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Editor's Note

The Real World

It's time for a confession. During medical school at the University of Pennsylvania, I always sat in the seat closest to the door of the lecture hall. After a few minutes of hearing a professorial incantation, I would decide whether it was worth listening or if I could learn more by reading textbooks and my colleagues' notes. More often than not, I was out the door.

My impatience with esoteric presentations that have minimal practical implications has continued, although the fast pace of ASCO and other scientific meetings prevents me from "giving the hook" to many speakers. My history of intolerance to boring educational formats led me to develop a CME group 20 years ago that constantly experiments with programs focusing on daily medical practice. The case discussions in this monograph typify the dilemmas faced by patients and physicians every day.

We held three working group meetings this year to identify the "real-world" issues in the care of women with breast cancer. One unusual facet of this initiative was that prior to the meetings, each participant submitted four breast cancer case write-ups from their respective practices.

These cases focused on one challenging treatment decision that the physician and patient faced, and our group carefully analyzed these to identify themes we could potentially address in our educational programs.

It was interesting that when we transposed a case from the typical nondescript "a 44-year-old female with a 2.2-cm, Grade II, ER/PR-positive, HER2-positive infiltrating ductal carcinoma and three positive nodes" to "a 44-year-old nurse with high-risk breast cancer who is a single mother of three children under the age of 10," the nature of the discussion at the meeting shifted as it related to the perspectives of patients and physicians about emerging clinical research data and participation in clinical trials.

This monograph consists of edited discussions from a number of the more than 500 de-identified cases submitted, including comments from the faculty members who participated in these meetings. Our goal is to provide a snapshot of the myriad of complex biopsychosocial issues that oncologists and surgeons face when recommending therapy for patients with breast cancer in the adjuvant or metastatic setting.

Although this is the era of "evidence-based medicine," these cases include many "anecdote-based" management practices. Our purpose is not to endorse these

approaches, but rather to acknowledge that clinicians often rely upon experience and intuition in making decisions when the research data are sparse or nonexistent.

Our CME group recently renamed ourselves, "Research to Practice," because the clinicians on our content development staff, including myself, wish to take a scientific approach to educating physicians about the potential clinical implications of emerging research data and ongoing clinical trials.

This includes a realistic assessment of the education needs of our audience, and we evaluate this using a somewhat complex and integrated model. First, we review the data published in journals and presented in meetings. We also follow the evolution of ongoing clinical trials and meet regularly with key investigators to learn of their "take" on emerging data.

We have also approached patients for input, and this year we held three "Breast Cancer Patients' Perspectives" meetings where more than 1,200 survivors utilized handheld keypads and portable computers to provide their input on controversial treatment decisions.

The three community physician working group meetings profiled in this monograph directly fit into this paradigm of CME needs assessment, in that we turned to these oncologists and surgeons to find out the issues they face in daily practice and how emerging research data and ongoing clinical trials are relevant.

We hope this discussion provides useful insight into some of the real-world challenges in translating oncology research into practice and that it will be an educational resource that helps us develop programs that prevent our physician audience from "bolting for the door."

—Neil Love, MD

Participants at the 2003 *Breast Cancer Update* Working Group Meetings

Surgeons — May 15, 2003, New York, New York

Faculty:

Patrick I Borgen, MD
Kevin R Fox, MD
Generosa Grana, MD
Eleftherios P Mamounas, MD

Attendees:

Thomas L Bauer, MD
Stephanie Bernik, MD
Marcy E Bernstein, MD
Michele Blackwood, MD, FACS
Aaron D Bleznak, MD, FACS
Susan K Boolbol, MD
Erna Busch-Devereaux, MD, FACS
Anthony C Cahan, MD
Charles C Conte, MD
Robert Dianni, MD
Thomas G Frazier, MD
Henry Frissora, MD
Mark A Gittleman, MD
Arthur H Glasgow, MD
Stephen H Green, MD
Susan E Lee, MD
Harvey J Lerner, MD
Margaret Levy, MD
Deepak P Merchant, MD
Alison D Mishkit, MD
Ann M Rogers, MD
Sharon M Rosenbaum-Smith, MD
Francis J Scarpa, MD
J Stanley Smith, MD
Paul I Tartter, MD
Elizabeth Tito, MD
Marshall Weiss, MD
Carol Woo, MD

Oncologists — May 16-17, 2003, New York, New York

Faculty:

Robert W Carlson, MD
Kevin R Fox, MD
Generosa Grana, MD
Hyman B Muss, MD
Leroy M Parker, MD
Eric Paul Winer, MD

Attendees:

Alan Astrow, MD
Sushil Bhardwaj, MD
David D Biggs, MD
Samuel N Bobrow, MD
Engracio P Cortes, MD, FACP
Ajit M Desai, MD
Leonard R Farber, MD
Neil M Friedberg, MD
David H Gallinson, DO
Paul B Gilman, MD
Michael D Henderson, MD
Barry H Kaplan, MD, PhD
Howard I Kesselheim, DO
Paula Klein, MD
Diana Lake, MD
Craig Lampert, MD
Stephen M Lichter, MD
Alan J Lippman, MD
Janice M Lu, MD, PhD
Stephen C Malamud, MD
Harish K Malhotra, MD, FACP
David M Mintzer, MD
Anne Moore, MD
Mary Ellen Moynahan, MD
Kenneth K Ng, MD
Yelena Novik, MD
Steven W Papish, MD
Michael E Rader, MD
John Rescigno, MD
Kert D Sabbath, MD
Grace R Tarabay, MD
Amy Tiersten, MD
Deborah Toppmeyer, MD
James M Vogel, MD
Paul L Weinstein, MD
Richard S Zelkowitz, MD

Oncologists — September 12-13, 2003, Miami, Florida

Faculty:

Lisa A Carey, MD
Robert W Carlson, MD
Generosa Grana, MD
Peter Ravdin, MD

Attendees:

Sarkis Y Anac, MD, PhD
Luis R Barreras, MD
Francisco Belette, MD
Arnold S Blaustein, MD
Rogelio Brito, DO
Thomas H Cartwright, MD
Enrique Davila, MD
David Mark Dresdner, MD
Douglas E Faig, MD
Gregory R Favis, MD
Lynn G Feun, MD
Eduardo A Garcia, MD
Roman A Gastesi, MD
Eduardo G Gomez, MD
Stephen A Grabelsky, MD
Gracy Joshua, MD
Thomas J Katta, MD
Brian K Kim, MD
Elisa Krill, MD
Richard M Levine, MD
Mark Steven Lewis, MD
Mathew Luke, MD
Joseph A McClure, MD, PhD
Mark S Rubin, MD
William Rymer, MD
Niramol Savaraj, MD
Sumit Sawhney, MD
Alka Sawhney, MD
Michael A Schwartz, MD
Leonard J Seigel, MD
Nikita C Shah, MD
Jane D Skelton, MD
Elizabeth Tan-Chiu, MD
Lawerence A Tepper, DO
Mary Jo Villar, DO
James K Weick, MD
Michael Wertheim, MD
Israel Wiznitzer, MD

Case 1: From the practice of Stephanie Bernik, MD

- 37-year-old premenopausal woman with four invasive ductal carcinomas (largest 1.5 cm), ER-positive, HER2-positive
- Underwent mastectomy: Seven positive axillary lymph nodes, no evidence of metastatic disease
- Participating in NSABP adjuvant trastuzumab study, randomized to receive chemotherapy plus trastuzumab; also on adjuvant tamoxifen

Dr Bernik: This 37-year-old woman was recently treated with a mastectomy for four invasive breast tumors, the largest of which was 1.5 centimeters. The tumor was ER-positive, HER2-positive and, on axillary dissection, there were seven positive nodes.

From the floor: Were these four separate tumors or was it intramammary spread? Were they exactly the same histologically?

Dr Bernik: They were histologically the same.

From the floor: Any information on her BRCA-1 and 2 status?

Dr Bernik: She did not undergo genetic testing.

From the floor: What about her family history?

Dr Bernik: She did not have a significant history.

Dr Love: Genny, would you do genetic testing in this situation?

Dr Grana: Absolutely, but I wouldn't do genetic testing at the time of surgery. I think there are many issues that are difficult to address at that point. I would mainly spend the time and the energy addressing the systemic issues. The genetic issues will come into play down the line.

Dr Love: Genny is one of the few oncologists who does both breast cancer treatment and prevention. This patient has no family history. What is making you think about genetic testing?

Dr Grana: The fact that she's 37. For breast cancer under age 40, the risk of genetic abnormalities is about 10 percent. The other thing that's very worrisome is the fact that she has multiple lesions.

From the floor: What about the metastatic work-up in this patient?

Dr Bernik: Her work-up showed no other evidence of disease.

Dr Love: What about the issue of reconstruction and timing of post-mastectomy radiation therapy? Pat?

Dr Borgen: This is something we struggle with all the time because it's largely a cosmetic issue, not an oncologic issue. In a very thin 37-year-old, an implant may be her only option for reconstruction. Very often, by not putting an implant in immediately, it's like saying, "You're not going to have a breast mound for the rest of your life."

The radiation oncologists tell us that the old fears of unpredictable scatter are probably overblown, and we'd

probably get the same local control with an implant, as not.

This is something that our group struggles with all the time. I think the trend has been for us to put tissue expanders in these patients, exchange them for implants because there's metal in the expander, and radiate. There's no science behind that, but that's sort of the direction that I see us heading in.

Dr Love: Dr. Bernik, can you talk about your discussions with this woman in terms of her risk for future recurrence?

Dr Bernik: She was diagnosed almost a year ago, and she's undergone a lot of her treatment. She was very motivated. When I walked in and I told her she had seven positive nodes, she said, "You know what? It is what it is. I just have to do whatever I have to do." So, she wanted to be very aggressive about her treatment. She has two children and she's very involved with their care. She's divorced and, as a single parent, she's raising these children pretty much on her own.

Dr Love: Kevin, in what kind of trials could she be enrolled?

Dr Fox: This woman would be eligible for what is, I think, in the minds of most of us, probably just about one of the most important clinical trials that we're doing, and that's basically a randomization of chemotherapy with or without trastuzumab. We would make a very, very strong case to have a woman like this participate. The study that we're doing is a clinical trial that evaluates AC followed by paclitaxel, with or without trastuzumab, and two-thirds of the patients are randomized to receive trastuzumab (Figure 1.1).

Figure 1.1

Open trials of adjuvant trastuzumab in the treatment of breast cancer

Study Name	Target Accrual	Randomization Arms
BCIRG-006	3,150	ARM 1: AC x 4 → docetaxel x 4 ARM 2: AC x 4 → docetaxel x 4 + H (qw x 12 weeks) → H (qw x 40 weeks) ARM 3: (Docetaxel + C) x 6 + H (qw x 18 weeks) → H (qw x 34 weeks)
NCCTG-N9831 CLB-49909 E-N9831 SWOG-N9831	3,300	ARM 1: AC x 4 → paclitaxel qw x 12 ARM 2: AC x 4 → paclitaxel qw x 12 → H (qw x 52 weeks) ARM 3: AC x 4 → (paclitaxel + H) qw x 12 → H qw x 40
BIG-01-01 EORTC-10011 HERA	3,192	(randomized after approved neoadjuvant or adjuvant chemotherapy) ARM 1: H q3w x 1 y ARM 2: H q3w x 2 y ARM 3: No H
NSABP-B-31	1,000 - 2,700	ARM 1: AC x 4 → paclitaxel x 4 ARM 1: AC x 4 → paclitaxel x 4 + H qw x 1y

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

SOURCE: NCI Physician Data Query, November 2003.

If she declines participation, the obvious question that follows is: Would we give a patient like this trastuzumab outside of a study? And I most certainly would not. This harkens back to the whole bone marrow transplant story and how we made a decade-long error in judgment by giving something that we thought was a good idea, which may not have been. So, I wouldn't give a patient like this trastuzumab outside of a study.

Dr Grana: I guess the other question is: If she does not enroll in one of the trastuzumab trials, what do you offer this patient? I think she would be a wonderful candidate for the dose-dense therapy regimens — either AC followed by paclitaxel at two-week intervals or A followed by T followed by C. I tend to use AC followed by paclitaxel, because it's four months of therapy as opposed to six. She would also be a good candidate for the TAC regimen.

The hormonal therapy issue is important. She's someone in whom I would not use an aromatase inhibitor unless I render her menopausal with oophorectomy, and even if she were to go into menopause with her chemotherapy, how comfortable are you that she's in a permanent menopause? I would give her tamoxifen. If she were to regain her menses, I might consider oophorectomy as a viable option in someone like this who is at such high risk.

Dr Love: Oophorectomy or LH-RH agonist?

Dr Grana: I find it hard to commit someone to five years of monthly injections, so I tend to be a proponent of oophorectomy. If she's interested in childbearing, you're going to have a problem, because if you commit her to tamoxifen, you're saying that she's not going to bear children for five years, at which time she's likely to be infertile anyway. So, if that's an option, you really need to sit down with her at the beginning and plan.

I would recommend tamoxifen unless I chose to take out her ovaries, in which case the genetic testing might also push me a little bit. If you don't remove her ovaries, I think tamoxifen should be the standard of care for someone like this.

The other issue that comes up is whether ovarian ablation on top of other endocrine therapy is beneficial as a systemic approach. I think the data is very limited. The Intergroup trial showed some tendency toward benefit in patients less than 40 years of age. That study was problematic in many ways. I don't recommend oophorectomy in the majority of patients, but in someone like this, who is at such high-risk, I would offer whatever I could to ameliorate that. So, in node-positive patients, if they resume menses, I would absolutely offer oopherectomy (Figure 1.2).

Dr Love: And there are clinical trials of hormonal therapy in premenopausal women, particularly looking at the issue of ovarian suppression and an aromatase inhibitor.

Dr Mamounas: The IBCSG is doing three trials. The most important one is the SOFT trial, in which the randomization is between tamoxifen alone, tamoxifen plus an LH-RH agonist, or any form of ovarian ablation versus ovarian ablation and an aromatase inhibitor. It's a three-arm

trial looking at whether ovarian ablation adds to tamoxifen and, after you ablate the ovaries, whether an aromatase inhibitor is better than tamoxifen (Figure 1.3).

Dr Love: The Austrians have looked at the strategy of an aromatase inhibitor and anastrozole, plus or minus a bisphosphonate, and they presented data on bone in these patients in San Antonio in 2002 (Figure 1.4). Kevin, any thoughts on that?

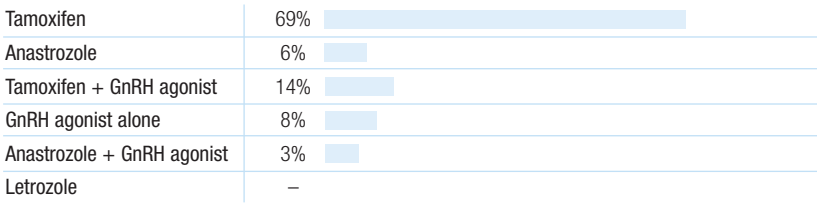
Dr Fox: That was my first exposure to that whole concept. The numbers were small, and the follow-up was short, but it was the first indication of what we all had hoped to see, which was that if we're going to prescribe

Figure 1.2

Random telephone survey of 100 medical oncologists: Adjuvant endocrine therapy in premenopausal women

Woman with 2.2-cm, ER-positive, HER2-negative IDC and 10 positive nodes: If you recommend adjuvant endocrine therapy, which agent(s) would you recommend?

33-year-old (premenopausal woman, menstruating after chemotherapy)



SOURCE: 2003 *Breast Cancer Update* Patterns of Care Study.

Figure 1.3

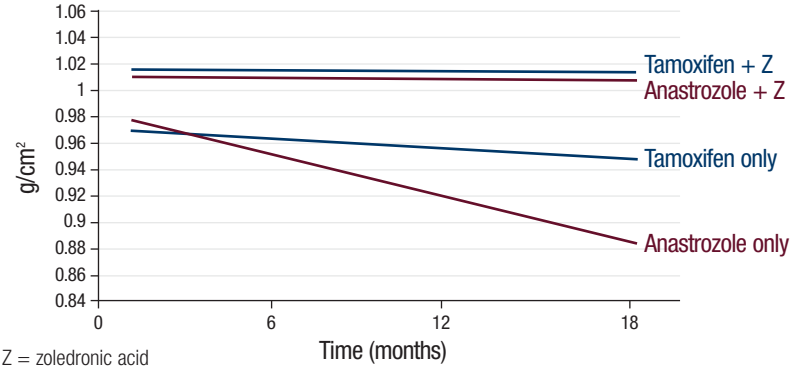
Ongoing trials of adjuvant endocrine therapy in premenopausal women

Study	Entry	Intervention	Target accrual
ABCSG-AU12	Stage I, II	Tamoxifen + goserelin ± zoledronate Anastrozole + goserelin ± zoledronate	1,250
IBCSG-24-02 (SOFT trial)	T1-T3, pN0-N2	Tamoxifen Ovarian suppression + tamoxifen Ovarian suppression + exemestane	3,000
IBCSG-25-02 (TEXT trial)	T1-T3, pN0-N2	Triptorelin + tamoxifen Ovarian suppression + tamoxifen	1,845
IBCSG-26-02 (PERCHE trial)	T1-T3, pN0-N2	Ovarian suppression + tamoxifen or exemestane Ovarian suppression + chemotherapy + tamoxifen or exemestane after chemotherapy	1,750

DERIVED FROM: NCI Physician Data Query, October 2003 and Gnant M et al. **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: Results of a randomized multicenter trial.** *Breast Cancer Res Treat* 2002;**Abstract 12.**

Figure 1.4

Changes in bone mineral density of the lumbar spine (LI-I4) caused by anastrozole or tamoxifen in combination with goserelin (± zoledronic acid) IN ABCSG-12



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

aromatase inhibitors to women who were either in menopause naturally or women whom we chose to make menopausal, at least we had some reassurance that bisphosphonates could offset the side effect that we fear the most, which is premature bone loss.

Dr Love: What actually happened to this patient?

Dr Bernik: She chose to participate in the NSABP adjuvant trastuzumab trial and received chemotherapy plus trastuzumab. She is also receiving tamoxifen.

Select publications

Clinical trials of adjuvant trastuzumab

Early Breast Cancer Trialists' Collaborative Group. **Adjuvant endocrine therapy in premenopausal women ovarian ablation for early breast cancer.** *Cochrane Database Syst Rev* 2000;CD000485. **Abstract**

Davidson N et al. **Effect of chemohormonal therapy in premenopausal, node (+), receptor (+) breast cancer: An Eastern Cooperative Oncology Group Phase III Intergroup trial (E5188, INT-0101).** *Proc ASCO* 1999;**Abstract 249A, 67A.**

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

Michaud LB, Buzdar AU. **Complete estrogen blockade for the treatment of metastatic and early stage breast cancer.** *Drugs Aging* 2000;16:261-71. **Abstract**

Seidman A et al. **Cardiac dysfunction in the trastuzumab clinical trials experience.** *J Clin Oncol* 2002;20(5):1215-21. **Abstract**

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

Case 2: From the practice of Thomas G Frazier, MD

- 72-year-old woman with a 5-mm area of suspicious calcifications on mammogram; biopsy reveals Grade II, ER-positive, HER2-positive infiltrating ductal carcinoma
- Segmental resection reveals no residual cancer, sentinel node is positive
- Enrolled in NSABP-B-32: Axillary dissection completed, nodes negative
- Patient concerned about lymphedema, prefers to avoid radiation therapy

Dr Frazier: This 72-year-old very healthy woman presented with a 5-mm area of suspicious calcifications on her mammogram. These were removed stereotactically and proved to be a Grade II, ER-positive, HER2-positive, infiltrating ductal carcinoma. We performed a segmental resection that showed no residual cancer, and she had a single sentinel node that was positive. This patient participated in the NSABP-B-32 trial (Figure 2.1), and as part of the study we completed the axillary dissection, which showed no additional tumor in her lymph nodes. The patient stated that she wished to avoid postlumpectomy radiation because of concerns about lymphedema.

Dr Lerner: She needs more treatment. Given a choice, I would prefer that she receive radiation to her breast to make sure another primary is not being missed. And there's no question she needs hormonal therapy plus or minus cytotoxic chemotherapy.

Dr Love: Where did this concern about lymphedema come from? Does she

Figure 2.1

Phase III Randomized Study of Sentinel Node Dissection with or without Conventional Axillary Dissection in Women with Clinically Node-Negative Breast Cancer Open Protocol

Protocol ID: NSABP-B-32
Accrual: 5,400 patients

Eligibility: Clinically node-negative breast cancer

ARM 1: Sentinel lymph node biopsy (SLNB) with axillary dissection

ARM 2: SLNB → positive → axillary dissection
SLNB → negative → no axillary dissection

Note: If no sentinel node is identified, then patients undergo axillary dissection. Patients with cytologically negative but histologically positive sentinel nodes undergo axillary dissection.

Study Contact:
David N Krag, Chair. Ph: 802-656-5830
National Surgical Adjuvant Breast and Bowel Project

SOURCE: NCI Physician Data Query, November 2003.

know someone who had lymphedema?

Dr Frazier: Yes. One of her best friends can't move her arm.

Dr Borgen: Was a clip placed at the stereo site, and were there biopsy changes in the specimen that you surgically removed? Do we know that the wire was in the right place and have we actually removed the area where the cancer was?

Dr Frazier: Yes. Absolutely. We place a little clip on all the stereos, and the clip was widely removed. And there was a hematoma, consistent with a biopsy cavity, in the middle of the specimen.

From the floor: In terms of lymphedema, once you break that chain along the axillary vein you are already at risk, as far as I'm concerned. Radiation therapy will not increase that risk substantially. I understand her concerns, but she already has undertaken the risk and she needs radiation.

Dr Love: Did she bring up the concern about lymphedema before surgery or after surgery?

Dr Frazier: After.

Dr Love: Terry, if a patient asks, "What's the chance I'm going to have lymphedema from having axillary dissection and breast radiation," what would you say?

Dr Mamounas: I think the chance for lymphedema after axillary dissection is probably in the range of five to 10 percent. With radiation, particularly if the tumor is in the upper outer quadrant and the tangents include some of the axilla, the range may go up a couple of percentage points, but not dramatically.

Dr Love: Do you think she would be willing to take a risk or compromise her therapy because of a slightly increased risk of lymphedema?

Dr Frazier: I think she'll probably do what we encourage her to do. That's sort of the way it is with most patients, but when a patient tells you that the one thing she doesn't want is lymphedema, and you have a tumor that's microscopic, the question is: "Will you be able to control second primaries in her breast with a hormonal approach?" I think we can decrease the risk with hormonal therapy alone, but probably not as much as we can with radiation.

Dr Love: Your take is that if she can get away without radiation, she will, but she doesn't want to compromise the treatment of the cancer?

Dr Frazier: She's more concerned, as I would be, about her survival, but I don't think, frankly, that radiation in a 72-year-old woman is going to increase her survival. It's probably going to decrease her chance of developing a second primary, but it is going to increase her chance of having lymphedema. Given the choice, she'd probably rather lose her breast later on than take a chance of developing lymphedema.

Dr Love: That's interesting. So, your take is she'd rather have a mastectomy than take a chance on lymphedema.

Dr Frazier: She doesn't need a mastectomy now, but, yes, that is my assessment.

From the floor: I don't want to be anecdotal about this, but in my practice I have about 20 older patients who have more medical problems than this patient, and I've just done a

lumpectomy and given tamoxifen. I have not seen any recurrences, and I'm seven or eight years down the line now. Many of these patients have completed their five years of tamoxifen.

Dr Love: The NSABP has studied that, because 10 to 15 years ago I think we hoped to avoid radiation therapy. Terry, what did those trials show?

Dr Mamounas: The NSABP-B-21 study clearly shows that the radiation therapy, even in the face of tamoxifen, reduces local recurrence by almost 50 percent (Figure 2.2). To put things in perspective — and I don't advocate not giving this woman radiation — but if you actually do a theoretical calculation of her mastectomy rate if she undergoes radiation now or if she undergoes it later, assuming that every time you give radiation after lumpectomy, you'll do a mastectomy when they recur, and assuming that you can do a lumpectomy and radiation later, if she recurs, the mastectomy rate is probably less if you don't give radiation.

It's complex, but if you don't do radiation, 10 percent of the patients will recur. That's what B-21 showed in small tumors.

If you then took that lump out and gave radiation at that time, assuming even a 20 percent risk of subsequent recurrence, that would be 20 percent of the 10 percent would have a mastectomy. That's two percent, overall.

If you did lumpectomy and radiation now, the rate is about five percent. And if then, the recurrence is five percent. That five percent should go to mastectomy, because they already have had radiation. Nobody's talked about that, but, in fact, that's true.

Dr Love: Pat, how much does fear of radiation therapy factor into patient preference for mastectomy?

Dr Borgen: This is a very common patient concern. In the 1990s when there were papers in the *New England*

Figure 2.2

Efficacy data from NSABP-B-21: Radiation versus tamoxifen versus the combination in the adjuvant treatment of invasive, node-negative breast cancer treated by lumpectomy

Therapy	Rate (per 1000 patients per year) of ipsilateral breast tumor recurrence
Tamoxifen	23.3
Radiation + placebo	11.7
Radiation + tamoxifen	3.4

"…evidence has been presented from NSABP-B-21, a trial evaluating radiation therapy (XRT) and/or TAM for the prevention of ipsilateral breast tumor recurrence (IBTR) after lumpectomy in women with tumors less than or equal to 1 cm. Findings have shown that XRT is superior to TAM and that XRT + TAM is superior to XRT alone for preventing IBTR."

DERIVED FROM: Fisher B et al. **Findings from recent National Surgical Adjuvant Breast and Bowel project adjuvant studies in Stage I breast cancer.** *J Natl Cancer Inst Monogr* 2001;(30):62-6. **Abstract**

Journal of Medicine evaluating our regional use of breast conservation therapy — and the group from Kentucky surveyed patients about why they didn't want breast conservation — fear of radiation was one of the most common reasons patients gave. This patient is telling us something that we've heard for a long time. I personally think that the added risk of lymphedema from the radiation is low, and I agree that having a Level 1 or 2 dissection certainly creates the lion's share of her risk.

One concern is not leaning towards undertreating this woman because the calendar says she's 72 years old. That's something we have to really avoid. New studies are using the Mammosite® regional radiation therapy. We have a trial using a single dose of intraoperative radiation therapy, using a high-dose after-loader, and this type of approach could make radiation therapy more palatable if we find that local control in the region is equal to external beam radiation therapy.

Dr Love: Dr. Frazier, we don't know what the chance of lymphedema would be with a Mammosite®, but do you think she might have been open to this type of experimental approach?

Dr Frazier: Yes, I think so.

Dr Borgen: This discussion is refreshing. What I hear people saying is, "Let's match the treatment with the patient." We've talked about the reality of the data and the reality of what the patient wants, but there's a third reality, and that is the medicolegal standard that we're held to. Two of my attending surgeons have gone through lawsuits when patients adamantly declined the recommended therapy, had terrible outcomes, and the physicians ended up in court. So this also becomes a documentation issue and a situation in which we might say, "Please get a second opinion."

None of us want to discharge these patients, but we really have to protect ourselves in cases like this if the patient doesn't follow the standard of care — because sometimes the patient's memory is a little different five years later than it might be today.

Dr Love: Let's discuss the issue of systemic management. This tumor was ER-positive and HER2-positive. She has one positive node. Kevin, how would you think through systemic therapy in this situation?

Dr Fox: First, I would like to comment about the point in this case at which all you had was a single positive sentinel node, and whether it was worth doing an axillary dissection. Most people agree that the standard of care is to do so, and I think this is a case where the performance of that axillary dissection turns out to be very useful to us in medical oncology — because the thing that drives this woman's risk of premature death from breast cancer, statistically, is her single positive lymph node.

That statistically overpowers virtually every other factor in her case. Now that we know she only has one, we can make more rational predictions about what the risks and benefits of systemic therapy are.

Having a single positive lymph node puts one at an ever-so-slightly higher risk than having no positive lymph nodes. She would be a low- to moderate-risk type of situation, and

we know that the greatest derivation of benefit with respect to survival will be from hormonal therapy.

All of us would happily prescribe some form of hormonal therapy to a patient like this. Which one you would choose is another topic. For us, the issue is what the contribution of systemic chemotherapy is to her long-term survival. If you look at the overview, which is our greatest data resource, quantitatively, the relative reduction in the risk of dying in a woman over the age of 50 with ER-positive, node-positive breast cancer goes down 10 percent with systemic chemotherapy in addition to hormonal therapy.

I personally would look at that 10 percent relative reduction in the risk of dying as being puny, and certainly would not present chemotherapy as a mandate to a patient like this.

Dr Love: How would you respond if this woman asked you, "What's the chance, if I don't do anything, that I'm going to relapse?"

Dr Fox: We're hampered a little bit by not knowing the exact size of her primary, and that's life in the world of stereotactic biopsies. She would, in the worse-case scenario, I think, have a risk of systemic recurrence and death of 30 percent with no treatment. We reduce that to somewhere around 20 percent by giving her hormonal therapy. Then, with chemotherapy, we would provide her with an additional reduction in the risk of dying of about three percent.

Dr Love: I'm curious, Dr Frazier, do you think she'd be the kind of woman who, for a very modest improvement in survival — a couple of percent — would want to go through, let's say, four cycles of chemotherapy?

Dr Frazier: I think she would take whatever we recommend to her, but I don't think that she's a person who would want chemotherapy for a one-percent improvement. I think she's more concerned about the quality of her life. She may very well say, "I don't want my hair falling out. Can you give me something mild for six months? I'll take treatment, but only if it won't make my hair fall out."

Dr Love: So, she's not grabbing you by the lapels, saying, "I want you to do everything possible to attack this tumor?"

Dr Frazier: Absolutely not. She's saying, "I've had a good life. I'm 72."

Dr Love: What's her lifestyle like?

Dr Frazier: She retired. She does hospital volunteer work.

Dr Love: Kevin, would you present the option of chemotherapy and discuss it with her?

Dr Fox: Absolutely, and I would try to give her an appraisal of the toxicity that was as honest and unbiased as I could.

Dr Love: How would you discuss the choice of hormonal therapy?

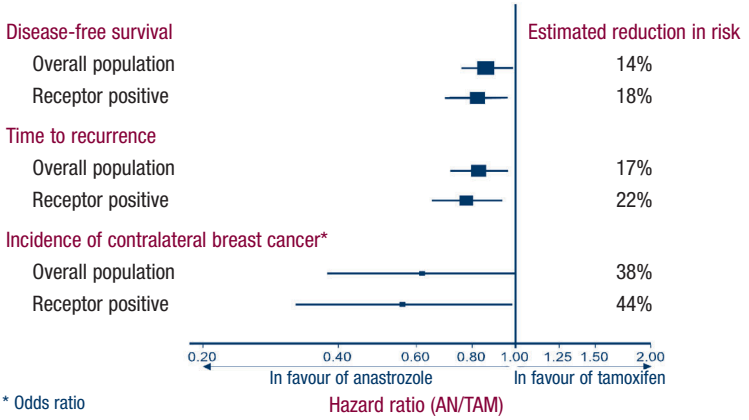
Dr Fox: I think we're at sort of a juncture now where we're all trying to decide how much the ATAC trial has altered our care standards (Figure 2.3). My own bias would be to prescribe an aromatase inhibitor to a patient like this, unless she had severe concurrent bone disease, symptomatic osteoporosis and complications thereof. In general, I believe the aromatase inhibitors have less of a

Figure 2.3

ATAC Trial: First Events in Overall Population

	Anastrozole n=3125 (%)	Tamoxifen n=3116 (%)
First event	413 (13.2)	472 (15.1)
Locoregional events	84 (2.7)	101 (3.2)
Distant events	195 (6.2)	222 (7.1)
Contralateral (invasive)	20 (0.6)	35 (1.1)
Contralateral (DCIS)	5 (0.2)	5 (0.2)
Deaths without recurrence	109 (3.5)	109 (3.5)

Summary I — Updated Analysis



SOURCE: The ATAC Trialists' Group. *Cancer* 2003;98(9):1802-10. **Abstract**

downside for all patients, and if we're going to give her a modest survival benefit, we might as well give her the treatment that is going to produce the least aggravation for her. I think that would be an aromatase inhibitor.

Dr Love: An aromatase inhibitor, or anastrozole?

Dr Fox: Well, if we have to dance with the one that brought us, we have to use anastrozole, because that's the drug for which we have the data. I would prescribe, specifically, anastrozole.

Dr Love: Genny, how would you think through this case and what would you say to this woman?

Dr Grana: I think along the same lines as Kevin. I would also take the positive HER2 status under consideration.

The data by Matt Ellis and others clearly demonstrates an association between HER2 status and hormonal therapy responsiveness (Figures 2.4, 2.5). That urges me more towards anastrozole than tamoxifen.

Dr Love: What about chemotherapy? Would you discuss it as an option?

Figure 2.4

ErbB status and response to neoadjuvant endocrine therapy in ER+ tumors

Marker status	Letrozole		Tamoxifen		*p*-value
	Responders	%	Responders	%	
ErbB-1/2 positive	15/17	88	4/19	21	0.0004
ErbB-1/2 negative	55/101	54	42/100	42	0.0780

DERIVED FROM: Ellis MJ et al. **Letrozole is more effective neo-adjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a Phase III randomized trial.** *J Clin Oncol* 2001;19(18):3808-16. **Abstract**

Figure 2.5

Response rates following neoadjuvant anastrozole in postmenopausal women with locally advanced breast cancer according to cerbB2 and Ki67 status

Tumor response	All patients n=112	CerbB2 negative n=79	CerbB2 positive n=33	Ki67 <10% n=61	Ki67 ≥10% n=51
Clinical complete response (cCR)	54.5%	60.8%	39.4%	63.9%	43.1%
Clinical partial response (cPR)	28.6%	34.2%	15.2%	32.8%	23.5%
Objective response (cCR + cPR)	83.0%	94.9%	54.5%	96.7%	66.7%
Pathological complete response	16.1%	21.5%	3.0%	23.0%	7.8%

DERIVED FROM: Milla-Santos A et al. **Anastrozole is an effective neoadjuvant therapy for patients with hormone-dependent, locally advanced breast cancer irrespective of cerbB2.** *Proc ASCO* 2003;Abstract 154.

Dr Grana: Yes, and also because of the HER2 status. In that light, if you're going to use chemotherapy, I don't see a real role for CMF — a milder, more gentle chemotherapy. I think this is a case in which you either use AC or you forego chemotherapy, and I think it's very much driven by the vigor of the woman. How young of a 72-year-old woman is she? Plenty of women like this have looked at the data and want everything; they will opt for chemotherapy and may want more than AC — they may want AC and a taxane.

Dr Love: She has a node-positive tumor and you mentioned a taxane. Would you discuss dose-dense chemotherapy as an option?

Dr Grana: I would be very reluctant to discuss dose-dense chemotherapy in someone of this relatively modest risk at this age. We have relatively limited information about the long-term sequelae of more intensive therapy in older women, so I would not present it as a viable option.

There's a wonderful CALGB randomized trial in older women that she may be eligible for. This study is being run by Hy Muss and randomly assigns women over age 65 to AC or CMF versus capecitabine, as an oral agent (Figure 2.6).

Dr Love: And that trial allows a woman to have hormonal therapy selected by the physician and patient?

Dr Grana: Yes.

Dr Love: Kevin, you said you were pleased that she had a full axillary dissection — that you wanted to see the axillary node status. If this patient had five positive nodes, how would that have changed your recommendation?

Dr Fox: If she had five positive lymph nodes, we would have to reinforce to this patient that her risk of dying prematurely from metastatic breast cancer was actually quite substantial. I think all medical oncologists generally would have greater enthusiasm for giving adjuvant systemic chemotherapy — which is inherently unpleasant to us, particularly in older women — and we would even go as far as telling a patient like this that the additional three months of taxane therapy might actually be meaningful, which is something I would be very reluctant to say if a patient had a single positive axillary lymph node.

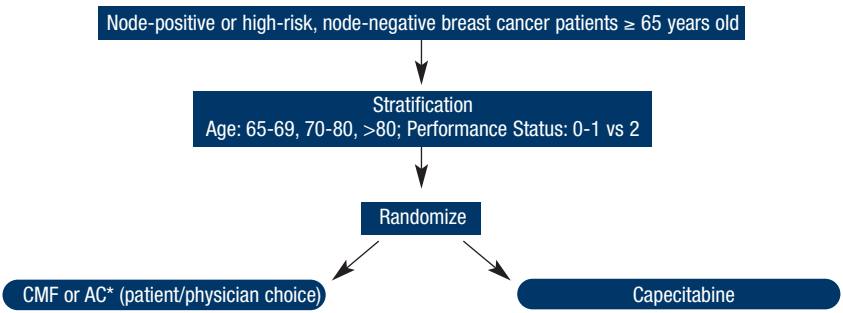
Dr Love: If the tumor had been 2.2 centimeters — a palpable tumor — and one positive node, how would that have changed your evaluation?

Dr Fox: It would not increase my enthusiasm about chemotherapy much because I still think, statistically, what drives this woman's predictable risk of recurrence and death is her axillary lymph node status.

Dr Love: Genny, you said that you would suggest or recommend anastrozole. Would you present the

Figure 2.6

CALGB-49907: A randomized trial of adjuvant chemotherapy with standard regimens (CMF or AC) versus capecitabine in women 65 years and older with node-positive or high-risk, node-negative breast cancer



* Patients whose LVEF is not within lower limits of normal must receive CMF, not AC.
All ER+ or PR+ patients receive tamoxifen or an aromatase inhibitor x 5 years.

SOURCE: CALGB 49907 Protocol.

option of tamoxifen, also?

Dr Grana: Absolutely, but based on the HER2 status, I would really push for anastrozole. Some women may come back to you and say, "I'm uncomfortable with the duration of follow-up on the ATAC trial and I'm uncomfortable with the bone density." Some of those women will elect tamoxifen, but this is where the HER2 status would drive my thinking.

Dr Love: How would you respond if the patient asked, "Can you tell me about the side effects and tolerability of the two approaches?"

Dr Grana: I think anastrozole is clearly more tolerable in terms of the significant toxicity of hormonal therapy and in terms of clotting and endometrial carcinoma (Figure 2.7). The hot flashes are probably not much better with anastrozole, maybe a little bit. The thing that often becomes important — and you only know it once you're in anastrozole therapy — is the arthralgias and myalgias, and that's something that you can only gauge once you've started.

Dr Love: What percent of patients have that?

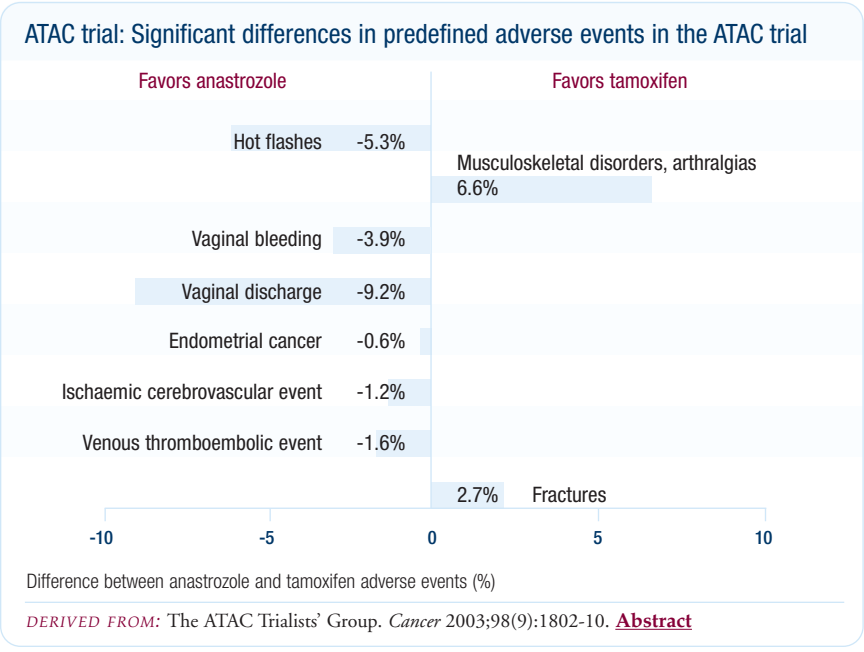
Dr Grana: If you look at the ATAC data, it was 27 percent versus 21, so a few percentage points more. What I think the ATAC trial failed to capture was the intensity. There are some women who become very intensely affected and have very significant arthralgias.

Dr Love: In your own experience, in what fraction of women is it a major problem?

Dr Grana: Five percent — ten percent, maybe, at most.

Dr Love: Another thing that's kind of

Figure 2.7



DERIVED FROM: The ATAC Trialists' Group. *Cancer* 2003;98(9):1802-10. **Abstract**

interesting, which I never understood, is that the NSABP has been telling us for years that tamoxifen doesn't cause weight gain, in contrast to what many practicing physicians and patients say. What's your take on that?

Dr Grana: I have many doubts about whether weight gain is significant with tamoxifen versus anastrozole. Many other factors effect weight gain in women with breast cancer, and I'm not sure I know what that means.

Dr Bauer: I want to explore something. Let's stereotype this patient, rightly or wrongly, as a woman who plays tennis, plays golf, is very concerned about her well-being, her appearance, and let's suppose she's my sister and I sent her to Kevin Fox and said, "She's 72 years old. She's very healthy. She wants to live a long time and continue to play tennis and golf. Kevin, advise me how she should be treated at this point. Should she have radiation? Should she have chemotherapy? And should she be on hormonal manipulation?"

Dr Fox: I would recommend that she have radiation therapy, because I think the contribution to her lymphedema risk, while we all agree that there is some, is very modest. I would recommend that she have adjuvant systemic chemotherapy, because she really does have a life expectancy, actuarially, that goes well beyond the age of 80. And I would recommend hormonal therapy and probably an aromatase inhibitor.

Dr Love: Just out of curiosity, Kevin, going back to the profile of the woman who said, "I want everything done. I'm not that concerned about toxicity, as long as it's not lethal toxicity," would you give her a taxane, also?

Dr Fox: I probably would not because, again, resorting to mathematics, the relative benefits of paclitaxel — the relative reduction in the risk of a woman like this dying — truly would be a single-digit number, and quite possibly one percent. The risk of this active, tennis-playing, golf-playing individual developing a significant and sustained neuropathy is probably as high as that, or greater. So, I would be much more reluctant to use taxanes in someone like this.

Dr Bauer: Thank you. If I had a sister with breast cancer, I'd send her to you!

Select publications

Adjuvant therapy in the elderly

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

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Grogan M et al. **Estimating the benefits of adjuvant systemic therapy for women with early breast cancer.** *Br J Surg* 2001;88(11):1513-8. **Abstract**

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Punglia RS et al. **Radiation therapy plus tamoxifen versus tamoxifen alone after breast-conserving surgery in postmenopausal women with stage I breast cancer: A decision analysis.** *J Clin Oncol* 2003;21(12):2260-7. **Abstract**

Woodard S et al. **Older women with breast carcinoma are less likely to receive adjuvant chemotherapy: Evidence of possible age bias?** *Cancer* 2003;98(6):1141-9. **Abstract**

Sentinel node biopsy

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Guenther JM et al. **Axillary dissection is not required for all patients with breast cancer and positive sentinel nodes.** *Arch Surg* 2003;138(1):52-6. **Abstract**

Jakub JW et al. **Current status of sentinel lymph node mapping and biopsy: Facts and controversies.** *Oncologist* 2003;8(1):59-68. **Abstract**

Mamounas EP. **Sentinel lymph node biopsy after neoadjuvant systemic therapy.** *Surg Clin North Am* 2003;83(4):931-42. **Abstract**

Reitsamer R et al. **Sentinel lymph node biopsy alone without axillary lymph node dissection — follow up of sentinel lymph node negative breast cancer patients.** *Eur J Surg Oncol* 2003;29(3):221-3. **Abstract**

Sanidas EE et al. **How many cases are enough for accreditation in sentinel lymph node biopsy in breast cancer?** *Am J Surg* 2003;185(3):202-10. **Abstract**

Schwartz GF et al. **Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast April 19 to 22, 2001, Philadelphia, Pennsylvania.** *Hum Pathol* 2002;33(6):579-89. **Abstract**

Veronesi U et al. **A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer.** *N Engl J Med* 2003;349(6):546-53. **Abstract**

Wilke LG, Giuliano A. **Sentinel lymph node biopsy in patients with early-stage breast cancer: Status of the National Clinical Trials.** *Surg Clin North Am* 2003;83(4):901-10. **Abstract**

Case 3: From the practice of Gracy Joshua, MD

- 73-year-old retired nurse with a 6.5-centimeter, poorly-differentiated, ER/PR-positive, HER2-negative, infiltrating ductal carcinoma
- Underwent mastectomy: Three out of 12 axillary lymph nodes positive

Dr Joshua: This is a 73-year-old woman whom I saw after she had a mastectomy for a 6.5-centimeter, ER/PR-positive, HER-2 negative, infiltrating, poorly differentiated ductal carcinoma. Three out of 12 axillary nodes were positive. The lesion had been detected on a screening mammogram. She was started on AC chemotherapy, which will be followed by docetaxel, chest wall radiation therapy and anastrozole.

Dr Love: Can you talk a little bit about this woman — how active she was and what her general condition was like?

Dr Joshua: She's a retired nurse. She is an otherwise healthy woman. I was a bit surprised that she had such a large tumor, and that it was only discovered on a mammogram. I only saw her after the surgery, and she absolutely denied having any palpable lumps. She's very active and intelligent and able to understand what's going on with her disease.

Dr Love: It's interesting that she was a nurse. What was her attitude towards the possibility of receiving chemotherapy? How concerned was she about toxicity or was she completely focused on the tumor?

Dr Joshua: She was not concerned about the alopecia. After explaining to her about the nausea, vomiting and the preventive medication we have today, she was not concerned about that either. She's on preventive growth factor and she's tolerated the treatment fairly well so far on AC.

Dr Love: And what was it that went into your decision to use AC, docetaxel and anastrozole?

Dr Joshua: She has a large tumor, positive lymph nodes and, in my opinion, she clearly would benefit from adjuvant chemotherapy. In terms of what drugs to choose, I thought about epirubicin instead of doxorubicin, but I'm much more used to using doxorubicin, and that's the first thing that came to mind. In terms of following that with docetaxel versus paclitaxel, I prefer docetaxel — especially in elderly women — because I think it's probably a better drug.

Dr Love: What about the decision of anastrozole versus tamoxifen? Did you present both options? And how did that discussion go?

Dr Joshua: I prefer anastrozole because of the ATAC trial, particularly because this woman is at a high risk of developing metastatic disease. I would certainly use an AI, and I would choose anastrozole.

I usually tell patients that anastrozole has fewer side effects, but if the patient has already had a hysterectomy, that is not such a major issue. We talk about bone density. We talk about uterine cancer.

I've used tamoxifen for many years and I only had one patient who was diagnosed with endometrial cancer, and she had a hysterectomy and did fine. So, I usually tell patients that even if they do develop endometrial cancer, the chance of dying from this is close to zero if the patient is followed carefully. In someone like this woman, with a large tumor and positive nodes, I prefer to use anastrozole.

Dr Love: So, in reviewing your practice, are you more likely to use anastrozole in a higher-risk situation, like this node-positive patient (Figures 3.1, 3.2)?

Dr Joshua: Yes.

From the floor: What about the issue of using taxanes in postmenopausal women with ER-positive tumors?

Dr Carlson: That issue and this entire case are complex, and it shows us how much we don't know. The patient is apparently in otherwise good health, but because she's over 70, the confidence we have that chemotherapy is of benefit is very low. For those of you who are historians, if you go back to the initial overview analysis of polychemotherapy, the only negative number in that entire paper was an increased death rate in

Figure 3.1

Random telephone survey of 100 medical oncologists: Counseling postmenopausal women about adjuvant endocrine therapy options

How do you generally counsel the following postmenopausal patients whom you are going to treat with endocrine therapy?

	Higher-risk, node-positive	Lower-risk, node-negative
Generally recommend tamoxifen, and don't discuss aromatase inhibitors as an option	2%	7%
Generally recommend tamoxifen, but discuss aromatase inhibitors as an option	33%	43%
Generally discuss tamoxifen and aromatase inhibitors as equal options	25%	20%
Generally recommend an aromatase inhibitor, but discuss tamoxifen as an option	33%	27%
Generally recommend an aromatase inhibitor, and don't discuss tamoxifen as an option	7%	3%

SOURCE: 2003 *Breast Cancer Update* Patterns of Care Study.

Figure 3.2

Random telephone survey of 100 medical oncologists: Change in adjuvant endocrine therapy use since 2002

65-year-old woman with 2.2-cm, ER-positive, HER2-negative IDC and 10 positive nodes: Which adjuvant endocrine therapy would you recommend?

	2002	2003
Tamoxifen	63%	35%
Anastrozole	31%	59%
Other aromatase inhibitor	6%	6%

SOURCE: 2002, 2003 *Breast Cancer Update* Patterns of Care Studies.

women over 70 given chemotherapy. It was the only negative number in the entire publication.

In the second and third overviews, they said they didn't have enough patients to comment. In the most recent, unpublished overview, there's a very small — a couple percent — risk reduction in chemotherapy in women over the age of 70, but it's not statistically significant. So, I have a lot of reservations about whether chemotherapy should be used or not. The patient's preference and how aggressive she wants to be is very important.

Because of the combination of concerns about toxicity, the hormone receptor positivity and so on, I personally would not add a taxane to this woman's therapy. If I used a taxane, I actually would prefer paclitaxel because I think that docetaxel is a difficult drug, especially in terms of myelosuppression, and especially in older women.

I think that older women have a much more difficult time with the prolonged courses of steroids that are required with the paclitaxel administration.

(Figure 3.3).

From the floor: I have a comment regarding age. It's always very controversial. One of the problems is that relatively few older women are enrolled in clinical trials. And then there's Hy Muss cheering the country on, saying, "Look, we are undertreating elderly women. We're already biased as physicians, not even presenting the option of chemotherapy because in our minds we're already against it and have decided not to offer it to them."

I think if we increase the number of elderly patients accrued into clinical trial, we would eventually have the data in elderly people. And what these elderly clinical trials should really be looking at is, in addition to disease-free and overall survival endpoints, we must consider comorbidities.

In our practice, for women who are 65 and older, we give them the option. If they're very healthy 65-year-olds — and we do have a lot of them here in southern Florida — we offer chemotherapy. I think it's their prerogative to know that the benefits

Figure 3.3

Random telephone survey of 100 medical oncologists: Impact of age on use of adjuvant chemotherapy

A woman with 2.2-cm, ER-positive, HER2-negative IDC and 10 positive nodes: Would you recommend adjuvant chemotherapy?

Patient age	33	43	55	65	77
Percent recommending chemotherapy	93%	93%	98%	95%	85%

If you recommend adjuvant chemotherapy, which regimen would you select?

	Patient age				
Chemo	33	43	55	65	77
AC-docetaxel	46%	46%	44%	41%	15%
AC-paclitaxel	40%	35%	36%	35%	23%
AC	11%	13%	10%	16%	26%
CMF	—	3%	2%	—	21%
FAC/FEC	3%	3%	8%	8%	3%
Docetaxel	—	—	—	—	12%

SOURCE: 2003 *Breast Cancer Update* Patterns of Care Study.

may be small and modest, but real. Just like we do with small increments as in adjuvant therapy altogether (Figure 3.4).

Dr Love: What about the issue of hormone therapy in postmenopausal women in clinical practice?

From the floor: We're using a lot more anastrozole. Now, there are women who read a lot and come with their thick Internet files, and they will demand either anastrozole or tamoxifen.

But we tend to use anastrozole unless they are already at increased risk for fracture because of osteoporosis. At that point, we back off on aromatase inhibitors.

Dr Carlson: Every time we come up with new clinical trial data set with the magnitude of the ATAC trial, it creates a crisis. There tends to be a chaos theory prevailing as we sort of respond to the new information and assimilate it.

I think what you're seeing right now is that there is this sort of mini-crisis as we try to understand whether anastrozole truly — when all is said and done — is going to be superior, not only in terms of disease-free survival, but also overall survival. And we're going to have problems interpreting data in the transition.

Dr Love: When you look at the choice between tamoxifen and anastrozole,

Figure 3.4

Under-representation of elderly women in recent CALGB adjuvant trials

Trial No. regimens	Total accrued	Age 70 and older
CLB-8541	1572	150 (10%)
CAF in three different doses		
CLB-9344	3170	182 (6%)
AC ± T		
CLB-9741	2005	162 (8%)
A → T → C vs AC → T		
in a q2 vs q3 wk schedule		

C = cyclophosphamide; A = doxorubicin; F = fluorouracil; T = paclitaxel

SOURCE: CALGB-49907 Protocol.

how much of a factor is it if the woman has a prior hysterectomy?

Dr Schwartz: I'm not really concerned about the uterine cancer. It really doesn't influence me. I am more concerned about cardiovascular risk factors that would cause me to stay away from tamoxifen. Generally, I'm using more and more aromatase inhibitors.

Dr Grana: I'm much more concerned about the thrombotic risk in the older woman. If I have a woman who's in her seventies or eighties, a CVA is a life-debilitating event. So, I weigh in thrombotic risk much more than I ever weigh in uterine cancer.

From the floor: Women make that choice and take that risk every day when they take hormone replacement therapy or oral contraceptives and they don't even think about it. But tamoxifen is such a studied drug, and it's so controversial that you have to present everything.

From the floor: Basically, I look at the entire patient. I personally like tamoxifen, but I discuss the literature about aromatase inhibitors with every patient. At the same time, a lot of these patients have limited funds.

It's very important that they take their medication, so their ability to pay or be reimbursed for the medication is a very important aspect. For some patients, aromatase inhibitors are prohibitively expensive.

Dr Grana: Just to bring up a related point, most of us would choose AC followed by paclitaxel for the same extra benefit that we see with anastrozole over tamoxifen. Adding paclitaxel to AC probably adds at least $10,000 to the cost and yet we accept it because the patient doesn't have to pay for it.

Select publications

Choice of hormonal therapy in the postmenopausal woman

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Ingle JN. **Adjuvant endocrine therapy in postmenopausal breast cancer.** *Clin Cancer Res* 2003;9(1 Pt 2):480S-5S. **Abstract**

Sainsbury R on behalf of the ATAC Trialists' Group. **Beneficial side-effect profile of anastrozole compared with tamoxifen confirmed by additional 7 months of exposure data: A safety update from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial.** *Breast Cancer Res Treat* 2002.**Abstract 633.**

Schmid M et al. **Randomized trial of tamoxifen versus tamoxifen plus aminoglutethimide as adjuvant treatment in postmenopausal breast cancer patients with hormone receptor-positive disease: Austrian breast and colorectal cancer study group trial 6.** *J Clin Oncol* 2003;21(6):984-90. **Abstract**

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Adjuvant chemotherapy

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

Robert JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study.** *Proc ASCO* 2002;**Abstract 141.**

Watters JM et al. **Functional status is well maintained in older women during adjuvant chemotherapy for breast cancer.** *Ann Oncol* 2003;14(12):1744-50. **Abstract**

Case 4: From the practice of David M Mintzer, MD

- 52-year-old woman with a T1N1M0, ER/PR-negative, HER2-negative infiltrating ductal carcinoma of the left breast
- Mastectomy followed by AC x 4, paclitaxel x 4
- Three years later: Presented with symptomatic pericardial effusion (compatible with recurrence) treated with pericardiectomy
- Biopsy: Adenocarcinoma
- Still with axillary nodes and pleural effusion

Dr Mintzer: This 55-year-old woman was treated three years ago for a T1N1M0, ER/PR-negative, HER2-negative left-breast cancer. She elected to undergo a mastectomy, which was followed by AC for four cycles and paclitaxel times four. She presented three years later, with symptomatic pericardial effusion, which was histologically confirmed to be recurrence.

She was managed with a pericardiectomy and is now asymptomatic and working full-time, but she still has evidence of disease in the contralateral right axillary nodes and small pleural effusions on CT scan.

Dr Winer: You're comfortable with the HER2 testing?

Dr Mintzer: Yes. She actually did have FISH, and it was negative, as was the IHC.

Dr Winer: I would use single-agent therapy, and I'm not convinced that there's an optimal sequence in which it should be given (Figure 4.1). Any of the active single agents are fine. I realize that the traditional choices are anthracyclines and taxanes. In this patient, given the fact that she's had four cycles of AC, most oncologists would probably use a taxane rather than an anthracycline. I probably wouldn't use a taxane, and would likely use something that is better tolerated. In these kinds of situations, these days, I actually often use capecitabine.

Dr Love: She received paclitaxel three years ago. What about docetaxel?

Dr Winer: Clearly, there are responses to docetaxel in patients who have been on paclitaxel, but there aren't a huge number. The response rate to docetaxel in the study that was reported a few years ago in patients who received paclitaxel was about 20 percent (Figure 4.2).

So there is some activity. In this situation, I would not view her disease as being either anthracycline- or taxane-resistant, and in practice, I consider going back to an anthracycline at some point. Going back to a taxane is also a possibility.

Dr Love: Dr. Mintzer, what was this woman's perspective on her situation?

Dr Mintzer: She basically left it up to me. The quandary here is that — although she had a pericardial effusion that could have been fatal — that is now relieved, and she's really asymptomatic. Do we approach this

like an aggressive symptomatic person or, now that she's asymptomatic, in a more indolent fashion? Because of the pericardiectomy, I think it's unlikely for her to have recurrent symptomatic pericardial disease. Most patients have prolonged relief after an adequate window, although some patients do fail that therapy. I'm a big believer that you can only make asymptomatic patients feel worse, not better.

Dr Love: Hy, how would you have thought through this case?

Dr Muss: I would actually use capecitabine in a patient like this outside of a clinical trial. We just did a trial evaluating oral chemotherapy, which was relatively nontoxic, but I think all of our therapy is palliative in these patients. That's the bottom line.

And I agree, you can't improve on being asymptomatic. So, I think capecitabine is a good choice. She

Figure 4.1

Random telephone survey of 100 medical oncologists: Sequencing of single agents in metastatic disease after adjuvant AC-paclitaxel

Postmenopausal women with ER/PR-negative, HER2-negative metastatic disease who received adjuvant AC-paclitaxel two years ago: What sequence of sequential single-agent chemotherapy do you typically use?

Agent	1st line	2nd line	3rd line
Docetaxel	68%	23%	5%
Capecitabine	18%	38%	15%
Vinorelbine	2%	23%	43%
Gemcitabine	7%	12%	35%
Doxorubicin	5%	2%	2%
Platinum	—	2%	—

SOURCE: 2003 *Breast Cancer Update* Patterns of Care Study.

Figure 4.2

Efficacy data from Phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer

Objective response (N=44)	18.1% (95% CI 6.7%-29.5%)
Response rate in patients previously treated with paclitaxel by 24-hour infusion (n=12)	0%
Response rate in patients previously treated with paclitaxel by 1-3-hour infusion (n=32)	25%
Median response duration	29 weeks
Median time to disease progression	10 weeks
Median survival	10.5 months

DERIVED FROM: Valero V et al. **A Phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer.** *J Clin Oncol* 1998;16(10):3362-8. **Abstract**

won't lose her hair again, she won't become myelosuppressed, and you can monitor her closely for hand-foot syndrome. I think capecitabine offers a good quality of life for a lot of these women. You can go back to the other agents later and, as Eric said, you can pick anything.

This patient had a three-year interval since her adjuvant chemotherapy. It's not great, but it's better than a one-year, disease-free interval, and I think the patient is likely to have a better quality of life with capecitabine than with IV taxanes or coming back for anthracyclines and having to buy another wig in two to three weeks. I would lean toward capecitabine.

From the floor: Did she have a mammogram to show that she doesn't have new onset disease on the right side?

Dr Mintzer: There was nothing clinically palpable in the right breast at that time. I did not do a mammogram because she had proven metastatic disease, so it would seem to have been relatively irrelevant. However, I will tell you that six months later she developed a mass in that right breast.

Dr Love: Did you have some kind of premonition about this? What made you ask the question and actually predict what happened?

From the floor: She had a three-year disease-free interval, and women certainly do develop bilateral breast cancer. She had a contralateral node. Maybe her metastatic disease is not the same as her primary disease. I think you have to figure out the options, so I would retest HER2 and I would probably do an MRI on the right breast.

Dr Love: The other issue would be whether her disease was resistant, or potentially resistant, to her prior adjuvant therapy. What happened with this woman?

Dr Mintzer: The right breast was biopsied and showed infiltrating ductal carcinoma that was ER/PR-negative and HER2-negative, just as the original contralateral primary tumor had been.

Dr Love: How did you manage her new contralateral primary cancer?

Dr Mintzer: After the pericardiectomy, I gave her capecitabine and she had stable disease for about three months. By four months, the new breast lesion had appeared and she had rising tumor markers. Then we put her on docetaxel and the new breast lesion shrank down. We debated whether or not she should have a mastectomy on the other side.

Dr Love: So, your conclusion was that she was progressing in the other breast while on capecitabine?

Dr Mintzer: She clearly was progressing. Whether she was progressing from her metastatic initial primary or whether she was progressing from a second primary was unclear.

Dr Winer: I'd like to go back to one of the prior points. The fact that she could have another primary illustrates the importance of retesting ER, PR and HER2 status, if there's any question. Knowing whether there's anything in that breast once you've re-tested ER, PR and HER2 may or may not make a difference in your treatment at this point.

The issue of resistance to AC and paclitaxel doesn't exist because it's a new primary, and chances are that primary was there when she received the AC and paclitaxel three years ago. So, I don't know that this would change my thinking either.

Dr Love: What is your plan in terms of this second primary?

Dr Mintzer: She had a contralateral mastectomy at her insistence two days ago.

Dr Love: And axillary dissection?

Dr Mintzer: No axillary dissection.

Dr Love: What went into her decision?

Dr Mintzer: She was actually very well-informed. I told her that the systemic disease might be more of a problem before she had local progression in that breast. I generally do not recommend mastectomy in the setting of metastatic disease, but I felt this was an unusual case (Figure 4.3).

Dr Love: Did she have reconstruction?

Dr Mintzer: No. She did not request it, and I did not recommend it.

Dr Love: What about the question of retesting metastatic disease for HER2 in a patient who has a HER2-negative primary?

Dr Muss: I don't routinely do it, but it's not an unreasonable thing to do. HER2 is usually consistent in the primary lesion and metastases. If you look at ER/PR status, it's vastly different. Studies show that you can divide a breast cancer into 12 sections and one part will be strongly ER-positive and another part will be stone-cold negative. I think HER2 is usually more consistent. We are trying to give every patient every break, so, depending on the clinical situation and how sick the patient is, it's not unreasonable to retest for HER2 (Figure 4.4).

A patient was recently referred to me whose HER2 was retested and was positive, and it really gave this patient another option for therapy. So, in selected patients, I think it's a reasonable thing to do.

Dr Winer: Ann Thor evaluated the

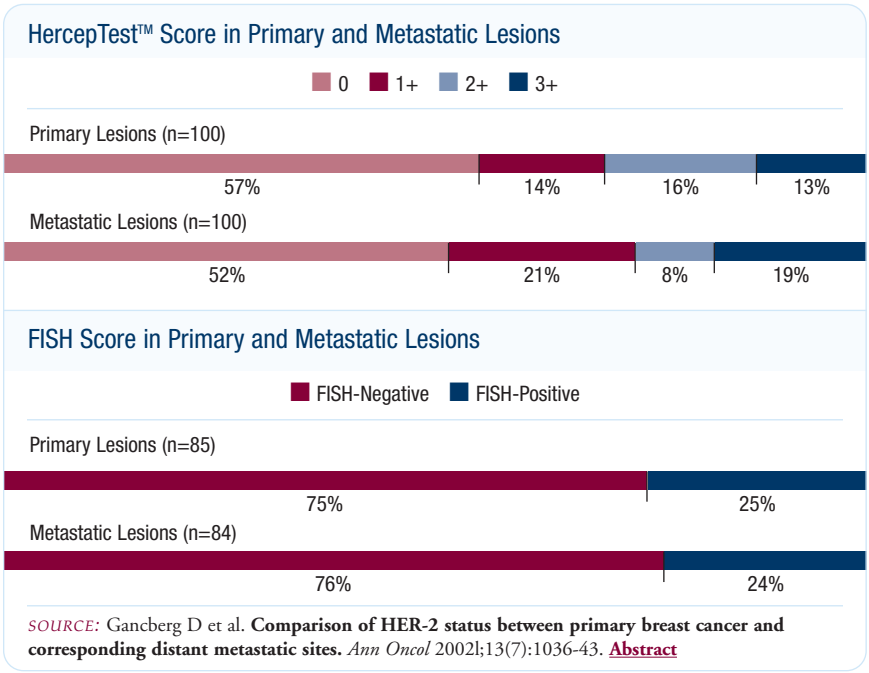
Figure 4.3

Impact of local therapy and margin status on survival in patients with metastatic disease: A review of 16,023 patients

	3-year survival	5-year survival	Median survival
No surgery	17.3%	6.7%	11.9 months
Clear margins			
Partial mastectomy	34.7%	16.6%	22.9 months
Total mastectomy	35.7%	18.4%	25.3 months
Involved margins			
Partial mastectomy	26.4%	11.3%	17.6 months
Total mastectomy	26.1%	11.5%	20.0 months

DERIVED FROM: Khan SA et al. **Does aggressive local therapy improve survival in metastatic breast cancer?** *Surgery* 2002;132(4):620-7. **Abstract**

Figure 4.4



SOURCE: Gancberg D et al. **Comparison of HER-2 status between primary breast cancer and corresponding distant metastatic sites.** *Ann Oncol* 2002l;13(7):1036-43. **Abstract**

concordance rate between the primary and the metastatic lesion. Her lab did the testing side by side on both of them, thereby eliminating the potential for false positives in some other lab. The concordance rate was 80 to 90 percent. It wasn't 100 percent, so they are different once in a while. I actually just treated a patient last week with recurrent disease that was progressing on trastuzumab. Her oncologist wanted to continue trastuzumab with something else. There had been some issues with the past testing, and I thought it was very likely not a HER2-positive tumor. We did a punch biopsy just to prove that it was HER2-negative, which one of the biopsies had shown before, and lo and behold, it was 3+ HER2-positive. I think we're still early enough in all of this testing that, if there's any question, it makes sense to obtain new tissue and retest.

From the floor: Would you routinely do FISH on any HER2 lesion that was zero on IHC?

Dr Winer: Very few patients whose biopsies are zero on IHC in a group lab have FISH-positive disease. With 1+, you start getting into the single digits, and I think that's where you really have to take into account their clinical situation. In patients with 2+ or 3+ disease, it makes sense to do FISH.

From the floor: What clinical setting would make you think that this disease was HER2-positive, despite a negative result?

Dr Winer: Nothing is absolute. A mix of different features — more common in

this setting of ER- and PR-negative disease (although probably 50 percent of HER2-positive disease is ER-positive), visceral disease, a patient presenting initially with DCIS with necrosis, and a short disease-free interval. You just have to use your judgment. And, if you're not sure, it's probably reasonable to re-test.

Select publications

Capecitabine in the metastatic setting

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Gradishar WJ. **Clinical status of capecitabine in the treatment of breast cancer.** *Oncology (Huntingt)* 2001;15(1 Suppl 2):69-71. **Abstract**

Jakob A et al. **Capecitabine in patients with breast cancer relapsing after high-dose chemotherapy plus autologous peripheral stem cell transplantation—-a Phase II study.** *Anticancer Drugs* 2002;13(4):405-10. **Abstract**

Maher JF, Villalona-Calero MA. **Taxanes and capecitabine in combination: Rationale and clinical results.** *Clin Breast Cancer* 2002;2(4):287-93. **Abstract**

O'Shaughnessy JA et al. **Randomized, open-label, Phase II trial of oral capecitabine (Xeloda) vs a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer.** *Ann Oncol* 2001;12(9):1247-54. **Abstract**

O'Shaughnessy J. **Clinical experience of capecitabine in metastatic breast cancer.** *Eur J Cancer* 2002 Feb;38 Suppl 2:10-4. **Abstract**

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

HER2 concordance between primary and metastatic breast cancer

Dittadi R et al. **Evaluation of HER-2/neu in serum and tissue of primary and metastatic breast cancer patients using an automated enzyme immunoassay.** *Int J Biol Markers* 2001;16(4):255-61. **Abstract**.

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Masood S, Bui MM. **Assessment of Her-2/neu overexpression in primary breast cancers and their metastatic lesions: An immunohistochemical study.** *Ann Clin Lab Sci* 2000;30(3):259-65. **Abstract**

Sekido Y et al. **Heterogeneous gene alterations in primary breast cancer contribute to discordance between primary and asynchronous metastatic/recurrent sites: HER2 gene amplification and p53 mutation.** *Int J Oncol* 2003;22(6):1225-32. **Abstract**

Simon R et al. **Patterns of her-2/neu amplification and overexpression in primary and metastatic breast cancer.** *J Natl Cancer Inst* 2001;93(15):1141-6. **Abstract**

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Vincent-Salomon A et al. **HER2 status in patients with breast carcinoma is not modified selectively by preoperative chemotherapy and is stable during the metastatic process.** *Cancer* 2002;94(8):2169-73. **Abstract**

Case 5: From the practice of Stephen A Grabelsky, MD

- 72-year-old woman with history of breast cancer at age 35, treated with radical mastectomy, chest wall radiation and adjuvant ovarian radiation
- 37 years later: Presented with minimal cough, bilateral pulmonary nodules on CT
- Biopsy revealed moderately well-differentiated adenocarcinoma, strongly ER-positive
- Received letrozole: The nodules decreased in size, tumor markers normalized. Received alendronate for diminution of bone density
- One year later: Markers rising, nodules enlarging

Dr Grabelsky: This 72-year-old woman became postmenopausal at age 35 as a result of a breast carcinoma. I don't have all the details because it was in 1962. She apparently had node-positive disease and underwent a radical mastectomy, chest wall radiation and ovarian radiation at that time, and she did well for 37 years.

In 1999, she presented with a minimal cough, which persisted despite a trial of antibiotics, et cetera, and was noted to have some small pulmonary nodules on chest X-ray, which were confirmed on CT scan. She underwent a bronchoscopy, at which time a small endobronchial lesion was noted and biopsied and revealed a moderately differentiated adenocarcinoma, which was strongly estrogen receptor-positive.

Dr Love: At that point, she was 72 years old and had undergone adjuvant ovarian radiation 37 years ago.

From the floor: What about her other breast?

Dr Grabelsky: She had mammography and MRI scanning of the breast, as well as a physical examination, and there was nothing abnormal.

Dr Love: How symptomatic was she at that point?

Dr Grabelsky: Minimally symptomatic, just a nonproductive cough. No shortness of breath. Excellent performance status.

Dr Love: And no other evidence of disease?

Dr Grabelsky: Complete staging workup, including PET scan, was negative.

Dr Love: Can you describe the pulmonary disease?

Dr Grabelsky: There were about eight to 10 nodules, bilaterally, mostly in the upper lobes, which were one to two centimeters. Also, her tumor markers, both CA 15-2 and CA 27-29, were elevated.

Dr Love: Lisa, what do you think you would do in this kind of situation?

Dr Carey: She's 72 years old and is asymptomatic with this odd picture of endobronchial lesions. I would use an aromatase inhibitor. You

don't want to make her sick, and she's asymptomatic with disease only in her lungs.

Dr Love: What did you do, Dr Grabelsky?

Dr Grabelsky: We gave her letrozole, and she had a very good response. The nodules shrank; they did not completely disappear but they were a subcentimeter. Her tumor markers completely corrected, and she did well for over a year until December of 2002.

Dr Love: What happened at that point?

Dr Grabelsky: At that time, her markers started going up and re-staging evaluation revealed that the nodules were enlarging again. No new nodules were identified and no metastatic disease anywhere else.

Dr Love: So, she's back kind of where she started from?

Dr Grabelsky: Again, minimally symptomatic, just a cough.

Dr Love: Genny?

Dr Grana: I have two issues to discuss. I haven't been in practice 35 years, so I can't say I've seen a relapse this far out. It is possible that this is a relapse of her first cancer. I guess it's also possible that this is a metastases from another cancer that you haven't found in the opposite breast. This is clearly a patient for whom genetic testing would have implications for her family, not for her at age 72.

At this point I would probably go back to tamoxifen and, again, it's that data from the anastrozole versus tamoxifen trial that tells us that, if you use an aromatase inhibitor first and you go to tamoxifen, about 60 percent of patients derive a clinical benefit. It was a retrospective look, not a built-in crossover, but I like tamoxifen.

Dr Love: Bob, what do you think you would do in this situation, progressing on an aromatase inhibitor?

Dr Carlson: I think the idea of tamoxifen is a great one, and that's probably what I would do.

The one thing you've told me that's very surprising is that she only had a two-year duration of response to an aromatase inhibitor. I would have expected a three-, four- or five-year duration of response.

Dr Love: What happened with this patient?

Dr Grabelsky: We had a discussion and at that point she actually was on several other medications, and we discussed tamoxifen versus fulvestrant, which had just become available. Because of financial issues about paying for medications, she elected to use fulvestrant. She had an excellent response. Nodules have decreased, tumor markers have again normalized, and she's stable after nine months on fulvestrant. My concern is that, if she's staying on fulvestrant, do we know what are the long-term toxicities of this agent?

My other question was: If she stops responding to fulvestrant, could you go back to something like tamoxifen?

Dr Carlson: We know that responses do occur to endocrine therapy after fulvestrant (Figures 5.1, 5.2). I don't

think we have really long-term data in terms of multiple years of fulvestrant treatment with follow-up. Certainly, the toxicity experience to date suggests that the toxicities are not cumulative with fulvestrant, and the toxicity experience at month 12 is similar to the toxicity experience at month four or six. Only a handful of patients have been on fulvestrant for longer than 18 months or so.

Dr Love: Is she receiving the two 2.5-cc injections?

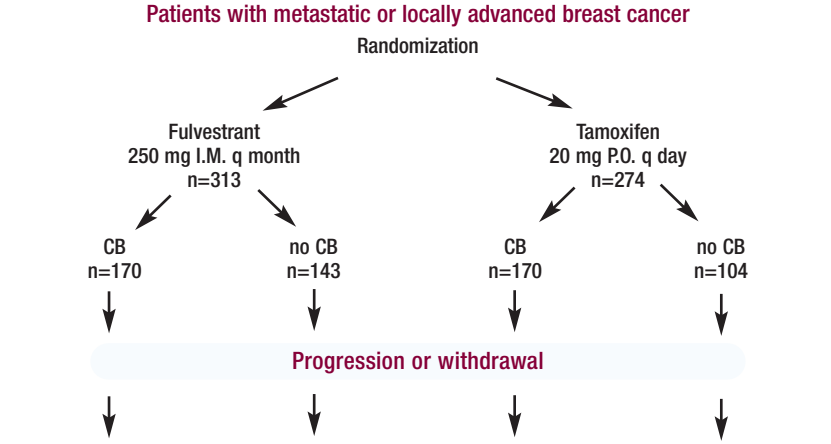
Dr Grabelsky: Yes, the two injections. She has had an occasional irritation in her buttock, but other than that, she's tolerating it extremely well and she's very active, traveling to visit her children and grandchildren. Her performance status is zero.

Dr Love: Is she thin, or not so thin?

Dr Grabelsky: Relatively thin. She is also on alendronate sodium (Fosamax®), so she comes in monthly for that and the fulvestrant (Faslodex®). She had some osteopenia, which developed in the

Figure 5.1

Response to endocrine therapy after fulvestrant or tamoxifen: A retrospective evaluation



Further therapy: n=35		Further therapy n=35		Further therapy n=31		Further therapy n=21	
	Fraction of patients with CB		Fraction of patients with CB		Fraction of patients with CB		Fraction of patients with CB
Endocrine therapy	20 / 35	Endocrine therapy	15 / 35	Endocrine therapy	19 / 31	Endocrine therapy	12 / 21
Anastrozole	9 / 16	Anastrozole	7 / 12	Anastrozole	9 / 15	Anastrozole	7 / 9
Letrozole	1 / 5	Letrozole	1 / 3	Letrozole	4 / 4	Letrozole	3 / 6
Tamoxifen	8 / 10	Tamoxifen	5 / 12	Fulvestrant	0 / 1	Other	2 / 6
Other	2 / 4	Other	2 / 8	Other	6 / 11		

CB = clinical benefit

DERIVED FROM: Howell A. Poster 251, San Antonio Breast Cancer Symposium, 2002.

interim when she was on the aromatase inhibitor.

She does not have true osteoporosis, but has had some diminution in her bone density so she was started on alendronate sodium at that time.

Figure 5.2

Overall response to fulvestrant 250 mg after progression on tamoxifen and aromatase inhibitors (N=32)

	Clinical benefit*	Partial response	Stable disease >24 weeks
Number of patients (%)	11 (34%)	2 (6%)	9 (28%)

*Partial response + stable disease

SOURCE: Perey L et al, Poster #249, San Antonio Breast Cancer Symposium 2002.

Select publications

Estrogen receptor downregulator, fulvestrant

Howell A. **Preliminary experience with pure antiestrogens.** *Clin Cancer Res* 2001;7(12 Suppl):4369s-4375s;discussion 4411s-4412s. **Abstract**

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

Howell A et al. **Fulvestrant versus anastrozole for the treatment of advanced breast cancer: Survival analysis from a Phase III trial.** *Proc ASCO* 2003;**Abstract 178.**

Jones SE. **A new estrogen receptor antagonist—-An overview of available data.** *Breast Cancer Res Treat* 2002;75 (Suppl 1)S19-21;discussion S33-5. **Abstract**

Mauriac L et al. **Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: Combined results from two multicentre trials.** *Eur J Cancer* 2003;39(9):1228-33. **Abstract**

Parker LM et al. **Greater duration of response in patients receiving fulvestrant ('Faslodex') compared with those receiving anastrozole ('Arimidex').** *Proc ASCO* 2002;**Abstract 160.**

Robertson JF. **Estrogen receptor downregulators: New antihormonal therapy for advanced breast cancer.** *Clin Ther* 2002;24 (Suppl A)A17-30. **Abstract**

Robertson JF, Harrison MP. **Equivalent single-dose pharmacokinetics of two different dosing methods of prolonged-release fulvestrant ('Faslodex') in postmenopausal women with advanced breast cancer.** *Cancer Chemother Pharmacol* 2003;52(4):346-8. **Abstract**

Case 6: From the practice of Elisa Krill, MD

- 58-year-old postmenopausal woman diagnosed with first breast cancer 12 years ago, (received adjuvant CMF followed by tamoxifen). A second cancer was removed surgically seven years ago, with no further treatment
- Four years ago: Recurred with bony metastases and developed carcinomatous meningitis; received radiation to the brain and intrathecal methotrexate
- Received anastrozole: Stable disease for two years, patient then developed multiple liver metastases and rising tumor markers (liver function remained normal)

Dr Krill: This 58-year-old postmenopausal woman has a history of bilateral breast cancer. She was diagnosed with her first breast cancer 12 years ago and her second breast cancer seven years ago.

The tumor recurred four years ago with bony metastases. She then developed carcinomatous meningitis, which, after treatment, appears miraculously gone and has not recurred since then. She was stable, had stable tumor markers and was on anastrozole for about two years when she developed liver metastases and rising tumor markers.

Dr Love: Did she have an objective response to anastrozole?

Dr Krill: Not really. She had bone-only metastases and it was very hard to measure. She also had a mildly elevated tumor marker, which remained stable on anastrozole, so I would say she had stable disease on anastrozole.

Dr Love: What was her general condition at that point?

Dr Krill: Outside of some memory deficit because of intrathecal chemotherapy, she was fine physically.

Dr Love: Asymptomatic?

Dr Krill: Completely.

Dr Love: In addition to anastrozole, what therapy did she have in the past?

Dr Krill: The only therapy she ever had was CMF adjuvant therapy 10 years before, followed by tamoxifen. She also received radiation to the brain and methotrexate intrathecally.

Dr Love: How extensive were the liver metastases?

Dr Krill: There were multiple liver metastases, some of which were sizable. Her liver function was normal.

Dr Love: Lisa, what are your thoughts about management at that point?

Dr Carey: Extensive liver metastases makes me a little bit nervous in a patient who's progressed on an aromatase inhibitor, having previously received adjuvant tamoxifen. You can watch her carefully and try another hormonal agent, like fulvestrant, but this is a patient in whom I would also think about using chemotherapy. You have the option of trying to cytoreduce the tumor with chemotherapy. Some patients with large liver metastases have normal liver function and are asymptomatic. The problem with liver metastases is that a lot of times the patient does not become symptomatic

until there is liver failure, and that's a real problem. You can use chemotherapy to try to cytoreduce the disease, and then try to maintain control with a hormonal agent.

Dr Love: What were her thoughts about treatment?

Dr Krill: This was two years ago. She was very nervous about any sort of chemotherapy. She did not want to lose her hair, and she had a very active lifestyle (Figure 6.1).

Dr Carey: The story about carcinomatous meningitis that resolves is a very unusual one. I don't think I've ever seen that happen as you described it.

Dr Krill: I agree. I was not taking care of her at that point in time, but we reviewed the pathology.

Dr Love: Lisa, very specifically, what do you think you would have done?

Dr Carey: Given her story, I would probably use weekly paclitaxel and then, if she's doing well and she's cytoreduced, I would try fulvestrant (Figure 6.2).

Dr Love: It's interesting how often you see that strategy of chemotherapy induction followed by hormonal therapy maintainance. Bob, what research evidence do we have on this?

Dr Carlson: There is relatively minimal or no supporting data, although it's a commonly utilized strategy.

This woman has relatively minimal liver disease and stable to slightly progressed bony disease. She's asymptomatic. She's fearful of chemotherapy. I would just use another hormone.

Dr Love: Which one?

Dr Carlson: Fulvestrant.

Dr Love: Peter, what do you think you would have done for this patient? A lot of people get nervous with liver metastases and hormone therapy.

Figure 6.1

Random telephone survey of 100 medical oncologists: Patient perspectives on therapy in the metastatic setting

What percentage of women with metastatic breast cancer in your practice are in the following categories?

Patients whose dominant concern is maintaining good quality of life and avoiding side effects from therapy	29%
Patients whose dominant concern is seeing a tumor response with minimal concern about toxicity	33%
Patients who are equally concerned about avoiding toxicity and having a response	38%

SOURCE: 2003 *Breast Cancer Update* Patterns of Care Study.

Figure 6.2

Efficacy of fulvestrant compared to anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy

	North American Trial (0021)			European Trial (0020)		
	Fulvestrant (n=206)	Anastrozole (n=194)		Fulvestrant (n=222)	Anastrozole (n=229)	
Disease progression	83.5%	86.1%	HR=0.92; 95.14% CI=0.74 to 1.14; *P*=0.43	82.4%	83.4%	HR=0.98; 95.14% CI=0.80 to 1.21; *P*=0.8
Median time to progression	5.4 months	3.4 months		5.5 months	5.1 months	
Treatment failures	79.6%	84%	HR=0.96; 95% CI=0.77 to 1.19; *P*=0.69	84.7%	85.6%	HR=0.97; 95% CI= 0.80 to 1.19; *P*=0.81
Objective response	17.5%	17.5%	*P*=NS	20.7%	15.7%	*P*=NS
Median duration of response	19.0 months	10.8 months		15.0 months	14.5 months	
Deaths	35.4%	33.5%		36.9%	36.2%	

DERIVED FROM: Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20:3386-95. **Abstract**

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

Dr Ravdin: Actually, as long as we're talking about evidence-based medicine, we did a large 300-patient study in the Southwest Oncology Group, evaluating response rates for tamoxifen and predictors of response. Patients with visceral disease — specifically hepatic disease — had just as good a response rate as patients with cancer in any other site, indicating that the site of the disease does not predict failure of therapy. If this patient had one or two liver metastases, I might try hormonal therapy again. But if she had, say, 10 small liver metastases and the markers had increased rapidly, I would probably treat such a patient with chemotherapy.

Dr Love: What type?

Dr Ravdin: I would treat this patient with an intensive chemotherapy — something that I expected to have about a 40- or 50-percent response rate — something like one of the taxane combinations. This case illustrates an interesting point that I find troubling. This is a patient who was picked up from someone else, who has a remote diagnosis of breast cancer and complicated events. If I'd been thinking about it *de novo*, it might have made me think about genetics. Here's

a woman with a premenopausal, bilateral breast cancer. I find it fruitful and sometimes a little bit humbling to go back and look at the history and realize that, if I'd seen that patient *de novo* today, I would be recommending that they see a genetics counselor.

From the floor: Do we really have any evidence-based medicine supporting the role of sequential hormonal therapy beyond tamoxifen for either an aromatase inhibitor or fulvestrant?

Dr Carlson: In the randomized trials of fulvestrant versus anastrozole, the investigators who accrued patients were asked to report on patients who had failed and crossed over to the other regimen. It was not a planned analysis. It was questionnaire-collected data — what I would call low-level evidence — but that low-level evidence indicated that responses were seen (Figure 6.3).

One of the difficulties here is that nobody is doing hormonal therapy trials as third-line, so everyone's trying to get first-line and second-line indications. We certainly know from experience that third- and fourth-line hormonal therapy responses certainly are observed, although they become less frequent with each generation of hormonal therapy. We'll probably never have high-level evidence about what to do with fourth- or fifth-line hormonal therapy.

Dr Love: If you have a patient who's progressed through a nonsteroidal aromatase inhibitor, who's had tamoxifen in the past, would you tend to use exemestane or fulvestrant in that situation?

Dr Grana: I don't know that either one is better, and that's exactly the question now being asked by an ongoing trial (Figure 6.4). This study is randomly assigning patients who failed on a nonsteroidal aromatase inhibitor to either exemestane or fulvestrant which include a loading program of 500 mg initially, and then 250 mg on day 14, and, 250 mg on day 28.

The idea is that you may need to load the drug to obtain better efficacy. I don't know what the right answer is, but I agree that I would ask the patient about their preference between

Figure 6.3

Response to endocrine therapy in patients in Trials 20 and 21 who derived clinical benefit from fulvestrant

	Number of patients with clinical benefit			
	PR	SD ≥24 weeks	Progression	Total
3rd generation AIs	3	12	24	39
Megestrol acetate	0	2	2	4

DERIVED FROM: Vergote I. *Breast Cancer Res Treat* 2001;69(3):**Abstract 446**.

Figure 6.4

The Evaluation of Faslodex® (fulvestrant) and Exemestane Clinical Trial (EFECT Trial)

Protocol IDs: EFECT, 9238IL/0048
Projected Accrual: 660

Eligibility: Postmenopausal, ER/PR-positive, locally advanced or metastatic breast cancer, progression on a nonsteroidal aromatase inhibitor (NSAI) or recurrence within six months of discontinuing NSAI therapy

ARM 1: Fulvestrant q 28 days*
ARM 2 Exemestane qd

*An initial 500 mg injection on day zero followed by 250 mg injection on days 14 and 28, and once monthly thereafter

Contact:

EFECT International Coordinating Investigator
William J Gradishar, MD, FACP

SOURCE: Sahmoud T. **Clinical trial designs for further development of fulvestrant (Faslodex®).** Poster, Lynn Sage Breast Cancer Symposium, September 2003; and NIH Clinical Trials.gov; AstraZeneca press release, August 2003.

injections and pills. Cost issues also come into play.

A small amount of data suggests that switching from a nonsteroidal to a steroidal aromatase inhibitor will lead to some responses.

Dr Carlson: The response rate was about 13 percent, but a substantial group of about another 20 percent had stable disease.

Dr Grana: It's not an earth-shattering number, but it is a response, and I think there's no right answer.

Dr Love: What happened to the patient? What did you end up doing?

Dr Krill: This was about a year and a half ago, before fulvestrant was easily available to us. She was very hesitant to receive intravenous chemotherapy. She's a very anxious person. And I prescribed capecitabine, which she's tolerated incredibly well. It's like she's not taking anything.

She's now been on capecitabine for a year and half, and her liver metastases nearly disappeared on CAT scan. Her tumor markers have stabilized, and they've been there for approximately a year now. I'm fearful to take her off, and yet I keep asking myself, "Should I take her off the capecitabine and observe her?

Should I take her off and put her on fulvestrant?" She has a performance status of zero, and she has no side effects from the capecitabine, whatsoever. So the question is: Do I just keep going on this or do I change tactics? Clinically, she's incredibly well.

Select publications

Sequencing of endocrine agents in the metastatic setting

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

Buzdar AU. **Endocrine therapy in the treatment of metastatic breast cancer.** *Semin Oncol* 2001;28(3):291-304. **Abstract**

Carlson RW. **Sequencing of endocrine therapies in breast cancer—integration of recent data.** *Breast Cancer Res Treat* 2002;75 (Suppl 1)S27-32;discussion S33-5. **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. **Postmenopausal women with advanced breast cancer who progress on fulvestrant or tamoxifen retain sensitivity to further endocrine therapies.** *Breast Cancer Res Treat* 2002;**Abstract 251**.

Morris C, Wakeling A. **Fulvestrant ('Faslodex')—A new treatment option for patients progressing on prior endocrine therapy.** *Endocr Relat Cancer* 2002;9(4):267-76. **Abstract**

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20(16):3386-95. **Abstract**

Parker LM. **Sequencing of hormonal therapy in postmenopausal women with metastatic breast cancer.** *Clin Ther* 2002;24 (Suppl C)43-57. **Abstract**

Perey L et al. **Fulvestrant ('Faslodex') as a hormonal treatment in postmenopausal patients with advanced breast cancer progressing after treatment with tamoxifen and non-steroidal aromatase inhibitors: An ongoing Phase II SAKK trial.** San Antonio Breast Cancer Symposium 2002;Poster 249.

Rose C. **A comparison of the efficacy of aromatase inhibitors in second-line treatment of metastatic breast cancer.** *Am J Clin Oncol* 2003;26(4 Suppl):S9-S16. **Abstract**

Carcinomatous meningitis

Boogerd W et al. **Response of leptomeningeal metastases from breast cancer to hormonal therapy.** *Neurology* 2000;55(1):117-9. **Abstract**

Gaur S. **Breast cancer relapsing as carcinomatous meningitis.** *South Med J* 2003;96(7):728. No abstract available.

Hara H et al. **Interventricular methotrexate therapy for carcinomatous meningitis due to breast cancer: A case with leukoencephalopathy.** *Breast Cancer* 2000;7(3):247-51. **Abstract**

Jaeckle KA et al. **Intrathecal treatment of neoplastic meningitis due to breast cancer with a slow-release formulation of cytarabine.** *Br J Cancer* 2001;84(2):157-63. **Abstract**

Kosmas C et al. **Isolated leptomeningeal carcinomatosis (carcinomatous meningitis) after taxane-induced major remission in patients with advanced breast cancer.** *Oncology* 2002;63(1):6-15. **Abstract**

Lauby G. **Carcinomatous meningitis in a patient with metastatic breast cancer.** *Clin Lab Sci* 2001;14(3):141-4. **Abstract**

Orlando L et al. **Intrathecal chemotherapy in carcinomatous meningitis from breast cancer.** *Anticancer Res* 2002;22(5):3057-9. **Abstract**

Robins HI et al. **Trastuzumab for breast cancer-related carcinomatous meningitis.** *Clin Breast Cancer* 2002;2(4):316. No abstract available.

Case 7: From the practice of Gregory R Favis, MD

- 76-year-old woman with a T3N1, ER-negative, PR-positive infiltrating ductal carcinoma in 1991
- Treated with mastectomy and reconstruction, radiation therapy, AC x 4, tamoxifen x 5 years
- Seven years later, relapsed in the skin and subcutaneous tissue (ten 1-cm lesions), metastatic work-up negative, otherwise asymptomatic
- Received an aromatase inhibitor, progressed within three months
- Lesion rebiopsied: ER-negative (similar histology to original tumor)
- Received capecitabine/docetaxel x 3 cycles: Minimal response and docetaxel discontinued
- Continued capecitabine: 50 percent response, remains on capecitabine for 18 months with no evidence of disease progression

Dr Favis: This 76-year-old woman had a T3N1 ER-negative, PR-positive breast tumor in 1991. She was treated with a mastectomy, AC for four cycles, radiation therapy and then tamoxifen for five years.

Seven years later, she relapsed in the subcutaneous tissues. She was started on an aromatase inhibitor and progressed in three months. We went back and rebiopsied one of the skin lesions, which we didn't do initially because it's so usual that somebody with such a long progression will have an ER-positive tumor. But we went back and rebiopsied one of these lesions, which was ER-negative.

Dr Love: Could you describe where these skin lesions were and what condition the patient was in?

Dr Favis: She was actually in pretty good condition. She and her husband were long-distance truck drivers, and she would go with him for two weeks at a time. She had been able to do that all along, so her performance status was completely normal. As for the skin lesions, there were about 10 of them, all about one centimeter in size but diffusely scattered over the back of her ears and her back. They weren't really bothering her, other than she knew they were there and they were slightly pruritic. There was no evidence of visceral organ involvement or other metastases in her work-up.

Dr Love: And so her original ER was in 1991, and that was ER-negative, PR-positive?

Dr Favis: Right.

Dr Love: And then you repeated it on the biopsy and it looked histologically like the same tumor?

Dr Favis: Yes, as best as we could tell.

Dr Love: The other breast was normal — no evidence of a new primary cancer?

Dr Favis: Correct. Her mammogram was negative.

Dr Love: You mentioned that she's a truck driver and she wanted to continue being able to take off for a couple of weeks at a time with her husband. Was this for personal or financial reasons, or both?

Dr Favis: Financially, it was not an issue. She just enjoyed going with him and it was part of their life together.

Dr Love: What was her reaction when she first was diagnosed with metastatic disease? How did she cope with that?

Dr Favis: I think women who have had breast cancer are always waiting for the other shoe to drop, so it wasn't that big of a surprise. But it had been 12 years since her initial diagnosis. She handled it well. A lot of people have blind faith that we can cure anything, and she kind of had that same feeling. I wish I had the same feeling.

Dr Love: To what extent were these skin lesions bothering her?

Dr Favis: They were starting to bother her cosmetically. That was her main concern.

Dr Love: Lisa, how would you have thought through this situation? This woman had prior AC 12 years ago, along with postmastectomy regional radiation therapy. She apparently has an ER-negative tumor with these skin lesions. What would you be thinking in terms of treating this 76-year-old woman?

Dr Carey: I think the first thing is that you probably can be somewhat reassuring by telling her that women who relapse after such a prolonged disease-free interval tend to live for a long time, and their disease tends to be easier to treat or at least more indolent. Regarding her treatment options, she has an active lifestyle; she's asymptomatic and wants to be able to leave town for a couple of weeks at a time. I think you can give her something that's likely to have low toxicity — perhaps capecitabine. I wouldn't give her the full dose, if you're trying to avoid toxicity. You can also consider paclitaxel.

Dr Love: Dr Favis, since Lisa mentioned capecitabine, how did you think she would be in terms of compliance? Did you think she would have reported back symptoms and taken the drug reliably.

Dr Favis: Yes. Absolutely. She was a really excellent patient in that regard.

Dr Love: Lisa, is that an important factor when you consider capecitabine?

Dr Carey: Absolutely. With any oral drug, you have to have a strong relationship with the patient and know that they're going to take it reliably and report back to you.

Dr Love: Peter?

Dr Ravdin: This is a case that Craig Allred would love. He would predict that this case would be ER-positive, even after hormone therapy failed. And so I guess one of the things I would do is retest her ER status. And I would consider, possibly going back and using tamoxifen, because there's something odd about this case with the very late recurrence.

Dr Love: Let's say you send the tumor to Craig Allred and he says, "It's absolutely zero. I don't see one ER-positive cell there." Would you still try a hormone?

Dr Ravdin: It's not out of the question.

This is the kind of patient who's going to have a long, slow progression and I would certainly think about it.

The other question I might ask — because we've all seen these patients, and there's no special reason why it seems to happen — is whether she's taking some root preparation or some other unconventional therapy. I'm always curious as to why somebody would develop multiple metastatic sites of disease 12 years after the fact.

Dr Love: Any suggestion of alternative approaches here?

Dr Favis: No. But she had reconstructive surgery and I've seen some peculiar patterns of recurrence after reconstructive surgery. One of the sites of recurrence initially was right at her suture line.

Dr Love: What happened with this lady?

Dr Favis: When she didn't respond to the aromatase inhibitor, it was roughly at the time during which Joyce O'Shaughnessy was talking about the capecitabine-docetaxel data (Figure 7.1), and so I decided to try her on that, even though she didn't seem very symptomatic. She went through three cycles of the docetaxel, and I really wasn't impressed by the response. These things are difficult because when you have a lot of subcutaneous things to measure, they're hard to quantitate. There didn't seem to be much of a response, so I left her on the capecitabine and she has had, I would say, about a 50 percent response. She's still on the capecitabine at 18 months and hasn't recurred in any other site. She likes the capecitabine because she can take it when she goes with her husband, and she's still out trucking with him.

Dr Love: How did you start the dosing and have you had to modify it?

Figure 7.1

Phase III trials comparing single-agent and combination chemotherapy for metastatic breast cancer

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

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

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

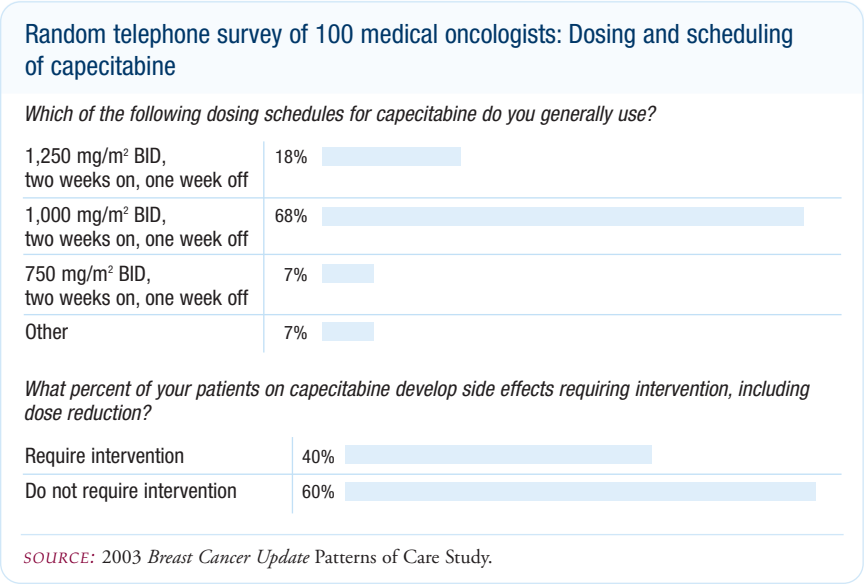
Dr Favis: I started at close to 2 g/m^2 per day in two divided doses for 14 days on with seven days off, and I've had to dose-reduce a little bit because of hand-foot syndrome, but not much (Figure 7.2).

Dr Love: It's interesting that in our patterns of care surveys, one of the things that we consistently observe in both community physicians and research leaders is that frequently they start their patients with ER-positive tumors on chemotherapy, and then, after the patient stabilizes, they switch to hormonal therapy. I've also heard about the strategy used in this case, in which you start off using the combination of capecitabine and docetaxel and then continue the capecitabine — sort an induction-maintenance approach. We presented a case like this to Joyce O'Shaughnessy at the last Miami Breast Cancer Conference and that was how she approached the patient. Lisa, is that a strategy you've used in your practice?

Dr Carey: Yes. I think, for the symptomatic patients, that's typically what we would do — use a combination. For someone who comes in with a lot of disease, use the combination to obtain the best response you can, but then continue them on something much less toxic as a single agent. If they've responded to the combination, we make our best guess as to which agent was the most important and most tolerable, and then continue with that. I'd say that's actually a very good paradigm.

From the floor: I was wondering, in a case like this where you have a 12-year, disease-free interval, would the histological grade on that biopsy help you? Let's say you found that it was a very well-differentiated tumor.

Figure 7.2



Even if the tumor was ER/PR-negative, would you be more apt to think it was positive and treat it as such?

Dr Love: Peter, that relates to what you were saying.

Dr Ravdin: I think you have nothing to lose by trying a hormone in a patient with indolent disease, and there are documented responses. There are clearly patients in whom the antibody doesn't pick up the fact that they have a functional estrogen receptor. Particularly in this case, to give it another spin would certainly be reasonable.

From the floor: There are clinical trials for first-line therapy in metastatic disease that should also be considered for a patient to enter. There's an ECOG study of paclitaxel plus or minus bevacizumab (Figure 7.3). It's an interesting study because second-line bevacizumab didn't work with capecitabine, but this is an ECOG first-line trial, and we'll see what happens. I have had patients on that trial and it's a relatively easy regimen for the patient.

From the floor: I have a question about the toxicity of the therapies and how much is necessary to obtain a response. I wonder why we subject everyone to the toxicity of the maximum dose of the therapy? I'm a bit of a therapeutic nihilist. I think that quality of life is important, particularly in the metastatic setting where treatment is palliative.

Dr Love: Bob?

Dr Carlson: With many of the agents that we use, including capecitabine, the evidence of a dose-response relationship is very poor. And if there is a dose-response curve, it's very shallow. I think that the FDA-approved dose of capecitabine of 2,500 mg/m^2 daily, divided into two daily doses, is much too toxic. I start it at

Figure 7.3

Phase III Randomized Study of Paclitaxel with or without Bevacizumab in Patients with Locally Recurrent or Metastatic Breast Cancer Open Protocol

Protocol IDs: E-2100, CTSU
Projected Accrual: 316-650 patients

Eligibility: Locally recurrent disease not amenable to resection with curative intent or metastatic disease.

ARM 1: Paclitaxel qw x 3 + bevacizumab q2w
ARM 2: Paclitaxel qw x 3

In both arms, treatment repeats q4w x 18 in the absence of disease progression or unacceptable toxicity.

Study Contacts:
Kathy Miller, Chair. Tel: 317-274-0920, ECOG
Edith Perez, Chair. Tel: 507-266-4997, NCCTG
Tamara Shenkier, Chair. Tel: 604-877-6000, NCIC
Melody A Cobleigh, Chair. Tel: 312-942-3240, NSABP

SOURCE: NCI Physician Data Query, October 2003.

2,000 mg/m^2 divided in two daily doses and, with that, my experience is that you usually end up rapidly dose de-escalating rather than escalating.

Another difficulty with dose escalating capecitabine is that the toxicity experience is often cumulative. If you dose escalate you sometimes think that the toxicity is because of the dose escalation, but it may be a result of the duration that the patient's been on therapy.

Select publications

Single agent versus combination chemotherapy in the metastatic setting

Ahn Sr, JH et al. **Phase II study of combination chemotherapy of capecitabine and vinorelbine in metastatic breast cancer with previous exposure to anthracycline and taxane: Preliminary results.** *Proc ASCO* 2002;**Abstract 2030.**

Alba E et al. **Multicenter Phase III randomized trial comparing sequential versus concomitant administration of doxorubicin (A) and docetaxel (T) as first-line treatment of metastatic breast cancer (MBC). GEICAM 9903 Study.** *Proc ASCO* 2003;**Abstract 27.**

Ghosn M et al. **Vinorelbine (Navelbine) IV and capecitabine (vinocap) as front-line chemotherapy in metastatic breast cancer (MBC).** *Proc ASCO* 2002;**Abstract 1978.**

Miles D et al. **Combination versus sequential single-agent therapy in metastatic breast cancer.** *Oncologist* 2002;7(Suppl 6):13-9. Erratum in: *Oncologist* 2003;8(1):127. **Abstract**

Miles D et al. **Survival benefit with Xeloda (capecitabine)/docetaxel vs docetaxel: Analysis of post-study therapy.** *Breast Cancer Res Treat* 2001;**Abstract 442.**

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

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

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

Tripathy D. **Overview: Gemcitabine as single-agent therapy for advanced breast cancer.** *Clin Breast Cancer* 2002;3 (Suppl 1)8-11. **Abstract**

Twelves C et al. **Adding Xeloda (capecitabine) to docetaxel significantly improves survival and does not compromise quality of life in patients with metastatic breast cancer.** *Breast Cancer Res Treat* 2001;**Abstract 542.**

Wright TL, Twelves CJ. **Improved survival in advanced breast cancer with docetaxel and capecitabine in combination: Biological synergy or an artifact of trial design?** *Eur J Cancer* 2002;38:1957-60. **Abstract**