. In addition to endocrine treatment, what would you recommend?



SOURCE: Miami Breast Cancer Conference Tumor Panel, Participant Polling, February 2006, Miami, Florida.

Select Excerpts from the Interview

Track 2

DR LOVE: George, would you provide an overview of the adjuvant trastuzumab trials that were presented in 2005?

DR SLEDGE: The two trials sponsored by the National Cancer Institute — NSABP-B-31 and NCCTG-N9831 — had somewhat overlapping schemas.

In the control arm, patients received AC followed by paclitaxel. In the second arm, they began trastuzumab concurrent with paclitaxel and then continued trastuzumab for a total of one year. The N9831 trial also had a third arm in which patients began trastuzumab subsequent to the completion of taxane-based chemotherapy.

The BCIRG 006 trial, an international study, also had a control arm of AC followed by a taxane, but in this case it was docetaxel. In the second arm, trastuzumab was added to the taxane, and the study had an interesting third arm in which patients received carboplatin/docetaxel/trastuzumab but no anthracycline.

In the HERA trial, performed largely in Europe, patients had completed all of their systemic chemotherapy prior to being randomly assigned to an observation arm versus one year of trastuzumab versus two years of trastuzumab.

Track 3

DR LOVE: Can you summarize the efficacy data that have been reported?

DR SLEDGE: Data from the HERA trial comparing observation versus one year of trastuzumab show a significant benefit in the addition of trastuzumab, with a risk reduction of about 50% and a strikingly positive *p*-value (Piccart-Gebhart 2005). Interestingly, this trial included no specified chemotherapy regimen, and approximately one third of the patients had node-negative disease.

In contrast to the HERA trial, early analysis of the N9831 trial demonstrated that the result from the sequential arm, in which trastuzumab was administered after completion of chemotherapy, was not statistically significant, with a *p*-value of 0.01 (Romond 2005). From a purely statistical standpoint, this did not meet the boundaries required for early reporting.

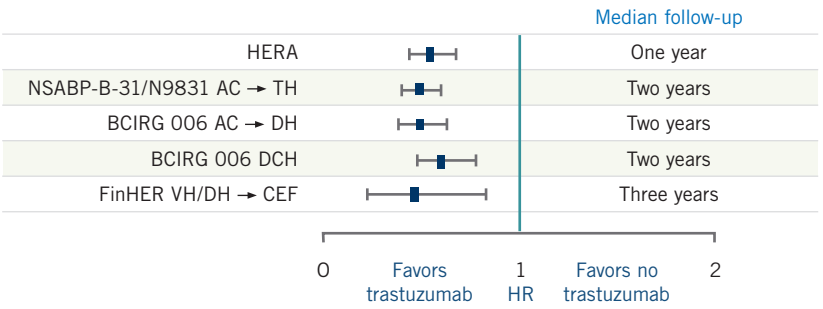
The median follow-up in this trial is very short, and the number of events is small, so which regimen is better is still an unanswered question. In the arm in which trastuzumab was administered concurrently with chemotherapy, the result was highly significant.

In the BCIRG 006 trial, both of the trastuzumab-containing arms were superior to the nontrastuzumab-containing arm (Slamon 2005). The nonanthracycline arm may be minimally inferior to the anthracycline-containing arm, but this is not yet a statistically significant difference and requires further follow-up.

If we examine all these trials as a group and include the FinHER trial, a small Finnish trial of adjuvant trastuzumab (Joensuu 2005), in every single study we see significant benefits with the addition of trastuzumab to chemotherapy (5.2). As a result, trastuzumab has become the standard of care for patients receiving adjuvant therapy who have HER2-positive disease.

5.2

Trastuzumab Disease-Free Survival



D = docetaxel; H = trastuzumab; T = paclitaxel; V = vinorelbine

SOURCE: Sledge GW. CME Satellite Symposium, Miami Breast Cancer Conference 2006. No abstract available

Track 5

DR LOVE: We know from our Patterns of Care studies that the most common chemotherapeutic regimen used in the United States for node-positive breast cancer is dose-dense AC followed by paclitaxel. That regimen was not evaluated in any of the adjuvant trastuzumab trials from which we have data, so physicians are questioning whether to use dose-dense AC → T with trastuzumab. Joyce, what are your thoughts?

DR O'SHAUGHNESSY: At the San Antonio Breast Cancer Symposium (2005), the Memorial group reported on cardiac safety data from approximately 55 patients who received dose-dense AC followed by paclitaxel with trastuzumab (Dang 2005).

Although some diminution occurred in LVEF, they saw no congestive heart failure and no significant LVEF decline (5.3).

Cliff Hudis also presented data on the dose-dense AC → paclitaxel trial, INT-C9741, reporting on five years of follow-up and showing no excess cardiac toxicity when the anthracycline is given every two weeks, which is encouraging (Hudis 2005).

I am comfortable with dose-dense AC, and I administer the taxane the way it was administered in the Intergroup or NSABP trials.

DR LOVE: Peter, what do you think about the Memorial data?

DR RAVDIN: The data from the Memorial Sloan-Kettering study are preliminary. The median follow-up was only about six months, so I would still say that we don't really know about the cardiac safety of that regimen.

5.3

Preliminary Cardiac Safety Results of Dose-Dense (DD) Doxorubicin/Cyclophosphamide (AC) Followed by Paclitaxel (T) with Trastuzumab (H)

Timing of MUGA*	N	Median LVEF	LVEF range
Baseline	70	68%	55%-81%
Month 2	61	67%	58%-79%
Month 6	35	66%	56%-75%
Month 9	9	64%	57%-69%

* MUGA obtained at baseline and repeated at months 2, 6, 9 and 18

SOURCE: Dang C et al. Poster. San Antonio Breast Cancer Symposium 2005;**Abstract 2041**.

Track 6

DR LOVE: George, Dennis Slamon presented a fascinating analysis of topoisomerase II-alpha (TOPO II) amplification examined in the BCIRG 006 trial (Slamon 2005; Press 2005). Can you comment on the data and whether you think they are clinically applicable at this time?

DR SLEDGE: TOPO II is one of the molecular targets for doxorubicin. It's found on chromosome 17, right next to where HER2 is located, so it's not uncommon for them to be coamplified.

We know from the BCIRG trial, as a result of careful analysis for TOPO II and HER2, that approximately a third of the breast cancers that are HER2 amplified by FISH are also amplified for TOPO II by FISH. A preliminary analysis of the data suggests that patients who benefit from an anthracycline/trastuzumab-containing regimen tend to be the patients who have the coamplification of TOPO II and HER2 (5.4).

Clearly, these data are preliminary, but they're fascinating and make sense biologically. Hopefully, in another year or two we'll have sufficient follow-up data to point us in one direction or another.

Track 11

DR LOVE: George, for a patient with a one- to two-centimeter, ER-positive, HER2-positive tumor, are you likely to recommend trastuzumab?

DR SLEDGE: Yes. That patient falls within the eligibility criteria of the HERA trial, so we have clinical trial data that say it's appropriate to use trastuzumab (Piccart-Gebhart 2005).

DR LOVE: Do you use trastuzumab if the tumor is less than one centimeter in size?

5.4 **BCIRG 006: Events Based on Treatment and Amplification of TOPO II**

Treatment	TOPO II amplified		Non-TOPO II amplified	
	N	Events	N	Events
AC → T	227	10%	458	20%
AC → TH	265	5%	472	10%
TCH	252	8%	446	12%

SOURCE: Slamon D et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

DR SLEDGE: Right or wrong, I don't. These trials included very few patients with tumors in the subcentimeter category.

DR LOVE: Joyce, how does tumor size affect your decision to use adjuvant trastuzumab for a patient with HER2-positive, node-negative breast cancer?

DR O'SHAUGHNESSY: If the tumor is greater than a centimeter in size and the patient has no contraindications to trastuzumab, I recommend it. For patients with tumors less than a centimeter, it depends on what I think their residual risk will be. For example, if a tumor is eight or nine millimeters but ER/PR-negative, Grade III and HER2-positive by FISH, I recommend trastuzumab.

For patients at higher risk, I always use AC followed by paclitaxel or docetaxel with trastuzumab, but for the patients at lower risk, I consider TCH because it has less cardiac toxicity. ■

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Joensuu H et al; FinHer Study Investigators. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. **Abstract**

Piccart-Gebhart MJ et al; Herceptin Adjuvant (HERA) Trial Study Team. **Trastuzumab after adjuvant chemotherapy in HER 2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

Press MF et al. **Topoisomerase II-alpha gene amplification as a predictor of responsiveness to anthracycline containing chemotherapy in the Cancer International Research Group 006 clinical trial of trastuzumab (herceptin) in the adjuvant setting.** San Antonio Breast Cancer Symposium 2005;**Abstract 1045**.

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER 2 positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. **Abstract**

Slamon D et al. **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 HER2 positive early breast cancer patients: BCIRG 006 study.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

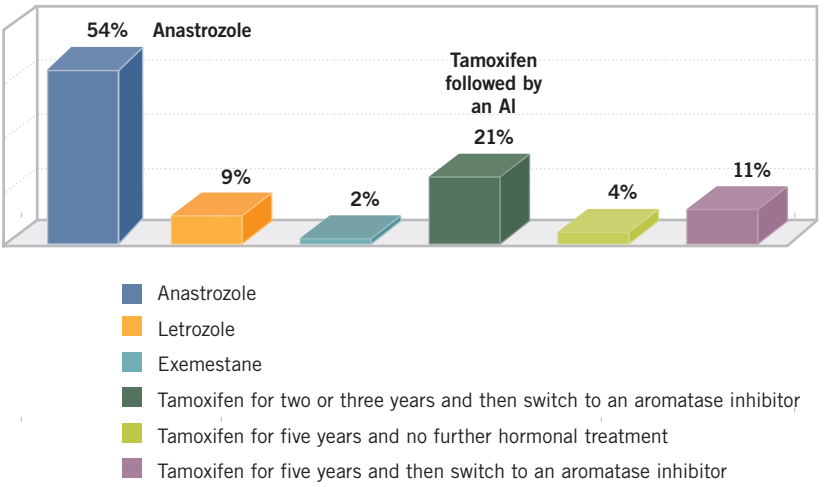
Adjuvant Endocrine Therapy for Patients with ER- and/or PR-Positive Disease

Tracks 1-7

Track 1	Clinical trials evaluating aromatase inhibitors in the neoadjuvant setting
Track 2	Overview of aromatase inhibitors trials
Track 3	Aromatase inhibitors versus tamoxifen
Track 4	Bone effects with aromatase inhibitors
Track 5	Gynecologic side effects with aromatase inhibitors and tamoxifen
Track 6	Time course of recurrence of ER/PR-positive disease
Track 7	Extended adjuvant therapy with aromatase inhibitors

6.1

Miami Breast Cancer Conference Poll Question: The Patient Is a 55-Year-Old Postmenopausal Woman in Average Health with a 1.2-Centimeter, Strongly (>80%) ER/PR-Positive, HER2-Negative, Grade II Tumor and Negative Lymph Nodes. What Do You Generally Think Would Be the Best Approach to Endocrine Therapy?



SOURCE: Miami Breast Cancer Conference Tumor Panel, Participant Polling, February 2006, Miami, Florida.

Select Excerpts from the Interview

Track 2

DR LOVE: Richard, can you summarize the data from the trials of adjuvant aromatase inhibitors?

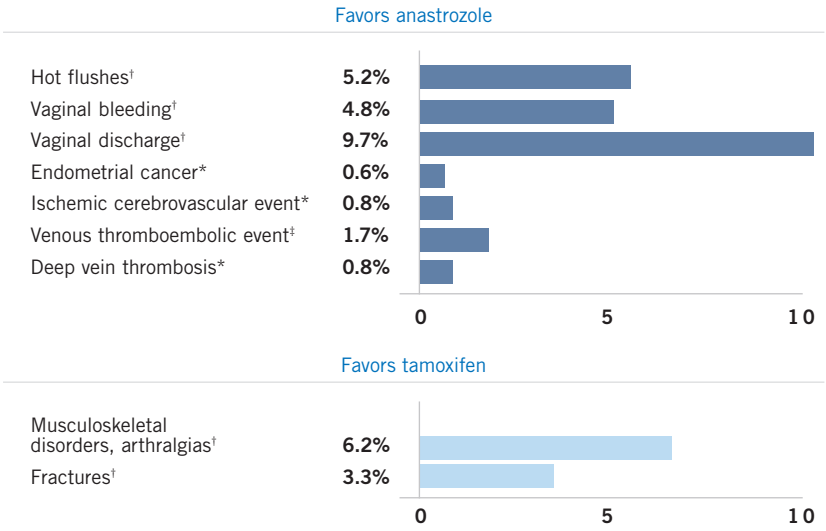
DR SAINSBURY: ATAC (Howell 2005) and BIG 1-98 (Thürlimann 2005) studied a population starting afresh. IES (Coombes 2004), ARNO 95 and ABCSG-8 (Jakesz 2005a) enrolled patients who had already received two or three years of adjuvant tamoxifen, and MA17 (Goss 2005) enrolled patients who completed five years of adjuvant tamoxifen.

So for some of these studies, you've already eliminated patients who had earlier relapses. Therefore, the studies are not strictly comparable and have to be considered in context.

ATAC (Howell 2005) and BIG 1-98 (Thürlimann 2005) both showed that up-front anastrozole and letrozole, respectively, were better than tamoxifen for disease-free survival. The ATAC study showed an apparent blunting of the early relapses, suggesting that to avoid recurrences you need to start the aromatase inhibitor early and not switch at two to three years.

6.2

Significant Differences Between Anastrozole and Tamoxifen in Predefined Adverse Events (Percent)



* $p < 0.05$; † $p < 0.0001$; ‡ $p = 0.0004$

DERIVED FROM: Howell A et al. *Lancet* 2005;365(9453):60-2. **Abstract**

We're obtaining increasing evidence that avoiding recurrences will affect mortality down the line. Both studies demonstrated different side effects, with generally reduced toxicities for the aromatase inhibitors compared to tamoxifen. Worry arose about the impact on bone, which is a manageable concern but something we still need to watch carefully (Howell 2005; Thürlimann 2005; [6.2]). Anastrozole has a slightly longer follow-up.

A retrospective analysis of ATAC indicated an apparent benefit for the subset with ER-positive, PR-negative disease (Dowsett 2005; [6.3]), which was not found in BIG 1-98, even when the tumors were reassessed centrally (Viale 2005; [6.4]). That is probably a fluke of subset analyses.

In the switching trials, the aromatase inhibitors are better than tamoxifen for relapse-free survival and have better side-effect profiles (Coombes 2004; Jakesz 2005a; Boccardo 2005). The combined analysis of ABCSG-8, ARNO 95 and the Italian study (ITA) demonstrated an overall survival benefit for anastrozole

6.3

Recurrence Rates in the ATAC Trial According to Estrogen and Progesterone Receptor Status

Receptor status	N	Anastrozole (%)	Tamoxifen (%)	Hazard ratio for anastrozole versus tamoxifen (95% CI)*
ER+/PR+	5,709	10	12	0.84 (0.69-1.02) $p = 0.07$
ER+/PR-	1,372	11	24	0.43 (0.31-0.61) $p < 0.0001$
ER-/PR+	220	27	33	0.79 (0.43-1.47) $p = 0.5$
ER-/PR-	703	28	32	0.90 (0.65-1.25) $p = 0.5$

* Hazard ratios less than one indicate values in favor of anastrozole.

SOURCE: Dowsett M et al. *J Clin Oncol* 2005;23(30):7512-7. **Abstract**

6.4

BIG 1-98 Central Review Project: Disease-Free Survival (DFS) in BIG 1-98 According to Hormone Receptor Status

Disease-free survival	HR	95% CI
All patients (N = 4,399)	0.71	—
According to ER/PR status		
ER+/PR+ (n = 3,330)	0.67	0.51-0.88
ER+/PR- (n = 832)	0.88	0.55-1.41

HR = hazard ratio for letrozole versus tamoxifen (<1.0 favors letrozole)

SOURCE: Viale G et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 44**.

6.5

Meta-Analysis of Trials Evaluating Switching to Anastrozole: ARNO 95, ABCSG-8 and ITA (n = 4,006)

	Hazard ratio [95% CI]	*p*-value
DFS (ITT population)	0.59 [0.48-0.74]	<0.0001
OS (ITT population)	0.71 [0.52-0.98]	0.038

DFS = disease-free survival; ITT = intention to treat; OS = overall survival

Hazard ratios are for anastrozole/tamoxifen.
Hazard ratio < 1.0 favors anastrozole.

"… This meta-analysis demonstrates that patients switched to anastrozole experience significantly fewer recurrences than those patients remaining on tamoxifen. These advantages translate into a benefit in the long-term endpoint of overall survival. Consistency of effect was seen between the three trials. … These data confirm that postmenopausal women currently receiving adjuvant tamoxifen should be switched to anastrozole."

SOURCE: Jonat W et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 18**.

(Jonat 2005; [6.5]); however, those studies were not intended to be combined, so I believe that survival benefit is artifactual.

Track 3

DR LOVE: George, what are your thoughts about the lack of a clear survival benefit in the trials of adjuvant aromatase inhibitors?

DR SLEDGE: I've not been as worried as others. In recent years, we've been fooled into thinking we should see survival advantages two or three years out on adjuvant trials. If one looks at the adjuvant tamoxifen trials from the 1980s, one sees that it was common for us to wait five, six or seven years to see a survival advantage.

So it doesn't at all surprise me that a lot of our trials haven't yet shown those advantages. I think they're going to emerge. If you significantly reduce a woman's likelihood of relapsing in her liver, lungs and bones, it will translate into a survival advantage unless these agents are significantly more toxic in some nonbreast cancer fashion.

DR LOVE: Peter, if the efficacy of the aromatase inhibitors were identical to tamoxifen, would they still be preferable because of the side-effect and toxicity profiles?

DR RAVDIN: Yes. For postmenopausal women in their sixties, the risk of cancer and the risk of thrombotic events are both very significant. I think if it were the other way around and we had the aromatase inhibitors first and we were trying to introduce tamoxifen, tamoxifen might not make the bar, except for premenopausal patients. I think toxicity is a major reason to select an aromatase inhibitor over tamoxifen.

Track 5

DR LOVE: Richard, can you comment on the gynecologic data from the ATAC trial that were presented at the 2005 San Antonio Breast Cancer Symposium (Duffy 2005)?

DR SAINSBURY: In the ATAC trial, the hysterectomy rate went down from six percent with tamoxifen to approximately two percent with anastrozole. That's a major health issue. Any woman on tamoxifen who has a bleed is investigated, which is expensive and invasive (Duffy 2005; [6.5]). Sean Duffy conducted the prospective endometrial study (Duffy 2006). In fact, we've gained a lot of information about what's happening in the uteri of these women that we didn't know about before. It's clear that the aromatase inhibitors are much less toxic to the uterus than tamoxifen is. ■

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Duffy S et al. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: First results of the endometrial sub-protocol following 2 years of treatment.** *Hum Reprod* 2006;21(2):545-53. **Abstract**

Duffy SR, Distler W, on behalf of the ATAC Trialists' Group. **Gynecologic interventions during adjuvant therapy with anastrozole or tamoxifen: Results from the ATAC trial.** Poster. 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 MA17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **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**

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Jonat W et al. **Switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-responsive early breast cancer: A meta-analysis of the ARNO 95 Trial, ABCSG Trial 8, and the ITA Trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 18**.

Thürlimann 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**

Viale G et al. **Central review of ER, PgR and HER-2 in BIG 1-98 evaluating letrozole vs tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 44**.

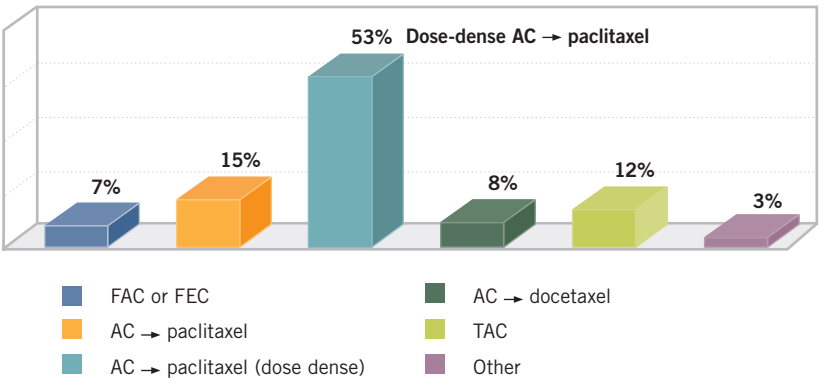
Selection and Schedule of Adjuvant Chemotherapy

Tracks 1-6

Track 1	Historical development of adjuvant chemotherapy	Track 4	US Oncology adjuvant trial comparing AC to TC
Track 2	ECOG-E1199 adjuvant trial: Evaluating type and schedule of taxanes	Track 5	Anthracycline- versus nonanthracycline-based adjuvant chemotherapy
Track 3	GEICAM 9906: Adjuvant $FE_{90}C$ versus $FE_{90}C$ followed by weekly paclitaxel	Track 6	Prediction of response to adjuvant chemotherapy

7.1

Miami Breast Cancer Conference Poll Question: The Patient Is a 55-Year-Old Woman in Average Health with a 1.2-Centimeter, ER 90%, PR 45%, HER2-Negative, Grade II Tumor and Three Positive Nodes. Which Chemotherapy Regimen, If Any, Would You Most Likely Recommend?



SOURCE: Miami Breast Cancer Conference Tumor Panel, Participant Polling, February 2006, Miami, Florida.

Select Excerpts from the Interview

Track 2

DR LOVE: Would you provide an overview of the adjuvant ECOG-E1199 trial that was presented at the 2005 San Antonio meeting?

DR RAVDIN: The ECOG-E1199 trial asked two questions: Which taxane and which schedule (Sparano 2005) are optimal as adjuvant therapy? Patients

received AC, and then the standard arm was paclitaxel every three weeks for four cycles. Another arm was a substitution of docetaxel for paclitaxel, and two arms evaluated these agents in weekly regimens.

If you look at paclitaxel versus docetaxel, you see no superiority in a two-by-two comparison between the two agents. If you look at every three weeks versus weekly, you see no difference in efficacy.

However, the devil is in the details, and as clinicians we all want to know the one-by-four comparisons. The results are consistent with what we've seen in metastatic disease.

The weekly paclitaxel regimen was the best, with almost a 20 percent better hazard ratio than the standard arm (7.2). Docetaxel, given every three weeks, also looked somewhat better.

In both of those cases, however, the difference was a trend and was not statistically significant. The weekly paclitaxel arm looked best in terms of overall survival, but this is a very early analysis not dignified by *p*-values.

What about toxicity? The weekly paclitaxel arm seemed to provide additional benefit without additional risk of febrile neutropenia, whereas the docetaxel arm was associated with additional febrile neutropenia (7.3).

A conclusion from this study has to be that weekly paclitaxel in adjuvant therapy appears promising, and the hazard ratios for the weekly arm of E1199 looked very similar to those of dose-dense therapy.

7.2

ECOG-E1199: AC Followed by Docetaxel (D) or Paclitaxel (P) Every Three Weeks (3) or Weekly (1) in Node-Positive or High-Risk Node-Negative Breast Cancer (Median Follow-Up = 46.5 Months)

Disease-free survival (DFS), primary comparisons	HR	95% CI	*p*-value
Paclitaxel vs docetaxel	0.985	0.84-1.15	0.83
Q3wk vs weekly	1.043	0.89-1.22	0.54
DFS, secondary comparisons	**HR**	**95% CI**	***p*-value**
P3 vs P1	1.20	0.99-1.46	0.06
P3 vs D3	1.13	0.94-1.36	0.20
P3 vs D1	1.03	0.85-1.23	0.78

SOURCE: Sparano JA et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 48**.

Track 4

DR LOVE: Could you briefly review the results of the US Oncology adjuvant trial comparing AC to docetaxel/cyclophosphamide (TC)?

DR RAVDIN: A striking improvement in disease-free survival and a large improvement in overall survival have been seen with TC in this study.

These improvements were obtained without a major difference in toxicity. A very slight increase occurs in neutropenia and fever rate with TC, but other advantages appear in the taxane-containing arm, with less nausea and vomiting (Jones 2005; [7.4]).

No major difference is seen between ER-positive and ER-negative disease in terms of the superiority of the taxane arm. A promising area in the development of adjuvant chemotherapy is that we may be able to substitute for the use of anthracyclines in adjuvant therapy, particularly in special populations, such as those who will be receiving trastuzumab.

7.3

ECOG-E1199: Most Common Grade III-IV Toxicities

	P3	P1	D3	D1
Neutropenia	4%	2%	46%	3%
Febrile neutropenia	<0.5%	1%	16%	1%
Infection	3%	4%	13%	5%
Stomatitis	<0.5%	0%	5%	2.5%
Fatigue	2%	3%	9%	11%
Neuropathy	5%	8%	4%	6%

P3 = paclitaxel every three weeks; P1 = paclitaxel weekly; D3 = docetaxel every three weeks
D1 = docetaxel weekly

SOURCE: Sparano JA et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 48**.

Track 5

DR LOVE: Joyce, can you comment on the study of adjuvant AC versus docetaxel/cyclophosphamide (TC) (Jones 2005)? We know from our Patterns of Care study that right now AC is the most common regimen used by oncologists for patients with node-negative disease.

DR O'SHAUGHNESSY: TC is definitely a better-tolerated regimen than AC. While it was not reported, any physician who took care of the patients on both arms is aware that less fatigue occurred with the TC because docetaxel at 75 mg/m^2 is not particularly fatiguing. With AC, you can get that kind of prolonged queasiness, and for some patients it brings them down for a week or so.

TC is much less nauseating and much better tolerated. It's a night and day difference, in my opinion. I have stopped using AC now for patients for whom I was using it. Now I use TC because of the six percent absolute improvement in disease-free survival. ■

7.4

Docetaxel and Cyclophosphamide (TC) versus Doxorubicin and Cyclophosphamide (AC) for Women with Early Breast Cancer (Median Follow-Up = 66 Months)

	TC (n = 506)	AC (n = 510)	Hazard ratio	*p*-value
Five-year disease-free survival	86%	80%	0.67	0.015
ER-/PR-	HR = 0.64 (95% CI: 0.38-1.04)			
ER+ or PR+	HR = 0.71 (95% CI: 0.47-1.03)			
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	0.131

Hazard ratios < 1 indicate values in favor of TC.

"Based on this trial, TC should now be considered a standard nonanthracycline adjuvant regimen for operable breast cancer."

Toxicities (Grades III/IV)	TC	AC	*p*-value
Neutropenia	59%	55%	NS
Neutropenic fever	6%	3%	0.03
Nausea	2%	7%	<0.01
Vomiting	<1%	5%	<0.01
CHF	0	0	NS

"TC was associated with more low-grade myalgias, arthralgias, edema and febrile neutropenia. AC was associated with significantly more nausea and vomiting."

SOURCE: Jones SE et al. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 40**.

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Doyle JJ et al. **Chemotherapy and cardiotoxicity in older breast cancer patients: A population-based study.** *J Clin Oncol* 2005;23(34):8597-605. **Abstract**

Duric VM et al. **Patients' preferences for adjuvant chemotherapy in early breast cancer: What makes AC and CMF worthwhile now?** *Ann Oncol* 2005;16(11):1786-94. **Abstract**

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Goldhirsch A et al. **Meeting highlights: International expert consensus on the primary therapy of early breast cancer 2005.** *Ann Oncol* 2005;16(10):1569-83. **Abstract**

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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**

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QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A meta-analysis reported at the 2005 San Antonio meeting by Dr Jonat demonstrated a survival advantage to switching to anastrozole as opposed to continuing tamoxifen.**
   a. True
   b. False
2. **In both the ATAC and BIG 1-98 trials, patients with ER-positive, PR-negative disease had a significantly greater risk reduction of recurrence with anastrozole than patients with ER/PR-positive disease.**
   a. True
   b. False
3. **In the BCIRG 006 adjuvant trastuzumab trial, coamplification of HER2 and topoisomerase II conferred an advantage for anthracycline-based chemotherapy regimens in combination with trastuzumab.**
   a. True
   b. False
4. **The ongoing XCaliBr trial is evaluating _____.**
   a. First-line capecitabine and bevacizumab
   b. Continued bevacizumab in combination with chemotherapy after disease progression
   c. Both a and b
5. **In the ECOG-E2100 trial, the addition of bevacizumab to _____ as first-line therapy resulted in significant improvements in disease-free survival for patients with metastatic breast cancer.**
   a. Capecitabine
   b. Docetaxel
   c. Paclitaxel
   d. *Nab* paclitaxel
6. **The US Oncology trial reported at the 2005 San Antonio meeting demonstrated a superior disease-free survival for adjuvant docetaxel/cyclophosphamide compared to standard AC.**
   a. True
   b. False
7. **The ECOG adjuvant trial E1199, reported at the 2005 San Antonio meeting, evaluated _____.**
   a. Paclitaxel with or without bevacizumab
   b. Schedule of taxanes
   c. Type of taxane
   d. Both a and b
   e. Both b and c
8. ***Nab* paclitaxel has the following advantage(s) over standard paclitaxel:**
   a. Eliminates the need for steroid premedication
   b. Infusion time is shorter
   c. Both a and b
   d. Neither a nor b
9. **In the pivotal trial, *nab* paclitaxel had a better response rate and time to tumor progression when compared to the original paclitaxel formulation.**
   a. True
   b. False
10. **Which of the following treatments are being compared in the SoFEA trial?**
    a. Exemestane
    b. Fulvestrant
    c. Fulvestrant with anastrozole
    d. Both a and b
    e. a, b and c
11. **Which of the following treatments are being compared in SWOG-S0226?**
    a. Anastrozole
    b. Fulvestrant
    c. Fulvestrant with anastrozole
    d. Both a and c
    e. a, b and c

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

EVALUATION FORM

Breast Cancer Update — Issue 3, 2006

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 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
- 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
Kevin R Fox, MD	5 4 3 2 1	5 4 3 2 1
William J Gradishar, MD	5 4 3 2 1	5 4 3 2 1
Professor John F R Robertson, MB, ChB, BSc, MD	5 4 3 2 1	5 4 3 2 1
Patrick I Borgen, MD	5 4 3 2 1	5 4 3 2 1
Joyce O'Shaughnessy, MD	5 4 3 2 1	5 4 3 2 1
Peter M Ravdin, MD, PhD	5 4 3 2 1	5 4 3 2 1
Richard Sainsbury, MD	5 4 3 2 1	5 4 3 2 1
Steven Shak, MD	5 4 3 2 1	5 4 3 2 1
George W Sledge Jr, 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

Which of the following audio formats of this program did you use?

☐ Audio CDs ☐ Audio tapes ☐ Downloaded MP3s from website

EVALUATION FORM

Breast Cancer Update — Issue 3, 2006

REQUEST FOR CREDIT — please print clearly

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

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:

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FOLLOW-UP

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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To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at BreastCancerUpdate.com/CME.

BCU306

Breast Cancer® UPDATE

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UPDATE

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