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Meet The Professors

A case-based discussion on the management of breast cancer in the adjuvant and metastatic settings

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Meet The Professors: A case-based discussion on the management of breast cancer in the adjuvant and metastatic settings

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. In order to incorporate research advances into developing treatment strategies for patients, the CME program *Meet The Professors* utilizes case-based discussions between community oncologists and research leaders.

LEARNING OBJECTIVES

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

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HOW TO USE THIS CME ACTIVITY

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes and complete the evaluation form in this booklet or on our website, **www.MeetTheProfessors.com**.

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Editor's Note

When to pull the trigger

At a *Breast Cancer Update* working group meeting a couple of years ago, a community-based oncologist presented the case of a woman in her thirties with newly diagnosed ER-positive, HER2 tic breast cancer. The patient, a nurse and a young mother of two small children, was like many or most people in this situation: desperate to do something aggressive against the tumor.

The physician, who understandably empathized with the patient's plight, initiated therapy with goserelin, anastrozole, trastuzumab, capecitabine and docetaxel. We know from our Patterns of Care studies over the years that few oncologists would recommend this type of untested "shotgun" approach even though an extensive clinical research base demonstrates the value of each of these therapies individually.

I asked the two breast cancer clinical investigators on the faculty for this working group event to respond to the doc's unusual treatment plan. Both gulped and tactfully indicated that they probably would not have taken the same approach and would more likely have chosen either conventional endocrine therapy (tamoxifen) or trastuzumab alone or with a taxane. However, the researchers and the other community docs in attendance commented that they understood the thinking behind the treatment decision made in this case.

So do I, and the topic of what constitutes evidence-based oncologic treatment is a constant theme in our CME programs. Clearly, we cannot require Phase III randomized trial evidence for every or even most decisions in cancer medicine, and we must be able to integrate input from a variety of resources and feel comfortable that the recommendations we make for patients are ethical.

The recent history of research and practice on adjuvant trastuzumab is perhaps the most dramatic example of the issue of when to "pull the trigger" on a highly promising yet unproven therapy that is part of major ongoing Phase III randomized trials. The adjuvant trastuzumab trials were initiated in 2000, following Dennis Slamon's pivotal randomized trial demonstrating a survival advantage when this monoclonal antibody was added to chemotherapy in the metastatic setting.

In dozens of interviews for our CME programs during the years following that historic study, I heard several very consistent messages from almost every breast cancer clinical investigator.

1. Although we had been disappointed in the past by therapies that seemed promising but failed to demonstrate value in randomized trials (eg, high-dose chemotherapy with stem-cell transplant), virtually all researchers expected adjuvant trastuzumab to work. This sentiment increased markedly after the ASCO 2004 meeting, when Aman Buzdar presented results of a trial of trastuzumab combined with neoadjuvant chemotherapy that demonstrated a 65 percent complete pathologic response rate, albeit in a very small number of patients.
2. Since Charles Geyer's presentation of the cardiac safety findings from NSABP-B-31 at the 2003 San Antonio Breast Cancer Symposium, we have had a generally accurate estimate

of the downside of adjuvant trastuzumab integrated into an anthracycline-based chemotherapy regimen.

Specifically, a three to four percent incidence of clinical congestive heart failure is associated with this sequence. We have also known for some time that trastuzumab is generally very well tolerated and does not seem to add to the other specific and nonspecific downsides of chemotherapy.

3. Until the recent release of the initial results of the major adjuvant trastuzumab trials, virtually all researchers strongly cautioned against using adjuvant trastuzumab outside a protocol setting, and our Patterns of Care surveys have consistently demonstrated that docs in practice supported this message. Even for women with multiple node-positive, HER2-positive tumors, trastuzumab was usually not raised as an adjuvant option.

One very notable exception was Dennis Slamon, who in an interview for the *Breast Cancer Update* audio series in 2002 told me about a number of patients who were not eligible for or did not wish to participate in his BCIRG 006 trial, whom he treated off protocol with trastuzumab. One of these patients was a marathon runner with node-negative, HER2-positive disease, who received TCH to protect her heart while still attacking the tumor.

Of course, things changed on April 25, 2005, when the NCI issued a press release announcing that the combined analysis of NSABP-B-31 and NCCTG-N9831 demonstrated a dramatic reduction in relapse rate and mortality when trastuzumab was added to chemotherapy. These data, along with the HERA trial data presented at ASCO in May, instantly changed breast cancer management as we knew it. Our most recent national Patterns of Care survey currently demonstrates that adjuvant trastuzumab is now the standard of care for most women with node-positive and higher-risk, node-negative, HER2-positive tumors.

OK, now I have to be the bad guy and, like some Monday-morning quarterback complaining that the Dolphins should have made a greater effort to push the ground game, ask the painful question: In the 18 months between Chuck Geyer's San Antonio presentation and the NCI press release in April 2005, should we have been more liberal about presenting the option of adjuvant trastuzumab to some patients?

I don't know the answer to that question, but I will mention another relevant anecdote: In 2003, our CME group conducted three breast cancer patient perspectives "town hall" meetings in New York, Miami and Houston. In total, we hosted about 1,200 breast cancer patients and their loved ones, all of whom listened to nationally recognized clinical investigators discuss a variety of clinical situations and then responded to a number of multiple choice questions, using electronic keypad polling, on how they viewed the risks and benefits of various interventions.

One of the most interesting scenarios we presented was that of a younger patient with a HER2-positive tumor and multiple positive lymph nodes. At each of the three meetings, a substantial number of patients in the audience indicated that if they were in that situation, they would want to receive adjuvant trastuzumab off protocol. What makes this finding even more intriguing is that this preference emerged in spite of the strong urging of the faculty at each meeting to utilize adjuvant trastuzumab only as part of a clinical trial.

The obvious difference between the perceptions of the investigators and the patients on this issue was particularly dramatic in Houston in November 2003, where local MD Anderson legend Gabriel Hortobagyi, along with panelists Peter Ravdin, Eva Singletary and Debu Tripathy, carefully explained the potential cardiac risks of trastuzumab and why they believed that adjuvant trastuzumab should not be utilized off study. Nonetheless, 44 percent of the patients indicated a preference for trastuzumab.

These meetings left me with an uncomfortable feeling about whether or not we were fulfilling our ethical obligation to patients. Then, in April we learned that, as predicted by the experts, the adjuvant trastuzumab trials demonstrated a major treatment benefit. While the early reported advantages are of greater magnitude than expected, there were essentially no surprises with these new data sets.

The point of this mental exercise is not to be critical. We are blessed with oncology leaders who — like their brethren and sistren in community practice — do the best they can and make recommendations to patients with the most sincere intent. However, the trastuzumab experience forces us to at least take a step back and rethink how we present treatment options to patients.

In this regard, Herbert Hurwitz — in a recent interview for our colorectal cancer series — made an interesting comment on the topic of when it's acceptable to discuss and utilize an unproven therapy. Herb was the principal investigator of the breakthrough IFL-bevacizumab trial in metastatic colon cancer that was presented at ASCO 2003 and led to the first FDA approval of this anti-VEGF agent.

As a result of these encouraging results in the metastatic setting, bevacizumab is following its older sister, trastuzumab, into the adjuvant setting and is currently being evaluated in large, randomized, adjuvant colorectal cancer trials in the United States and elsewhere, including NSABP-C-08, which randomly assigns patients with Stage II and III disease to FOLFOX alone or with bevacizumab.

My question to Herb was, "In view of the trastuzumab experience, should clinicians consider raising the issue of bevacizumab as a point of discussion in select patients with colorectal cancer in the adjuvant setting?" I have discussed this issue with many other colorectal cancer investigators as part of our audio programs, and like the breast cancer specialists commenting earlier this year on nonprotocol trastuzumab, virtually all have said that they would not support the consideration of bevacizumab off protocol for such patients. Herb had a somewhat more open approach:

"For me, the issue of whether or not to treat a patient off protocol with an experimental approach depends on the nature of the protocol. I usually do not treat a patient off protocol with therapies being tested in Phase I or Phase II studies, with all the literature biases and other biases in that setting. However, when a regimen has been credentialed enough to be part of a Phase III regimen, I'm more than willing to talk in detail with a patient about considering that directly — including how much we don't know, the inconveniences and the fiscal and biological toxicities that accrue by taking the treatment. I think the less we know about the effects of a therapy, the more we need to spend time being sure the patient is fully informed of what the pros and cons of that management strategy would entail."

Herb's point about the unknown is key, and clinical investigators including Herb express far less certainty that bevacizumab will be effective and safe adjuvant therapy than was expressed in 2004 about trastuzumab.

With these difficult-to-answer issues as a background, the enclosed audio program features a panel of community-based medical oncologists presenting cases from their practices to clinical investigators Drs Aman Buzdar, Kevin Fox, Gershon Locker and Eric Winer. The issue of when to pull the trigger surfaces here numerous times in discussions about challenges such as the use of adjuvant aromatase inhibitors combined with ovarian suppression in premenopausal patients and the management of patients with visceral metastatic crisis. Herb Hurwitz provides a construct for us to begin to evaluate these dilemmas, and his advice to involve the patient is perhaps the key to clinical decision-making in these situations.

— Neil Love, MD
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December 12, 2005

CASE 1:

A 40-year-old woman with a palpable, high-grade, ER/PR-negative, strongly HER2-positive invasive ductal carcinoma with four separate tumors at mastectomy and 2/19 positive nodes *(from the practice of Dr Barbara G Fallon)*.

Edited excerpts from the discussion:

DR FALLON: This woman presented in March 2003 at the age of 40 with a palpable tumor in the right breast. The mammogram showed several areas of suspicion, and the ultrasound showed one large mass and possibly a second mass. On stereotactic biopsy, she had high-grade, invasive ductal, ER-negative, PR-negative, strongly HER2-positive breast cancer. At mastectomy, four separate areas of invasive tumor were found, measuring 0.6 centimeter, 0.9 centimeter, one centimeter, and another measuring 2.4 centimeters with a margin less than two millimeters deep. Two out of 19 lymph nodes were positive, and no extracapsular spread was observed on the lymph nodes.

The patient underwent modified radical mastectomy and immediate implant reconstruction. She enrolled on NSABP-B-31 and had hoped to receive trastuzumab but in fact was randomly assigned to receive AC times four followed by paclitaxel times four, without trastuzumab.

She received chest wall radiation therapy because of the close margin. By the end of the trial, she was doing extremely well. She finished her doctorate in special education and got a new job as principal of a grammar school. This summer she climbed the Adirondacks with her sister, which was about a three-week hike.

She called me in June to ask whether she could receive trastuzumab at this point, and I told her I would look into it. She didn't want to do anything until she got back in August, and by that time the NSABP told us they would allow trastuzumab only to those who were randomly assigned after April 2004, but she was randomly assigned in April of 2003.

DR LOVE: How long has it been since she completed chemotherapy?

DR FALLON: Approximately two and a half years.

DR LOVE: Eric, would you recommend trastuzumab off study for this patient?

DR WINER: I would be inclined not to administer trastuzumab at the moment for two reasons. One is that whether trastuzumab works as a single agent when given two years after diagnosis is unknown. Second, whatever her risk of recurrence was in 2003, she has a somewhat lower risk of recurrence, perhaps a substantially lower risk, two years later.

Unlike ER-positive breast cancer, in which events are strung out over the course of 10 to 15 years, in HER2-positive breast cancer most of the events occur in the first five years and a lot of them occur in the first couple of years. That is part of the reason why, in each of these studies, we saw a dramatic benefit early on, even in the first year (Perez 2005b; Piccart-Gebhart 2005; Romond 2005).

DR LOVE: What would you say if this patient asked you what her risk of recurrence was from this point on?

DR WINER: I don't think we can give her a hard number, but I believe it's more than 10 percent.

DR LOVE: Dr Fallon, do you think if this woman knew she had a 10 percent risk of recurrence, she would want therapy despite the potential risks?

DR FALLON: She's asking for the therapy, but she's very philosophical and she agreed that if we don't know how much benefit she

would gain at this point in time, she may just wait and use it if she needs it.

DR WINER: Initially, this patient's risk of recurrence was in the range of 50 percent in the absence of any therapy. AC followed by paclitaxel decreased that by about 50 percent, so at the end of therapy, her recurrence risk was approximately 25 percent.

DR LOVE: Over two years have passed since this patient completed chemotherapy. What is risk of recurrence now?

DR WINER: I suspect that at least a third of all of the events occur in the first couple of years, but none of us can give you an exact answer, partially because we just don't have a great database on patients with HER2-positive disease treated only with AC followed by paclitaxel.

DR LOVE: How would you respond if the patient asked, "I know we don't have any data, but do you believe my relapse rate would be decreased if I take trastuzumab now?"

DR WINER: I think it's unknown, but if you invoke the HERA data (Piccart-Gebhart 2005), you would conclude that single-agent trastuzumab given immediately after the completion of chemotherapy is a very effective approach (1.1).

If you look at Edith Perez's data from the N9831 study, there are questions about how much benefit a patient would receive from single-agent trastuzumab (Perez 2005). Additionally, some small risk of cardiac toxicity clearly exists, in addition to the unknown risks of long-term trastuzumab after an anthracycline-based regimen.

DR LOVE: This patient is 42 years old. Assuming she has a normal ejection fraction, what is her risk of cardiomyopathy or cardiac failure with trastuzumab?

DR WINER: It's in the range of one to four percent.

DR FALLON: I think it's important to remind patients that MUGAs don't prevent cardiac toxicity. I did one on a patient whom I started on trastuzumab after doxorubicin and cyclophosphamide for locally advanced disease. After day one of trastuzumab and day two of paclitaxel, she presented with an unmeasurable ejection fraction. She had received full-dose doxorubicin, but she had a normal MUGA at the beginning and end of doxorubicin and then she suddenly developed acute cardiotoxicity.

When she then came back with metastatic disease, I treated her with docetaxel alone. Since her cardiac condition had reversed, eventually I was tempted to administer trastuzumab again. I administered it to her with vinorelbine, but her ejection fraction again decreased, so now she's on vinorelbine alone.

So while I do think cardiac dysfuction with trastuzumab is more reversible than doxorubicin-induced cardiac failure, it's not a walk in the park. I do think it's reasonable with the patient I presented today. But she wants to be active — that's a big part of her lifestyle — so it's a balance of unknown benefit against possible risk.

1.1 First Results of HERA: Trastuzumab for One versus Two Years versus Placebo After Chemotherapy for HER2-Positive Breast Cancer

Efficacy (One-year median follow-up)	Placebo (n = 1,693)	Trastuzumab for one year (n = 1,694)	Hazard ratio [95% CI]	*p*-value
Two-year disease-free survival	77.4%	85.8%	0.54 [0.43-0.67]	<0.0001
Distant recurrence-free survival	82.8%	90.6%	0.49 [0.38-0.63]	<0.0001
Overall survival	95.1%	96.0%	0.76 [0.47-1.23]	0.26

SOURCE: Piccart-Gebhart MJ et al; Herceptin Adjuvant (HERA) Trial Study Team. *N Engl J Med* 2005;353(16):1659-72. **Abstract**

DR LOVE: Eric, what are your thoughts about the use of trastuzumab without chemotherapy in the adjuvant setting for patients in whom you are reluctant to use chemotherapy, either because of age or comorbidities?

DR WINER: I wouldn't do it. As tempted as we all might be, there simply aren't data from any of the trials. That said, I think that a regimen of some chemotherapy followed by trastuzumab, based on HERA, is justifiable (Piccart-Gebhart 2005). In this woman, I think the key issue is making sure that she's comfortable with the decision. I try not to draw a line in the sand and say, "We can't cross this line" but to really help patients make the decision with me. The fact is that this patient could have a recurrence no matter what you do. If she receives trastuzumab, she could develop heart failure. You just can't predict all of this.

DR LOVE: Kevin, would you administer delayed adjuvant trastuzumab to this patient (1.2)?

DR FOX: I find that when I've been confronted with these agonizing situations that present an impossible calculation of risk and benefit, I have at times taken the "oh, what the heck" approach. I have administered delayed trastuzumab a couple of times, but I would not if I felt the risk of recurrence were so absurdly small that I couldn't justify it — for example, the one-centimeter, HER2-positive cancer that was treated five years ago. That would be an easier case to decide than this one. I have to confess I've been a little bit "fast and loose" with delayed trastuzumab.

DR LOVE: Eric, in the data from the BCIRG 006 study, we see that patients on the TCH [docetaxel/carboplatin or cisplatin/trastuzumab] arm had a 39 percent reduction in their relapse rate, whereas patients who received AC followed by TH [docetaxel/trastuzumab] had a 51 percent reduction (Slamon 2005; [1.3]). The conclusion was that both of the arms were better than the nontrastuzumab arm, and it was stated that there weren't enough data to compare the two trastuzumab arms. What are your thoughts regarding these data?

DR WINER: Assuming the hazard ratios hold up and nothing further shows up in the data, I'm struck that while TCH clearly reduced the risk of disease recurrence, a trend for a better outcome occurred in the women who received AC followed by TH. It was said that these are not different from

1.2 Use of Delayed Adjuvant Trastuzumab: National Patterns of Care Survey

- *55-year-old woman with normal ejection fraction who received prior adjuvant AC/paclitaxel*
- *2.4-cm, Grade II tumor*
- *ER-negative/PR-negative, HER2-positive*
- *Node status specified below*

Would you recommend adjuvant trastuzumab at each of the following time points?

	Node-negative		3 positive nodes		10 positive nodes	
Six months after completion of chemotherapy	76%	58%	96%	82%	96%	84%
One year after completion of chemotherapy	50%	32%	70%	54%	82%	58%
Two years after completion of chemotherapy	2%	8%	14%	14%	36%	38%
Four years after completion of chemotherapy	—	4%	5%	8%	9%	22%

Breast cancer specialists (n = 45) General oncologists (n = 50)

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

one another; however, I think it is unlikely that TCH will be better. At the moment, I would use TCH only for patients in whom I am particularly concerned about cardiac toxicity.

I'll also add that the TCH regimen used in the BCIRG study is not an easy regimen to get a patient through, and so apart from the cardiac issues, I think it's a more toxic regimen than AC followed by docetaxel.

1.3 BCIRG 006 Interim Efficacy Analysis: Risk of Relapse Relative to AC → T (n = 3,222)

	Median follow-up	AC-docetaxel/ trastuzumab	Docetaxel/ carboplatin/trastuzumab
Relative reduction in risk of relapse	23 months	51% (95% CI: 35-63%)	39% (95% CI: 21-53%)

SOURCE: www.bcirg.org/Internet/Press+Releases, December 2005.

Select publications

Burstein HJ. **The distinctive nature of HER2-positive breast cancers.** *N Engl J Med* 2005;353(16):1652-4. No abstract available

Ewer MS et al. **Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment.** *J Clin Oncol* 2005;23(31):7820-6. **Abstract**

Hortobagyi GN. **Trastuzumab in the treatment of breast cancer.** *N Engl J Med* 2005;353(16):1734-6. No abstract available

Joensuu H et al. **Trastuzumab in combination with docetaxel or vinorelbine as adjuvant treatment of breast cancer: The FinHer trial.** San Antonio Breast Cancer Symposium 2005;**Abstract 2**.

Perez EA et al. **Exploratory analysis from NCCTG N9831: Do clinical and laboratory characteristics predict cardiac toxicity of trastuzumab when administered as a component of adjuvant therapy?** San Antonio Breast Cancer Symposium 2005a;**Abstract 2038**.

Perez EA et al. **NCCTG N9831: May 2005 update.** Presentation. ASCO 2005b;**Abstract 556**.

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**

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. **BCIRG006 — Randomized Phase III trial comparing AC-T vs AC-TH vs TCH in HER2 positive node positive or high risk node negative breast cancer.** Presentation. NSABP meeting. September 2005. No abstract available

Slamon D et al. **Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study.** San Antonio Breast Cancer Symposium 2005;**Abstract 1**.

Tan-Chiu E et al. **Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.** *J Clin Oncol* 2005;23(31):7811-9. **Abstract**

CASE 2:

A 46-year-old perimenopausal woman with a 1.4-centimeter, Grade II, three-node-positive, ER-positive/PR-negative, HER2-positive infiltrating ductal carcinoma who was accepted to the Intergroup adjuvant trastuzumab trial *(from the practice of Dr Frederick P Smith)*.

Edited excerpts from the discussion:

DR SMITH: My patient is a 46-year-old intramenopausal woman with irregular periods. She developed a 1.4-centimeter, Grade II infiltrating ductal carcinoma, which was ER-positive, PR-negative and HER2-positive — IHC 3+ and amplification by FISH. She had three positive lymph nodes and was accepted into the Intergroup adjuvant trastuzumab trial, but when randomly assigned to the nontrastuzumab arm, she insisted on receiving trastuzumab and dropped out of the trial.

DR LOVE: Were you surprised that this patient dropped out of the clinical trial?

DR SMITH: I was surprised and a little annoyed, since it confounds the trial results. Initially, I persuaded her to stay on study, but then she sought other opinions until she found someone who would put her on trastuzumab and then returned to me. This actually occurred about a month before the adjuvant trastuzumab data were released last April.

I administered four cycles of AC followed by weekly paclitaxel with concomitant trastuzumab and, upon conclusion of the paclitaxel, continued trastuzumab every three weeks. I also have her on tamoxifen.

DR LOVE: Interesting. Can you tell us a bit more about this woman and her situation?

DR SMITH: The patient is married and has two children. She is a psychiatrist and her sister is a radiologist. As many of these patients do, she went on the internet, made the rounds, and carefully read the study consent.

DR LOVE: Gersh, what are your thoughts regarding this patient enrolling and then dropping out of the clinical trial in order to receive adjuvant trastuzumab?

DR LOCKER: I wish I could say that this was an isolated phenomenon, but this is a common problem. In every consent form it states that patients can withdraw consent at any time, and a lot of patients do avail themselves of that right. I do think you were dealing with a patient who was perhaps a little more educated or did a little more homework than most.

DR LOVE: This case raises the question, "When do we use a therapy that has not been proven?" We know from our Patterns of Care studies that in clinical practice, physicians had not been using adjuvant trastuzumab prior to the data becoming available, and every time I interview a breast cancer researcher they strongly discourage it.

Maybe this patient read Aman's paper on neoadjuvant trastuzumab and got excited about the idea of adjuvant therapy (Buzdar 2005; [2.1]).

DR SMITH: She actually did read Aman's paper.

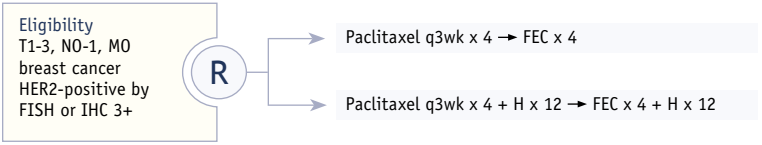
DR LOVE: Aman, why do you think physicians were so hesitant to use adjuvant trastuzumab off protocol?

DR BUZDAR: I think one of the major concerns was that trastuzumab has a known risk of cardiotoxicity and we didn't know the degree of benefit, so we didn't know whether the risk-benefit ratio would favor treatment.

However, the results from our neoadjuvant study showed substantial improvement in pathological complete response, and I think that, provided indirect evidence, the adjuvant trials would be positive.

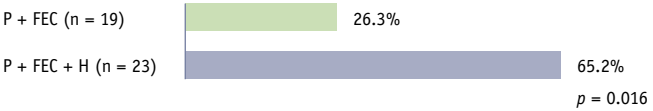
2.1 MD Anderson Phase III Trial of Neoadjuvant Trastuzumab/Chemotherapy

Accrual: 42 (Early closure by DSMB)

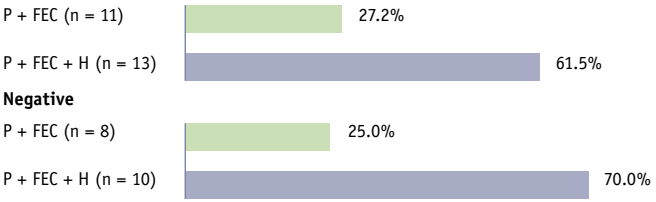


H = trastuzumab 4 mg/kg on day 1, then 2 mg/kg weekly

Overall pathologic complete response



Pathologic complete response by hormonal receptor status



"These results represent the highest reported pCR rate in this patient population. The most logical explanation for this high pCR rate is the use of two potentially noncross-resistant chemotherapies administered sequentially in combination with trastuzumab. Other possibilities include longer duration of neoadjuvant therapy compared with earlier studies."

P = paclitaxel

SOURCE: Buzdar AU et al. *J Clin Oncol* 2005;23(16):3676-85. **Abstract**

DR LOVE: It's interesting that this educated woman who was very aggressive about wanting trastuzumab is content with tamoxifen, which in a patient with three positive nodes and HER2-positive disease, is not aggressive hormone therapy. Has the issue of ovarian suppression been raised in this case?

DR SMITH: Yes, it's been raised and she is struggling with the thought of using leuprolide or goserelin. I think what she'll probably do is have an oophorectomy.

If this patient opted not to do that, I'd like to query what one would do with this patient who is intramenopausal. She stopped menstruating after the second or third cycle of AC, but I don't think she can be considered permanently postmenopausal.

DR LOVE: This is a vexing and common question. Aman, how do you approach endocrine intervention in perimenopausal patients who stop menstruating during chemotherapy, particularly in the high-risk, HER2-positive populations?

DR BUZDAR: There is no good way to define these patients. The best thing we can do is serial evaluations of the patient's LH, FSH and serum estradiol levels. If her LH and FSH levels remain high and the serum estradiol levels remain very low in the postmenopausal range, chances are she will not resume her cycles. Still, I think that if she

does not want ovarian suppression, then it is reasonable to start with tamoxifen.

DR LOCKER: I think we need to put this all in context. We are discussing this issue because women with ER-positive, PR-negative disease and with HER overexpressed tumors are two subsets of patients who, based on several studies, don't do as well as the average patient on tamoxifen. Data from ATAC and other trials and, in the case of HER2-positive disease, data in the neoadjuvant setting, demonstrate that these patients do better on an aromatase inhibitor (AI). So we'd like to see this patient on an AI, but she can't be on it unless she's clearly postmenopausal.

DR LOVE: Aman, what would you do if this patient came to you requesting an LHRH agonist and an aromatase inhibitor?

DR BUZDAR: The role of an LHRH agonist with an aromatase inhibitor in premenopausal women is under study, and a number of protocols are ongoing. We know the safety data. However, we don't know the efficacy of this regimen, and until we see those data, I do not like to see it used in clinical practice.

DR LOVE: What if the same patient came to you requesting aromatase inhibitors after an oophorectomy?

DR BUZDAR: Then there is no question that I would put her on an aromatase inhibitor, because she would then be postmenopausal.

DR LOVE: Aman, about half of the patients in the adjuvant trastuzumab studies presented at ASCO 2005 had ER-positive tumors, although we don't know the quantitative levels. Did trastuzumab impact these patients any differently?

DR BUZDAR: No. For these patients, appropriate endocrine therapy should be offered, because there is no question that endocrine therapy can substantially change the natural history of the disease in these patients, too.

DR LOVE: What do we know about combining hormonal therapy and trastuzumab, in terms of safety?

DR BUZDAR: In the NSABP study, patients who received endocrine therapy received trastuzumab concomitantly. No experimental data exist to suggest any adverse interactions, and none were reported.

DR LOVE: Gersh, it appears most physicians are waiting until the patient completes chemotherapy and then giving hormone therapy along with trastuzumab, as they did in the clinical trials.

DR LOCKER: Yes. In patients with HER2-positive disease, recurrences occur early. In the ATAC trial, an early blip was clear in time to recurrence, even with hormone receptor-positive disease. So you want to use your best guns early — meaning hormonal therapy and trastuzumab. I'd be very uncomfortable waiting a year until trastuzumab is completed.

DR LOVE: Let's talk about chemotherapy in patients with HER2-negative tumors and positive nodes. How do you approach those patients?

DR LOCKER: If the tumor were ER/PR-positive and HER2-negative with multiple positive nodes and the patient understood the limited benefit of chemotherapy beyond the benefit she gains from hormonal therapy, I would use AC times four. I'm not even convinced that adding paclitaxel makes a difference. Now, if I were going to be more aggressive for whatever reason — say she has 20 nodes and wants to be as aggressive as possible — then perhaps I would use TAC, but that's about as far as I'd go.

DR LOVE: What if the tumor were ER/PR-negative?

DR LOCKER: In a healthy patient with an ER/PR-negative tumor and multiple positive nodes, I would use TAC.

DR BUZDAR: TAC is a good combination, but when you combine either docetaxel or paclitaxel with other drugs, you increase the morbidity. I think patients tolerate sequential administration better, and you don't have to use growth factors to overcome some of the side effects. My personal choice would be to administer anthracycline-based therapy followed by a taxane-based therapy in these patients.

DR LOVE: How does the relative efficacy of docetaxel compare with paclitaxel?

DR BUZDAR: In my judgment, the efficacy of docetaxel every three weeks is similar to weekly paclitaxel, whereas a study has shown paclitaxel every three weeks is inferior to docetaxel every three weeks in the metastatic setting (Jones 2005).

DR LOVE: Gersh, do you think at some point AC followed by nanoparticle albumin-bound (*nab*) paclitaxel will be used?

DR LOCKER: It's possible. *Nab* paclitaxel has some advantages, but I'm not sure whether the difference in efficacy, if there is any, would warrant it. I think the bigger issue is whether we're going to be doing stratification by receptors in terms of chemotherapy choices, the way we do stratification by receptors for hormonal therapy choices.

DR LOVE: Aman, if we find *nab* paclitaxel is equal to paclitaxel in efficacy, will the advantages of a shorter infusion time and the ability to administer it without premedication justify a shift in practice?

DR BUZDAR: Yes. I think the advantage of *nab* paclitaxel is that you don't have to use steroids. When we use taxanes, one of the major complaints from patients, besides the neurotoxicity, is the weight gain and side effects related to steroids. If you can avoid that, you are actually enhancing the quality of life of these patients. Even if the antitumor activity of *nab* paclitaxel is identical to paclitaxel, I think it has a better safety profile.

Select publications

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

Eiermann W et al. **Phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed by docetaxel (ACT) in HER-2/neu negative early breast cancer patients with positive axillary lymph nodes: Interim analysis of the BCIRG 005 study.** San Antonio Breast Cancer Symposium 2005;**Abstract 1069**.

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. **Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer.** *J Clin Oncol* 2005;23(24):5542-51. **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**.

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**.

CASE 3:

A 45-year-old woman who presented in 1999 with ER/PR-positive, HER2-negative, node-negative bilateral breast tumors (right: 2.4 centimeters; left: 1.2 centimeters). After bilateral mastectomy, AC chemotherapy and five years of tamoxifen, she presented in 2005 with extensive ER/PR-negative, HER2-negative metastatic disease *(from the practice of Dr Paul K Marcom)*.

Edited excerpts from the discussion:

DR MARCOM: This patient is a 45-year-old woman, who presented first in May 1999 with bilateral breast cancer. She had a right breast tumor that was a T2 lesion, about 2.4 centimeters, Grade II, ER 10 percent, PR 10 percent, HER2 1+. She also had a contralateral breast tumor that was 1.2 centimeters and was also node-negative, ER and PR also 10 percent and HER2-negative.

She underwent bilateral mastectomies, very much at her preference, and received four cycles of AC. She was premenopausal and was placed on tamoxifen for borderline hormone receptor-positive breast cancer.

She did well and stayed on tamoxifen for five full years, but then presented in May 2005 to her internist with severe right upper quadrant abdominal pain. She had the clinical appearances of metastatic disease that, in my opinion, was bordering on visceral crisis.

She had essentially complete replacement of her left hepatic lobe and significant disease in her right hepatic lobe also. Her baseline alkaline phosphatase was 205, SGOT was 166 and SGPT was 61, but she was in quite a bit of discomfort. She also had some retroperitoneal mediastinal lymph nodes.

We biopsied the liver lesions, which were ER- and PR-negative and HER2-negative — 1+ by IHC and FISH negative. A PET scan also revealed a pericardiac mass that was not hemodynamically compromising, retroperitoneal nodes and a right adnexal mass.

DR LOVE: Can you talk about her lifestyle and family situation?

DR MARCOM: She's a "salt-of-the-earth" person. She's a stay-at-home mother. Her husband has a blue-collar job, and her children are nine and 12 years old. She's just a very solid woman, one of these tragic cases that we all see in young women with aggressive metastatic breast cancer in the midst of trying to raise their families.

DR LOVE: Therapy was initiated on May 26th of 2005, which was just 10 days after the bevacizumab presentation at the ASCO meeting (Miller 2005a; [3.1]). With that in mind, Gersh, how would you treat this unusual case of a young patient in visceral crisis with metastatic disease?

DR LOCKER: It's a good point, because in the average patient with metastatic disease that's ER-negative, there is little advantage to using anything other than sequential single-agent chemotherapy. The only advantage to using combinations is a higher response rate and probably a quicker response rate. So in this case, a taxane is a given — it's the most active drug that she hasn't already received — and this would be a patient for whom I would add something to a taxane. One key issue is her liver function.

In a patient such as this, the liver enzymes are a good reason to use a low-dose weekly paclitaxel regimen, because you're going to get into less trouble than giving either docetaxel or paclitaxel every three weeks. Now, what would I add to low-dose weekly paclitaxel? Data were presented at ASCO in favor of adding bevacizumab and that's one alternative (Miller 2005a). The other would

3.1 ECOG-E2100: First Planned Interim Analysis of Primary and Secondary Efficacy Endpoints

	Paclitaxel + bevacizumab (n = 330)	Paclitaxel (n = 316)	*p*-value
Response rate			
All patients	28.2%	14.2%	<0.0001
Measurable disease	34.3%	16.4%	<0.0001
Progression-free survival	10.97 months	6.11 months	
	Hazard ratio = 0.498 (CI: 0.401-0.618)		<0.001
Overall survival	Hazard ratio = 0.674 (CI: 0.495-0.917)		0.01

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

be to add something like a fluoropyrimidine, since there's data on capecitabine (Susnjar 2005; Uhlmann 2004).

To be honest, I'm not certain what I would do. Even though I was there for the presentation of the bevacizumab data, I'd probably add a second chemotherapeutic agent, understanding it probably will not impact survival. It's just going to allow you to treat her quicker and get a greater response. Fluoropyrimidines are attractive because they don't need liver metabolism. Doxorubicin is perfectly reasonable to combine with docetaxel, but not in a patient with liver disease.

DR LOVE: Would you treat her any differently if she had not received any prior chemotherapy?

DR LOCKER: Again, the most active regimen probably is a combination of a taxane and doxorubicin, specifically docetaxel/doxorubicin in this case, but my big concern is the liver function. You are going to have problems with stomatitis and GI toxicity if you do that, even if you administer cytokines. I think I would use low-dose weekly paclitaxel and 5-FU or capecitabine, and less likely bevacizumab.

DR BUZDAR: For this lady I would discuss various options, but I would recommend combination chemotherapy. The other option I would discuss with this patient is paclitaxel with bevacizumab. This patient has extensive replacement of the liver and I think it would be appropriate to utilize combination therapy to get a quick response, such as capecitabine or gemcitabine with a taxane.

DR LOVE: What about combination chemotherapy and bevacizumab?

DR BUZDAR: We don't have any safety or efficacy data on the combination of bevacizumab with two drugs. If we had even Phase I data indicating that you could combine the drugs, I would have gone with that (Miller 2005a, 2005b).

DR LOVE: Dr Marcom, what happened with this patient?

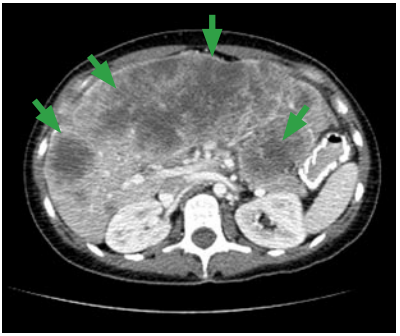
DR MARCOM: I would generally use single-agent therapy and I don't think of myself as somebody who pushes the envelope too much, but I had just returned from ASCO and seen the bevacizumab data. In my opinion, this case was a kind of the basal-like breast cancer subtype. I fully discounted her original ER and PR and saw her case as aggressive and I felt she needed combination chemotherapy.

With all that said, I gave her weekly paclitaxel along with capecitabine and bevacizumab. She actually has had quite a remarkable response and has tolerated therapy extremely well (3.2). I was part of Bill Gradishar's capecitabine plus paclitaxel study and was impressed that it was a pretty well-tolerated regimen (Gradishar 2004; [3.3]), and we have safety data on the combination of capecitabine and bevacizumab in breast cancer (Miller 2005b), so I felt I had a leg to stand on.

DR LOVE: How many courses has she received?

DR MARCOM: She's received four cycles altogether now. She had very quick symptomatic improvement about halfway through the

3.2 Case 3: Marked Reduction in Hepatic Tumor Burden Following Four Cycles of Paclitaxel, Capecitabine and Bevacizumab



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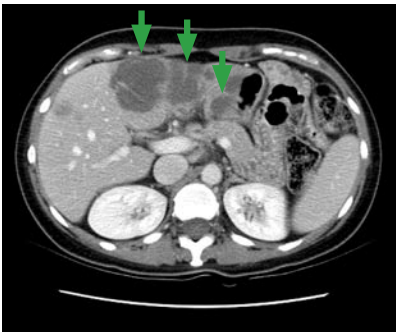

9/29/05

SOURCE: From the practice of Paul K Marcom, MD

3.3 Multicenter Phase II Study of Capecitabine with Paclitaxel as First-Line Therapy for Metastatic Breast Cancer (n = 47)

Efficacy endpoints	**Number of responders**	**Response rate**
Overall response (90% CI)	24	51% (38, 64)
Complete response	7	15%
Partial response	17	36%
Stable disease ≥6 months	9	19%
Clinical benefit (95% CI)	33	70% (55, 83)
Grade III/IV adverse events	**Number of patients**	**Percent**
Neutropenia	7	15
Alopecia	6	13
Hand-foot syndrome	5	11
Fatigue	4	9
Dyspnea	4	9
Paraesthesia	3	6
Peripheral neuropathy	3	6

Capecitabine = 825 mg/m^2 twice daily, days 1-14, every three weeks
Paclitaxel = 175 mg/m^2 every three weeks

SOURCE: Gradishar WJ et al. *J Clin Oncol* 2004;22(12):2321-7. **Abstract**

second cycle. Her right upper quadrant pain decreased quite dramatically. My plan was that I would drop the capecitabine at some point once I had gotten a response.

DR LOVE: Have you considered stopping the paclitaxel or even both chemotherapy agents?

DR MARCOM: That's a very good question. Looking at ECOG data on paclitaxel plus bevacizumab, I think I have the best justification for stopping the capecitabine, at least initially. I would be hesitant to stop all chemotherapy and have her on just single-agent bevacizumab, given the response that we have for that (Cobleigh 2003).

DR LOVE: Aman, if this patient came to you for a second opinion a few months from now and she'd had a great response, and she were stable, what would you recommend at that point?

DR BUZDAR: Our approach is that if she were not experiencing excessive toxicity, we would advise her to continue the therapy, unless she had a complete clinical response.

DR MARCOM: For what it's worth, her CA15-3 started at 331 U/mL and has normalized now. Hopefully, her scans will fully catch up with that if this is necrotic tumor left in her left lobe.

DR LOVE: In talking to Bill Gradishar about the capecitabine/paclitaxel study and Joanne Blum from US Oncology who looked at a similar regimen, it seemed they felt the combination was not necessarily more effective than other combinations — for example, docetaxel combinations — but that it was better tolerated. What was your impression?

DR MARCOM: It's been my general sense that that is the case.

DR LOVE: Aman, you're evaluating capecitabine with docetaxel in your neoadjuvant/adjuvant trial. Can you talk about that study and what you've observed in terms of tolerance and the dose?

DR BUZDAR: We started that study a couple of years ago with 1,000 mg/m^2 twice daily of capecitabine, but after we treated a few patients, we had to modify the dose due to toxicities. The current dose of capecitabine is 750 mg/m^2 twice a day for two of three weeks with docetaxel 75 mg/m^2 every three weeks. That regimen is fairly well tolerated and we have now treated a sizable number of patients. Also, this regimen can be given on an outpatient basis. I don't think 1,250 mg/m^2, the package insert dose of capecitabine, can be tolerated by most patients (3.4).

3.4 Therapeutic Index of Lower-Dose Capecitabine in Metastatic Disease: MD Anderson Experience

"We retrospectively reviewed the records of 141 consecutive patients with metastatic breast cancer identified from pharmacy records as receiving capecitabine outside of a clinical trial between May 1998 and February 1999... .

"It is apparent that the toxic effects associated with capecitabine therapy at 2500 mg/m^2/day cause morbidity in a relatively high proportion of patients, necessitating frequent dose reduction. This is consistent with our experience. Since the most important goal of the treatment of metastatic breast cancer is symptom palliation, therapy associated with considerable morbidity defeats the purpose. Reduction of the capecitabine dose has been shown to improve drug tolerability in most cases. Moreover, retrospective analysis of many of the capecitabine trials [referenced here] has found that dose reduction for adverse events related to capecitabine did not have an impact on efficacy of the drug. This is supported by our data. In our experience, the mean tolerated dose of capecitabine is 2040 mg/m^2/day. Thus, it seems appropriate to use the drug at a lower starting dose, perhaps 2000 mg/m^2/day in two divided doses."

SOURCE: Hennessy BT et al. *Ann Oncol* 2005;16(8):1289-96. **Abstract**

Select publications

Batista N et al. **Phase II study of capecitabine in combination with paclitaxel in patients with anthracycline-pretreated advanced/metastatic breast cancer.** *Br J Cancer* 2004;90(9):1740-6. **Abstract**

Cobleigh MA et al. **A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer.** *Semin Oncol* 2003;30(5 Suppl 16):117-24. **Abstract**

Di Costanzo F et al. **Weekly paclitaxel plus capecitabine in advanced breast cancer patients: Dose-finding trial of GOIRC and GOL.** *Ann Oncol* 2006;17(1):79-84. **Abstract**

El-Helw L, Coleman RE. **Reduced dose capecitabine is an effective and well-tolerated treatment in patients with metastatic breast cancer.** *Breast* 2005;14(5):368-74. **Abstract**

Friedrich M et al. **Taxanes in the first-line chemotherapy of metastatic breast cancer: Review.** *Eur J Gynaecol Oncol* 2004;25(1):66-70. **Abstract**

Gradishar WJ et al. **Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: A multicenter phase II study.** *J Clin Oncol* 2004;22(12):2321-7. **Abstract**

Hennessy BT et al. **Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: Retrospective analysis of patients treated at MD Anderson Cancer Center and a review of capecitabine toxicity in the literature.** *Ann Oncol* 2005;16(8):1289-96. **Abstract**

Ignoffo RJ. **Overview of bevacizumab: A new cancer therapeutic strategy targeting vascular endothelial growth factor.** *Am J Health Syst Pharm* 2004;61(21 Suppl 5):21-6. **Abstract**

Kaklamani V, O'Regan RM. **New targeted therapies in breast cancer.** *Semin Oncol* 2004;31(2 Suppl 4):20-5. **Abstract**

Mackey JR et al. **Final results of a phase II clinical trial of weekly docetaxel in combination with capecitabine in anthracycline-pretreated metastatic breast cancer.** *Clin Breast Cancer* 2004;5(4):287-92. **Abstract**

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

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

Pagani O et al. **Dose-finding study of weekly docetaxel, anthracyclines plus fluoropyrimidines as first-line treatment in advanced breast cancer.** *Ann Oncol* 2005;16(10):1609-17. **Abstract**

Rugo HS. **Bevacizumab in the treatment of breast cancer: Rationale and current data.** *Oncologist.* 2004;(9 Suppl 1):43-9. **Abstract**

Susnjar S et al. **Weekly paclitaxel (TAX) and capecitabine (CAP) for metastatic breast cancer (MBC) patients (PTS) previously treated with anthracycline-containing therapy: A phase I dose-finding study.** *Proc ASCO* 2005;**Abstract 851**.

Tubiana-Hulin M. **How to maximize the efficacy of taxanes in breast cancer.** *Cancer Treat Rev* 2005;31(Suppl 4):3-9. **Abstract**

Uhlmann C et al. **Capecitabine with weekly paclitaxel for advanced breast cancer: A phase I dose-finding trial.** *Oncology* 2004;67(2):117-22. **Abstract**

Walko CM, Lindley C. **Capecitabine: A review.** *Clin Ther* 2005;27(1):23-44. **Abstract**

CASE 4:

A 38-year-old woman with a 1.5-centimeter, poorly differentiated, ER-positive/PR-negative, HER2-negative intraductal breast tumor with vascular invasion and four positive nodes *(from the practice of Dr Doron Weiner)*.

Edited excerpts from the discussion:

DR WEINER: This 38-year-old woman presented in January 2004 with a 1.5-centimeter, poorly differentiated, ER-positive, PR-negative, HER2-negative, intraductal breast cancer. Vascular invasion was noted, and four lymph nodes were positive.

She was initially treated with dose-dense AC followed by paclitaxel and radiation therapy to the left breast and axilla. She was prescribed tamoxifen, 20 milligrams daily. Her last menstrual period was at the onset of chemotherapy.

DR LOVE: Kevin, this patient's last menstrual period was less than a year ago and she's on tamoxifen. Would it be appropriate to switch her to an aromatase inhibitor?

DR FOX: I think it would be appropriate to switch a patient from tamoxifen to an aromatase inhibitor after two years of therapy. However, that requires that the patient be in true menopause, which brings up a very important issue in this case: When can you be assured that this patient is truly in menopause? I think it's safe to say that, for the first time this year, we were given some information that gives us a clue as to the natural history of chemotherapy-induced amenorrhea and its permanence, or lack of permanence, in women. I had never seen much on this issue before.

The late Dr Jeanne Petrek from Memorial was one of the organizers of a multi-institutional study, wherein newly diagnosed patients were recruited during or shortly after they completed adjuvant therapy. All that the study required was menstrual histories from these patients, essentially on a daily basis, for a three-year period. The data presented at ASCO (Petrek 2005) gave us an idea about how often women became amenorrheic and how often their menstrual periods resumed. Without belaboring the details, the most compelling observation was that if you looked at the percentage of patients after chemotherapy who were in a state of amenorrhea, the data were convincing that no reversibility remained after the second year.

On the other hand, quite a bit of reversibility was evident after the first year, especially in women under the age of 40. The point being that the premature prescription of an aromatase inhibitor might result in a therapeutic failure if the patient still has ovarian function.

What we've done, as an unofficial policy, is that if we need to confirm the patient's menstrual status, we check their estradiol and FSH levels, for all its faults. We haven't been burned thus far.

DR LOVE: Eric, this is a 38-year-old woman with four positive nodes. We know that in the postmenopausal woman, aromatase inhibitors reduce recurrence risk more than tamoxifen. What are your thoughts on how best to treat this perimenopausal patient?

DR WINER: The truth is, in a woman who is premenopausal at diagnosis, we don't know that any aromatase inhibitor used in the first five years is better than tamoxifen. No such patients were included in the trials, other than the MA17 trial, which involved treatment after five years of tamoxifen. If you think about it, a premenopausal woman experiences ovarian suppression from chemotherapy, and if she is on tamoxifen she has received essentially two hormonal therapies, one of which is substantially

lowering her estrogen levels.

It's an important and unanswered question as to whether, in a premenopausal woman, ovarian suppression and an aromatase inhibitor are better than ovarian suppression with tamoxifen. That is the question being asked in the TEXT and SOFT trials, and I could imagine the results going either way — showing the aromatase inhibitor combination to be superior or inferior to the tamoxifen combination (4.1).

DR LOVE: Do you think that ovarian ablation and tamoxifen will be better than tamoxifen?

DR WINER: I suspect that it may be, but that wouldn't keep me from enrolling someone in the study, because I'm not sufficiently convinced. The decision to add ovarian suppression and tamoxifen to treat a woman who's still premenopausal after chemotherapy is a tough decision outside of a trial.

I do it occasionally, and sufficient data exist to make me comfortable with that, but at the same time, I wouldn't say it's the standard. However, I would be worried that this woman might start cycling again if you switch her too soon, and we don't know that switching at any point in time will improve her outcome.

DR LOVE: If she came to see you in another couple of years and had now not menstruated for three years, would you switch her then?

DR WINER: I'm still a little nervous in a 38-year-old woman. If she were 48, had received AC followed by T and had not menstruated for three years, I'd be pretty comfortable. Although I realize those patients weren't included in IES or the ABCSG ARNO study, I tend to switch those patients (Coombes 2004; Jakesz 2005). On the other hand, if this 38-year-old patient were menopausal at the four- to five-year point, I would switch to an AI then or perhaps sooner if we have additional data before then.

DR LOVE: Eric, our Patterns of Care study has shown us that the most common chemotherapy right now in the United States for a patient like this is dose-dense AC followed by T, exactly what she received. What are reasonable alternatives for a patient like this?

DR WINER: I think any of the so-called third-generation regimens are reasonable. I can't tell you that one is better than the other, because they haven't been compared to each other. The two main regimens are AC followed by paclitaxel given in a dose-dense fashion, based on the results of the CALGB Intergroup study (Citron 2003), or TAC (Martin 2005). I think whatever you're most comfortable using as a third-genera-

4.1 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%	Tamoxifen x 5y OFS + tamoxifen x 5y OFS + exemestane x 5y
IBCSG-25-02 (TEXT trial)	1,845 (open)	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	Triptorelin ± chemotherapy + tamoxifen x 5y Triptorelin ± chemotherapy + exemestane x 5y
IBCSG-26-02 (PERCHE trial)	1,750 (closed with accrual) as of December 16, 2005 = 15/1,750	Premenopausal ER ≥ 10% and/or PgR ≥ 10%	OFS + tamoxifen or exemestane x 5y OFS + any chemotherapy + tamoxifen or exemestane x 5y

OFS = ovarian function suppression with triptorelin or surgical oophorectomy or ovarian irradiation

SOURCES: www.ibcsg.org; NCI Physician Data Query, December 2005.

tion regimen is the regimen that you should use (4.2).

DR LOVE: What about AC followed by docetaxel? Our Patterns of Care studies show that is the second most common regimen used in a case like this.

DR WINER: Why give something that hasn't been shown to be effective, although there's every reason to think that it will be? Why not give the regimen as it was given in a trial? Now, if you have a patient who's getting AC followed by paclitaxel and she's having severe neuropathy, it's reasonable to use docetaxel if you want to continue the taxane and you think it may be better tolerated from a neuropathy standpoint.

DR LOVE: Kevin, what regimen would you use in a patient like this?

DR FOX: We participated in the CALGB-9741 trial and became somewhat familiar with the dose-dense concept. When that trial was reported as a positive study, we began asking, "Why not give dose-dense therapy?" Gaining more experience with dose density after the study, we saw no unique toxicities.

It was virtually always assured that patients could stay on schedule, which trimmed eight weeks off their course of therapy. Cost issues of growth factors notwithstanding, I still haven't come up with a good reason not to do it, so it has been our standard approach outside of a clinical trial.

4.2 Indirect Comparison of Adjuvant Clinical Trial Results in Patients with Node-Positive Breast Cancer: BCIRG-001 (TAC versus FAC) and CALGB-9741 (Dose-Dense [DD] versus Conventional Scheduling [CS] Chemotherapy)

	BCIRG-001[1]		CALGB-9741[2]	
Number of patients	1,491		2,005	
Median follow-up	55 months		36 months	
	Relative reduction TAC/FAC	Percent reduction	Relative reduction DD/CS	Percent reduction
Disease-free survival	HR = 0.72 p = 0.001	28	RR = 0.74 p = 0.010	26
Overall survival	HR = 0.70 p = 0.008	30	RR = 0.69 p = 0.013	31

SOURCES: [1] Martin M et al. *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 43**; [2] Citron ML et al. *J Clin Oncol* 2003;21(8):1431-9. **Abstract**

Select publications

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Kaklamani VG, Gradishar WJ. **Adjuvant therapy of breast cancer.** *Cancer Invest* 2005;23(6):548-60. **Abstract**

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Pritchard K. **Endocrinology and hormone therapy in breast cancer: Endocrine therapy in premenopausal women.** *Breast Cancer Res* 2005;7(2):70-6. **Abstract**

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CASE 5:

A 70-year-old woman with a 2.5-centimeter, Stage II, ER/PR-positive, HER2-negative adenocarcinoma with two positive nodes *(from the practice of Dr Robert Goldberg).*

Edited excerpts from the discussion:

DR GOLDBERG: This 70-year-old woman presented with Stage II breast cancer. She had an ER/PR-positive, HER2-negative, 2.5-centimeter adenocarcinoma with two positive lymph nodes. She received adjuvant CAF chemotherapy and then went on to tamoxifen for five years. After completing tamoxifen, she was put on anastrozole. She's been on anastrozole for about a year and she's doing well.

DR LOVE: Gersh, can you discuss how you approach these patients who have completed five years of tamoxifen in terms of deciding whether to use an AI and which one?

DR LOCKER: If their tumors are node-positive, they should go on an AI, unless they have severe osteoporosis. I use letrozole because that was used in the original study, and I'm trying to be evidence based. I suspect the other AIs would be just as good. Data from Europe support anastrozole after five years of tamoxifen (Jakesz 2005a).

In a woman with node-negative disease, if there were any negative prognostic features, such as a large tumor, then I would switch to letrozole after tamoxifen. I do not routinely switch breast cancer patients with T1-B, ER-positive, node-negative tumors. In that group of women, tamoxifen is as much a chemopreventative as it is an adjuvant therapy, and I'm not sure whether the potential side effects, in terms of bone or the need for bisphosphonates, merit it. On the other hand, if the tumor is a T1-C/N0, I probably would start them on letrozole at five years.

DR LOVE: How would you manage a patient who had five or 10 positive nodes initially and completed adjuvant tamoxifen more than a year or two ago?

DR LOCKER: I have "sinned" and put patients with 20 positive nodes on letrozole five years after completing tamoxifen. I know I will burn in hell for this, but they had 20 nodes and I don't care. For someone who's node-negative, I won't do it that late.

DR LOVE: Incidentally, would you start a patient with HER2-positive disease and 20 positive nodes on adjuvant trastuzumab five years later?

DR LOCKER: No, I would not. One of the things about HER2-positive disease is that the side effects are bad and can be bad early. A few patients will probably have a recurrence late, but I think the greatest concern is with those who have a recurrence earlier.

DR LOVE: Would you treat that same patient with adjuvant trastuzumab two years after diagnosis?

DR LOCKER: Probably.

DR LOVE: Aman, how do you think exemestane, letrozole and anastrozole compare with regard to serious toxicities?

DR BUZDAR: That's an important issue we need to discuss with patients. Even though these studies did not compare one aromatase inhibitor head-on with another, the ATAC study, which has the longest follow-up, has not shown any increase in cardiovascular events with anastrozole, and substantial reduction was apparent in cerebrovascular events (Howell 2005), whereas with the letrozole in BIG-1-98, an increased risk of cerebrovascular accidents was apparent and also an increased risk of fatal myocardial infarcts (Thürlimann 2005b). These numbers are small but of some concern. The same

thing was seen with the myocardial events in the exemestane study (Coombes 2004). I am concerned, but I discuss the data with the patient and use the aromatase inhibitor for the setting in which the most data are available.

We now have some of the data from the Austrian study, in which anastrozole was used after five years of tamoxifen (Jakesz 2005a). We see a similar proportional reduction in the risk of recurrence, which gives us one more piece of information that suggests we may be able to use anastrozole in this setting.

DR LOVE: At this time, what do you think is the most defensible aromatase inhibitor to use initially and after two to three years, Gersh?

DR LOCKER: Up front, it's clearly anastrozole. Until we have five or six years of data in the BIG I-98 study, anastrozole is the drug that is most reasonable up front (5.1). After five years, letrozole should be used. I have no doubt that anastrozole will probably be just as good, but I act on the data that we have.

In terms of the switching studies, the IES data certainly support exemestane, while the German-Austrian and the Italian data support anastrozole (Coombes 2004; Jakesz 2005b; Boccardo 2005; [5.2]). I think either one is acceptable. I would probably use anastrozole, only because I have more experience with it in the adjuvant setting.

When the BIG I-98 trial reports on the two switching arms — and I'm praying they are not underpowered — then we will have an answer as to whether letrozole should be used after two years of tamoxifen. However, for now I go with the most mature studies that address the specific situations.

DR LOVE: Aman, do you agree with Gershon as to which AI should be used initially and when switching after two to three years?

DR BUZDAR: My feeling is that if you look at the efficacy, either up front or after two to three years, or even after five years, all these aromatase inhibitors show similar efficacy. Differences in safety exist, but you have to keep in mind that you are looking across the trials, not at a head-on comparison. One study is comparing anastrozole with exemestane, and that will provide head-on safety data.

However, I totally agree with Gershon that we have the most mature safety data for anastrozole, which has the longest follow-up, and the efficacy data of BIG-1-98 is almost a mirror image at the two-year follow-up. That study, at least, confirms the ATAC data, in which at two and a half years we saw a similar proportional reduction in risk of recurrence.

DR DESAI: When you do switch patients after two or three years of tamoxifen, patients ask whether a total of five years

5.1 BIG 1-98 (N = 8,010) and ATAC (N = 9,366) Efficacy Data

Endpoint	BIG 1-98[1] hazard ratio (25.8 months)	ATAC[2] hazard ratio (68.0 months)
Disease-free survival	0.81	0.87
Time to recurrence	0.72	0.79
Time to distant recurrence	0.73	0.86
Time to breast cancer death	NR	0.88
Overall survival	0.86*	0.97*

* Not significant; NR = not reported

SOURCES: [1] Thürlimann B for the BIG 1-98 Collaborative Group. Presentation. St Gallen Breast Cancer Conference 2005. *Breast* 2005a;14(Suppl 1):3;S4.
[2] Howell A et al; ATAC Trialists' Group. *Lancet* 2005;365(9453):60-2. **Abstract**

5.2 Evaluating the Strategy of Switching from Adjuvant Tamoxifen to an Aromatase Inhibitor

Study	N	Randomization	Study endpoints	Hazard ratio
ABCSG-8/ ARNO 95	3,224	TAM (T) x 2y → anastrozole (A) x 3y TAM x 2y → TAM x 3y	EFS DRFS OS	A/T = 0.60 (p = 0.0009) A/T = 0.61 (p = 0.0067) A/T = 0.76 (p = 0.16)
IBCSG-18-98/ EU-99022/ IBCSG-1-98	8,010	TAM x 5y Letrozole (L) x 5y TAM x 2y → letrozole x 3y Letrozole x 2y → TAM x 3y	DFS* OS*	L/T = 0.81 (p = 0.003) L/T = 0.86 (p = 0.16) NR NR
IES/ICCG-960 EXE031-C1396-BIG9702	4,742	TAM x 5y TAM x 2-3y → exemestane (E) x 2-3y	DFS BCFS OS Time to contralateral breast cancer	E/T = 0.68 (p < 0.001) E/T = 0.63 (p < 0.001) E/T = 0.88 (p = 0.37) E/T = 0.44 (p = 0.04)
Italian (ITA)	426	TAM x 2-3y → anastrozole x 2-3y TAM x 2-3y → TAM x 2-3y	Relapse Death	A/T = 0.36 (p = 0.006) A/T = 0.18 (p = 0.07)
GROCTA 4B	380	TAM x 3y → aminoglutethimide (AG) x 2y TAM x 3y → TAM x 2y	EFS	AG/T = 1 (p = 0.6)

TAM = tamoxifen; EFS = event-free survival; DRFS = distant relapse-free survival; OS = overall survival; DFS = disease-free survival; NR = not yet reported; BCFS = breast cancer-free survival

* Endpoint for monotherapy; analysis of sequential endocrine treatment not yet completed; HR < 1.0 favors aromatase inhibitors

Extended Adjuvant Hormonal Therapy with Aromatase Inhibitors After Five Years of Tamoxifen

Study	N	Randomization	Study endpoints	Hazard ratio
SWOG-NCIC-MA17/ CAN-NCIC-MA17/ IBCSG-BIG97-01/ CALGB-49805	5,187	TAM x 4.5-6y → letrozole x 5y = 0.76 TAM x 4.5-6y → placebo x 5y	Relapse Death	L/P = 0.57 (p = 0.00008) L/P = 0.76 (p = 0.25)
ABCSG-6a	856	GROCTA 4B → anastrozole x 3y GROCTA 4B → no treatment x 3y	EFS	Anastrozole/ no treatment = 0.64 (p = 0.047)

TAM = tamoxifen; EFS = event-free survival

SOURCES: Boccardo F et al. *Proc SABCS* 2003;**Abstract 3**; Boccardo F et al. *J Clin Oncol* 2001;19(22):4209-15. **Abstract**; Boccardo F et al. *J Clin Oncol* 2005;23(22):5138-47. **Abstract**; Jakesz R et al. Presentation. San Antonio Breast Cancer Symposium 2004;**Abstract 2**; Thürlimann BJ et al. BIG 1-98. Presentation. ASCO 2005b;**Abstract 511**; Jakesz R et al. *Proc ASCO* 2005;**Abstract 527**; NCI Physician Data Query, September 2005; Goss PE et al. *N Engl J Med* 2003;349(19):1793-802. **Abstract**; Coombes RC et al. *N Engl J Med* 2004;350(11):1081-92. **Abstract**; NSABP website, **www.nsabp.pitt.edu**; **www.ibcsg.org**.

of endocrine therapy is enough. They want to continue therapy. What do we do about those patients?

DR LOCKER: The switching trials are problematic, because the implication is that if you switch, you stop therapy at five years. Does it make sense that we give five years of tamoxifen followed by five years of letrozole, but when we switch, we give only five years of therapy — two years of tamoxifen followed by three years of anastrozole or exemestane?

I don't know what to do with those patients. I use the "20-node rule." If they had a lot of positive nodes and I'm really worried, then they're going to receive hormones until they die. If they are node-negative, I think you should just go by what the studies say.

DR BUZDAR: I totally disagree with Gershon on this point. If you look at the hazard ratios for patients who have 20 versus zero positive nodes, the risk of recurrence in the first two to five years becomes very high as the number of nodes increases. As time passes, the risk of recurrence for the two groups becomes very close. The patient who has survived five years disease free has a risk close to that of the patient who had maybe one or no positive nodes (Saphner 1996).

DR LOCKER: What about looking at receptor status within that subset? I know it's a subset of a subset analysis, but the women who had 20 positive nodes and are receptor-positive are not the same as the women who had 20 positive nodes and are receptor-negative.

DR BUZDAR: The recurrence risk is regardless of the receptor status. Patients are at increased risk in the first several years, and after that, while the risk is there, the differences between a high number of positive nodes and negative nodes or a low number of positive nodes tend to become blurred.

DR LOCKER: Well, having said that, remember that for a woman with node-positive disease, from year five to year 10 after tamoxifen, the absolute yearly risk for recurrence is two percent per year.

DR LOVE: Do you agree with that, Aman?

DR BUZDAR: It is true that there is a risk and it is higher than the normal patient population, but my point is that when comparing the risk between 20 versus two positive nodes, the differences become very close.

DR DRAGON: My understanding in looking at the trial of letrozole after tamoxifen is that 20 percent of the recurrences occur after five years. How does that impact decision-making for node-negative patients, where you're talking about a relatively small number of women who recur, and then reducing that by 40 percent? We're talking about a one or two percent benefit for five years of letrozole, which is, by my calculation, about $14,000 per patient. So you're treating 100 women at $14,000 per patient to reduce, perhaps to eliminate, one or two recurrences over the next five years. Is that a rational thought process?

DR LOVE: It is not uncommon to see adjuvant chemotherapy used under similar circumstances.

DR LOCKER: Other issues arise with the patients with node-negative disease in the MA17 trial. For example, the odd survival data, showing a statistically significant survival advantage in patients with node-positive disease, but no survival advantage in women with node-negative disease. In fact, it's trending the wrong way. I think Dr Dragon's point is very well taken. In patients with node-negative disease, you have to be selective as to whom you treat with letrozole after tamoxifen.

DR SMITH: There seems to be a bit of a schism between those who would start patients on anastrozole or letrozole initially versus those who would give tamoxifen for two or three years and then switch the patient to an aromatase inhibitor.

DR BUZDAR: You bring up a very important point. At MD Anderson, we do not use tamoxifen up front on any patient who is postmenopausal. Right now, in 2005, I do not think we can say that any subset of postmenopausal patients with ER-positive

disease should start on an anti-estrogen and switch to an aromatase inhibitor after two or five years. I think the data we have are very convincing that starting with an aromatase inhibitor is better. It reduces the risk of recurrence and the overall safety profile of the therapy is better. I think the question is whether a subset exists in which it is better to start on tamoxifen and then switch later. This is a research question and the studies are ongoing.

DR LOVE: Gersh, when deciding on an adjuvant therapy, how much of an issue is the risk of endometrial cancer and thrombosis?

DR LOCKER: I remember sitting with Aman when they presented the ATAC hysterectomy data, which was a curveball. It showed that seven percent of women on tamoxifen underwent a hysterectomy during five years of treatment, compared to a couple percent, at the most, for the patients taking anastrozole. I think, in terms of the switching versus starting, that is a number you cannot escape. One out of every 100 women who receives tamoxifen for two or two and a half years and then switches to anastrozole will recur and presumably die, who would not have if they were on anastrozole initially. What do you say to that one patient? I don't think anybody can predict who that one woman is, such that you can start her on anastrozole and start everybody else on tamoxifen.

DR LOVE: Aman, do you think we will see a survival advantage for aromatase inhibitors over tamoxifen?

DR BUZDAR: I think that you will see a survival advantage once these studies mature. I think if you did a meta-analysis of the data from the current studies, you would see a significant survival advantage. I just want to remind some of you that initially when tamoxifen was being evaluated, only one or two trials showed a survival advantage. It was the first Oxford meta-analysis that showed a dramatic reduction in the risk of death because you need a lot of events. In these postmenopausal patients with ER-positive disease, it takes much longer for the events that contribute to the survival advantage to develop. Major competing causes of death play a role and breast cancer becomes a secondary cause of death, so you need a large number of patients and longer follow-up.

DR STEINECKER: Should we be a little more attuned to following lipid profiles in patients on aromatase inhibitors?

DR BUZDAR: It would be reasonable — at least with letrozole and exemestane, for which we have data indicating that those agents change the lipid profile adversely in a sizable number of patients — to have baseline information and to re-evaluate the lipids several months down the line. If they are being affected adversely, then maybe an appropriate intervention should be made before any major event related to that effect develops.

I would like to come back to this issue of cost. Patients don't come to us because they want us to manage their financial affairs. They are coming to receive the best treatment for their cancer. We need to tell them what we think is the best and most effective treatment and then if the cost is an issue, we need to help them. Some of the patients who bring up the issue of cost have a bag full of other, alternative "health medications" for which they may be paying twice as much per month as the difference in costs between these two drugs.

Select publications

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**

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Proc SABCS* 2003;**Abstract 3**.

Boccardo F et al. **Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: Results of an Italian cooperative study.** *J Clin Oncol* 2001;19(22):4209-15. **Abstract**

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

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. **NCIC CTG MA17: Disease free survival according to estrogen receptor and progesterone receptor status of the primary tumor.** San Antonio Breast Cancer Symposium 2005;**Abstract 2042**.

Goss PE et al. **Updated analysis of NCIC CTG MA.17 (letrozole vs. placebo to letrozole vs placebo) post unblinding.** San Antonio Breast Cancer Symposium 2005;**Abstract 16**.

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

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

Ingle JN et al. **Analysis of duration of letrozole extended adjuvant therapy as measured by hazard ratios of disease recurrence over time for patients on NCIC CTG MA.17.** San Antonio Breast Cancer Symposium 2005;**Abstract 17**.

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

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

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

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**.

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 for the BIG 1-98 Collaborative Group. **Letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. First results of IBCSG 18-98/ BIG 1-98.** Presentation. St Gallen Breast Cancer Conference 2005. *Breast* 2005a;14(Suppl 1):3;S4.

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

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.** San Antonio Breast Cancer Symposium 2005;**Abstract 44**.

CASE 6:

A 55-year-old woman who presented with a locally advanced ER/PR-positive left breast tumor and bone metastases *(from the practice of Dr Leon H Dragon)*.

Edited excerpts from the discussion:

DR DRAGON: This 55-year-old woman presented with a locally advanced, ER-positive, PR-positive, left breast tumor and bone metastases approximately three years ago. She underwent a subtotal mastectomy, axillary dissection and reconstruction. She was given tamoxifen, to which she responded, and then letrozole, which also resulted in significant disease control.

DR LOVE: Did this patient know she had breast cancer and neglect it or was she just one of those cases that presents with metastatic disease?

DR DRAGON: She was very frightened. She had been treated for DCIS a number of years earlier with a right mastectomy and then had reconstruction. She knew there was something wrong in her left breast and she did not want to deal with having another episode of breast cancer.

DR LOVE: Was the left breast tumor an obvious lesion?

DR DRAGON: At the time I saw her, she had a four-centimeter mass that was fixed to the skin and clearly obvious as a breast cancer, and she knew that.

DR LOVE: Did she have bone pain from the metastases?

DR DRAGON: No.

DR LOVE: What was her life situation at that time?

DR DRAGON: She is a fashion model in her second marriage with two kids. Her son is a medical resident at a university center. She travels internationally on a regular basis. Her husband is a businessman in the community. They are independent financially and very secure.

DR LOVE: When she presented with locally advanced disease, how would you describe her mental state?

DR DRAGON: That's an interesting question. When she first presented to the breast surgeon and he sat down with her to explain that this looked like breast cancer, she became very unstable emotionally and actually had to be hospitalized for a couple of days.

She went directly from the surgeon's office to an inpatient psychiatric unit. She improved very rapidly, then came to see me and was ready to hear about how to get better.

DR LOVE: What was her psychological and medical history?

DR DRAGON: She had never had any medical or psychiatric illnesses before, except for the DCIS.

DR LOVE: How did she react to the idea of hormonal therapy?

DR DRAGON: Hormonal therapy fit in very well with her lifestyle. She was able to maintain an active travel schedule, seeing me between her travels to Europe, the Far East and Hawaii. This is a woman who was used to traveling a great deal and continued to do so while on therapy.

DR LOVE: How did she do emotionally after her initial reaction?

DR DRAGON: During periods when her disease was clearly beginning to progress, she would become tearful, but with a little bit of support and emphasis about the potential control of her disease with other therapies, she readily compensated within the span of an office visit and was able to go back to normal functioning.

DR LOVE: What hormonal therapy did she receive?

DR DRAGON: We started with tamoxifen and she achieved excellent disease control. When we reached an optimal level of control in the breast, the surgeon did a wide excision and cleaned out her axilla for local control, because initially this was an ulcerated lesion. We did not radiate the local area. She had excellent control of her bone metastases as well.

DR LOVE: What prompted the decision to use tamoxifen initially as opposed to an aromatase inhibitor?

DR DRAGON: It's a good question. We began therapy five years ago. If I saw this patient today, I would probably start with an aromatase inhibitor.

DR LOVE: After tamoxifen she received letrozole. How did she tolerate endocrine therapy?

DR DRAGON: She did not experience any toxicity with either agent. When she progressed, it was primarily in the breast. She never developed more bone metastases or pain.

We then started fulvestrant, which was approximately 18 months ago. She received fulvestrant for four months, and we did not give her a loading dose. She clearly progressed on the chest wall and in the axilla and at that point, we began discussing systemic chemotherapy.

DR LOVE: Eric, what options would you have presented to this patient at this point?

DR WINER: I wouldn't have totally ruled out using another hormone, but it's certainly reasonable to move on to chemotherapy at this point.

I would like to comment on fulvestrant. It's perplexing to a lot of people that it doesn't perform better given that in the randomized trials it was at least as good as, if not a little bit better than anastrozole (6.1). Some of that may relate to the setting. There's some concern that using it after an aromatase inhibitor may not be the optimal setting for this agent, although it's the way we all give it. Ongoing studies are evaluating estrogen priming for brief periods of time after an aromatase inhibitor followed by fulvestrant. Then there's the issue of a loading dose. It may turn out that one of the problems is that it just takes a long time to get to an optimal therapeutic level.

DR LOVE: Do you use a loading dose?

DR WINER: I haven't outside of a study (6.2). I don't think we know yet the optimal way to administer fulvestrant, and there's a lot of interest in learning the most effective way to use it. One reason why there have been delays in initiating any type of large adjuvant trial with fulvestrant is that until we define the optimal way to use this drug, we're just shooting ourselves in the foot if we try to start a trial sooner.

DR LOVE: If you were to begin chemotherapy at this time, what regimen would you choose?

DR WINER: As a general rule, I'm a single-agent guy and I'm not convinced that combination therapy is superior to giving single agents sequentially. The two trials that have shown that combination therapy may be superior — that is, the docetaxel with or without capecitabine study and the paclitaxel with or without gemcitabine trial — are both flawed in that there was not an appropriate crossover (O'Shaughnessy 2002; Albain 2004). In the studies that have evaluated crossover, there is absolutely no difference in survival between single agents and combination therapy (Sledge 2003).

So, in this woman who is not terribly symptomatic and for whom you want to do your best to minimize the impact of therapy on her quality of life, be as specific as you can with the therapy and eliminate drugs that aren't working, I would definitely use single-agent chemotherapy. In my view, it almost doesn't matter whether you use capecitabine or a taxane or an anthracycline. For that matter, you could probably use gemcitabine or vinorelbine, although they're less commonly used in this situation. I believe that response rates and time to progression are more dependent on when you administer the drug than on which drug it is.

6.1 Combined Analysis of Two Phase III Multicenter Trials Comparing Fulvestrant to Anastrozole in Postmenopausal Women with Advanced Breast Cancer

	Fulvestrant (n = 428)	Anastrozole (n = 423)	*p*-value
Complete response rate	4.7%	2.6%	—
Partial response rate	14.5%	13.9%	—
Objective response rate	19.2%	16.5%	0.31
Clinical benefit rate*	43.5%	40.9%	0.51
Estimated median time to progression	5.5 months	4.1 months	0.48
Median duration of response in those responding	16.7 months	13.7 months	—
Death rate (median follow-up, n = 27.2 months)	74.5%	76.1%	—
Median time to death	27.4 months	27.7 months	0.81

* Clinical benefit = complete response + partial response + stable disease ≥24 weeks

SOURCES: Robertson JF et al. *Cancer* 2003;98(2):229-38. **Abstract**
Pippen J et al. Poster. San Antonio Breast Cancer Symposium 2003;**Abstract 426**.

DR LOVE: Would you consider incorporating bevacizumab?

DR WINER: This patient would have been eligible for the ECOG trial with bevacizumab. The results presented at ASCO showed approximately a five-month improvement in time to progression and a doubling of the response rate (Miller 2005a). Unfortunately, bevacizumab is a very expensive drug, for which we don't have an identified target. We just don't know who benefits and who doesn't, or perhaps everybody benefits a little bit.

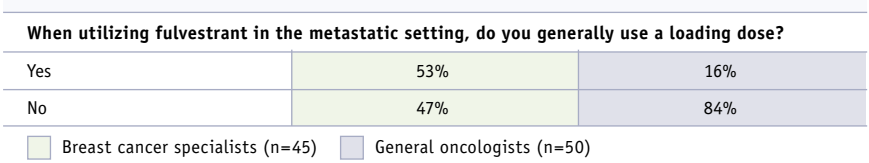
If I were going to use bevacizumab, I would give bevacizumab in combination with paclitaxel, the way it was done in the ECOG trial.

DR LOVE: Dr Dragon, what happened with this patient?

DR DRAGON: This predated the bevacizumab data, which I still don't know what to do with. We talked about the options and had a similar conversation about the many different choices of sequential single agents and agreed that ultimately she would probably see a lot of different drugs. We offered capecitabine as a reasonable option that would allow her to maintain her lifestyle, and she found an oral agent to be very appealing.

DR LOVE: How important was the issue of alopecia for her?

6.2 Use of a Loading Dose with Fulvestrant



SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

DR DRAGON: At this point, very important. She understands that, at some point, that's going to be an issue, but the availability of drugs — including vinorelbine, gemcitabine and capecitabine — that don't cause significant alopecia basically allowed her to compensate for the loss of control in her life.

DR LOVE: Eric, if you had seen this woman before the bevacizumab data were presented, what therapy would you have used?

DR WINER: Capecitabine.

DR LOVE: Would that change now that we have the bevacizumab data?

DR WINER: Since those data became available, I tend to somewhat cautiously use bevacizumab in this setting, and when I do, I'm a little uncomfortable combining it with capecitabine, given the negative data from Kathy Miller's previous study (Miller 2005b).

Now, I don't know if that trial was negative because bevacizumab isn't as effective in combination with capecitabine as it is with paclitaxel or whether it's because of the setting — that is, first line versus not first line. I tend to think it's probably not agent specific but rather more related to the fact that the ECOG paclitaxel trial was conducted with patients who had not received prior treatment in the metastatic setting.

I think that even today, I probably would pick capecitabine alone and hold off on doing anything else in this particular patient.

DR LOVE: Kevin, how would you think through this decision?

DR FOX: The same way. The decision would rest entirely upon which drug fits the patient's lifestyle, desires and limitations. This patient seems like a logical and almost perfect candidate for capecitabine.

DR LOVE: Eric, I think a lot of physicians share Dr Dragon's concern about not knowing how to apply the bevacizumab data (6.3). How would you respond to this concern?

DR WINER: I think part of the reason that people are uncertain is that we don't have a huge amount of data on bevacizumab. We have these two studies and we don't know much about bevacizumab with other agents. We'll probably learn more in the next few years.

My other comment is that this is a woman who has never received any chemotherapy before, so even if she receives capecitabine initially and you plan to use bevacizumab in the second-line setting, she's still more like the ECOG patients, and so I don't think you're burning any bridges by giving her single-agent capecitabine.

DR LOVE: Kevin, what do you think about using bevacizumab in the second-line setting in a patient who has received no prior adjuvant therapy?

DR FOX: I think it makes perfectly logical sense. I don't think we ought to make blanket rules about the use of bevacizumab exclusively as first-line therapy, because not every patient will be like the patients who were actually in the clinical trial.

DR LOVE: Dr Dragon, can you follow up on what happened with this woman?

DR DRAGON: She was started on capecitabine 10 months ago and had a very rapid and gratifying response. The node went away and the skin disease disappeared. Her bone disease was already asymptomatic. The response continued for more than nine months, and just this last month, her node became palpable. Her skin disease has still not recurred, but I think she's starting to progress.

DR LOVE: Eric, what are your thoughts about the dosing of capecitabine?

DR WINER: I usually don't bother calculating a precise dose per meter squared. I never use the 150-milligram pills. I'd start a normal-sized woman at 1,500 milligrams twice a day, and then adjust as necessary. Clearly, responses are seen at those doses.

I know that Larry Norton has been talking about some interesting scheduling ideas on capecitabine dosing. It may be a drug that will be more effective with different dosing, but at the moment, I think we're left dosing it with a modification of the package insert,

6.3 Incorporation of Bevacizumab into Treatment of Breast Cancer: A Survey of US Oncologists (n = 50) and Breast Cancer Specialists (n = 45), September 2005

Utilized bevacizumab to treat breast cancer off protocol	73%	4%
Have not utilized bevacizumab but intend to use it	18%	64%
Have not utilized and have no immediate intention to use it	9%	32%
If utilized, for what duration?		
Until disease progression	81%	74%
Beyond disease progression	14%	20%
Other	5%	6%

Breast Cancer Specialists General Oncologists

SOURCE: *Breast Cancer Update* Patterns of Care Survey, September 2005.

meaning two weeks on, one week off, but with lower doses.

DR LOVE: What about other taxanes, docetaxel and *nab* paclitaxel, in combination with bevacizumab?

DR WINER: I tend to be somebody who likes to see a little data. I don't see a reason for giving *nab* paclitaxel with bevacizumab at the moment. Once there are some safety data with the combination, and I don't have any reason to think that it won't be safe, then I think that's fine.

DR FOX: Eric, do you foresee using single-agent bevacizumab under any circumstances?

DR WINER: Well, in the study that Melody Cobleigh, George Sledge and Kathy Miller did evaluating bevacizumab as a single agent, it showed a bit of single-agent activity, mostly in heavily pretreated patients (Cobleigh 2003). I probably wouldn't be in a rush to do that at the moment, but I think it's a question to be asked in clinical trials.

One other thing I want to mention about the ECOG trial is that unlike most of the previous studies we have evaluating paclitaxel or any agent, the ECOG trial is one of the first that actually systematically excluded patients with HER2-positive disease. As we winnow down the patient populations, there may be somewhat unexpected findings in terms of response rate and time to progression. So in that ECOG trial, two-thirds of the patients had ER-positive disease, like this patient, and a third of the patients had ER-negative disease, which in that study, by definition, was triple-negative disease.

DR DESAI: Eric, do you feel the ECOG study data should change the way we practice?

DR WINER: I think that we're not quite sure what to do with the data. In my talk at ASCO, I carefully chose my words and said that it was reasonable to use bevacizumab in settings similar to the ECOG trial. However, it's not mandatory, and different people will approach this question in different ways. Hopefully we'll have some more data in the not-distant future.

DR LOVE: It's been interesting to see how in breast cancer the reaction to the bevacizumab data has been completely different from what we saw in colon and lung cancer. In colon cancer, people jumped on the data and actually started using it with FOLFOX, even though the trial was with IFL. In lung cancer, reimbursement issues exist, but the researchers feel that once it is reimbursable, they'll begin using it.

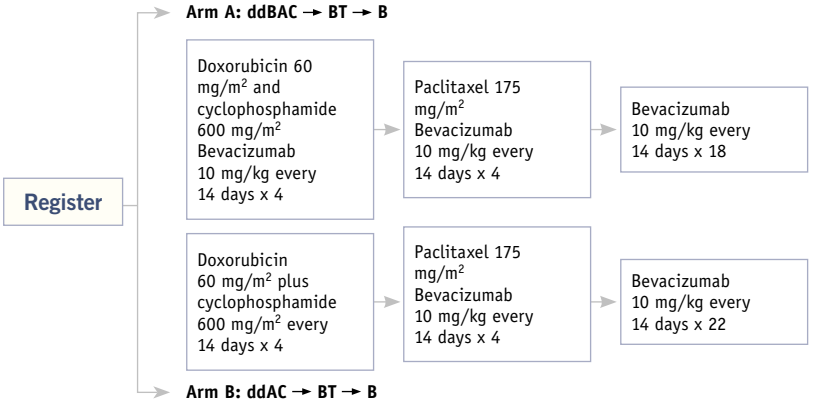
DR FOX: I think this stems from the fact that in the treatment of metastatic breast cancer we have lots of choices, whereas up until recently there were few choices, and even fewer good choices, in treating lung and colon cancer. As a result, we tend to be

a little bit more circumspect with respect to what we're going to use and what kinds of toxicities we're willing to accept.

DR LOVE: Eric, when do you think we'll begin to see adjuvant bevacizumab breast trials?

DR WINER: In the not-too-distant future. ECOG will be sponsoring a pilot study similar to the pilot feasibility study we saw with trastuzumab many years ago. A Phase III concept has already been submitted to the NCI from ECOG, so I suspect that study will open in 12 to 24 months, and I think it's a reasonable study (6.4).

6.4 E2104 Adjuvant Pilot Trial



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

Select publications

Adams GP, Weiner LM. **Monoclonal antibody therapy of cancer.** *Nat Biotechnol* 2005;23(9):1147-57. **Abstract**

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

Choueiri TK et al. **Role of aromatase inhibitors in the treatment of breast cancer.** *Clin Ther* 2004;26(8):1199-214. **Abstract**

Cobleigh MA et al. **A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer.** *Semin Oncol* 2003;30(5 Suppl 16):117-24. **Abstract**

Franco S et al. **Response to fulvestrant in heavily pretreated postmenopausal women: A single-center experience.** *Breast Cancer Res Treat* 2004;88(2):103-8. **Abstract**

Gralow JR. **Optimizing the treatment of metastatic breast cancer.** *Breast Cancer Res Treat* 2005;89(Suppl 1):9-15. **Abstract**

Howell SJ et al. **The use of selective estrogen receptor modulators and selective estrogen receptor down-regulators in breast cancer.** *Best Pract Res Clin Endocrinol Metab* 2004;18(1):47-66. **Abstract**

Hussain SA et al. **Endocrine therapy and other targeted therapies for metastatic breast cancer.** *Expert Rev Anticancer Ther* 2004;4(6):1179-95. **Abstract**

Hudis CA. **Clinical implications of antiangiogenic therapies.** *Oncology (Williston Park)* 2005;19(4 Suppl 3):26-31. **Abstract**

Ignoffo RJ. **Overview of bevacizumab: A new cancer therapeutic strategy targeting vascular endothelial growth factor.** *Am J Health Syst Pharm* 2004;61(21 Suppl 5):21-6. **Abstract**

Janicke F. **Are all aromatase inhibitors the same? A review of the current evidence.** *Breast* 2004;13(Suppl 1):10-8. **Abstract**

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

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

O'Shaughnessy J. **Extending survival with chemotherapy in metastatic breast cancer.** *Oncologist* 2005;10(Suppl 3):20-9. **Abstract**

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

Pegram MD et al. **Phase I combined biological therapy of breast cancer using two humanized monoclonal antibodies directed against HER2 proto-oncogene and vascular endothelial growth factor (VEGF).** San Antonio Breast Cancer Symposium 2004;**Abstract 3039**.

Pippen J et al. **Fulvestrant (Faslodex) versus anastrozole (Arimidex) for the treatment of advanced breast cancer: A prospective combined survival analysis of two multicenter trials.** Poster. San Antonio Breast Cancer Symposium 2003;**Abstract 426**.

Rhee J, Hoff PM. **Angiogenesis inhibitors in the treatment of cancer.** *Expert Opin Pharmacother* 2005;6(10):1701-11. **Abstract**

Rieber AG, Theriault RL. **Aromatase inhibitors in postmenopausal breast cancer patients.** *J Natl Compr Canc Netw* 2005;3(3):309-14. **Abstract**

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38. **Abstract**

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

Slimane K et al. **Risk factors for brain relapse in patients with metastatic breast cancer.** *Ann Oncol* 2004;15(11):1640-4. **Abstract**

Sundar S et al. **Management of endocrine resistant breast cancer.** *J Br Menopause Soc* 2004;10(1):16-23. **Abstract**

CASE 7:

A 68-year-old woman who presented in 1997 with a four-centimeter, node-negative, ER-positive intraductal carcinoma with a small focus of microinvasion. One year later, she developed and was treated for a fallopian tube carcinoma. In 2002, she had an ER-positive chest wall recurrence *(from the practice of Dr William G Reeves)*.

Edited excerpts from the discussion:

DR REEVES: This is a 68-year-old mother of one of my previous patients who had breast cancer. In 1997, she developed breast cancer, but it was primarily an intraductal carcinoma. It was four centimeters, node-negative, estrogen receptor-positive, with one small focus of microinvasion. She had a mastectomy with clear margins and did not receive any additional treatment.

DR LOVE: Aman, what about the approach to the patient who has a tiny focus of invasion in the tumor?

DR BUZDAR: In these patients who have a small tumor with microinvasion that is one or two millimeters and the tumor is ER-positive, you can offer appropriate endocrine therapy to reduce the risk of a contralateral or ipsilateral cancer. If the patient has an ER/PR-negative tumor with multiple areas of microinvasion, we need to discuss the risks with those patients, but overall only two to three percent of patients with DCIS develop disseminated disease and die from metastatic disease. The highest risk is developing an invasive cancer in the ipsilateral and contralateral breast.

DR LOVE: That was back in 1997. Dr Reeves, what happened with this patient?

DR REEVES: In 1998, she had a fallopian tube carcinoma, which was completely resected. She received six cycles of adjuvant carboplatin and paclitaxel, which she tolerated very well.

In October of 2002 — four years after treatment of the fallopian tube cancer and five years from the original breast cancer — she experienced a local chest wall recurrence, which was completely resected. All margins were clear, and once again, the tumor was estrogen receptor-positive. She received chest wall irradiation and was started on letrozole.

DR LOVE: Gersh, how would you approach treatment in this Stage IV NED situation?

DR LOCKER: It's easy when the patients are ER/PR-positive. You put them on hormones. The question is, What do you do with these patients who, 10 years later, are still on hormones and haven't recurred? Do you continue it forever, or do you stop? I have been inconsistent.

The problem is the patient who has ER/PR-negative disease, has a local recurrence and is NED. Do you give them "adjuvant chemotherapy"? I've done it. I have no data to support it, but I believe a lot of people do it. This lady is particularly interesting because she had carboplatin/paclitaxel adjuvant therapy for her breast cancer, and it recurred again. So if she were ER/PR-negative, I'm not sure which chemotherapy I would have given her. I believe putting her on an AI after resection is reasonable.

DR LOVE: Aman, how do you approach patients with Stage IV NED disease whose tumors are ER-positive versus ER-negative?

DR BUZDAR: Considering the natural history of these patients who have an isolated chest wall recurrence, we used to believe that just doing local therapy cured these patients. Actually, 70 to 80 percent of the patients will develop a second recurrence somewhere else within a year if they don't receive any systemic therapy.

At MD Anderson, we've been offering these patients systemic therapy. In our initial

experience with six cycles of a FAC-type of combination with this type of patient, about a third are alive and free of disease beyond 20 years. The natural history would be that within a year or two, close to 90 percent of the patients would have developed recurrent disease.

We conducted another study in which most of the patients had been treated with anthracycline-based chemotherapy in the adjuvant setting. If they had an isolated recurrence, we administered six cycles of docetaxel, and if they had an ER-positive tumor, we put them on hormonal therapy. Again, in that subset of patients, about a third of the patients are alive and free of disease.

So I think in this patient population, the risk of recurrence is great, and the addition of systemic therapy can substantially improve their odds and a sizable fraction of these patients can remain alive, free of disease, five, 10 and 20 years down the line.

DR LOVE: Dr Reeves, would you update us further on what happened to this patient?

DR REEVES: She started letrozole and was on that for almost eight months when depression became an issue for her, and she believed it was drug related. We discontinued the letrozole for a month and she felt better. She switched to exemestane, but after about four months on exemestane, her liver function tests began to rise. We checked the CAT scan, and it was fine. There was no evidence of any intrahepatic abnormality. We stopped the exemestane and within a month, the LFTs were normal again. So we went back to the letrozole. She fought with that for about six months, and finally, after about 18 months of hormonal therapy, she didn't want to take anything.

Four months after that, in October 2004, metastases in the bone, liver and lung were identified. We started her on capecitabine at that point — initially at 2,000 mg/m^2/day. Within two cycles, we reduced her dose because of palmar-plantar erythema, and by three cycles, we reduced the dose a second time. A significant reduction occurred in the size of the three liver metastases and a significant improvement in the pulmonary metastases.

Her second daughter was then diagnosed with breast cancer in a distant town, and she said she couldn't continue with treatment. She went to help her daughter, who is single. We lost track of her for about three months. She returned off treatment and was feeling okay, but because of restaging, the lung metastases had worsened again. She went back on capecitabine and responded. Improvement occurred after another three months of capecitabine. The liver metastases were completely resolved, the lung metastases were stable, but the palmar-plantar erythema was a bit of a bother to her, so we switched to fulvestrant in June 2005. She's been on fulvestrant for about four months and seems to be tolerating it reasonably well, except her tumor markers are just starting to rise, and they had come down significantly with capecitabine.

DR LOVE: What was the dose and schedule of fulvestrant?

DR REEVES: Initially, we gave her 250 milligrams every two weeks times three and now she receives it monthly. So we did give her a loading dose — a "miniload," if you will.

DR LOVE: Aman, you talked before about the differential effect of LFTs and exemestane. What are your thoughts about what happened here?

DR BUZDAR: One of the metabolites of exemestane has androgenic properties, so it's theoretically possible that some of the LFT abnormalities may be related to the metabolite of exemestane. It could be that she had subclinical disease, which was causing all the problems and was being blamed on the drug.

DR LOVE: Have you seen depression associated with the AIs?

DR BUZDAR: I have not seen depression with any of the AIs.

DR LOVE: Was it evaluated in the ATAC trial?

DR BUZDAR: In the ATAC trial, where we have 99-plus percent safety data, depression was not an issue.

DR LOCKER: There were no mental status changes of any kind.

DR LOVE: The other thing that's interesting about this case is the response to capecitabine with liver metastases. Any comments, Aman?

DR BUZDAR: Capecitabine is an effective drug, and when it works, it works very well. Hand-foot syndrome is a problem in some patients, and transiently stopping the therapy was a reasonable option in this patient, but now it looks as if she's resistant. I would not change her therapy from an endocrine agent because her tumor markers are changing, because I can tell you that in some of these patients, if you continue with the same therapy, these markers continue to fluctuate. If they were consistently going up, I would say that it may be time to change therapy. I have some patients whose markers are about three to four times the normal value of our lab, and I have followed one lady more than six or eight years, and she has not yet developed any metastases.

DR LOVE: What dose and schedule of fulvestrant do you use?

DR BUZDAR: Data suggest that if you use the package insert dose, which is 250 milligrams every four weeks, it takes about two to three months to get a steady state therapeutic level. So we give a 500-milligram loading dose, and then in another two weeks we give another 250 milligrams, and then treat every four weeks. This is being evaluated in a prospective study because an important question is, are we losing some patients before we get to the therapeutic level and the disease is progressing because the patient does not have enough drug in their system?

DR LOVE: Gersh, one of the things that's being evaluated in clinical trials is the concept of an AI plus fulvestrant — the idea being that fulvestrant competes with estrogen. One way would be to load up, get a higher dose up front, but another way might be to decrease the ligand through the AI. It's being studied in clinical trials like SoFEA (7.1). A number of oncologists actually do that in their practices, particularly for a patient who's on an AI and progresses. Some people will keep the AI going and add the fulvestrant. What are your thoughts?

DR LOCKER: A very elegant study in *Cancer Research* in June 2005 from Angela Brodie (Jelovac 2005) evaluated a preclinical model and found that if you combine an AI with fulvestrant, you get incredible suppression, destruction and disappearance of the estrogen receptor and great responses.

One of the things that stimulates the estrogen receptor is the presence of estrogen. If you take estrogen away, then destroy the receptor with fulvestrant, you don't get replenishment. Some data from the group at Mass General show that with this combination, the receptor goes away for as long as fulvestrant is present.

Anecdotal data suggest that the combination works, and clinical trials are about to commence that will study the combination. I've administered it only once, and I'm almost embarrassed to say that, because I'm evidence-based. I think this is the wave of the future and may be the way to make fulvestrant more effective.

DR BUZDAR: I believe it may be the wave of the future, but at the present time, no data support doing that. Unless we have clinical data to support this wave of the future, I would discourage the utilization of two endocrine agents.

DR LOCKER: I'm in complete agreement with Dr Buzdar. Extenuating circumstances applied to the one patient with whom I used it. When the studies come out, I would strongly urge patient enrollment.

DR LOVE: I've got to challenge Aman a little bit about combined endocrine therapy. You've got a premenopausal patient who's received adjuvant tamoxifen. She develops a relapse. She's put on ovarian suppression, has a good response, and then progresses. Are you going to keep the suppression going and add in an AI?

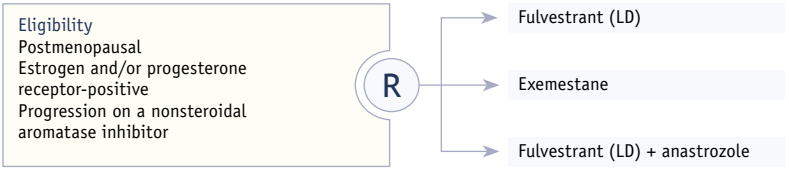
DR BUZDAR: Yes. In a Phase II study published by John Robertson, an LHRH agonist with an AI showed high response

rates in the metastatic setting (Forward 2004).

DR LOVE: Bob Carlson has also looked at that and found pretty much the same thing (Carslon 2004).

7.1 Phase III Study of Fulvestrant with or without Anastrozole versus Exemestane

Protocol ID: SoFEA
Target Accrual: 750 (Open)



LD = loading dose (500 mg at day 0, 250 mg at days 14 and 28, then 250 mg qm)

Study Chair:
Dr Stephen Johnston
Royal Marsden Hospital
NHS Trust and Institute of Cancer Research
Phone: 44 (0) 20 7808 2745

SOURCES: Institute of Cancer Research, **www.icr.ac.uk/ctsu**, September 2005; Gradishar WJ, Sahmoud T. *Clin Breast Cancer* 2005;6(Suppl 1):23-9. **Abstract**

Select publications

Abram P et al. **Case studies of fulvestrant ("Faslodex") in postmenopausal women with advanced breast cancer.** *Cancer Treat Rev* 2005;31(Suppl 2):17-25. **Abstract**

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Bertelli G. **Sequencing of aromatase inhibitors.** *Br J Cancer* 2005;93(Suppl 1):6-9. **Abstract**

Buzdar AU, Blumenschein GR et al. **Adjuvant chemoimmunotherapy following regional therapy for isolated recurrences of breast cancer (stage IV NED).** *J Surg Oncol* 1979;12(1):27-40. **Abstract**

Carlson RW et al. **Goserelin plus anastrozole for the treatment of premenopausal women with hormone receptor positive, recurrent/metastatic breast cancer.** San Antonio Breast Cancer Symposium 2004;**Abstract 6052**.

Dodwell D, Vergote I. **A comparison of fulvestrant and the third-generation aromatase inhibitors in the second-line treatment of postmenopausal women with advanced breast cancer.** *Cancer Treat Rev* 2005;31(4):274-82. **Abstract**

El-Helw L, Coleman RE. **Reduced dose capecitabine is an effective and well-tolerated treatment in patients with metastatic breast cancer.** *Breast* 2005;14(5):368-74. **Abstract**

Forward DP et al. **Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer.** *Br J Cancer* 2004;90(3):590-4. **Abstract**

Franco S et al. **Response to fulvestrant in heavily pretreated postmenopausal women: A single-center experience.** *Breast Cancer Res Treat* 2004;88(2):103-8. **Abstract**

Gradishar WJ, Sahmoud T. **Current and future perspectives on fulvestrant.** *Clin Breast Cancer* 2005;6(Suppl 1):23-9. **Abstract**

Hennessy BT et al. **Lower dose capecitabine has a more favorable therapeutic index in metastatic breast cancer: Retrospective analysis of patients treated at MD Anderson Cancer Center and a review of capecitabine toxicity in the literature.** *Ann Oncol* 2005;16(8):1289-96. **Abstract**

Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *J Clin Oncol* 2004;22(9):1605-13. **Abstract**

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20(16):3396-403. **Abstract**

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CASE 8:

A 77-year-old woman diagnosed with a 3.5-centimeter, Grade III ER/PR-negative, HER2-positive infiltrating ductal carcinoma one year after undergoing MRM for a Grade III DCIS *(from the practice of Dr Gary A Steinecker)*.

Edited excerpts from the discussion:

DR STEINEKER: This woman was 76 years old and presented a year ago in July 2004 with a Grade III DCIS in the left breast, for which she had a modified radical mastectomy.

In February 2005, she was diagnosed with an infiltrating ductal carcinoma, and a right modified radical mastectomy was performed, showing a Grade III ER/PR-negative, HER2-positive tumor. The disease was staged as T2/N0/M0, and her primary tumor was 3.5 centimeters.

I recommended the CALGB protocol 49909, with chemotherapy and trastuzumab. She was randomly assigned to Arm B, which was AC followed by paclitaxel followed by trastuzumab. That trial is a little bit of a challenge because the investigators want to check the FISH results, so the patient doesn't find out until they're pretty far into the protocol whether or not they're going to receive the trastuzumab.

She was treated with AC and had a lot of trouble with that. I have not seen colitis before, but she had diarrhea to the point where we had to hospitalize her for a week. She did have a preexisting history of diverticulosis but did not have any particular problem with that. According to the protocol, we had to reduce her doses, and she completed four cycles of AC. She then started on paclitaxel. At the time I wrote this up, she was into her ninth week, with a fair amount of colitis and diarrhea despite Imodium®. In fact, we had to hold the paclitaxel for one week to let her recover. Her blood counts were always good.

The dilemma is that, according to the protocol, after the AC she needed a MUGA. Compared to before the chemotherapy, her MUGA had dropped from 66 to 50 percent, and the protocol had a cutoff of 15 percentage points. She was therefore excluded from consideration for trastuzumab, no matter what happened to the ejection fractions.

Out of curiosity, though, I repeated her MUGA one month after the AC and her MUGA showed 71 percent left ventricular ejection fraction, but to be careful, I did a 2-D Echo, and this showed 45 percent. Anyway, according to the protocol, she can't receive trastuzumab. She was at relatively low risk, because she was lymph node-negative.

DR LOVE: Eric, what do we know about variations in ejection fractions and 2-D Echos?

DR WINER: I don't pretend to be an expert in terms of the cardiac toxicity of these agents. Clearly, measurements of cardiac function can bounce around, and as Barbara said earlier, getting MUGAs doesn't prevent heart failure, although it gives us some clues about who may be at greater risk. I would be concerned about giving her trastuzumab, given the fact that in the study the only data we have in terms of cardiac toxicity are from patients whose ejection fractions didn't drop 15-plus percent. Although you had that reassuring second MUGA, you have an Echo that gives you a very different result. So I think there is reason to believe that her ejection fraction has dropped with the anthracycline.

The issue of age is hard to deal with, because on one hand, one doesn't want to discriminate against older women. On the other hand, you want to include that information appropriately in your decision-making. Given the fact that events in HER2-positive patients do tend to be earlier

rather than later, it is likely that her life expectancy will be such that she will not die before she has a recurrence, if she's destined to have a recurrence. On the other hand, this issue of toxicity is a big one, and toxicity with one agent often correlates with toxicity with another. I would just be quite concerned.

I think the more interesting situation would be if she were 45 years old or if she were 76 and had 10 positive lymph nodes. In those situations, I would probably cautiously and with a lot of discussion think about using trastuzumab.

DR LOVE: Kevin, how are you approaching the issue of trastuzumab for patients with node-negative tumors?

DR FOX: NCCTG-N9831 did include node-negative patients, although not many. My feeling is that if they meet the criteria for entry onto the study, they should be entitled to the benefits of the therapy, if there are no extenuating circumstances.

With respect to your patient, something came to mind that I think everybody probably has seen by now. When the NSABP did their detailed cardiac analysis of the first 1,000 patients, this grid was produced that has made the rounds, which perhaps you've seen, which tries to identify the patients who are at the highest risk for developing trastuzumab-related cardiac problems. In that grid, they positioned patients based on their post-AC ejection fraction, and if someone had fallen into the range of 50 to 54 percent, from another number, if they had not fallen more than 15 points, they were still eligible to go on, and they did.

If they fell to an ejection fraction range between 50 and 54 percent and were over the age of 50, in that small group of patients, of which there were 47, the cardiac event rate was 20 percent. That was the subset that stood out as being uniquely susceptible to the ill effects of trastuzumab. Your patient is elderly and showed a substantial drop in ejection fraction from AC alone. That alone would raise a red flag, that she has the potential, even under the best of circumstances, for trouble later on. So I, too, would be inherently reluctant to use trastuzumab.

However, since we're confessing things today, I have had two younger patients on clinical trials whose ejection fraction dropped as yours did, unacceptably, and were denied trastuzumab on the clinical trial. These were people who, getting back to the other case, were enrolled in 2003 and now are presenting with normalized ejection fractions and the same question that your patient asked.

DR WINER: It would be a more interesting dilemma if she had a number of positive lymph nodes or if she were much younger. In those situations, I think that I would approach this situation a little bit less stringently. In this case, I think that I'd fall back on the guidelines in the trial and probably not use trastuzumab.

DR STEINECKER: This lady had so much trouble, she was so happy to hear she wouldn't be getting the trastuzumab once a week for the next year that she was smiling from ear to ear — for better or worse.

DR WINER: The CALGB has had this ongoing trial that is slowly accruing older women, comparing capecitabine with either CMF or AC — "dealer's choice." Presumably, most patients will get AC. This study is of women over the age of 65 and now allows women to receive trastuzumab after the completion of chemotherapy. If I were seeing this woman today, I might well encourage her to enroll in the trial with the idea that after the completion of chemotherapy, with the knowledge of HERA, we would use trastuzumab as a single agent at that point.

DR REEVES: I'm concerned about subclinical heart disease with trastuzumab. Should we be considering substituting epirubicin for doxorubicin? Or should we be considering dexrazoxane to protect people, if it's going to exclude our use of trastuzumab, which we know now makes such a difference in patients with HER2-positive disease?

DR WINER: This is a good question. The results of the BCIRG trial imply that we're not ready to get rid of an anthracycline

8.1 Protocol-Defined Cardiac Events in Adjuvant Trastuzumab Trials

Trial	Arm of study	Protocol-defined cardiac event rate*
BCIRG 006[1]	AC → D AC → DH CDH	1.2% 2.3% 1.2%
NSABP-B-31[2]	AC → TH AC → T	4.1% 0.8%
NCCTG-N9831[3]	AC → T AC → T → H AC → TH → H	0% 2.2% 3.3%
BIG 1-01, HERA[4]	Observation One year H	0% 0.60%

* Note that the definition of cardiac events varied between protocols.
AC = doxorubicin/cyclophosphamide; D = docetaxel; H = trastuzumab; C = carboplatin; T = paclitaxel

SOURCES: [1] Slamon DJ. NSABP Annual Meeting Satellite Symposium 2005. No abstract available; [2] Romond EH et al. *N Engl J Med* 2005;353:1673-84. **Abstract**; [3] Perez EA et al. NCCTG N9831 May 2005 Update. Presentation. ASCO 2005;**Abstract 556**; [4] Gelber RD for the HERA Study Team. Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 11**.

yet, and I think an important question is whether we can make the anthracycline less toxic. The CALGB had a study that enrolled all of two patients about six years ago, evaluating dexrazoxane and a variety of other questions in the locally advanced setting with trastuzumab. MD Anderson has been using epirubicin concurrently with trastuzumab. Other, less toxic anthracyclines, the liposomal preparations, both Doxil® and a drug that's commonly called D-99, have yet to be approved in the United States, and may or may not ever be approved. I believe it's an important question and, of course, if you could get the benefit from an anthracycline with less concern about cardiac toxicity, so much the better. Outside of a trial, I wouldn't be in a rush to give dexrazoxane, but I think it's an important research question.

Everybody was hoping that the BCIRG study would make this simple — that TCH would be better, we wouldn't be giving anthracyclines any more and we'd be moving on to a new era, in which preclinical assays would predict how patients were going to do on a routine basis. I don't think we're quite there.

DR LOVE: It never works out that easily, does it?

DR FOX: I don't want this to come out wrong, but how many people were really put in harm's way, clinically, by the cardiotoxicity (8.1)? I'm not diminishing the fact that there were a couple of cardiac deaths. In the HERA trial, the rate of congestive heart failure for those who received sequential therapy was remarkably low, and maybe we ought not allow this to be more of a concern than it merits. This was a large clinical trial where far fewer people came into harm's way from cardiac toxicity than they did from recurrence and death from breast cancer had they not received trastuzumab.

With stringent monitoring, if we all just adhere consistently to the protocol criteria and we pay close attention to this post-AC ejection fraction, which appears maybe to be quite important, I don't think we'll have too much trouble, and we won't need to use more expensive therapies like epirubicin and dexrazoxane to offset the problem.

DR LOVE: Eric, what kind of clinical scenario in terms of risk for cardiovascular disease would have you considering TCH right now, and how much of a clinical history would make you say, even in a node-positive patient, "I'm not going to use trastuzumab"?

DR WINER: As long as a patient had an acceptable ejection fraction level, there isn't any cardiac risk factor that would push me in the direction of not using trastuzumab in that setting.

I think where this becomes an issue is with a patient with a 1.3-centimeter ER/PR-negative, node-negative tumor, who was just barely eligible both for HERA and for the Intergroup trial, or the patient who's got a slightly larger ER-positive tumor, who might have been eligible for HERA but wasn't eligible for the Intergroup trial. In those situations, there's good reason to think that the relative risk reduction with trastuzumab will be the same across the board, but it's not relative risk reduction that should push us to decide to give a therapy. It's the absolute reduction. That's where you've got to really think about the toxicity issues.

DR LOVE: So what about a patient with normal ejection fraction but a history of a couple of MIs and hypertension?

DR WINER: In the setting of a normal ejection fraction in somebody who's got a relatively high risk of recurrence — node-positive disease — I would probably use trastuzumab in those patients who were eligible for the trial.

DR LOVE: Which chemotherapy?

DR WINER: Would I give TCH or AC followed by paclitaxel? The problem is that I think TCH is a pretty toxic regimen, and I'm not sure in which patients I would use it.

I suppose I would use it in a younger woman who I thought could tolerate the other toxicities, other than the cardiac issues, who either has a borderline ejection fraction — and occasionally, you'll come across somebody, a 38- or 42-year-old woman, who has an ejection fraction of 48 percent — or someone, perhaps, who's had Hodgkin's disease before and had mantle irradiation, and I'm more concerned about cardiac issues. At the moment, I'm not quite sure for whom I would use it.

DR FOX: With these questions in mind, there was actually a case that's come up just in the last week. I treated a patient in 1989 for a T2/N1, ER-negative right breast cancer. She received six cycles of CAF, 360 mg/m^2 of doxorubicin and has been fine. She has a normal ejection fraction currently but has a contralateral breast cancer that is 2.5 centimeters, ER-negative, HER2-positive, node-negative. I'm not going to give her anthracyclines. Would I administer TCH? It looks like maybe it's my default position, as much as my enthusiasm for doing it has gone down.

DR WINER: I think Kevin's case is perhaps the best of all of them in terms of the situation in which I would administer TCH, which is for someone who can't receive an anthracycline. It's not even an issue. You're not going to give it to this woman who's had 360 mg/m^2 of doxorubicin. At the moment, this is someone to whom I absolutely would give TCH.

DR FOX: Now, had I treated her two years later, when the patterns of care were changing a bit, I probably would have given her AC, and then it would be 240 mg/m^2. Would that make you feel any differently?

DR WINER: I think I'd still give her TCH today.

DR LOVE: Would you have given her TCH before the press release came out from the BCIRG?

DR WINER: I probably would have because, at a minimum, you can't give her an anthracycline, and it's a regimen that we know has been given to a large group of women, and so there's at least a toxicity experience that's been amassed.

DR LOVE: Would you be surprised if it turns out that TCH is not as effective as the anthracycline-containing regimen?

DR WINER: Right now, we don't know that it isn't as effective. But if it turns out to be the case, I think the real question will be which patients need an anthracycline in the HER2-positive setting and which don't.

It doesn't surprise me that a subgroup of patients exists who benefit from an anthracycline, given all of the data that suggest that the benefits of anthracycline-based regimens, compared to CMF, are

largely confined to women with HER2-positive disease, albeit retrospective — but convincing — analyses.

We need to spend time focusing on molecular predictors of resistance to trastuzumab. As a medical community and a breast cancer research community, it's almost shameful that we haven't figured this out, in spite of the fact that we've been using trastuzumab in the metastatic setting for seven or eight years.

Much of the problem relates to the fact that it just hasn't been in our practice approach to perform biopsies at the time of relapse. If we had 100 patients who had been on trastuzumab and experienced disease progression, had biopsies, and we had interrogated the tissue, we might have some clues. But we do have clues based on preclinical data.

DR LOVE: The C-Myc data done by Soonmyung Paik was able to separate out a group that had a greater than 90 percent chance of remaining disease free, as opposed to a group whose chance of remaining disease free was in the 60s. It reminds me of some of the work he's done with Genomic Health, which has some teeth to it in terms of decision-making. Maybe we'll have trials that'll focus on the people who we think have high relapse rates.

DR WINER: Right, and those are the patients for whom you might consider strategies such as other HER2-directed therapies in place of trastuzumab or therapies in addition to trastuzumab.

DR LOVE: Kevin, what were your thoughts about Edith Perez's NCCTG data suggesting an advantage to concurrent versus sequential chemo-trastuzumab?

DR FOX: She did, indeed, draw that conclusion, but I think she was quick to point out that at that point in time, the number of recurrences was very small. So it's too early to conclude that we know the worth or lack of worth of sequential versus concurrent treatment. We just don't know.

DR LOVE: There is a lot of confusion about this exact point, because the HERA study, which is seemingly a similar sequential strategy, showed a 50-percent reduction in relapse rate.

DR WINER: I think the HERA results are impressive and stand on their own without a lot of difficulty. It is quite possible that concurrent may be better than sequential, but we don't know that at the moment. The only reason we know anything from N9831 about sequential versus concurrent therapy is that when the DSMV met and decided to release the data about trastuzumab, as a practice management question in terms of what to tell doctors whose patients were on the trial, they asked to look at those two arms, so that they could give doctors a sense of what to do for those patients who had been treated on the trial and didn't receive trastuzumab.

While there is a statistically significant difference between the concurrent and sequential arms on Edith's trial, and the sequential arm wasn't significantly better than no trastuzumab, it did not meet any boundary in terms of early stopping. I think that we just need more data.

DR STEINECKER: So if Edith's study shows no benefit for that sequence, then the timing of one year, two years, is shot.

DR WINER: We know there's benefit from HERA. The risk reduction in HERA was similar to what we've seen in all of the studies. All of these studies — other than that one arm in N9831 — have shown that the use of trastuzumab either with or following chemotherapy reduces the risk of disease recurrence by about half, and the results are shockingly consistent.

DR LOVE: At the NSABP meeting, people were talking about the fact that most of the HERA patients did not receive taxanes. Could that be confounding this? If you're going to give the patient a taxane, isn't it going to bump up the efficacy and, in some way, dampen what you'd see with trastuzumab?

DR WINER: Perhaps. What has been stated incorrectly is that most of the patients in HERA didn't receive an anthracycline. In

fact, 92 or 94 percent of patients in HERA received an anthracycline, and I think about a third of them received a taxane.

It's very difficult to compare across trials. I think there's a signal from Edith's trial. I'm not saying it should be ignored, but I would not conclude, based on her data, particularly considering HERA, that trastuzumab after chemotherapy is ineffective. That would be an inappropriate conclusion. I think an appropriate conclusion is that — particularly if you're giving a taxane — sequential therapy isn't as good as concurrent, but we have to see.

DR GOLDBERG: The schedule of how the paclitaxel was administered originally was weekly, and then every three weeks. Does that make a difference?

DR WINER: In N9831, it was administered as a weekly regimen. In the NSABP trial, it was initially administered every three weeks, and then the study was amended and it was allowed to be administered weekly. I don't know whether it matters or not. Certainly the suggestion exists that weekly paclitaxel is better than every three-week paclitaxel. Whether that matters in the context of HER2-positive disease and with concurrent or sequential trastuzumab, we don't know. If I were going to use it, I would tend to use the weekly schedule as was done in the studies.

Select publications

Campone M et al. **Cardiac dysfunction induced by trastuzumab.** *Bull Cancer* 2004;91(Suppl 3):166-73. **Abstract**

Cvetkovic RS, Scott LJ. **Dexrazoxane: A review of its use for cardioprotection during anthracycline chemotherapy.** *Drugs* 2005;65(7):1005-24. **Abstract**

Ewer MS et al. **Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment.** *J Clin Oncol* 2005;23(31):7820-6. **Abstract**

Gelber RD for the HERA Study Team. **Trastuzumab following adjuvant chemotherapy significantly improves disease-free survival in HER2-positive early breast cancer. The HERA trial.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 11**.

Kim C et al. **Trastuzumab sensitivity of breast cancer with co-amplification of HER2 and cMYC suggests pro-apoptotic function of dysregulated cMYC in vivo.** San Antonio Breast Cancer Symposium 2005;**Abstract 46**.

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Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353:1659-72. **Abstract**

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**

Tan-Chiu E et al. **Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.** *J Clin Oncol* 2005;23(31):7811-9. **Abstract**

Tripathy D et al. **Effect of cardiac dysfunction on treatment outcomes in women receiving trastuzumab for HER2-overexpressing metastatic breast cancer.** *Clin Breast Cancer* 2004;5(4):293-8. **Abstract**

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

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Kevin R Fox, MD	5 4 3 2 1	5 4 3 2 1
Gershon Locker, MD	5 4 3 2 1	5 4 3 2 1
Eric P Winer, MD	5 4 3 2 1	5 4 3 2 1

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