

Controversies in Systemic Therapy of Breast Cancer

Breast Cancer[®]
U P D A T E

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Breast Cancer Update

A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. To bridge the gap between research and patient care, this special edition of *Breast Cancer Update* utilizes case-based discussions held between community oncologists and research leaders at two live CME meetings to demonstrate the integration of clinical research data into clinical practice.

GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data, patterns of care data and patients' perspectives on breast cancer treatment decisions.
- Counsel women with low-risk invasive disease about the absolute risks and benefits of adjuvant systemic chemotherapy, and describe the potential utility of a predictive assay to help guide these discussions.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and about switching or sequencing aromatase inhibitors after tamoxifen.
- Counsel premenopausal women about the risks and benefits of adjuvant ovarian ablation in combination with tamoxifen or aromatase inhibition.
- Distinguish the risk-to-benefit profiles of chemotherapeutic agents and combinations to determine a management algorithm for metastatic breast cancer.
- Develop and explain a management strategy for therapy for patients with ER-positive, metastatic disease including sequencing of hormonal therapies.
- Describe and implement an algorithm for treatment of HER2-positive breast cancer.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of this special edition of *Breast Cancer Update* is to support these global objectives by offering the perspectives of the faculty on the integration of emerging clinical research data into the management of breast cancer.

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EDITOR'S NOTE

Neil Love, MD

Common questions about breast cancer from oncologists in community practice

The enclosed audio program contains highlights from two case-based daylong CME meetings our group hosted for medical oncologists in Los Angeles and New York City. Like all of our live events, the primary purpose of these gatherings was for us to interact with physicians in practice to better understand their education needs.

To better accomplish this goal, we commonly utilize an innovative wireless “chat room” setup that provides each attendee with a portable computer throughout the event. This allows participants to continuously provide input to our faculty panel, but even more importantly, it encourages them to pose questions that are usually answered by investigators as part of the meeting or typed in the chat room. Below, find a sampling of the most common queries and comments that emerged, many of which are discussed in the enclosed program.

— Neil Love, MD
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January 10, 2006

Adjuvant and neoadjuvant endocrine and monoclonal antibody therapy

- How do you approach endocrine therapy in patients with chemotherapy-induced menopause?
- In the absence of randomized trial data, please comment on the use of adjuvant tamoxifen versus an AI with goserelin in premenopausal patients.
- It is recommended that tamoxifen not be given at the same time as adjuvant chemotherapy; is the recommendation for AIs different? Can AIs be used concurrently with radiation therapy?
- Is there any value in administering an AI for two years and then switching to tamoxifen?
- Is tamoxifen dead for postmenopausal patients?
- A lot of the safety benefit of an AI is based on decreased gynecological symptoms. Is the toxicity profile of an AI better for women who have had a hysterectomy?

Adjuvant and neoadjuvant endocrine and monoclonal antibody therapy (continued)

- Should an AI be used in the treatment of DCIS instead of tamoxifen? Are we justified in using anastrozole as chemoprevention for patients at high risk for breast cancer?
- Was it the weight loss or the decreased fat intake that led to the reduced breast cancer relapse rate in the WINS trial? Why were the benefits seen mainly in the patients with ER-negative disease? Is there any reason not to believe that a low-fat diet might be beneficial to patients with other types of malignancies?
- Should the impressive results of the WINS trial of dietary fat reduction be discussed with patients at this point? If we had seen these results in a study in which patients took a drug to achieve this, we would have seen a lot more excitement about them.
- Do aspirin or statins decrease the risk for stroke or MI in patients receiving anti-estrogen therapy? For a patient with an adverse lipid profile and osteoporosis, which aromatase inhibitor do you use?
- Do you use the *Oncotype DX* in your patients? Is it covered by insurance?
- What do you recommend for osteoporosis prevention when using an AI, and at what point do you stop the AI based on a change in bone density?
- If a woman already has osteoporosis before starting anastrozole, what is your choice of bisphosphonate for her?
- If you switch from tamoxifen to an AI after two years, do you continue the AI for three years or five years? Can a patient be at low enough risk of relapse not to switch to letrozole after five years of tamoxifen?
- Has anybody looked at the use of COX-2 inhibitors in patients with letrozole-induced arthralgias? Perhaps this, rather than the altered lipids that letrozole induced, contributed to the high incidence of cardiac death in the BIG study.
- Are the musculoskeletal side effects the same with all AIs? In other words, if a woman is taking one AI and not tolerating it due to these symptoms, might she do better with another AI? Why do AIs cause these symptoms?
- How often do you measure bone density in patients who are on AIs? Do you put them on bisphosphonates and calcium supplements if they have osteopenia?
- Would cardiac echo be more accurate than a MUGA scan in determining LVEF in patients on adjuvant trastuzumab? How about adding a cardioprotective agent?
- Is it reasonable to use dose-dense adjuvant chemotherapy with trastuzumab?
- What is the difference between AC followed by paclitaxel/trastuzumab and AC followed by docetaxel/trastuzumab? Does docetaxel/trastuzumab result in less cardiac toxicity?

Adjuvant and neoadjuvant endocrine and monoclonal antibody therapy (continued)

- Do you give adjuvant trastuzumab weekly or every three weeks?
- Would you use trastuzumab as part of neoadjuvant therapy in which the nodal status isn't assessed pathologically? If so, would you look at something like PET to assess the axilla?
- What is the explanation for the high incidence of brain metastases in women on trastuzumab? Is this due to blood-brain barrier issues or the development of resistant clones?
- How reliable is IHC for assessing HER2 status? When must we use FISH?
- Close monitoring of cardiac function is recommended for patients receiving trastuzumab and chemotherapy. In fact, monitoring neither prevents nor predicts congestive cardiomyopathy; it merely confirms it.
- What medical options are available for the woman with HER2-positive breast cancer who demonstrates declining EF while on trastuzumab?

Systemic therapy for metastatic disease

- The ECOG-1193 study shows no advantage to combining paclitaxel/doxorubicin. However, this does not mean other combinations are not superior. There is little reason to think AT would be superior (no synergism, overlapping toxicities, inability to administer full therapeutic doses in combination). On the other hand, a rationale does exist for regimens such as DC and GT.
- One of the goals of chemotherapy for metastatic disease is palliation. In general, response (or control of disease) is associated with palliation. As combination regimens have higher response rates (and better control of disease), one can assume they will be associated with better palliation too.
- Are data available on gemcitabine/capecitabine for metastatic breast cancer?
- Does anyone use the European approach of starting capecitabine at full dose but closely monitoring the patient during capecitabine administration and reducing the dose in the middle of a cycle?
- The cost of capecitabine is an issue for patients because many do not have prescription coverage and are ineligible for patient assistance programs. This is a common reason for patients preferring IV chemotherapy to capecitabine despite physician recommendation of capecitabine.
- Some California senior-care HMOs cover only generic forms of oral medications, and for both capecitabine and etoposide, no generic form exists, and they are not covered. This is an excuse. Are there any recommendations for dealing with this issue?

Systemic therapy for metastatic disease (continued)

- We make a big fuss about the lack of crossover design in many chemotherapy trials for metastatic disease. However, for other tumor sites (eg, colon, lung), combination therapy is the standard, with no crossover design studies.
- Sometimes when we change the dose of capecitabine, pharmacists see the prescription for 14 days given every 21 days, and either the patient or the pharmacy seems to be confused as to how many pills constitute a “30-day supply.” Also, if we have prescribed 500-mg tabs and want to change to the smaller-dose tabs halfway through the month, we have difficulty doing this because preauthorization from insurance companies takes four to five days or longer if they require a dictated note to make any changes.
- What would your choice of therapy be for patients who had received AC/paclitaxel/trastuzumab as adjuvant therapy and then relapsed after one year? Would you retreat with trastuzumab-based therapy or go to anti-VEGF-based therapy?
- A main reason for continuing trastuzumab beyond progression is the preclinical synergism between trastuzumab and many chemotherapy drugs. Do any preclinical data show that tumors that become resistant to trastuzumab still benefit from continuing trastuzumab?
- Does the degree of HER2 amplification matter? Isn't positive just positive?
- What is the role of tumor markers, bone scans, CT scans, etc, in the routine follow-up of breast cancer? NCCN has issued guidelines, but are they being followed?
- Has capecitabine been combined with weekly paclitaxel in any studies? Do you think this regimen would make any difference compared to three-weekly paclitaxel in terms of efficacy and safety?
- Is there a rationale for combining fulvestrant with an AI? Do any preclinical models show synergism?
- Is there an optimal dose and/or schedule for fulvestrant? Should patients be “loaded” with a loading dose?
- What is your first choice of hormonal therapy for the premenopausal patient with metastatic, ER-positive disease?

Case 1: From the practice of Dr Martha A Tracy, Berkeley, California

An active 79-year-old woman with a 7.5-centimeter, Grade II, ER/PR-positive, HER2-negative breast cancer with lymphovascular invasion and three positive nodes

► **DR TRACY:** I saw a 79-year-old woman, very active skier, who discovered a right breast mass, which was four centimeters or greater in diameter.

Her mammogram and ultrasound were both pathologic. She had a mastectomy, which revealed a 7.5-centimeter, Grade II tumor with lymphovascular invasion. The tumor was ER/PR-positive and HER2-negative, and three of seven nodes were positive.

She had some mild hypothyroidism and absolutely no major comorbidities. She experienced some mild chronic pain as the result of a minor motor vehicle accident that caused a back injury. Her family was described as very long-lived.

Her physical exam was completely negative, with a well-healing chest wall scar. The staging studies included a bone scan, which was normal except for mild degenerative changes, and full CAT scans, because of the size of her tumor, which were negative.

► **DR LOVE:** So, she's a 79-year-old woman who sounds about as healthy as one can be at 79. Was she a proactive patient who wanted to do everything she could with regard to treatment?

► **DR TRACY:** No. She was not.

► **DR LOVE:** So she was concerned about the side effects of treatment?

► **DR TRACY:** Absolutely.

► **DR LOVE:** Peter, how do you approach the question of adjuvant chemotherapy in older patients?

► **DR RAVDIN:** I think when we see an older patient, we view things a little differently. That isn't necessarily a reflection of us being ageists but rather that we recognize, and patients themselves recognize, that they have less remaining life expectancy and, overall, a lot more competing problems. In fact, most people with node-negative disease, even if they're fairly young, end up dying of something other than breast cancer. Sometimes looking at the competing mortality — for this patient it's in the range of 30 to 40 percent, even though she is a skier — puts things in context, and many patients recognize that and are less enthusiastic about aggressive therapy.

The other thing to be said is that there are some uncertainties as to how effective adjuvant chemotherapy is in older patients, not because we have any deep biological rationale for why it shouldn't work but because we have less data on that patient population.

There's an excellent paper in *JAMA* by Dr Hy Muss that points out that older patients have about as much benefit as the younger patients, although they do have more toxicity (Muss 2005). So, for decisions where it's difficult for us to know what to do, engaging the patient in the decision is reasonable because often, when they see the numbers and think about it, it actually helps them have a clearer view of what they want.

► **DR LOVE:** How much additional survival benefit would this patient

experience by receiving chemotherapy in addition to an aromatase inhibitor?

► **DR RAVDIN:** The overview suggests that a chemotherapy regimen like CMF has little activity in postmenopausal women with ER-positive breast cancer (Early Breast Cancer Trialists' Collaborative Group 1998), but other trials suggest adjuvant chemotherapy with anthracycline-based regimens actually has a 20 to 30 percent proportional risk reduction in this population. In terms of mortality reduction, chemotherapy — even that kind of chemotherapy — isn't quite as good as hormonal therapy, but for a patient like this, it could mean approximately a five percent difference in mortality.

I think that it isn't out of the question to treat healthy women in their seventies and eighties with adjuvant chemotherapy. I'd like to point out that this has been studied in other adjuvant scenarios such as colon cancer, and you can clearly see people older than 70 benefiting as much from adjuvant chemotherapy as younger patients.

► **DR OSBORNE:** Peter, one of the problems with programs like your Adjuvant! Online model is that you can't consider every single nuance of every single patient, so you have to generalize a bit. The program doesn't consider PR, and I don't think it takes into account quantitative ER, maybe because the data on those factors are still new, but I think both are becoming extremely important. Data from the SWOG-8814 study show that patients with high ER/PR-positive tumors receive no benefit from FAC (Albain 2004). Data from the Ludwig Breast Cancer Study Group similarly show that patients with highly endocrine-responsive disease receive little or no benefit from chemotherapy of any kind (Colleoni 2000), and there's no benefit for dose-dense chemotherapy in

the patients with strongly ER-positive disease.

In terms of endocrine therapy for this patient, the only prospective marker trial was conducted in the 1980s by Peter and showed that PR negativity does, at least in metastatic disease, predict for less response to tamoxifen (Ravdin 1992).

There are now three modeling studies of long-term endocrine therapy of postmenopausal patients. All three — Jack Cuzick's, our own with statistician Sue Hilsenback, and Dana-Farber's — have modeled whether it's better to give an aromatase inhibitor or tamoxifen first. We can't necessarily go by models, but I think they can tell us that jumping over to an aromatase inhibitor may not be, at 10 or 15 years, a better strategy.

► **DR LOVE:** Aman, what are your thoughts regarding these modeling studies, and what do you think is the best long-term strategy?

► **DR BUZDAR:** I think modeling studies are good to keep the biostatisticians busy until we generate the clinical data, but you have to go with the facts that are in front of you. The proper sequence is an interesting question, but it's a research question, and until we have the answers, we have to use the data we have. We have data showing that in patients who are newly diagnosed, it's better to start with an aromatase inhibitor rather than waiting two to three years. We don't have data to show it's better to start with tamoxifen and then switch. I think the major shortcoming of all three models is that they do not take into account the adverse effects in those first two to three years, which could be life changing for the patient.

► **DR LOVE:** Kent, do these models bring in the toxicity issues with tamoxifen,

including deep vein thrombosis, stroke and endometrial cancer?

► **DR OSBORNE:** No. They're not built into the models, but the mortality from those events is, so death from them would be an issue. We have data on tamoxifen followed by an aromatase inhibitor and we see a certain benefit there. We also have data comparing an aromatase inhibitor to tamoxifen in the first five years. So we do have clinical data. What we don't have is what happens, side effect- and benefit-wise, to the patient after being treated for five years with an aromatase inhibitor and then off. We have no data for that, not even modeling data.

► **DR BUZDAR:** We pick the numbers that we like to believe. The first publication on the ATAC trial reported a proportional reduction in hazard rate at year one, year two and year three. In year two, the reduction in the risk of events was about 39 percent. When you look at the curves, you are looking at the overall effect, and when you look at hazard rates, you look at a certain point.

► **DR GRADISHAR:** In terms of how I would approach this 79-year-old patient, I would probably utilize the data that we have on up-front therapy — the ATAC data set and more modest follow-up in the BIG 1-98 trial — and begin the patient on anastrozole or letrozole (1.1).

► **DR LOVE:** Do you prefer one or the other — anastrozole or letrozole — or do you consider them to be equal?

► **DR GRADISHAR:** The long-term data at this point — the more mature data — are with anastrozole, looking at follow-up of patients from the ATAC data set.

► **DR LOVE:** What about the issue of chemotherapy in this patient, Bill?

► **DR GRADISHAR:** The obvious caveat is that the patient has to be engaged in the discussion. This patient has been described as the super-athlete 79-year-old with a clear mindset about what she wants to do in her life, not only in sports but probably day to day in terms of tolerating certain side effects that are going to inhibit her activities.

So I would feel comfortable discussing chemotherapy with her, but she sounds like somebody who's going to think about the numbers carefully and realize that the added contribution of chemotherapy, despite her relatively poor prognosis, is still going to be modest, and she may elect to get endocrine therapy alone.

► **DR LOVE:** Would you be comfortable giving this woman chemotherapy?

► **DR GRADISHAR:** I would, based on how she was described in terms of performance status.

► **DR LOVE:** What if she were 85 years old?

► **DR GRADISHAR:** I think you have to look at the competing morbidities and mortalities as a patient ages. Peter's Adjuvant! Online model takes you out to 10 years, so when we are talking about the added contribution of chemotherapy in an 85-year-old patient, we have to think about her odds of being alive at 95. Then I think it becomes a different issue.

► **DR LOVE:** Peter, there was a paper in the *JCO* that evaluated the validity of the Adjuvant! Online program (Olivotto 2005). I understand that not only were the numbers related to breast cancer validated, but your nonbreast cancer mortality numbers were also validated.

► **DR RAVDIN:** We had an interest in validating the model, which is derived

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: ¹Thürlimann B for the BIG 1-98 Collaborative Group. St Gallen Breast Cancer Conference 2005. *Breast* 2005a;14(Suppl 1):3;S4.

²Howell A et al; ATAC Trialists' Group. *Lancet* 2005;365(9453):60-2. [Abstract](#)

largely from US data. The group in British Columbia has, perhaps, one of the larger North American databases, with very complete clinical data, so they sent us blinded information about the patients and their tumors. We then projected outcomes for those patients, sent the data back and they compared that to the actual outcomes of those patients.

Overall, it was a very tight fit. There were some groups where we were a little bit off. For instance, in younger women it appears that perhaps the classic pathologic variables don't tell us everything that's different about that population in that they had a somewhat worse prognosis than we had projected.

- ▶ **DR LOVE:** What specifically would this 79-year-old woman most likely be treated with in your clinic, Peter?
- ▶ **DR RAVDIN:** Hormonal therapy with an aromatase inhibitor. This is also a very active woman who's probably going to be taking a few falls, and the one thing worth emphasizing is that she'd have to be told about the osteoporosis risk and actually evaluated for that.
- ▶ **DR LOVE:** Which aromatase inhibitor?

▶ **DR RAVDIN:** I'd probably treat her with anastrozole, although there are substantial data for letrozole also. However, the anastrozole data in up-front therapy is actually more robust, because it's based on almost six years of follow-up now, so that's encouraging.

▶ **DR LOVE:** Aman, there is no survival difference at this point in the ATAC trial. How do you think the risk-benefit stacks up without survival differences, and what are your thoughts about cost?

▶ **DR BUZDAR:** At this point, none of these studies show any statistically significant survival advantage. However, there is a trend in the same direction in every study: With aromatase inhibitors there are fewer breast cancer deaths, whether they are used up front, in the middle, or down the line.

Why hasn't the ATAC trial, which has the longest follow-up, shown a statistically significant effect on survival? Because the patients in that trial are the most favorable subset of women in that the majority are node-negative, and it takes a much longer time to see a survival effect. Even the NSABP study, which consisted of patients with node-negative disease treated with tamoxifen,

took more than seven or eight years to show a survival advantage (Fisher 1989). I think if the therapy is effective and it prevents recurrence, eventually it will manifest a reduction in mortality down the line.

► **DR LOVE:** Dr Tracy, what happened with your patient?

► **DR TRACY:** We discussed these issues, although a little less scientifically, and she did not want chemotherapy. We discussed the slight potential benefit and the side effects of the different categories of drugs. Her two sons were in favor of chemotherapy, but she chose no chemotherapy. She did receive radia-

tion therapy to her chest wall and her draining lymphatics and has not had any sign of local recurrence.

We put her on anastrozole, and she's tolerated it beautifully with no musculoskeletal side effects. She's been on it for more than two and a half years and has no evidence of metastatic disease.

We did do a bone mineral density scan initially, and she had very mild osteopenia and worked with her primary care physician on that. She did not, however, choose to take a bisphosphonate. She and her family are very happy with her decisions. ■

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Case 2: From the practice of Dr Herbert I Rappaport, Los Angeles, California

A 41-year-old premenopausal woman with an ER/PR-positive, HER2-positive infiltrating ductal carcinoma and six positive lymph nodes

► **DR RAPPAPORT:** This is a 41-year-old, premenopausal woman with infiltrating ductal carcinoma of the breast, metastatic to six lymph nodes. She had a modified radical mastectomy and has been treated with four cycles of AC at this point. The tumor is ER- and PR-positive and HER2-positive by FISH.

► **DR LOVE:** Aman, how would you treat this patient?

► **DR BUZDAR:** For this young lady, who has a very high risk of recurrence, we have an effective therapy that has been shown to reduce the risk of recurrence. I would discuss with her the potential benefits of trastuzumab and that convincing evidence exists that we can reduce her risk of recurrence by more than 50 percent. In spite of chemotherapy and the positive hormone receptor status, she still has a very high risk of recurrence and I, personally, would be very much in favor of using trastuzumab as an addition to her therapy.

► **DR LOVE:** What specific chemotherapy and when would you add the trastuzumab?

► **DR BUZDAR:** If she just was finishing the last of four cycles of AC, I would give trastuzumab with a taxane, and most of the data we have are with paclitaxel (Perez 2005, Romond 2005). I personally would use trastuzumab concomitantly with the taxane-based therapy because of the positive impact when given concurrently and the lack

of benefit when it was given sequentially that we saw in the Intergroup trial. That is one area of discordance between the US trial, in which I have more faith, and the European HERA trial, which shows a very similar degree of benefit to the combined analysis (Piccart-Gebhart 2005). In the HERA trial, the choice of chemotherapy was up to the physician.

► **DR LOVE:** When would you start hormonal therapy in this patient, and what agent would you use?

► **DR BUZDAR:** My understanding is that in these trials, hormonal therapies were started after the completion of chemotherapy concomitantly with trastuzumab. We have utilized that approach in the neoadjuvant and adjuvant settings.

► **DR LOVE:** If this patient continues to menstruate through the chemotherapy, what hormonal therapy would you use?

► **DR BUZDAR:** In a patient who continues to menstruate, I still believe that tamoxifen is the standard of care. Of course, there are a number of ongoing randomized adjuvant trials in which pharmacological intervention and the substitution of tamoxifen with an aromatase inhibitor and an LHRH agonist is being evaluated; we should have some preliminary data from these in the next year or so.

► **DR LOVE:** I assume you would use trastuzumab for a total of one year, as was used in the adjuvant trials.

► **DR BUZDAR:** Yes, because we need to use the therapy as it was used in the study where the data were collected.

► **DR LOVE:** Bill, how do you approach patients who have been treated in the past for HER2-positive disease and have not received trastuzumab?

► **DR GRADISHAR:** This harkens back to the release of the MA17 data and then seeing patients who completed adjuvant tamoxifen six months or a year ago. Do you institute another endocrine maneuver? I think that's one of the big questions we are going to be facing with delayed trastuzumab. The data we have from trials long ago, tracking the recurrence of breast cancer over time, are instructive because we know that even after five years — be they node-negative or node-positive, but particularly if they are node-positive — there's a fraction of patients who are going to continue to be at risk for recurrence, even though the peak recurrence may be within the first few years.

So with that as the background, I think for a patient who has completed chemotherapy, it is reasonable to consider trastuzumab. The big question is, How long since the completion of chemotherapy? Six months? A year? Two years? If a patient had six or 10 positive nodes and were out six months or a year, I would still have the discussion about the data and consider adding trastuzumab, even though it doesn't directly duplicate the trial design.

► **DR LOVE:** In terms of hormonal therapy, do you agree with Aman that in this patient you would use tamoxifen alone? I'm not certain whether this patient would be eligible for the TEXT or SOFT trials, but would you consider ovarian suppression and an aromatase inhibitor in this patient off protocol?

► **DR GRADISHAR:** I believe tamoxifen remains the standard for this type of

patient. The data we have available on ovarian suppression with tamoxifen or an aromatase inhibitor are still relatively limited, so I would still view tamoxifen as the optimal therapy.

► **DR LOVE:** Kent, there were a fair number of patients in the HERA study who had node-negative disease but not too many in the combined NSABP/NCCTG analysis. Do you think that the concept of relative risk should be applied when considering trastuzumab in patients with node-negative disease who have received chemotherapy and hormonal therapy?

► **DR OSBORNE:** First of all, we should stop stratifying patients for treatment by node-negative versus node-positive disease. That's only one of many factors. A patient with a high-grade, large tumor that is node-negative may have a much worse prognosis than a patient with node-positive disease and two positive receptors. I would look at the patient's risk of recurrence and base my decision on the risk of recurrence, and even though she's node-negative, I'd treat her.

► **DR LOVE:** Dr Rappaport, would you follow up with what happened to this patient?

► **DR RAPPAPORT:** I plan to talk to her about starting a taxane and trastuzumab concomitantly. I am wondering whether we should give her an LHRH agonist, or should we use tamoxifen? Also, if she is on an LHRH agonist, do we start either tamoxifen or an aromatase inhibitor?

► **DR LOVE:** Peter, what about the issue of patients who cease menstruating with chemotherapy? How do we determine whether they're postmenopausal and whether to consider an AI?

► **DR RAVDIN:** One of the things that's been frustrating is to use serum estradiol and gonadotrophin levels to define the

menopausal status of women who have become postmenopausal on chemotherapy. This patient is relatively young, so if she stops menstruating, there's a reasonable chance that she's going to start menstruating again.

In this type of patient, I still prefer tamoxifen rather than an aromatase inhibitor. If she receives tamoxifen, and at the end of two years she hasn't menstruated and her estradiol levels are

low, then you can switch her. Incidentally, tamoxifen usually pushes up the estradiol levels and makes it more obvious that a patient is premenopausal, so that if you drew an estradiol level after two years and it was in the postmenopausal range, and you wanted to start her on an aromatase inhibitor, I think there's very little chance that she would start menstruating at that point (2.1). ■

2.1

Incidence of Long-Term Amenorrhea Following Chemotherapy in Patients with Stage I-III Breast Cancer (n = 595)

Treatment	Amenorrhea for 12 months	Subsequent bleeding in the next 4 years
AC	31%	42%
ACT	20%	33%
CMF	29%	16%
Treatment	Amenorrhea for 24 months	Subsequent bleeding in the next 3 years
All regimens (AC, ACT, CMF)	22%	9%

AC = doxorubicin/cyclophosphamide; ACT = doxorubicin/cyclophosphamide/paclitaxel
 CMF = cyclophosphamide/methotrexate/5-FU

SOURCE: Sukumvanich P et al. *Proc ASCO* 2005; [Abstract 575](#).

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Case 3: From the practice of Dr Ghaleb A Saab, Riverside, California

A 68-year-old woman with disease progression 10 years after presenting with hormone receptor-positive diffuse metastatic disease to the bone

► **DR SAAB:** Ten years ago, at the age of 58, this patient presented with a right breast lump, which was breast cancer. She was found to have diffuse metastatic disease to the bones and was in such pain that she needed radiation therapy to various areas of the skeleton over the subsequent 18 months. The tumor was hormone receptor-positive, and her prior oncologist started her on tamoxifen. Over the ensuing two years, she didn't respond very well, was found to be resistant to tamoxifen and needed a substantial amount of radiation therapy. She was switched to anastrozole, which again was determined not to be effective.

Eventually, she was offered chemotherapy, which she had declined initially. She was given CMF with filgrastim support over a period of six months. Toward the end of 1999, again because of rising tumor markers, it was determined that the chemotherapy wasn't working. Her oncologist then tried low-dose paclitaxel every week for three months, and he determined that it didn't work well.

This lady required morphine all this time, despite radiation therapy. In January 2000, she was started on capecitabine, and she has been on it ever since. For a full five years on capecitabine, she had been morphine-free and pain-free, until three months ago, when her tumor markers started rising again and her pain started to

develop in different areas. Obviously, her cancer was coming back. I then started her on docetaxel every three weeks. After the second cycle, her tumor markers went down and she experienced symptom improvement.

► **DR OSBORNE:** When she experienced progression of disease on the hormone therapy, how long had she been on it, and was it more than just markers going up that led to the discontinuation?

► **DR SAAB:** Her symptoms, including pain, persisted, and her markers continued to rise. The CA27.29 and CA15-3 were elevated around 150 to 180 and her CEA was a little higher.

► **DR GRADISHAR:** This patient has had a remarkable course on capecitabine. Capecitabine is one of my favorite chemotherapy drugs. I believe it was probably underrated initially until we learned how to properly dose it and utilize it effectively in both older and younger patients. I think one of the issues is whether combining drugs is better than using single agents in sequence and how you actually define superiority.

One experience, presented by Joanne Blum, evaluated capecitabine plus a weekly schedule of paclitaxel (Blum 2004). When you compare the clinical endpoints in that trial to the every three-week schedule of paclitaxel in both the European and US studies, you see a response rate in the 50 percent

Phase II Studies of Capecitabine Plus Paclitaxel in the Treatment of Patients with Metastatic Disease

Study	Response rate	Stable disease	Median time to disease progression	Median overall survival
Batista et al ¹ (n = 73)	52%*	29%	8.1 months	16.5 months
Gradishar et al ² (n = 47)	51%*	19%	10.6 months	29.9 months
Blum et al ³ (n = 44)	52.3% [†]	29.5%	NR	NR

* Objective response rate; [†] Partial response rate

¹ (Capecitabine 1,000 mg/m² BID days 1-14 + paclitaxel 175 mg/m² day 1) q3wk

² (Capecitabine 825 mg/m² BID days 1-14 + paclitaxel 175 mg/m² day 1) q3wk

³ (Capecitabine 825 mg/m² BID days 1-14 + paclitaxel 80 mg/m² days 1, 8) q3wk

SOURCES: ¹ Batista N et al. *Br J Cancer* 2004;90(9):1740-6. **Abstract**; ² Gradishar WJ et al. *J Clin Oncol* 2004;22(12):2321-7. **Abstract**; ³ Blum JL et al. San Antonio Breast Cancer Symposium 2004; **Abstract 5053**.

range (3.1). In terms of adverse events, they're modest, with the most prominent one being hand-foot syndrome, and then hematologic toxicities, which were fairly predictable.

► **DR LOVE:** Peter, we have found that clinical research leaders much more commonly use capecitabine than clinicians in practice. What has been your experience with capecitabine?

► **DR RAVDIN:** Capecitabine has some attractive features. I view it, in terms of toxicity and response, as something that bridges the gap between hormonal therapy and intravenous chemotherapy. Particularly when dosed a bit lower than the package insert dose, it's tolerable for most patients, and they don't experience nausea, vomiting or hair loss, almost as if they were receiving an endocrine agent. It's an oral agent, we don't have to put in a line, so it's easier for patients to accept. I think all those features make it an attractive agent.

Actually, I'm a little surprised that it isn't more commonly used in the community, because I think it's one of those agents that is generally tolerated with repeated use. With a lot of other

agents, patients begin to get tired when you get in six cycles.

► **DR LOVE:** Aman, what was your take on the bevacizumab/paclitaxel data initially presented by Kathy Miller at ASCO (Miller 2005a)?

► **DR BUZDAR:** I think if you put it in context, it's very similar to the data we saw when trastuzumab was combined in the first-line setting: There is a significantly higher response rate, longer control of disease and early evidence that it may have a favorable impact on survival (3.2). Its side-effect profile is unique, but I think most of the side effects are very manageable, and no new side effects were seen in this study.

With regard to this specific patient, would I consider adding a biologic agent to her therapy? The data on capecitabine combined with bevacizumab, unfortunately, did not show a longer time to progression or any favorable impact on survival, although a higher number of patients had an objective response to the therapy (Miller 2005b). So I think these therapies may need to be utilized early on to get the benefit.

ECOG-E2100 Efficacy Results

	Paclitaxel + bevacizumab (n = 341)	Paclitaxel (n = 339)	p-value
Response rate	29.9%	13.8%	<0.0001
Progression-free survival	11.4 months	6.11 months	<0.0001
Overall survival	Hazard ratio = 0.84 (CI, 0.64-1.05)		0.12

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

SOURCE: Miller KD et al. Presentation. San Antonio Breast Cancer Symposium 2005; [Abstract 3](#).

► **DR LOVE:** Are you using bevacizumab and paclitaxel in the first-line setting?

► **DR BUZDAR:** I think the data are very compelling, and I feel that it is our responsibility to share that information with every patient who has similar eligibility criteria as those in that ECOG study.

► **DR LOVE:** Kent, what are your thoughts on this?

► **DR OSBORNE:** I certainly wouldn't use bevacizumab in any situation other than first-line therapy, since that's where the data came from, so I wouldn't use it in this patient. But I'm very concerned about the cost of treatment for a few extra months in time to progression. If I had insurance that paid 80 percent, I'm not sure I would elect to receive bevacizumab because 20 percent of a lot of money is a lot of money. I'm very concerned about the cost issue.

► **DR LOVE:** Peter, do you agree with Kent that you would only use it in that specific situation?

Our group has been tracking the bevacizumab story in colorectal cancer. The initial data were presented two years ago with IFL, and yet everybody immediately started using it with FOLFOX, and eventually that combination was shown to be effective. What are your thoughts about using bevacizumab in breast cancer, and what agents would you combine it with?

► **DR RAVDIN:** I largely agree with what Kent has said in that while a lot of expense, and even sometimes a lot of toxicity, is justified in the adjuvant arena, in the metastatic disease arena, enormous expense is sometimes added to the cost of therapy for a relatively small impact. Data from one trial that's not a crossover trial are not strong enough to make me consider it the standard of care as front-line therapy for everyone with hormone refractory, metastatic breast cancer because I think that would actually break the back of the healthcare system. ■

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Case 4: From the practice of Dr Juliann M Smith, Rancho Mirage, California

A 91-year-old woman with dementia who was diagnosed with Stage II, ER-positive, lymph node-negative breast cancer 15 years ago and now has diffuse bone metastases

► **DR SMITH:** This is a 91-year-old lady with Stage II breast cancer, diagnosed in 1990. At the time, her tumor was 2.4 centimeters, estrogen receptor-positive, but lymph node-negative. She underwent mastectomy and took adjuvant tamoxifen for seven years.

Since that time she's developed mild to moderate dementia and, according to her family, she may forget to take her pills from time to time. The patient herself is not aware of this.

She did quite well until September 2004, when she presented with right hip pain. A bone scan showed diffuse bone metastases, mostly involving the hips and femurs, bilaterally, with a right superior pubic ramus fracture.

A CT scan showed multiple liver metastases, five in number, with the largest one being three centimeters in size, and no other sites of disease.

The pubic ramus fracture was irradiated, which resolved her pain, and she was started on pamidronate and fulvestrant, with stabilization of her disease for eight months.

► **DR LOVE:** You mentioned that the patient has dementia. Were you able to discuss treatment with her in a way that she understood?

► **DR SMITH:** She did understand that her cancer had returned and that she needed some treatment.

► **DR LOVE:** Did her symptomatology improve on the fulvestrant?

► **DR SMITH:** Yes, her pain resolved and that was the only symptom she was having.

► **DR LOVE:** Dr Osborne, what are your thoughts on the use of fulvestrant?

► **DR OSBORNE:** Two clinical trials were conducted comparing fulvestrant versus anastrozole for second-line therapy in patients who had received tamoxifen in the adjuvant or metastatic setting (Pippen 2003; Robertson 2003; [4.1]). One study was conducted in North America and the other in Europe and the rest of the world. The data from both trials were very similar. The complete response rate was slightly higher with fulvestrant, whereas the partial and objective response rates were very similar. In terms of stable disease and clinical benefit, fulvestrant was a tiny bit better than anastrozole. In one of the trials, duration of response favored fulvestrant, but by and large, the drugs were very similar.

How does fulvestrant compare with tamoxifen in the front-line setting? All the preclinical data suggested that fulvestrant would be significantly better than tamoxifen, so a trial was conducted comparing these two endocrine agents. In the receptor-positive group, fulvestrant and tamoxifen were similar in response and time to treatment failure,

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 = 27.0 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.**

but overall, tamoxifen looked slightly better in some of the parameters.

► **DR LOVE:** Would you have used fulvestrant in this patient?

► **DR OSBORNE:** Because of the data showing superiority of aromatase inhibitors relative to tamoxifen, in a previously untreated patient I would tend to go with an aromatase inhibitor first. However, in this patient, who has received tamoxifen and suffers from dementia and may not be taking her pills correctly, I think she's a perfect candidate for fulvestrant, and I totally agree with its use in this situation.

► **DR GRADISHAR:** One of the issues is whether there's a particular sequence of endocrine therapy that's optimal, in terms of prolonging time to disease progression or overall survival. The EFECT trial is one effort to look at patients who have progressed through a nonsteroidal aromatase inhibitor, be it anastrozole or letrozole, and are then randomly assigned to receive either fulvestrant or the steroidal aromatase inhibitor exemestane. There are no data

from that trial yet; it's probably three quarters of the way to its accrual goal at this point.

► **DR LOVE:** Kent, the SoFEA trial in Europe is evaluating another strategy in patients who are progressing on aromatase inhibitors. Those patients are randomly assigned to fulvestrant, exemestane or fulvestrant plus anastrozole. I know there are oncologists in practice who have continued an aromatase inhibitor and added fulvestrant. What do you think of that strategy in the clinical setting?

► **DR OSBORNE:** I think it's a good idea, but as you know, there are no data. I have to say I have done it in a few patients based on two preclinical studies that have evaluated this: my own and Angela Brody's. Fulvestrant seems to work much better when there's no estrogen around. Even though postmenopausal women have lower estrogen levels in the blood, their tumors don't necessarily have lower estrogen levels, and fulvestrant seems to be more effective when estrogen is low.

It would be interesting to see the results of a clinical trial evaluating that.

► **DR LOVE:** A lot of people have talked about the issue of how to dose fulvestrant. My simplified understanding of it is that since it's a competitive inhibitor for estrogen, you could increase dose or get rid of the estrogen.

► **DR OSBORNE:** Yes, you could do it either way, but I am concerned that in premenopausal women, it doesn't work very well. Obviously, they have a lot of estrogen in their blood, and we know it doesn't work well for conditions like benign endometriosis. I think the estrogen in the premenopausal woman is too much to be competitively inhibited with the fulvestrant dose that we're now using. Plus it takes three to

six months to get the dose to steady state when you start at 250 mg a month, and that's a problem. Some patients may be taken off fulvestrant after only two months of therapy, before the blood levels are even high enough to make a difference.

Ongoing trials are evaluating fulvestrant at doses of 500 mg on day one, 250 mg on days 14 and 28, and then once a month. That's based on a computer model of the pharmacokinetics of the drug. Whether insurance companies will pay for that loading dose outside of that trial is another issue.

► **DR LOVE:** Do you use that strategy in a clinical setting?

► **DR OSBORNE:** Yes. I do. ■

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Case 5: From the practice of Dr Herbert I Rappaport, Los Angeles, California

A 41-year-old surgically postmenopausal woman with a 3.5-centimeter, ER/PR-positive, HER2-positive tumor and two positive lymph nodes

► **DR RAPPAPORT:** This is a 41-year-old woman who previously had a hysterectomy and bilateral oophorectomy for menometrorrhagia four years ago at the age of 37. She underwent a radical mastectomy for a 3.5-centimeter, poorly differentiated adenocarcinoma, metastatic to two lymph nodes.

She was treated with FAC times six, and currently is on tamoxifen, which she has taken for three and a half years. The tumor is both ER- and PR-positive and overexpresses HER2 by FISH.

► **DR LOVE:** This case raises the issue as to the optimal long-term endocrine treatment strategy in postmenopausal women. A number of theoretical models have been proposed to estimate whether an aromatase inhibitor initially or tamoxifen followed by an aromatase inhibitor is the optimal schedule (5.1). Dr Chlebowski, could you comment on these models?

► **DR CHLEBOWSKI:** The problem I have with the models is they all assume they know what's going to happen if you randomly assigned patients at first versus in the middle. I don't think you can take those numbers in the middle and tack them onto a model. The models are interesting but not very informative.

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

► **DR LOVE:** Can you discuss the trial reported at ASCO 2005 evalu-

ating anastrozole in patients who had completed five years of tamoxifen?

► **DR CHLEBOWSKI:** The Austrian trial, ABCSG-6a, looked at patients who had received tamoxifen with or without aminoglutethimide for five years. The patients were then randomly assigned to anastrozole or no treatment for three years. This extended adjuvant trial also showed a benefit from anastrozole.

► **DR LOVE:** How did those data compare to what was seen in the MA17 trial with letrozole?

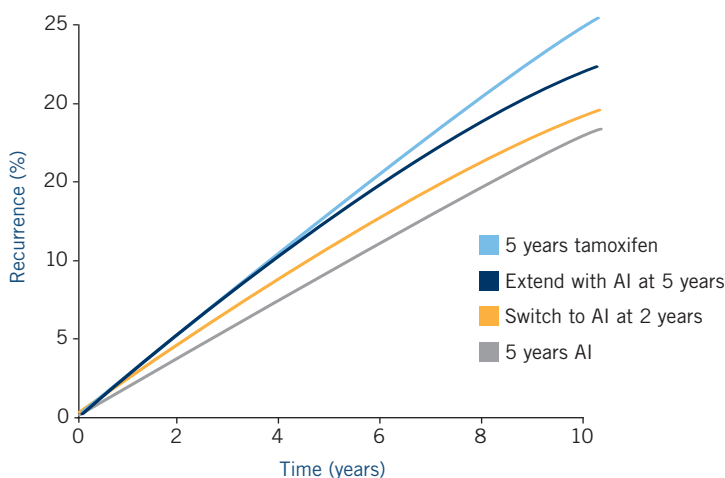
► **DR CHLEBOWSKI:** The data looked about the same. Of course, in the letrozole trial, we talk about five years of letrozole, but it was reported after two and a half years of treatment.

► **DR LOVE:** What you were saying about the models makes sense in terms of the point of randomization and the fact that looking at how relapse rate is affected at two or five years does not take into account all the recurrences and adverse events that occurred before that time.

► **DR CHLEBOWSKI:** To me, that's a big black box, to make that assumption. The other part of it is, when you look at the assumptions, trying to compare Jack Cuzick's and Hal Burstein's model, they get completely different answers.

Burstein used the primary studies' main endpoints and Cuzick used a little different endpoint, and you get a totally different result, based on what you put in the model.

Cuzick's Model of AI/Tamoxifen Effect



SOURCE: Cuzick J, Howell A. Presentation. ASCO 2005; [Abstract 658](#).

► **DR LOVE:** Dan, from a clinical point of view, the idea of starting tamoxifen and switching to an AI requires clinicians to tell patients, “Here’s my long-term strategy for you. You’re going to go on a therapy that, for the first two or three years, is going to expose you to a greater risk of relapse, but in the long run, you’ll have fewer relapses.”

► **DR HAYES:** In my own practice, I believe that for patients who have a reasonably good prognosis, tamoxifen alone is a perfectly adequate start. I actually disagree a bit with Rowan in that I’m not sure we know about long-term follow-up of women who have complete estrogen depletion. It took us a long time to see some of the unanticipated effects of tamoxifen.

Tamoxifen is a good drug. It’s not like we should throw it out. In patients who start out with a good prognosis, the maximum potential added benefit of an AI over tamoxifen can’t be more than

one or two percent absolute survival over 10 years or so. Given what we know about tamoxifen and the benefits of it, I have started with that.

On the other hand, in this patient with positive nodes, I would consider starting with an aromatase inhibitor initially. She has a high risk of relapse up front, so the potential added proportional reduction in recurrences and death by using an AI is amplified. In addition, if you want to bring Kent’s biology into it, she’s HER2-positive, and one would believe that estrogen depletion should be a more effective strategy than a SERM in such a patient.

► **DR LOVE:** Would you describe the type of patient you would treat with tamoxifen up front and discuss the issue of excess toxicities, such as endometrial cancer and stroke?

► **DR HAYES:** First of all, let’s be clear that we’re talking about postmenopausal women only, not premenopausal

patients. A postmenopausal woman with ER-positive, node-negative disease, especially if her tumor is two or three centimeters or less, I believe has a very good prognosis, and that's the type of patient in whom I would recommend tamoxifen. I tell my patients that there's no question in my mind that the AIs are more effective than tamoxifen, although the amplification of that benefit in a very good-prognosis patient is very small in terms of the added proportional reduction over tamoxifen.

With an AI, bone fractures are a risk. Granted, the fracture curves look like they are coming together, but you have to recall that there are precious few patients out in that tail beyond five years (5.2). That's a very unstable statistical tail. Most of those patients are to the left of that, between three and four years.

► **DR LOVE:** Chuck, where are you on the debate of tamoxifen versus aromatase inhibitors?

► **DR VOGEL:** I've listened to everybody, and I actually agree with everything that's been said. We worry about the

cost issues, and there's no question that I treat some patients with tamoxifen solely on the basis of cost.

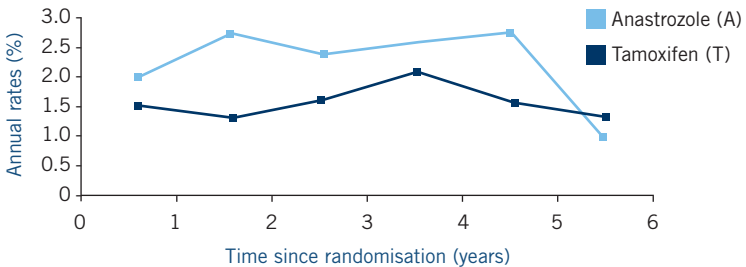
I think that looking at the overall results, the aromatase inhibitors have a better toxicity profile, except for two areas, and they probably have slightly more efficacy. On the other hand, they are more costly.

So, in practice, I discuss all of these things with my patients. I have no problem if a patient elects to receive tamoxifen because of cost or whatever. It's a very good drug. But, cost notwithstanding — and with the proviso that I don't like starting the osteoporotic patients on aromatase inhibitors — I start with an aromatase inhibitor. I switch from tamoxifen to an aromatase inhibitor at two years, and I switch to letrozole at five years.

► **DR RAVDIN:** I absolutely agree with the ASCO Technology Assessment statement that basically, for postmenopausal women with ER-positive disease, an aromatase inhibitor should be part of their adjuvant hormonal therapy (Winer 2005). I think it's quite clear that these

5.2

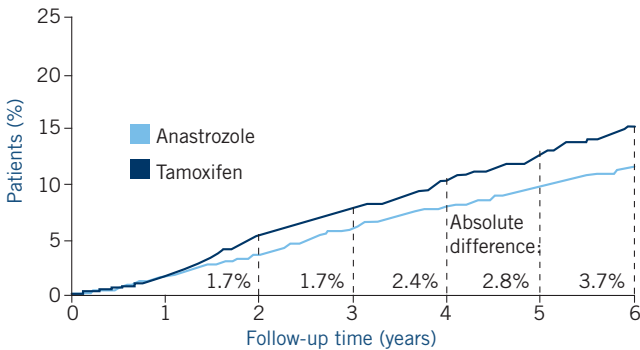
The Long-Term Fracture Risk with Anastrozole Is Predictable and Manageable



SOURCE: With permission from Howell A. Presentation. San Antonio Breast Cancer Symposium 2004; [Abstract 1](#).

ATAC: Time to Recurrence Curves Shown for HR+ Patients

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



At risk:

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

SOURCE: With permission from Howell A. Presentation. San Antonio Breast Cancer Symposium 2004; [Abstract 1](#).

agents reduce the risk of relapse. Every single one of the major trials, all five of them, show marked reduction in the risk of relapse with aromatase inhibitors.

► **DR CHLEBOWSKI:** Looking at the toxicity profile and the fact that you're getting more recurrences if you start with tamoxifen first, I would rather start with an aromatase inhibitor and have fewer relapses, because those are not recoverable in a major sense.

I think it's possible that shorter durations of hormone therapies will be better. We had more signals on that at ASCO this year with the two- versus five-year tamoxifen randomized trial showing absolutely no difference in survival after 10 years of follow-up (Valentini 2005).

► **DR RAVDIN:** The clinical data are what drive things. And the same way that nobody could anticipate what the combined arm of ATAC was going to show, we don't know what will be revealed with these switching strategies.

► **DR CHLEBOWSKI:** I agree that the empirical data will rule, but what happens is you're going to be behind for sure in terms of recurrences if you start with tamoxifen first, and in many cases that's a terminal disease that you can't recover from. I think you'll have time to see what the empirical data will be for the majority of your patients because we'll get some kind of signal from BIG FEMTA. We'll have that result in probably three years. ■

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Case 6: From the practice of Dr Steven W Papish, Morristown, New Jersey

A 45-year-old premenopausal woman with a 0.7-cm, ER/PR-positive, HER2-positive tumor with 25 percent high-grade DCIS and an *Oncotype DX* recurrence score of 16

► **DR PAPISH:** This patient is the 45-year-old premenopausal wife of a physician in our community who presented with a left breast abnormality that she felt on examination. She underwent mammography, which was negative, but an ultrasound revealed a seven-millimeter nodule at approximately five o'clock. She ultimately underwent an excisional biopsy for a 0.7-centimeter, poorly differentiated, invasive ductal carcinoma that contained approximately 25 percent high-grade DCIS.

The tumor was strongly ER-positive (90 percent on IHC), PR-positive (80 percent), and HER2-positive (amplified by FISH). She subsequently underwent bilateral breast MRIs, which were negative. Her family history is negative for breast cancer and ovarian cancer, but she is of Ashkenazi heritage and underwent both BRCA1 and BRCA2 testing for the three Ashkenazi genes.

► **DR LOVE:** John, if this woman turned out to be BRCA1- or BRCA2-positive, would you approach her local breast cancer therapy any differently?

► **DR MACKEY:** When we see a patient who is BRCA1-positive, we often have the discussion that they're at quite high risk of local recurrence or a second primary cancer. Even though this is a small tumor, the woman should be given the discussion regarding prophylactic mastectomy, as well as perhaps a completion mastectomy on the affected side.

► **DR PAPISH:** She then underwent a re-excision and sentinel node biopsy. The re-excision revealed a residual two-millimeter area of just high-grade DCIS with no other invasive tumor. Three sentinel lymph nodes were negative by IHC and H&E.

► **DR LOVE:** What was her attitude? Was she more of the proactive, "I want to do everything possible," or was she more concerned about toxicity?

► **DR PAPISH:** There was a clear-cut difference between the patient and her husband. She is a long-distance runner. She was very worried about anything that might impact on her cardiovascular health. She truly did not want to receive any aggressive therapy if it were not warranted. However, she's bright enough to understand that if it were needed, she would accept it.

► **DR LOVE:** Aman, would you bring up the use of the *Oncotype DX* assay in this woman?

► **DR BUZDAR:** The tumor is relatively small, and the risk in this woman of this breast cancer causing a problem is relatively small. But if she has one breast cancer, she has at least a 0.6 percent risk of developing contralateral breast cancer on a yearly basis, and she's young. She may have another 30 or 40 years of lifespan left. So that also has to be taken into account.

► **DR LOVE:** So how did you approach this patient?

Ten-Year Distant Recurrence-Free Survival According to a 21-Gene Recurrence Score

Risk group	Tamoxifen (n = 227)	Tamoxifen + chemotherapy (n = 424)	p-value
Low (RS < 18)	96%	95%	0.76
Intermediate (RS = 18-30)	90%	89%	0.71
High (RS ≥ 31)	60%	88%	0.001

Chemotherapy = MF or CMF; RS = recurrence score

SOURCE: Paik S et al. Presentation. San Antonio Breast Cancer Symposium 2004. [Abstract 104](#)

► **DR PAPHIS:** We discussed the *Oncotype DX* assay. My bias was that with a poorly differentiated tumor and borderline but HER2-positive amplification, we would probably see a high or a high-intermediate recurrence score. The recurrence score was 16 (6.1).

► **DR LOVE:** Her recurrence score was 16, which is low risk. What did you decide to do?

► **DR PAPHIS:** She was started on tamoxifen and breast irradiation. We had previously discussed that if the recurrence score from the *Oncotype DX* assay was low, we would use hormonal therapy.

I explained that I had a bias about possibly using an aromatase inhibitor and ovarian ablation but did not feel strongly that it needed to be done at the moment. She's perimenopausal, so she clearly would not be a candidate for an aromatase inhibitor alone at present. They have an appointment next week, and her husband still thinks he may want her to have chemotherapy. But I think the patient is very comfortable with hormonal therapy.

► **DR LOVE:** If you're thinking about chemotherapy, potentially you also might be talking about trastuzumab.

► **DR PAPHIS:** The tumor is FISH-positive, but I don't know whether the

Oncotype DX assay trumps the HER2 positivity in the sense that we have a relatively low recurrence score. I would presume that if she had an increase in genes coding for HER2 positivity, she would have had a higher recurrence score and certainly a more proliferative tumor.

► **DR LOVE:** John, I'm curious. Is it possible that the HER2 positivity is from the DCIS?

► **DR MACKKEY:** There's generally a high degree of concordance between the HER2 status of DCIS and invasive disease. In general, the two travel together. However, when one does FISH, the person who's reading it should be trained enough to score only the invasive nuclei, as opposed to the in situ component.

► **DR LOVE:** Andy, what would you say to this woman?

► **DR SEIDMAN:** I think we need to be cognizant of what the real benefit is and lead with the data rather than the emotional response. I would absolutely give this woman tamoxifen and talk to her about participation in a trial of ovarian function suppression.

► **DR LOVE:** You're going to knock down the relapse rate a little bit with trastuzumab. Of course, following an anthracycline base, we're looking at probably a

three or four percent risk of cardiomyopathy. A young woman who's a jogger probably has normal cardiac function. If the husband brings that up, Andy, how would you respond?

► **DR SEIDMAN:** I think the only meaningful data we have regarding trastuzumab's role in patients with node-negative breast cancer come from the HERA trial, in which there were 1,100 such patients randomly assigned to trastuzumab or not (Piccart-Gebhart 2005). They had to have T1C or greater tumors; this woman clearly doesn't fit that category. The incidence of cardiac events is probably very close to the potential benefit she would receive. It would be easy to defend not giving her trastuzumab.

► **DR LOVE:** Aman, how would you approach the issue of chemotherapy and maybe even trastuzumab in this patient?

► **DR BUZDAR:** I think the trastuzumab part is a little tricky, because she has a small tumor where 20 or 25 percent of the tumor is DCIS. I agree with John, that pathologists have to carefully look at and make sure that this overamplification of HER2 is indeed in the invasive component. Sometimes our pathologists at MD Anderson will say, "Yes, there is overamplification, but it is only confined in the DCIS area." We should not be misguided and overtreat the patient.

What is interesting and intriguing about this patient is that she is young — she's 45 — so she has a fairly long lifespan. But the tumor is very small and is strongly ER/PR-positive. The addition of chemotherapy in patients with strongly ER/PR-positive disease is marginal at best; most of the benefit in this patient would be from endocrine intervention.

► **DR RAVDIN:** This case represents where

molecular characterization comes into play in terms of treatment sensitivity. Even though this patient had a low-risk *Oncotype* DX score — seven percent rate of distant recurrence — that range includes patients with as low as two percent or as high as 10 percent risk. And a 10 percent risk of distant recurrence is — if you're the one facing it — a substantial risk.

The Overview says chemotherapy adds to such patients about a 30 percent relative benefit. Now, a lot of that benefit — at least half of it — is probably an endocrine ablation type of benefit. But nonetheless, it is a benefit. So you could argue rationally that such a patient should be treated if you believe that she would get 30 percent of 10 percent, or a three percent net benefit.

However, a proportional benefit for this woman is likely to be less than that 30 percent benefit. In the future, I think if you look at it as a three percent possible benefit, that would be attractive to a number of people. So I don't think you can discount the idea that such a patient would be treated even if all you know is the prognostic information.

► **DR LOVE:** One final question for Aman. Does the fact that this patient has FISH-positive disease make you concerned about using just tamoxifen as opposed to an LHRH agonist or an LHRH agonist plus an aromatase inhibitor?

► **DR BUZDAR:** There are small but definite data emerging that suggest that patients who have HER2-positive disease may have better disease-free survival when treated with an aromatase inhibitor — both in the metastatic and the adjuvant settings, or even in the neoadjuvant setting (Dowsett 2005, Smith 2005). ■

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Case 7: From the practice of Dr Pamela Drullinsky, Rockville Center, New York

A woman who presented in 1989 with an infiltrating lobular carcinoma and 21 positive nodes and was treated with adjuvant chemotherapy and tamoxifen and then develops metastatic disease and is treated over the next 11 years with a variety of chemotherapeutic and hormonal agents

► **DR DRULLINSKY:** This patient first presented in 1989 with an infiltrating lobular carcinoma and 21 positive lymph nodes. She was treated at a local hospital with CMF and etoposide in the adjuvant setting and placed on tamoxifen for five years.

Then she was watched for several months and developed bone metastases. At this point, she was switched to an aromatase inhibitor, anastrozole. Then she quickly developed aggressive disease, mostly extending to the bones, and she had mild ascites.

At this point, 11 years after presentation, she has been through all the hormones, all the aromatase inhibitors, and fulvestrant. She has had a number of chemotherapy agents, including capecitabine, gemcitabine, vinorelbine, and every three-week docetaxel.

At the end of last year, she developed extensive bone marrow involvement, complicated by anemia and thrombocytopenia requiring transfusions. Her baseline platelet count last year was nine, and her hemoglobin was five.

The only treatment she hadn't received was an anthracycline. So I gave her liposomal doxorubicin, and she had a one-year response. She became transfusion-free from both red blood cells and platelets. Now I'm faced with the fact that she's progressed on liposomal

doxorubicin, and she's again thrombocytopenic, anemic and dependent on transfusions.

► **DR LOVE:** What about her symptomatology and performance status?

► **DR DRULLINSKY:** She is completely asymptomatic. She does not take any narcotics at all, and her performance status is 90 percent.

► **DR LOVE:** Has she experienced any bleeding?

► **DR DRULLINSKY:** No.

► **DR LOVE:** Which taxanes has she received?

► **DR DRULLINSKY:** She's only had every three-week docetaxel. And with that, she actually had stable disease.

► **DR LOVE:** What are you thinking about at this point?

► **DR DRULLINSKY:** Well, she has not yet received the platinum and weekly taxanes. Given the data with bevacizumab, I was considering that. The problem is she's very thrombocytopenic, with a platelet count under 10.

► **DR LOVE:** Aman, any thoughts about her case?

► **DR BUZDAR:** One thing you may consider is weekly paclitaxel or *nab* paclitaxel. With weekly paclitaxel, myelosuppression is not one of the side effects. She may benefit, even though

she has been treated with docetaxel. There is a partial lack of cross-resistance between these two agents, and the lack of myelotoxicity might be worthwhile. The same is true with *nab* paclitaxel, which may be another option for you to consider.

► **DR LOVE:** You mentioned that she had a good response to liposomal doxorubicin. Along the way, as she's gotten these various therapies, is there anything else that she had a good response to?

► **DR DRULLINSKY:** Every therapy she has had has worked.

► **DR LOVE:** How did she do on capecitabine?

► **DR DRULLINSKY:** Capecitabine worked for one year. Every treatment regimen worked for approximately nine months to one year.

► **DR LOVE:** John, what are your thoughts?

► **DR MACKEY:** Perhaps this is heresy, but at some point you have to have a conversation with the patient about what realistically she can expect from further chemotherapy. You could kill this woman with your next cycle, potentially. She has to be aware of that. In our center in Edmonton, we have a world-class palliative care team. At this point, we would hand over this woman's care to the palliative care team.

► **DR SEIDMAN:** Having just completed a two-week stint as the inpatient attending at Memorial Sloan-Kettering, I wish I were in Canada right now with Dr Mackey. Obviously, no further chemotherapy and best supportive care certainly should be part of a discussion with someone when they're facing their sixth line of therapy. Despite the dangerously low platelet count that Pam described, I did get a sense that this patient has a high functional

status and is living a good quality of life. She has repeatedly had at least transient responses to every chemotherapy regimen she's been exposed to. I think an overall difference in orientation exists toward breast cancer and the utility and futility of chemotherapy between Canada and the US.

► **DR LOVE:** What, specifically, would you recommend, Andy?

► **DR SEIDMAN:** I would include in a discussion the possibility that chemotherapy could lead to life-threatening hemorrhagic complications. If the patient still wanted to proceed, the regimens that would likely not contribute further to thrombocytopenia — weekly paclitaxel or weekly *nab* paclitaxel — are reasonable options. Other drugs I would consider, if she had a healthier bone marrow, include agents like irinotecan, for which we have Phase II data in the anthracycline/taxane-refractory population (Perez 2004). Even agents such as pemetrexed, for which there are Phase II data (O'Shaughnessy 2005).

► **DR RAVDIN:** I would largely agree with what has already been said. I think that weekly taxane therapy would be my first pick in this patient. The one thing I would also keep in the back of my mind is the possibility, when her platelets are back at 100,000, of rebiopsying her tumor. There are times, particularly over long periods, where the biology of the tumor can drift. Maybe she's actually HER2-positive at this point.

► **DR DRULLINSKY:** I do have the bone marrow from a year and a half ago, and it was completely packed, so maybe we could test that.

► **DR LOVE:** Do we know what the incidence is of switching from HER2-negative to HER2-positive, or an original false negative that you would now identify as positive? Andy?

► **DR SEIDMAN:** Lindsey Harris and others have reported on this. Dr Luftner from Germany recently reported that the incidence is in the range of 10 to 15 percent discordance (Luftner 2004). More commonly, the direction tends to be negative to positive, rather than positive to negative. This probably does warrant rebiopsying patients, specifically when you're running out of options and when a biopsy doesn't represent a major ordeal for the patient.

► **DR LOVE:** Let's talk about the typical case of a patient who doesn't have rapidly progressive, visceral, symptomatic metastatic disease that requires an immediate response — the patient who's had AC/paclitaxel, a very common adjuvant regimen in patients who relapse. Starting with John, in patients with ER-negative, HER2-negative disease, how have you thought through the decision at that point? And did your thought process change after you saw the bevacizumab data (Miller 2005a)?

► **DR MACKEY:** The reality is, we have a lot of patients treated with an anthracycline and a taxane in the adjuvant setting who relapse. At the time of relapse, it's always nice to be able to offer them an option where they don't lose their hair and they can have outpatient oral therapy. So we've made a major shift to first-line capecitabine. It's a well-tolerated, often very effective option. Unlike the data we're getting from the vinorelbine and the gemcitabine studies, some of these patients have a tremendous prolonged response. I'm not saying the median times to progression are substantially greater, but we are seeing at two and a half and three and four years people who are still on at cycle 70 of capecitabine.

► **DR LOVE:** We know there are reimbursement and cost issues that enter

into this, but looking at the pure science in terms of decision-making, John, what about bevacizumab? Would you combine it with capecitabine? Where, right now, would you utilize it in the metastatic setting?

► **DR MACKEY:** There are two ways to look at the bevacizumab data. What makes it particularly exciting is that it's a new therapeutic target. We've introduced antiangiogenic therapy. But if you look at ways of beating single-agent paclitaxel at 175 mg/m² every three weeks, bevacizumab is number six on the list. The excitement is because of the possibility of a new mechanism, almost as much as the improved progression-free and overall survival (Miller 2005a). Until such time as we have bevacizumab available for breast cancer treatment in Canada, which it currently is not, we are stuck with looking at what provides optimal survival with the agents that we have. I apologize. We have a pragmatic barrier here.

► **DR LOVE:** Andy, how do you approach patients like this, and where does bevacizumab fit in?

► **DR SEIDMAN:** Clearly, there are patients who have minimal and sometimes no symptoms of disease for whom hormones are just not the right choice. Their disease is ER/PR-negative, or you've exhausted all of your reasonable hormonal options. In an effort not to make the treatment worse than the disease, oral capecitabine is a very attractive option. Patients live their lives at home, not in your oncology clinic.

We will have some data on this from a Mexican oncology group trial that was unfortunately presented way too prematurely at ASCO within the last couple of years (Soto 2003). This was a randomized study of capecitabine

first, followed by taxane, a taxane first followed by capecitabine, or the combination of taxane and capecitabine. With mature results from that trial, maybe we'll be more reassured that using capecitabine as monotherapy, as chapter one, is perfectly appropriate.

► **DR LOVE:** Andy, you're saying that in patients who've had prior dose-dense ACT, in general, you're going to start with capecitabine. Is bevacizumab going to work its way into the algorithm of a patient like that?

► **DR SEIDMAN:** When I think about what to use after adjuvant anthracycline/taxane-based therapy, the thing I think mostly about is how long it has been since they've completed that therapy.

If it's been a relatively short period of time — there's nothing magic about one year, but we often use that as a benchmark — I'm not that enthusiastic about going back and using a taxane or an anthracycline again. At that particular moment in time, capecitabine is an obvious default option. Given the increased response rate seen with bevacizumab when added to capecitabine (Miller 2005b; [7.1]), as long as your insurance companies will recognize the benefits seen with this drug in combination with other agents, and in other diseases, and in combination with paclitaxel in the first-line setting for metastatic disease, it definitely seems to be a rational option.

► **DR LOVE:** With bevacizumab, the cost and reimbursement issues obviously are out on the table. We don't know how that's going to play out. We're focused on the science today, but I think, obviously, that's a huge issue. Aman, same question: Patient has had prior AC/paclitaxel, asymptomatic metastatic disease. What's your algorithm? And is bevacizumab going to fit into it?

► **DR BUZDAR:** I discuss the data, which were presented by Kathy Miller, with these types of patients. I think the point that Andy made is very important: If the patient failed very shortly after receiving the taxane in the adjuvant setting, then I think capecitabine might be a better option, and the taxane might not be the appropriate option. But if the patient has a longer disease-free interval, I think we need to discuss that because of two points. There is substantial improvement in time to progression and early evidence to suggest that bevacizumab may have a favorable impact on survival (Miller 2005a).

► **DR LOVE:** Again, cost aside, Aman, would you bring up the issue of bevacizumab plus capecitabine?

► **DR BUZDAR:** With bevacizumab and capecitabine, I think the data, which were in a somewhat more heavily treated patient population, unfortunately, did not pan out into longer control of disease or any favorable impact on the survival. Although investigator-reported data and independently peer-reviewed data did show that women who received the combination of bevacizumab and capecitabine had a higher objective regression of their disease, it somehow did not translate into a time to progression or survival benefit (Miller 2005b; [7.1]).

► **DR LOVE:** Peter, how do you approach the choice of chemotherapy in a patient who received prior AC/paclitaxel?

► **DR RAVDIN:** Actually, capecitabine is my first choice because of all the reasons that have already been stated: low toxicity and the sometimes very long duration of responses. One thing I've been doing more is thinking about new agents in Phase I testing very early in those patients who don't have threatening disease. I always used to give these as fifth- and sixth-line therapy,

but by then, eligibility issues come up: central nervous system metastases, bone marrow problems.

I've recently become aware of how many people have been disappointed in the idea that they wanted to receive something new, but it was only thought of when they were so far down the road and had other comorbid problems that they were no longer eligible. So I often tell people who are two or three treatments in: If we're going to try a wild card, now is the time to try it, when you're in relatively good shape; let's not wait until your eligibility might be in question. ■

7.1

Phase III Randomized Trial of Capecitabine with or without Bevacizumab in Patients with Previously Treated Metastatic Breast Cancer

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

Cap = capecitabine; bev = bevacizumab
ORR = overall response rate; inv = investigator
IRF = independent review facility

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

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Case 8: From the practice of Dr Pamela Drullinsky, Rockville Center, New York

A 35-year-old woman with a 3.5-cm, ER/PR-positive, HER2-positive infiltrating ductal carcinoma and two positive sentinel lymph nodes treated on the nontrastuzumab-containing arm of the Intergroup N9831 trial

► **DR DRULLINSKY:** This 35-year-old woman developed a mass during her third pregnancy, which was ignored by her obstetrician because it was felt to be related to pregnancy changes. Then, after delivery, the mass persisted. It turned out to be a 3.5-centimeter, moderately differentiated infiltrating ductal cancer, with two sentinel lymph nodes positive for cancer. It was estrogen receptor-positive, progesterone receptor-positive, and HER2-positive by FISH.

We were participating in the CALGB trial of adjuvant trastuzumab, and she agreed to enter the study. She was randomly assigned to no trastuzumab, and she received AC times four and weekly paclitaxel for 12 weeks. She finished her therapy in January 2005, at which point she was premenopausal, and the question came up of whether we should go with tamoxifen or anastrozole and goserelin.

Since the tumor was 3.5 centimeters, two lymph nodes were positive and she had not received trastuzumab, I put her on anastrozole and goserelin, knowing that it's not standard practice in this country but based on some preliminary information on aromatase inhibitors in HER2-positive disease. Then, after the ASCO meeting, we actually called her back, and she's being provided trastuzumab for a year.

► **DR LOVE:** A number of questions come up about this case. First, let's start with

the hormone therapy. Even though, as you said, it's certainly not standard, I can tell you from our Patterns of Care studies that probably about a third of the oncologists in the United States would have done what was done here, in terms of using an LHRH agonist plus an aromatase inhibitor in a high-risk younger woman with a HER2-positive tumor. Rowan, what are your thoughts about that, off protocol?

► **DR CHLEBOWSKI:** The data you have to support it are a couple of Phase II trials in metastatic disease with less than 100 patients. So, in a certain sense, there's very limited information. Alternatively, you could give ovarian suppression plus tamoxifen. That's what we've been doing. You deviate off these protocols in various different ways. In women under 40 with hormone receptor-positive disease, we're routinely doing ovarian suppression with tamoxifen. We haven't utilized the combination of aromatase inhibitors with ovarian suppression yet. But I can see how it may not be an unreasonable extrapolation to do so.

People should also know about a trial in the abstract book from the San Antonio Breast Cancer Conference a couple years ago. It was a randomized trial in metastatic disease, showing a benefit for ovarian suppression plus anastrozole versus ovarian suppression plus tamoxifen (Milla-Santos 2000). But that was a withdrawn abstract. It's gotten into

Medscape, and it's very difficult to pull it once it's out on the internet.

► **DR LOVE:** This also gets into the issue of when to pull the trigger on a therapy that hasn't been proven in a Phase III study. For the last few years prior to the release of the data from the adjuvant trastuzumab trials, I was asking research leaders on our audio series about patients like these, "Should you use trastuzumab off study?" They very strongly said, "No. Put the patient on a trial. If not, you don't use trastuzumab."

Now it's been proven to reduce the relapse rate, and it raises the question of how much evidence is enough when you are dealing with a patient like this woman, with a very high risk of relapse.

So, even though you say there are only 100 patients in these Phase II trials, there are also thousands of postmenopausal women who have benefited from the aromatase inhibitors, and other people would say, "We're making the patient postmenopausal, so let's use the best hormonal therapy for postmenopausal women."

Tom, what are your thoughts about this — not just specifically of a premenopausal woman with high-risk ER-positive disease — but when do we pull the trigger?

► **DR BUDD:** It is an interesting question. I think we have no option but to try to be evidence-based, when we have evidence. Now, there are all too many situations in clinical medicine where we don't have data. And we have to reason in other ways — by analogy to similar situations, by what we know about the biology of the disease and so on.

In the adjuvant treatment of any disease, you can't monitor the disease to see what's happening. The only way to approach this scientifically is with randomized trials that have

control groups. So in clinical practice in general, I try to stick to what's been proven. We've gone through this many other times with adjuvant chemotherapy for node-negative breast cancer and so on.

What was the wrong thing to do 10 or 15 years ago is now the right thing to do. You're going to make mistakes if you don't go on the basis of evidence. Where you have evidence, you ought to follow it. And where you don't have evidence, that's where you can be more creative.

► **DR LOVE:** With this woman's disease being HER2-positive, you have the question of whether tamoxifen is going to be a little less effective. What specific hormone therapy, in general, would you be utilizing off protocol?

► **DR BUDD:** I don't want to criticize, and I understand where you're coming from. I think it's quite possible — maybe even probable — that an AI and LHRH agonist will turn out to be the best treatment for this patient, and the International Breast Cancer Study Group has shown these younger patients with ER-positive disease have a bad prognosis, so some improvement in hormonal therapy is needed.

Off protocol, in general, I use tamoxifen in premenopausal women. Whether ovarian ablation adds — in terms of efficacy — to chemotherapy or tamoxifen, I don't think we know. We do know it adds toxicity. That's what this ECOG trial (E3193) in node-negative breast cancer showed (Robert 2003). It's quite possible that it will end up adding efficacy, if we can select the right patient population, unconfounded by early menopause from chemotherapy.

► **DR LOVE:** Any situations like this where you might use an LHRH agonist plus an aromatase inhibitor off study, Jenny?

► **DR CHANG:** We'll try not to and try to put them on a study. We have several ongoing studies, including the SOFT study (8.1) to consider. We like to practice evidence-based medicine, and yes, I tend to agree with Dr Budd, but it's very difficult. I understand where you're coming from, and you're probably making the right choice, but it's not evidence-based.

► **DR LOVE:** Eric?

► **DR WINER:** I wouldn't go so far as to say that it's the right choice. I think that it is a choice. I think there are really four choices. One is tamoxifen. One is tamoxifen plus ovarian suppression. The third is ovarian suppression alone, which you would argue to do if you thought tamoxifen might have a stimulatory effect on the tumor, and you acknowledge that we don't know that adding an aromatase inhibitor to ovarian suppression in a premenopausal woman improves outcome. The fourth is doing what you've done.

Trials examining these various issues are ongoing. I don't think there's a

right or wrong. I probably would give her ovarian suppression and tamoxifen outside of a trial. She might be the type of person whom I would switch to an aromatase inhibitor with ovarian suppression after a couple of years, even though she was premenopausal at the time of diagnosis.

I think this is a trap that we all fall into — and I'm not suggesting that you did any more than anyone else — to bring a lot of emotion into the picture when you're dealing with a young woman. I just think we have to make sure that doesn't influence us to make decisions that we would later regret.

► **DR LOVE:** Let's discuss adjuvant trastuzumab. Would you consider adjuvant trastuzumab for a small (under a centimeter) node-negative tumor? Clearly, that patient would not have fallen into the eligibility criteria of the studies that were reported.

► **DR CHANG:** Basically, it depends on her risk of relapse. If she has a small tumor with a low risk of relapse, then

8.1 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)	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

* The PERCHE trial has closed. Accrual as of December 16, 2005 = 15/1,750.

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

the addition of trastuzumab probably adds very little.

▶ **DR LOVE:** Eric?

▶ **DR WINER:** I don't believe the benefits of trastuzumab will vary according to nodal status, but the risk of recurrence will vary according to nodal status and tumor size. I find it very hard to imagine treating a woman with a T1a-N0 cancer with either chemotherapy or trastuzumab.

Apart from that, I'm generally comfortable with the use of adjuvant trastuzumab in the majority of patients, based on what we know so far, although I think we have to watch the toxicity profile closely over time. One group that I do still have some concerns about are women with relatively small — under two to three centimeters — ER-positive, HER2-positive cancers because I'm not so clear that I know the event rate and the benefits of hormonal therapy, specifically the aromatase inhibitors, in that group of women.

▶ **DR LOVE:** How about the issue of delayed trastuzumab in patients treated previously?

▶ **DR WINER:** In terms of the woman with five positive nodes who is some time out, we've generally taken the approach that within six months we would offer treatment. Up to a year we'd consider it. I have trouble doing it beyond a year. One can't be too rigid here. I think the thing to remember is, for that woman with five positive nodes who is now two years out, her risk of recurrence is actually substantially lower than it was at the time of diagnosis because events in HER2-positive patients occur early on. So there is good reason to think that the benefit may be much less for her.

▶ **DR LOVE:** Tom?

▶ **DR BUDD:** I'd use adjuvant trastuzumab in patients with tumors that are T1c and above and within six months post-treatment.

▶ **DR LOVE:** Rowan?

▶ **DR CHLEBOWSKI:** It would be size-dependent, and six months is also my cutoff. The other thing for me is ejection fraction, especially dealing with the older individual. In an older individual, I like to see a higher ejection fraction to put that into the risk-benefit calculation.

▶ **DR LOVE:** We've really become sensitized to the time course of recurrence because of the aromatase inhibitor data. I wonder if, as time goes on, postadjuvant trastuzumab is going to start to fit into that model, just like we're looking now whether to start letrozole at six years. We're looking at the risk and risk reduction. Are we going to fall into the same type of model?

▶ **DR WINER:** I think the fundamental difference here and the reason we saw such big differences early on is that events occur early in patients with HER2-positive disease and ER-negative breast cancer. We're really talking about somewhat different diseases than the patient who has ER/PR-positive, HER2-negative breast cancer. So I think we're just going to have to see over time.

The other comment is that there is great interest in looking at nonanthracycline-containing regimens. The whole way we look at this may be different in a few years because, in fact, for that patient at low risk, on some level — not that I would do this at the moment — I'm more interested in giving her trastuzumab than doxorubicin. We'll have to see how all this plays out.

▶ **DR LOVE:** In the trastuzumab studies, about half of those patients were also

ER-positive. What about the natural history of ER-positive, HER2-positive disease?

► **DR WINER:** We know much less about that than we would like to. The one thing we do know from the metastatic trials, the preoperative trials and now the adjuvant trials is that the benefits of trastuzumab seem to be similar in ER-negative and ER-positive disease. I think

what we're less clear about is the risk of recurrence because we're still not sure how much hormonal therapy adds in that situation, particularly if the aromatase inhibitors turn out to be as effective in HER2-positive as in HER2-negative disease. Then those women are starting from a much lower risk of recurrence than the patient with ER-negative, HER2-positive breast cancer. ■

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EVALUATION FORM

Proceedings from Two 2005 *Breast Cancer Update* Medical Oncology Educational Forums

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GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data, patterns of care data and patients' perspectives on breast cancer treatment decisions. 5 4 3 2 1 N/A
- Counsel women with low-risk invasive disease about the absolute risks and benefits of adjuvant systemic chemotherapy, and describe the potential utility of a predictive assay to help guide these discussions. 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 about switching or sequencing aromatase inhibitors after tamoxifen. 5 4 3 2 1 N/A
- Counsel premenopausal women about the risks and benefits of adjuvant ovarian ablation in combination with tamoxifen or aromatase inhibition. 5 4 3 2 1 N/A
- Distinguish the risk-to-benefit profiles of chemotherapeutic agents and combinations to determine a management algorithm for metastatic breast cancer. 5 4 3 2 1 N/A
- Develop and explain a management strategy for therapy for patients with ER-positive, metastatic disease including sequencing of hormonal therapies. 5 4 3 2 1 N/A
- Describe and implement an algorithm for treatment of HER2-positive breast cancer. 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of subject matter	Effectiveness as an educator
G Thomas Budd, MD	5 4 3 2 1	5 4 3 2 1
Aman U Buzdar, MD	5 4 3 2 1	5 4 3 2 1
Jenny C Chang, MD	5 4 3 2 1	5 4 3 2 1
Rowan T Chlebowski, MD, PhD	5 4 3 2 1	5 4 3 2 1
William J Gradishar, MD	5 4 3 2 1	5 4 3 2 1
Daniel F Hayes, MD	5 4 3 2 1	5 4 3 2 1
John Mackey, MD	5 4 3 2 1	5 4 3 2 1
Kathy D Miller, MD	5 4 3 2 1	5 4 3 2 1
C Kent Osborne, MD	5 4 3 2 1	5 4 3 2 1
Peter M Ravdin, MD, PhD	5 4 3 2 1	5 4 3 2 1
Andrew D Seidman, MD	5 4 3 2 1	5 4 3 2 1
Charles L Vogel, 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

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

EVALUATION FORM

Proceedings from Two 2005 *Breast Cancer Update* Medical Oncology Educational Forums

REQUEST FOR CREDIT — please print clearly

Name: Specialty:

Degree:

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

Medical License/ME Number: Last 4 Digits of SSN (required):

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Telephone: Fax:

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

Signature: Date:

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

Yes No

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

.....

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

.....

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

.....

Additional comments about this activity:

.....

FOLLOW-UP

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

Yes, I am willing to participate in a follow-up survey. No, I am not willing to participate in a follow-up survey.

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Breast Cancer®

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