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Patterns of Care in Medical Oncology

Management of Breast Cancer in the Adjuvant and Metastatic Settings

Adjuvant Chemotherapy

Adjuvant Hormonal Therapy

Chemotherapy for Metastatic Disease

Hormonal Therapy for Metastatic Disease

HER2-Positive Disease

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FROM THE PUBLISHERS OF:

Breast Cancer™ UPDATE

Colorectal Cancer™ UPDATE

Lung Cancer™ UPDATE

Non-Hodgkin's Lymphoma™ UPDATE

Prostate Cancer™ UPDATE

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Patterns of Care: A CME Series Activity

STATEMENT OF NEED/TARGET AUDIENCE

Medical oncology is one of the most rapidly evolving fields in medicine. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care, the practicing medical oncologist must be well informed of these advances and aware of the ever-expanding spectrum of options available to treat their patients.

It is also important for practicing oncologists to be aware of similarities and differences between his or her practice patterns, those of others in community practice and those of breast cancer clinical research leaders. While there is often agreement, it is important for oncologists to recognize the heterogeneity that exists in the oncology community, especially in clinical situations for which there is suboptimal existing research evidence.

This program focuses on the self-described practice patterns of randomly selected medical oncologists on a variety of key clinical issues in cancer. Also included is research leader commentary and references addressing these issues. This CME program will provide medical oncologists with information on national patterns of cancer care in order to assist with the development of clinical management strategies.

GLOBAL LEARNING OBJECTIVES FOR THE *PATTERNS OF CARE* SERIES

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

- Compare and contrast a management strategy for the treatment of cancer patients to that of other community oncologists and cancer research leaders.
- Discuss cancer management issues for which there is relative agreement and those for which there is heterogeneity in patterns of care.
- Counsel cancer patients about multiple acceptable treatment options when they exist.

PURPOSE OF THIS ISSUE OF *PATTERNS OF CARE*

The purpose of this issue of *Patterns of Care* is to support these objectives by offering the perspectives of 200 randomly selected medical oncologists interviewed at length in August of 2004 regarding their practice patterns in the management of breast cancer as well as the perspectives of Drs Carlson and O'Shaughnessy on these issues.

HOW TO USE THIS MONOGRAPH

This monograph is one issue of a CME series activity. To receive credit for this issue, the participant should read the monograph and complete the evaluation located in the back of this book or on our website **BreastCancerUpdate.com/POC**. PowerPoint files of the graphics contained in this document can be downloaded at **BreastCancerUpdate.com/POC**.

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Editor's Note: Phase II

I am sure that Dennis Slamon and his trastuzumab colleague investigators struggled mightily when that fascinating therapeutic agent first became available, and only through trial and error did they eventually define a safe and effective protocol for administration. Educational researchers (is that what I am?) also need time to tailor their new "interventions," and this edition of *Patterns of Care* involves a modest but important change in plan.

As with our first issue, we conducted random telephone surveys of community-based oncologists throughout the country. Two hundred brave souls were willing to give up 45 minutes of their day for a modest honorarium to provide us their perspectives, opinions and treatment recommendations. The data are once again presented in easy-to-read graphics.

The major change for this issue has to do with the commentary supporting these graphics. Last time around we compiled related quotes generated from the *Breast Cancer Update* audio series. While these were an effective adjunct, we thought it would be interesting to obtain specific perspectives on the actual survey data. To this end, we recruited two renowned research leaders and former *Breast Cancer Update* interviewees — Drs Joyce O'Shaughnessy and Robert Carlson — to provide their thoughts. To make this happen, I emailed Joyce and Bob the results of the survey, which included a minimum of 100 physician responses to each question. We then chatted about the data in a series of in-depth teleconferences. Edited smatterings of these conversations are interspersed throughout this monograph.

With regard to the survey, we really don't know if what the participating physicians say they do is, in fact, what they actually do in clinical practice. We expect and hope that these responses are closely correlated with intended treatment plans. Note that oncologist responses are totally anonymous. We do hope to expand our quest to define how patients are treated and perhaps someday include data documented by medical records. Meanwhile, we see many new and interesting trends in the current survey data, including the following:

1. **Adjuvant taxane-containing regimens** — either dose dense AC → paclitaxel, TAC, or AC → docetaxel — have quickly become standard of care for women with node-positive or high-risk node-negative tumors. This reflects a similar consensus among clinical research leaders including Drs O'Shaughnessy and Carlson.
2. **Aromatase inhibitors** are now clearly preferred to tamoxifen as adjuvant therapy for postmenopausal women with ER-positive tumors. Anastrozole as up-front therapy, exemestane and anastrozole for women who have had two to three years of tamoxifen, and letrozole after five years of tamoxifen are now common treatment approaches. Clearly, 2004 is "the year of the aromatase inhibitors."
3. **Peter Ravdin has changed the clinical face of breast cancer.** Our survey clearly reflects that Peter's Adjuvant! model has permeated into oncologic practices nationwide. Adjuvant! calculates the risk of relapse and mortality and the impact of systemic agents and regimens. The incorporation of this now validated model has changed the discussions and decisions regarding adjuvant systemic therapy. In particular, oncologists now use Adjuvant! to assist in assessing the potential use of chemotherapy in borderline situations such as elderly patients and those with node-negative disease. Another valuable aspect of the Adjuvant! model is the way it factors in competing causes of mortality in older patients.
4. **Systemic management of metastatic disease is variable.** Dr Carlson noted that available clinical research data does not clearly define preferred agents and regimens. In his opinion, new studies should be conducted to address this important issue. He also provides an intriguing comment about his soon-to-be-presented (in San Antonio) paper on LHRH agonist suppression plus anastrozole in premenopausal women with ER-positive metastatic disease. "It is the highest response rate to hormonal therapy that I have ever seen," he said.

Meanwhile, postmenopausal women with ER-positive disease may be treated in just about any sequence that includes tamoxifen, a steroidal and nonsteroidal aromatase inhibitor and fulvestrant. A survey our group conducted involving more than 200 women with metastatic breast cancer suggests that perhaps a third of patients prefer a monthly injection to a daily pill. Fulvestrant is a particularly salient consideration in patients already coming in monthly for bisphosphonate therapy.

Turning to the other key breast cancer molecular target, the management of HER2-positive metastatic disease now clearly includes trastuzumab from day one, although in the uncommon situation of ER-positive, HER2-positive disease, some physicians will utilize endocrine therapy prior to starting trastuzumab. It is interesting that physicians in this survey tend to use trastuzumab monotherapy a bit less than some of the more experienced clinical researchers in the field. Many research leaders, such as Melody Cobleigh, will not add chemotherapy until they are sure that trastuzumab alone is not controlling the tumor.

The next issue of our series will take a similar approach to this one, and three new research leaders (Cliff Hudis, Debu Tripathy and Gershon Locker) boldly comment on survey data for the record. We shall then re-evaluate and move forward. Your thoughts and suggestions are most welcome.

— Neil Love, MD
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Introduction: Breast Cancer in Community-Based Practice

FIGURE 1

Demographics

What percent of your work is patient care?

	Percent of physicians
50-70%	2%
71-80%	7%
81-90%	23%
91-99%	37%
100%	31%

FIGURE 2

Demographics

Percentage of patients that you see for office visits who have breast cancer	30%
Percent of the total patients in your practice who have breast cancer	31%
Percent of your total breast cancer patients who have metastatic disease	33%
Number of new breast cancer patients you evaluate in a typical month	13

DR LOVE: We've been doing patterns of care studies with oncologists for several years via national telephone surveys and using keypads and laptop computers at meetings. We've been gathering information on how oncologists practice — or how they say they practice. The information we gathered led to this new publication called *Patterns of Care*.

We conducted a national telephone survey of 200 medical oncologists from approximately 37 states randomly selected from the ASCO mailing list of oncologists in practice. Each question was asked of either 100 or all 200 physicians, so we are fairly confident in the numbers.

I'd like to present and discuss some of the results with you. According to the data (Figure 2) — and we have seen this from several other studies as well — about one third of general oncology practice is dedicated to breast cancer. Does that surprise you?

DR CARLSON: It doesn't surprise me based on the number of therapies that are available to women with breast cancer and the intensity of the interactions that are required. My expectation is that we are going to see those numbers decline over the next year or two as information about the advances in colorectal cancer and lung cancer are distributed throughout the community.

DR LOVE: That's a good point. I imagine that adjuvant therapy is creating a lot of the office visits for breast cancer patients, and it seems that adjuvant therapy for colon cancer and lung cancer is changing very rapidly.

DR CARLSON: I am sure a lot of it is adjuvant therapy but a lot of it is the weekly therapies we use for recurrent disease. Add in bisphosphonates and all the growth factors we are now using in the metastatic setting and it equals a lot of office visits.

DR LOVE: Before we discuss clinical scenarios, I'd like to ask you some questions that we asked the surveyed physicians relating to more psychosocial and quality-of-life aspects of patients with metastatic breast cancer and their predictions for how patients would rate their experiences with oncologists and oncology nurses.

Joyce, how many breast cancer patients in your practice have died in the last three months (Figures 3 and 4)?

DR O'SHAUGHNESSY: Oh, it has been terrible. I have lost many patients in the last six months. In the last three months, I would say approximately six patients have died. My practice is all breast cancer so they were all breast cancer patients.

DR LOVE: You said you had a terrible six months. How does that affect you?

DR O'SHAUGHNESSY: I have been in Dallas for seven and a half years. Many of these women have been my patients for five, six, seven years. They live a long time and you get to know them. It is really a complicated question because aside from my love for my family, taking care of breast cancer patients is the most enhancing thing in my life.

I've learned over the years — and it has taken me a long time to understand this — that truly caring about somebody, wanting to solve problems on that person's behalf and struggling to do everything you can to help that person — is the most empowering and energizing emotion I know. It is extremely positive.

Human beings are built for service; we are absolutely hard-wired for it. It is good for us, motivates us, energizes us

FIGURE 3

Patient Mortality

How many patients in your practice have died in the past three months?

Mean	17

FIGURE 4

Patient Mortality

Of those patients, how many have died of each of the following types of primary cancer?

Breast	18%
Colorectal	16%
Lung	32%
Non-Hodgkin's Lymphoma	7%
Prostate	7%
Other types	20%

FIGURE 5

Patient Mortality

Do you ever attend funerals for your cancer patients?

Yes, I have attended funerals for my patients	57%

FIGURE 6

Patient Mortality

In the last two years, how many funerals for patients, if any, have you attended?

Mean	5

FIGURE 7

Clinical Visits for Women with Metastatic Breast Cancer

How many office visits and clinical appointments do you believe the typical metastatic breast cancer patient has had in the past three months?

Mean	7

and brings out the best in us, so getting to know patients, caring about them and seeing these women is absolutely one of the most enhancing things in my life.

Thankfully, in breast cancer, we often have the opportunity to celebrate remissions. But you know darn well, Neil, that patients die. When you see the inexorable progression, start running out of options and watch as the symptoms become debilitating, it is very sad and it makes you feel helpless. It also spurs you to do the very best you can for early-stage breast cancer patients and become the strongest of salespeople when it comes to recommending and keeping women on therapy.

Patients tell me all the time, and it amazes me, that the best palliation by far comes from pills — antiestrogens or capecitabine. For HER2-positive disease, drugs like vinorelbine or trastuzumab provide enormously wonderful palliation for long periods of time as well.

However, in these patients who have prolonged periods of excellent quality of life and then go on to have horrendous difficulty with progression, lots of symptomatology and suffer the side effects of chemotherapy when they die, their families look at me and say, "You gave her five more years."

I have had several patients, and two come to mind, who died particularly difficult deaths. Both experienced complications from chemotherapy and died in the hospital instead of at home with hospice. However, both families expressed their appreciation for the extra years they had with their loved ones. That is enormously powerful.

DR LOVE: What do you do personally to deal with some of the stress and these feelings of helplessness?

DR O'SHAUGHNESSY: The way I deal with these feelings is to funnel them right back into breast cancer. I listen and

FIGURE 8

Clinical Visits for Women with Metastatic Breast Cancer

How long do you think the typical metastatic breast cancer patient spends in the waiting room during an office visit?

Mean time (minutes)	30

FIGURE 9

Clinical Visits for Women with Metastatic Breast Cancer

How long do you think these patients spend on a typical office visit from the time they arrive at the office until the time they leave?

Mean time (minutes)	86

FIGURE 10

Clinical Visits for Women with Metastatic Breast Cancer

How long do you think these patients spend with their oncologist during a typical office visit?

Mean time (minutes)	15

FIGURE 11

Clinical Visits for Women with Metastatic Breast Cancer

What percent of these patients have beneficial conversations with other patients during office visits or clinical appointments?

Mean	54%

FIGURE 12

Oncology Report Card

If these patients were asked to grade their oncologists in a number of areas, what do you think the overall grade point average for oncologists would be?

Mean grade point average	3.2

What do you think the overall grade point average for oncology nurses would be?

Mean grade point average	3.6

give respect to my own evolving observations about patterns of care and what works. I try to outsmart the cancer. I don't have "willy-nilly" algorithms for how to treat metastatic disease. I try to psyche it out.

The other thing I do is research. For example, these horrendous triple-negative (ER/PR/HER2-negative) breast tumors are very drug resistant. Some we cure in the adjuvant setting but the ones that come back are horrendous. We are hoping to start a new clinical trial of CPT-11/carboplatin with or without cetuximab because about 50 percent of these tumors have EGFR overexpression.

DR LOVE: How many clinical visits do you think the average woman with metastatic breast cancer has over a three-month period of time (Figure 7)?

DR O'SHAUGHNESSY: If we are including visits with the doctor, appointments for hematopoietic growth factors and everything else that patients come in for, I would have to agree with what the physicians said — seven or eight, on average.

DR LOVE: How long do you think the typical patient with metastatic breast cancer spends in your waiting room (Figure 8) and how long do you think she spends at your office from the time she arrives until the time she leaves (Figure 9)?

DR O'SHAUGHNESSY: I think she waits about 45 minutes to see me. When we add in the treatment time, the blood work and the consultation with me, I think each visit is probably two hours in total.

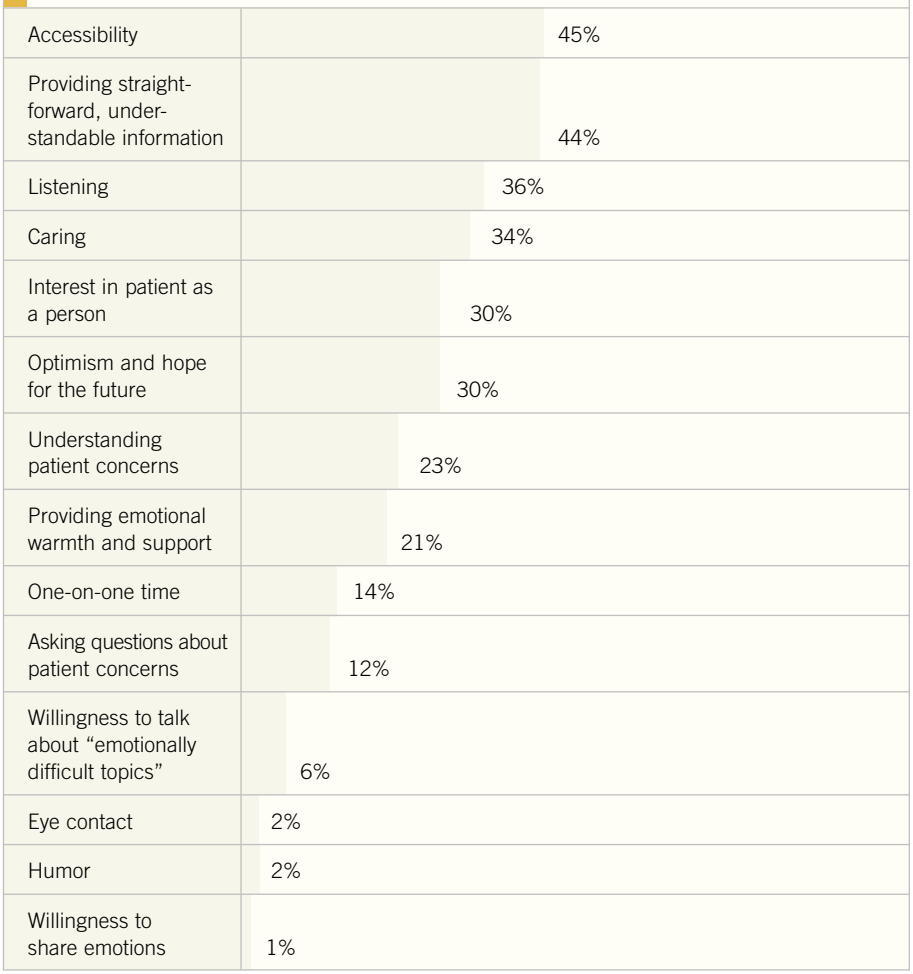
DR LOVE: That leads us to the next question, how long do you typically spend with a patient with metastatic breast cancer (Figure 10)?

DR O'SHAUGHNESSY: I would say a typical, relatively uncomplicated visit would probably last approximately 12 to 15 minutes.

FIGURE 13

Physician Behaviors

Of the physician behaviors listed, which three do you think patients with metastases would identify as the most important characteristics of medical oncologists?



DR LOVE: One of the other interesting aspects of this survey is that we asked physicians how their patients would grade them in terms of their overall care (Figure 12). What makes this so interesting is, in a similar survey we conducted of metastatic breast cancer patients, we asked them to actually grade their oncologists and oncology nurses using a 4-point scale.

We have recently prepared an abstract about this for presentation at the 2004 San Antonio Breast Cancer Symposium. What grade point averages do you think patients gave their oncologists and oncology nurses?

DR O'SHAUGHNESSY: I am going to guess that patients, on average, scored their doctors a 3.8 and their oncology nurses a 4.0.

DR LOVE: They were actually both about 3.5 and support the overall theme of the abstract, which is that patients think very highly of their doctors and nurses.

I asked this question in conversations at ASCO and a variety of other places, and I found that at least half of the oncologists I spoke with think their patients would give them a "C". Many underestimated how much patients appreciate their work.

DR O'SHAUGHNESSY: I think patients love their healthcare team, Neil; I think doctors and nurses become enormously important people in the lives of metastatic breast cancer patients and their entire families. These people spend a lot of time thinking about their doctor and when they see kindness and true caring from the doctor, they truly appreciate it.

DR LOVE: This is another very interesting question. What percent of patients do you think fired their oncologists because they weren't happy?

DR O'SHAUGHNESSY: A very small number. I would say five percent.

DR LOVE: It was 21 percent.

DR O'SHAUGHNESSY: That is the actual number from the patients?

DR LOVE: Yes. Twenty-one percent of these women left their oncologist because they were not happy. Part of the reason patients are so satisfied is because they seek satisfaction.

DR O'SHAUGHNESSY: They sought out what they needed. Good for them. Wow, that number is very high.

DR LOVE: Which of these characteristics do you think patients would view as most important (Figure 13)?

DR O'SHAUGHNESSY: Wow, these are all important. If I had to rate the highest, I would say it is a toss-up between providing straightforward information and caring, with providing straightforward information coming first.

SELECT PUBLICATIONS

Gourdji I et al. **Patients' satisfaction and importance ratings of quality in an outpatient oncology center.** *J Nurs Care Qual* 2003;18(1):43-55. Abstract

Gray RE et al. **Supportive care provided by physicians and nurses to women with breast cancer. Results from a population-based survey.** *Support Care Cancer* 2002;10(8):647-52. Abstract

Runge C et al. **The pasqoc study - patient satisfaction and quality of life in oncological care.** *Proc ASCO* 2003;Abstract 2215.

Adjuvant Chemotherapy

FIGURE 14

Use of Computer Models in Clinical Practice

How often do you use computer models/programs in your practice to evaluate individual patients in the adjuvant setting?

Always	—
Sometimes	86%
Rarely	14%
Never	—

FIGURE 15

Use of Computer Models in Clinical Practice

Which of the following models do you use to estimate your breast cancer patients' risk of relapse and/or mortality?

Peter Ravdin's Adjuvant! model	25%
Charles Loprinzi's Mayo Clinic model	12%
Both	22%
Neither	41%

FIGURE 16

Use of Computer Models in Clinical Practice

In which of the following situations do you tend to use these models?

To review risk estimates with patients	98%
To decide whether to use chemotherapy in node-negative cases	81%
To decide whether to use endocrine therapy in node-negative cases	44%
To select type of chemotherapy to use	19%
To select type of endocrine therapy to use	10%
Other situations	5%

DR LOVE: The use of Peter Ravdin's Adjuvant! program and some of the other computer models is a recent phenomenon. Interestingly, it now looks like more than half of all oncologists either have used or are using these models. Joyce, do you use a computer model in making clinical decisions (Figures 14-16)?

DR O'SHAUGHNESSY: I sometimes use the Ravdin model. I'm surprised to see that over half of the oncologists who responded have used these models — that's higher than I would have expected.

DR LOVE: You can see that in addition to providing patients with risk estimates, the most common use is treatment decisions in node-negative cases. What do you think that means?

DR O'SHAUGHNESSY: I believe it reflects that clinicians are struggling with treatment decisions, particularly in the patients with receptor-positive, node-negative breast cancer. I use Ravdin's model to give patients a quantitative estimate of their risk based on an authoritative source rather than just my opinion, particularly in these gray areas.

DR LOVE: Bob, do you have any additional thoughts on these numbers or the use of these models?

DR CARLSON: I am really pleased that the percentage of practitioners actually using computer-based models is as high as 60 percent. My expectation is that the number is rapidly increasing and it seems that people who have used these models in practice use them quite frequently. What made the use of Adjuvant! widespread was distribution — a diskette version is available at no cost to medical oncologists across the country.

I have found that it is difficult to convince practitioners to try these models; however, when they do, I believe that they see the power of the numbers and how the presentation of absolute benefits to the patient can make decision-making an easier and much more objective process.

DR LOVE: I believe these models have changed the culture of medical oncology especially with regard to the way the benefits of adjuvant therapy are being presented in terms of absolute versus relative risk.

FIGURE 17

Accuracy of Estimated Risk of Relapse and Mortality

The patient is a 65-year-old woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH) Grade II tumor and negative lymph nodes. How would you estimate this patient's 10-year risk of relapse and mortality?

Therapy	Estimated 10-year risk of relapse	Actual 10-year risk of relapse	Estimated 10-year risk of mortality	Actual 10-year risk of mortality
With no systemic therapy	20%	23%	12%	7%
With hormonal therapy alone	13%	Anastrozole 13% Tamoxifen 15%	8%	Tamoxifen 6%
With both hormonal therapy and chemotherapy (AC x 4)	10%	Anastrozole 11% Tamoxifen 14%	6%	Tamoxifen 5%

DR CARLSON: I think you're right. Historically, most of us tried to present both the relative and the absolute benefits of therapy. But when it boils down to decision-making, patients really don't care about relative benefits. They want to know the absolute numbers. Having a model like Adjuvant! allows us to estimate absolute benefit much faster and more reliably.

DR O'SHAUGHNESSY: I believe that's true, particularly in the low-risk scenario. In the node-positive, higher-risk situation, I still use the relative risk, but when it comes down to one, two or three points, I always use absolute. While too many variables exist for these models to be totally germane to one patient, I believe as a general rule they are very positive.

DR LOVE: Do you use the models yourself?

DR CARLSON: I use these models for every patient who comes to me for a discussion of adjuvant therapy. For the past two years I have printed out the results and I usually give them to the patient. I love the Adjuvant! model because it helps me avoid biases. Many factors influence how physicians think about a specific patient — personality type, type of relationship that is established, referral source — these models totally remove those from the equation.

DR LOVE: We presented a case in this survey (Figure 17) in which we asked doctors how they would estimate the patient's 10-year risk of relapse and mortality and then we calculated the numbers using the Adjuvant! model. It's interesting how closely they match.

DR CARLSON: That surprises me too. It makes me wonder if the use of these models has resulted in more education and now physicians are able to estimate the absolute risk of relapse and of death more accurately.

It would be fascinating to see this table broken into two parts: one evaluating the 60 percent of the practitioners who said that they have used the computer-based models and the other showing the 40 percent who have not used them. My prediction is that we would see more accuracy and consistency in the group that uses these models than we do in the group that does not.

DR LOVE: We actually did compare those groups and, surprisingly, we did not find many differences. Joyce, how would you estimate the risk of relapse in this patient?

DR O'SHAUGHNESSY: Without adjuvant therapy, I believe this patient has approximately a 12 percent risk. Adjuvant therapy would cut that risk in half; however, she would receive little benefit from chemotherapy — possibly zero benefit.

DR LOVE: The physicians who responded, and Adjuvant!, gave higher estimates of risk. Are they overestimating the risk?

DR O'SHAUGHNESSY: I fine tune risk a bit more. The size difference in Adjuvant! is between a 1.1-centimeter tumor and a 1.9-centimeter tumor. I estimate that a one-centimeter tumor has a 10 percent risk of relapse and a 12-millimeter tumor has a 12 percent risk of relapse.

DR LOVE: Regarding the question of chemotherapy (Figures 18 and 19), I am interested in your perspective on what physicians are doing in practice — especially the number that are using dose-dense AC. Also what would be your choices for chemotherapy in this situation at varying ages?

DR CARLSON: I am surprised by how many physicians are using AC alone, especially for a very young woman with what I would view as a substantial risk of relapse. I would have thought people would be more aggressive, either adding a taxane or considering dose-dense adjuvant therapy. While all of these therapies offer proportional risk reductions, the addition of a taxane or dose-dense therapy does increase that risk reduction.

For me it would be a 50-50 split between AC for four cycles every three weeks and dose-dense AC followed by paclitaxel. I have not used dose-dense AC without paclitaxel in part because I believe if the risk is great enough to warrant the use of dose-dense therapy, then it is presumably great enough to add the taxane. I am cautious because we don't have any prospective randomized data evaluating the utility of dose-dense AC by itself.

FIGURE 18

Adjuvant Chemotherapy for Node-Negative Disease

The patient is a woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH) Grade II tumor and negative lymph nodes. Which chemotherapy regimen, if any, would you most likely recommend for this patient?

	Age 35	Age 45	Age 55	Age 65	Age 75	Age 85
AC x 4 q3wk	50%	49%	42%	32%	15%	7%
AC x 4 q2wk with pegfilgrastim	8%	9%	7%	4%	2%	—
AC x 4 q2wk with filgrastim	1%	1%	—	—	—	—
FAC or FEC x 6	12%	12%	8%	5%	2%	1%
AC x 4 followed by paclitaxel x 4 q3wk	6%	6%	5%	3%	1%	1%
AC x 4 followed by paclitaxel x 4 q2wk with pegfilgrastim	3%	3%	3%	—	—	—
AC x 4 followed by paclitaxel x 4 q2wk with filgrastim	1%	1%	—	—	—	—
AC x 4 followed by docetaxel x 4 without growth factors	5%	6%	3%	3%	1%	—
AC x 4 followed by docetaxel x 4 with growth factors	2%	1%	2%	1%	—	—
CMF	7%	7%	7%	8%	6%	1%
TAC (docetaxel) x 6 without growth factors	1%	1%	1%	1%	—	—
TAC (docetaxel) x 6 with growth factors	1%	1%	1%	—	—	—
Would not recommend chemotherapy	3%	3%	21%	43%	73%	90%

FIGURE 19

Which treatment strategy would you most likely recommend in the above case?

	Age 35	Age 45	Age 55	Age 65	Age 75	Age 85
Chemotherapy alone	2%	2%	—	—	—	—
Chemotherapy + endocrine therapy	95%	95%	79%	57%	27%	10%
Endocrine therapy alone	3%	3%	21%	43%	72%	74%
No therapy	—	—	—	—	1%	16%

As the age of the patient increases, obviously the magnitude of absolute benefit decreases; therefore, I think as women grow older, fewer are willing to accept chemotherapy.

However, if you compare AC every three weeks to AC followed by paclitaxel in a dose-dense fashion, the magnitude of benefit that you achieve by using AC is at least matched by the addition of the taxane and the dose-dense application of it.

I think that most women who are willing to accept AC for the absolute improvement in benefit would also be willing to accept the addition of a taxane in a dose-dense fashion.

In my practice a 65-year-old woman would receive chemotherapy because the benefits are relatively substantial. I would offer her two alternatives — AC or dose-dense AC followed by paclitaxel. For an 85-year-old woman, however, I think few of us would be anxious to give her AC because of toxicity concerns.

DR LOVE: What about at age 75?

DR CARLSON: At age seventy-five it is a tough discussion and is influenced by comorbidities that may or may not exist, the woman's philosophy of life and how much toxicity she would be willing to tolerate for a very modest, but presumably real, gain.

DR LOVE: Joyce, which chemotherapy would you use in this clinical scenario?

DR O'SHAUGHNESSY: I generally don't use chemotherapy in postmenopausal patients with ER-positive, node-negative disease unless bad prognostic factors exist, such as a tumor that is HER2-positive, has a high proliferative fraction or is Grade III.

DR LOVE: When you use chemotherapy in a node-negative patient, which regimen do you use?

DR O'SHAUGHNESSY: I generally use six cycles of FAC. In the younger patient, age 55 or younger, I discuss TAC with the patient.

FIGURE 20

Adjuvant Chemotherapy for Patients with Node-Negative, HER2-Positive Disease

The patient is a woman in average health with a 1.2-centimeter, ER-positive, HER2-positive (as confirmed by FISH) Grade II tumor and negative lymph nodes. Which chemotherapy regimen, if any, would you most likely recommend for this patient?

	Age 35	Age 45	Age 55	Age 65	Age 75	Age 85
AC x 4 q3wk	42%	42%	41%	36%	18%	8%
AC x 4 q2wk with pegfilgrastim	8%	8%	4%	3%	2%	—
AC x 4 q2wk with filgrastim	1%	1%	1%	2%	—	—
FAC or FEC x 6	14%	15%	14%	9%	6%	1%
AC x 4 followed by paclitaxel x 4 q3wk	7%	6%	7%	4%	—	—
AC x 4 followed by paclitaxel x 4 q2wk with pegfilgrastim	8%	7%	6%	3%	1%	—
AC x 4 followed by paclitaxel x 4 q2wk with filgrastim	2%	1%	—	—	—	—
AC x 4 q3wk followed by weekly paclitaxel x 12	—	1%	—	1%	1%	—
AC x 4 followed by docetaxel x 4 without growth factors	13%	14%	12%	10%	1%	—
AC x 4 followed by docetaxel x 4 with growth factors	3%	2%	4%	3%	1%	1%
CMF	—	—	—	3%	4%	1%
TAC (docetaxel) x 6 with pegfilgrastim	1%	1%	1%	—	—	—
Other chemotherapy	1%	1%	—	—	—	—
Would not recommend chemotherapy	—	1%	10%	26%	66%	89%

DR LOVE: Why TAC as opposed to AC/docetaxel?

DR O'SHAUGHNESSY: When I use TAC in that situation, I sometimes use only four cycles. AC/docetaxel is six months of therapy and if a patient is eligible for that regimen, then I usually enroll her in our clinical trial. I tend to use AC/docetaxel in patients with higher-volume breast cancer, either T2 or node-positive. For patients age 65 and older, I generally don't use chemotherapy in this scenario.

DR LOVE: How would you treat the same patient if the tumor was HER2-positive (Figure 20)?

DR O'SHAUGHNESSY: I would use an anthracycline-based regimen for the patient with HER2-positive breast cancer.

DR CARLSON: It appears as though physicians are much more likely to use a taxane or dose-dense therapy for patients with HER2-positive disease. I think that is likely due to the perception that women with HER2-overexpressed breast cancer have a higher probability of recurrence.

DR LOVE: Do you agree with that?

DR CARLSON: I think it is probably true, but the available studies that have examined the issue retrospectively are somewhat contradictory. If we evaluate this in one univaried analysis, HER2 is definitely prognostic. But after you correct for lymph-node status, tumor size, degree of differentiation and so on, whether or not it remains independently prognostic, I am not yet convinced.

DR LOVE: In your own practice, do you tend to push your patients toward taxanes a little bit more if their tumor is HER2-positive?

DR CARLSON: I do, and I tell them what I just told you. I also provide an Adjuvant! estimate and explain that the estimate does not incorporate the level of HER2-overexpression. If their tumor is HER2-overexpressed, the estimates from Adjuvant! in terms of outcome are high and, therefore, the estimates for benefit from therapy are probably slightly low.

DR LOVE: The next case (Figure 21) is a woman in average health with a 1.2-centimeter, ER-positive, HER2-negative tumor and three positive nodes. This is another situation in which we asked physicians to estimate risk of relapse, and here we see some disparity at least in terms of the baseline risk of recurrence.

I would have guessed it would be a little higher. Do you think a 34 percent risk of relapse sounds right for this patient?

DR CARLSON: That is what I would tell my patients because I quite literally use Adjuvant! for every adjuvant patient I see.

FIGURE 21

Accuracy of Estimated Risk of Relapse and Mortality

The patient is a 65-year-old woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH) Grade II tumor and 3 positive lymph nodes. How would you estimate this patient's 10-year risk of relapse and mortality?

Therapy	Estimated 10-year risk of relapse	Actual 10-year risk of relapse	Estimated 10-year risk of mortality	Actual 10-year risk of mortality
With no systemic therapy	46%	34%	32%	16%
With hormonal therapy alone	30%	Anastrozole 20% Tamoxifen 23%	21%	Anastrozole 12% Tamoxifen 12%
With both hormonal therapy and chemotherapy (AC x 4)	23%	Anastrozole 18% Tamoxifen 21%	15%	Anastrozole 11% Tamoxifen 11%

FIGURE 22

Adjuvant Chemotherapy for Node-Positive Disease

Which chemotherapy regimen, if any, would you most likely recommend?

	Age 35	Age 55	Age 65	Age 75
AC x 4 q3wk	3%	4%	7%	11%
AC x 4 q2wk with pegfilgrastim	3%	3%	2%	2%
AC x 4 q2wk with filgrastim	1%	1%	—	—
FAC or FEC x 6	2%	3%	4%	7%
AC x 4 followed by paclitaxel x 4 q3wk	7%	8%	13%	7%
AC x 4 followed by paclitaxel x 4 q2wk with pegfilgrastim	38%	33%	26%	11%
AC x 4 followed by paclitaxel x 4 q2wk with filgrastim	7%	7%	5%	3%
AC x 4 q3wk followed by weekly paclitaxel x 12	2%	1%	3%	5%
AC x 4 followed by docetaxel x 4 without growth factors	15%	17%	16%	8%
AC x 4 followed by docetaxel x 4 with growth factors	11%	10%	10%	6%
CMF	—	—	—	10%
TAC (docetaxel) x 6 with pegfilgrastim	9%	9%	7%	2%
Other chemotherapy	2%	2%	2%	2%
Would not recommend chemotherapy	—	2%	5%	26%

DR LOVE: It suggests that maybe a prognosis of node-positive disease is not as bad as we thought.

DR CARLSON: I think what it tells us is that axillary lymph node status in isolation is not as strongly predictive as we would have expected.

In women with positive lymph nodes, the degree of differentiation, hormone-receptor status, size of the tumor and so forth are also independently prognostic and perhaps have a greater influence on the ultimate prognosis than we previously gave them credit for.

DR LOVE: That's interesting. When you use Adjuvant! within the node-positive population do you notice significant shifts based on grade and tumor size? I have never played around with the model in that respect.

DR CARLSON: Yes, you do see shifts and it is not difficult to find patients who are node-negative who have a risk of recurrence that is greater than some of the node-positive subsets.

I expect as these models are used more and more over the next few years we will see a culture shift and won't be stratifying patients in our brains or in our practices based on nodal status as much as we will base it on a risk estimate.

DR LOVE: Joyce, which chemotherapy regimen would you use for a patient like this with three positive nodes (Figure 22)?

DR O'SHAUGHNESSY: My standard treatment in this case would be AC followed by docetaxel. I offer the same regimen to patients ages 70 and over, but I usually begin the docetaxel at 75 mg/m^2 rather than 100 mg/m^2. If they do well, then I increase the docetaxel to 85 mg/m^2.

One study I'm intrigued with is a trial that Denise Yardley and Skip Burris are planning, of TAC versus dose-dense chemotherapy starting with docetaxel at 100 mg/m^2 every two weeks for four

FIGURE 23

Adjuvant Chemotherapy for Patients with Node-Positive, HER2-Positive Disease

The patient is a woman in average health with a 1.2-centimeter, ER-positive, Grade II tumor and 3 positive lymph nodes but her tumor is HER2-positive (as confirmed by FISH). Which chemotherapy regimen, if any, would you most likely recommend for this patient?

	Age 35	Age 65
AC x 4 q3wk	1%	6%
AC x 4 q2wk with pegfilgrastim	1%	1%
AC x 4 q2wk with filgrastim	1%	1%
FAC or FEC x 6	2%	2%
AC x 4 followed by paclitaxel x 4 q3wk	9%	16%
AC x 4 followed by paclitaxel x 4 q2wk with pegfilgrastim	32%	24%
AC x 4 followed by paclitaxel x 4 q2wk with filgrastim	7%	6%
AC x 4 q3wk followed by weekly paclitaxel x 12	3%	4%
AC x 4 followed by docetaxel x 4 without growth factors	15%	21%
AC x 4 followed by docetaxel x 4 with growth factors	15%	6%
TAC (docetaxel) x 6 with pegfilgrastim	12%	6%
Other chemotherapy	2%	2%
Would not recommend chemotherapy	—	5%

cycles followed by AC every two weeks for four cycles. Filgrastim is used in this trial.

DR LOVE: Wow! Has docetaxel every two weeks been evaluated?

DR O'SHAUGHNESSY: Yes. George Raptis published a paper in *Anti-Cancer Drugs* evaluating preoperative docetaxel 100 mg/m^2 every two weeks with a good PCR rate demonstrating feasibility.

However, docetaxel 100 mg/m^2 every two weeks following AC is not feasible because of skin toxicity, but you can administer the docetaxel first. This results in some skin toxicity, but it's at the tolerable level.

DR LOVE: What strikes me about the use of chemotherapy for this type of patient with node-positive disease is the amount of dose-dense AC → T being used and a reasonable amount of docetaxel given in different ways.

DR CARLSON: It is interesting to me how quickly dose-dense AC → T has become adopted and how widely it is used. I view that as good news because it looks like we're doing a good job of translating research findings into community practice in a timely fashion.

DR LOVE: Joyce, what are your thoughts about the dose-dense data?

DR O'SHAUGHNESSY: I'm the principal investigator of the US Oncology trial of AC followed by docetaxel versus AC followed by docetaxel/capecitabine, so I spend a lot of my day cheerleading for that study. Therefore, I'm biased.

I've used dose-dense AC followed by paclitaxel, but I tend to use it only in patients whose disease is not high enough risk to enroll in our clinical trial. I have a patient who is a 40-year-old nurse with a one-centimeter, Grade III, Ki-67, 80 to 90 percent, ER-/PR- and HER2-negative tumor and negative nodes.

While that's not a "good" cancer, she was not eligible for our trial because the tumor was not staged as T1C. If her tumor had been 1.1 centimeter, she would have been eligible, but she wasn't eligible and I wasn't going to treat her with AC or FAC. She has a "bad" cancer, so I gave her dose-dense AC followed by paclitaxel.

I have another patient with multiple myeloma in addition to breast cancer. I plan to use hematopoetic growth factor support, so I'm treating her with dose-dense AC followed by paclitaxel.

So, yes, I do use the dose-dense regimen for selected patients.

DR LOVE: Bob, would you present AC alone or CMF to a patient in this situation as options?

DR CARLSON: If a woman who has three positive lymph nodes has a risk of recurrence that is substantial enough in an absolute sense to warrant the use of chemotherapy, then the addition of the taxane or a dose-dense regimen or both provides an advantage that is at least equivalent to the addition of AC or CMF.

If a woman is willing to accept AC for four cycles for the absolute benefit she will derive, then she is almost certainly going to accept another four cycles of treatment with a taxane.

DR LOVE: Do you ever use TAC off protocol?

DR CARLSON: No, I don't.

DR LOVE: It's interesting that people almost always use growth factors when they use TAC. It seems that the message has gotten through.

FIGURE 24

Frequency of Adjuvant Taxane Use

About how many times a month do you start a breast cancer patient on a taxane-containing adjuvant regimen?

Mean	7

FIGURE 25

Use of Adjuvant AC Followed by Docetaxel

When you utilize adjuvant taxanes, how frequently do you use AC followed by docetaxel?

Never	10%
Rarely/occasionally	32%
About half the time	16%
Usually	23%
Always	19%

FIGURE 26

Use of Growth Factors with Adjuvant Docetaxel

When using adjuvant AC followed by docetaxel, which of the following best describes your dosing of docetaxel and use of growth factors?

75 mg/m^2 without growth factors	18%
75 mg/m^2 with filgrastim	8%
75 mg/m^2 with pegfilgrastim	29%
100 mg/m^2 without growth factors	12%
100 mg/m^2 with filgrastim	3%
100 mg/m^2 with pegfilgrastim	23%
Other	7%

DR CARLSON: I think that is probably one of the reasons why the TAC regimen is not more widely used. People initially didn't use growth factors and had bad experiences.

DR LOVE: Joyce, if this same patient were HER2-positive, I assume that wouldn't change your treatment plan with chemotherapy. Is that correct (Figure 23)?

DR O'SHAUGHNESSY: Correct.

DR LOVE: We asked these clinicians how many times a month they start a breast cancer patient on a taxane-containing adjuvant regimen, the response was about twice a week (Figure 24). A significant percentage of clinicians reported they use AC followed by docetaxel for adjuvant taxane therapy (Figure 25). Is that your practice?

DR O'SHAUGHNESSY: In a nonprotocol setting, my standard regimen is AC followed by docetaxel.

DR LOVE: What has been your experience with nanoparticle paclitaxel?

DR O'SHAUGHNESSY: I have treated approximately seven patients with this agent and I've found it's extremely well tolerated, particularly at the 100 mg/m^2 dose. In the Phase II trial with 125 mg/m^2, I had two patients who experienced either significant fatigue or some neuropathy with this higher dose.

I like the 100 mg/m^2 dose because I see very little myelosuppression or fatigue and I can't recall any patients experiencing peripheral neuropathy.

DR LOVE: I assume you don't premedicate patients receiving nanoparticle paclitaxel with the taxane.

DR O'SHAUGHNESSY: That is correct; I don't believe weekly dexamethasone is good for patients — it tires them and has a crash effect. Avoiding the premedication may be one of the reasons why we don't see significant side effects with nanoparticle paclitaxel.

DR LOVE: Would you use nanoparticle paclitaxel in the adjuvant setting off protocol?

DR O'SHAUGHNESSY: Without data, I am not generally willing to substitute nanoparticle paclitaxel for docetaxel off protocol in the adjuvant setting. In a middle-aged patient with numerous comorbidities whom I can't give TAC because of the risk of febrile neutropenia and other complications, I would

consider every three-week nanoparticle paclitaxel because it would be more tolerable than docetaxel 100 mg/m^2 and I don't feel dose-dense therapy is right for every patient.

We are considering an adjuvant trial comparing dose-dense AC followed by dose-dense paclitaxel versus dose-dense AC followed by dose-dense nanoparticle paclitaxel.

I generally use docetaxel 100 mg/m^2 in the adjuvant setting. If I had a patient who had been treated for early breast cancer and had a recurrence with a small, solitary lung metastasis that was biopsy-positive — a pseudoadjuvant setting — I would still use docetaxel.

I have two patients who have experienced long-term complete responses after six doses of docetaxel at 100 mg/m^2; however, in patients who clearly have metastatic disease, I am moving toward using nanoparticle paclitaxel if it is available.

DR LOVE: How do you think nanoparticle paclitaxel compares with paclitaxel and docetaxel in terms of efficacy?

DR O'SHAUGHNESSY: I believe nanoparticle paclitaxel 260 mg/m^2 is superior to paclitaxel 175 mg/m^2 in terms of response rate and time to progression. The data in the pivotal trial of nanoparticle paclitaxel in anthracycline-pretreated patients basically shows it to be as efficacious as docetaxel in terms of response rates.

DR LOVE: When you use adjuvant docetaxel, what dose do you use and when do you use growth factors (Figure 26)?

DR O'SHAUGHNESSY: I generally use 100 mg/m^2 of docetaxel. If I start any lower, I begin with 85 mg/m^2, particularly in patients who are older, frail or have multiple comorbid conditions.

I have started as low as 75 mg/m^2, although that is rare. I only use growth factors if a patient requires it during AC treatment and then I use pegfilgrastim while continuing the AC. I never use filgrastim.

DR LOVE: Can you comment on the recent data regarding the incidence of febrile neutropenia at 100 mg/m^2 dose?

DR O'SHAUGHNESSY: In a large trial of docetaxel 100 mg/m^2 with over 700 patients, the 19 percent rate of febrile neutropenia was reduced to one percent with pegfilgrastim. I believe it included patients with metastatic disease. We use AC followed by docetaxel in the adjuvant setting and less than 10 percent, maybe eight or nine percent, of our patients experience febrile neutropenia.

DR LOVE: Why is febrile neutropenia more common in metastatic disease?

DR O'SHAUGHNESSY: A number of possibilities exist. With liver metastases, even if the patient's liver function studies are normal, we still wonder about their metabolism. Also, if the patient has received other chemotherapeutic agents, the integrity of the mucous membranes in the gut may not be 100 percent.

Also, we know that as a patient's performance status declines, drug metabolism and excretion may not be as robust and if a patient is symptomatic from their breast cancer, their nutritional status may not be optimal.

DR LOVE: If you could reduce the rate of febrile neutropenia from eight or nine percent to one percent in the adjuvant setting, why not use growth factors?

DR O'SHAUGHNESSY: Whenever we treat a patient, we want to have an evidence-based reason to do so and we have little data on these agents in the adjuvant setting.

We have a good deal of experience in using hematopoietic growth factors in metastatic patients, but, unfortunately, their life spans are too short to determine the long-term effects of these agents.

In the adjuvant setting, most of these patients will be cured, but they're receiving alkylators, anthracyclines and many receive radiation therapy and the long-term risk of leukemia is unknown. Filgrastim was used in the NSABP studies B-22 and B-25 and elevated risks of leukemia occurred, but they were also using high doses of cyclophosphamide. In addition, it doesn't make economic sense to use an agent in all patients that is not needed 90 percent of the time.

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FIGURE 27

Adjuvant Hormonal Therapy in Premenopausal Patients with Node-Negative Disease

The patient is a woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH) Grade II tumor and negative lymph nodes. Which hormonal therapy would you most likely recommend for this patient if she is actually menstruating after chemotherapy?

	Age 35	Age 45
Tamoxifen	73%	76%
Aromatase inhibitor + LHRH agonist or ovarian ablation	4%	4%
Tamoxifen + LHRH agonist or ovarian ablation	14%	9%
LHRH agonist or ovarian ablation	2%	2%
Other endocrine therapy	5%	7%
Would not recommend endocrine therapy	2%	2%

FIGURE 28

Aromatase Inhibitors and Ovarian Suppression in Premenopausal Patients

Have you prescribed an adjuvant aromatase inhibitor plus an LHRH agonist in the following premenopausal patients?

	Percent answering "yes"
Those with contraindication to tamoxifen (clotting, etcetera)	54%
Those who cannot tolerate tamoxifen due to side effects in the adjuvant setting	49%
Those with multiple positive axillary nodes	45%
Those with locally advanced disease after local therapy	41%

DR LOVE: Joyce, what are your thoughts about using LHRH agonists plus aromatase inhibitors as adjuvant therapy off protocol in premenopausal women (Figure 28)?

DR O'SHAUGHNESSY: I have combined an LHRH agonist with an aromatase inhibitor but it's rare because for women that I consider high enough risk for that therapy — multiple positive nodes or even node-positive, HER2-positive breast cancer — I generally recommend oophorectomy and then I'm comfortable with an aromatase inhibitor.

DR LOVE: Do you think the responses would have been different if we replaced LHRH agonists with oophorectomy in this question?

DR O'SHAUGHNESSY: Yes. We have little data on LHRH agonists and aromatase inhibitors. Robertson and his colleagues reported on a small, 16-patient study in metastatic breast cancer. The Austrian Breast Cancer Study Group has some data regarding estrogen levels in the adjuvant setting, but we have no efficacy data. The problem with the LHRH agonists is that they're a little "squirrelly" in their pharmacodynamics and how long they last.

I find that when I use the every three-month depo-goserelin, it doesn't always last a full three months, so I give it routinely every 10 or 11 weeks. At that point patients begin noticing premenstrual symptoms, but after they receive the injection they experience their menopausal symptoms all over again.

I don't find that to be the case on the every four-week goserelin, which was approved by the FDA based on good pharmacodynamic data of estrogen suppression over a four-week period. I don't have much experience with leuprolide acetate because it's not approved for breast cancer and reimbursement can be difficult, so I use goserelin.

Occasionally I see a young patient who has not yet had children, so I use an LHRH agonist plus an aromatase inhibitor for four or five years. Then I stop treatment and allow her ovaries to recover to give her a chance at having children, but that's a rare scenario.

DR LOVE: Which hormonal therapy would you most likely use in this situation (Figure 27)?

DR O'SHAUGHNESSY: In addition to the information provided, to decide between an aromatase inhibitor and tamoxifen, I would consider the percent of cells staining positive for ER and/or PR, the intensity of the staining and the Ki-67.

Patients with a Ki-67 of less than five percent may not relapse for 12 years; however, this tumor is Grade II, so the Ki-67 is probably midrange and if the patient is premenopausal, I would use tamoxifen.

DR LOVE: What about the patient with a HER2-positive tumor?

FIGURE 29

Adjuvant Hormonal Therapy in Postmenopausal Patients with Node-Negative Disease

The patient is a woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH) Grade II tumor and negative lymph nodes. Which hormonal therapy would you most likely recommend for this patient?

	Age 55	Age 65	Age 75	Age 85
Anastrozole	74%	74%	70%	55%
Exemestane	—	1%	1%	2%
Letrozole	7%	9%	10%	8%
Tamoxifen	19%	16%	18%	19%
Would not recommend endocrine therapy	—	—	1%	16%

DR O'SHAUGHNESSY: In this premenopausal patient, I would use tamoxifen. In these patients, the estrogen levels are high and the estrogen is acting as a cofactor with the HER2. I imagine the ER in the plasma membrane or the cell membrane cross-talking with the HER2 and when that ligand is occupied by either tamoxifen or estrogen, that can cross-talk with that growth factor signaling pathway.

I believe tamoxifen is beneficial in premenopausal women with HER2-positive disease; however, I worry about tamoxifen in postmenopausal women with HER2-positive breast cancer. I believe tamoxifen has a greater likelihood of acting as an agonist in that scenario.

DR LOVE: And you, Bob?

DR CARLSON: My practice patterns are consistent with the majority of respondents and I tend to use tamoxifen as a single agent in premenopausal women with estrogen receptor-positive disease.

DR LOVE: What about the postmenopausal patient, Joyce (Figure 29)?

DR O'SHAUGHNESSY: In that scenario, I use aromatase inhibitors — mostly anastrozole. However, I find that patients who were peri- or premenopausal before chemotherapy and have recently become postmenopausal, or who have recently stopped hormone-replacement therapy after a long period of use, are the patients who suffer from arthralgias while on aromatase inhibitors. I have no problem giving them two years of tamoxifen and then switching to an aromatase inhibitor.

DR LOVE: How long do you continue the aromatase inhibitors?

DR O'SHAUGHNESSY: Five years. We participate in the ATAC trial and that is an ongoing trial. Some of my patients are just completing their five years of therapy and, if they are at very high risk, I'm advising them to continue the anastrozole until we know more.

DR LOVE: Bob?

DR CARLSON: With the majority of postmenopausal patients, I too tend to use an aromatase inhibitor, generally anastrozole, in the adjuvant setting. If a contraindication or resistance to using an aromatase inhibitor exists, my second option is tamoxifen. I guess I'm surprised that today so many postmenopausal women are receiving an aromatase inhibitor as first-line adjuvant hormonal therapy. That is a huge shift from what we saw just a couple of years ago.

I'm also somewhat surprised that aromatase inhibitors seem to be used less as patients reach the age of 85. I would have expected the opposite.

DR LOVE: It looks like that shift is from anastrozole to no treatment. Only 55 percent of oncologists said they would use anastrozole to treat an 85-year-old woman?

DR CARLSON: That surprises me because I generally recommend hormonal therapy and use anastrozole unless the patient has substantial comorbidities. The patient's expected survival would have to be quite short to make me think the mild toxicity of the hormonal therapy wasn't warranted.

DR LOVE: Joyce, what do you tend to do for women with ER-positive, HER2-positive disease? Do you take into account HER2 status when you make a decision about adjuvant hormonal therapy (Figures 30-32)?

DR O'SHAUGHNESSY: Yes, I do. I use an aromatase inhibitor for postmenopausal patients with ER-positive, HER2-positive disease. I feel strongly about that mainly based on the small amount of preoperative data we have from IMPACT and Matt Ellis' work.

In premenopausal women, this is much more complicated. I saw an interesting poster at ASCO from Kent Osborne's group. They burdened animals with human breast cancer cell lines that were ER-positive and HER2-positive.

They then treated the animals with tamoxifen, which had a stimulatory effect in the absence of exogenous estradiol pellets. What I thought I saw in that preclinical work was, when they made these animals premenopausal by giving them estrogen pellets, the tamoxifen was inhibitory. This suggests that it depends on the estrogen milieu of the patient as to whether tamoxifen will be an agonist or an antagonist.

FIGURE 30

Adjuvant Hormonal Therapy in Premenopausal Patients with HER2-Positive, Node-Negative Disease

The patient is a woman in average health with a 1.2-centimeter, ER-positive, HER2-positive (as confirmed by FISH) Grade II tumor and negative lymph nodes. Which hormonal therapy, if any, would you most likely recommend for this patient who continues to menstruate after receiving chemotherapy?

	Age 35	Age 45
Tamoxifen	60%	64%
Aromatase inhibitor + LHRH agonist or ovarian ablation	12%	13%
Tamoxifen + LHRH agonist or ovarian ablation	17%	11%
LHRH agonist or ovarian ablation	2%	2%
Other endocrine therapy	7%	8%
Would not recommend endocrine therapy	2%	2%

FIGURE 31

Adjuvant Hormonal Therapy in Postmenopausal Patients with HER2-Positive, Node-Negative Disease

The patient is a woman in average health with a 1.2-centimeter, ER-positive, HER2-positive (as confirmed by FISH) Grade II tumor and negative lymph nodes. Which hormonal therapy, if any, would you most likely recommend for this patient?

	Age 55	Age 65	Age 75	Age 85
Anastrozole	71%	74%	71%	60%
Exemestane	—	—	1%	2%
Letrozole	12%	13%	13%	11%
Tamoxifen	16%	12%	15%	15%
Would not recommend endocrine therapy	1%	1%	—	12%

This makes a lot of sense to me. If you have breast cancer that is being signaled by HER2, and the ER is sitting next to it in the plasma membrane occupied by estrogen in premenopausal women, you can imagine that some crosstalk may occur between the ER (which can hetero- or homodimerize when it is occupied by the ligand) and the HER2.

If you then introduce tamoxifen into that setting, the drug will compete with estrogen for that estrogen receptor. It may not signal quite as strongly or be as good as removing the estrogen altogether like an aromatase inhibitor, but tamoxifen still may be of benefit in premenopausal women with ER-positive, HER2-positive disease. It is interesting and I think we need to analyze these studies carefully and separate the data from pre- and postmenopausal women.

Neil, for a premenopausal woman at low risk with a small, ER-positive, HER2-positive tumor with no positive nodes, I would treat her with tamoxifen. If she is at higher risk, has positive nodes or a T2-N0 tumor and has received chemotherapy and is still premenopausal, my first choice would be oophorectomy and an aromatase inhibitor. If it is not feasible for her to undergo an oophorectomy because she has not had children or completed childbearing, I will treat her with goserelin and anastrozole, but I have rarely done this.

DR LOVE: And you, Bob?

DR CARLSON: I tend to use tamoxifen in premenopausal women with ER-positive, HER2-positive disease, as the majority of physicians do. I think that the argument for ovarian suppression or ablation plus the addition of an aromatase inhibitor in this cohort of women is pretty compelling given the data that suggests aromatase inhibitors may be more effective in HER2-overexpressed breast cancer. However, I think we have to be cautious before we jump to that conclusion.

Breast tumors presenting during the premenopausal state may, in fact, respond quite differently to a hormonal intervention than breast tumors that appear in postmenopausal women; therefore, I don't think we know whether the data suggesting the superiority of the aromatase inhibitors in HER2-overexpressing breast cancer is applicable to premenopausal women.

In the postmenopausal setting, physicians seem to be shifting away from tamoxifen toward the aromatase inhibitors, and shifting away from anastrozole toward letrozole. Presumably that trend is a result of Matt Ellis' study evaluating tamoxifen versus letrozole. In that study, women with HER2-positive breast cancer appeared to have a superior response rate with letrozole.

FIGURE 32

Adjuvant Hormonal Therapy with Node-Positive, HER2-Positive Disease

The patient is a woman in average health with a 1.2-centimeter, ER-positive, HER2-positive, (as confirmed by FISH) Grade II tumor and 3 positive lymph nodes. Which hormonal therapy, if any, would you most likely recommend for this patient?

	Age 35*	Age 65
Anastrozole	3%	76%
Exemestane	—	2%
Letrozole	1%	10%
Tamoxifen	50%	11%
Aromatase inhibitor + LHRH agonist or ovarian ablation	16%	—
Tamoxifen + LHRH agonist or ovarian ablation	25%	—
LHRH agonist or ovarian ablation	2%	—
Other endocrine therapy	1%	1%
Would not recommend endocrine therapy	2%	—

* Still menstruating after chemotherapy

FIGURE 33

Adjuvant Hormonal Therapy with Node-Positive, HER2-Negative Disease

The patient is a woman in average health with a 1.2-centimeter, ER-positive Grade II tumor and 3 positive lymph nodes, but now the tumor is HER2-negative (as confirmed by FISH). Which hormonal therapy, if any, would you most likely recommend for this patient?

	Age 35	Age 55	Age 65	Age 75
Anastrozole	3%	66%	76%	75%
Exemestane	—	1%	2%	2%
Letrozole	1%	7%	7%	9%
Tamoxifen	53%	21%	14%	14%
Aromatase inhibitor + LHRH agonist or ovarian ablation	12%	1%	—	—
Tamoxifen + LHRH agonist or ovarian ablation	26%	2%	—	—
LHRH agonist or ovarian ablation	2%	—	—	—
Other endocrine therapy	1%	1%	1%	—
Would not recommend endocrine therapy	2%	1%	—	—

This is a situation in which physicians may be making a drug-based conclusion that outweighs what I would call a disease-state conclusion. In HER2-overexpressed breast cancer, we do not have as much data for anastrozole as we do for letrozole; however, because their mechanisms of action are essentially identical, my expectation is that we are going to see identical outcomes from the two drugs.

DR LOVE: Moving on to the next case, I think it is pretty interesting that 40 percent of the doctors we surveyed would use an LHRH agonist off study in the adjuvant setting for premenopausal women with positive nodes. Bob, what do you think about that (Figures 32 and 33)?

DR CARLSON: That number seems much higher than I would have expected. I think data exist to justify that approach and to argue against it. That seems to be a much higher frequency than I see in my community.

One of the difficulties in using ovarian ablation in this population is that you can't take it back. It is such a huge shift for the woman — not only physiologically, but also psychologically — that I find it a very difficult step to take, especially with the uncertainty of all the data.

Ovarian suppression also requires monthly injections and substantial increased expense, and I believe that this is one of those situations in which an oncologist's preconceived notions strongly influence the patient's decision-making process.

DR LOVE: I take it that in this situation you are generally using tamoxifen in the younger woman and anastrozole in the older woman?

DR CARLSON: That's correct.

DR LOVE: Joyce, from our discussions, I assume you would use anastrozole or an aromatase inhibitor for endocrine therapy in these patients.

FIGURE 34

Sequencing Aromatase Inhibitors after Tamoxifen

The patient is a 65-year-old woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH) Grade II tumor and 3 positive lymph nodes on tamoxifen for 2 years. ***The patient is not having any severe side effects or problems with tamoxifen.*** *Which of the following best describes how you would manage this patient's therapy?*

Continue tamoxifen	45%
Stop tamoxifen	—
Stop tamoxifen and switch to anastrozole	12%
Stop tamoxifen and switch to letrozole	11%
Stop tamoxifen and switch to exemestane	32%

FIGURE 35

Sequencing Aromatase Inhibitors after Tamoxifen

The patient is a 65-year-old woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH) Grade II tumor and 3 positive lymph nodes on tamoxifen for 2 years. ***The patient complains of a 20-pound weight gain since starting tamoxifen.*** *Which of the following best describes how you would manage the patient's therapy at this point?*

Continue tamoxifen	17%
Stop tamoxifen	—
Stop tamoxifen and switch to anastrozole	35%
Stop tamoxifen and switch to letrozole	16%
Stop tamoxifen and switch to exemestane	32%

DR O'SHAUGHNESSY: Yes, definitely.

DR LOVE: Let's discuss the issue of sequencing hormonal therapy. If the patient described here (Figure 34), who is not having any difficulty tolerating tamoxifen, came to you for a second opinion, what would you recommend?

DR O'SHAUGHNESSY: I discuss switching to an aromatase inhibitor with all my patients. Even if a patient's systemic risk is incredibly low, the risk reduction for a new primary lesion is improved by switching to an aromatase inhibitor. For a patient who has taken adjuvant tamoxifen for two years, I use exemestane. For the patient who has taken tamoxifen for five years, or close to that, I use letrozole.

I am doing this pretty much across the board. I believe switching women from tamoxifen to exemestane has a huge upside and almost no downside. It is safer and allows us to avoid that low incidence of endometrial cancer. Switching is also efficacious.

Even for women who are at very low risk, their risk for second primary breast lesions is reduced by switching to an aromatase inhibitor, so I strongly favor it and I do it routinely.

DR LOVE: Do you do it at any time during the first five years?

DR O'SHAUGHNESSY: Every time I see a patient who is on tamoxifen, I evaluate whether I should switch her at that point or wait until the two- to three-year window. Rightly or wrongly, I think it boils down to which patient is going to have a late relapse and which one is going to have an early relapse.

My best guess is that it may have to do with grade and proliferation. If I have a patient with a strongly ER/PR-positive, Grade I-II tumor with a low proliferative rate, I believe she may be more at risk for a late relapse, so I tend to give that woman three years of tamoxifen and tell her to count on five years of an aromatase inhibitor.

However, when I see a patient on tamoxifen who has ER-positive, PR-negative, Grade II disease with a higher proliferative rate and more aggressive biology, I tend to switch sooner rather than later. I don't necessarily wait two years. Most of these women start on an aromatase inhibitor from the beginning anyhow, so it is becoming a moot point, but if she were on tamoxifen for whatever reason, I would switch her as soon as I could.

DR LOVE: Which aromatase inhibitor would you use in a patient who has been on adjuvant tamoxifen for only six months?

DR O'SHAUGHNESSY: If I didn't agree with the tamoxifen and if I wanted her on an aromatase inhibitor, I'd probably use anastrozole.

FIGURE 36

Sequencing Aromatase Inhibitors after Tamoxifen

The patient is a 65-year-old woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH) Grade II tumor and 3 positive lymph nodes on tamoxifen for 2 years. ***The patient complains of moderate hot flashes since starting tamoxifen, which are refractory to nonhormonal therapy.*** *Which of the following best describes how you would manage the patient's therapy at this point?*

Continue tamoxifen	16%
Stop tamoxifen	—
Stop tamoxifen and switch to anastrozole	36%
Stop tamoxifen and switch to letrozole	12%
Stop tamoxifen and switch to exemestane	36%

DR LOVE: Bob, how do you think the physicians in our survey did in managing this patient, and how do you approach this type of situation in your practice?

DR CARLSON: The numbers are certainly consistent with what I see in my community, but I think that they are going to change rapidly. In another year or two, I bet you will find 80 percent switching to an aromatase inhibitor.

In my practice, starting at two to three years, I begin to talk with women about the option of switching from tamoxifen to an aromatase inhibitor. I typically recommend a switch to exemestane, although I also talk about anastrozole because those are the two agents that we have data for in this specific situation.

I tell them that if they decline the switch at this point in time, when we reach the five-year time point we'll have the discussion again, based on the extended adjuvant endocrine therapy data we have from the MA17 trial. To date, of women to whom I offer a switch, the vast majority are switching.

DR LOVE: What do you do if a woman has been on tamoxifen for six months or a year?

DR CARLSON: I recommend that she continue tamoxifen until the two- to three-year time point. We don't fully understand whether the larger proportional risk reductions that we see with switching to the aromatase inhibitor compared with an aromatase inhibitor or tamoxifen up front, are related to selection of patients who do not have a recurrence and, therefore, are more likely to have hormone-responsive disease.

We also do not know if tamoxifen is somehow interacting with the biology of the tumor and changing it in such a way that it is more sensitive to the profound estrogen deprivation seen with an aromatase inhibitor. Until we sort these issues out, I think we should try to model our clinical decisions as closely to the clinical trials as we can.

DR LOVE: It's interesting that we see shifts toward aromatase inhibitors in women with excessive weight gain and hot flashes. What do you think about that (Figures 35 and 36)?

DR CARLSON: With regard to weight gain, I think this is a great example of people thinking with their biases as opposed to thinking with science. Randomized trials consistently show that tamoxifen does not cause weight gain, at least in comparison with placebo, and therefore switching to an aromatase inhibitor in this circumstance would be wishful thinking.

Women certainly have hot flashes on aromatase inhibitors, but I think they occur less often and are less intense than they are with tamoxifen. However, I tend to ignore hot flashes as a reason to switch or not switch from tamoxifen.

DR LOVE: Joyce, how does your practice compare with these responses (Figure 37)?

DR O'SHAUGHNESSY: I estimate that 50 percent of my patients on tamoxifen receive treatment for vasomotor symptoms, which is much higher than the responses you received. I consider an intervention when the patient experiences significant sleep disturbances. I find that women who are well rested can put up with hot flashes during the day, but if the therapy is causing symptoms such as night sweats, to the point of interrupting their sleep, the patient becomes exhausted and less able to tolerate these side effects. I treat these problems with trazodone, escitalopram oxalate or venlafaxine.

DR LOVE: And what is your experience with weight gain and tamoxifen (Figure 38)?

DR O'SHAUGHNESSY: I believe tamoxifen causes weight gain. The randomized data from NSABP-P-1 and even NSABP-B-14 showed that all the patients gained weight, whether they received the placebo or tamoxifen. We know that women after menopause gain weight every year, even if they eat and exercise exactly the same, because their metabolism slows. I believe tamoxifen exacerbates that in a subset of patients, despite the randomized data, and in general it seems to affect the patients who already have a weight problem.

DR LOVE: Do you discuss the issue of weight gain when you recommend tamoxifen therapy to these patients?

FIGURE 37

Vasomotor Symptoms and Tamoxifen

What percent of the patients you start on tamoxifen have significant vasomotor symptoms to the point that you consider interventions such as SSRI antidepressants?

Mean	26%

FIGURE 38

Tamoxifen and Weight Gain

Do you believe that tamoxifen can cause weight gain?

Yes	77%
No	22%
Not sure	1%

FIGURE 39

Tamoxifen and Weight Gain

What percent of your patients started on tamoxifen have significant weight gain while taking this agent?

Mean	20%

FIGURE 40

Endocrine Therapy after Five Years of Tamoxifen

The patient is a 65-year-old woman in average health with a 1.2-centimeter, ER-positive, HER2-negative (as confirmed by FISH) Grade II tumor and 3 positive lymph nodes who has completed 5 years of tamoxifen therapy. Which of the following best describes how you would manage this patient's endocrine therapy?

	Has just completed 5 years of tamoxifen	Completed 5 years of tamoxifen 1 year ago	Completed 5 years of tamoxifen 3 years ago
Continue tamoxifen	—	—	—
Start anastrozole	16%	14%	4%
Start letrozole	77%	58%	19%
Start exemestane	1%	—	—
Use no further hormonal therapy	6%	28%	77%

DR O'SHAUGHNESSY: I don't bring it up, but the patients always do.

DR LOVE: What percent of patients in your practice have this problem (Figure 39)?

DR O'SHAUGHNESSY: During and after breast cancer treatment, whether the therapy is hormonal, chemotherapy or both, 80 percent of my patients gain weight. It's a huge issue and it needs to be investigated. Also, I believe another 20 percent of patients gain weight if they are on tamoxifen.

DR LOVE: Moving on to the next case (Figure 40), how do you manage the patient who has completed five years of tamoxifen?

DR O'SHAUGHNESSY: After five years of tamoxifen, the only patients for whom I don't recommend switching to letrozole are the older, postmenopausal women with low-risk disease — tiny lesions, node-negative — for whom I'm less concerned about the systemic risk for relapse. While patients over the age of 65 are still at risk for new primary lesions, they have had the benefit of five years of tamoxifen, so I don't ask them to take more drugs.

DR LOVE: How do you decide on therapy for a patient who has been off adjuvant tamoxifen for one to three years?

DR O'SHAUGHNESSY: I treat them the same as the patient who has just completed tamoxifen. If I think they might benefit from a risk-reduction standpoint, that's enough of a reason for me to consider further therapy.

DR LOVE: What would be your cutoff?

DR O'SHAUGHNESSY: It depends on the patient's risk status. In a low-risk patient, I think five years would be my cut-off, but in a patient at high risk with multiple positive nodes, I probably have no time limit.

DR LOVE: Bob, what do you recommend to similar patients in these three situations?

FIGURE 41

Bone Mineral Density Measurement

Would you obtain baseline or follow-up bone mineral density measurements for a 40-year-old premenopausal woman being started on the following agents? (Percent answering "yes")

	Baseline bone mineral density measurement	Follow-up bone mineral density measurement
LHRH agonist	71%	79%
LHRH agonist and tamoxifen	61%	75%
LHRH agonist and aromatase inhibitor	83%	89%

FIGURE 42

Bone Mineral Density Measurement

Would you obtain baseline or follow-up bone mineral density measurements for postmenopausal women of the following ages being started on an aromatase inhibitor? (Percent answering "yes")

Age	Baseline bone mineral density measurement	Follow-up bone mineral density measurement
55	90%	92%
65	92%	92%
75	87%	84%
85	76%	74%

DR CARLSON: I'm consistent with what these statistics show. After 5 years, I use letrozole as the preferred agent because that is where we have data.

About a year after stopping tamoxifen, I tend to not encourage crossing over to an aromatase inhibitor.

As more time passes after discontinuing tamoxifen, the further you get from the selection criteria used to justify the subsequent aromatase inhibitor in the clinical trials. I am not surprised that we see a drop in the frequency of aromatase inhibitor use.

DR LOVE: Joyce, do you perform bone mineral density studies in these scenarios and in women of these varying ages (Figures 41 and 42)?

DR O'SHAUGHNESSY: Yes. I obtain baseline and follow-up bone mineral densities in patients receiving LHRH agonists, tamoxifen and aromatase inhibitors.

DR LOVE: Have you incorporated bone health into your care of breast cancer patients in general, or just those receiving endocrine intervention?

DR O'SHAUGHNESSY: If their primary physician is following their bone density, then I don't, but if I have them on hormonal therapy then I feel obligated to do so.

DR LOVE: It appears from these responses that physicians are less likely to assess bone density in patients on tamoxifen. Do you agree with that practice?

DR O'SHAUGHNESSY: I don't evaluate the bone as frequently in patients on tamoxifen; however, if the patient is also on an LHRH agonist, then I always assess their bone density. It's been shown that this combination can cause bone loss and some postmenopausal women lose bone on just tamoxifen. Also, patients are generally not on tamoxifen for long and it's important to have a baseline in case we switch them to an aromatase inhibitor later.

DR LOVE: With regard to the ER/PR status in patients with DCIS, what's your practice and what do you think about these numbers (Figure 43)?

DR O'SHAUGHNESSY: We began assessing patients' ER and PR status approximately four or five years ago and now we do it routinely. When Craig Allred presented his tamoxifen data from NSABP-B-24 at the 2002 San Antonio Breast Cancer Symposium, it solidified our practice. Prior to this data, we didn't always insist on establishing the ER/PR status in patients we saw for second opinions, and we put them all on tamoxifen.

However, as we saw those women in follow-up, we checked their ER/PR status and I've since stopped tamoxifen in patients whose tumors were negative, even if they had been on it for a couple of years. Now I use tamoxifen only in patients with DCIS who are ER- and/or PR-positive and DCIS clinical trials like NSABP-B-35, in which patients are randomly assigned to tamoxifen versus anastrozole, restrict eligibility to patients with receptor-positive disease.

I reviewed this issue recently as I wrote a chapter on systemic therapy for DCIS for Martine Piccart's book, which examines molecularly targeted breast cancer treatment. In the data from NSABP-B-24, little evidence indicates that patients with truly ER/PR-negative disease derived benefit from tamoxifen.

While relatively little data exists, based on what we do have, I don't believe

FIGURE 43

Hormone Receptor Assays for DCIS

Which of the following best describes how often you consider ER/PR results in deciding whether to use tamoxifen in ductal carcinoma in situ*?*

Always	58%
Occasionally	25%
Never	17%

FIGURE 44

Endocrine Therapy for DCIS

About what percentage of your patients with DCIS receive tamoxifen?

Receive tamoxifen	71%

FIGURE 45

Endocrine Therapy for DCIS

Which one of the following best describes how you have used an aromatase inhibitor outside of a clinical trial in a patient with DCIS?

Have not used an aromatase inhibitor in a patient with DCIS	40%
Have used an aromatase inhibitor in a patient with DCIS	5%
Have used an aromatase inhibitor in a patient with DCIS but only in patients who have problems with or contraindications to tamoxifen	55%

we should expect tamoxifen to benefit patients with ER/PR-negative DCIS — in preventing in-breast recurrences or reducing the risk of a contralateral breast cancer — just as it doesn't benefit patients with ER/PR-negative breast cancer. Given the risks associated with tamoxifen, I'd like to see more clinicians considering the ER and PR status when deciding whether to use tamoxifen in patients with DCIS.

DR LOVE: In your practice, what percent of patients with DCIS actually receive tamoxifen (Figure 44)?

DR O'SHAUGHNESSY: I would estimate that 75 to 80 percent of my patients with DCIS receive tamoxifen. If the disease was treated by lumpectomy and radiation therapy, I tend to use tamoxifen to prevent an in-breast recurrence and a new primary lesion.

In a woman over the age of 60 with ER-positive DCIS, who has undergone a mastectomy, I would estimate the risk of a new primary lesion or a contralateral occurrence to be in the neighborhood of 0.5 to 0.8 percent per year. In the next 20 to 25 years, she has approximately a 10 to 16 percent risk of developing a new second primary lesion. Tamoxifen reduces that risk by 50 percent; however, I don't recommend tamoxifen for all of these patients. If the risk of a new primary lesion or DCIS is only 10 percent or less, I worry more about the risks of tamoxifen — thromboembolic risk, stroke, CVAs, DVTs — particularly in women over the age of 60.

I also consider the tissue background. In a patient who undergoes a mastectomy, we have a good deal of tissue to examine. If the background is relatively bland, I am less inclined to recommend tamoxifen to protect the contralateral breast.

On the other hand, if a good deal of atypia or LCIS is present, for example, I worry more about the contralateral breast. Likewise, if a patient has a strong family history of breast cancer, I'm more inclined to worry about a contralateral new primary lesion.

DR LOVE: How do you feel about the off-protocol use of aromatase inhibitors for DCIS in patients who can't take tamoxifen (Figure 45)?

DR O'SHAUGHNESSY: I have used them sparingly in patients at very high risk, such as those with multifocal DCIS, but only when tamoxifen is absolutely contraindicated. We have very little data on this issue.

DR LOVE: If clinical trials like NSABP-B-35 show the efficacy of aromatase inhibitors to be equal to, but not greater than, tamoxifen, would you switch your patients to these agents given their side-effect profiles?

DR O'SHAUGHNESSY: Definitely, because in the risk-reduction setting, we don't want patients to experience any unnecessary side effects.

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FIGURE 46

Treatment of Receptor-Negative Disease in Asymptomatic Chemotherapy-Naïve Patients

The patient is a woman with no prior systemic therapy who has an ER-negative, HER2-negative tumor with rising tumor markers and asymptomatic bone metastases. What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	6%	5%	4%	4%	1%	2%
Docetaxel	16%	16%	16%	17%	10%	15%
Paclitaxel	17%	9%	18%	8%	19%	8%
Carboplatinum + taxane	4%	5%	4%	5%	1%	1%
Capecitabine	12%	17%	14%	19%	27%	26%
Gemcitabine	—	16%	—	18%	4%	15%
Vinorelbine	—	16%	—	16%	5%	15%
AC	15%	8%	15%	5%	6%	2%
AC + docetaxel	14%	—	13%	—	3%	—
AC + paclitaxel	2%	1%	3%	1%	—	—
Doxorubicin	—	1%	—	1%	1%	1%
Other chemotherapy	6%	3%	7%	3%	5%	2%
No chemotherapy	8%	3%	6%	3%	18%	13%

DR LOVE: Bob, I'll go through a few of these metastatic disease scenarios with you. For a patient with ER-negative, HER2-negative metastatic disease with asymptomatic bone metastases who has never received systemic therapy, which regimens would you typically use first- and second-line (Figure 46)?

DR CARLSON: I think I am consistent with the responses to the survey, in that I am remarkably inconsistent and do not follow a single regimen. Little evidence exists to suggest that any one chemotherapy regimen provides a meaningful advantage to the woman in terms of response rates, duration of response, survival and so on, relative to other combinations or single agents.

I tend to discuss what she expects from her treatment, how much toxicity she is willing to tolerate and when she would be willing to do so; however, in an asymptomatic woman, I try to minimize toxicity. Why should I make a woman sick when she feels well?

In this situation, I often start with an agent such as capecitabine, and that would be independent of age. However, I can't be critical of any of the choices that have been made.

DR LOVE: What tends to be your second-line therapy?

DR CARLSON: A taxane.

DR LOVE: Which one?

DR CARLSON: Again, I discuss the type of experience she wants and try to gauge how "toxic" she views coming to my office. When I use paclitaxel, I tend to use it weekly and when I use docetaxel, I tend to use it every three weeks.

In general, I think docetaxel is a slightly more toxic agent than paclitaxel, so, to some extent, it becomes an issue of toxicity of treatment versus the number of visits the patient is willing make.

DR LOVE: How much, if any, is your decision-making influenced by age?

DR CARLSON: Age influences me primarily in the same way that it does the survey respondents. The older a woman is, the more likely I am to use a single agent because single agents alone tend to be less toxic.

DR LOVE: Looks like there's a shift toward capecitabine with increasing age. Is that your approach?

DR CARLSON: Sure, because I will shift to a single agent due to toxicity concerns. Capecitabine tends to have manageable toxicity. Although, I do think it is a mistake to look at capecitabine as a nontoxic chemotherapy.

DR LOVE: Approximately one third of these docs picked combination therapy as their first-line choice for an asymptomatic 40-year-old woman. Do you think that is a reasonable recommendation?

DR CARLSON: I think it's reasonable in that there is no data to show that it is a disadvantage to the woman with regard to the most important endpoint — survival. In fact, limited data from imperfect studies suggest combination chemotherapy may provide a slight survival advantage. I guess I'm surprised

FIGURE 47

Treatment of Receptor-Negative Disease in Symptomatic Chemotherapy-Naïve Patients

The patient is a woman with no prior systemic therapy who has an ER-negative, HER2-negative tumor with bone and lung metastases and is very symptomatic. What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	15%	9%	14%	5%	12%	4%
Docetaxel	4%	15%	7%	15%	15%	18%
Paclitaxel	2%	8%	3%	10%	15%	8%
Carboplatinum + taxane	16%	12%	17%	8%	12%	—
Capecitabine	—	9%	—	11%	12%	20%
Gemcitabine	—	13%	—	15%	4%	17%
Vinorelbine	—	8%	—	10%	5%	23%
AC	23%	8%	22%	9%	15%	3%
AC + docetaxel	30%	1%	27%	1%	6%	—
AC + paclitaxel	4%	1%	4%	1%	1%	—
Doxorubicin	—	4%	—	4%	—	3%
Other chemotherapy	6%	12%	6%	11%	3%	3%
No chemotherapy	—	—	—	—	—	1%

that people would step up to the plate with aggressive combination regimens in an asymptomatic woman with bone-only metastatic disease, especially with bone being such a favorable site for metastases.

DR LOVE: If nanoparticle albumin-bound paclitaxel were available, would you use it as first-line therapy in the metastatic setting?

DR CARLSON: Yes. Data indicate that nanoparticle paclitaxel is at least as efficacious as paclitaxel, and perhaps slightly more so. The toxicity experience with this new agent is also convincing, especially in terms of hypersensitivity reactions. I think it would be beneficial if we could diminish the need for relatively expensive antihypersensitivity medication. As far as neuropathy, I think we are going to need a lot more data to really understand whether nanoparticle paclitaxel has either less, or more, rapidly reversed neuropathy than paclitaxel.

DR LOVE: Any guess on efficacy or side effects with nanoparticle paclitaxel compared to docetaxel?

DR CARLSON: My expectation is that it will be similar to the data with paclitaxel. Docetaxel has frequent hypersensitivity reactions, just like paclitaxel, and being able to avoid dexamethasone, diphenhydramine and so forth, is a very reasonable goal, if we can accomplish it.

DR LOVE: You talked about the cost savings involved in avoiding hypersensitivity medications, what about the quality-of-life impact of avoiding these side effects? How much of a benefit would that be?

DR CARLSON: I think the side effects of those medications are an issue. It doesn't take many cases of aseptic necrosis to make avoiding dexamethasone a really good goal. Likewise the sedation that goes along with diphenhydramine is also a potential problem we would like to eliminate.

DR LOVE: If it were available, are there any circumstances that would lead you to use adjuvant nanoparticle paclitaxel in a nonprotocol situation? If not, would it be your first-line taxane in the metastatic setting?

DR CARLSON: I would not use it in the adjuvant setting; however, I think it would be a reasonable first-line choice for metastatic disease. Whether or not I would use it in the six months after it became approved, rather than paclitaxel and docetaxel, with which we have an incredible wealth of experience, I guess I'd have to see.

DR LOVE: Let's go to the next case. How would you approach a symptomatic patient like this one and what would your first- and second-line therapies be (Figure 47)?

DR CARLSON: I would certainly be much more inclined to use combination chemotherapy because the probability of response goes up, and it sounds like this patient needs a response. I would personally use AC, CAF or FAC, one of those types of regimens as first-line therapy.

DR LOVE: How about in a 75-year-old woman?

DR CARLSON: A 75-year-old woman obviously presents a much more difficult situation. Again, you need to consider how sick you are going to make her compared to how sick she is feeling.

FIGURE 48

Treatment of Asymptomatic, Receptor-Negative Disease after Adjuvant AC → Paclitaxel

The patient is a woman treated two years ago with adjuvant AC → paclitaxel for an ER-negative, HER2-negative tumor ***with rising tumor markers and asymptomatic bone metastases.*** *What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?*

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	11%	3%	9%	2%	3%	2%
Docetaxel	29%	14%	29%	14%	15%	12%
Paclitaxel	8%	4%	8%	4%	6%	3%
Carboplatinum + taxane	6%	4%	6%	3%	1%	—
Capecitabine	18%	20%	20%	19%	36%	25%
Gemcitabine	8%	25%	9%	26%	8%	25%
Vinorelbine	8%	14%	7%	18%	11%	18%
AC	—	2%	—	2%	—	—
AC + docetaxel	3%	—	3%	—	—	—
Doxorubicin	—	3%	—	3%	—	1%
Other chemotherapy	2%	7%	2%	5%	3%	—
No chemotherapy	7%	4%	7%	4%	17%	14%

In that situation I would probably go with AC.

DR LOVE: Here (Figure 48) we have a situation similar to one we talked about before — an asymptomatic patient with bone metastases. However, this patient received adjuvant AC → paclitaxel two years ago. In general, what would you be inclined to do with this patient?

DR CARLSON: A spectrum of options exist. Given her prior exposure, I think it makes sense that respondents tend to use fewer anthracycline-based regimens. I'm surprised by the frequency of use of the taxanes.

Data suggest that complete cross resistance does not occur between paclitaxel and docetaxel, but some cross resistance does occur. In general, I would use capecitabine as my first-line therapy.

DR LOVE: It's interesting to see so much variation in all of these cases. You can almost imagine a woman going to five different doctors and receiving five different therapies.

DR CARLSON: Yes, but that is not surprising. When you look at the endpoints that are most important — survival and progression-free survival — little data show that these regimens differ from one another. What shapes these decisions are the complex motivations of patients and physicians.

DR LOVE: One of the things I noticed was a big shift to capecitabine/docetaxel when we asked about the symptomatic patient previously treated with adjuvant AC → paclitaxel.

DR CARLSON: I find capecitabine to be an active agent that is relatively easy to administer, and I would consider using it as a single agent. If you are going to add a taxane, which is a reasonable thing to do, I think docetaxel makes more sense than paclitaxel.

I am surprised by the frequent use of carboplatin, in combination with a taxane. These types of regimens are modestly toxic and very expensive. If you are going to use combination therapy and accept a fair amount of toxicity, then the carboplatin/paclitaxel in preference to capecitabine/docetaxel doesn't make a lot of sense to me.

I haven't seen patterns of care data like this, other than some relatively modest data from National Comprehensive Cancer Network (NCCN) centers. I think this type of information is interesting and can help highlight where the educational opportunities are and what the future research questions should be.

A great example is the issue we just talked about — should we try to better define the optimal first-line regimens for metastatic disease? I think that is a good question, and your data tells us that this is a problem.

DR LOVE: This type of survey may also help us determine what data is needed to help docs make better decisions. Trials that extend survival and progression-free survival have always been emphasized, but quality-of-life issues exist for which I'm not sure we have much data.

DR CARLSON: We don't, and that is a very important point. It is actually my major consideration in trying to help a woman with metastatic breast cancer select one chemotherapy versus another.

FIGURE 49

Treatment of Symptomatic, Receptor-Negative Disease after Adjuvant AC → Paclitaxel

The patient is a woman treated two years ago with adjuvant AC → paclitaxel for an ER-negative, HER2-negative tumor who now has bone and lung metastases and is symptomatic. What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Capecitabine + docetaxel	41%	9%	41%	7%	17%	4%
Docetaxel	9%	5%	10%	5%	18%	8%
Paclitaxel	1%	—	1%	1%	7%	1%
Carboplatinum + taxane	24%	2%	24%	4%	9%	—
Capecitabine	1%	16%	1%	17%	17%	29%
Gemcitabine	6%	29%	6%	31%	15%	29%
Vinorelbine	—	22%	—	21%	8%	22%
Carboplatinum	1%	—	1%	—	—	1%
AC	1%	2%	1%	1%	—	—
AC + docetaxel	4%	—	4%	—	—	—
AC + paclitaxel	1%	—	1%	—	—	—
Cyclophosphamide	1%	—	1%	—	—	—
Doxorubicin	—	—	—	—	—	1%
Other chemotherapy	10%	15%	9%	13%	9%	4%
No chemotherapy	—	—	—	—	—	1%

I tell patients up front that they are going to receive a list of drugs over the course of their treatment, and that the major issue we will deal with is not which drugs, but the sequence in which they will be used. For the most part, the sequence is based more on toxicity considerations than on efficacy.

DR LOVE: The next case (Figure 49) involves a symptomatic patient with metastatic disease who has previously been treated with AC → paclitaxel in the adjuvant setting. The number of physicians treating with chemotherapy combinations (capecitabine/docetaxel and a platinum/taxane combination) is much greater in a patient like this.

Joyce, could you comment on the recent data from the randomized study of paclitaxel with or without gemcitabine in women with metastatic breast cancer?

DR O'SHAUGHNESSY: This trial demonstrated a survival advantage for adding gemcitabine. It was an interim survival analysis requested by the FDA prior to the registration of gemcitabine. This positive survival advantage is important because it gives us another agent that can impact the natural history of metastatic disease, and the current list of efficacious agents in this setting is short.

It's now important to study gemcitabine in the adjuvant setting, which is being done in the TANGO trial in the United Kingdom and NSABP-B-38.

In the metastatic setting, we still need to know whether we should treat patients with this combination up front, as was done in this trial, or further down the line. I believe either option is appropriate and selection depends on the tumor burden and symptomatology.

DR LOVE: How do you feel about this combination in the nonprotocol setting as opposed to capecitabine/docetaxel or capecitabine/paclitaxel as recently reported by Gradishar?

DR O'SHAUGHNESSY: I don't generally use paclitaxel every three weeks as Bill Gradishar did in his Phase II trial. We are conducting a Phase II trial of weekly paclitaxel 80 mg/m^2 on days one and eight, with day 15 off in a 21-day cycle, along with capecitabine 1,650 mg/m^2 daily, 14 days on and seven days off.

We have completed the front-line cohort in patients who are taxane-naïve, and Joanne Blum will present those data in a poster at the 2004 San Antonio Breast Cancer Symposium. It's a wonderful combination — active and safe. As for the cohort of patients who are taxane pretreated, we have 15 more patients to accrue.

In my practice, whether I use capecitabine in combination with docetaxel, or paclitaxel alone, depends on which taxane the patient has already received. Historically, I've been using capecitabine/docetaxel in patients with a heavier tumor burden or patients who are very concerned about their metastatic disease and want the best chance for a durable remission.

FIGURE 50

Use of Docetaxel in the Metastatic Setting

	Yes
Do you use single-agent docetaxel in the metastatic setting at 100 mg/m^2 every three weeks?	36%

FIGURE 51

Use of Growth Factors with Docetaxel in the Metastatic Setting

Which of the following best describes your frequency of use of up-front preventive growth factors (filgrastim or pegfilgrastim) with this docetaxel regimen?

Always	26%
Commonly	29%
Occasionally	19%
Rarely	26%

For patients with indolent disease, I generally use single-agent capecitabine followed by a taxane.

The gemcitabine/paclitaxel data is relatively new and I'm still trying to determine the best use of that regimen. Until now, I've been saving gemcitabine to combine with carboplatin.

That's an active combination and I've been pleased with the responses, particularly in drug-resistant patients; however, I'm finding cumulative thrombocytopenia to be a problem after three to five treatments.

This toxicity requires prolonging the interval between cycles and then the patients lose their response.

While gemcitabine and carboplatin are both important drugs, I'm rethinking which agents to combine them with and I find I'm swinging back to combining gemcitabine with a taxane or vinorelbine, as I did a year and a half or two years ago.

Gemcitabine partners well with other agents because it doesn't add substantially to toxicity. I've used it either with docetaxel, paclitaxel or vinorelbine, generally as second- or third-line therapy for metastatic disease. These are well-tolerated active combinations.

DR LOVE: What about the combination of gemcitabine with either capecitabine or nanoparticle paclitaxel?

DR O'SHAUGHNESSY: The combination of capecitabine with paclitaxel for two out of three weeks is active and well tolerated. I believe gemcitabine or carboplatin combined with nanoparticle paclitaxel will provide nice palliation for patients. The combination of nanoparticle paclitaxel/carboplatin is also being studied with trastuzumab.

DR LOVE: Joyce, let's look at more data on the use of docetaxel in the metastatic setting. How do you dose this agent for patients with metastatic disease (Figure 50)?

DR O'SHAUGHNESSY: It depends on the setting. With chronic use, I give 75 to 85 mg/m^2 every three weeks to avoid the neurotoxicity we see with weekly use; however, if I'm only going to give patients four to six cycles, I use 100 mg/m^2.

DR LOVE: And would you use prophylactic growth factors with docetaxel in the metastatic setting (Figure 51)?

DR O'SHAUGHNESSY: Based on the data showing a 19 percent rate of febrile neutropenia in metastatic disease, I would definitely use prophylactic growth factors with docetaxel 100 mg/m^2. On the other hand, I find 75 mg/m^2 is well tolerated; I've not seen a significant incidence of myelosuppression with that dose.

DR LOVE: Where do you see nanoparticle paclitaxel being utilized in the treatment of breast cancer over the next couple of years?

DR O'SHAUGHNESSY: I believe physicians will use nanoparticle paclitaxel for palliation in the metastatic setting in patients whom they want to experience as few side effects as possible. I expect it will be used weekly at 100 mg/m^2 for three weeks, followed by one week off, as in Joanne Blum's study.

I believe it will be a popular choice to avoid the on-again, off-again fatigue of weekly dexamethasone and for patients with any kind of peripheral neuropathy. It's so well tolerated overall that I expect it will be favored over weekly paclitaxel.

DR LOVE: Do you believe physicians will prefer it over docetaxel?

DR O'SHAUGHNESSY: I'm not certain how it will compare with docetaxel. Often a patient with metastatic breast cancer has received both taxanes — one in the adjuvant setting and the other in metastatic disease.

If a patient has received adjuvant paclitaxel, depending on how long ago she received it, I believe weekly nanoparticle paclitaxel will be seriously considered over docetaxel because of its tolerability.

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FIGURE 52

Hormonal Therapy after Progression on Adjuvant Tamoxifen

The patient is a woman who has been on adjuvant tamoxifen for four years for an ER-positive, HER2-negative tumor and now has rising tumor markers and asymptomatic bone metastases. What is your first-line endocrine treatment for this patient, and your second-line endocrine treatment if she had objective progression over several months but was clinically the same?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Anastrozole	8%	8%	46%	9%	45%	8%
Exemestane	3%	11%	7%	30%	6%	28%
Letrozole	11%	6%	37%	7%	39%	6%
Tamoxifen	2%	1%	1%	1%	1%	1%
Fulvestrant	6%	36%	4%	47%	6%	51%
Aromatase inhibitor + LHRH agonist or ovarian ablation	52%	9%	3%	—	1%	—
Tamoxifen + LHRH agonist or ovarian ablation	6%	3%	—	1%	—	—
LHRH agonist or ovarian ablation	9%	2%	—	—	—	1%
Other endocrine therapy	—	10%	—	2%	—	2%
No endocrine therapy	3%	14%	2%	3%	2%	3%

DR LOVE: Bob, how do you approach women with ER-positive disease who relapse while on adjuvant tamoxifen (Figure 52)?

DR CARLSON: This case shows us that we have a tremendous educational opportunity. Over 20 percent of oncologists are recommending one of the aromatase inhibitors without ovarian ablation to a 40-year-old premenopausal woman.

This suggests that at least one in five women in this situation is being offered an inactive first-line or second-line agent.

I think these data are probably accurate and reflect an important problem. In my practice, I would offer such a woman enrollment in a clinical trial in which we are looking to discover the benefit of goserelin plus anastrozole in young premenopausal women.

We initiated this trial because we realized many people were using this approach despite a paucity of data about it. We will have a poster at the 2004 San Antonio Breast Cancer Symposium reporting on the first 22 or 23 women enrolled in the trial.

DR LOVE: How many responses were seen?

DR CARLSON: The data is embargoed, but I can tell you that it is the highest response rate to hormonal therapy that I have ever seen.

DR LOVE: Interesting. What do you tend to do in these three situations in a nonprotocol setting?

DR CARLSON: For a premenopausal woman, I typically use ovarian ablation and add an aromatase inhibitor. I do not use ovarian suppression because I expect to keep this woman on hormonal therapies for a long time.

The most active hormonal therapies we have are either active only in postmenopausal women or have been studied primarily in postmenopausal women. If a woman is functionally postmenopausal, decision-making is easier and more options are available. I also believe that most women are likely to tolerate a one-shot laparoscopic oophorectomy better than years of monthly LHRH agonist injections.

In a postmenopausal woman, I present an aromatase inhibitor and fulvestrant as options. I go over the data comparing anastrozole and fulvestrant and explain that perhaps fulvestrant offers a slight improvement in duration of clinical benefit, but that no known differences exist with regard to survival and few with regard to quality of life.

Probably one third of these women will choose fulvestrant and the others will select an aromatase inhibitor. I use anastrozole as my first-line aromatase inhibitor, but I actually believe that they are all created equal in terms of antitumor efficacy and toxicity. I tend to always use the same one so I won't get

FIGURE 53

Approach to Therapy in Symptomatic Patients with ER-Positive Disease

The patient is a woman who has been on adjuvant tamoxifen for four years for an ER-positive, HER2-negative tumor and now has bone and lung metastases and is symptomatic. Which of the following best describes which general approach to therapy you would take in selecting treatment for each of these patients?

	Age 40 (premenopausal)	Age 57	Age 75
Chemotherapy alone	26%	18%	12%
Chemotherapy until disease stabilization, then hormone therapy "maintenance"	71%	76%	61%
Hormone therapy alone	3%	6%	27%

FIGURE 54

Hormonal Therapy after Progression on Adjuvant Tamoxifen

If you would use endocrine therapy for this symptomatic patient, what is your first-line endocrine treatment, and your second-line endocrine treatment if she had objective progression over several months but was clinically the same?

	Age 40 (premenopausal)		Age 57		Age 75	
	1st-line	2nd-line	1st-line	2nd-line	1st-line	2nd-line
Anastrozole	9%	4%	45%	2%	45%	4%
Exemestane	4%	8%	5%	38%	7%	32%
Letrozole	8%	4%	46%	6%	42%	8%
Tamoxifen	14%	—	1%	2%	1%	2%
Fulvestrant	5%	40%	3%	49%	5%	52%
Aromatase inhibitor + LHRH agonist or ovarian ablation	46%	9%	—	—	—	—
Tamoxifen + LHRH agonist or ovarian ablation	3%	9%	—	—	—	—
LHRH agonist or ovarian ablation	11%	4%	—	1%	—	1%
Other endocrine therapy	—	7%	—	1%	—	—
No endocrine therapy	—	15%	—	1%	—	1%

confused. That is truly the only reason I prefer one instead of the other.

DR LOVE: It's interesting that you present both options and about one third of your patients select fulvestrant. A more typical answer I hear from oncologists is, "I present an aromatase inhibitor because it is more convenient."

DR CARLSON: I think it is a question of for whom it is convenient and why. It relates back to the issue of chemotherapy and choosing toxicity. I always talk to women and ask, "Which of these toxicities is least concerning to you?"

DR LOVE: The most common strategy we see for the symptomatic patient with ER-positive disease is initiating chemotherapy until the patient is stabilized, and then switching to hormonal maintenance (Figures 53 and 54). Is that a strategy you use?

DR CARLSON: For a symptomatic patient, starting with chemotherapy is a reasonable strategy, and one that I would use with this type of patient.

Hopefully, if the patient does well and becomes substantially less symptomatic due to response, the issue of toxicity will become much more important. Switching her to hormonal therapy at that point in time is reasonable. I agree fully with the majority of respondents with regard to this question.

DR LOVE: Joyce, for a patient who is gravely ill with a high tumor burden, do you use the strategy of chemotherapy to induce a remission and then maintenance hormones?

DR O'SHAUGHNESSY: I just did that with a patient, but I do not do it often. This particular woman was young, premenopausal and presented with a heavy liver burden and bone disease.

She also had some adenopathy in her axilla. I gave her six cycles of TAC and she had a good response.

I knew I could not give her TAC forever, so I stopped it. She is postmenopausal

FIGURE 55

Hormonal Therapy for Premenopausal Patients

The patient is a 40-year-old premenopausal woman who has been on adjuvant tamoxifen plus an LHRH agonist for four years for an ER-positive, HER2-negative tumor and now presents with one of the following clinical situations. What is your first-line endocrine treatment for this patient, and your second-line endocrine treatment if she had objective progression over several months but was clinically the same?

	Rising tumor markers and asymptomatic bone metastases		Bone and lung metastases and is symptomatic	
	1st-line	2nd-line	1st-line	2nd-line
Anastrozole	15%	2%	15%	6%
Exemestane	6%	16%	3%	13%
Letrozole	12%	5%	12%	5%
Tamoxifen	—	2%	6%	—
Fulvestrant	8%	33%	13%	34%
Aromatase inhibitor + LHRH agonist or ovarian ablation	46%	5%	43%	9%
Tamoxifen + LHRH agonist or ovarian ablation	2%	1%	2%	5%
LHRH agonist or ovarian ablation	1%	—	3%	3%
Other endocrine therapy	1%	13%	3%	12%
No endocrine therapy	9%	23%	—	13%

now and is on letrozole. I am watching her estradiol closely. I use this strategy only for the sickest of patients and it is not common.

DR LOVE: Bob, you chair the NCCN Breast Committee. What do they say about this?

DR CARLSON: The practice of initially treating patients who have ER-positive breast cancer with chemotherapy and then switching to hormonal therapy is not addressed in the NCCN guidelines; however, it's a common strategy that makes sense.

In general, the NCCN guidelines classify women into two groups: those who should be given endocrine therapy until they sequence through all of them or develop organ impairment, and those who should be given chemotherapy until they have exhausted all of the reasonable chemotherapy options.

The guidelines do, however, recommend that women who have substantial organ dysfunction — even those with hormone receptor-positive disease — be treated initially with cytotoxic chemotherapy.

DR LOVE: We often see premenopausal patients such as these who experience relapse on adjuvant tamoxifen. Joyce, I am curious about how you generally approach a patient with ER-positive, HER2-negative disease who has been on tamoxifen for two or three years and develops metastases?

DR O'SHAUGHNESSY: In general, I think we should treat those patients with hormonal therapy. They have been on tamoxifen for two or three years. That is not a terribly long disease-free interval but it is not bad either. I would consider hormonal therapy unless the patient was approaching or in visceral crisis. If the patient was not horrendously tumor-burdened and horribly symptomatic and postmenopausal, then I would favor hormonal therapy and go right on to an aromatase inhibitor.

In premenopausal patients (Figure 55), I have had a phenomenal success rate with LHRH analogs or oophorectomy along with an aromatase inhibitor. I personally find that premenopausal women benefit from oophorectomy followed by an aromatase inhibitor and that is what I do first line.

DR LOVE: What is your usual second-line therapy for patients who progress on the aromatase inhibitor?

DR O'SHAUGHNESSY: I either use exemestane or tamoxifen — depending on when (or if) the patient last had tamoxifen. In a woman who progressed after only two or three years on tamoxifen, I would not use tamoxifen again, but if she had tamoxifen many years ago, I would probably go back to it.

I also use fulvestrant but I do not use it often right after an aromatase inhibitor. Neil, we all come up with our own hunches on things, and the good responses to fulvestrant that I have seen have not been immediately following an aromatase inhibitor. They have been in postmenopausal women whose bodies have come back to homeostasis, if you will, with regard to their estrogen levels.

I'll give you an example. I have this remarkable patient with metastatic disease whom I met about five years ago. She was 65 years old at the time and had been on tamoxifen for 20 years for metastatic bone disease.

FIGURE 56

Patients Preferences for Oral versus Parenteral Therapy

What percentage of your patients with metastatic breast cancer would prefer to receive a monthly injection of fulvestrant rather than a daily oral endocrine agent like an aromatase inhibitor or tamoxifen?

Mean	34%

FIGURE 57

Sequencing Endocrine Therapy in Hormonal Therapy-Naïve Patients

How do you normally sequence endocrine therapy in postmenopausal patients with metastases and no prior endocrine therapy?

	1st-line	2nd-line	3rd-line	4th-line
Tamoxifen	19%	27%	8%	13%
Anastrozole	42%	13%	5%	—
Letrozole	36%	13%	8%	3%
Exemestane	3%	27%	23%	16%
Fulvestrant	—	18%	48%	26%
Megestrol acetate	—	—	4%	24%
High-dose estrogen	—	—	1%	2%
Other endocrine therapy	—	1%	—	2%
No endocrine therapy	—	1%	3%	14%

DR LOVE: Wow.

DR O'SHAUGHNESSY: Twenty years! She was Steve Jones' patient and I inherited her. The cancer progressed in her bones so I initiated anastrozole and she did well for about two and a half to three years. Then she became symptomatic and crippled with bone pain. Fulvestrant was not yet available.

She was chemotherapy-naïve so I started her on vinorelbine. She had a good response but after a while had difficulty handling the toxicity of the chemotherapy. We stopped it and she had a nice remission for nine months.

She then progressed again, so I started her on fulvestrant and she has been in a remission for almost two years.

I am so pleased with how well she has done, and maybe she would have done just as well on fulvestrant if I had brought it in after an aromatase inhibitor, but I don't have any similar success stories to report after an aromatase inhibitor.

We all try to strategize about our hormonal therapies to figure out when to introduce these truly important agents at the most opportune time. That is why we call it "practice." But I am trying to use fulvestrant away from an aromatase inhibitor to let the body return to homeostasis.

DR LOVE: Joyce, if we could speak for a moment about how these agents are administered, what percentage of your patients with metastatic breast cancer do you believe would rather receive a monthly injection of a hormonal agent, such as fulvestrant, versus taking a pill daily, such as an aromatase inhibitor or tamoxifen (Figure 56)?

DR O'SHAUGHNESSY: I believe approximately 30 percent of my patients would prefer to receive the injection. I find that maybe a third of my patients struggle with insurance coverage for oral medications, so they would prefer an injection.

DR LOVE: We have found that when posing this question to oncologists, oncology nurses and patients, they consistently answer between 30 to 40 percent. We also did a telephone survey of 260 patients with metastatic breast cancer, and about a third preferred parenteral therapy

In asking patients why they would prefer an injection, we were unable to establish a clear profile — some find it more convenient, some believe injections are more effective and some just don't like taking pills or have a problem remembering them. However, it appears physicians assume patients would prefer an oral medication because of the convenience and may not present the injection option, yet a third of patients prefer it.

DR O'SHAUGHNESSY: That's interesting. My endocrine therapy of choice in a patient progressing on tamoxifen is an aromatase inhibitor because of the vast data available. All three of the aromatase inhibitors look great after tamoxifen, and while we have the fulvestrant versus anastrozole data, that's only one trial.

DR LOVE: How do you feel about the responses regarding sequencing endocrine therapy (Figure 57)?

DR O'SHAUGHNESSY: Most of the clinicians chose an aromatase inhibitor up front and the data suggest that is probably optimal.

FIGURE 58

Sequencing Endocrine Therapy after Adjuvant Tamoxifen

How do you normally sequence endocrine therapy in postmenopausal patients with metastases who completed adjuvant tamoxifen four years previously?

	1st-line	2nd-line	3rd-line	4th-line
Tamoxifen	2%	3%	3%	9%
Anastrozole	44%	6%	1%	2%
Letrozole	49%	11%	4%	5%
Exemestane	3%	38%	34%	5%
Fulvestrant	2%	38%	39%	13%
Megestrol acetate	—	2%	9%	37%
High-dose estrogen	—	—	3%	5%
Other endocrine therapy	—	—	1%	2%
No endocrine therapy	—	2%	6%	22%

FIGURE 59

Sequencing Endocrine Therapy after Adjuvant Aromatase Inhibitors

How do you normally sequence endocrine therapy in postmenopausal patients with metastases who completed adjuvant anastrozole one year previously?

	1st-line	2nd-line	3rd-line	4th-line
Tamoxifen	38%	7%	16%	8%
Anastrozole	1%	—	—	2%
Letrozole	16%	9%	6%	8%
Exemestane	22%	31%	17%	8%
Fulvestrant	22%	43%	23%	7%
Megestrol acetate	1%	6%	20%	26%
High-dose estrogen	—	—	2%	6%
Other endocrine therapy	—	—	2%	2%
No endocrine therapy	—	4%	14%	33%

DR LOVE: What do you use after the aromatase inhibitor?

DR O'SHAUGHNESSY: I use tamoxifen or exemestane, depending on what the patient has had before, and for the next line of therapy, I use fulvestrant.

DR LOVE: Would you treat this patient who received adjuvant tamoxifen the same way (Figure 58)?

DR O'SHAUGHNESSY: I would use a nonsteroidal aromatase inhibitor, and after that I would be inclined to use exemestane. I'm not using fulvestrant after aromatase inhibitors, even though some small studies show efficacy — I just haven't seen good responses from that sequence.

In select patients who have a relatively small tumor burden, I consider high-dose estrogen therapy, particularly after the aromatase inhibitors. If the patient is heavily burdened with tumor, I select a gentle chemotherapeutic agent, my first choice being capecitabine.

DR LOVE: And how would you treat the patient who had taken adjuvant anastrozole (Figure 59)?

DR O'SHAUGHNESSY: In a patient who completed five years of an aromatase inhibitor, I would use tamoxifen. After tamoxifen, I'd probably use exemestane or fulvestrant.

DR LOVE: Bob, what are your thoughts about the sequencing of endocrine therapy in metastatic disease, specifically with regard to response to fulvestrant?

DR CARLSON: Women with breast cancer who fail on tamoxifen can clearly respond to fulvestrant, and the rate of response is equivalent to that seen with anastrozole. Also, in women with disease that has failed anastrozole who then cross over to fulvestrant, the rate of clinical benefit is substantial and in the range of about 40 percent. Patients who cross over from fulvestrant to aromatase inhibitors also show response rates around 40 percent.

Surprisingly, the magnitude of benefit from fulvestrant does not predict whether the cancer will respond to a subsequent hormonal maneuver. One rule of thumb in the past has been that the magnitude and duration of response to the most recent hormonal therapy predicts the likelihood of response for subsequent hormonal therapies. A small retrospective study suggests that may not be the case with fulvestrant.

In addition, an increasing body of preclinical evidence suggests that breast cancer that becomes resistant to tamoxifen or fulvestrant has upregulation of epidermal growth factor receptor (EGFR) and HER2 expression. As those endocrine-sensitive cells become endocrine-resistant and the EGFR and HER2 upregulate, some of the sensitivity to the endocrine agents may return if those cells are exposed to EGFR inhibitors.

Series of trials are being conducted to evaluate the role of fulvestrant or other hormonal agents in combination with gefitinib. ECOG is conducting a Phase II randomized trial comparing fulvestrant/gefitinib to anastrozole/gefitinib.

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FIGURE 60

Trastuzumab Use in Asymptomatic Premenopausal Patients

*The patient is a **40-year-old** premenopausal woman with no prior systemic therapy who has an ER-negative, HER2-positive tumor with rising tumor markers and asymptomatic bone metastases. What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?*

	1st-line	2nd-line
Chemotherapy alone	7%	17%
Trastuzumab alone	19%	3%
Trastuzumab + chemotherapy	70%	77%
Capecitabine + docetaxel	*2%*	*2%*
Docetaxel	*14%*	*17%*
Paclitaxel	*15%*	*9%*
Carboplatinum + taxane	*15%*	*7%*
Capecitabine	*3%*	*5%*
Gemcitabine	*1%*	*10%*
Vinorelbine	*9%*	*23%*
Carboplatinum	—	*1%*
AC	*6%*	—
Other chemotherapy	*5%*	*3%*
No therapy	4%	3%

FIGURE 61

Continuation of Trastuzumab after Disease Progression

For this 40-year-old patient, if you use first-line trastuzumab (with or without chemotherapy), would you continue trastuzumab upon disease progression?

Percent continuing trastuzumab upon disease progression	84%

DR LOVE: Bob, how do you typically manage asymptomatic patients with ER-negative, HER2-positive tumors (Figures 60-65)?

DR CARLSON: For a younger woman, I would use trastuzumab and would discuss with her whether or not to add a taxane — most likely paclitaxel. For a 75-year-old woman, I would typically use trastuzumab as a single agent.

DR LOVE: For how long do you continue the paclitaxel?

DR CARLSON: That is a tough decision to make. I consider the magnitude and rapidity of response and toxicity experience. The more impressive the response or the less tolerable the regimen, the more inclined I am to stop the taxane sooner rather than later; however, I try to give everyone at least six months of therapy before I stop the cytotoxic part of the regimen.

DR LOVE: It is interesting that almost all of these docs continue trastuzumab when the patient progresses to second-line therapy. Is that what you do?

DR CARLSON: In the absence of data, that is what I do. Some of that is West Coast bias, but patients are influential in this regard. Many of them, correctly or incorrectly, believe that once trastuzumab is started, it should never be stopped.

At times, we find ourselves encouraging patients to stop, and they just tell us "No." There is a very powerful patient network in this area, and in this population I tend to continue trastuzumab indefinitely.

DR LOVE: Let me take a step back here for a moment to talk about HER2 testing. Joyce, when you are considering trastuzumab in any setting, how do you approach HER2 testing?

DR O'SHAUGHNESSY: We routinely order IHC on pathology specimens. For patients with metastatic breast cancer, if the IHC is 3+ I do not generally follow up with FISH, provided the tumor stains 3+ in 75 to 100 percent of cells.

I also determine whether the cancer is high grade and has a high proliferative fraction. Particularly in those cases, I do not order FISH for metastatic disease.

I order a FISH assay when I use adjuvant trastuzumab because in that setting I want documentation that the patient has FISH-positive disease. I also always order a FISH if the IHC is 1+ or 2+.

FIGURE 62

Trastuzumab Use in Asymptomatic Patients

*The patient is a **57-year-old** woman with no prior systemic therapy who has an ER-negative, HER2-positive tumor with rising tumor markers and asymptomatic bone metastases. What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?*

	1st-line	2nd-line
Chemotherapy alone	6%	17%
Trastuzumab alone	20%	3%
Trastuzumab + chemotherapy	71%	77%
Capecitabine + docetaxel	*1%*	*2%*
Docetaxel	*15%*	*15%*
Paclitaxel	*16%*	*8%*
Carboplatinum + taxane	*15%*	*6%*
Capecitabine	*3%*	*5%*
Gemcitabine	*1%*	*12%*
Vinorelbine	*9%*	*25%*
Carboplatinum	—	*1%*
AC	*6%*	—
Other chemotherapy	*5%*	*3%*
No therapy	3%	3%

FIGURE 63

Continuation of Trastuzumab after Disease Progression

For this 57-year-old patient, if you use first-line trastuzumab (with or without chemotherapy), would you continue trastuzumab upon disease progression?

Percent continuing trastuzumab upon disease progression	85%

DR LOVE: We had an interesting case presented for our *Meet The Professors* audio series. The patient's tumor was found to be IHC 0, but the doctor decided to do a FISH and it came back positive. He started trastuzumab and the woman responded very well. Do you FISH test IHC 0 tumors?

DR O'SHAUGHNESSY: I sometimes do. I do not in the adjuvant setting when I'm trying to decide between tamoxifen and an aromatase inhibitor, but in metastatic disease, I test everybody.

I believe every patient with metastatic disease needs one FISH assay in her lifetime. I actually had a patient whose tumor was labeled FISH-negative at a very large major cancer center. She moved to Dallas and her files were delayed in the mail, so I ordered a FISH test and it came back positive. She has derived benefit from trastuzumab.

These are not perfect tests by any means, and it is worthwhile to make sure you are comfortable with the results.

DR LOVE: Wow, that is a really scary case.

DR O'SHAUGHNESSY: It is a really scary case because the test was done at a very important center. The other thing I will tell you is that one woman I treated with adjuvant trastuzumab had over 10 positive nodes, a huge amount of axillary disease and an ER/PR-negative, HER2-positive tumor (3+ by IHC). It was definitely 3+ but also FISH-negative.

I emailed Soon Paik for guidance on this because I was uncertain about what to do. He told me that in the original series, some patients fell into this category. We don't know why, nor whether a post-translational modification exists that is not amplified at the DNA level but nonetheless results in a ton of protein.

The pivotal trials evaluated the 3+ versus the 1+ or 2+, and a benefit was shown in the 3+ population. Dr Paik believes that the bulk of our data are with IHC methodology and, therefore, it is perfectly justifiable to treat this type of patient with trastuzumab.

DR LOVE: Getting back to our cases, Bob, how do you treat symptomatic patients with ER-negative, HER2-positive tumors (Figures 66-71)?

DR CARLSON: In this situation I would use trastuzumab in combination with a taxane and I would consider adding carboplatin; however, in a 75-year-old woman I would be hesitant to use the triplet and would typically use trastuzumab combined with paclitaxel.

DR LOVE: We talked before about nanoparticle paclitaxel. Would you consider using that with trastuzumab?

DR CARLSON: Good question. I would certainly consider it, but I have not seen

FIGURE 64

Trastuzumab Use in Asymptomatic Elderly Patients

*The patient is a **75-year-old** woman with no prior systemic therapy who has an ER-negative, HER2-positive tumor with rising tumor markers and asymptomatic bone metastases. What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?*

	1st-line	2nd-line
Chemotherapy alone	8%	18%
Trastuzumab alone	23%	10%
Trastuzumab + chemotherapy	61%	68%
Docetaxel	*11%*	*8%*
Paclitaxel	*18%*	*11%*
Carboplatinum + taxane	*5%*	*3%*
Capecitabine	*9%*	*8%*
Gemcitabine	*5%*	*10%*
Vinorelbine	*11%*	*27%*
AC	*2%*	*1%*
No therapy	8%	4%

FIGURE 65

Continuation of trastuzumab after disease progression

For this 75-year-old patient, if you use first-line trastuzumab (with or without chemotherapy), would you continue trastuzumab upon disease progression?

Percent continuing trastuzumab upon disease progression	86%

any data on that combination. One of the issues with nanoparticle paclitaxel is that its delivery mechanism is different, so it is not totally clear whether the drug equivalence to paclitaxel or docetaxel will generalize to all settings.

I would be hesitant to use it until we have prospective data suggesting that the additive or synergistic interaction of trastuzumab and the taxanes also exists for this newer agent.

DR LOVE: What would be your second-line choice after the taxane?

DR CARLSON: Vinorelbine. Approximately one fourth of patients receiving vinorelbine develop asthenia or pulmonary symptoms and have to be taken off the drug quickly, but for the rest it is a well-tolerated medication.

DR LOVE: Another issue that arises is the combination of capecitabine and trastuzumab. Will you ever use that combination?

DR CARLSON: Historically, concerns arose about incorporating a fluoropyrimidine with trastuzumab, but I think more recent data specifically evaluating capecitabine and trastuzumab suggest they are at least additive and perhaps synergistic in efficacy.

DR LOVE: When you say data, is that laboratory or clinical?

DR CARLSON: This is preclinical data in animal models that examine the issue of additive or synergistic cytotoxicity. A smattering of small Phase II trials suggest response rates at least as good as you would expect from the combination as opposed to single-agent capecitabine.

DR LOVE: What about the strategy using single-agent trastuzumab in the asymptomatic patient and then adding a chemotherapeutic agent if the patient doesn't respond?

DR CARLSON: I have used that strategy — especially in older patients. Chuck Vogel's data suggest that response rates, at least in the women who have FISH-positive tumors, are going to be as high as 45 to 50 percent.

DR LOVE: How do you handle cardiac monitoring for patients receiving trastuzumab?

DR CARLSON: I typically do a baseline ejection fraction and I prefer to use MUGA scans rather than ECHOs, but either is appropriate. For asymptomatic patients with good cardiac function, I typically monitor them about every six months. Drops in ejection fraction or clinical heart failure rarely occur.

DR LOVE: What do you do when a patient's ejection fraction drops?

DR CARLSON: I stop the trastuzumab. If the patient is symptomatic, I refer her to one of my cardiology colleagues to optimize her cardiac medication. Typically, the cardiac function will improve. I have actually rechallenged a few of these patients with trastuzumab. Interestingly, the cardiac toxicity often does not reappear.

DR LOVE: Interesting. Have you seen tumor responses?

FIGURE 66

Trastuzumab Use in Symptomatic Premenopausal Patients

*The patient is a **40-year-old** premenopausal woman with no prior systemic therapy who has an ER-negative, HER2-positive tumor with bone and lung metastases and is symptomatic. What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?*

	1st-line	2nd-line
Chemotherapy alone	7%	11%
Trastuzumab alone	1%	—
Trastuzumab + chemotherapy	92%	89%
Capecitabine + docetaxel	*6%*	*5%*
Docetaxel	*11%*	*5%*
Paclitaxel	*9%*	*4%*
Carboplatinum + taxane	*49%*	*7%*
Capecitabine	*—*	*2%*
Gemcitabine	*—*	*16%*
Vinorelbine	*1%*	*43%*
Carboplatinum	*1%*	*—*
AC	*5%*	*1%*
AC + docetaxel	*5%*	*—*
Other chemotherapy	*5%*	*6%*

FIGURE 67

Continuation of Trastuzumab after Disease Progression

For this 40-year-old patient, if you use first-line trastuzumab (with or without chemotherapy), would you continue trastuzumab upon disease progression?

Percent continuing trastuzumab upon disease progression	90%

DR CARLSON: It is hard to separate whether secondary tumor responses occur, because almost all of these patients are going to be continuing anti-tumor therapy on an ongoing basis.

DR LOVE: Alright, we've talked about trastuzumab in the metastatic setting. In a moment I am going to ask you to comment on data from the adjuvant setting, but I want to ask Joyce her opinion about the MD Anderson data presented by Dr Buzdar at ASCO this year.

DR O'SHAUGHNESSY: I think it is extremely exciting and a nice step forward. I give Aman Buzdar a lot of credit for sticking with it because this was not an easy study to initiate. It took a couple of years to get off the ground because people were very concerned about combining epirubicin with trastuzumab. Aman's solution was to lower the dose of epirubicin and keep it going for four cycles based on some work by Luca Gianni.

Luca combined doxorubicin 240 mg/m^2 with trastuzumab and had a low rate of cardiac toxicity. At any rate, I think the high PCR rate of 65 percent reported from this trial indicates the anthracyclines and trastuzumab may have some important synergy.

In my practice I have been cautious about that particular combination and have not had the occasion to utilize it since the time Aman presented the data. It is something I would consider using off study if the patient was at extremely high risk with, for example, inflammatory breast cancer.

DR LOVE: What if the patient had locally advanced disease?

DR O'SHAUGHNESSY: Neil, I would consider it. I think we have to tell patients that the data is only from approximately 20 patients. Aman has more experience with this regimen than the ASCO presentation reflects, and the trastuzumab-containing arm of the trial continues to accrue. When I spoke with him recently, he had treated approximately six more patients and he is not seeing problems with the heart.

However, NSABP-B-28 reported a 4.28 percent rate of congestive heart failure with trastuzumab following AC. Out of about 20 patients, this is only 0.8 patients. In other words, he may have not yet accrued enough patients to see one congestive heart failure.

I think we have to give patients enough information so they can give good informed consent. The B-28 data are enormously helpful to doctors, and I think I would have to apply those to Aman's data to help decide what I am going to do.

FIGURE 68

Trastuzumab Use in Symptomatic Patients

*The patient is a **57-year-old** woman with no prior systemic therapy who has an ER-negative, HER2-positive tumor with bone and lung metastases and is symptomatic. What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?*

	1st-line	2nd-line
Chemotherapy alone	7%	11%
Trastuzumab alone	1%	1%
Trastuzumab + chemotherapy	92%	88%
Capecitabine + docetaxel	*6%*	*4%*
Docetaxel	*12%*	*4%*
Paclitaxel	*10%*	*5%*
Carboplatinum + taxane	*46%*	*6%*
Capecitabine	—	*2%*
Gemcitabine	—	*17%*
Vinorelbine	*1%*	*40%*
Carboplatinum	*1%*	*2%*
AC	*5%*	*2%*
AC + docetaxel	*5%*	—
Other chemotherapy	*6%*	*6%*

FIGURE 69

Continuation of Trastuzumab after Disease Progression

For this 57-year-old patient, if you use first-line trastuzumab (with or without chemotherapy), would you continue trastuzumab upon disease progression?

Percent continuing trastuzumab upon disease progression	90%

Interestingly, Frankie Holmes is the principal investigator for a preoperative trial of FEC 100 for four cycles followed by capecitabine/docetaxel (XT). Frankie would like to amend the protocol for HER2-positive patients to make it FEC 75 for four cycles followed by XT combined with trastuzumab. The goal is to gain trial experience adding trastuzumab to chemotherapy, including FEC 75, in the preoperative setting.

DR LOVE: That is fascinating. Have you used neoadjuvant trastuzumab off protocol for inflammatory and locally advanced disease?

DR O'SHAUGHNESSY: No, I have not. Usually, I use CAF preoperatively for patients with locally advanced or inflammatory disease. Then they undergo surgery and if they have residual disease, I start docetaxel/trastuzumab or paclitaxel/carboplatin/trastuzumab.

DR LOVE: Let's talk briefly now about adjuvant trastuzumab (Figure 72). Based on the data, it seems that very few physicians would recommend trastuzumab off study for a patient with HER2-positive disease and three positive nodes, but a relatively high number would recommend a clinical trial. Do you have any thoughts about that?

DR CARLSON: I find it somewhat surprising but very reassuring that physicians are not prescribing trastuzumab off protocol without high-level evidence that the benefits exceed the long-term toxicities — especially with regard to cardiac toxicity.

DR LOVE: We have been doing these kinds of surveys for many years and it appears that physicians' approaches to treatment are becoming much more in line with what research leaders are doing. I'm not sure why that is happening — maybe it is better education.

DR CARLSON: It might be the "Bezwoda effect" and physicians' experiences with high-dose chemotherapy. Many community physicians took information that was a little bit disconnected, put it together and concluded that high-dose therapy was superior to standard full-dose therapy. When they eventually were burned by fraudulent trial results, I think many of them paused and thought, "How many women died because of my recommendation, albeit well intentioned, about how to treat their breast cancer?"

DR LOVE: Joyce, what are your thoughts about the current clinical trials evaluating adjuvant trastuzumab?

DR O'SHAUGHNESSY: Neil, I cannot wait until we have the first data analyses. Frankly, I think that this is the most important question on the table right now. I have no doubt that it has the

FIGURE 70

Trastuzumab Use in Symptomatic Elderly Patients

*The patient is a **75-year-old** woman with no prior systemic therapy who has an ER-negative, HER2-positive tumor with bone and lung metastases and is symptomatic. What is your first-line treatment for this patient, and your second-line treatment if she had objective progression over several months but was clinically the same?*

	1st-line	2nd-line
Chemotherapy alone	9%	13%
Trastuzumab alone	3%	5%
Trastuzumab + chemotherapy	88%	82%
Capecitabine + docetaxel	*5%*	*1%*
Docetaxel	*21%*	*7%*
Paclitaxel	*22%*	*5%*
Carboplatinum + taxane	*16%*	*1%*
Capecitabine	*2%*	*8%*
Gemcitabine	*2%*	*19%*
Vinorelbine	*12%*	*38%*
Carboplatinum	*1%*	—
AC	*3%*	*1%*
Other chemotherapy	*4%*	*2%*

FIGURE 71

Continuation of Trastuzumab after Disease Progression

For this 75-year-old patient, if you use first-line trastuzumab (with or without chemotherapy), would you continue trastuzumab upon disease progression?

Percent continuing trastuzumab upon disease progression	91%

biggest potential impact on women and that it is the next quantum leap in terms of disease-free and overall survival in the adjuvant setting. I think it is going to have a huge impact on changing the natural history of the disease and, therefore, nothing is of greater urgency.

I am going to be a little controversial here and say I hope that after we have these adjuvant data, the breast cancer community can take a look at the future and decide whether or not we really need to wait five or six years to do very large adjuvant trials in women at high risk to be able to apply positive data from the metastatic setting.

Personally, I would probably not make a leap into the lower-risk adjuvant setting where there is a smaller benefit and greater concern about risk-to-benefit ratios; however, I think the higher-risk adjuvant setting — meaning node-positive or locally advanced breast cancer — is the greatest ethical dilemma I have faced in my career in breast cancer.

History tells us that every substantial, definitive survival advantage in metastatic breast cancer translates into improved disease-free and overall survival in the adjuvant setting. I am not aware of any exception to that rule, and it makes sense. When treating metastatic disease, often the tumor burden can be reduced by half a log or a log. If we can impact survival with that kind of cytoreduction, we should be able to make a similar impact in the locally advanced or node-positive setting. I think this is a huge priority.

I understand that the NSABP and Intergroup may try to pool the events from their ongoing trials. Both trials have similar designs — AC followed by paclitaxel with or without trastuzumab. To my knowledge both trials are still accruing and discussions are underway to combine events, which I think would be a great contribution.

The BCIRG trial has finished accrual. We are a year to 18 months away from having enough events, but I think we may have answers a little bit earlier. Unfortunately, HER2-positive breast cancer conveys a poor prognosis and a number of events may occur in women with HER2-positive breast cancer in the control arm without trastuzumab.

DR LOVE: Based on what you are saying, for a woman at very high risk — 5 to 10 positive nodes, HER2-positive disease — do you consider nonprotocol adjuvant trastuzumab?

DR O'SHAUGHNESSY: As I mentioned, this is the issue that gives me the most grief. In the past three to four years, I have treated no more than 10 or 12 women at high risk in the adjuvant setting with trastuzumab.

They have been either patients with inflammatory breast cancer or 10 or

FIGURE 72

Clinical Use of Adjuvant Trastuzumab

The patient is a woman in average health with a 1.2-centimeter, ER-positive, Grade II tumor and 3 positive lymph nodes but her tumor is HER2-positive (as confirmed by FISH). Would you utilize trastuzumab for this patient? (Percent responding "yes")

	35 years old	65 years old
Trastuzumab off protocol	6%	4%
Trastuzumab clinical trial	75%	70%

Would you be likely to recommend adjuvant trastuzumab to a 65-year-old otherwise healthy woman with an ER-negative, HER2-positive tumor with 10 positive nodes?

No	82%
Yes	18%

more positive nodes. Generally, they are in the ER/PR-negative, FISH-positive group.

I treated one woman who had bulky adenopathy and eight positive nodes, and another woman with large, bulky, macrometastases, adenopathy and five positive nodes. Both of these women were young, vigorous and healthy, and had ER/PR-negative and HER2-positive disease by FISH.

I have used adjuvant trastuzumab extremely judiciously, recognizing the risks that I was taking, and I have had extremely good success. Of the 10 or 12 patients I've treated, only one patient has experienced relapse, and, frankly, in that case I brought the trastuzumab in late.

I gave that patient preoperative CAF followed by docetaxel without trastuzumab. She went to surgery and still had an extraordinary bulk of disease. I started vinorelbine and trastuzumab afterward and I'm afraid I was too late with the trastuzumab; she developed metastatic disease.

With the others, I started docetaxel/trastuzumab or docetaxel/carboplatin/trastuzumab right after the CAF or the AC and none of those patients has experienced relapse.

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Pharmaceutical Agents Discussed in this Program

Generic	Trade	Manufacturer
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cetuximab	Erbitux™	ImClone Systems
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan® Neosar®	Bristol-Myers Squibb Company Pfizer Inc
dexamethasone	Various	Various
diphenhydramine	Benadryl® Benylin®	Warner-Lambert Company Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin® Rubex®	Pfizer Inc Bristol-Myers Squibb Company
epirubicin hydrochloride	Ellence®	Pfizer Inc
escitalopram oxalate	Lexapro®	Lundbeck/Forest Laboratories
exemestane	Aromasin®	Pfizer Inc
filgrastim	Neupogen®	Amgen Inc
fluorouracil (5-FU)	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly and Company
goserelin acetate	Zoladex®	AstraZeneca Pharmaceuticals LP
goserelin acetate implant	Zoladex® LA	AstraZeneca Pharmaceuticals LP
irinotecan, CPT-11	Camptosar®	Pfizer Inc
letrozole	Femara®	Novartis Pharmaceuticals
leuprolide acetate implant	Viadur™ Lupron Depot®	ALZA Corporation TAP Pharmaceuticals Inc
megestrol acetate	Megace®	Bristol-Myers Squibb Company
methotrexate	Various	Various
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pegfilgrastim	Neulasta®	Amgen Inc
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech BioOncology
trazodone	Desyrel	Pfizer
venlafaxine	Effexor®	Wyeth
vinorelbine	Navelbine®	GlaxoSmithKline

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

- Compare and contrast a management strategy for the treatment of cancer patients to that of other community oncologists and cancer research leaders. 5 4 3 2 1
- Discuss cancer management issues for which there is relative agreement and those for which there is heterogeneity in patterns of care. 5 4 3 2 1
- Counsel cancer patients about multiple acceptable treatment options when they exist. 5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1

Related to my practice needs. 5 4 3 2 1

Will influence how I practice 5 4 3 2 1

Will help me improve patient care 5 4 3 2 1

Stimulated my intellectual curiosity 5 4 3 2 1

Overall quality of material. 5 4 3 2 1

Overall, the activity met my expectations 5 4 3 2 1

Avoided commercial bias or influence 5 4 3 2 1

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Robert W Carlson, MD	5 4 3 2 1	5 4 3 2 1
Joyce A O'Shaughnessy, MD	5 4 3 2 1	5 4 3 2 1

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Patterns of Care in Medical Oncology

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