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Meet The Professors

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

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

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of these advances. In order to incorporate research advances into developing treatment strategies for patients, the CME program *Meet The Professors* utilizes case-based discussions between community oncologists and research leaders.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- 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 with ER-positive breast cancer about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the relevance to patients considering adjuvant chemotherapy regimens.
- Identify patients with metastatic breast cancer for whom single-agent versus combination chemotherapy would be and counsel them regarding the risk/benefit profiles of chemotherapeutic agents/regimens.
- Develop and explain a management strategy for treatment of ER-positive breast cancer in the metastatic setting.
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant and metastatic settings.

EDUCATIONAL METHOD

To receive CME credit, the participant should listen to the CDs or tapes, review the monograph and complete the evaluation form.

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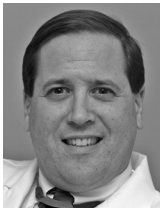

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
aminoglutethimide	Cytadren®	Novartis Pharmaceuticals
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan® Neosar®	Bristol-Myers Squibb Company Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin® Rubex®	Pfizer Inc Bristol-Myers Squibb Company
epirubicin hydrochloride	Ellence®	Pfizer Inc
exemestane	Aromasin®	Pfizer Inc
filgrastim	Neupogen®	Amgen Inc
fluorouracil (5-FU)	Various	Various
fluoxymesterone	Halotestin®	Pfizer Inc
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly and Company
goserelin acetate	Zoladex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals
megestrol acetate	Megace®	Bristol-Myers Squibb Company
methotrexate	Various	Various
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pegfilgrastim	Neulasta®	Amgen Inc
risedronate	Actonel®	Procter and Gamble
rofecoxib	Vioxx®*	Merck and Company Inc
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
temozolomide	Temodar®	Schering-Plough Corporation
trastuzumab	Herceptin®	Genentech BioOncology
triptorelin pamoate	Trelstar™	Pfizer Inc
vinorelbine	Navelbine®	GlaxoSmithKline
zoledronic acid	Zometa®	Novartis Pharmaceuticals

* Discontinued by manufacturer

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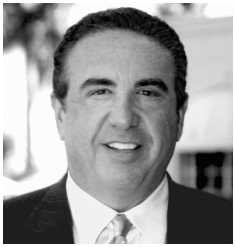

Editor's Note

Looking for pearls

From my perspective, the most enjoyable part of our *Meet The Professors* audio series is the individual premeeting teleconferences I hold with the community-based oncologists who will be presenting cases to faculty members during our recording sessions. Sure the daylong events themselves are exciting and thought-provoking, but these one-on-one conversations — during which we sift through a variety of potential patient histories and try to pick out the most controversial and instructive to spring upon the unknowing research leaders — are truly what I look forward to most.

The reason for this is simple: Our CME group has been fortunate to work with many very astute practitioners who seem to share my passion for delving deeply into the critical issues that shape oncology education and practice. Each time we attempt to identify actual cases, I am amazed at how adept these physicians are at selecting interesting patients. Recently, after hearing Dr Jim Wade's saga of an 83-year-old woman with ER-negative, "HER2-negative" breast cancer, I knew we had another winner.

This woman's case — like many of those presented by these knowledgeable clinicians — is far more instructive than any journal article or meeting presentation. From the moment this woman was diagnosed with Stage II disease, her situation posed a fortunately uncommon dilemma. During the discussion, faculty members Adam Brufsky and Dan Budman quickly pulled out their Palm Pilots to "run the numbers" using Peter Ravdin's Adjuvant! program. Based on these assessments, both believed that adjuvant chemotherapy would have minimal impact on long-term mortality because of the woman's age and competing causes of mortality.

The research leaders then suggested that they would have discouraged this patient from being treated, and Leon Dragon — another community oncologist at the meeting — noted that even if the patient wished to have treatment, chemotherapy had an adverse therapeutic risk-to-benefit ratio and consumed resources that might better be utilized elsewhere.

Nonetheless, after discussing the marginal benefits of treatment, Dr Wade and his patient embarked on four courses of AC, which she tolerated without any problems. Like many selfless older people, this patient's primary concern regarding therapy was that it might cause side effects that would interfere with her ability to provide care for her infirm husband.

I set up the geriatrics education program at the University of Miami School of Medicine in the mid-1980s, and perhaps the most important message from that experience is that you can't make generalizations about older patients any more than you can about younger ones, and that most people tend to retain their attitudes and personalities with time.

Nonproductive people don't suddenly get motivated when they become older, and go-getters remain go-getters regardless of age. This woman obviously was a dynamo all her life and was so motivated to avoid mastectomy that she commuted 40 miles each way to receive postlumpectomy radiation therapy.

The story becomes even more complicated three years after initial diagnosis, when the patient developed metastatic disease. Again facing chemotherapy, this woman's physician (Dr Wade) had a hypothesis that, if confirmed, would greatly impact her quality of life and ability to provide care for her husband.

In spite of an IHC assay that was read as "0", Dr Wade ordered a FISH test that subsequently revealed HER2 gene amplification. The patient was treated with trastuzumab — both monotherapy and in combination with chemotherapy — and experienced significant tumor response with minimal treatment-related morbidity. Like many patients successfully treated with trastuzumab for metastatic disease, this woman's ultimate problem was CNS metastases, and Dr Wade comments on her valor in facing this situation:

"She's a profile in courage. She is strong, stoic and proud. The best example is positioning her furniture around the house so she wouldn't have to use a cane or a walker. She's a remarkable woman who has taught us a lot about how brave many of these more senior citizens are. I don't know if I could have done nearly what she has during the course of her illness."

All of us learn early on after medical school that optimal continuing education is a combination of studying data, listening to the perspectives of our colleagues and just taking care of patients. This case history typifies the management gems that we hope to uncover during these *Meet The Professors* programs, and it is gratifying to be able to make such instructive discussions available to so many clinicians in practice.

—Neil Love, MD
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Select publications

Herrero A et al. **High incidence of brain metastases at the time of death in women with metastatic breast cancer treated with trastuzumab.** *Proc ASCO* 2004;**Abstract 765**.

Kirsch DG et al. **Brain metastases from breast cancer: Survival by HER2 status in the trastuzumab era.** *Proc ASCO* 2004;**Abstract 779**.

Lindrud S et al. **Central nervous system progression during systemic response to trastuzumab, humanized anti-HER-2/neu antibody, plus paclitaxel in a woman with refractory metastatic breast cancer.** *Breast J* 2003;9(2):116-9. **Abstract**

Osoba D et al. **Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer.** *J Clin Oncol* 2002;20(14):3106-13. **Abstract**

Paik S et al. **Real world performance of HER2 testing — National Surgical Adjuvant Breast and Bowel Project experience.** *J Natl Cancer Inst* 2002;94(11):852-4. **Abstract**

Ravdin PM et al. **Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.** *J Clin Oncol* 2001;19(4):980-91. **Abstract**

Roche PC et al. **Concordance between local and central laboratory HER2 testing in the breast Intergroup trial N9831.** *J Natl Cancer Inst* 2002;94(11):855-7. **Abstract**

Shmueli E et al. **Central nervous system progression among patients with metastatic breast cancer responding to trastuzumab treatment.** *Eur J Cancer* 2004;40(3):379-82. **Abstract**

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-92. **Abstract**

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. **Abstract**

CASE 1: A 38-year-old premenopausal patient with ER-positive, PR-negative, HER2-positive, node-positive breast cancer (from the practice of Dr Rafat H Ansari)

- Presented with a palpable lesion in her left breast
- Mammography revealed 1.7-centimeter, 1.5-centimeter and 0.8-centimeter lesions in the same quadrant
- Underwent a modified radical mastectomy
- SLNB-positive, with 12/14 axillary lymph nodes involved
- ER was 10 percent; PR was negative
- HER2-positive via FISH
- Metastatic workup including a normal bone scan, CT scan of the chest and abdomen, and echocardiogram

Key discussion points:

1. Protocol and nonprotocol options for adjuvant trastuzumab
2. Role of adjuvant ovarian ablation in addition to tamoxifen or an aromatase inhibitor in premenopausal patients
3. Use and selection of growth factor support
4. Switching patients from tamoxifen to an aromatase inhibitor

DR ANSARI: This 38-year-old premenopausal woman presented with a palpable lesion in her left breast. Mammography demonstrated three lesions in the same quadrant: 1.7-centimeter, 1.5-centimeter and 0.8-centimeter.

She underwent a modified radical mastectomy, with sentinel lymph node biopsy and complete axillary dissection. Twelve out of 14 axillary lymph nodes were positive for metastases. Her tumor was 10 percent ER-positive, PR-negative, and HER2 gene amplification by FISH was positive.

DR LOVE: Can you describe her lifestyle and life circumstances?

DR ANSARI: She was married and had three small children; the youngest was about six years old at the time of her diagnosis.

She was concerned about her appearance and after the mastectomy, she underwent immediate reconstruction, including a tummy tuck and flap. She was a manager of a store and wanted to maintain her appearance for her job.

DR LOVE: Adam, this is a very challenging case involving a young woman with 12 positive nodes. What are your thoughts?

DR BRUFSKY: We have clinical trials available for her, with trastuzumab in some of the arms. BCIRG trial 006 — AC/docetaxel, AC/docetaxel plus one year of trastuzumab, or carboplatin/docetaxel plus trastuzumab — would have been our first choice, but that trial just closed. At our institution

Trials of Adjuvant Trastuzumab in the Treatment of Breast Cancer

Study name	Target accrual	Arms
BCIRG-006 (Closed)	3,150	ARM 1: AC x 4 → docetaxel x 4 ARM 2: AC x 4 → docetaxel x 4 + H (qwk x 12) → H (qwk x 40) ARM 3: (docetaxel + C) x 6 + H (qwk x 18) → H (qwk x 34)
NCCTG-N9831 CLB-49909 E-N9831 SWOG-N9831	3,300	ARM 1: AC x 4 → paclitaxel qwk x 12 ARM 2: AC x 4 → paclitaxel qwk x 12 → H (qwk x 52) ARM 3: AC x 4 → (paclitaxel + H) qwk x 12 → H qwk x 40
BIG-01-01 EORTC-10011 HERA	4,482	(Randomization after approved neoadjuvant or adjuvant chemotherapy) ARM 1: H q3wk x 1 y ARM 2: H q3wk x 2 y ARM 3: No H
NSABP-B-31	2,700	ARM 1: AC x 4 → paclitaxel q3wk x 4 or paclitaxel qwk x 12 ARM 2: AC x 4 → q3wk + H qwk x 1 y

AC = doxorubicin/cyclophosphamide; C = cisplatin or carboplatin; H = trastuzumab

SOURCE: NCI Physician Data Query, October 2004.

we would offer her participation in NSABP-B-31, which randomly assigns patients to AC followed by paclitaxel alone or with one year of trastuzumab.

I would not utilize adjuvant trastuzumab in this woman off protocol because the data from NSABP-B-31 presented at the 2003 San Antonio Breast Cancer Symposium suggested that women receiving AC → paclitaxel plus trastuzumab had a clinical congestive heart failure or cardiac death rate of approximately 3.5 percent.

I would probably administer a regimen containing AC and a taxane. The TAC regimen would be reasonable or AC followed by paclitaxel or docetaxel. I'll leave the dose-dense issue for Dr Budman.

DR LOVE: What about endocrine therapy?

DR BRUFSKY: We consider her ER-positive. In fact, the most recent St Gallen consensus conference indicated that staining over one percent was considered positive, so she was clearly ER-positive. I would treat her with tamoxifen after the chemotherapy.

Whether to use ovarian ablation in addition to tamoxifen is a controversial question. No has yet shown ovarian ablation after chemotherapy provides any benefit.

DR LOVE: Dan, would you use trastuzumab? What type of chemotherapy? What type of hormonal therapy? Let's assume she's still actively menstruating after chemotherapy.

DR BUDMAN: This is a difficult case. I assume you're going to stage her carefully, because having 12 positive nodes is almost tantamount to metastatic disease.

DR LOVE: Dr Ansari?

DR ANSARI: She had a metastatic workup done, which included a bone scan, CT scan of the chest and abdomen and an echocardiogram, and all were normal.

DR BUDMAN: For this woman we would strongly recommend Edith Perez's study, NCCTG-9831, in which the patient has two out of three chances of receiving trastuzumab. The cardiac events are noted very carefully in that trial. Patients are randomly assigned to AC followed by paclitaxel with or without trastuzumab, or AC followed by paclitaxel followed by trastuzumab. If anybody needs this type of study, it's this woman.

If that's not possible, I would offer dose-dense chemotherapy. In the New York area, we've been indoctrinated in dose-dense chemotherapy, and I think it's a very reason-

Three-Year Results of CALGB-9741, a Phase III Randomized Study Comparing Dose-Dense versus Conventional Scheduling and Sequential versus Combination Adjuvant Chemotherapy for Node-Positive Breast Cancer

Protocol IDs: CLB-9741, E-C9741, NCCTG-C9741, SWOG-C9741 (Closed)

ARM 1: A q3wk x 4 → T q3wk x 4 → C q3wk x 4
ARM 2: A q2wk x 4 → T q2wk x 4 → C q2wk x 4*
ARM 3: AC q3wk x 4 → T q3wk x 4
ARM 4: AC q2wk x 4 → T q2wk x 4*

*Filgrastim (G-CSF) is administered on days three through 10 after each dose of doxorubicin, paclitaxel and cyclophosphamide.

A = doxorubicin; T = paclitaxel; C = cyclophosphamide

Parameters	Dose-dense scheduling	Conventional scheduling	Response rate (*p*-value)
Disease-free survival	85%	81%	0.74 (0.010)
Overall survival	92%	90%	0.69 (0.013)

SOURCE: Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003; 21(8):1431-9. **Abstract**

able therapy. More than 3,000 patients were enrolled in CALGB-9741, and the dose-dense schedule clearly offers a benefit.

DR LOVE: Dose-dense AC followed by paclitaxel or sequential single agents?

DR BUDMAN: It's "dealer's choice" whether you use AC followed by paclitaxel or sequential. In young women, I usually administer AC together followed by paclitaxel. The combination frequently causes anemia, but younger women tolerate it well and it's over faster.

DR LOVE: Would you utilize filgrastim or pegfilgrastim?

DR BUDMAN: I use pegfilgrastim. Enough evolving data exist from the CHOP data, and we've never had a problem with pegfilgrastim. It makes quality of life better.

In terms of endocrine therapy, no evidence exists that castration following chemotherapy is effective. A very interesting trial that should be a very high priority is the SOFT trial. Women who remain premenopausal after chemotherapy receive tamoxifen, ovarian ablation with tamoxifen, or ovarian ablation with exemestane. The SOFT trial would also be a good choice for her, and it's available through CTSU.

DR LOVE: What about using that strategy in a nonprotocol situation, with an LHRH agonist plus an aromatase inhibitor? This woman has an ER-positive, PgR-negative tumor. We had some interesting data presented from the ATAC trial at the 2003 San Antonio meeting showing a particularly dramatic decrease in relapse rate using anastrozole. Any thoughts about that?

DR BUDMAN: We don't have the answer. We have no long-term data with aromatase inhibitors in young women. On the other hand, if anybody's at high risk for relapse, it's this woman.

DR WADE: I'd like to ask a question of Dr Budman or Dr Brufsky regarding equipoise in the Perez trial, recognizing that the standard arm is still the standard schedule of AC followed by paclitaxel. Another

Results of Analysis of Time to Recurrence in the ATAC Trial According to Estrogen and Progesterone Receptor Status

Receptor status	N	Anastrozole vs tamoxifen*
ER-positive, PgR-positive	5,704	0.82 (0.65-1.03)
ER-positive, PgR-negative	1,370	0.48 (0.33-0.71)
ER-negative, PgR-positive	220	0.79 (0.40-1.5)
ER-negative, PgR-negative	699	1.04 (0.73-1.47)

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

SOURCE: Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;**Abstract 4**.

randomized trial shows a modest but measurable improvement with the dose-dense utilization of those same drugs.

DR BUDMAN: In Edith's trial, the taxane is administered weekly. It may be that giving the weekly taxane is better than administering it every two weeks. We don't know that. At our institutions, we feel that it's a very reasonable therapy to offer.

DR LOVE: Dr Dragon?

DR DRAGON: Jim Wade brought up a very interesting point that was highlighted by a patient I put on NSABP-B-31 last week. She is a public health professional with a PhD, and she knew as much about the ongoing clinical trials as most physicians.

When I offered her participation in NSABP-B-31 and we discussed the arms and the dose-dense chemotherapy option, she pointed out that the nontrastuzumab arm did not receive dose-dense chemotherapy.

Was this a reasonable trial in which to be enrolled? I pointed out to her that NSABP-B-31 gives the treating physician the choice of paclitaxel schedule — either every three weeks or every week, which we have to elect at the time of randomization.

I felt that was a justifiable adjustment in the schedule, which may be most of the benefit in the dose-dense regimen. The Seidman study in the metastatic setting clearly highlights that paclitaxel every 21 days for four cycles is probably not the best administration schedule, which we've known for a long time.

It is a point of equipoise. If we push dose-dense chemotherapy to its limit, we will have to terminate most of the ongoing randomized clinical trials that have a standard treatment arm of AC followed by paclitaxel. It would be very disappointing to be in that position.

DR BERRY: Many patients don't want to enroll in clinical trials because often the trials don't address their concerns. With regard to targeted therapy, such as trastuzumab, I've actually taken the plunge and treated a number of women off study because they've had a horrible potential outcome like this woman.

I have given the taxanes in a dose-dense fashion along with the weekly trastuzumab until the taxane was finished, and then continued with trastuzumab every three weeks for a full year. Anecdotally, the three or four patients whom I've treated have been doing well.

It's a matter of being honest with the patients and making sure they understand that what we're doing is not a standard practice. We must make it clear that we are making a value judgment based on the risks.

We do not present it to women who are not willing to enroll in clinical trials. I've not

run into any trouble with cardiotoxicity. I monitor the MUGA scan every six months, and it has not been an issue.

I question whether 12 months is the correct duration of trastuzumab, and, in fact, the HERA study is evaluating 12 versus 24 months of trastuzumab. That's another question beyond whether you should use trastuzumab at all.

DR LOVE: Dan, in a woman who is still menstruating after chemotherapy, do you consider ovarian ablation an option? Do you consider ovarian ablation plus an aromatase inhibitor an option in this situation?

DR BUDMAN: No good data exist for ovarian ablation alone after chemotherapy. On the other hand, I believe the SOFT trial is the most interesting ongoing investigation and I would try to enroll that woman in it.

If she refuses I would have no objection to an aromatase inhibitor plus ovarian suppression or ablation because she has 12 positive nodes and we need to try everything possible.

DR DRAGON: I struggle over whether to offer adjuvant trastuzumab or not, because intuitively I have the sense it's the right thing to do.

We've been down that road before with bone marrow transplant, and we don't want to do that again. I would be reluctant to be drawn. We're attempting to be driven by data, and using clinical trial data is important to us. I think we need to learn the lesson one time only.

DR LOVE: Adam, what does the Adjuvant! model say? This woman is going to receive a taxane-containing chemotherapy regimen and tamoxifen. What's her risk of relapse and death?

DR BRUFSKY: Within 10 years, her risk of relapse is 88 to 89 percent with no therapy. AC followed by a taxane every three weeks followed by tamoxifen results in a risk reduction of about 42 percent.

DR LOVE: So she still has a residual relapse rate of 46 percent? Is anyone using endocrine therapy other than tamoxifen alone in this situation?

DR MERKEL: Outside of the constraints of NSABP-B-31, which would be my first choice, I would actually push for ovarian ablation with an aromatase inhibitor, because this HER2-positive tumor is the tumor phenotype for which I would least trust tamoxifen to provide any benefit.

DR LOVE: If she is still menstruating at the end of chemotherapy, you would use an LHRH agonist plus an aromatase inhibitor?

DR MERKEL: Yes.

DR NABHAN: Approximately 10 years ago, it would have been considered cruel not to offer a bone marrow transplant. We're being careful and not even offering ovarian ablation and an aromatase inhibitor when the risk of dying of breast cancer is significantly high. I would tend to offer ovarian ablation in this setting.

DR BERRY: I agree with Dr Merkel. If I were seriously thinking about utilizing ovarian ablation for this woman, I'd give an aromatase inhibitor as the follow-through.

DR LOVE: Adam, the woman has an ER-positive, PgR-negative, HER2-positive tumor. Are you more inclined to consider an LHRH agonist plus an aromatase inhibitor?

DR BRUFSKY: Before listening to the discussion, I wasn't thinking about an aromatase inhibitor, but I think the downside risk is not that high.

This woman's major cause of mortality in the next 10 years is breast cancer, and I'd probably want to be as aggressive as possible, understanding that we don't know the long-term cognitive effects of aromatase inhibitors in young women.

In her case an aromatase inhibitor is probably superior, at least in the postmenopausal setting, so I have no problem giving this woman an aromatase inhibitor and an LHRH agonist.

Before the NSABP-B-31 data came out, I treated 10 to 20 patients like this woman with trastuzumab off study. A few have had their ejection fractions go down.

Case follow-up:

- Elected to participate in BCIRG-006 but HER2 was FISH-negative by UCLA pathologists
- Received AC every two weeks for four cycles with growth factor support followed by paclitaxel every two weeks for four cycles
- Still menstruating after chemotherapy
- Received tamoxifen and goserelin
- Received risedronate due to declines in bone mineral density
- Currently doing well three years after diagnosis

Since B-31, I've stopped that, but two or three years from now when the data is complete, the docetaxel/carboplatin/trastuzumab arm of BCIRG-006 may become the standard of care for these women. That's something to consider if you're thinking of off-study therapy.

DR LOVE: Dr Ansari, can you give us a follow-up on what happened with this woman?

DR ANSARI: This lady was diagnosed in October 2001, so some of the trials and trial results we're talking about were not available at that time.

When I saw her, we had two trials available: BCIRG-006 and NSABP-B-31. The patient chose our BCIRG trial. According to that trial, her HER2 slides had to be sent to UCLA, and the results were available in five days. When we received the results, her HER2 was negative at UCLA, so she didn't qualify for that trial. She was treated outside the clinical trial with doxorubicin and cyclophosphamide every two weeks for four cycles with growth factor support followed by paclitaxel in a three-hour infusion every two weeks for four cycles. This was before the dose-dense regimen was published, but she did receive a dose-dense regimen.

At the conclusion of her chemotherapy, she was still menstruating and I started her on tamoxifen and goserelin. Her last follow-up visit with me was about three weeks ago and she is still on goserelin and tamoxifen. She's been receiving risedronate because her yearly bone mineral density assessment revealed some bone loss, but her scans are normal right now.

DR LOVE: I was fascinated by the fact that this woman received dose-dense AC → T before the 9741 trial was reported. I thought Dr Ansari had psychic abilities. Maybe you can talk a little bit about how this woman ended up receiving that therapy.

DR ANSARI: At that time, we were impressed by the data from Memorial Sloan-Kettering on the dose-dense regimen, even though it was not a randomized trial. We thought if we want to give her the most benefit outside of a clinical trial, maybe the dose-dense regimen would be appropriate.

She tolerated it very well. Since then we've had a lot of experience administering dose-dense chemotherapy, especially in patients with multiple positive lymph nodes. My experience is that with growth factor support — and we almost universally use pegfilgrastim — they tolerate therapy very well — probably better than with the every three-week schedule. Today, I would definitely offer these patients participation in B-31.

DR LOVE: Dan, a theme of this whole discussion is, "What are reasonable, evidence-based options to consider?" In this compelling situation involving a young mother with a poor prognosis after standard therapy,

is trastuzumab an option. It was a false-positive HER2, so trastuzumab is not an option. Another issue of dose-dense chemotherapy arose before the data was published.

As risk increases and age decreases, do you see people leaning more toward therapies that aren't fully proven? What are your thoughts about the approach to adjuvant therapy from that perspective?

DR BUDMAN: Well, you're "damned if you do and damned if you don't." Unfortunately, we have a fair idea of what the biology of this disease is, even though we don't know how to treat it well. Without trying to be conservative I always worry that we've gone down lots of paths before with a lot of different types of tumors and said, "This is the answer," and then it turns out that it really offers no major benefit.

It's nice to see that a winner can be picked out now and then. On the other hand, we do not have mature data. We've been wrong before, and we could be wrong again.

I would have pushed this woman as hard as I could to participate in a clinical trial. We desperately need to finish these trials in real time, which we're not doing.

DR LOVE: Any final comments on this case?

DR ANSARI: She has had three years of tamoxifen, and she's on goserelin. She is about 42 years old. New data coming out indicate that two to three years of tamoxifen followed by an aromatase inhibitor looks better than continuation of tamoxifen: Is it time to discontinue tamoxifen and put her on an aromatase inhibitor?

DR LOVE: You're talking about the switching issue, but this is a woman who's been made menopausal by an LHRH agonist. We're really getting out there a little bit. Adam?

DR BRUFSKY: What about convincing her to undergo an oophorectomy and then putting her on an aromatase inhibitor?

DR LOVE: Do you feel better about oophorectomy than just keeping her on goserelin?

DR BRUFSKY: Yeah, I do. It's more permanent. I've had women who were borderline suppressed in whom I've given an aromatase inhibitor and they actually began to menstruate again.

Aromatase inhibitors inhibit peripheral aromatase, so feedback on the ovaries is lost. Although the LHRH agonist causes suppression, in certain rare cases that may be overcome and menstruation resumes. For example, I've treated women who were perimenopausal from their chemotherapy who began to menstruate when switched to an aromatase inhibitor.

DR LOVE: So what would you do after the oophorectomy?

DR BRUFSKY: I would offer her an aromatase inhibitor.

DR LOVE: Would you have done that up front if she had an oophorectomy?

DR BRUFSKY: Yes.

DR LOVE: Dan?

DR BUDMAN: I probably would have given her tamoxifen in that setting. In light of her high risk, I'm not averse to giving her an aromatase inhibitor, as long as she is aware that we really don't know how it's going to affect a 40-year-old woman 20 years later.

DR LOVE: She's been on tamoxifen for three years. Would you switch her to an aromatase inhibitor?

DR BUDMAN: At that point, I would have done an oophorectomy because of quality-of-life issues. She doesn't have to worry about shots or whether she's going to break through on the LHRH agonist. Oophorectomy is eminently reasonable, and I'd probably give her an aromatase inhibitor as long as she's willing to accept the risk.

DR LOVE: Adam, the whole thought process has changed in the last year with the MA17 data evaluating letrozole after five years of tamoxifen. Now two trials have evaluated aromatase inhibitors after two or three years of tamoxifen — one with anastrozole, the other with exemestane.

The patient's residual risk over time becomes

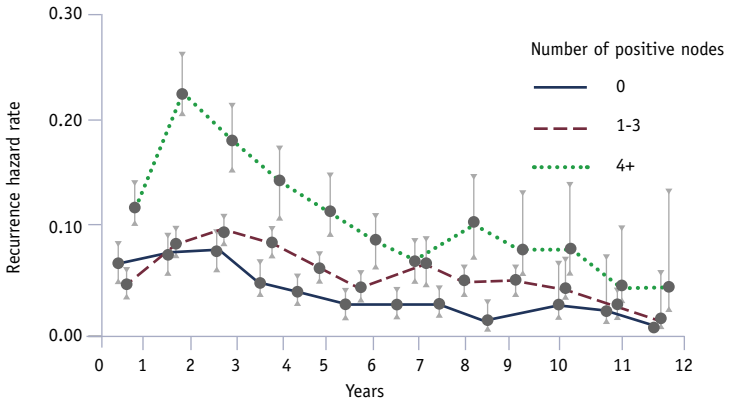
an important issue. This woman has 12 positive nodes, and she's made it three years free of disease. How much more residual risk of relapse does she have now? What would it be in five years, seven years, 10 years, and how does that factor into your decision-making?

DR BRUFSKY: I still think the residual risk with 12 nodes positive is substantial — even up to 10 years — and she would be a perfect candidate for MA17. She would definitely benefit from continued aromatase inhibition for five more years.

DR LOVE: Dan, any predictions about her relapse rate over time if she just continued with goserelin and tamoxifen for five years? How would that affect her risk for relapse?

DR BUDMAN: For patients with ER-positive disease, late relapses are not uncommon. The concern with the MA17 data is whether ER-positive patients with the best prognosis were selected because they are more likely to survive five years. That's a different issue because if this patient survives five years, I would be worried that her relapse rate would still be substantial because of her significant nodal status.

Annual Hazard Rates of Recurrence for Breast Cancer after Primary Therapy



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

Select publications

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Proc SABCS* 2003(Suppl 1);Abstract 3.

Castiglione-Gertsch M et al. **Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: A randomized trial.** *J Natl Cancer Inst* 2003;95(24):1833-46. Abstract

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. Abstract

Colleoni M et al. **Randomized comparison of adjuvant tamoxifen (Tam) versus no hormonal treatment for premenopausal women with node-positive (N+), early stage breast cancer: First results of International Breast Cancer Study Group Trial 13-93.** *Proc ASCO* 2004;**Abstract 532**.

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

Crawford J. **Once-per-cycle pegfilgrastim (Neulasta) for the management of chemotherapy-induced neutropenia.** *Semin Oncol* 2003;30(4 Suppl 13):24-30. **Abstract**

Davidson NE et al. **Chemohormonal therapy in premenopausal, node-positive, receptor-positive breast cancer: An Eastern Cooperative Oncology Group Phase III Intergroup trial (E5188,INT-0101).** *Proc ASCO* 2003;**Abstract 15**.

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Proc SABCS* 2003;82(Suppl 1);**Abstract 4**.

George S et al. **Fixed-dose pegfilgrastim is safe and allows neutrophil recovery in patients with non-Hodgkin's lymphoma.** *Leuk Lymphoma* 2003;44(10):1691-6. **Abstract**

Geyer CE Jr et al. **Cardiac safety analysis of the first stage of NSABP B-31, a randomized trial comparing the safety and efficacy of Adriamycin and cyclophosphamide (AC) followed by Taxol to that of AC followed by Taxol plus Herceptin in patients (Pts) with operable, node-positive (N+), HER-2 overexpressing breast cancer (HER2+BC).** *Proc SABCS* 2003;**Abstract 23**.

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

Grigg A et al. **Open-label, randomized study of pegfilgrastim vs. daily filgrastim as an adjunct to chemotherapy in elderly patients with non-Hodgkin's lymphoma.** *Leuk Lymphoma* 2003;44(9):1503-8. **Abstract**

Kaufmann M et al; Zoladex Early Breast Cancer Research Association (ZEBRA) Trialists' Group. **Survival analyses from the ZEBRA study. Goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer.** *Eur J Cancer* 2003;39(12):1711-7. **Abstract**

Perez EA et al. **Effect of doxorubicin plus cyclophosphamide on left ventricular ejection fraction in patients with breast cancer in the North Central Cancer Treatment Group N9831 Intergroup Adjuvant Trial.** *J Clin Oncol* 2004;22(18):3700-4. **Abstract**

Proceedings of the 8th International Conference on Primary Therapy of Early Breast Cancer. **St. Gallen, Switzerland, 12-15 March 2003.** *Breast* 2003;12(6):349-582. No abstract available

Ravdin PM et al. **Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.** *J Clin Oncol* 2001;19(4):980-91. **Abstract**

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Tan AR, Swain SM. **Ongoing adjuvant trials with trastuzumab in breast cancer.** *Semin Oncol* 2003;30(5 Suppl 16):54-64. **Abstract**

Tan-Chiu E, Piccart M. **Moving forward: Herceptin in the adjuvant setting.** *Oncology* 2002;63(Suppl 1):57-63. **Abstract**

CASE 2: A 57-year-old woman with ER/PR-positive, HER2-negative, node-negative breast cancer who gained 75 pounds while receiving adjuvant tamoxifen (from the practice of Dr John Berry)

- Presented with an abnormal mammogram
- Underwent lumpectomy with axillary node dissection for 3.2-centimeter tumor and no positive lymph nodes
- Tumor was 60 percent ER-positive, 40 percent PR-positive and HER2-negative by IHC
- Received adjuvant radiation therapy, AC x 4 followed by tamoxifen

Key discussion points:

1. Role of Onco*type* DX™ assay in clinical practice
2. Use of the Ravdin Adjuvant! model
3. Selection of adjuvant chemotherapy for patients with node-negative disease
4. Tamoxifen-associated weight gain
5. Side effects of adjuvant aromatase inhibitors and tamoxifen
6. Use of bisphosphonates in postmenopausal patients treated with an aromatase inhibitor

DR BERRY: The patient was 57 years old and working full time as a sales assistant. She is a rather large lady — approximately 5'8" and 180 pounds. She originally presented with an abnormal mammogram and subsequently went on to have a lumpectomy during which a 3.2-centimeter, T2 tumor was discovered. She also had an axillary dissection that revealed no positive lymph nodes. The tumor's ER was 60 percent positive, PR was 40 percent positive, and the Ki67 was eight percent. HER2 was negative by immunohistochemistry.

Overall, this woman had a positive attitude and was keen to have breast conservation. She was willing to undergo the rigors of radiation therapy and wanted to do anything she could to reduce her risk of recurrence.

DR LOVE: Adam, in general, how would you have thought through this situation?

DR BRUFSKY: My general approach in postmenopausal women with T2 tumors who are under 65 or 70 years of age is to offer them chemotherapy and an aromatase inhibitor. However, I think this is a case for which you could consider using the Onco*type* DX™ test.

DR LOVE: Can you talk a little bit more about that test?

DR BRUFSKY: It is a reverse transcriptase, PCR-based test based on paraffin-embedded tissue. A group in California selected 21 genes as the basis for the test. Expression

Ten-Year Distant Recurrence Rate According to Risk Group

Risk group	Percent of patients	10-y distant recurrence rate	95% confidence interval
Low	51%	6.8%*	4.0-9.6%
Intermediate	22%	14.3%	8.3-20.3%
High	27%	30.5%*	23.6-37.4%

*p < 0.00001 for comparison between high- and low-risk groups

SOURCE: Paik S. **Development and validation of a multi-gene RT-PCR assay for predicting recurrence in node negative, ER+, tamoxifen-treated breast cancer patients NSABP studies B-20 and B-14.** Presentation. San Antonio Breast Cancer Symposium, 2003;**Abstract 16**.

of this 21-gene set is converted into a recurrence score. This has been validated based on retrospective data from an NSABP study. If your recurrence score is high, then you have about a 30 percent chance of relapse with tamoxifen alone, versus 10 percent if your recurrence score is low. The idea is that you can then offer chemotherapy to women with higher recurrence scores.

DR LOVE: Let's say a woman fell into the high-risk range because of this assay or her tumor size, what type of chemotherapy would you recommend?

DR BRUFSKY: Generally, in postmenopausal women, I've offered anthracycline-based chemotherapy, such as AC x 4 or FEC 100 x 6 in a non-dose-dense fashion.

DR LOVE: Dan, do you use taxanes in patients with node-negative disease and if so, in what situations?

DR BUDMAN: At our institution, we are not convinced that this test, which costs more than $3,000, offers anything over Peter Ravdin's Adjuvant! program, which is free.

In the New York area, it depends on whom you talk to. Many of the physicians at Memorial believe a continuum exists between node-positive and node-negative disease and are even treating high-risk, node-negative disease off protocol with dose-dense AC → T. At our institution, we have been more conservative and are using the AC x 4 regimen.

Information from thousands of patients indicates that an aromatase inhibitor is good adjuvant therapy for a postmenopausal woman with ER-positive disease. Is there a downside? Sure. But I'm surprised that ASCO has not picked up on this more strongly, because if this were a chemotherapy drug, we'd be jumping up and down and saying, "Look how good it is!"

I am curious to know what the community experience is with the aromatase inhibitors. In my practice, they are exceedingly well tolerated, but a cohort of women has articular complaints and some are severe. I have taken two patients off of an aromatase inhibitor because they just could not tolerate it. Usually, these symptoms are reversible, but quality of life for those patients was poor.

DR LOVE: I'd like to hear from Dr Merkel because I know he had a very interesting point in this regard.

DR MERKEL: When I was enrolling patients in the ATAC trial, patients occasionally complained of aches and pains very much like what was reported. But as soon as the data became available and I started using anastrozole as first-line adjuvant hormonal therapy, I found I was seeing a lot more articular problems than earlier on.

It was only later that I realized I was using it in a different population of patients. When I was enrolling patients in ATAC, my particular referral pattern was to recommend the trial only to women who were not receiving chemotherapy.

Many of the women I have treated with anastrozole in the last two years received it after chemotherapy. Women can develop postchemotherapy arthralgia, typically three to six months after treatment. That is also the time when they finish their radiation therapy, if they're receiving it, and then their first month or two of anastrozole.

I think some of the aches and pains that I've been blaming on anastrozole are actually old chemotherapy-related arthralgias. Anastrozole may not always be at fault, and we need to try to help people through that three- to six-month window in hopes that things will improve.

DR LOVE: Adam, I thought that was a fascinating point. I had not previously heard anybody mention this as a possibility. What are your thoughts about it?

DR BRUFSKY: This is the first time I've heard it. I think it is an interesting point. The other point to make is that sometimes the arthralgias appear, at least anecdotally in my practice, to be idiosyncratic to a particular aromatase inhibitor.

DR LOVE: Dan, what are your thoughts on that?

DR BUDMAN: I have not heard of it before either, but I think it is particularly interesting. Also, it may be that the cytotoxics sensitize the joints in some manner that we are unaware of, but I have no biologic mechanism to account for that.

In my practice, if a patient is intolerant of a nonsteroidal aromatase inhibitor I try them on a steroidal one, or vice versa, and hope for the best. I have seen at least two women who went to a rheumatologist, underwent a complete workup and improved when we stopped the aromatase inhibitor.

DR LOVE: I want to discuss the issue of bisphosphonates with anastrozole. Adam, we do not have much data, but a presentation from the Austrian group at the 2002 San Antonio Breast Cancer Symposium showed a lot, if not all, of the bone loss associated with an aromatase inhibitor — in this situation an LHRH agonist plus anastrozole — was ameliorated using intravenous bisphosphonates. What are your thoughts about that study and where do you think this is all heading?

DR BRUFSKY: The Austrian study was conducted in premenopausal women who were made postmenopausal by an LHRH agonist. Every woman enrolled in the study received an LHRH agonist, and one half received tamoxifen and the other half received anastrozole. These patients then underwent a second randomization to zoledronic acid or observation, and the women who received zoledronic acid in that trial had less bone loss.

DR LOVE: If you see a woman with node-positive disease who has osteopenia or even osteoporosis, would you use anastrozole plus a bisphosphonate up front?

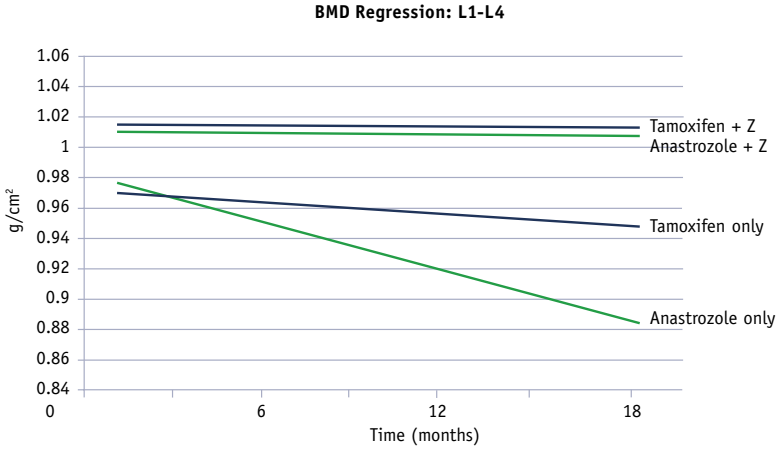
DR BRUFSKY: I think it depends on the degree of osteopenia and whether the woman has had fractures in the past. If someone comes in with a T-score of minus two and a half and has not had a fracture, I probably would treat her with a bisphosphonate and an aromatase inhibitor. I would hesitate in a woman with a T-score of minus three who already had a couple of fractures. In my opinion it is really a matter of degree more than anything.

DR LOVE: Dr Shulman?

DR SHULMAN: Dr Brufsky, you mentioned that you would consider using an aromatase inhibitor for a patient who has osteopenia. You also mentioned that you would not give an aromatase inhibitor to a woman who has already had bone fractures. I see a lot of women who have osteoporosis but do not have fractures yet. Right now, I'm staying away from adjuvant aromatase inhibitors in those patients, but what would you suggest?

DR BRUFSKY: It's a great question. If a woman is already taking a bisphosphonate, calcium and vitamin D, and you follow her closely, I don't see any reason why you could not give her an aromatase inhibitor as long as you use care. I think it is a reasonable thing to do because, in my opinion, the

Changes in Bone Mineral Density Caused by Anastrozole or Tamoxifen in Combination with Goserelin (± Zoledronic Acid) as Adjuvant Treatment for Hormone Receptor-Positive, Premenopausal Breast Cancer: Results of a Randomized Multicenter Trial (ABCSG-12).



Z = zoledronic acid

SOURCE: Gnant M. Presentation. San Antonio Breast Cancer Symposium, 2002.

benefits of aromatase inhibitors over tamoxifen in the adjuvant setting are starting to become substantial. We are now talking about absolute differences of three percent over tamoxifen. I think that is nearing the point at which I am willing to risk a little bit of bone loss.

DR LOVE: Dr Ansari?

DR ANSARI: In a patient with osteopenia or osteoporosis, will you select one aromatase inhibitor over the others because it seems to be less toxic to the bone?

DR LOVE: Adam, at one point we hoped that exemestane might be bone-sparing, but the recent study by Coombes suggested that may not be the case.

DR BRUFSKY: We hoped that because exemestane was steroidal and had some androgenic effects, it somehow would be less osteoporosis-inducing. However, it looks like exemestane does cause bone loss.

DR LOVE: Dr Berry, this woman was diagnosed prior to the ATAC study, what happened with her?

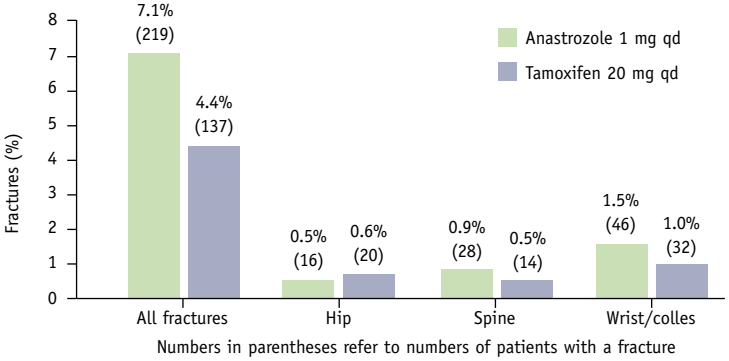
DR BERRY: She received four cycles of AC and, at that time, commenced on tamoxifen. She tolerated it well, but over the next two years she gained 75 pounds. She tried to diet and exercise, but was absolutely disgusted by her weight gain. Then, on routine follow-up examination in May of 2000, she developed obvious hepatomegaly.

DR LOVE: Did she describe a history of eating the same amount and yet gaining 75 pounds?

DR BERRY: No change occured in her lifestyle. She was working full time and was adamant that she had not increased her caloric intake. In fact, she was trying to reduce her eating and increase her exercising. Nonetheless, she steadily gained weight.

DR LOVE: Did any symptoms suggest metastatic disease?

Bone Fracture Adverse Events at the Updated Safety Analysis



SOURCE: Locker G. Poster. Lynn Sage Breast Cancer Symposium, 2003.

Case follow-up:

- Tolerated tamoxifen well but gained 75 pounds
- Weight loss unsuccessful with diet and exercise
- Developed hepatomegaly
- Discontinued tamoxifen and started on anastrozole off protocol
- Hepatomegaly resolved and over a two-year period she lost 60 pounds

DR BERRY: None whatsoever. She had no arthralgia, did not complain of shortness of breath, and no signs suggested that her performance status was deteriorating — other than the weight gain itself.

Her liver function tests were absolutely normal at that point in time, but on routine physical examination, I was able to appreciate a liver edge, which I had not appreciated before.

DR LOVE: Adam, how would you have thought through this situation?

DR BRUFSKY: In a woman who has had modestly high-risk breast cancer and hepatomegaly, even in the setting of a normal liver function test, I would think this is liver metastases and I would order a CT of the abdomen.

DR LOVE: What are your thoughts about the weight gain?

DR BRUFSKY: I think that we all debate the real cause of weight gain from tamoxifen. A lot of trials enrolled women who were perimenopausal and became postmenopausal, and it is often difficult to determine whether weight gain is attributable to becoming postmenopausal or caused by tamoxifen.

Anecdotally, in my practice I have treated several women who have gained 70 to 100 pounds or more while taking tamoxifen. Most initially weighed over 200 to 300

pounds, but when I've discontinued tamoxifen, they have lost the weight.

DR LOVE: Dan, I can remember a panel discussion at the Miami Breast Cancer Conference during which we were talking about tamoxifen and weight gain. Richard Margolese from the NSABP was in the audience and almost jumped out of his chair, "Tamoxifen doesn't cause weight gain. We have placebo-controlled studies." Does tamoxifen cause weight gain, Dan?

DR BUDMAN: Good question. The literature tells us that if weight gain occurs, it is usually 10 to 15 pounds at most, so this is particularly unusual. That is not to say that it cannot happen, but other factors may be involved.

DR LOVE: Dr Shulman?

DR SHULMAN: I had a patient who gained about 30 pounds, and when she stopped tamoxifen, she gradually returned to her baseline weight and refused to take the drug anymore.

DR LOVE: Let's find out what happened to this patient. Dr Berry?

DR BERRY: She had a CT scan that showed pronounced fatty infiltration of the liver. I have seen this before in a number of other patients, but not with such dramatic weight gain.

I suggested that we discontinue the tamoxifen and, because she was only a couple of years out, I offered her anastrozole as an alternative to reduce her risk of recurrence. She was willing to try that approach and started on anastrozole.

Within two follow-up office visits her liver, clinically, returned to normal and over the course of two years, she lost 60 pounds without a great deal of change in her diet and activity level. I'm convinced it was causally related and have seen a number of other women who have gained 25 to 30 pounds. The majority of women do not gain large amounts of weight on tamoxifen, but it happens often enough that I am not surprised to see it in this setting.

Select publications

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

Gnant M et al. **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: Results of a randomized multicenter trial.** *Breast Cancer Res Treat* 2002;**Abstract 12**.

Paik S et al. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** *Breast Cancer Res Treat* 2003;82(Suppl 1):10;**Abstract 16**.

Ravdin PM et al. **Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.** *J Clin Oncol* 2001;19(4):980-91. **Abstract**

CASE 3: A 47-year-old premenopausal woman with ER/PR-positive, HER2-positive, node-positive breast cancer (from the practice of Dean Tsarwhas, MD)

- Presented at 44 years of age with 1.8-centimeter primary tumor that was ER/PR-positive, HER2-positive (3+ by IHC)
- Four out of 31 lymph nodes were positive
- Treated with lumpectomy, adjuvant AC x 4 and radiation therapy
- Menstruation ceased after chemotherapy
- Treated with adjuvant tamoxifen

Key discussion points:

1. Role of ovarian ablation in premenopausal patients at high risk
2. Switching to an aromatase inhibitor after three years of tamoxifen versus up-front use of adjuvant aromatase inhibitors
3. Selection of hormonal therapy for the patient with HER2-positive disease
4. Choice of adjuvant chemotherapy for the patient with positive lymph nodes

DR TSARWHAS: This woman presented a few years ago. At that time, she was in her mid-forties and had Stage II breast cancer. Her primary tumor was 1.8 centimeters, ER/PR-positive and HER2-positive (3+ by IHC). She had four out of 31 lymph nodes involved. She was premenopausal and was treated with lumpectomy.

DR LOVE: Hy, if she presented today, how would you think through her therapy?

DR MUSS: I would try to enroll her in a clinical trial, but if she wasn't interested, several options for chemotherapy. Dose-dense AC → T or TAC are leading the pack in terms of the data, so I would pick one of those two regimens.

She would undergo breast irradiation and then I would try to enroll her in the SOFT trial. SOFT is for premenopausal women who maintain their menses, and the randomization is tamoxifen, tamoxifen/ovarian ablation, or ovarian ablation and an aromatase inhibitor. I think it's a very good trial because it's trying to answer some of the questions that we all want answered.

In a patient with four positive nodes, I would probably recommend ovarian ablation and either put her on tamoxifen or an aromatase inhibitor after discussing the pros and cons. Tamoxifen alone would also be perfectly reasonable. I would not put her on trastuzumab outside of a clinical trial, even though her tumor is IHC 3+.

I think the ovarian ablation data is going to eventually show that it helps a little bit, but I don't think it is going to be any type of "home run." However, in someone with four positive nodes and a tumor like this, I would lean toward making the jump. I really don't think it is going to have a drastic effect on

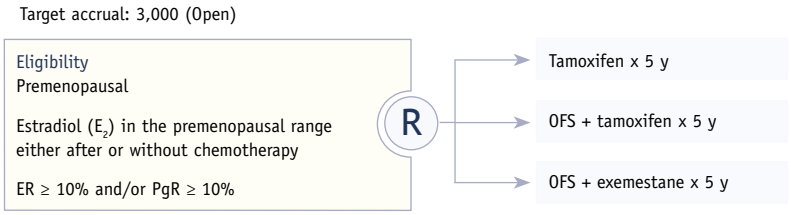
Comparison of Adjuvant Clinical Trial Results in Patients with Node-Positive Breast Cancer: BCIRG-001 (TAC versus FAC) and CALGB-9741 (Dose-Dense [DD] versus Conventional Scheduling [CS] Chemotherapy)

	BCIRG-001*		CALGB-9741**	
No. of patients **Median follow-up**	**1,491** **55 months** **TAC/FAC**		**1,973** **36 months** **DD/CS**	
	Risk ratio (*p*-value)	Percent reduction	Risk ratio (*p*-value)	Percent reduction
Disease-free survival	0.72 (0.001)	28%	0.74 (0.010)	26%
Overall survival	0.70 (0.008)	30%	0.69 (0.013)	31%

DD = dose dense
CS = conventional schedule

SOURCES: *Martin M. Presentation. San Antonio Breast Cancer Symposium, 2003;**Abstract 43**.
Citron M et al. *J Clin Oncol* 2003;21(7):1-9. **Abstract

Suppression of Ovarian Function Trial (SOFT)



OFS = ovarian function suppression using triptorelin x 5 years or surgical oophorectomy or ovarian irradiation

SOURCE: **www.ibcsg.org**

quality of life in the long run, but you might give her a few percent edge.

DR LOVE: Does the HER2 status affect your choice of hormonal therapy?

DR MUSS: I would say it does. Compelling preclinical data indicate that HER2 is involved in phosphorylating receptors and activating them even without a ligand and bypassing the effects of drugs like tamoxifen. Clinical data from trials in metastatic disease show patients with HER2-positive disease are slightly more resistant to endocrine therapy, whether it's an aromatase inhibitor or tamoxifen. An aromatase inhibitor may be a better choice up front in patients with HER2-positive disease.

DR LOVE: Tom, how would you have approached this woman?

DR BUDD: At that time, I would have used an anthracycline/taxane-containing regimen. For the hormonal regimen, the thought that HER2 positivity might be a reason to think about something other than tamoxifen is interesting, but for standard

clinical practice I would probably use tamoxifen alone as the standard of care.

The combination of ovarian ablation and tamoxifen has never been compared to tamoxifen alone, so we don't have a true comparison. Clearly, tamoxifen and chemotherapy act independently and add to each other's effects, so the question is whether ovarian ablation adds to that — and we just don't know the answer.

From the Intergroup trial in patients at lower risk who were randomly assigned to ovarian ablation plus tamoxifen versus tamoxifen alone, we know that ovarian ablation adds toxicity. For that reason, I tend to use tamoxifen alone as adjuvant treatment, and even though the HER2 positivity worries me a bit, I think I would go ahead with tamoxifen.

DR LOVE: You're the principal investigator of a new Intergroup SWOG study that is a follow-up to the CALGB-9741 dose-dense study — can you tell us about the design of that trial and its rationale?

DR BUDD: Dose-dense therapy seems to be the optimal way to administer the combination of AC/paclitaxel. If that's the anthracycline/taxane-containing regimen you're using, I would tend to use dose-dense therapy in most cases.

SWOG-S0221 is based on the dose-dense CALGB-9741 trial, some SWOG studies and some studies done at the University of Washington evaluating a different regimen of doxorubicin/cyclophosphamide. In that regimen, cyclophosphamide is given orally continuously for 15 weeks, and doxorubicin is given weekly. To maintain the dose, it's necessary to give G-CSF every day except on the days of intravenous drug administration.

This regimen produced very promising results in a pilot adjuvant trial and a pathologic complete response rate of approximately 24 percent in locally advanced disease in the Southwest Oncology Group. Based on those preliminary data, that regimen is being compared to dose-dense AC given for six weeks in order to compare equivalent durations of therapy — 15 weeks versus 12 weeks. It also has a randomization between dose-dense paclitaxel every two weeks for six cycles and weekly paclitaxel for 12 weeks.

DR LOVE: What's the growth factor support being used in this study?

Phase III Trial of Continuous Schedule AC + G versus the Every Two-Week Schedule of AC Followed by Paclitaxel Given Either Every Two Weeks or Weekly for 12 Weeks as Postoperative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer

Protocol ID: SWOG-S0221
Accrual: 4,500 patients (Open)

Eligibility:
Stage I - III invasive breast cancer, node-positive or high-risk node-negative, with no prior cytotoxic chemotherapy or radiation therapy

R

- AC q2wk + PEG-G x 6 cycles → T q2wk + PEG-G x 6
- Continuous AC + G x 15 weeks → T q2wk + PEG-G x 6
- AC q2wk + PEG-G x 6 cycles → T qwk x 12
- Continuous AC + G x 15 weeks → T qwk x 12

G = filgrastim; T = paclitaxel; PEG-G = pegfilgrastim; continuous AC = weekly doxorubicin + daily, oral cyclophosphamide

Southwest Oncology Group Study Coordinators:
G Thomas Budd, MD; Tel: 216-444-6480
Halle CF Moore, MD; Tel: 216-444-2644

SOURCE: NCI Physician Data Query, July 2004.

DR BUDD: For the every two-week treatments, it's pegfilgrastim, and for the daily and weekly treatments, it is filgrastim.

DR LOVE: What happened to this patient, Dr Tsarwhas?

DR TSARWHAS: This patient originally presented at approximately the same time that CALGB-9344 was presented, and at that point we discussed the benefit of a taxane in patients who were ER-positive and went on to receive tamoxifen. In fact, one of our thought leaders in Chicago was not recommending the addition of a taxane in that setting.

Obviously, thinking has changed over the years, but at that point I treated her with four cycles of AC. She stopped menstruating after chemotherapy and went on to receive adjuvant radiation therapy. She then started on tamoxifen.

She did well for a couple of years, but recently came to the office with some complaints of back pain. My initial thought was, "She's three years out now. She didn't received a taxane. She was IHC 3+ for HER2 overexpression and I have her on tamoxifen. I missed my chance, and her cancer has recurred."

We did a bone scan and an MRI. I don't routinely check markers, but if a patient has symptoms, I check them and I did in this case. Everything came out normal. She had some arthritis in her lower back so I prescribed 25 mg of rofecoxib and her symptoms improved immediately.

Reviewing this case again prompted me to bring up the idea of switching to an aromatase inhibitor, as I now discuss it as an option with any patient who is either on tamoxifen or completing tamoxifen. She is an intelligent patient and we discussed the fact that her tumor was HER2-positive, she didn't receive a taxane and maybe she would benefit from switching. Given both our concerns, we made the switch from tamoxifen to exemestane.

DR LOVE: Let's talk about the continuum of hormonal therapy. I think we're all much more sensitive to it with the emergence of these switching reports. Hy, how do you approach patients who are in their first five years of adjuvant tamoxifen? Do you routinely bring up the issue of switching? How do you determine when you're going to switch therapies?

DR MUSS: This is a work in progress and my views have changed a lot this year, based on the fact that now we have several trials — ATAC, the Intergroup exemestane trial, the NCIC trial with letrozole after five years of tamoxifen and a smaller Italian trial — all showing the relative superiority of the aromatase inhibitors.

I thought Dr Goss' presentation of the letrozole trial at ASCO was very impressive. Even with all the design issues, with distant metastases as the initial endpoint, patients with positive nodes have a statistically significant survival advantage with letrozole. I have to believe that the exemestane study, which actually had more events than the initial letrozole trial, will probably also show a survival advantage, and I have been discussing the aromatase inhibitor data with the majority of my patients.

Case follow-up:

- After three years, the patient developed suspicious lower back pain
- Bone scan, MRI and tumor markers were normal
- Treated with rofecoxib and switched to exemestane

In this patient with four positive nodes and HER2-positive disease, I would probably encourage her to switch to an aromatase inhibitor, and what I generally do is I pick the aromatase inhibitor that matches the patient's status. This patient has had two to three years of tamoxifen, so I would use exemestane. If she had five years of tamoxifen, I would use letrozole, and if this was *de novo* disease, I would pick anastrozole. I think that is a reasonable approach, even though I don't believe the three differ much biologically or in terms of overall effectiveness.

DR LOVE: One of the questions I've been asked since the switching data has emerged is, in the long run, would patients be better off having tamoxifen for two to three years or five years and then switching, as opposed to starting on an aromatase inhibitor up front?

DR MUSS: I don't think it makes great sense to do that because in all of these studies the relapse rates and the rates of distant metastases have been higher in the tamoxifen arms. Whether you begin up front, in the middle or out back, the aromatase inhibitors are doing better than tamoxifen in every study. Mathematically, I think it is a better strategy to use your best first. Otherwise, you lose a few patients to distant relapse that you might have salvaged with the aromatase inhibitor.

DR TSARWHAS: How long do you leave a patient on the aromatase inhibitor if you switch in the middle?

DR MUSS: Great question. I don't know the answer. I'm going to probably use it for five years provided no accelerated bone loss occurs.

Clinical Trials Comparing Up-Front, Switching or Sequential Adjuvant Aromatase Inhibitors to Tamoxifen

Trial	N	Randomization	Disease-free survival
ATAC[1]	9,366	TAM vs ANA vs TAM/ANA x 5 y	HR = 0.86 95% CI 0.76-0.99
ITA[2]	426	TAM x 2-3 y → ANA vs TAM x 2-3 y	HR = 0.36 95% CI 0.17-0.75
CRC-TU-TEAM[3]	4,742	TAM x 2-3 y → EXE vs TAM x 2-3 y	HR = 0.68 95% CI 0.56-0.82
NCIC-CAN-MA17[4]	5,187	TAM x 5 y → LET vs Placebo x 5 y	HR = 0.57 95% CI 0.43-0.75

Median follow-up = 47 months[1]; 24 months[2]; 31 months[3]; 29 months[4]
TAM = tamoxifen; ANA = anastrozole; EXE = exemestane; LET = letrozole

SOURCES: [1] Baum M et al. *Cancer* 2003;98:1802-10. **Abstract** [2] Boccardo et al. *Proc* SABCS 2003;**Abstract 3**. [3] Coombes RC et al. *N Engl J Med* 2004;350(11):1081-92. **Abstract** [4] Goss P et al. *N Engl J Med* 2003;349(19):1793-1802. **Abstract**

Select publications

Baum M et al; The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses.** *Cancer* 2003;98(9):1802-10. **Abstract**

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Proc SABCS* 2003(Suppl 1);**Abstract 3**.

Carlson RW, Henderson IC. **Sequential hormonal therapy for metastatic breast cancer after adjuvant tamoxifen or anastrozole.** *Breast Cancer Res Treat* 2003;80(Suppl 1):19-26. **Abstract**

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. **Abstract**

Coleman R et al. **Association between prior chemotherapy and the adverse event (AE) profile of adjuvant anastrozole (A) or tamoxifen (T): A retrospective analysis from the ATAC trial.** *Proc ASCO* 2004;**Abstract 767**.

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

Distler W et al. **Impact of age on the gynecologic adverse event (AE) profile of anastrozole (A) or tamoxifen (T) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2004;**Abstract 770**.

Dixon JM. **Exemestane and aromatase inhibitors in the management of advanced breast cancer.** *Expert Opin Pharmacother* 2004;5(2):307-16. **Abstract**

Gnant M et al. **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: Results of a randomized multicenter trial.** *Breast Cancer Res Treat* 2002;**Abstract 12**.

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

Goss PE et al. **Updated analysis of the NCIC CTG MA.17 randomized placebo (P) controlled trial of letrozole (L) after five years of tamoxifen in postmenopausal women with early stage breast cancer.** *Proc ASCO* 2004;**Abstract 847**.

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

Ingle JN. **Sequencing of endocrine therapy in postmenopausal women with advanced breast cancer.** *Clin Cancer Res* 2004;10(1 Pt 2):362S-7S. **Abstract**

Locker GY et al. **The time course of bone fractures observed in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2003;**Abstract 98**.

Mouridsen HT et al. **Challenges in the endocrine management of breast cancer.** *Breast* 2003;12 (Suppl 2):2-19. **Abstract**

Paridaens R et al; European Organization for the Research and Treatment of Cancer (EORTC)-Investigational Drug Branch for Breast Cancer (IDBBC). **Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer.** *Ann Oncol* 2003;14(9):1391-8. **Abstract**

Whelan T et al. **Assessment of quality of life (QOL) in MA.17, a randomized placebo-controlled trial of letrozole in postmenopausal women following five years of tamoxifen.** *Proc ASCO* 2004;**Abstract 517**.

CASE 4: A 56-year-old woman with ER/PR-negative, HER2-negative, node-positive breast cancer with elevated tumor markers after adjuvant chemoradiation therapy (from the practice of Bharat H Barai, MD)

- Presented at 51 years of age with ER/PR-negative, HER2-negative breast cancer and four positive lymph nodes
- Underwent lumpectomy and radiation therapy and received four cycles of AC followed by paclitaxel
- Followed with routine CA 27.29 and remained asymptomatic for approximately 3.5 years
- CA 27.29 began to rise but no metastatic disease was discovered
- Six months later a CT scan revealed multiple liver metastases

Key discussion points:

1. Evaluation and treatment of a woman with very high-risk breast cancer
2. Role of tumor markers in following patients at high risk after adjuvant therapy
3. Selection of first-line chemotherapy in the metastatic setting
4. Selection and use of single-agent versus combination chemotherapy for metastatic disease

DR BARAI: When this woman was first diagnosed with breast cancer she was 51 years old. Her tumor was ER/PR-negative with HER2 1+ by immunocytochemistry. At that time she also had four positive nodes. She underwent lumpectomy and radiation therapy and then received four cycles of AC followed by paclitaxel.

At approximately three and a half or four years' follow-up, she was asymptomatic but her CA 27.29 started rising. I repeated the CA 27.29 tumor marker test, and it was still up around 100+ U/mL. At that point I did a metastatic workup on her, which was negative. I expressed my concern and told her that no detectable disease was present at that point.

Six months later she was not feeling well and had started to lose weight. I repeated the CA 27.29 and this time it was about 350 U/mL. This, along with her symptoms, made me suspicious that something was going on — perhaps viscerally.

I checked her X-ray and bone scan, which were both okay, but a CT scan showed multiple lesions in her liver. I went back and asked the pathologist to test her tissue block with FISH even though it was 1+ by immunocytochemistry. The FISH results were negative.

DR LOVE: Tom, I'm curious about your thoughts.

DR BUDD: In some ways, this case shows why I personally do not use tumor markers. I know many people find them useful, but they tell you that someone is at increased risk to have a recurrence sometime in the next few months. It's not a 100 percent

chance, and I'm not always sure that is information you want to know.

If a patient is asymptomatic and you follow a strategy of evaluating the patient and aggressively working up any persistent symptoms, I think you will arrive at a diagnosis at the same time.

I don't think any data show that aggressive monitoring with scans or markers will detect recurrences soon enough that you can improve survival by instituting treatment at that point, so, in general, I don't follow markers.

In this case, given that she was symptomatic and the markers were going up, I think the workup was appropriate.

DR LOVE: How would you approach her therapy at this point?

DR BUDD: Can you quantify the magnitude of the liver involvement?

DR BARAI: She had at least four or five lesions and they were on both lobes of the liver, probably measuring about one or one and one half centimeters in size.

DR BUDD: This is a patient in whom I would probably use sequential single agents. I do not think you have to use combination chemotherapy, although I would not quibble if you did, given that she was losing weight and had some ominous symptoms.

It has been five years since her initial diagnosis and she has already had AC → paclitaxel. I think the choices would include docetaxel, capecitabine and vinorelbine. I do not think one right answer exists. I would probably give her capecitabine, but this is one of those situations in which I discuss the alternatives with the patient because I think the toxicities and her lifestyle will influence her choice.

DR LOVE: Hy, same question. Would you have used tumor markers? How would you approach her at the point that she only had tumor marker elevation? And at this point, how would you manage her overt metastatic disease?

DR MUSS: I do not routinely use tumor markers. A fair amount of false-positives occur with CA 27.29 testing, but they are not usually with levels above 100 U/mL. I would think that this patient had metastatic disease because with a number as high as 150 U/mL, it's likely to be breast cancer. It is also very common to have lead times of three to six months. I was involved in the initial study of CA 27.29, and in many instances it took six months or even a year to see the tumors.

As far as treatment of metastatic disease, my philosophy is that it is all palliative care, and the goals are quality of life and disease control. It sounds trite, but it's true, and I think the overwhelming number of randomized trials have suggested that sequential single agents have the same survival outcomes. Although virtually all the combinations have a little bit higher response rates, they do not transfer into survival. Many trials have shown that quality of life is worse in people who have combination therapy.

I like Tom's choice of capecitabine. Most of these patients have lost their hair in the past, and I think capecitabine gives them a chance to deal with the fact that they now have an incurable disease without the trauma of more hair loss. Whether you like a taxane or gemcitabine first, I don't think the sequence effects survival. Therefore, I tend to start with the agent that is easiest on patients, and I like capecitabine because it is well tolerated.

DR LOVE: How much of an issue is alopecia in the metastatic and adjuvant settings, and how much of an advantage is it to have an agent that does not cause hair loss?

DR MUSS: From speaking with many patients, including my cousin who has metastatic breast cancer, I think hair loss is a big deal. When you are talking about palliative therapy, I believe alopecia is a major side effect to go through — especially for a relatively asymptomatic patient whose disease was found on a scan. I think it is helpful to patients if you can avoid alopecia for a while.

Phase III Trials Comparing Single-Agent and Combination Chemotherapy for Metastatic Breast Cancer

	XT trial: Comparing docetaxel monotherapy and combination capecitabine/docetaxel		Intergroup trial E1193: Comparing doxorubicin, paclitaxel and combination doxorubicin/paclitaxel		
Treatment	Docetaxel	Capecitabine/ docetaxel	Doxorubicin	Paclitaxel	Doxorubicin/ paclitaxel
Objective response	30%	42%	36% (20% response to crossover)	34% (22% response to crossover)	47%
Median survival	11.5 months	14.5 months	18.9 months	22.2 months	22.0 months

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

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

Case follow-up:

- Received capecitabine and docetaxel but developed severe mucositis
- Switched to doxorubicin and docetaxel but MUGA scan declined to 50 percent
- Switched to carboplatin and docetaxel
- Tumor markers decreased to normal
- CT of the liver was normal
- Treatment discontinued
- After 12 months the patient became symptomatic and had rising tumor markers
- Carboplatin/docetaxel was reinitiated and a decrease in tumor markers and reduction in liver lesions occured
- Patient died of sudden death, probably of cardiac origin

DR LOVE: This woman had adjuvant AC and a taxane. Suppose she was completely naïve to chemotherapy — would you still use capecitabine as first-line therapy?

DR MUSS: I would not be swayed by the fact that a patient may not have had chemotherapy. The data suggest that she is not going to do any better having an anthracycline or a taxane up front, so I don't think the sequence matters as much as the agents being active, and I think these are all active agents. Therefore, it becomes a measure of the quality of life you achieve with a drug, and capecitabine offers a better quality of life for patients like this.

DR LOVE: Can you talk about what happened to this patient?

DR BARAI: I initially started this patient on capecitabine and docetaxel, but she developed severe mucositis and quickly said, "I'm not going to take this anymore." Her MUGA scan was okay, so I decided to start her

on doxorubicin and docetaxel. By the third cycle her MUGA scan came in around 50 percent so I stopped the doxorubicin.

During this time her CA 27.29 started coming down. I switched her to carboplatin and docetaxel, and her tumor markers became normal. Computed tomography of her liver was normal, so we knew that at least most of the gross disease was gone. At that point, I proposed stopping the treatment and continuing with observation.

Believe it or not, she stayed asymptomatic, gained weight, and her markers stayed relatively normal for about 12 months. Then they started rising again, and I followed her for a few months. She again became symptomatic and the markers rose to approximately 150 U/mL. I put her back on carboplatin and docetaxel, and she started responding again. Her markers came down to approximately 51 U/mL, and her liver lesions decreased in size.

One morning she drove herself to my office for her chemotherapy and while she was waiting for her blood to be drawn, she suddenly collapsed in the chemo chair. In spite of resuscitation attempts, unfortunately, the patient died.

DR LOVE: So, she had sudden death in the chemo room before she received her chemotherapy?

DR BARAI: Yes. We did not request an autopsy, but we think she might have had a pulmonary embolus.

DR LOVE: Tom, any thoughts about this case?

DR BUDD: It is interesting that she still seemed to retain some responsiveness to the taxane. I think using docetaxel was reasonable, particularly given the long time period.

DR LOVE: How do you approach the use of sequential single agents? How do you decide which one to try first, second, third? Dr Berry?

DR BERRY: Unless a person has a visceral crisis, I go with sequential single-agent therapy. One of the caveats addressed at last year's ASCO was the continuity of chemotherapy. It seems counterintuitive, but quality of life, etcetera, tend to be better with maintenance therapy.

This particular patient enjoyed an interval of about 12 months of stable disease before she became symptomatic again. How you select drugs often enables you to carry on with continuous therapy, and I think it is easier to carry on with something like capecitabine than it is for some of the taxanes. The reality is that all of these drugs have a cumulative toxicity. Sometimes what you end up doing isn't just a question of the disease progression but also limiting toxicities that can go along with treatment. I think that can be a very significant factor in your choice.

DR LOVE: Dr Barai?

DR BARAI: Three or four patients who have switched to my practice have commented that their previous oncologist never monitored their tumor markers. Patients are surfing the Internet and learning all their options, and they're starting to view you as an inferior oncologist if you are not doing everything that is available.

DR MUSS: I think it depends on your style with patients. I tell them that one third of patients with metastatic disease do not have positive tumor markers, and that is right out of the data. I also tell them that CA 27.29 is not of any real value for screening as it's almost never positive in a primary tumor.

I generally try to explain that we have randomized trials showing that discovering small metastases early when you're feeling well does not make your life longer or better. I try to talk patients out of tumor markers, but you are never going to convince all of them. As a general rule, I don't order tumor markers, and I think we have a sound basis for not using them.

DR DRAGON: I agree with Dr Muss and I don't routinely use tumor markers, but as you pointed out, you can't talk all of your patients out of them. The worst thing is engaging in a Socratic discussion with

your patient about the meaning of life and these markers. Sometimes when I see that resistance coming, I believe it is not worth trying to teach a patient that early diagnosis for recurrent breast cancer doesn't matter.

Select publications

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

Bast RC Jr et al. **2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: Clinical practice guidelines of the American Society of Clinical Oncology.** *J Clin Oncol* 2001;19(6):1865-78. **Abstract**

Bria E et al. **Impact of taxanes in association with anthracyclines in 1st line chemotherapy for metastatic breast cancer (MBC): Comprehensive review of 2805 patients in 7 phase III trials.** *Proc ASCO* 2004;**Abstract 659**.

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

Jones S et al. **Randomized trial comparing docetaxel and paclitaxel in patients with metastatic breast cancer.** *Breast Cancer Res Treat* 2003;**Abstract 10**.

Nabholtz JM et al; TAX 306 Study Group. **Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: Results of a randomized, multicenter, phase III trial.** *J Clin Oncol* 2003;21(6):968-75. **Abstract**

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

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

Talbot DC et al. **Randomised, phase II trial comparing oral capecitabine (Xeloda) with paclitaxel in patients with metastatic/advanced breast cancer pretreated with anthracyclines.** *Br J Cancer* 2002;86(9):1367-72. **Abstract**

Winer EP et al. **Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: Cancer and leukemia group B trial 9342.** *J Clin Oncol* 2004;22(11):2061-8. **Abstract**

CASE 5: An 83-year-old woman with an ER/PR-negative, HER2-negative, node-positive breast cancer (from the practice of James L Wade, MD)

- Mammographic abnormality and palpable mass in the right breast
- Lumpectomy with SLNB and axillary dissection revealed a 1.5-centimeter, Grade III invasive ductal carcinoma with lymphovascular invasion and one positive lymph node
- ER/PR-negative, HER2-negative by IHC
- Frequency of cell mitosis is 25
- No comorbid illnesses
- Treated with lumpectomy, AC for 4 cycles and radiation therapy without difficulty

Key discussion points:

1. Role of adjuvant systemic therapy in healthy elderly patients with high-risk ER/PR-negative, HER2-negative disease
2. Use of chemotherapy in elderly patients with visceral metastatic disease
3. Reassessment of tumor HER2 status in patients with metastatic disease
4. Use of nonprotocol trastuzumab-based therapy in patients with ER/PR-negative, HER2-positive disease

DR WADE: This 83-year-old woman initially presented in December 2000 with a palpable mass and mammographic abnormality in the right breast. After a needle biopsy, sentinel node evaluation and a subsequent lumpectomy with axillary dissection, she was diagnosed with a 1.5-centimeter, Grade III invasive ductal carcinoma with lymphovascular invasion.

One sentinel node out of a total of nine lymph nodes was involved with ductal carcinoma, but no extracapsular extension was present. She was ER-negative, PR-negative, and HER2-negative by IHC. Parenthetically, she had 25 mitoses per 10 high-power fields on microscopy.

DR LOVE: Was she a healthy 83-year-old? Did she have any comorbid illnesses?

DR WADE: I'd put her performance status somewhere between one and two. She was ambulatory and was reluctant to consider any type of aggressive therapy. Her husband was debilitated and spent most of his time in a wheelchair. Her primary concern was undergoing any kind of treatments that would weaken her and make her unable to care for him.

DR LOVE: Did she have any specific illnesses that were causing her problems?

DR WADE: She didn't have any major problems with hypertension, cardiovascular disease or diabetes at that time, but she did have arthritis.

DR BUDMAN: Is she cognitively intact? Do you think you could trust this woman with

oral medication or would you be uncertain about whether she's taking it? What medications is she taking? Drug interactions are a major issue that we acknowledge, but really don't deal with it in oncology because people are on polypharmacies all the time. The husband's debilitation is obviously a major issue, but does she have any other family support?

DR WADE: Dan, her cognition was fine. She had good memory and understood the issues we were discussing. She was the primary caregiver in the family, and no children were present who could help out. She managed most of the activities of daily living — grocery shopping, housecleaning, dishes and meal preparation.

DR LOVE: What is your assessment of how she might have tolerated different types of chemotherapy?

DR WADE: Usually it's "put your toe in the water" and find out. Her renal function was adequate, and you might predict that she'd tolerate therapy okay, with the caveat that some patients beginning cytotoxic therapy — particularly agents associated with a lot of mucositis — will have a lot of secondary problems, and you may need to back out quickly.

DR LOVE: In this woman, who has ER-negative, node-positive disease, chemotherapy is an issue that must be considered, which was part of the rationale for Hyman Muss to develop the CALGB trial comparing capecitabine to either CA or CMF. That trial has just begun. Dan, how would you have thought through whether to use chemotherapy and, if so, what type?

DR BUDMAN: I would have taken a step back first. Peter Ravdin's Adjuvant! program is really superb, and I use it all the time. At the last ASCO meeting it was nice to see that the people in British Columbia Cancer Registry actually validated Adjuvant! with 10,000 patients, and it was within one percent.

The only area in which it wasn't particularly accurate was for patients under 35 years old, which is obviously not a concern in this patient. I would plug this patient's information into Peter's program to obtain an idea of what type of benefits we're considering in a woman who has major social responsibilities and no support structure?

DR LOVE: Dr Wade, after you explained the situation to her, do you think she would have been comfortable receiving no adjuvant therapy?

DR WADE: We discussed no adjuvant systemic therapy. She was torn between the lack of toxicity with no therapy weighed against the concern she would become ill and be unable to care for her husband.

DR LOVE: Adam, would you have used chemotherapy in this situation? If so, what type?

DR BRUFSKY: I would not use chemotherapy in this situation. We actually plugged her information into the Adjuvant! Palm Pilot program. From standard CMF-based chemotherapy, she would probably have a benefit of approximately 1.4 percent due to competing causes of mortality.

If she was seriously considering chemotherapy, and said "I really want to do everything possible, even if it's a one percent benefit for my relapse rate in five years," I would consider the capecitabine trial or a mild regimen such as CMF.

DR LOVE: If the capecitabine trial data were available and demonstrated equivalent benefit for CMF and AC, would you use capecitabine or CMF?

DR BRUFSKY: If the data were available, I would use capecitabine.

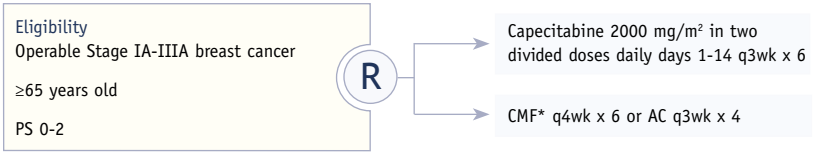
DR LOVE: Dan?

DR BUDMAN: The CALGB breast community was very interested in this study, perhaps not in an 83-year-old patient, but in patients up to 75 years old with a little more social support.

The problem is we're waiting for the data. Capecitabine is very attractive. I believe this is an important study, but we don't have the answer yet.

Phase III Study of CMF or AC versus Oral Capecitabine in Elderly Women

Protocol IDs: CALGB-49907, CAN-NCIC-CALGB-49907, ECOG-CALGB-49907, SWOG-CALGB-49907, CTSU
Target Accrual: 600-1,800



*CMF with oral cyclophosphamide

Note: Patients with insufficient LVEF must receive CMF; otherwise, choice of AC or CMF is at physician's discretion

SOURCE: NCI Physician Data Query, October 2004.

DR LOVE: Dan, how do you approach dosing with capecitabine?

DR BUDMAN: I look at it a little differently because we know that women have slightly lower DPD levels than men. In fact, when we did a Phase I study, our dose of capecitabine was lower than the dose utilized by the Europeans, because they were enrolling male patients with rectal cancer in their study, whereas we enrolled only breast cancer patients in our study.

We also know that capecitabine becomes more toxic if you have renal insufficiency. As these patients age, they develop end organ dysfunction, so we don't know whether a dose-response curve really exists. The suggestion from retrospective data, mainly from Joyce O'Shaughnessy, is that the dose-response curve is relatively flat.

Even at 50 percent of the initial dose that she used in the metastatic setting, patients responded. I'd "chicken out" in this case. In an elderly lady, I would probably start at 1,500 mg/m^2 per day. If any toxicity occured, I would consider reducing the dose.

DR LOVE: Let's find out what happened to this patient, at least at that point. Can you talk about your conversation and what ended up happening, Dr Wade?

DR WADE: I discussed the competing issues with her. Would she tolerate therapy? Would it tear her down, or would her disease catch up with her? Keeping in mind that she had a Grade III malignancy, we even discussed whether or not the addition of a taxane would add any additional benefit for her, because she had node-positive disease.

We eventually decided to try one dose of AC and see how she did. She tolerated it with practically no side effects. She went on to receive four doses of AC and then breast irradiation.

The question of performing lumpectomy versus mastectomy was appropriate because she had to drive about 40 miles to receive radiation therapy. However, I saw her after those decisions were already made, and she made it clear to the surgeon that, if possible, she wanted to have breast-conserving therapy. She went through her radiation therapy without difficulty and drove herself back and forth for six weeks.

DR LOVE: Overall, how did she tolerate the AC?

DR WADE: She tolerated the AC fine and received therapy on schedule without dose reduction or mucositis.

DR LOVE: Was she able to continue to take care of her husband?

DR WADE: Yes.

DR LOVE: Dan, the dose-dense CALGB trial 9741 has resulted in a lot of physicians using dose-dense AC → T every two weeks. Interestingly, the node-negative Intergroup trial that followed the report of 9741 switched to using dose-dense AC every two weeks. What are your thoughts about that strategy? Would you have considered it in this woman if she wanted to receive AC?

DR BUDMAN: One of the concerns around the country is that the taxanes, especially paclitaxel, seem to be more efficacious if given more frequently. Andy Seidman's study in the metastatic setting demonstrated paclitaxel administered weekly was superior to the every three-week schedule. My suspicion is that part of the difference is due to the taxane scheduling.

An Intergroup study that is closed to accrual evaluated every three-week versus weekly paclitaxel and docetaxel. Joe Sparano informed me that, hopefully, the data will be mature enough by next year's ASCO. Hopefully, that will also add to our knowledge about how to use these drugs.

I am a little wary of giving dose-dense chemotherapy to the elderly. Most of the patients in the CALGB trials are under 65 years old, and the average age in CALGB-9741 was 55 years.

DR LOVE: Dr Dragon, how do you use growth factors in the older patient? Do you use dose-dense chemotherapy, and would you have considered dose-dense AC in this woman?

DR DRAGON: With regard to using growth factors, much of what I've done in my practice is based on the CHOP experience in elderly patients. The only way to effectively and safely give CHOP in patients over the age of 65 has generally been with the regular use of growth factors, so when I treat older patients with AC, I typically administer growth factor support.

Let me play the devil's advocate. In the meta-analysis, very little data exists for treating patients over the age of 70 years. In patients over the age of 50, the benefits of adjuvant chemotherapy are often quite marginal, and they seem to be even further attenuated in patients over the age of 60 and, we presume, over the age of 70. I can't explain why this occurs, but nonetheless we have to recognize that a diminution in the effectiveness of adjuvant chemotherapy occurs in elderly patients with breast cancer.

In a patient like this, I wouldn't ask the question, "Can we treat her?" I'd ask, "Should we treat her?" Frankly, I'd be reluctant to treat this patient with chemotherapy.

DR LOVE: Would you discuss the option with the patient?

DR DRAGON: No, I would not, and my habit is to discuss all the options with patients. Postmenopausal patients will have a two to three percent disease-free survival advantage from chemotherapy. In my experience, the older the patient, the less they want to hear and the more confused they are when they hear the actual statistics. They just want to know, "What should I do, Doctor?"

I would be reluctant to treat this patient, not because I don't think we can do it safely, but because I'm just not sure we can justify the effort and the utilization of resources.

DR LOVE: We are about to make this a little more complicated, so let's take it to the next point in this case.

DR WADE: She completed four cycles of AC without difficulty and had breast radiation therapy.

We followed her clinically and I obtained routine annual chest X-rays. She reported some fatigue and back pain. In February 2003, her chest X-ray showed the new appearance of multiple pulmonary nodules. Subsequent imaging showed "plus-minus" for bone metastases but demonstrated the presence of hepatic metastases. We performed a biopsy of her liver, which demonstrated a small area of adenocarcinoma consistent with the original primary tumor.

DR LOVE: What was her functioning at that point?

Case follow-up:

- Two years and two months after adjuvant therapy, routine chest X-ray revealed multiple pulmonary nodules, possible bone metastases and hepatic metastases
- Patient had a good performance status
- Re-evaluated her primary tumor via FISH, which revealed positive gene amplification
- Initiated trastuzumab monotherapy with a partial response
- Progressed and was treated with capecitabine/trastuzumab
- Progressed after seven months and was switched to paclitaxel/trastuzumab, but after five months she developed severe numbness in her hands
- CT revealed multiple cerebral metastases
- Brain irradiation and steroids were initiated

DR WADE: She was functioning well and was still providing most of the support in the household. She was still driving, able to move around the home and do the cleaning, laundry, etcetera.

DR LOVE: Now she had the experience of having gone through chemotherapy. When you began discussions with her, what was her attitude about the possibility of being re-treated?

DR WADE: Now that she was facing visceral metastatic disease, she wanted to stay alive as long as possible. She did not want just comfort measures only — she wanted active therapy.

DR LOVE: Adam, it becomes more difficult.

DR BRUFSKY: Well, in this case, she is clearly indicating she wants something done. Could she come in for weekly therapy?

DR WADE: She's close to one of our satellite offices, so we could see her weekly.

DR BRUFSKY: Given her ability to come in weekly, the choices I would probably present are a weekly taxane, either paclitaxel or docetaxel, which would be my first choice if she could tolerate it. The alternative would be capecitabine.

DR LOVE: Dan, what are your thoughts?

DR BUDMAN: Well, I would tend to agree that the database of evidence supports offering an oral fluoropyrimidine, such as capecitabine, or a taxane. In regard to the weekly taxane data, I would differ a little, in that docetaxel offers no real advantage for the weekly over the every three-week schedule, and other problems occur with the nails and the eyes. I would choose weekly paclitaxel, with the hope that some of the water-soluble paclitaxel agents become available soon and will be less toxic.

DR LOVE: If she was treated with weekly paclitaxel and didn't respond, or progressed, what would be your next therapeutic maneuver?

DR BUDMAN: I could just as easily give her capecitabine first and save the taxane for later treatment. Treatment in this situation is really for palliation and quality of life.

DR LOVE: Adam, what would you do in the same situation, except the patient is 37 years old?

DR BRUFSKY: In a younger patient with visceral disease, I would favor combination therapy. Several regimens are available. The latest regimen — gemcitabine/paclitaxel — was presented at ASCO this year. You could also utilize capecitabine/paclitaxel. Usually I'm a big believer in sequential single agents, but in a patient who has an impending visceral crisis I would vote for a

combination therapy.

DR LOVE: Dan, same situation; she's 37 years old.

DR BUDMAN: I totally agree. I would administer combination chemotherapy to cytoreduce and then, if a response occurs, I would switch to a single agent for quality of life because we know we're not changing survival.

DR LOVE: Which combination would you use and how would you handle switching to a single agent?

DR BUDMAN: For a response in this setting after failing anthracyclines, the best data right now would be for a combination of docetaxel and capecitabine, and then maintaining her on an oral agent such as capecitabine.

DR LOVE: So, you started off with the docetaxel/capecitabine and after three or four cycles, she had a partial response. At that point, do you switch?

DR BUDMAN: The problem with Joyce O'Shaughnessy's study is the early death rate on the single-agent arm, which she didn't correlate with tumor bulk. Most of us are suspicious that visceral crisis is a measure of high tumor bulk, and you want to reduce it as quickly as you can to prevent end-organ damage. You may not have time to use another single agent in that circumstance, which is very different than chest wall or soft tissue disease for which we have plenty of time to play with the drugs.

DR LOVE: Joyce actually talked to me about this strategy of starting with docetaxel and capecitabine, then going on to maintenance capecitabine — a similar strategy to starting out with chemotherapy and switching to hormonal therapy. Is that something that you've done in your practice, Adam?

DR BRUFSKY: Yes, we've done that. Generally, we'll administer four to six cycles of combination chemotherapy and then stop or maintain them on single-agent chemotherapy.

DR STEINECKER: Was her ER/PR and HER2 rechecked at the liver biopsy?

DR LOVE: That's a good question. Dr Wade, can you follow up with what actually happened with this woman?

DR WADE: We didn't have enough tissue from the liver biopsy to go back and recheck those things. Because her disease appeared to be recurring in such an aggressive fashion, I had the breast tumor sent for FISH analysis.

DR LOVE: What was her original IHC score?

DR WADE: Zero.

DR LOVE: Okay, so you "FISHed" it anyhow?

DR WADE: Yes, and it turned out that she had gene amplification — 5.8 copies — so she was FISH-positive.

DR LOVE: Then what happened?

DR WADE: I met with her and told her that we could try single-agent trastuzumab as an option. It would have relatively little toxicity, and data demonstrated a reasonable response rate. If it worked, it would allow us to avoid cytotoxic therapy for awhile.

DR LOVE: When we talked on the phone, I asked the same question that Dr Steinecker asked: "Did you retest the ER status?" You told me you had not done that.

DR WADE: That's correct.

DR LOVE: Adam, what are your thoughts about this patient?

DR BRUFSKY: We know from the original pivotal trial of trastuzumab that about 10 percent of women whose tumors are scored as IHC zero or one-plus will test FISH-positive, and obviously she is one of those women.

A lot of discrepancy and discordance exist between community laboratories and central laboratories in IHC testing. I'm assuming this was done in a community laboratory?

DR WADE: The hospital where she actually had the surgery done was not where the test was performed. It was sent to Memorial Medical Center in Springfield, which is a fairly large institution with 800 beds and

Efficacy of XT versus T in Patients with Anthracycline-Pretreated Metastatic Breast Cancer

	Capecitabine/Docetaxel (XT) n=255	Docetaxel (T) n=256	*p*-value
Median time to progression	6.1 mo [95% CI: 5.4-6.5]	4.2 mo [95% CI:3.4-4.5]	Log rank 0.0001
Objective tumor reponse	42% [95% CI:36-48]	30% [95% CI:24-36]	0.006
Stable disease	38% [95% CI:32-44]	44% [95% CI:38-50]	
Median survival	14.5 mo [95% CI:12.3-16.3]	11.5 mo [95% CI:9.8-12.7]	Log rank 0.0126

DERIVED FROM: O'Shaughnessy J et al. **Superior survival with capecitabine and docetaxel combination chemotherapy in anthracycline-pretreated patients with advanced breast cancer.** *J Clin Oncol* 2002;20:2812–23. Abstract

the pathology team for the medical school has a fair amount of experience.

DR BRUFSKY: So this is probably one of those 10 percent who are really not expressing the protein, but actually have gene amplification.

For this patient, single-agent trastuzumab is a very reasonable therapy. In the Phase II study conducted by Chuck Vogel, the response rate was approximately 26 to 30 percent with trastuzumab monotherapy. I would consider trastuzumab and vinorelbine in someone this old who wanted therapy. A lot of very good Phase II experience with the combination exists, and response rates occur in 60 to 70 percent of patients. That's probably what I would offer this woman.

DR LOVE: Adam, when you were discussing adjuvant therapy with her, would you have considered treating her with trastuzumab if you had known she was HER2-positive?

DR BRUFSKY: No, I would not. At the time her adjuvant therapy was selected, Chuck Vogel's monotherapy data wasn't available. In addition, cardiomyopathy from adjuvant trastuzumab clearly occurs, and that's causing me to hesitate about using trastuzumab off protocol in the adjuvant setting.

DR LOVE: Dan, in the metastatic setting, now that you know she has a FISH-positive tumor, how would you have thought through her therapy? Also, would you have considered trastuzumab in the adjuvant setting if you had known she was FISH-positive?

DR BUDMAN: No data in the adjuvant setting exists, and we're waiting for Edith Perez's study, which I believe is going to close in the next six months, to at least give us some early data.

Data was presented on several thousand patients who had IHC compared to FISH, and for patients with an IHC of zero, two to three percent had FISH-positive tumors, so this patient is unusual.

In her study, Edith has noted frequent discordance between the local and central laboratory HER2 results. It's worrisome, because we're obviously dependent upon our local laboratories.

I would approach therapeutic decision-making in the same way as Dr Brufsky. Vinorelbine administered at a reasonable dose is well tolerated in the elderly, and the Farber group has a lot of data suggesting synergism between vinorelbine and trastuzumab.

This patient has significant visceral disease, which I'd like to try to down-stage and then maintain her on trastuzumab monotherapy for quality of life.

DR LOVE: Would you bring us up to date on this woman, Dr Wade?

DR WADE: One advantage of trastuzumab alone is that you can administer it on a 21-day schedule, which we did. After three cycles, we repeated CTs and she had a partial response in her liver and lung. We checked it again after another three cycles, and she was starting to progress in the same locations.

After discussing the various options, including one that is not fully rooted in the literature, capecitabine was added to trastuzumab in June 2003; she began treatment for metastatic disease in February 2003. She responded again and continued on a three-week schedule until January 2004, when she had progression in the liver and breast pain on the treated side.

Capecitabine was discontinued, and she was treated with weekly paclitaxel plus trastuzumab from January until June 2004. She had a partial response after two cycles and was re-evaluated with the intent to stop the paclitaxel and continue on trastuzumab alone.

Over the last two months, she has developed increasing numbness in her fingers and toes, and has more and more trouble moving around. She has to use a walker and needs to position furniture around the house so she can lean on it to move around the house. She didn't want to use a walker or a cane in her home. After she finished the last round of therapy and came in, she needed to use a wheelchair. I thought, "I've really done it with the paclitaxel peripheral neuropathy."

Computed tomography of her head revealed multiple cerebral metastases, while chest and hepatic CTs still showed a partial response.

DR LOVE: What are you thinking at this point? Does she have any neurologic symptoms centrally, as opposed to peripheral neuropathy?

DR WADE: She has weakness in her right arm to the extent that she can't write anymore.

DR LOVE: Did you start her on steroids and radiation therapy?

Efficacy of First-Line Trastuzumab in HER2-Overexpressing Metastatic Breast Cancer

Subset	Objective response	Clinical benefit*
All assessable patients (n=111)	26%	38%
Trastuzumab		
2 mg/kg weekly (n=58)	24%	34%
4 mg/kg weekly (n=53)	28%	42%
Estrogen receptor		
Positive (n=52)	23%	36%
Negative (n=54)	30%	39%
HER2		
IHC 3+ (n=84)	35%	48%
IHC 2+ (n=27)	0%	7%
FISH		
Positive (n=79)	34%	48%
Negative (n=29)	7%	10%
Previous adjuvant doxorubicin (n=57)	32%	41%

* Clinical benefit = complete, partial or minor response or stable disease >6 months

DERIVED FROM: Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20:719-26. Abstract

DR WADE: She started on steroids and after 24 hours, her right arm improved. She's undergoing whole brain irradiation, and when she completes it, we'll probably sit down and talk about her entering hospice.

DR LOVE: Any comments, Adam?

DR BRUFSKY: As far as we know, trastuzumab doesn't cross the blood-brain barrier. Based on data from a number of abstracts presented at ASCO over the last year or two, approximately half of women who are on trastuzumab-containing therapies will relapse with brain metastases.

I don't know what my colleagues do, but in my practice I've started to order screening head CTs every six months in patients with HER2-positive metastatic disease.

DR LOVE: Dan, it sounds like this woman had a response to capecitabine and trastuzumab. Initially, there was discussion about Dennis Slamon's work in vitro. Now I'm hearing more people talking about that combination. What are your thoughts about that?

DR BUDMAN: Two years ago we presented data in San Antonio, but depending on which cell lines are utilized and the model, different results are obtained. In our data we were able to show at least synergism in vitro between trastuzumab and capecitabine. The Japanese also demonstrated synergism in a xenograft model. Does that prove anything in humans? Of course not.

Perhaps the whole "kick" you saw was capecitabine, and she didn't need the trastuzumab at all. This is a very frustrating area in clinical practice because I'm always on the fence when I have a patient who's been on trastuzumab and failed that regimen. What should I do? Should I still give it to them or should I stop it? No guidelines are available to tell us what to do.

DR LOVE: Dr Wade, how did she tolerate the capecitabine?

DR WADE: Very well. She had minimal problems with tenderness in her hands and feet.

DR LOVE: Did you ever have to dose-reduce?

DR WADE: No.

DR LOVE: Dr Berry?

DR BERRY: Did this patient truly have a visceral crisis simply because she had liver, lung and bone metastases? If she was FISH-positive, it would not be unreasonable to deliver trastuzumab as a single agent because the response rates are in excess of 30 percent. My experience with paclitaxel in the elderly, no matter how it is administered, has shown a high incidence of neurotoxicity.

If I experience a lack of response with trastuzumab, I add vinorelbine. Assuming eventual resistance, I would consider an equally less toxic agent, such as gemcitabine. I'm not sure I would use systemic chemotherapy by itself in a patient who's HER2-positive. If she remained FISH-negative, you have little recourse to using the capecitabine-based regimen.

DR LOVE: I set up the geriatrics program at the University of Miami in the mid-1980s, and one of the things that Hyman Muss has talked about over the years is the myth of aging and the importance of being careful generalizing about patients who are in their eighties. This woman, as you said from the beginning, decided she wanted a lumpectomy and was willing to drive 40 miles for radiation therapy. This is not the type of personality that most people think about when they hear about 87-year-old patients.

DR STEINECKER: I don't know if anybody has ever tried temozolomide with trastuzumab, but it might be worthwhile if your patient wanted to continue therapy. I've had some patients who have been long-term survivors, even with brain metastases and breast cancer. I know it's going to be hard if she's elderly and weak, but that might be one consideration.

DR LOVE: That's a great thought. Adam?

DR BRUFSKY: Less enthusiasm exists for temozolomide, because a Canadian Phase II trial that used temozolomide for brain metastases and breast cancer didn't have

good results. Temozolomide didn't add much benefit, so little enthusiasm exists to repeat that study in the United States.

However, I think the combination of some sort of agent that penetrates the central nervous system in HER2-positive disease is very important. We have to find that agent. Is temozolomide the right agent? I take an aggressive approach to brain metastases, especially in patients with HER2-positive disease who have their visceral disease under control. I do whole-brain radiation and gamma knife radiosurgery, and in a few cases I have used temozolomide in that setting and have had mixed results, but it is of interest.

Select publications

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

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. **Abstract**

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

Paik S et al. **Real world performance of HER2 testing — National Surgical Adjuvant Breast and Bowel Project experience.** *J Natl Cancer Inst* 2002;94(11):852-4. **Abstract**

Pegram MD et al. **Trastuzumab and chemotherapeutics: Drug interactions and synergies.** *Semin Oncol* 2000;27(6 Suppl 11):21-5. **Abstract**

Roche PC et al. **Concordance between local and central laboratory HER2 testing in the breast Intergroup trial N9831.** *J Natl Cancer Inst* 2002;94(11):855-7. **Abstract**

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

Shmueli E et al. **Central nervous system progression among patients with metastatic breast cancer responding to trastuzumab treatment.** *Eur J Cancer* 2004;40(3):379-82. **Abstract**

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-92. **Abstract**

Tripathy D et al. **Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression.** *J Clin Oncol* 2004;22(6):1063-70. **Abstract**

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. **Abstract**

CASE 6: A 48-year-old premenopausal woman presenting to the emergency room with an ER/PR-positive fungating infiltrating ductal carcinoma with "automastectomy" of the right breast and bone metastases (from the practice of Dr Gary Steinecker)

- Treated with surgical oophorectomy plus tamoxifen and radiation therapy to the spine
- Patient developed back pain and her tumor markers were rising
- Switched to anastrozole and had tumor control for three years

Key discussion points:

1. Selection and sequencing of endocrine therapy in the metastatic setting
2. Use of bisphosphonates in patients with metastatic bone lesions

DR STEINECKER: This is a woman I followed for almost 10 years. I first saw her in 1995, at which time she came into the emergency room complaining of severe back pain.

The emergency room staff observed a fungating tumor in the right breast with literally an automastectomy. It was reddened, raised and ulcerated, and her studies at that time showed bone metastases.

DR LOVE: Can you talk more about this woman and her history in terms of the evolution of this breast lesion?

DR STEINECKER: Where I practice we see one patient every year or two who presents with neglected tumors. She told me she had something in her breast for three to four months, but her records indicate she told her surgeon that she had changes in her breast for four to five years. I'm uncertain about the psychodynamics involved.

DR LOVE: I've often heard physicians describe cases like this in which the woman is responsible and takes care of herself in all aspects except this one isolated area of denial. Would that describe this woman?

DR STEINECKER: I think so. She had a family with children, and she was living with her husband and working regularly.

DR LOVE: What did you do at that point?

DR STEINECKER: Clinically, she had Stage IV breast cancer and was still menstruating at the age of 48. Her biopsies revealed ER/PR-positive infiltrating ductal carcinoma. I recommended a surgical oophorectomy and tamoxifen.

She did well. Her automastectomy healed, the breast shriveled and the tumor disappeared. Her bone lesions seemed to regress and her pain went away.

She became quite active. She underwent radiation therapy to her spine and did well for about five years before having a relapse in the bone.

DR LOVE: At that point, what was her situation?

DR STEINECKER: She had more back pain, and her CA 27.29 tumor marker had risen. We thought her disease was progressing. She switched to anastrozole and did well for about three years, and her pain was under control.

Case follow-up:

- Developed severe pain and received radiation therapy; developed osteoporosis, vertebrae collapse and rising tumor markers
- Switched to fulvestrant and zoledronic acid

Gradually, her disease began to relapse and ended up in the hospital with really severe pain. She had significant osteoporosis and collapse of vertebrae. In retrospect, before the ATAC trials we probably didn't realize the amount of osteoporosis caused by aromatase inhibitors. Bone scans clearly revealed bone progression and lytic disease, and she had elevated tumor markers.

She received radiation therapy to the painful areas. Her lytic lesions in the acetabulum and the femurs were such that the orthopedic physicians did not think they could perform prophylactic surgery. She avoided weight-bearing activity for almost six months and responded to a change in her hormone treatment to fulvestrant and zoledronic acid.

After six months, she has gradually resumed weight-bearing activity. It's been about a year now, and she's doing well. She comes to the office with her husband and is continuing on monthly fulvestrant and zoledronic acid.

DR LOVE: It has now been about 10 years since she presented with automastectomy?

DR STEINECKER: Yes.

DR LOVE: She has metastatic disease and has never been treated with chemotherapy?

DR STEINECKER: She never had chemotherapy and has disease isolated to the bones.

DR LOVE: What does her breast look like right now?

DR STEINECKER: It hasn't changed much in the last couple of months. I thought I noticed a slight red raised area, which I'm keeping an eye on, but her automastectomy area is the same as it's been for 10 years, which is basically scar tissue.

DR LOVE: So she has gone from oophorectomy/tamoxifen to anastrozole to fulvestrant over a period of 10 years?

DR STEINECKER: Yes.

DR LOVE: How has she functioned over that entire time period?

DR STEINECKER: She's been functioning well, working regularly up until the last couple of years when her pain started becoming worse. Now, she stays at home and her husband is very supportive. He took time off work to be with her for six months.

DR LOVE: Dan, what are your thoughts about this case?

DR BUDMAN: This is fairly classical ER-positive disease, which is mainly bone dominant. It's gratifying to see the initial response was rather good. If you evaluate hormonal therapy in the neoadjuvant setting, the actual complete response rate is not particularly high. To achieve a complete response rate in the chest and a good response in the bones, obviously, makes everyone happy.

Craig Henderson wrote a nice editorial in the *Journal of Clinical Oncology* approximately three years ago about the utility of being able to cycle hormones from one to the other, which is basically what we've done with this patient. An advantage in breast cancer is that it's a chronic disease and is hormonally responsive at many levels, and hormonal therapy has minimal toxicity and potentially a lot of benefit.

One question that might be asked is whether the EGFR superfamily has become over-

expressed and the patent has developed endocrine resistance. Alternative methods exist to activate the estrogen receptor. Perhaps that's why fulvestrant worked, because it destroyed the estrogen receptor. It might be worthwhile in this case to re-biopsy the lesion and evaluate it for both HER2 and EGFR expression. Ongoing studies are evaluating blocking both HER2 and EGFR expression to determine whether or not they are of value in patients who have failed primary endocrine therapy.

DR LOVE: Adam, what are your thoughts?

DR BRUFSKY: My thoughts were essentially the same. This woman has lived 10 years with endocrine-responsive disease, and you still have agents available after fulvestrant, including megestrol acetate, aminoglutethimide and even fluoxymesterone, if you could find it somewhere. Clearly, several other options are available for this woman before chemotherapy.

DR LOVE: Dan was talking about some of the new trial strategies evaluating hormonal therapy and biologic agents. Trastuzumab and fulvestrant is one that I've heard about. Adam, what are your thoughts about that clinical research strategy?

DR BRUFSKY: I think it's a good one. Good preclinical data suggest that members of the EGFR superfamily have receptor crosstalk with members of the steroid receptor superfamily.

Clinical trials with gefitinib and tamoxifen or trastuzumab and fulvestrant are ongoing. Newer agents, such as 2C4, actually inhibit some of the interaction between the HER1 and HER2, and HER2 and other members of the superfamily, HER3 and HER4. As soon as 2C4 can be evaluated as combination therapy, it will likely be combined with hormonal therapy.

DR LOVE: Adam, this woman had a good response to fulvestrant. What is your experience with this agent?

DR BRUFSKY: I've mostly used fulvestrant as third-line therapy. Occasionally, I've used it first-line in patients who cannot afford an aromatase inhibitor or in whom I have concerns about compliance.

In my experience with fulvestrant, I've probably seen more disease stabilization than clinical response. I've treated women who had nonprogression for three to four months, generally in the third-line setting. I've seen a few patients with disease stabilization for years, but in most patients it's only been for months.

DR LOVE: When I ask research leaders and community-based physicians, they often report using fulvestrant third-line due to convenience. They agree that it seems to be at least equivalent to anastrozole. How often do you see patients in your practice who, if you offer either a once-a-month intramuscular injection or a daily pill, would prefer the injection?

DR BUDMAN: I think it varies throughout the country. We were involved in one of the initial studies of fulvestrant, and our major concern was that women wouldn't like the injection. The toxicity was not an issue.

On the other hand, I use fulvestrant commonly now, although it's mainly in patients who have failed primary endocrine therapy. Many physicians tell me their patients have no problems with the injection. In fact, women prefer it because they don't have to worry about taking a pill. It varies throughout the country, and it may vary among the patient population you're treating.

DR LOVE: We surveyed 239 women who had metastatic breast cancer, and we asked them, "If you were faced with the choice between a monthly intramuscular injection or a daily pill, assuming the same side effects, which would you prefer?" Thirty-four percent preferred to have the injection. Does that surprise you, Dan?

DR BUDMAN: We know geographic differences exist in terms of whether patients prefer hormonal therapy or chemotherapy.

DR LOVE: I was surprised, because I don't hear about physicians offering these as options. Typically, physicians will say, "Well,

patients would rather have a pill," yet, if a third of women would rather have an injection, why are we not presenting that as an option? Adam?

DR BRUFSKY: Fulvestrant is especially interesting because the patients are coming in monthly for zoledronic acid anyway. Why not just add in the fulvestrant?

Select publications

Argiris A et al. **Synergistic interactions between tamoxifen and trastuzumab (Herceptin).** *Clin Cancer Res* 2004;10(4):1409-20. **Abstract**

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Henderson IC. **A rose is no longer a rose.** *J Clin Oncol* 2002;20(16):3365-8. No abstract available

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Ropero S et al. **Trastuzumab plus tamoxifen: Anti-proliferative and molecular interactions in breast carcinoma.** *Breast Cancer Res Treat* 2004;86(2):125-37. **Abstract**

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GLOBAL LEARNING OBJECTIVES

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

- 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 with ER-positive breast cancer about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions . . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the relevance to patients considering adjuvant chemotherapy regimens . . . . . 5 4 3 2 1 N/A
- Identify patients with metastatic breast cancer for whom single-agent versus combination chemotherapy would be and counsel them regarding the risk/benefit profiles of chemotherapeutic agents/regimens. . . . . 5 4 3 2 1 N/A
- Develop and explain a management strategy for treatment of ER-positive breast cancer in the metastatic setting. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
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G Thomas Budd, MD	5 4 3 2 1	5 4 3 2 1
Daniel R Budman, MD, FACP	5 4 3 2 1	5 4 3 2 1
Hyman B Muss, 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
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity. 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations. 5 4 3 2 1
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