Meet The Professors

A case-based discussion on the management of women with metastatic breast cancer

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STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well-informed of these advances. 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:

- Describe and implement a management strategy integrating chemotherapy, endocrine therapy and biologic therapy into the treatment of metastatic breast cancer in women.
- Determine the clinical implications of emerging data on the use of trastuzumab in combination with chemotherapy in the management of HER2-positive, metastatic breast cancer in women.
- Determine the adjuvant and neoadjuvant role of chemotherapy for patients diagnosed with locally advanced breast cancer.
- Discuss the use of sequential single-agent versus combination chemotherapy for the treatment of metastatic breast cancer.

EDUCATIONAL METHOD

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

ACCREDITATION STATEMENT

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CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 4 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity.

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Various	Various
epirubicin hydrochloride	Ellence®	Pfizer Inc
5-fluorouracil, 5-FU	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly & Company
imatinib	Gleevec®	Novartis Pharmaceuticals Corporation
letrozole	Femara®	Novartis Pharmaceuticals Corporation
liposome-encapsulated doxorubicin	Doxil®	Ortho Biotech
methotrexate	Various	Various
nonpegylated liposomal doxorubicin	MyocetTM	Elan Corporation plc
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pamidronate	Aredia®	Novartis Pharmaceuticals Corporation
porfimer sodium	Photofrin®	Axcan Scandipharm Inc QLT Phototherapeutics
simvastatin	Zocor®	Merck & Company Inc
tamoxifen citrate	Various	Various
trastuzumab	Herceptin®	Genentech BioOncology
vinorelbine	Navelbine®	GlaxoSmithKline
zoledronic acid	Zometa®	Novartis Pharmaceuticals Corporation

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Editor's Note

The bond that heals

For women with metastatic breast cancer, no therapy is more powerful than the doctor-patient relationship. Most of these patients have received prior adjuvant systemic therapy, and the moment a relapse is diagnosed demands extreme courage in the face of a failed attempt to remain cancer free.

This "Meet the Professor" (MTP) program is our group's second attempt to provide a continuing medical education platform that addresses the complex issues associated with this clinical scenario. As with our prior MTP program, we gathered about a dozen community-based oncologists and asked them to present de-identified cases from their practices to a faculty panel of four national research leaders.

Our first meeting was held in Dallas, Texas. To provide some geographic variation, we visited New York City for this second foray into the art and science of oncology. This monograph provides abridged and edited versions of five of the 10 cases presented on the enclosed audiotapes and CDs. We have also included relevant clinical trials, research results and journal citations.

One of the major factors in our decision to bring back this educational platform was the extensive positive feedback we received on our inaugural issue. However, an email from an oncologist in Austin, Texas, proved that not everyone was satisfied. This physician is a longstanding and regular listener to our *Breast Cancer Update* series, but he did not like the "anecdotal nature" of the discussion on the MTP program.

As CME providers, we must balance the need to provide realistic and relevant clinical content with the imprimatur to deliver evidence-based research data, and we believe that there is a benefit to allowing oncologists to see how their colleagues manage situations in which research evidence is inconclusive.

In preparation for audio taping this second program, I first conducted individual teleconferences with the participating community-based physicians to help identify potential cases from their practices. As we explored tumor characteristics, imaging results and other standard clinical data, another factor emerged with overwhelming intensity — these physicians all had deep concern for the well being of their patients.

About 10 years ago I produced a video about the doctor-patient relationship called "The Bond That Heals." Working with the physicians in this MTP program helped me realize that this concept continues to hold relevance and importance. Hopefully, the deep humanness of these bonds is evident in the enclosed case discussions. And while the spiels of our research leader faculty are informative, we are optimistic that the anecdotes of the community panel will allow our listeners and readers the opportunity to compare notes and discover how others in similar situations face unanswerable dilemmas.

—Neil Love, MD

CASE 1: A 67-year-old woman with hepatic metastases 26 years after primary breast cancer (from the practice of Dr Myron Bednar)

- Patient underwent mastectomy in 1977, followed by CMF and one year of tamoxifen.
- While followed for rising liver function tests, attributed to simvastatin, patient developed fatigue and right upper quadrant pain.
- Ultrasound revealed multiple hepatic lesions.
- Biopsy of hepatic lesions revealed ductal carcinoma that was ER/PR-negative, HER2-positive (IHC 3+). Original pathology from 1977 was unavailable.
- Mammogram and clinical exam of the contralateral breast were negative.

Key discussion points:

1. Quality control in ER/PR and HER2 assays
2. Selection of chemotherapy in combination with trastuzumab in patients with HER2-positive metastatic disease
3. Endocrine therapy in patients with ER-positive, HER2-positive metastatic disease
4. Duration of trastuzumab therapy
5. Monitoring cardiac function in patients on trastuzumab

DR BEDNAR: This 67-year-old woman was originally taken care of by a physician who later retired from our practice. In 1977, the patient had a left mastectomy and then received CMF. She also took tamoxifen for about a year, and had not seen an oncologist in a long time.

Over the years, she developed hypertension and hypercholesterolemia. A couple of years ago she started taking simvastatin and then began to develop rising liver function tests. These were attributed to the simvastatin and she was simply followed. The patient then developed fatigue and right upper quadrant pain. An ultrasound demonstrated multiple hepatic lesions. Biopsy revealed ductal-type cells that were ER/PR-negative and IHC 3+ for HER2. Mammogram and physical examination of the contralateral breast were both negative.

DR LOVE: Were you able to obtain the original pathology from 1977 and compare it to the liver biopsy specimen?

DR BEDNAR: No, I was not.

DR LOVE: Harold, can you share with us how you would think through this patient's situation.

DR BURSTEIN: Well, the whole thing doesn't make much sense. It's not inconceivable that these metastases are from the original tumor, but it is certainly unusual. I would consider FISH in this situation, especially with a liver needle biopsy specimen.

DR VOGEL: I would send samples for estrogen receptor assay to two different reference labs, and I would be sure to obtain a FISH. One of the best correlates we have with hormone receptor-positive disease is disease-free interval. I published a paper in the 1980s on the response of tamoxifen in ER-negative disease. We had about a 25 percent response rate, and most of that was due to false-negatives. I would make absolutely certain that both of these assays were accurate before making any kind of decision with regard to treatment.

DR BILSKY: But even if the ER/PR receptors were positive and FISH confirmed HER2 overexpression, in someone with visceral disease, you'd be hard pressed to give hormonal therapy anyway.

DR VOGEL: Correct. If she had less severe liver problems and wasn't particularly symptomatic, I would probably try hormonal therapy despite the receptor negativity. I still want to know the receptor status because ultimately her cancer will recur and it would be nice to have hormones to fall back on.

DR LOVE: Chuck, assuming she is both FISH-positive and ER-negative, what specific systemic regimen would you recommend?

Trastuzumab Plus Chemotherapy Trials in Women with HER2-Positive Metastatic Breast Cancer

	Number of subjects	Overall response rate
Paclitaxel/trastuzumab with or without carboplatin Robert N. *Breast Cancer Res Treat* 2002;35.	160	57% versus 38%
Weekly versus every-three-week paclitaxel/carboplatin/trastuzumab Perez EA. *Breast Cancer Res Treat* 2003;216.	36	Response rate maintained > 4 weeks 78% versus 50%
Docetaxel/carboplatin/trastuzumab Crown J. *Breast Cancer Res Treat* 2003; 79(SI):S11-S18.	55	56%
Docetaxel/cisplatin/trastuzumab Pienkowski T. *Proc ASCO* 2001;2030.	34	76%
Docetaxel/trastuzumab Raab G. *Breast Cancer Res Treat* 2002;443. Uber K. *Proc ASCO* 2001;1949. Meden H. *Proc ASCO* 2001;1987. Esteva FJ. *JCO* 2002;20:1800-8.	24 19 12 30	63% 63% 50% 63%
Weekly paclitaxel/trastuzumab Fountzilas G. *Ann Oncol* 2001;12:1545-51. Seidman AD. *JCO* 2001;19:2587-95.	34 50	62% 67%-81%
Paclitaxel/gemcitabine/trastuzumab Miller KD. *Oncology (Huntingt)* 2001;15 (2 Suppl 3):38-40.	27	Not reported
Weekly vinorelbine/trastuzumab Burstein HJ. *Proc ASCO* 2002;211. Burstein HJ. *JCO* 2001;19:2722-30. Jahanzeb M. *Proc ASCO* 2001;1986.	50 40 20	64% 75% 60%
Liposomal anthracycline/trastuzumab Theodoulou M. *Proc ASCO* 2002;216.	33	58%

DR VOGEL: All of the chemo-trastuzumab regimens produce excellent response rates between 60 and 70 percent. We're going to need an adjuvant-like trial to produce sufficient power to prove that one regimen is superior to another. Outside of the context of a clinical trial, you can take your pick of weekly paclitaxel, weekly docetaxel, gemcitabine, vinorelbine or carboplatin/paclitaxel in combination with trastuzumab. I make the decision on the basis of toxicity after counseling and discussion with the patient.

DR LOVE: If this patient had an ER-positive, HER2-positive tumor, how might your approach change?

DR BURSTEIN: In a symptomatic patient like this one, I would probably induce her with chemotherapy and trastuzumab and then hopefully consolidate with hormone therapy later. In someone with minimally symptomatic metastatic disease, I would certainly feel comfortable starting with and obtaining as much mileage as I could out of endocrine therapy before pulling the chemotherapy/trastuzumab trigger.

There's no data in that setting to tell us whether continuing trastuzumab after stopping chemotherapy and adding hormones is clinically beneficial or not. In clinical practice, it is frequently difficult to get patients to discontinue trastuzumab, especially if they've had a good clinical response. I am comfortable giving a treatment break or switching to an every three-week schedule and adding an endocrine agent with trastuzumab.

DR VOGEL: Let me just make one other point because it is controversial. Until the ongoing clinical trials show unequivocal benefit of combining trastuzumab with endocrine therapy, I will treat HER2-positive, ER-positive patients with minimal disease with hormones up front without trastuzumab; however, Steve Jones, Mark Pegram and I agree to disagree on this topic. They use combination trastuzumab and hormonal therapy in these patients.

DR BURSTEIN: I'll just add that in the subset analysis of the pivotal trastuzumab trial, prior hormonal therapy did not adversely affect the outcomes with chemotherapy and trastuzumab together. For that reason, as does Chuck, I feel very comfortable offering endocrine therapy without trastuzumab, as long as it's clinically indicated, and then bringing in the trastuzumab later.

Many clinical trials are evaluating aromatase inhibitors plus or minus trastuzumab. Everyone expects to increase the response rate and time to progression by adding the trastuzumab early because it's an active drug in and of itself.

However, I assume that these studies are never going to answer whether or not there

Active Phase II and III Trials of Endocrine Therapy and Trastuzumab in Postmenopausal Women with Hormone-Receptor Positive, HER2-Positive Breast Cancer

Protocol IDs	Eligibility criteria	Projected accrual	Schema
ROCHE-B016216	Postmenopausal, metastatic, ER/PR+, HER2+ (FISH or IHC 3+)	202	Trastuzumab + anastrozole versus anastrozole
NU-01B4	Postmenopausal, metastatic or locally advanced, ER/PR+, HER2+ (FISH or IHC 3+)	18-60	Trastuzumab + exemestane

SOURCE: NCI Physician Data Query, January 2004.

Case follow-up:

- Patient was treated with weekly paclitaxel/trastuzumab.
- Right, upper quadrant pain and smaller hepatic lesions resolved, dominant lesion was reduced by 50 percent and fatigue improved.
- After six months, treatment was discontinued.
- Three months later, CAT scan revealed that the dominant hepatic lesion had increased in size and smaller lesions redeveloped. CA 27-29 increased 15 to 20 points.
- Treated with trastuzumab monotherapy every three weeks.
- Eighteen months later, the patient was doing well with no toxicity and hepatic lesions shrinking on CAT.

will be a survival benefit because they are relatively small and weren't designed to have that much follow-up. I think this question will be on the table for a long time.

DR LOVE: Dr Bednar, what happened with this woman?

DR BEDNAR: I gave her weekly paclitaxel and trastuzumab and she actually did quite well. Her smaller hepatic lesions resolved, and the dominant one was reduced by over 50 percent. Her right upper quadrant discomfort also resolved and she felt generally improved. By the end of six months, she was starting to feel some fatigue and some cumulative chemotherapy effects. I was treating her weekly, giving her some weeks off here and there, but she had two children who lived in another state and she wanted to travel and not come in as frequently. I decided to give her a treatment break and I stopped treating her altogether.

DR GREENBERG: Did you stop the trastuzumab?

DR BEDNAR: I stopped everything and I followed her with CAT scans and checks of her CA 27-29 levels which were initially over 100 but then normalized. About three months later, on routine follow-up, the CT scan revealed that the dominant hepatic nodule started to increase in size, some other small nodules redeveloped and her CA 27-29 went up about 15 to 20 points.

Symptomatically, she was still fine, but I started her on trastuzumab alone every three weeks. She's been on that for about a year and half now, and she continues to do very well. I did another CAT scan about a month ago and her lesions continue to shrink. Symptomatically, she's doing very well and has no toxicity.

DR LOVE: Chuck, what's your usual approach to the patient who's responding to chemotherapy and trastuzumab in whom you want to discontinue the chemotherapy? Do you continue the trastuzumab?

DR VOGEL: Yes, we continue the trastuzumab, and we usually give it every three weeks. At the point at which they then progress on trastuzumab alone, we either reinstitute the original chemotherapy or switch to a different one along with the trastuzumab. This patient never failed the original chemotherapy so it would be reasonable to go back to that.

DR LOWENTHAL: When you are maintaining a patient for a long time on trastuzumab and she is doing well and has no symptomatic cardiac disease, how often do you do surveillance MUGAs?

DR BURSTEIN: We looked at that issue in one of our trastuzumab and vinorelbine trials. We

did a baseline MUGA and then a follow-up at 16 weeks. Among those patients who had preserved left ventricular ejection fraction (LVEF) of 50 percent or greater at 16 weeks, none of them went on to subsequently develop symptoms of heart failure or significant declines in LVEF.

By contrast, in two of the patients who had declines in LVEF at 16 weeks, we saw problems. One actually developed heart failure and the other had a drop in ejection fraction to about 40 percent. While this data only applies to that specific regimen, this has become our routine algorithm.

Anecdotally, I have not seen any late-onset heart failure or changes in LVEF once patients get past the first few months of trastuzumab-based therapy. In my experience, cardiac changes usually occur in the first two or three months of therapy, so I think if you recheck the MUGA around three and four months and the patient is clinically stable, you don't need to frequently check it again.

DR LIPSHUTZ: From a practical standpoint, when you see a patient's ejection fraction fall, I assume you withhold trastuzumab. I also assume that because this is metastatic disease that's responding to trastuzumab, you have a strong desire to resume the trastuzumab after the ejection fraction has improved. What has happened to patients for whom you've employed that strategy?

DR BURSTEIN: Well, fortunately, there aren't many patients like this. Even the incidence of asymptomatic declines in LVEF, in our experience with taxanes or vinca-based therapies, is much less than five percent. For this type of case, I typically stop the trastuzumab, have the patient see a cardiologist, work on optimizing her hemodynamics, and then see what happens with her cancer using other non-trastuzumab-based approaches like hormones or other chemotherapy. At some point, if her EF has recovered, and it certainly may, I will rechallenge her with trastuzumab if the clinical circumstances demand.

I have heard anecdotes of physicians treating through asymptomatic LVEFs in the thirties, and that the LVEF will come back over time once you stop the trastuzumab. I don't know that you can authoritatively say that it's always reversible, so that's just not something I've done. When a patient's LVEF gets below 45 or 50 percent, I get more squeamish.

DR LOVE: Chuck, what's your approach to cardiac monitoring and dealing with drops in ejection fractions?

DR VOGEL: We've actually just adopted a policy of doing MUGAs every six months for a couple of years. As far as treating through, we don't worry too much until the LVEF reaches about 40 percent in a responding patient. If you have somebody with liver metastases that is well controlled but she also has a slowly dropping ejection fraction, it's a good idea to do echocardiograms more frequently and keep her on trastuzumab as long as she's working closely with the cardiologist.

DR BURSTEIN: Chuck, could you elaborate on that? I have not seen patients in whom the LVEF drops steadily from 62 to 57 to 52 to 48 to 43. In my experience, patients are doing well, doing well, doing well, and then the LVEF just drops. By contrast, I can't think of any patient on trastuzumab in whom I've seen a drop after six months. Have you seen those cases?

DR VOGEL: Yes, I had one patient who was on trastuzumab for six years when she developed clinical congestive cardiac failure. She was so far out that we weren't doing routine MUGAs.

DR FRIEDBERG: Harold, is it true that patients treated with prior anthracyclines and then trastuzumab do not recover cardiac function as quickly?

DR BURSTEIN: I don't know enough about cardiac toxicity to say that, but I've certainly

had patients who have received prior anthracyclines — either in the adjuvant or metastatic setting — and have developed heart failure while taking trastuzumab. Some of those patients have experienced lingering problems with heart failure. I don't know if we have a pure enough population of anthracycline-naïve patients who have had trastuzumab-related cardiomyopathy and then got better to truly answer that question.

DR VOGEL: That's really the issue. When you start talking about people who haven't recovered, I think it's very difficult to differentiate between the anthracycline cardiotoxicity and the additional toxicity of the trastuzumab.

DR BURSTEIN: One of the things that Andy Seidman found when he did his comprehensive review of cardiac toxicity of trastuzumab was that prior anthracycline exposure was clearly a risk factor. Some data indicate that trastuzumab may actually interfere with the heart's normal myocyte repair, so adding an anthracycline hit to the trastuzumab may produce a particularly vulnerable situation. How that plays out in the clinical setting is really not known.

DR LOVE: I'm curious, Dr Bednar, has the experience with this patient in any way changed your algorithm or approach to management of HER2-positive breast cancers?

DR BEDNAR: Yes. I think perhaps, after induction with chemotherapy and trastuzumab, I might keep patients on trastuzumab as maintenance.

DR LOVE: It's interesting how sometimes one patient or one experience will have more effect on us than reading all the literature in the world.

It reminds me a little bit about the early days of adjuvant tamoxifen when we treated patients for a year or two and we saw women coming back and then relapsing. Same situation: We re-treated them and they responded. You only had to see one patient like that to start thinking about using tamoxifen for a little longer.

Cardiac Effects of Trastuzumab

"A large randomized phase III pivotal trial comparing chemotherapy alone versus chemotherapy plus trastuzumab showed that the addition of trastuzumab improved objective response rates, median duration of response, and overall survival. Unfortunately, myocardial dysfunction was markedly increased in the patients who were receiving concurrent anthracycline-based therapy…. When trastuzumab was approved by the US Food and Drug Administration in September 1998 for the treatment of women with metastatic breast cancer whose tumors overexpress HER2, it was approved as a single agent in the salvage setting or as first-line treatment in combination with paclitaxel. It is universally accepted that trastuzumab is not recommended in combination with anthracyclines. An independent Cardiac Review and Evaluation Committee reported on several trastuzumab trials. The findings supported the observations that trastuzumab was associated with an increased risk of cardiac toxicity, and age was associated with increased risk in the anthracycline-treated subset. It is important to note that in the pivotal trial, the subset treated with trastuzumab and anthracyclines still had a treatment advantage with an improved response rate (64.9% v 42.1%) and a survival benefit."

SOURCE: Theodoulou M, Seidman AD. **Cardiac effects of adjuvant therapy for early breast cancer.** *Semin Oncol* 2003;30(6):730-9. **Abstract**

Trastuzumab Cardiotoxicity in the Pivotal Trial Comparing Chemotherapy Plus or Minus Trastuzumab

	AC (n=138)	ACT (n=143)	P (n=96)	PT (n=92)
LVEF (n)	11	39	1	12
↓LVEF (%)	8	27	1	13
Class III/IV (%)	3	16	1	2

A = anthracycline; C = cyclophosphamide; P = paclitaxel; T = trastuzumab; LVEF = left ventricular ejection fraction

SOURCE: Theodoulou M, Seidman AD. **Cardiac effects of adjuvant therapy for early breast cancer.** *Semin Oncol* 2003;30(6):730-9. **Abstract**

Select publications: ***Clinical use of trastuzumab***

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Burstein HJ et al. **Multicenter phase II study of trastuzumab (herceptin; H) and vinorelbine (navelbine; N) as first-line therapy for HER2 overexpressing metastatic breast cancer (HER2+ MBC).** *Proc ASCO* 2002;**Abstract#211.**

Esteva FJ et al. **Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(7):1800-8. **Abstract**

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Perez EA, Rodeheffer R. **Clinical cardiac tolerability of trastuzumab.** *J Clin Oncol* 2004;22(2):322-9. **Abstract**

Pienkowski T et al. **Taxotere, cisplatin and herceptin (TCH) in first-line HER2 positive metastatic breast cancer (MBC) patients, a Phase II pilot study by the Breast Cancer International Research Group (BCIRG 101).** *Proc ASCO* 2001;**Abstract 2030.**

Raab G et al. **Multicenter randomized phase II study of docetaxel (Doc) given q3w vs q1w plus trastuzumab (Tra) as first line therapy for HER2 overexpressing adjuvant anthracycline pretreated metastatic breast cancer (MBC).** *Breast Cancer Res Treat* 2002;**Abstract 443.**

Robert N et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 35.**

Seidman AD et al. **Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification.** *J Clin Oncol* 2001;19(10):2587-95. **Abstract**

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Theodoulou M et al. **TLC D99 (D, Myocet) and herceptin (H) is safe in advanced breast cancer (ABC): Final cardiac safety and efficacy analysis.** *Proc ASCO* 2002;**Abstract 216**

Uber KA et al. **A Phase II trial of weekly docetaxel (D) and herceptin (H) as first- or second-line treatment in HER2 over-expressing metastatic breast cancer.** *Proc ASCO* 2001;**Abstract 1949.**

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**

Vogel CL et al. **Response to tamoxifen in estrogen receptor-poor metastatic breast cancer.** *Cancer* 1987;6096):1184-9. **Abstract**

CASE 2: A 58-year-old woman with postmastectomy chest wall recurrence while receiving chest wall radiation therapy (from the practice of Dr Ranjana Tavorath)

- This 58-year-old woman presented with a palpable breast mass, adenopathy and a 1- to 1.5-cm supraclavicular lymph node.
- Breast biopsy revealed ER/PR-negative, HER2-negative (FISH) invasive ductal carcinoma with lymphatic invasion.
- CT and bone scans were negative.
- Patient received AC x 4.
- Regression was noted in breast mass and the node.
- Patient underwent mastectomy (residual cancer in breast) and axillary node dissection (two positive nodes).
- She received docetaxel and chest wall irradiation.
- Two weeks into radiation treatment, skin changes were noted on chest wall.
- Radiation therapy was completed with an extra boost to the chest wall and supraclavicular node.
- Biopsy of macular rash along mastectomy scar revealed ER/PR-negative, HER2-negative invasive cancer.
- No further treatment; patient was under observation for 14 months with no change in the first six to eight months, and now has localized progression.

Key discussion points:

1. Staging of patients with positive supraclavicular nodes
2. Adjuvant therapy for ER/PR-negative, HER2-negative disease
3. Neoadjuvant chemotherapy for locally advanced disease
4. Treatment of chest wall recurrence

DR LOVE: We've been talking about HER2-positive disease, so lets discuss Dr Tavorath's case as I think it presents a particularly interesting dilemma — ER/PR-negative, HER2-negative disease.

DR TAVORATH: This is a very healthy 60-year-old special-ed teacher who presented to me when she was 58. She hadn't seen a doctor for many years and suddenly noticed that there was pinkness and a change in texture on her right breast. She finally decided to see a doctor and was subsequently referred to a breast surgeon who found a palpable mass, adenopathy and a 1- to 1.5-cm supraclavicular lymph node. A biopsy of the mass revealed invasive ductal carcinoma with some lymphatic invasion. The supraclavicular

node was also positive. The tumor was tested and found to be ER/PR-negative and HER2-negative by FISH. She was staged with routine CT and bone scans and everything was fine.

The dilemma at that time was whether to categorize this as locally advanced Stage III or Stage IV breast cancer. She wanted to be treated as aggressively as possible, which I thought was appropriate. She received four doses of AC, which she tolerated extremely well, and had a very nice regression in the breast and the lymph nodes. There was nothing else in terms of metastatic disease.

DR LOVE: Dr Burstein, what are your thoughts about what had been done up to this point, and how would you proceed?

DR BURSTEIN: If this woman were diagnosed in 2001, we would have considered her to have metastatic disease. But if the diagnosis took place in late 2002 or 2003, this would be Stage III disease according to the revised American Joint Committee on Cancer (AJCC) Staging Manual, sixth edition. I think this reflects the idea that this is the ultimate extreme of locally advanced disease. We generally treat these patients with adjuvant type therapies with curative intent. Based on a variety of trials, I would offer her both an anthracycline and a taxane-based regimen.

This type of biology really shows you the power of targeted therapy because when you don't have a target, it's really hard to know what to offer. One of the challenges of hormone receptor-negative, HER2-negative breast cancer is developing such targets. If you look at the gene chip array analyses and other molecular expression profiling, these types of breast cancers consistently appear to be a relatively novel and distinctive set of tumors probably from a slightly different cell of origin. They are frequently called baseloid or basel-like breast cancers and I suspect within the next few years, that's what we are going to call them. Perhaps we'll also have different treatment algorithms for them just as we do for other types of cancer.

Limited data suggest that ER-negative, HER2-negative cancers may have more genetic instability or poorer DNA repair mechanisms than other types of breast cancer. For that reason, we have been developing a platinum-based chemotherapy program for these types of cases.

There may be a particular benefit from alkylator- or platinum-based chemotherapy,

American Joint Committee on Cancer's Breast Cancer Staging Revisions: Fifth versus Sixth Edition

Summary of Changes:

- *Micrometastases are distinguished from isolated tumor cells on the basis of size and histologic evidence of malignant activity.*
- *Identifiers have been added to indicate the use of sentinel lymph node dissection and immunohistochemical or molecular techniques.*
- *Major classifications of lymph node status are designated according to the number of involved axillary lymph nodes as determined by routine hematoxylin and eosin staining (preferred method) or by immunohistochemical staining.*
- *The classification of metastasis to the infraclavicular lymph nodes has been added as N3.*
- *Metastasis to the internal mammary nodes, based on the method of detection and the presence or absence of axillary nodal involvement, has been reclassified.*
- *Metastasis to the supraclavicular lymph nodes has been reclassified as N3 rather than M1.*

SOURCE: American Joint Committee on Cancer. **Comparison Guide: Cancer Staging Manual Fifth Versus Sixth Edition. www.cancerstaging.org**.

although that is purely conjecture at this time.

DR LOVE: Chuck, what would your management plan for this patient have been initially, and then after she had a good response to the pre-op anthracycline?

DR VOGEL: Neoadjuvant therapy with curative intent is what we would have done. Based on our relationship with Judy Hurley at the University of Miami, and the work she has done with platinum-based therapy, we've actually been using platinum-based neoadjuvant therapy in our practice.

We currently have an early investigational neoadjuvant program with weekly carboplatin, docetaxel and capecitabine. I think that neoadjuvant programs using anthracyclines followed by taxanes with pathologic complete response rates in the 27- to 30-percent range are really "standard" therapies based on the NSABP and MD Anderson data.

DR BURSTEIN: She responded to anthracyclines, so the question arises whether you should push on with the anthracyclines or cross her over to something else. The only real data we have to answer that is from the Aberdeen trial.

In that relatively small neoadjuvant trial, women received a CVAP- or CHOP-based anthracycline regimen for four cycles. Patients in response were then randomized to more anthracycline-based chemotherapy or crossed over to a taxane. In that trial, women who crossed over did better in the long run.

That doesn't tell us whether she needs two more doses of anthracyclines and then a

Pathologic Complete Response in Recently Completed Comparative Clinical Trials of Neoadjuvant Chemotherapy

Study	No. of evaluable patients (OR)	Therapy	pCR	OR
NSABP-B-27[1]	752[4]	AC x 4 → docetaxel x 4	26%	91%
	1,534[4]	AC x 4	14%	86%
Aberdeen Trial[2]		CVAP x 4		66%
		Responders		
		Randomized		
	49	→ CVAP x 4	15%	64%
	42	→ docetaxel x 4	31%	85%
MD Anderson[3]		Paclitaxel qw → FAC		
	50	Node-positive	28%	NA
	68	Node-negative	29%	NA
		Paclitaxel q3w → FAC		
	51	Node-positive	14%	NA
	67	Node-negative	13%	NA

[2]At a median follow up of 65 months, the survival rates were 93% in the docetaxel group versus 78% in the CVAP group ($p = 0.04$).
[4]These numbers reflect pCR; number of evaluable patients for OR is 722 for AC → T and (1,533) for AC.
pCR = pathological complete response; OR = objective response (complete + partial clinical response)

SOURCES: [1]Bear H et al. **The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2003;21(22):4165-74. [2]Hutcheon AW et al. **Docetaxel primary chemotherapy in breast cancer: A five year update of the Aberdeen trial.** Presented at SABCS 2003. *Breast Cancer Res Treat* 2003;**Abstract 6**. [3]Green MC et al. **Weekly (wkly) paclitaxel (P) followed by FAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC- final results of a prospective phase III randomized trial.** *Proc ASCO* 2002;**Abstract 135**.

taxane or something like that, and we don't have any concrete data to help guide us.

However, this trial has led most of us to think that, as opposed to sticking purely with an anthracycline-based regimen, we should at some point offer a taxane. If this patient was a surgical candidate you could take her to surgery and then come back with a taxane, or you could offer her the taxane in the preoperative setting.

DR LOVE: Can you talk about what happened at that point?

DR TAVORATH: She had such a good response that we decided to proceed with a mastectomy and axillary lymph node dissection. She had some residual cancer in the breast, but there was a lot of treatment effect. She also had two positive lymph nodes and the supraclavicular node was not palpable.

After the mastectomy, she received four cycles of docetaxel followed by chest wall radiation. Two weeks into her radiation treatment, the radiation oncologist felt a small pimply area on the chest wall that had not been noticed before.

Despite the possibility that this could be local recurrence in the midst of her radiation, the radiation oncologist didn't want to stop radiation halfway through. Radiation was continued until completion with an extra boost to about 6,300 Rad to the chest wall and the supraclavicular node.

When I saw her after the radiation she had a vague macular-like rash along the mastectomy scar. There was not much that I could feel. I decided to send her back to her surgeon. She underwent a biopsy that showed invasive cancer. The profile was exactly the same as the original tumor — ER/PR-negative and HER2-negative. Since all she had was a minimal rash on her chest wall, at this point we opted to continue observation and nothing else. She was very comfortable with that.

DR LOVE: How long was she on observation and what happened to her rash or lesions? Did they progress?

DR TAVORATH: She's been on observation for 14 months. For the first six to eight months, there was almost no change in her disease and she remained well. Over the past three to four months, there's been definite progression. The disease is still localized across her scar but there are certain areas that are really visible and slightly crusted on the surface. It has also become more palpable with more nodularity. At this point, since she has a slow progression, we've been having an ongoing discussion about what to do next.

DR BILSKY: I don't know whether there's really any good solution. Because she relapsed so quickly after appropriate treatment, I think this patient has a rather poor prognosis. I would consider something like capecitabine. I think she could tolerate it well and I don't think it would interfere with her lifestyle. We can use her chest wall as a therapeutic parameter to determine whether it's a reasonable maintenance treatment.

DR LOVE: Chuck, can you talk a little bit about the strategy of observing women with recurrent or metastatic disease? Is that something you do in your practice? How would you think through this situation?

DR VOGEL: We occasional observe patients who have relatively indolent metastatic disease or patients in whom we don't know if their disease is going to be indolent. I would agree that capecitabine is a very good drug as long as you don't use the package insert dose. We use a fixed dose of two grams total dose per day.

In these types of cases you really have a set of options that is limited to chemotherapy with all the attendant toxicities. Rather than putting patients on something that's going to make them sick, we try to observe the tempo of the disease. In the case we've just discussed, you've gotten 14 months out of no treatment. Knowing that she had metastatic disease, you could have been making her sick with chemotherapy. I agree that there are

Treatment Histories of Patients with Taxane-Pretreated Metastatic Breast Cancer Enrolled in Capecitabine Clinical Trials

	Pivotal US trial (n=162)	US/French trial (n=74)	German trial (n=136)	French trial (n=126)
Prior therapy (%)				
Paclitaxel	100	73	49	21
Docetaxel	0	47	46	84
Anthracycline	91	96	93	96
5-FU	82	n/a	n/a	90

Efficacy of Capecitabine in Patients with Heavily Pretreated Metastatic Breast Cancer

	N	Overall response rate	Disease control rate	Median overall survival
Pivotal US trial	162	20%	63%	11.6 months
US/French trial	74	26%	57%	12.2 months
German trial	136	15%	62%	10.4 months
French trial	126	25%	54%	15.2 months

SOURCE: Seidman AD et al. **Single-agent capecitabine: A reference treatment for taxane-pretreated metastatic breast cancer?** *The Oncologist* 2002;7(Suppl 6):20-8

certainly patients for whom observation is a reasonable strategy.

We also try to get these types of patients on investigational therapies. Many new studies are evaluating dual tyrosine kinase and pan tyrosine kinase inhibitors. In our practice, this patient would probably be offered that type of investigational approach or a drug holiday until the tempo of the disease was such that we were pushed to do something more.

DR BURSTEIN: I admire Dr Tavorath's restraint. I don't think most oncologists would have managed the patient this way. More likely, I think the majority would have put her on a drug and 14 months later attributed her relatively stable disease to the drug. Clinical medicine is quite a varied and marvelous thing, and we are constantly learning amazing things about the natural history of breast cancer.

DR LOVE: Dr Tavorath, were you comfortable observing this patient without treatment? How did she feel about it?

DR TAVORATH: I was very comfortable because I follow my patients very closely. As long as a dialogue is ongoing and the patient is comfortable, I always give them that option. I think learning the biology of these cancers really helps you manage them better. Sometimes we jump in and do things because the tumor is there and we feel we have to try to get rid of it. Fourteen months ago, I honestly thought this patient was going to develop metastatic disease before anything else could happen, but that has not happened. I was following her every month and then it became every two months. It's important to accept that every cancer is not the same. I have followed a lot of patients, sometimes with more disease than this. I think a lot of it has to do with the comfort level of the patient. If there's an ongoing discussion and the patient feels comfortable, it's a reasonable thing to do.

DR LOWENTHAL: I just wondered if this chest wall recurrence, albeit very early on, was amenable to any type of local approach. I have read and heard about photodynamic therapy. Would this have been an appropriate situation for that?

DR LOVE: Does anyone have experience with photodynamic therapy?

DR VOGEL: I haven't been impressed with what I've seen with photodynamic therapy. Basically, there are a number of different approaches either with porfimer sodium or other types of porphyrins. Some studies have led to significant areas of ulceration. I remember reviewing a new investigational approach and was appalled that the patient was left with ulcers that took three to four months to heal. During that time her quality of life was compromised.

Select publications: ***Treatment for local recurrence after primary mastectomy***

Arends J, Unger C. **Excellent response to gemcitabine in a massively pre-treated woman with extensive cutaneous involvement after recurrence of breast cancer.** *Invest New Drugs* 2001;19(1):93-100. **Abstract**

Bartelink H et al. **European Organization for Research and Treatment of Cancer Radiotherapy and Breast Cancer Groups. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation.** *N Engl J Med* 2001;345(19):1378-87. **Abstract**

Carlson GW et al. **Local recurrence after skin-sparing mastectomy: Tumor biology or surgical conservatism?** *Ann Surg Oncol* 2003;10(2):108-12. **Abstract**

Fernando IN. **The role of radiotherapy in patients undergoing mastectomy for carcinoma of the breast.** *Clin Oncol (R Coll Radiol)* 2000;12(3):158-65. **Abstract**

Freedman GM, Fowble BL. **Local recurrence after mastectomy or breast-conserving surgery and radiation.** *Oncology (Huntingt)* 2000;14(11):1561-81; discussion 1581-2,1582-4. **Abstract**

Haffty BG et al. **Molecular markers for prognosis after isolated postmastectomy chest wall recurrence.** *Cancer* 2004;100(2):252-63. **Abstract**

Harms W et al. **Results of chest wall reirradiation using pulsed-dose-rate (PDR) brachytherapy molds for breast cancer local recurrences.** *Int J Radiat Oncol Biol Phys* 2001;49(1):205-10. **Abstract**

Janni W et al. **Radiotherapy of the chest wall following mastectomy for early-stage breast cancer: Impact on local recurrence and overall survival.** *Int J Radiat Oncol Biol Phys* 2000;48(4):967-75. **Abstract**

Kroll SS et al. **Local recurrence risk after skin-sparing and conventional mastectomy: A 6-year follow-up.** *Plast Reconstr Surg* 1999;104(2):421-5. **Abstract**

Le MG et al. **Prognostic factors for death after an isolated local recurrence in patients with early-stage breast carcinoma.** *Cancer* 2002;94(11):2813-20. **Abstract**

Rangan AM et al. **Local recurrence after mastectomy and adjuvant CMF: Implications for adjuvant radiation therapy.** *Aust N Z J Surg.* 2000;70(9):649-55. **Abstract**

Schuck A et al. **Radiotherapy in the treatment of locoregional relapses of breast cancer.** *Br J Radiol* 2002;75(896):663-9. **Abstract**

CASE 3: A patient with metastatic disease and bipolar disorder (from the practice of Dr Anna Gattani)

- Eight years ago, a woman in her forties underwent mastectomy with lymph node dissection (7/23 nodes positive) for Grade II, ER/PR-negative, multifocal, invasive ductal carcinoma.
- Patient has bipolar disorder with manic-depressive episodes.
- She refused adjuvant chemotherapy and radiation therapy.
- Five years after diagnosis, the patient developed dypsnea (pleural effusion) and extensive chest wall recurrence.
- Thorocoscopic pleural and chest wall biopsies both showed ER/PR-negative, HER2-positive (IHC 3+), metastatic breast carcinoma.
- She received trastuzumab monotherapy and pamidronate with excellent tumor response.
- Upon progression, chemotherapeutic agents were added to trastuzumab, including docetaxel, vinorelbine, carboplatin and gemcitabine, and eventually weekly doxorubicin, to which she responded.
- The patient has been receiving trastuzumab monotherapy for approximately 18 months with stable disease, but progression was recently noted in two chest wall nodules.

Key discussion points:

1. Treatment of patients averse to traditional therapy
2. Selection of chemotherapeutic agents in combination with trastuzumab
3. Continuation of trastuzumab following progression
4. Sequential single agents versus combination chemotherapy

DR GATTANI: The patient is 52 years old. She presented to a different oncologist in April of 1995. According to her chart, she had bloody nipple discharge from her right breast on and off for four years, but never sought help. This patient has bipolar disorder with manic-depressive episodes, which may have contributed to her overlooking this situation.

The medical oncologist at that time sent her to a surgeon, who did a right nipple smear. The cytology was positive for malignant cells. A few weeks later a right breast excisional biopsy showed multifocal, invasive ductal carcinoma, the largest being about three millimeters.

It was Grade II and ER/PR-negative. In July of 1995 a right modified radical mastectomy

with lymph node dissection revealed further invasive disease; the largest lesion was 12 millimeters and seven out of 23 lymph nodes were positive for metastatic disease.

According to the chart and what the patient told me, she was offered adjuvant chemotherapy and radiation therapy. She refused both treatments and decided to pursue alternative and complementary medicine.

I picked up her care in 1997, at which time she only wanted to follow her complementary doctor based in Seattle. She consulted with him regularly via telephone. I told her that I would have no problem talking with him and since then have had to pass pretty much everything by him. I knew I had to tread carefully with this woman or she was just going to run off, so I didn't push the issue.

She came back to see me another time, and again wanted no treatments. She refused scans, but physical and clinical exam revealed no evidence of disease. I gave her a follow-up appointment and some time in 1998 I received a phone call from this young woman in distress. She was on the side of the road with no clothes and was asking me what to do. Having no idea where she was, I told her to call 911. Then there was a click, and that was the last I heard from her.

In March of 2000, her family ushered her into my office. She had dyspnea and lesions on the right chest wall. Clinical exam revealed a pleural effusion about halfway up the chest wall. The lesions were crusted and appeared to be metastatic disease. She was admitted to the hospital. The pleural effusion was drained, and a thorocoscopic pleural biopsy and a biopsy of the chest wall were performed. Both showed metastatic breast carcinoma that was ER/PR-negative and HER2-positive and 3+ by immunohistochemistry.

At this time she was still not in favor of chemotherapy, and the data showing the advantage of chemotherapy and trastuzumab were not out. From a medical and ethical point of view, I felt that trastuzumab monotherapy was a good option for her. I had to tread carefully and

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

SOURCE: 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**

told her she needed some form of systemic therapy, but I emphasized that trastuzumab was not chemotherapy.

I never lied to her, but unless she asked me a question, I didn't give her a full picture. I explained everything to her sister, brother and her aunt, but I knew that I couldn't tell her the prognosis and what we were dealing with because she would just pick up and run off again. I had to be careful and was very thankful that she agreed to allow me to use trastuzumab as a mode of treatment at that time.

DR LOVE: Did you feel that trastuzumab was going to be more acceptable to her because of the toxicity and side effects profile or because of the idea that it wasn't chemotherapy?

DR GATTANI: The idea that it wasn't chemotherapy was important, and that she would be able to come back and initiate treatment after she was discharged from the hospital.

DR LOVE: So, at that point, she had already refused chemotherapy and radiation therapy in the past, but you were able to convince her to start treatment?

DR GATTANI: I talked her into trastuzumab, and in April of 2000 she agreed to take it along with pamidronate because her bone scan was positive in multiple areas. Amazingly, with single-modality treatment, she had a complete remission of her chest wall lesion and the pleural effusion did not recur. This lasted for several months from about April to September of 2000. At that time, I noted that her chest wall lesions were beginning to recur.

DR LOVE: What was her reaction when she saw the tumor going away?

DR GATTANI: I think she became a believer and began to trust me more. We bonded and I was able to learn that she wanted to be in control. She felt that her family was always making decisions for her, so I made it a point to make her the person making each decision, and not her brother or sister who came with her to every weekly treatment. I told her that although we were successful for a while, we might need to move on to additional treatment with trastuzumab, because it was not working anymore.

I also explained to her the philosophy that oncologists have with regard to metastatic disease and that this disease would not be cured. I suggested that she look at it as chronic disease and although she probably wasn't going to die tomorrow, she would be on some form of treatment pretty much for the rest of her life — like diabetics and people with hypertension. I think because she had seen a response and how much better she felt, I earned her trust.

DR LOVE: What happened from then until now?

DR GATTANI: She has since allowed me to add chemotherapeutic agents, including docetaxel, vinorelbine, carboplatin and gemcitabine. When she failed carboplatin-gemcitabine, she actually begged me for doxorubicin, which I was keeping for last because of the cardiac toxicity. I gave her the weekly doxorubicin and she responded. We could measure the effectiveness by looking at the chest wall, and we were able to see when things got better or worse much quicker than we could with scans.

In January of 2002, she received doxorubicin, and I thought she should stop taking chemotherapy. She wanted more, but we made the decision to continue the trastuzumab alone and she continues to do so. In August of this year, after about one and a half years of monotherapy, I noted two chest wall nodules that were slowly but definitely progressing. Now we are discussing what to add.

DR THEODOULOU: The psychological makeup of the human being is fascinating. I think what was said earlier about different regimens being discussed based on different patient profiles and the sense that we have about our patients really rings true. It is so

complex that sometimes it seems like we are walking on water, and we get wet a lot because we really can't solve all of these issues that are often 40 years or, in my practice, 60 years in the making. That's just a commentary. But it is incredible that you were able to gain the kind of trust that you did in this woman.

DR LOVE: That's what really struck me when I heard this story. I think that a lot of physicians who encounter a woman who doesn't follow their recommendation might have been uncomfortable taking care of that patient and might even ask her to go to another doctor. What I heard from you was a true commitment to this woman. She called you when she was naked in the street, and you had never even treated her.

DR GATTANI: Receiving that phone call definitely shocked me because I had only seen her twice in follow-up. I was just so impressed that she would call me, even though I was helpless. I didn't know where she was and couldn't help her at all.

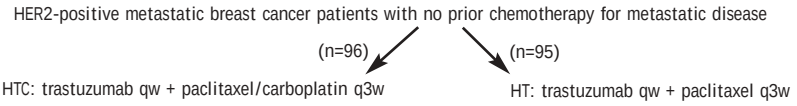
DR LOVE: So now you have a patient who wants to know what your advice is and she has a decision to make. Skip, can you talk about some of the combinations that might be considered and what your thoughts are? You've done a lot of clinical research on trastuzumab-containing triplets, so maybe you can review some of the combinations we have data on and what some options might be for this woman?

DR BURRIS: I think the data has evolved and is very provocative, and I'm intrigued by the fact that the platinums are so synergistic with trastuzumab. Several different centers have reported on giving a taxane and a platinum together with trastuzumab. Gemcitabine-platinum-trastuzumab combinations are being looked at as well.

We've done some work with paclitaxel, carboplatin and trastuzumab, and other studies with similar combinations have had response rates sufficient enough for patients to get a longer chemo holiday.

Mark Pegram and I have talked about that and are presenting some data that show three or four months of slightly more aggressive chemotherapy up front often resulted in the patient being able to take trastuzumab alone for six, 12 or even 18 months or longer and truly be on a chemo holiday. I wouldn't put trastuzumab in a class with chemotherapy drugs.

Phase III Study Comparing Trastuzumab and Paclitaxel with and without Carboplatin in Patients with HER2-Positive Advanced Breast Cancer



Study Results

Parameters	HTC regimen	HT regimen	p-value
Response rate (RR)	48/92 52%	34/94 36%	$p = 0.04$
RR in HER2 IHC 3+	35/61 57%	23/63 37%	$p = 0.03$
Time to progression (TTP)	11.2 mo	6.9 mo	$p = 0.007$
TTP in HER2 IHC 3+	13.5 mo	7.2 mo	$p = 0.006$

HTC = trastuzumab, paclitaxel, carboplatin; HT = trastuzumab, paclitaxel

SOURCE: Robert N. **Presentation, San Antonio Breast Cancer Symposium 2002. Abstract 35.**

My nurses get so excited nowadays if a metastatic breast cancer patient's pathology comes back HER2-positive because they feel greater comfort that the patient's going to do better for a longer period of time. Not a lot of data exists in this setting and certainly no randomized data on continuing trastuzumab after initial progression.

It's interesting, the survival curves from the initial Slamon presentation have crept up from two years to three years and, in some trials, median survival has not been reached by three years. You have to credit some of that stretching of the curve to the fact that we all continue trastuzumab after progression. It's an anecdotal look at that data, but it's very consistent in all of the studies, that the survival curve has moved to the right.

The other point is that we don't have a great next option for this patient. In my patients who have taken trastuzumab for a long period of time and then stop it, very often I've lost control of the disease. In those cases, things go poorly very quickly, and I have a difficult time getting them to re-respond, not become symptomatic and not have a rapid fatal outcome.

Since this patient has not been on capecitabine, I think that would likely be the agent that I would go to next in this setting. I think that the data from the early preclinical and clinical work was misinterpreted in terms of 5FU being questionably antagonistic or less than additive. I believe that was really a mathematical model issue, so I think chronic oral capecitabine with trastuzumab would be a reasonable option for this patient.

DR GATTANI: Actually, before I gave her doxorubicin, I recommended capecitabine; however, I have to balance my recommendations with her complementary doctor's suggestions. He read literature and said that there was no synergy or response with the trastuzumab-capecitabine combination. I have been trying to explain to her that everyone needs to be treated individually. Incidentally, his recommendation was imatinib.

DR BURRIS: The asymptomatic nature of this woman's situation is another vote in this direction, and I think staying with a relatively nontoxic chemotherapy at this point would certainly be advantageous. We've all been concerned about anthracyclines and trastuzumab, but another drug that I sometimes go back to is liposome-encapsulated doxorubicin (Doxil®) at a modest dose of 30 mg/m^2 every three weeks or 40 mg/m^2 every four weeks.

We know from some of the adjuvant retrospective studies that HER2-overexpressing patients seem to be sensitive to the anthracyclines or at least obtain an additional benefit from them.

I also have had the good fortune of doing some Phase I and II trials with some of the newer EGFR and pan inhibitors affecting the HER1 and HER2 pathways. If you had the option of trying something investigational to block the pathway, you could consider EGFR or pan inhibitors. However, patients who have truly responded to trastuzumab and have been on it for a long period of time often do poorly when it is stopped. That may be just the nature of the disease.

DR GATTANI: I refuse to stop the trastuzumab in this woman because I saw the response that she had. Her pleural effusion has not recurred, and she mainly has just a chest wall lesion.

DR THEODOULOU: Skip's comment about survival being lengthened from Slamon's pivotal trial is really interesting. We sometimes lose sight of the fact that not only do we have a survival benefit that is continuing to be documented, but we're also seeing a survival benefit in a particularly bad player in breast cancer.

These were the patients who would present, flare, burn and die on us, often within a

year or a year and a half. It's just astounding how much headway we have made in breast medicine.

In this patient I would favor capecitabine as a treatment option. I think the 5FU-trastuzumab *in vitro* data tainted us against capecitabine, but Mark Pegram will be the first to say that this is a totally different drug with totally different properties of metabolism and clearance. Capecitabine would be my selection.

Because we've seen not only response but also improvements in time to progression, duration of response and survival in patients who received AC or EC with trastuzumab in the pivotal trial, I'm a big fan of bringing safer anthracyclines into the clinical setting.

We are about to publish the final results of a 40-person, Phase I/Phase II trial looking at the safety of nonpegylated liposomal doxorubicin (TLCD99) in 40 patients. In looking for cardiac safety, we were surprised to see efficacy in a heavily pretreated patient population who had previously received both trastuzumab and anthracyclines. The response rates were in the mid-fifties, with a clinical benefit of 79 percent. Hopefully, trials like this one will open up that venue of treatment.

DR LOVE: Skip, you were talking about the platinum-containing triplets that have emerged. What factors do you consider when deciding to use a triplet as opposed to a doublet?

DR BURRIS: That's a very key point. The decision is similar to the decision of how aggressive to be in the adjuvant setting. I tend to put patients into three categories—low risk, intermediate risk and high risk. I look at the low-risk category as an opportunity to give trastuzumab by itself. As the risk increases, I add more agents. My double-agent combination has generally been a taxane and trastuzumab, while my three-drug combination has been taxane-platinum-trastuzumab.

If a patient is fairly asymptomatic and doesn't have much disease, I offer her trastuzumab by itself and see how it goes. Anecdotally, I have had some patients do very well with trastuzumab monotherapy.

We conducted a trial in which patients had the opportunity to have a lead-in induction with trastuzumab. Patients who had stable disease or better remained on trastuzumab for eight weeks and then received an additional eight weeks of treatment.

In patients who had evidence of progressive disease, paclitaxel and carboplatin were added to the trastuzumab. It was a small trial of 63 patients, but if you look back and see how the patients fared, we didn't lose any ground during that first eight weeks in patients who didn't benefit from trastuzumab.

For a patient who clearly has visceral metastases and is symptomatic, I use the three-drug combination with the platinum included. The other patients fall in the mix,

Efficacy of First-Line Paclitaxel/Carboplatin/Trastuzumab in Patients with HER2-Overexpressing Metastatic Breast Cancer

	ORR	TTP	Median survival
All (IHC 2+, 3+; n=61)	66%	12 mo	29 mo
FISH+	89%	19 mo	30+ mo*
FISH-	44%	8.5 mo	19 mo

* Median survival not reached at 30 mo; ORR = objective response rate; TTP = time to progression

SOURCE: Yardley DA et al. **Final results of the Minnie Pearl Cancer Research Network first-line trial of weekly paclitaxel/carboplatin/trastuzumab in metastatic breast cancer.** *Breast Cancer Res Treat* 2002. **Abstract 439**

and we discuss which one to start with and how aggressive to be.

DR BILSKY: A lot of the data with the platinum-taxane-trastuzumab triplets suggest greater response rates and longer response durations. The advocates of sequential single-agent therapies say that when you recapture a response and add the two sequential therapies together, you're pretty much where you were with the response of triplet.

If a patient is young and has aggressive visceral disease, I use a triplet. But if a patient has HER2-negative disease, more often than not I use sequential single agents. This is a big controversy right now.

DR LOVE: Maria, in the last five years we've seen a huge shift in clinical practice in using singleagent chemotherapy for HER2-negative metastatic disease. Is that the way you practice?

DR THEODOULOU: In our group we are big fans of sequential single-agent therapies and trying to milk the responses for all we can before we go on to the next regimen. However, other than the ECOG trial that George Sledge presented, we really haven't examined this issue very well. Even in the Sledge study, we saw some response advantage at least in terms of time to progression for combination therapy, but when you look at the data, there was no survival advantage.

I think you need to look at your window of opportunity and if you have a patient with visceral disease and multiple lesions in her liver and lungs, who is symptomatic and is not going to be around in two months, there's no question I'm going to use the triplet of carboplatin, paclitaxel and trastuzumab.

I tend to use the weekly regimen because the side-effect profile is more favorable, and based on the data that was presented this past spring from Rowland, we don't lose anything by way of response. Once I get a response and I know we're out of hot water, then I'll tailor my regimens to trastuzumab with one of the single agents. Eventually the goal is to get the patient on trastuzumab alone.

DR LOVE: I want to ask Dr Tavorath for a comment on this case because earlier she presented an incredible case of a woman with locally recurrent disease that she's observed for 14 months. We all thought that took a lot of patience, and I was curious about her thoughts on this unusual case.

DR TAVORATH: Actually, I was thinking about a patient I just saw about a month or two ago. She was exactly the same — a young woman with six positive nodes, ER/PR-negative, HER2-positive. She underwent surgery but absolutely refused chemotherapy and, essentially, was sent to me to receive adjuvant trastuzumab monotherapy.

DR LOVE: Were you willing to give her trastuzumab?

DR TAVORATH: I thought about it, and at one point I felt that maybe it was better

Intergroup Trial 1193: Comparing Doxorubicin, Paclitaxel and Combination Doxorubicin/Paclitaxel

	Doxorubicin	Paclitaxel	Doxorubicin/paclitaxel
Objective response	36% (20% response to crossover)	34% (22% response to crossover)	47%
Median Survival	19.1 mo	22.5 mo	22.4 mo

SOURCE: 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**

Phase II Trial of Weekly versus Every Three-Week Paclitaxel, Carboplatin and Trastuzumab in Women with HER2-Positive Metastatic Breast Cancer: Efficacy and Toxicity Data

Interim efficacy analysis (n=36)	Every three-week	Weekly
Response rate maintained >4 weeks	50% (95% CI 26-74%)	78% (95% CI 52-94%)
Median progression-free survival	8.8 mo	13.4 mo
1-year progression-free survival	27% (95% CI 13-59%)	56% (95% CI 37-87%)
Grade 3/4 toxicities (n=84)		
Neutropenia	88%	52%
Leukopenia	70%	27%
Thrombocytopenia	30%	2%
RBC transfusion	25%	5%
Neurosensory	20%	2%
Febrile neutropenia	18%	0%
Anemia	15%	5%
Myalgia	15%	0%
Arthralgia	13%	2%

SOURCE: Perez EA et al. **N98-32-52: Efficacy and tolerability of two schedules of paclitaxel, carboplatin and trastuzumab in women with HER2-positive metastatic breast cancer: A North Central Cancer Treatment Group randomized Phase II trial.** *Breast Cancer Res Treat* 2003;**Abstract 216**.

than nothing, but I couldn't convince myself and she didn't want it. When she heard about the treatments out there, she basically said, "I know I have bad disease. I'll probably relapse and die, but I don't want treatment like this." She has been seeing me every few months on follow-up and actually came in last week crying because she suddenly developed pain in her shoulder.

I think she has radiation-related irritation of the brachial plexus, but the point is that if she had metastatic disease, she probably would have agreed to be treated. It's sometimes difficult to know when to really push what you think is right for the patient. I think you have to build up a level of comfort and trust to the point where you can tell them the right way to do it. But they have to make the decision about what's right for them.

DR LOWENTHAL: When patients are fearful of chemotherapy, those fears are often based on the old public perception of terrible nausea, hair loss and hospitalizations. Sometimes, by offering a regimen that may not be my first-line regimen, but one I think can reduce their risk of hair loss, nausea and other side effects, I've been able to work through the fear. Obviously, the higher the risk, the more inclined I am to push things. But for patients for whom chemotherapy is indicated, but who refuse chemotherapy under any circumstance, I always try to work with them.

Select publications: *Chemotherapy in the treatment of HER2-positive metastatic disease*

Baselga J. **Herceptin alone or in combination with chemotherapy in the treatment of HER2-positive metastatic breast cancer: Pivotal trials.** *Oncology* 2001;61(Suppl 2):14-21. **Abstract**

Burris HA 3rd. **Docetaxel (Taxotere) plus trastuzumab (Herceptin) in breast cancer.** *Semin Oncol* 2001;28(1 Suppl 3):38-44. **Abstract**

Burstein HJ et al. **Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2001;19(10):2722-30. **Abstract**

Christodoulou C et al. **Prolonged administration of weekly paclitaxel and trastuzumab in patients with advanced breast cancer.** *Anticancer Res* 2003;23(1B):737-44. **Abstract**

Eiermann W; International Herceptin Study Group. **Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: Pivotal trial data.** *Ann Oncol* 2001;12(Suppl 1)57-62. **Abstract**

Leyland-Jones B. **Trastuzumab: Hopes and realities.** *Lancet Oncol* 2002;3(3):137-44. **Abstract**

Ligibel JA, Winer EP. **Trastuzumab/chemotherapy combinations in metastatic breast cancer.** *Semin Oncol* 2002;29(3 Suppl 11):38-43. **Abstract**

Miller KD et al. **Gemcitabine, paclitaxel, and trastuzumab in metastatic breast cancer.** *Oncology (Huntingt)* 2001;15(2 Suppl 3):38-40. **Abstract**

Montemurro F et al. **Safety and activity of docetaxel and trastuzumab in HER2-overexpressing metastatic breast cancer: A pilot Phase II study.** *Am J Clin Oncol* 2003;26(1):95-7. **Abstract**

O'Shaughnessy J. **Gemcitabine and trastuzumab in metastatic breast cancer.** *Semin Oncol* 2003;30(2 Suppl 3):22-6. **Abstract**

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Seidman AD et al. **Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification.** *J Clin Oncol* 2001;19(10):2587-95. **Abstract**

Sledge GW Jr. **Gemcitabine combined with paclitaxel or paclitaxel/trastuzumab in metastatic breast cancer.** *Semin Oncol* 2003;30(2 Suppl 3):19-21. **Abstract**

Winer EP, Burstein HJ. **New combinations with Herceptin in metastatic breast cancer.** *Oncology* 2001;61(Suppl 2)50-7. **Abstract**

CASE 4: A 63-year-old woman presenting with locally advanced breast cancer and metastases (from the practice of Dr Bilsky)

- Two years ago, this 63-year-old woman presented with a large, ulcerated breast lesion and a palpable supraclavicular node.
- Bone scan was positive in multiple locations.
- CAT scan of the chest and abdomen were negative.
- Breast biopsy revealed ER-positive, HER2-negative, infiltrating ductal carcinoma.
- Received pamidronate and docetaxel/doxorubicin x 6 and had an excellent response.
- Patient is now on maintenance letrozole.

Key discussion points:

1. Psychosocial issues in treating women with metastatic disease
2. Goals of treating metastatic disease
3. Chemotherapy versus hormonal therapy for patients with locally advanced breast cancer

DR LOVE: Before we continue with the case discussions, let's take a moment to reflect on some of the psychosocial issues in decision-making in the metastatic setting. Maria, how do you approach this?

DR THEODOULOU: From the moment you meet a patient with — or make a diagnosis of — metastatic disease, you're dealing with a life-threatening illness. From the very onset, you define your goals of treatment, hopefully in a team effort with the patient. Together you decide whether the goal is cure, palliation, quality of life or supportive care. We've all listened to the lectures, read the algorithms and talked about it with our patients.

This is not something that's esoteric or sophisticated for any of us. But, we know that we're dealing with a life-threatening disease, and sometimes the patient is willing to take on toxicities and a compromise in quality of life to get to a better place.

DR LIPSHUTZ: One of the reasons meetings like these are so successful is because, as oncologists, we constantly have competing anxieties. We are worried about so many things: causing harm to our patients, being state-of-the-art, medicolegal issues, psychosocial issues. We are even worried about our own lifestyle, our own ability to assimilate the data that comes down the line and our ability to deliver state-of-the-art care.

We have more options available, which is making consults much lengthier and leading to more difficult discussions. All of that weighs heavily on us. Many of us have been doing this for many years and when we finished our fellowships, we believed that we were going to see cures in our lifetime. I think all of us were optimists and thought we were going to see major advances, and that's why we went into oncology.

However, the advances have been painstakingly slow. They are real, but they require a long-sighted vision over a long period of time to see them. People want the latest, greatest and best therapies immediately, and that causes a tremendous amount of strain. If

you add government regulations, bureaucratic demands and difficulty with reimbursements for what we consider to be the best of treatment, there is tremendous strain, stress and anxiety on the oncologist.

DR LOVE: Dr Burris, Dr Theodoulou talked about setting realistic goals for the woman with metastatic breast cancer. Can you talk about how you do that in your practice?

DR BURRIS: As Maria was alluding to, the conversation in the metastatic setting is more difficult in terms of how old the patient is, what her performance status is and whether she is having symptoms. A few years ago, the Southwest Oncology Group was trying to do a trial with two different paclitaxel arms for patients who were symptomatic or asymptomatic.

The asymptomatic arm closed very quickly because there were so many patients who relapsed with relatively asymptomatic disease. This gets to an interesting point: I've recently seen several women with metastatic breast cancer recurrences who have been diagnosed by laboratory, a chest X-ray or something that another physician did to get the test result. These patients were not symptomatic and not feeling poorly. In these cases you are left with the decision of how bad should you make the patient feel to get rid of some tumor to potentially prolong life?

So you sit down and you talk with patients about where they want to be and what they want to do. Some older patients have very short-term goals like living to see a grandchild or to watch somebody get married.

These patients are sometimes easier to work with than those with longer-term goals. I saw a woman the other day who was 47 years old with little girls in junior high school. Her goals were probably unrealistic, but her main focus every day was preventing her family's life from being disrupted by her illness.

DR LOVE: What is it like to take care of a 47-year-old woman who has a couple of teenage kids and an extremely serious, noncurable problem? How do you deal with it as an oncologist?

DR GREENBERG: Personally, the first thing I do is talk with the patient to get a sense of what is important to her. Many times she will want to be able to spend time with her children. Generally I have found that patients fall into two populations. One population says, "I want to live, and I don't care what I have to do."

They will walk on hot coals for you, if you think it will buy them one more week. The other population says, "I'm not having that much of a problem now, so just keep me comfortable and don't disrupt my quality of life. Let me enjoy my family because I don't think you're going to cure me."

You need to discuss what the realistic chances are that you're going to tremendously impact their survival and balance that against what they will have to go through to get what benefit. I think that's an important discussion to have.

DR LOVE: Dr Theodoulou, how does the doctor deal with it, personally.

DR THEODOULOU: One of the things I encountered when I was going through my fellowship was the whole concept of being comfortable with death and dying, and that you are never going to get bonus points or a pat on the back for successfully treating a patient, because that patient will eventually die in your care.

It's important to really identify what your comfort level is. Personally, I'm very comfortable in the arena of death and dying. I knew it as a medical student, an intern and a fellow. I come from an environment where family members die at home with their families around them, so I was never uncomfortable in that situation.

Due to the sadness of it, I don't think this is the kind of work that you can ever leave behind at the office. But we have to be very careful not to let one patient experience — even if it's a devastating or tragic one — influence the next patient experience that we

have the following day or the next week.

I don't think there are enough venues like this one where we talk to one another. How many times do we talk about how recently we cried, felt guilty, felt frustrated, felt failure or felt like, "Boy, that was a successful death, and thank God I was around to do something good"? I try to open up these types of discussions at the end of the day with my fellows because it is really a huge topic that needs to be addressed more often.

DR RAJDEV: I actually find that young women with metastatic disease are more complex with more emotional issues. Older people are more resigned to dying, whereas younger women, particularly those who have children, have a harder time. I think younger patients with very advanced disease are more demanding on oncologists, at least to me they are.

I had a patient who was in her fifties and didn't want to die before seeing her daughter get married. Every time I went on vacation, she got sick. She started telling me not to go on vacation. Then, she passed away. Later on, I can recall one time when I was about to go on vacation when suddenly, she came back to me. It was like she was telling me again not to go on vacation. I think oncologists are affected, but you have to pick up and move on. It is a way of life, but patients do have an impact on you.

DR LOVE: How do you personally cope with these kinds of things?

DR RAJDEV: It's hard to brush off people. You realize that these are such important issues that you just sort of make the time and talk to patients about them. You can actually see that the more you treat them, the greater confidence they tend to have in you. They develop a rapport with you, even on a social basis, and the more you treat them the more you learn about their lives.

DR LIPSHUTZ: As oncologists I think we're all very different, just like people are in general. I think we have different psychological makeups, backbones and ways we cope. Personally, I think hospice was a major advance that has allowed oncologists to continue to practice oncology. In the days before hospice, we used to spend too much time taking care of dying people, and the futility of it from a medical oncology standpoint would be frustrating.

I have hobbies and interests that help me divorce myself from the practice of medicine. I am able to move away from it, and yet devote 100 percent of my attention when I'm in the office. I can make that separation, go home and not think about what's going on until the next day when the next problem arises. Friends, family and neighbors call you all the time and ask you for help or advice, so you're really never away from it even on vacation, but I think you need some other interests.

DR LOVE: Dr Bilsky, would you present your case?

DR BILSKY: This patient is an otherwise healthy 63-year-old who looks like she's 53. In June of 2002, she presented with a large, crusted ulcerating right breast lesion and a palpable right supraclavicular lymph node. The work-up revealed bone metastases on bone scan, but she had no bone pain. Her CAT scans failed to reveal any areas of visceral disease in her chest or abdomen. Her breast biopsy revealed ER-positive, HER2-negative, infiltrating ductal carcinoma. Her performance status was excellent and her past medical history was essentially benign.

DR LOVE: Did you have the feeling that she neglected this breast lesion?

DR BILSKY: Oh, yes. She is an intelligent lady. She is a divorcee with a very supportive daughter. I think she was more concerned about being a mother to her daughter and trying to protect her daughter from the idea that this might be a serious significant illness than she was about her own mortality.

DR LOVE: What were you thinking at that point?

DR BILSKY: After the biopsy I knew what her status was pathologically, and I really wanted

to just get rid of this horrible right-breast lesion. I treated her fairly aggressively and started her on pamidronate and six courses of docetaxel and doxorubicin. She responded beautifully. The right breast lesion and the ulceration absolutely dried up and the crusting disappeared. Her right supraclavicular lymph node became barely palpable.

In December of that year, I switched her to maintenance letrozole. I never recommended radiation therapy. I felt that I had controlled the primary tumor pretty well systemically, and I was concerned that the amount of radiation therapy she would require might cause radiation-induced vasculitis that would have been a problem — particularly if she were to ulcerate again.

DR LOVE: I want to go back to your decision to use combination chemotherapy and ask Skip Burris how he would have thought through this case, because another alternative would have been to try hormonal therapy first and see what would happen.

DR BURRIS: I would have probably gone with the same approach as Dr Bilsky. In situations where you can see a tumor like this one in front of you, I think the goal is usually to get rid of it as quickly as possible. In Europe and other parts of the world, hormonal therapy certainly would have been considered. I know that the BCIRG has been trying to get some neoadjuvant hormonal therapy trials rolling, but our doctors in Nashville didn't think they would ever enroll a patient in that type of study. I don't know if the trial is still moving forward — maybe it's more of an American reaction.

I think docetaxel and doxorubicin are two very active drugs, and the odds of responding are 60, 70, 80 percent and up. Within two or three treatments you're going to have a dramatic response, so I think that was a very logical approach. It's probably what I would have done.

DR LOVE: She is in good condition and this is not an emergent situation, but she does have a disturbing breast lesion. Maria, what about neoadjuvant endocrine therapy?

DR THEODOULOU: I think hormonal therapy is the foundation of our treatment and the gold standard in metastatic disease. But hormonal therapy is slow. It doesn't kick in for three, four or five weeks; sometimes it takes two months or even 10 weeks. Here we have a fairly significant ulceration and a crusted lesion that's going to be amenable to infection and oozing, which could make it all the more difficult to treat.

I probably would have been inclined to use chemotherapy for local control, and then once I got the response I needed, switched over to hormonal therapy. I have used hormonal therapy in Stage IV *de novo* locally advanced breast cancer, but this is the kind of lesion that would have pushed me to treat with chemotherapy.

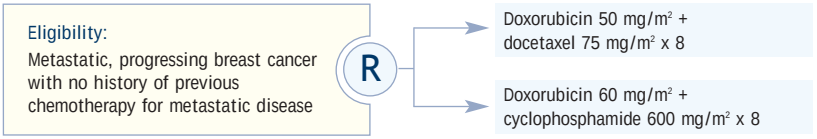
Select Phase II Trials of Doxorubicin (A) Plus Docetaxel (T)

Author	Regimen (mg/m^2)	N	ORR (%)	TTP (months)	Survival (months)
Sparano	A 60 T 60	51	57	7.6	27.5
Dieras	A 50 T 75	39	74	NR	NR
Baltali	A 60 T 80	42	79	8.0	NR

ORR = objective response rate; TTP = time to progression; NR = not reported

SOURCE: Nabholtz JM. **Docetaxel-anthracycline combinations in metastatic breast cancer.** *Breast Cancer Res Treat* 2003;79(Suppl 1):3-9. **Abstract**

Randomized, Multicenter, Phase III Trial Comparing Docetaxel/Doxorubicin with Doxorubicin/Cyclophosphamide as First-Line Chemotherapy for Metastatic Breast Cancer



Actual Accrual: 429

Efficacy data	AT (n=214)	AC (n=215)	*p*-value
Median TTP	37.3 weeks	31.9 weeks	0.014
Median TTF	25.6 weeks	23.7 weeks	0.048
Overall response	59%	47%	0.009
Complete response	10%	7%	
Partial response	49%	89%	

TTP = Time to progression; TTF = Time to treatment failure
Overall survival was comparable in both arms.

SOURCE: Nabholtz J-M et al. **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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Dickenson DL. **Are medical ethicists out of touch? Practitioner attitudes in the US and UK towards decisions at the end of life.** *J Med Ethics* 2000;26(4):254-60. **Abstract**

Dickinson GE. **A quarter century of end-of-life issues in U.S. medical schools.** *Death Stud* 2002;26(8):635-46. **Abstract**

Dickinson GE et al. **Twenty years beyond medical school: Physicians' attitudes toward death and terminally ill patients.** *Arch Intern Med* 1999;159(15):1741-4. **Abstract**

Downe-Wamboldt B, Tamlyn D. **An international survey of death education trends in faculties of nursing and medicine.** *Death Stud* 1997;21(2):177-88. **Abstract**

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Holstein M. **Reflections on death and dying.** *Acad Med* 1997;72(10):848-55. **Abstract**

Kash KM et al. **Stress and burnout in oncology.** *Oncology (Huntingt)* 2000;14(11):1621-33; discussion 1633-4, 1636-7. **Abstract**

Leland JY. **Death and dying: Management of patients with end-stage disease.** *Clin Geriatr Med* 2000;16(4):875-94. **Abstract**

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Sand RB et al. **A survey of physicians' education in caring for the dying: Identified training needs.** *J Cancer Educ* 1998;13(4):242-7. **Abstract**

Seligman PA et al. **Practicing physicians' assessments of the impact of their medical-school clinical hospice experience.** *J Cancer Educ* 1999;14(3):144-7. Abstract

Sotile WM, Sotile MO. **Beyond physician burnout: Keys to effective emotional management.** *J Med Pract Manage* 2003;18(6):314-8. **Abstract**

Steinhauser KE et al. **Preparing for the end of life: Preferences of patients, families, physicians, and other care providers.** *J Pain Symptom Manage* 2001;22(3):727-37. **Abstract**

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Vachon ML. **Reflections on the history of occupational stress in hospice/palliative care.** *Hosp J* 1999;14(3-4): 229-46. **Abstract**

Webster J, Kristjanson LJ. **"But isn't it depressing?" The vitality of palliative care.** *J Palliat Care* 2002;18(1):15-24. **Abstract**

CASE 5: Multiple metastases in an elderly, asymptomatic patient (from the practice of Dr Richard Zelkowitz)

- A 65-year-old woman was treated with lumpectomy, adjuvant CMF, radiation and five years of tamoxifen for a 1.3-cm, ER/PR-positive, HER2-negative breast tumor with negative nodes.
- At age 70, the patient noted skin lesions on her hand, shoulder and abdomen that were biopsied and found to be metastases.
- Metastatic work-up revealed three bone lesions and a 2-cm hepatic lesion.
- Patient is asymptomatic and is receiving letrozole and a bisphosphonate.

Key discussion points:

1. Treatment of the asymptomatic, elderly patient with ER-positive metastatic disease
2. Efficacy and tolerability of fulvestrant

DR ZELKOWITZ: I saw this patient initially in 1998 when she was 65 years old. She had a 1.3-cm ER/PR-positive, HER2-negative tumor with negative nodes. After much discussion, she received adjuvant CMF, radiation to the breast and tamoxifen.

She recently completed her five years of tamoxifen and presented to the office for a routine follow-up visit. She had no complaints. On her way out she mentioned that she had a few funny "little things" on her skin. I've seen many skin metastases over the years, but these were very small and innocuous looking. I had done a complete physical examination and just passed by these lesions.

One was on the hand, another on the shoulder and one was on her abdomen. I wasn't sure what they were, so I sent her to her surgeon who removed them. Lo and behold, they turned out to be skin metastases.

DR LOVE: Were you expecting the surgeon to remove all three lesions?

DR ZELKOWITZ: No. I figured they would biopsy one. Frankly, I did not think this was metastatic disease. In retrospect, I wish he had left one so I would have a marker lesion.

So, obviously, this was metastatic disease. She is now almost 70 years old and totally asymptomatic. She spends a good part of her time on her boat with her husband. We repeated the ER/PR and HER2 assays, which remained the same — ER/PR-positive and HER2-negative. We did an extent of disease workup and found three solitary bone lesions — one in her sternum, one in her right hip with a negative plain film and a third in her rib. None of her bone lesions are symptomatic. She also has a 2-cm hepatic lesion. We didn't biopsy anything. Her chest CT was negative.

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

DR THEODOULOU: She's asymptomatic, 70 years old and ER-positive. I would treat her with an aromatase inhibitor or fulvestrant.

DR ZELKOWITZ: We put her on letrozole and a bisphosphonate.

DR THEODOULOU: That's all reasonable. The question is: Would I treat her with chemotherapy? She had a five-year, disease-free interval, so I would be very comfortable treating her hormonally.

DR BURRIS: I would agree with that, too. The fulvestrant comment is interesting. My nurses have really gotten into the mode of Medicare patients thinking about the question of prescription benefits and are aware of the coverage for fulvestrant, which we consider even more strongly if the patient is going to receive bisphosphonates.

I have a number of patients who come in and receive once-a-month zoledronic acid and fulvestrant. It's a shame. It's probably a greater cost to the system, but it saves the patient a lot of money.

There are plenty of Medicare patients out there who don't have that set-up, and fulvestrant works well in that scenario. I've had some very good results with fulvestrant, and certainly it's very reasonable to use.

Efficacy of Fulvestrant Compared to Anastrozole in Postmenopausal Women with Advanced Breast Cancer Progressing on Prior Endocrine Therapy

	Combined analysis[1]		European trial (0020)[3]		North American trial (0021)[5]	
	Fulvestrant (n=428)	Anastrozole (n=423)	Fulvestrant (n=222)	Anastrozole (n=229)	Fulvestrant (n=206)	Anastrozole (n=194)
Disease progression			82.4%	83.4%	83.5%	86.1%
Median time to progression	5.4 mo	4.1 mo	5.5 mo	5.1 mo	5.4 mo	3.4 mo
Treatment failures			84.7%	85.6%	79.6%	84%
Objective response	19.6%[2]	17.3%[2]	20.7%	15.7%	17.5%	17.5%
Clinical benefit (CR + PR + SD ≥ 24 w)	43.7%[2]	41.1%[2]	99 (44.6%)	103 (45.0%)	87 (42.2%)	70 (36.1%)
Median duration of response in those responding	16.7 mo*	13.6 mo*	15.0 mo	14.5 mo	19.0 mo	10.8 mo
Median time to death			26.5 mo[4]	24.3 mo[4]		

*In addition to reporting median duration of response (DOR) in those responding, a newly developed statistical analysis of DOR was performed, defined for responders as the time from onset of response to disease progression and for non-responders as zero. In this analysis, DOR was significantly greater (ratio of average response durations = 1.30; 95% CI 1.13 to 1.50; p=0.0003) for fulvestrant versus anastrozole.

SOURCES: [1]Parker LM et al. *Proc ASCO* 2002;**Abstract 160** [2]Mauriac L et al. *Eur J Cancer* 2003;39(9):1228-33. [3]Howell A et al. *J Clin Oncol* 2002;20:3396-403. [4]Howell A et al. *Proc ASCO* 2003: **Abstract 178** [5]Osborne CK et al. *J Clin Oncol* 2002;20:3386-95.

Select publications: ***First-line endocrine therapy in metastatic disease***

Buzdar AU. **Advances in endocrine treatments for postmenopausal women with metastatic and early breast cancer.** *Oncologist* 2003;8(4):335-41. **Abstract**

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; discussion 27-8. **Abstract**

Howell A et al. **A review of the efficacy of anastrozole in postmenopausal women with advanced breast cancer with visceral metastases.** *Breast Cancer Res Treat* 2003;82(3):215-22. **Abstract**

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

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Pritchard KI. **Endocrine therapy of advanced disease: Analysis and implications of the existing data.** *Clin Cancer Res* 2003;9(1 Pt 2):460S-7S. **Abstract**

Simons WR et al. **Cost-effectiveness of anastrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer.** *Clin Ther* 2003;25(11):2972-87. **Abstract**

Wong ZW, Ellis MJ. **First-line endocrine treatment of breast cancer: Aromatase inhibitor or antioestrogen?** *Br J Cancer* 2004;90(1):20-5. **Abstract**

Post-test: Meet The Professors, Issue 1, 2004

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The pivotal Phase III trial comparing chemotherapy alone versus chemotherapy plus trastuzumab showed the addition of trastuzumab improved overall survival.

a. True
b. False

2. In the sixth edition of the American Joint Committee on Cancer staging system for breast cancer, metastasis to the supraclavicular lymph nodes has been reclassified as N3 rather than M1.

a. True
b. False

3. In the randomized Phase III trial comparing docetaxel/doxorubicin with doxorubicin/cyclophosphamide as first-line chemotherapy for metastatic breast cancer, the docetaxel/doxorubicin combination was superior in all of the following except:

a. Median time to progression
b. Median time to treatment failure
c. Overall response
d. Overall survival

4. In the pivotal trastuzumab trial, a subset analysis showed prior hormonal therapy did not adversely affect the outcomes with chemotherapy and trastuzumab combined.

a. True
b. False

5. In Seidman's comprehensive review of cardiac toxicity of trastuzumab, he found that prior anthracycline exposure was a risk factor.

a. True
b. False

6. Which of the following statements is true about the results from the trial comparing trastuzumab plus paclitaxel with or without carboplatin?

a. There was an improvement in response rate for trastuzumab plus paclitaxel plus carboplatin.
b. There was no difference in response rate for trastuzumab plus paclitaxel plus carboplatin compared to trastuzumab plus paclitaxel.
c. There was an improvement in time to progression for trastuzumab plus paclitaxel plus carboplatin.
d. b and c
e. a and c

7. The usual and optimal first-line therapy for a woman with HER2-positive metastatic breast cancer who has not received prior chemotherapy is a doxorubicin-based regimen.

a. True
b. False

8. Clinical trials have proven that continuing trastuzumab after stopping chemotherapy and adding hormones results in improved survival in patients with HER2-positive metastatic disease.

a. True
b. False

9. Trastuzumab and capecitabine have adverse drug interactions and should not be used simultaneously.

a. True
b. False

Post-test Answer Key: 1a, 2a, 3d, 4a, 5a, 6e, 7b, 8b, 9b

Evaluation Form: Meet The Professors, Issue 1, 2004

Research To Practice respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued upon receipt of your completed evaluation form.

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5 = *Outstanding*	4 = *Good*	3 = *Satisfactory*	2 = *Fair*	1 = *Poor*	NA = *not applicable to this issue of MTP*

GLOBAL LEARNING OBJECTIVES

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

- Describe and implement a management strategy integrating chemotherapy, endocrine therapy and biologic therapy in the treatment of women with metastatic breast cancer . . . . . 5 4 3 2 1 NA
- Determine the clinical implications of emerging data on the use of trastuzumab in combination with chemotherapy in the management of HER2-positive, metastatic breast cancer in women . . . . . 5 4 3 2 1 NA
- Determine the adjuvant and neoadjuvant role of chemotherapy for patients diagnosed with locally advanced breast cancer . . . . . 5 4 3 2 1 NA
- Discuss the use of sequential single agents versus combination chemotherapy for the treatment of metastatic breast cancer . . . . . 5 4 3 2 1 NA

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Howard A Burris III, MD	5 4 3 2 1	5 4 3 2 1
Harold J Burstein, MD, PhD	5 4 3 2 1	5 4 3 2 1
Maria Theodoulou, MD	5 4 3 2 1	5 4 3 2 1
Charles L Vogel, MD, FACP	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
Avoided commercial bias or influence 5 4 3 2 1

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This program is supported by an education grant from Genentech BioOncology.

This program is supported by an education grant from Genentech BioOncology.

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Sponsored by Research To Practice.

This activity has been planned and produced in accordance with the ACCME Essential Areas and Policies.

Last review date: February 2004
Release date: February 2004
Expiration date: February 2005
Estimated time to complete: 4 hours