

Patterns of Care

in Medical Oncology

Management of Breast Cancer in the Adjuvant and Metastatic Settings

Adjuvant Systemic Therapy

Chemotherapy for Metastatic Disease

Hormonal Therapy for Metastatic Disease

HER2-Positive Disease

Editor

Neil Love, MD

Special Edition:

**A Case Survey Comparing
Practices of Breast
Cancer Specialists and
General Oncologists**



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PowerPoint files of the graphics contained in this document can be downloaded at PatternsOfCare.com.

STATEMENT OF NEED/TARGET AUDIENCE

It is 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. It is also important for oncologists to recognize that heterogeneity exists in the oncology community, especially in clinical situations for which there is suboptimal 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 cancer patterns of care 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 management strategies of community oncologists and cancer research leaders for the treatment of cancer.
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care.
- Counsel cancer patients about multiple acceptable treatment options when they exist.

PURPOSE OF THIS ISSUE

The purpose of this issue of *Patterns of Care* is to support these objectives by comparing the perspectives of 200 randomly selected community medical oncologists interviewed in depth in August of 2004 with those of 31 breast cancer researchers surveyed, and to offer in-depth commentary from faculty regarding their practice patterns in the management of breast cancer.

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COMMERCIAL SUPPORT

This program is supported by education grants from Abraxis Oncology, AstraZeneca Pharmaceuticals LP and Genentech BioOncology.

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PHARMACEUTICAL AGENTS DISCUSSED IN THIS PROGRAM

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UPCOMING EDUCATIONAL EVENTS

Breast Cancer Update Medical Oncology Educational Forum: Controversies in Systemic Therapy of Breast Cancer
May 21, 2005

Beverly Hills, California

Event website: www.breastcancerupdate.com/cmemeetings

Breast Cancer Update Medical Oncology Educational Forum
June 25, 2005

New York, New York

Event website: www.breastcancerupdate.com/cmemeetings

For many years, our CME oncology group has attempted to utilize educational objectives that bridge what we call "the gap" — the difference between "standard of care" as defined by cancer research leaders and oncologic care delivered by community-based oncologists. In the many audio interviews and CME meetings with breast cancer specialists (BCS) over the years, we have noted a great deal of homogeneity in their approach to patient care. Their practices also generally closely reflect NCCN and ASCO guidelines.

There are relatively few researchers in any given tumor type, and these oncologists are frequently interacting together on education panels and in research planning meetings. This results in a continuous informal consensus process. Community-based oncologists (CBO) are not nearly as connected, and there is much more heterogeneity in their practice patterns. One can argue that for many clinical situations, there are multiple evidence-based options, and perhaps the judgment of CBO is more astute than that of researchers. However, I suspect that many CBO do not have the necessary time to adequately review the available research data on the many

tumors they must treat and this is the most likely cause for differences in care patterns.

For this special issue of *Patterns of Care*, we attempt to quantify the "gap" for a number of common clinical scenarios in the management of breast cancer. In February 2005, 74 clinical researchers who specialize in breast cancer were invited to complete the same case-based survey that was given to 200 medical oncologists randomly recruited from a national mail list six months earlier (see Volume 1, Issue 3 of this publication). Thirty-one of these investigators — most of whom have previously been interviewed for our audio series — completed the surveys (see next page for complete list of respondents).

A number of these research leaders also participated in hour-long follow-up telephone interviews, which were transcribed and edited as commentary for this issue. This issue also includes relevant comments from other researchers that were gleaned from our audio programs.

The two sets of survey results demonstrate that while there is general concordance about medical management of breast cancer, there also are a number of

clinical situations where significant differences exist between these two groups (see Figure 1, below, for examples).

Perhaps the most interesting finding from the comparison of these two surveys was that the number of breast cancer patients treated by BCS is about the same as those treated by CBO. This occurrence is likely unique in contemporary oncology. Typically, research leaders who specialize in specific tumor types have a great deal more clinical experience with those diseases than CBO do.

For example, I recently interviewed Steven Rosen from Northwestern University for our series in non-Hodgkin's lymphoma. Dr Rosen has a particular research and practice interest in cutaneous lymphomas, which represent less than 2,000 cases annually in the United States. Every day, he sees patients with these tumors, which are very rare in general oncology practice. This has important implications for education, as practitioners commonly seek "pearls" about caring for patients with these uncommon tumors from specialists like Steve.

During the interview, we reviewed a number of Dr Rosen's second opinion cases, and in several instances, there

FIGURE 1

Striking Differences in Practice Patterns between Breast Cancer Specialists and Community Oncologists

	Breast cancer specialists	General oncologists
Oncologists who would recommend switching to an aromatase inhibitor after 2 years of tamoxifen (65-year-old woman with a 1.2-centimeter, node-negative, ER-positive tumor)	93%	55%
Oncologists who would recommend an aromatase inhibitor after completing 5 years of tamoxifen one year ago (65-year-old woman with a 1.2-centimeter, node-negative, ER-positive tumor and 3 positive nodes)	84%	58%
Oncologists who would recommend adjuvant chemotherapy for a 75-year-old woman with a 1.2-centimeter, node-negative, ER-positive tumor	0%	27%
Oncologists who would recommend first-line trastuzumab without chemotherapy (57-year-old woman with HER2-positive disease and asymptomatic bone mets)	74%	20%
Oncologists who would recommend first-line capecitabine (57-year-old woman with asymptomatic bone mets and ER-negative, HER2-negative metastatic disease who received adjuvant AC → paclitaxel 2 years ago)	88%	20%

was a marked difference in his recommendation compared to the first. In one case, a patient was recommended to have high-dose chemotherapy with stem cell support, but Steve recommended watchful waiting, an approach the patient continues to take 12 years later without difficulty. While such disparities are uncommon in breast cancer, the enclosed breast cancer survey demonstrates many common clinical situations where significant differences exist between research leaders and oncologists in practice.

From a public health perspective, the most important example relates to

switching a postmenopausal woman on adjuvant tamoxifen during the first five years of treatment to an aromatase inhibitor. Two major randomized trials and one smaller one now clearly demonstrate that both exemestane and anastrozole present a much more favorable risk-benefit ratio than tamoxifen to these patients, and one can make the argument that perhaps hundreds of thousands of women are currently receiving treatment that is totally unsupported by breast cancer researchers, and that this exposes them to a 35-40% greater risk of relapse, and a greater chance for serious adverse effects.

This is not good and needs to change as soon as possible.

We will be presenting and discussing the data from the surveys at many future live CME education forums so that we can obtain feedback on these trends. We will also continue to track these fascinating practices over time, as new research results emerge and will soon launch a "Phase II study" in this initiative. It will be interesting to follow these trends as new research results emerge.

— Neil Love, MD
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FIGURE 2

Breast Cancer Specialists Completing the Survey

<p>Alan Astrow, MD The Saint Vincent's Comprehensive Cancer Center New York, New York</p> <p>Joanne L Blum, MD, PhD Baylor-Charles A Sammons Cancer Center Dallas, Texas</p> <p>Adam M Brufsky, MD, PhD University of Pittsburgh Pittsburgh, Pennsylvania</p> <p>Harold J Burstein, MD, PhD Harvard Medical School Dana-Farber Cancer Institute Boston, Massachusetts</p> <p>Lisa A Carey, MD University of North Carolina Chapel Hill, North Carolina</p> <p>Robert W Carlson, MD Stanford University Medical Center Stanford, California</p> <p>Jenny C Chang, MD Baylor College of Medicine Houston, Texas</p> <p>Ellen Chuang, MD Weill Medical College of Cornell University New York, New York</p> <p>Richard M Elledge, MD Baylor College of Medicine Houston, Texas</p> <p>Kevin R Fox, MD University of Pennsylvania Cancer Center Philadelphia, Pennsylvania</p> <p>Julie R Gralow, MD University of Washington and Fred Hutchinson Cancer Research Center Seattle, Washington</p>	<p>Generosa Grana, MD UMDNJ/Robert Wood Johnson School of Medicine Cooper Hospital Camden, New Jersey</p> <p>Jennifer Griggs, MD, MPH University of Rochester Rochester, New York</p> <p>Daniel F Hayes, MD University of Michigan Comprehensive Cancer Center Ann Arbor, Michigan</p> <p>Clifford Hudis, MD Memorial Sloan-Kettering Cancer Center New York, New York</p> <p>Stephen E Jones, MD Charles A Sammons Cancer Center Baylor University Medical Center Dallas, Texas</p> <p>Allan Lipton, MD Hershey Medical Center Hershey, Pennsylvania</p> <p>Gershon Locker, MD Northwestern University Evanston, Illinois</p> <p>Charles L Loprinzi, MD Mayo Clinic College of Medicine Rochester, Minnesota</p> <p>Gary H Lyman, MD, MPH James P Wilmot Cancer Center University of Rochester Medical Center Rochester, New York</p> <p>Anne Moore, MD Weill-Cornell Medical College New York Presbyterian Hospital New York, New York</p>	<p>C Kent Osborne, MD Baylor College of Medicine Houston, Texas</p> <p>Leroy Parker, MD Harvard Medical School Boston, Massachusetts</p> <p>Ann H Partridge, MD, MPH Harvard Medical School Boston, Massachusetts</p> <p>John Pippen, MD Baylor University Medical Center Dallas, Texas</p> <p>Lajos Pusztai, MD, PhD The University of Texas MD Anderson Cancer Center Houston, Texas</p> <p>Hope Rugo, MD Carol Franc Buck Breast Care Center University of California, San Francisco Comprehensive Cancer Center San Francisco, California</p> <p>Michelle Shayne, MD Beth Israel Deaconess Medical Center Boston, Massachusetts</p> <p>Debu Tripathy, MD University of Texas Southwestern Medical Center Dallas, Texas</p> <p>Vicente Valero, MD The University of Texas MD Anderson Cancer Center Houston, Texas</p> <p>Charles L Vogel, MD Cancer Research Network Inc Miami, Florida</p>
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EDITOR'S COMMENT

Our previous surveys have repeatedly demonstrated that breast cancer cases comprise approximately one third of patient visits to community oncologists' offices. However, since these physicians treat many more total patients than researchers, the number of monthly breast cancer clinical encounters is virtually the same for both groups. On average, both groups of physicians begin adjuvant systemic therapy for early breast cancer about twice a week and start or switch systemic therapy for patients with metastatic disease also about twice a week.

There are no major differences in the education methods used by both groups to keep up to date with new research findings, but oncologists in practice must follow research developments in a plethora of tumor types.

FIGURE 3

Demographics

What fraction of your work is patient care?

≤30%	10%	0%
31-40%	20%	0%
41-50%	17%	1%
51-60%	3%	0%
61-70%	20%	1%
71-80%	17%	7%
81-90%	3%	23%
91-99%	7%	37%
100%	3%	31%

FIGURE 4

Demographics

How many years have you been in practice?	17.2 yrs	15.3 yrs
What percent of your patients are in HMOs?	21%	27%
What percent of your overall practice is breast cancer (BCA)?	88%	33%
How many new BCA patients do you see per month?	16.7	13.5
How many BCA patients do you start on adjuvant therapy per month?	8.9	9.3
In how many BCA patients per month do you start or switch systemic therapy for metastases?	9	8

■ BREAST CANCER SPECIALISTS □ GENERAL ONCOLOGISTS

Differences between academic and community practice

I view myself primarily as a researcher and secondarily as a treating physician. For most community practitioners, it is probably reversed. I think generally your perspective is based on the time you spend doing specific activities.

The amount of time I spend taking care of patients is probably considerably less than the time spent by most private oncologists, and, therefore, the volume of patients I see is less. However, in terms of complexity, some of my colleagues in practice send me the more difficult, problematic, puzzling cases.

So I see a somewhat different spectrum of patients, but I'm asking the same questions as my community-based colleagues. We both want to translate the same recent research findings into state-of-the-art patient care. So there are probably more similarities than differences.

— Gary Lyman, MD, MPH

Everybody wants the same thing in the end, but we all know there are different ways of achieving it and in general, I think the community oncologist and the research oncologist face different pressures. The community oncologist faces the pressure of getting people in and out of the office for understandable economic reasons while the research oncologist faces pressures related to doing research and following institutional values.

Clinical practice at a research institution tends to be more sub-specialized and therefore you find experts in one particular area whereas, in the commu-

FIGURE 5

Time Spent in Continuing Education Activities*How much time in a typical month do you spend doing the following?*

	Mean time spent (hours)	
Reading any type of medical educational materials	12.0	15.7
Specifically reading medical journals	10.3	10.8
Searching for and reading oncology information on the Internet	4.9	4.4
Listening to any type of medical educational programs on tape or CD	1.2	3.4
Specifically listening to interviews with cancer research leaders	1.1	2.5

FIGURE 6

Utilization of Medical Journals

	Mean	
How many medical journals do you subscribe to?	5.7	4.3
How many of these journals do you typically read or skim per month?	5.2	4.1
What percent of the articles do you actually read?	17%	25%

FIGURE 7

Use of Peer-Reviewed Medical Journals*Do you read or skim the following journals each month?*

<i>Journal of Clinical Oncology</i>	100%	99%
<i>Journal of the National Cancer Institute</i>	57%	31%
<i>The Lancet</i>	23%	22%
<i>Cancer</i>	40%	37%
<i>New England Journal of Medicine</i>	83%	87%
<i>Journal of the American Medical Association</i>	43%	58%

nity oncology setting, a physician may be good at a lot of different things, but may not be up to speed on everything. So it depends on the patient and the situation. For some bread-and-butter type cases, I think a community oncologist might be as effective, if not more effective, than a research oncologist in terms of caring for the patient. However, when there are more esoteric situations where a research study may be a better option or one of

the only options, then someone might be better served in a research setting.

— Ann Partridge, MD

I believe the medical oncologist who treats only breast cancer and attends either the San Antonio Breast Cancer Symposium or the breast cancer portion of the ASCO meeting is better able to extract small details that will change their practice patterns than the general

oncologist who needs to attend lectures on others cancers as well. In addition, general oncologists don't attend meetings on translational biology and may not be in tune with new studies that are evolving. We are beginning to evaluate treatments for subsets of patients rather than treating all patients with the same approach. General oncologists may be seeing patients in these subsets, but may not be aware that one treatment is

FIGURE 8

Participation in Breast Cancer Research

Do you enter patients in clinical trials?

Yes	100%	73%
<i>For those answering "yes," what type of trials?</i>		
Cooperative Group	97%	68%
Industry	93%	52%
<i>How many patients a year do you enroll in trials?</i>		
Mean	43	11

superior until that information becomes widely disseminated. There may be a time delay in changing practice patterns for the general oncologist versus the medical oncologist who specializes in breast cancer.

— Joanne L Blum, MD

Staying up to date with emerging data

More and more, I look at journals electronically. In fact, I'm changing all my subscriptions because electronic access has been revolutionary, allowing me to download an electronic copy onto my hard drive to keep in a filing system. Personally, I've found that this has increased my ability to scan the literature and to organize my references.

Having said that, the number of medical and scientific journals continues to mushroom. There are tens of thousands of journals, and one has to prioritize. I have my internal list of the major publications, both general medical and oncology specific, that I feel I have time to personally access.

I also scan Medline, looking for the types of data that my group works with, particularly meta-analyses, systematic reviews and randomized controlled trials. Fortunately, the filter mechanisms available through the National Library of Medicine narrow down the number of articles each month so that I can scan through them, at least with regard to breast cancer.

However, trying to keep up with the

literature is still a major challenge, so like everyone else, I turn to medical education programs, particularly those where leaders in the field whom I respect communicate their impressions and interpret what's most relevant and what's the take-away message. Even in breast cancer, it's virtually impossible to stay current with every issue that's actively being discussed and researched.

— Gary Lyman, MD, MPH

I spend a lot of time reading medical journals, including the *Journal of the American Medical Association*, the *New England Journal of Medicine* and the *Journal of Clinical Oncology*. I read all of the articles related to breast cancer, but I also try to read some of the review articles and articles on new drugs. I read articles on diseases other than breast cancer, but I don't spend nearly as much time on those.

I read select articles in *Nature* and *Science* to stay abreast of the basic science issues. I read a lot of the news and views articles from both of those journals. I also read *Cancer Research*, although very selectively. I may read the cover article and possibly one or two articles related to breast cancer. I receive the *American Journal of Human Genetics* and *Nature Genetics* because I'm involved with the genetic counseling program at our institution and I look for articles related to BRCA-1 and BRCA-2.

— Joanne L Blum, MD

I rely on four journals. I read *JCO* thor-

oughly every month and scan the *JNCI*, the *New England Journal of Medicine* and *JAMA* for cancer-related articles. Sometimes the web-based publication summaries catch my attention.

— Generosa Grana, MD

I keep up-to-date through my clinical practice and discussing cases with the core group at my institution. I also speak at a number of meetings, where I have the opportunity to hear other faculty present. Finally, I peruse the *Journal of Clinical Oncology* fairly religiously and review articles submitted for publication.

— Charles L Loprinzi, MD

Participation in clinical trials

I supervise most of the breast cancer clinical trials in oncology at my center. I participate in Phase II and Phase III studies in both the adjuvant and metastatic setting. I've had minimal involvement in Phase I trials as well. I'm also involved in studies on the psychological implications of genetic counseling for patients. I direct the genetic counseling program at our institution, and we have approximately four collaborative studies with other centers that deal with genetics.

— Joanne L Blum, MD

SELECT PUBLICATIONS

Bloom BS et al. **Breast cancer treatment in clinical practice compared to best evidence and practice guidelines.** *Br J Cancer* 2004;90(1):26-30. [Abstract](#)

Cervero RM. **Place matters in physician practice and learning.** *J Contin Educ Health Prof* 2003;23(Suppl 1):10-8. [Abstract](#)

Ebell MH, Shaughnessy A. **Information mastery: Integrating continuing medical education with the information needs of clinicians.** *J Contin Educ Health Prof* 2003;23(Suppl 1):53-62. [Abstract](#)

Parochka J, Paprockas K. **A continuing medical education lecture and workshop, physician behavior, and barriers to change.** *J Contin Educ Health Prof* 2001;21(2):110-6. [Abstract](#)

Partridge MR. **Translating research into practice: How are guidelines implemented?** *Eur Respir J Suppl* 2003;39:23-29. [Abstract](#)

Stancic N et al. **Continuing medical education: What delivery format do physicians prefer?** *J Contin Educ Health Prof* 2003;23(3):162-7. [Abstract](#)

EDITOR'S COMMENT

Breast cancer specialists (BCS) more commonly use computer models — particularly Peter Ravdin's Adjuvant! — to calculate the expected benefits of adjuvant therapy. BCS also use chemotherapy less frequently for node-negative cases. For node-positive disease, researchers use less AC followed by docetaxel, although this difference may relate to the recently reported NSABP B-27 data on this regimen, which was presented in between these two surveys. BCS also more commonly recommend ovarian suppression plus an aromatase inhibitor (AI) for premenopausal patients. For both groups, anastrozole is by far the most common choice for an upfront AI in postmenopausal patients. BCS more commonly switch patients on tamoxifen for two years to an AI (usually exemestane) and more commonly start an AI (usually letrozole) after five years of tamoxifen.

FIGURE 9

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	23%	0%
Sometimes	50%	86%
Rarely	20%	14%
Never	7%	0%

FIGURE 10

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	70%	25%
Charles Loprinzi's Mayo Clinic model	0%	12%
Both	20%	22%
Neither	10%	41%

FIGURE 11

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	82%	98%
To decide whether to use chemotherapy in node-negative cases	70%	81%
To decide whether to use endocrine therapy in node-negative cases	17%	44%
To select type of chemotherapy to use	7%	19%
To select type of endocrine therapy to use	0%	10%

Computerized risk models

Peter Ravdin and I did a lot of this work together, and we published a paper several years ago in the *Journal of the NCCN*, which compared and contrasted the two tools. These programs are becoming increasingly established among community oncologists. Peter's program Adjuvant! has been validated against the natural experience of the British Columbia Group, which was presented in abstract form at ASCO 2004.

The advantage to having both tools out there is that it allows some honesty between the people developing them and keeping them updated. The Mayo Clinic program is quite user-friendly, but you could also argue that it doesn't have as much flexibility and as many nuances as Adjuvant!.

— Charles L Loprinzi, MD

My group is very involved in developing and validating risk models from a methodological, statistical standpoint because these models are very easy to produce, but not easy to produce right. The one model that's captured everybody's imagination more than any other is Peter Ravdin's Adjuvant! program. We use Adjuvant! virtually on a daily basis.

What is often misunderstood about these models is that the estimates they generate — while probably better than what we've had in the past — are still estimates. They're based on extrapolations often from highly selected patients put through very formal clinical research trials. In some cases they can be extrapolated to the general population or to

FIGURE 12

Accuracy of Estimated Risk of Relapse and Mortality

- 65-year-old woman in average health
- 1.2-centimeter, Grade II tumor
- ER-positive, HER2-negative
- Negative nodes

What would you estimate to be 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	17%	20%	23%	9%	12%	7%
With hormonal therapy alone	10%	13%	Anastrozole 13% Tamoxifen 15%	6%	8%	Tamoxifen 6%
With both hormonal therapy and chemotherapy (AC x 4)	9%	10%	Anastrozole 11% Tamoxifen 14%	5%	6%	Tamoxifen 5%

patients who wouldn't have been in those trials. Peter has attempted to adjust for co-morbidities, but the adjustment there is pretty crude and broad and has to be interpreted by the patient's treating oncologist.

— Gary Lyman, MD, MPH

I have book marked both the Mayo Clinic and the Adjuvant! Online program in all the clinic's computers. I'm using Adjuvant! Online most commonly, especially when I think a patient could really benefit from seeing some numbers. Sometimes I need some help sorting out exactly what added risk reduction would be predicted from the data, for example in adding chemotherapy to hormone therapy — I'm always looking for support not to give chemotherapy.

— Julie Gralow, MD

Adjuvant chemotherapy for node-negative disease

Ultimately, most women with node-negative, ER-positive disease who go to see an oncologist are asking: "What would chemotherapy add to my care?" A number of parameters need to be factored into this discussion, including tumor size, HER2 status, tumor grade in some cases, the presence of lympho-

vascular invasion and, of course, the patient's age and comorbidities.

All of these elements are considered, but usually it comes down to a discussion of whether chemotherapy adds enough to standard care — usually a hormonal manipulation — to justify the added toxicity. This is a situation where an aid like Adjuvant! is helpful. You can use the results from the model to say to a patient, "Here's your risk with or without adjuvant chemotherapy and here's your risk with or without adjuvant hormonal therapy."

I also feel very strongly that we need to incorporate the patient's value system into the discussion and the final decision. What I believe is a reasonable benefit needed to accept the toxicity from a chemotherapy regimen may be very different from what a patient views as reasonable, particularly when we are talking about just a few percentage points.

— Gary Lyman, MD, MPH

My current approach to patients with ER-positive, node-negative disease is to look at tumor size and other prognostic factors to decide whether or not to add chemotherapy to hormone therapy. I foresee that in the next six to 12 months, I will be using the Genomic Health information in making those decisions

for some of these patients.

Right now, I'm not using that information in my practice because of logistical issues such as reimbursement, technology acceptance and turnaround time.

I factor the patient's age into my choice of hormonal therapy and whether or not to use chemotherapy. With a young woman in a node-negative setting, I'm much more likely to use chemotherapy, and I may go with four cycles of AC or even add paclitaxel to AC with a larger or high-grade tumor.

In elderly patients, I think the Adjuvant! Online program performs very well because it allows you to take into account age and their co-morbidities in determining the impact of treatment. So, these are patients that I am likely to plug into Adjuvant! to get a handle on the impact of the disease and treatment.

— Generosa Grana, MD

I try very hard not to give chemotherapy to patients with ER-positive, node-negative disease. But there are things like tumor size (over a centimeter, especially if it's high grade) HER2-positivity, lymphovascular invasion or other features that may push me to give chemotherapy.

I think the preponderance of data to date shows us that people who benefit the most from chemotherapy are those with

FIGURE 13

Adjuvant Chemotherapy for Node-Negative Disease

- 65-year-old woman in average health
- 1.2-centimeter, Grade II tumor
- ER-positive, HER2-negative
- Negative nodes

Which treatment strategy would you most likely recommend?

	Age 35		Age 45		Age 55		Age 65		Age 75		Age 85	
Chemotherapy alone	0%	2%	0%	2%	0%	0%	0%	0%	0%	0%	0%	0%
Chemotherapy + endocrine therapy	87%	95%	87%	95%	60%	79%	17%	57%	0%	27%	0%	10%
Endocrine therapy alone	13%	3%	13%	3%	40%	21%	83%	43%	97%	72%	77%	74%
No therapy	0%	0%	0%	0%	0%	0%	0%	0%	3%	1%	23%	16%

FIGURE 14

Adjuvant Chemotherapy for Node-Negative Disease

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

	Age 35		Age 45		Age 55		Age 65		Age 75		Age 85	
AC q3wk x 4	44%	50%	40%	49%	27%	42%	10%	32%	0%	15%	0%	7%
AC q2wk x 4 with growth factors	13%	9%	13%	10%	10%	7%	3%	4%	0%	2%	0%	0%
FAC or FEC x 6	7%	12%	7%	12%	3%	8%	0%	5%	0%	2%	0%	1%
AC x 4 followed by paclitaxel q3wk x 4	0%	6%	0%	6%	0%	5%	0%	3%	0%	1%	0%	1%
AC x 4 followed by paclitaxel q2wk x 4 with growth factors	17%	4%	17%	4%	13%	3%	3%	0%	0%	0%	0%	0%
AC x 4 followed by docetaxel x 4	0%	7%	0%	7%	0%	5%	0%	4%	0%	1%	0%	0%
CMF	3%	7%	7%	7%	3%	7%	3%	8%	0%	6%	0%	1%
TAC	3%	2%	3%	2%	3%	2%	0%	1%	0%	0%	0%	0%
Other	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Would not recommend chemotherapy	13%	3%	13%	3%	41%	21%	81%	43%	100%	73%	100%	90%

higher-risk tumors, which tend to be the ER-negative or HER2-positive. That's not to say that people with ER-positive or HER2-negative cancers don't benefit from chemotherapy, but rather they seem to benefit less. So for me, it's really a mat-

ter of weighing the risks and benefits, including the risk of the cancer itself.

— Ann Partridge, MD

For adjuvant chemotherapy in the lower-risk, node-negative setting, I generally

use four cycles of AC. The controversial issue at this point is whether to use the traditional every three-week schedule or dose-dense therapy with hematopoietic growth factor support.

Dose-dense schedules are intriguing

FIGURE 15

Adjuvant Hormonal Therapy in Postmenopausal Patients with Node-Negative Disease*Tumor is 1.2 centimeters, ER-positive, node-negative**Which hormonal therapy, if any, would you most likely recommend?*

	Age 55		Age 65		Age 75		Age 85	
Anastrozole	64%	74%	67%	74%	70%	70%	57%	55%
Exemestane	0%	0%	0%	1%	0%	1%	0%	2%
Letrozole	3%	7%	3%	9%	7%	10%	3%	8%
Tamoxifen	33%	19%	30%	16%	20%	18%	20%	19%
Would not recommend endocrine therapy	0%	0%	0%	0%	3%	1%	20%	16%

in that they are somewhat better tolerated because of the growth factors and the patient finishes therapy faster. They come with, of course, a great deal of additional cost.

Most importantly, however, we probably could benefit from additional validation that AC given every two weeks has an advantage over an every three-week administration. Clearly, dose-dense AC → paclitaxel showed an advantage in CALGB-9741 that most oncologists have accepted. But whether we can convert that benefit to a lower-risk, node-negative setting with AC times four alone is controversial.

In my own practice, I discuss with patients the benefits of quicker therapy, the downside in terms of additional injections and cost, and the uncertainty regarding the additional benefit of dose-dense AC. I'm very comfortable, however, if a patient chooses to go that route, that we're not doing her any harm.

— Gary Lyman, MD, MPH

ATAC trial update

The ATAC trial has reached an important point in its evolution with a median follow-up of 68 months. Almost all of the patients are now off therapy, and we have one year of follow-up after the therapy is completed.

The progress of this trial is important for two reasons: it makes me comfortable about the efficacy and the hypotheti-

cal “carry-over effect” we've seen with tamoxifen, and I'm also more comfortable with the toxicities and tolerability of anastrozole.

I believe this is probably the most important of the three ATAC analyses, and it allows me, as a practicing clinician, to change practice. I speak not only as a practicing clinician but also as the past principal investigator of the trial.

The simplest interpretation of the results is that anastrozole prevents one in four of the relapses we see in postmenopausal patients on tamoxifen. That translates into highly significant improvements in disease-free survival, recurrence-free survival and distant disease-free survival.

The absolute number for difference in recurrence-free survival in the patients with receptor-positive disease at six years is close to four percent. It is important to remember that this trial included a group of patients with a relatively good prognosis.

In terms of relative risk reductions, we have no reason to suppose that the relative risk reductions will be different in any subgroup, and if that one in four relative risk reduction is across the board, then in a subgroup of patients with, for example, a 40 percent chance of relapse at six years, the absolute reduction is about 10 percent, not four percent, as was seen in the ATAC trial.

— Michael Baum, MD, ChM

The use of anastrozole instead of tamoxifen does not impair quality of life. We can also say, with confidence, that the gynecological symptoms linked to tamoxifen have now translated into a fourfold increase in hysterectomy rates with tamoxifen compared to anastrozole.

That is a dramatic observation, which we nearly missed. I was persistent about tracking down all the hysterectomies in women who had their wombs at the time of randomization. We came up with an extraordinary figure — I believe it's the most extreme relative risk I've encountered in clinical trials.

The absolute numbers of hysterectomy were 1.3 percent versus 5.1 percent for anastrozole and tamoxifen, respectively. This has a profound economic impact. I also don't know how many hysteroscopies are being performed for every hysterectomy or how much the workup costs to decide whether a woman should have a hysterectomy, but these are big cost issues.

The update doesn't give us any new information with regard to other pre-specified adverse events, and no other adverse event is emerging with a frequency of more than one percent.

The fracture rate incidence is becoming a little more reassuring. An excess fracture rate occurs in the first two or three years, but then the lines are beginning to come together. As patients stop taking anastrozole, the fracture rate

FIGURE 16

Impact of Tumor Size on Approach to Adjuvant Therapy in Patients with Negative Lymph Nodes

- 65-year-old woman in average health
- Grade II tumor
- ER-positive, HER2-negative
- Negative nodes

Which treatment strategy would you most likely recommend?

	0.8-cm tumor		2.4-cm tumor	
Chemotherapy alone	0%	0%	0%	1%
Chemotherapy + endocrine therapy	3%	11%	87%	91%
Endocrine therapy alone	90%	83%	13%	8%
No therapy	7%	6%	0%	0%

Impact of Tumor Size on Selection of Adjuvant Chemotherapy in Patients with Negative Lymph Nodes

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

	0.8-cm tumor		2.4-cm tumor	
Would not recommend chemotherapy	93%	89%	13%	8%
AC q3wk x 4	7%	6%	44%	42%
AC q2wk x 4 with growth factors	0%	2%	7%	5%
FAC or FEC x 6	0%	0%	7%	12%
AC x 4 followed by paclitaxel q3wk x 4	0%	0%	0%	6%
AC x 4 followed by paclitaxel q2wk x 4 with growth factors	0%	1%	13%	8%
AC x 4 followed by docetaxel x 4	0%	1%	3%	8%
CMF	0%	1%	3%	8%
Other	0%	0%	10%	3%

returns to that of the patients randomized to tamoxifen.

Thus, so far, no difference has occurred in fractures of the neck or femur, which are of particular concern.

I think the issue of bone is easy to manage. We should monitor bone mineral density, perhaps exclude patients who have established osteoporosis, and then be ready to intervene with a bisphosphonate when the patient becomes osteopenic.

The polyarthralgia with anastrozole remains a problem. We don't understand it, and it occasionally leads to withdrawal of treatment; however, the bottom line is

that a significant difference exists favoring anastrozole for patients withdrawing from treatment because of side effects.

If you evaluate the totality of side effects, anastrozole does better. If you consider the issue of the gynecological symptoms leading to hysterectomy, I believe the new drug — anastrozole — has the better tolerability profile.

— Michael Baum, MD, ChM

Adjuvant endocrine therapy in postmenopausal women

Five major studies examining three different patient populations have reported

on aromatase inhibitors in the adjuvant setting. First are the studies of initial therapy comparing tamoxifen versus an aromatase inhibitor. This includes the ATAC trial with anastrozole and the BIG-01-98 trial with letrozole.

The sequential therapy trials examine patients who have been on adjuvant tamoxifen for two to three years and are then randomly assigned to continue tamoxifen or switch to an aromatase inhibitor. The three trials that have been reported are the Intergroup study with exemestane, the ARNO trial with anastrozole and a smaller study with anastrozole presented by Boccardo.

FIGURE 17

Adjuvant Endocrine Therapy in Women with Node-Positive, HER2-Positive Tumors

- Woman in average health
- 1.2-centimeter, Grade II tumor
- ER-positive, HER2-positive
- 3 positive nodes

What hormonal therapy, if any, would you most likely recommend?

	Age 55		Age 75	
Anastrozole	82%	69%	85%	74%
Exemestane	0%	2%	0%	2%
Letrozole	15%	8%	15%	12%
Tamoxifen	3%	20%	0%	12%
Would not recommend endocrine therapy	0%	1%	0%	0%

The extended endocrine therapy trial, MA17, evaluated patients who had taken tamoxifen for four-and-a-half to six years and were randomly assigned to no further endocrine therapy versus switching to letrozole.

It's important to point out that none of these strategies have been compared head-to-head, so we don't know whether it would be best to use aromatase inhibitors up front, after two to three years or after five years of tamoxifen. We also don't know the optimal duration of treatment with aromatase inhibitors.

However, the trend in all of these trials has been that women who received an aromatase inhibitor had a lower risk of disease recurrence than women who remained on tamoxifen or, as in MA17, received no further endocrine therapy. That led the ASCO technology assessment panel to recommend that postmenopausal women with hormone receptor-positive breast cancer should receive an aromatase inhibitor at some point in their treatment.

Despite the major questions that remain — including scheduling and duration of treatment — clearly, aromatase inhibitors have a role in treating postmenopausal women with breast cancer.

— Harold J Burstein MD, PhD

We have two studies using an aromatase inhibitor up front — ATAC with anastrozole and BIG 1-98 with letrozole; however, we have more data on anastrozole with more than five years of follow-up. There doesn't appear to be any difference, so far, in efficacy, so I would use anastrozole off study because of the toxicity profiles.

I believe that one should use an aromatase inhibitor after two to three years of tamoxifen because of the IES and ARNO/ABCSG data. The ARNO/ABCSG trial with anastrozole is a good study with 1,600 patients in each arm, and if you compare the data to the IES study, the agents are very similar in terms of efficacy. The hazard ratio for relapse-free survival in the IES study was 0.68 and in the ARNO study it was 0.59. I would utilize exemestane, but I believe these two agents are equivalent, and we now have data to support either anastrozole or exemestane after two or three years of tamoxifen.

After five years of tamoxifen, we have only the MA17 trial, so I believe letrozole should be used in this setting. However, if the cardiac concerns continue and they are confined to exemestane and letrozole, that may change my view.

— Anthony Howell, MD

The data from the ATAC trial and the BIG-FEMTA trial are very difficult to compare for a number of reasons. There are different numbers of patients with positive nodes in the two studies, and different percentages who received chemotherapy. Another point is that the BIG-FEMTA is a short-term analysis of data at the present time. For the core group, the followup is only 25.8 months, whereas the current data for anastrozole are beyond five years.

The other concern about the letrozole data is the high incidence of hypercholesterolemia and greater number of cardiac deaths, despite small numbers of events. We also saw excessive cardiac events with exemestane in the IES study.

The data from ATAC on cardiac events will be presented this year, but if letrozole is more potent — and I think it is — you may not want the most potent drug in the adjuvant setting, because it may have more adverse events. We clearly need longer-term data before we start using letrozole upfront for five years.

At this point, in terms of optimal hormonal therapy for ER-positive, postmenopausal patients, the current data indicate that for most women, anastrozole should probably be first line. I think we need more data on letrozole.

— J Michael Dixon, MD

It's very exciting that we've got lots of choices now in hormonal treatments and several categories of very active drugs with very good toxicity profiles. But it's confusing to know exactly what to do in terms of our postmenopausal, hormone-receptor-positive women. Should we start with an AI? Should we give tamoxifen for two years or five years, if we're giving it at all?

I do agree with the ASCO Tech Assessment that says that for the majority of postmenopausal, hormone receptor-positive women, at some point an adjuvant AI is absolutely indicated. But I'm not starting everybody, up front, on an AI.

If a patient has strongly ER/PR-positive, HER2-negative disease and no history of clotting, for example, and if she has osteoporosis or hyperlipidemia, I would probably start her on tamoxifen. Whereas if a patient has a PR-negative or HER2-positive tumor, settings where there's at least some hints that maybe the AI's are clearly superior, then I'm going to start the patient on an up-front AI. I still discuss both tamoxifen and the AIs with my patients.

— Julie Gralow, MD

In the past, adjuvant endocrine treatment in postmenopausal women was really easy, because everyone was treated with tamoxifen. Today the decision is fairly complicated because you need to consider individual patient issues and factors, like cost, risk for heart disease and strokes and risk of the disease itself.

A patient with a tiny node-negative cancer isn't going to derive much benefit from anastrozole compared to tamoxifen, whereas higher-risk patients with multiple positive nodes should probably be treated with an aromatase inhibitor from the beginning. Generally, that is my preference unless the patient is intolerant or refuses.

So I certainly would consider an aromatase inhibitor up front, and we have a choice of two now — anastrozole and letrozole — with the most data on anastrozole. Starting with an aromatase inhibitor is a proven treatment option, but it's not the only one. Another option

would be to treat with tamoxifen for a couple of years and then switch to an aromatase inhibitor. In US Oncology, we're about to reopen a trial investigating those two treatment options; an aromatase inhibitor from the beginning versus a couple of years of tamoxifen followed by an aromatase inhibitor. According to the ASCO tech assessment on aromatase inhibitors, both options are very reasonable.

The argument against initial treatment with tamoxifen and switching to an aromatase inhibitor is the chance you will lose patients between day one and year two by not putting them on an aromatase inhibitor. For the patients who relapse in the first six to 12 months, I don't believe the choice of endocrine treatment will make a difference. There is probably a point where it will begin to make a difference if you don't switch from tamoxifen to an aromatase inhibitor, which seems to be around two years.

— Stephen E Jones, MD

Management of premenopausal women to maintain fertility

For premenopausal women with ER-negative disease interested in preserving fertility, there is currently a study being run through SWOG evaluating whether or not ovarian suppression can protect ovarian function through chemotherapy. If the woman has ER-positive disease and is not a candidate for that study, I would talk to her about the availability of leuprolide acetate and the lack of data that it actually works, but that it might. I'd prefer to do it on study, but if a person wants everything, I'd say okay.

First and foremost though, I would think about the need for chemotherapy and how much the benefits for the cancer compare to the risks of becoming infertile. I would look at age and think about which treatment to give a patient.

I would lean more towards AC, certainly more than CMF, because oral cyclophosphamide-containing regimens are much more likely to cause people to go into premature menopause. I would also try to stay away from the longer regimens

with much more cyclophosphamide such as CEF or CAF compared to AC.

I also sometimes send patients to a reproductive endocrinologist, if it's something that's very important to them and/or they have a high likelihood of going through menopause with treatment.

— Ann Partridge, MD

We see many younger patients who wish to preserve their fertility, as we have a very active research program for embryo preservation prior to starting chemotherapy.

Our recommendation for patients in the adjuvant setting is very age-dependent. We generally recommend chemotherapy to most of our very young patients (30 or under), and we usually counsel them that the chemotherapy probably won't affect their fertility. We advise our patients who are 40 or over that the chemotherapy probably will affect their fertility. Generally, we speak to the women in the 30 to 40 range about our research program in embryo preservation prior to chemotherapy.

— Anne Moore, MD

Adjuvant endocrine therapy in premenopausal patients

In premenopausal patients, the endocrine therapy of choice for adjuvant therapy is still tamoxifen. In select high-risk patients — those very young patients with many positive nodes where chemotherapy has not rendered them menopausal, I do consider ovarian suppression.

If the chemotherapy has put the patient in limbo for a while, I would treat for a couple of years with tamoxifen, checking periodically to confirm — by low estradiol levels and high FSH levels — that they really are postmenopausal, then switch to an aromatase inhibitor.

In the higher-risk premenopausal patient, where I consider ovarian suppression, I would probably use an aromatase inhibitor along with ovarian suppression — although there is no data to support this approach. Two studies indicate that aromatase inhibitors are better than tamoxifen up front, so I'm going to pick one of those agents, and I would prob-

FIGURE 18

Aromatase Inhibitors with or without Ovarian Suppression in Premenopausal Patients

Have you prescribed aromatase inhibitors in premenopausal women with or without ovarian suppression/ablation (OSA)?

	Adjuvant setting		Metastatic setting	
No	37%	66%	10%	49%
Yes, alone	0%	4%	0%	8%
Yes, with OSA	63%	30%	90%	37%
Yes, both alone and with OSA	0%	0%	0%	6%

FIGURE 19

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)	70%	54%
Those who cannot tolerate tamoxifen due to side effects in the adjuvant setting	50%	49%
Those with multiple positive axillary nodes	47%	45%
Those with locally advanced disease	47%	41%

FIGURE 20

Adjuvant Endocrine Therapy for Premenopausal Women

- 35-year-old woman in average health
- 1.2-centimeter, Grade II tumor
- ER-positive, HER2-negative
- Nodal status varies

What hormonal therapy, if any, would you most likely recommend?

	Node-negative		1 positive node		10 positive nodes	
Tamoxifen	86%	73%	86%	59%	34%	43%
Aromatase inhibitor + LHRH agonist or ovarian ablation	7%	4%	7%	10%	33%	18%
Tamoxifen + LHRH agonist or ovarian ablation	7%	14%	7%	22%	33%	31%
LHRH agonist or ovarian ablation	0%	2%	0%	2%	0%	2%
Other endocrine therapy	0%	5%	0%	5%	0%	4%
Would not recommend endocrine therapy	0%	2%	0%	2%	0%	2%

FIGURE 21

Adjuvant Chemotherapy for Node-Positive Disease

- Woman in average health
- 1.2-centimeter, Grade II tumor
- ER-positive, HER2-negative
- 3 positive nodes

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

	Age 35		Age 55		Age 65		Age 75	
AC q3wk x 4	0%	3%	0%	4%	0%	7%	17%	11%
AC q2wk x 4 with growth factors	3%	4%	3%	4%	7%	2%	0%	2%
FAC or FEC x 6	0%	2%	0%	3%	0%	4%	0%	7%
AC x 4 followed by paclitaxel q3wk x 4	3%	7%	3%	8%	13%	13%	3%	7%
AC x 4 followed by paclitaxel q2wk x 4 with growth factors	64%	45%	64%	40%	61%	31%	37%	14%
AC q3wk x 4 followed by weekly paclitaxel x 12	0%	2%	0%	1%	3%	3%	3%	5%
AC x 4 followed by docetaxel x 4	3%	26%	3%	27%	0%	26%	0%	14%
CMF	0%	0%	0%	0%	0%	0%	3%	10%
TAC	24%	9%	24%	9%	13%	7%	7%	2%
Other	3%	2%	3%	2%	3%	2%	7%	2%
Would not recommend chemotherapy	0%	0%	0%	2%	0%	5%	23%	26%

ably go with anastrozole because there's more data.

— Stephen E Jones, MD

There is tremendous interest in the role of aromatase inhibitors with ovarian ablation or suppression in premenopausal women in the adjuvant setting. It is a very exciting possibility for the future, and I'm willing to put patients on clinical trials addressing this, but I am unwilling to apply this to clinical practice until I have some clarification on the true benefit and risk. We have no data on the ultimate effectiveness of that strategy, and we do know there is a significant price to be paid in terms of bone, based on Dr Gnant's data.

In premenopausal women, I tend to use tamoxifen alone for low-risk disease

and tamoxifen and chemotherapy for higher-risk disease. I will use ovarian suppression and tamoxifen for women who don't want chemotherapy and for those who continue to menstruate following chemotherapy.

— Generosa Grana, MD

Aromatase inhibitors are contraindicated in premenopausal women because they don't work in this population. Aromatase inhibitors suppress nonovarian sources of the aromatase enzyme and, if the woman has a functional ovarian reserve, then when exposed to an aromatase inhibitor, her ovary makes more aromatase enzyme to overcome that effect.

My colleagues at Dana-Farber and MD Anderson and I have been collecting a series of women who were premeno-

pausal when given aromatase inhibitors inappropriately. Typically, these are women who had chemotherapy-induced amenorrhea, began an aromatase inhibitor and then, anywhere from six to 36 months later, began to menstruate again, including one woman who became pregnant while on aromatase inhibitors. These agents are not at all appropriate for premenopausal women.

The importance of ovarian suppression in premenopausal patients is unknown and is not widely utilized in the United States. It's more commonly used in Europe. Some very important trials of ovarian suppression are ongoing, most notably the SOFT trial, which is a randomized study of tamoxifen alone versus tamoxifen plus ovarian suppression versus an aromatase inhibitor plus

FIGURE 22

Adjuvant Hormonal Therapy for Node-Positive Disease

Same case

Which hormonal therapy, if any, would you most likely recommend?

	Age 55		Age 65		Age 75	
	Breast Cancer Specialists	General Oncologists	Breast Cancer Specialists	General Oncologists	Breast Cancer Specialists	General Oncologists
Anastrozole	63%	66%	67%	76%	67%	75%
Exemestane	0%	1%	0%	2%	0%	2%
Letrozole	10%	7%	10%	7%	10%	9%
Tamoxifen	27%	21%	20%	14%	20%	14%
Other	0%	4%	0%	1%	0%	0%
Would not recommend endocrine therapy	0%	1%	0%	0%	0%	0%
Anastrozole, exemestane or letrozole	—	—	3%	—	3%	—

FIGURE 23

Use of Adjuvant Aromatase Inhibitors

When you use an aromatase inhibitor as initial adjuvant therapy, what percentage of this use is generally with each of the following agents?

Anastrozole	85%	84%
Letrozole	12%	14%
Exemestane	3%	2%

ovarian suppression as primary endocrine therapy for premenopausal women.

The SOFT trial is being conducted by the IBCSG, and I am involved in measuring the quality of life in that study. It's a very important trial that will define whether ovarian suppression is essential.

At the present time, tamoxifen is the standard for adjuvant therapy in premenopausal women. While the benefit of adding ovarian suppression is uncertain, it clearly accelerates side effects such as hot flashes, osteoporosis, vaginal dryness and sexual dysfunction.

— Harold J Burstein MD, PhD

For adjuvant systemic therapy in premenopausal women with early stage disease, we generally use tamoxifen alone or with chemotherapy. Sometimes we also use tamoxifen plus ovarian suppres-

sion instead of chemotherapy.

Part of this decision is related to patient preference. In a patient with low-risk disease for whom the chemotherapy is going to provide a very small benefit, I'm perfectly comfortable using ovarian suppression for two years as a substitute for chemotherapy.

— Anne Moore, MD

Chemotherapy for patients with node-positive disease

For patients with ER-positive disease and multiple nodes positive, I usually use AC with or without a taxane — often dose dense. As we learn more about the biology of these diseases and separate out the cancers by more than just ER-positive and ER-negative, I hope that we can give fewer people chemotherapy.

— Ann Partridge, MD

The situation sometimes arises in older patients with high-risk disease, in whom you may not want to utilize adjuvant chemotherapy. I received an email about an 83-year-old woman with an ER/PR-negative tumor and three positive nodes from a physician who felt a great deal of pressure to use chemotherapy. I think about the only thing that can happen there is a disaster. There are patients in whom the age and general condition just does not permit the use of adjuvant chemotherapy. In these patients, you've got to accept that and move on. Our first goal is to do no harm.

Having said that, adjuvant chemotherapy is an individual decision. I certainly have comfortably used chemotherapy in women up into their seventies. In these women, I'm much more likely, regardless of the nodal status, to use AC times four. AC → paclitaxel is also pretty well tolerated in the older group of women.

In younger women, we have a number of different choices for adjuvant chemotherapy. I am not a dose-dense person. We have one study demonstrating a fairly small difference, and in Don Berry's presentation in San Antonio, we saw that dose-dense therapy didn't seem to work in the ER-positive group. Almost all of the treatment effect was in the ER-nega-

FIGURE 24

Sequencing Aromatase Inhibitors after Tamoxifen

- 65-year-old woman in average health on tamoxifen x 2 years, tolerating tamoxifen as described below
- 1.2-centimeter, Grade II tumor
- ER-positive, HER2-negative
- 3 positive nodes

How would you manage this patient's therapy?

	Without severe side effects		Complains of 20 pound weight gain		Complains of moderate hot flashes refractory to nonhormonal therapy	
Continue tamoxifen	7%	45%	7%	17%	7%	16%
Stop tamoxifen and switch to anastrozole	15%	12%	25%	35%	24%	36%
Stop tamoxifen and switch to letrozole	8%	11%	8%	16%	10%	12%
Stop tamoxifen and switch to exemestane	70%	32%	70%	32%	59%	36%

tive subset. So in my practice, I wouldn't consider dose-dense chemotherapy in a patient with ER-positive disease.

I do think AC → docetaxel — the control arm in our current US Oncology study — is a very reasonable treatment that doesn't require growth factors. TAC would also be an option. TAC does require growth factors but has about the same treatment duration as dose-dense therapy, and I would use this regimen.

We also saw in San Antonio that FEC-docetaxel was significantly better than the standard six cycles of FEC. So this is also a very legitimate treatment option. In the higher risk patient, I would pick one of these regimens, and I tend to use AC → docetaxel.

— Stephen E Jones, MD

The simplest adjuvant chemotherapy regimen is AC or AC followed by paclitaxel. I'm a believer that dose-dense scheduling does have a role to play in terms of improving outcome. It's less toxic in terms of myelosuppression. It is more expensive, but that's the route I go. I haven't been using TAC. Nobody has any good evidence that TAC is better than AC followed by paclitaxel or AC followed by dose-dense paclitaxel.

— Charles L Loprinzi, MD

Switching from tamoxifen to aromatase inhibitors

Generally I believe postmenopausal patients with ER-positive disease on tamoxifen for several years would benefit from switching to an aromatase inhibitor. You have a choice of exemestane or anastrozole. It's difficult from the data at the present time to do a direct comparison between the two studies, but we can say that they're both effective.

After five years of tamoxifen, our view is that any patient, other than somebody with a Grade I node-negative breast cancer, would benefit from extended adjuvant treatment with letrozole. If a patient with high-risk disease has been off tamoxifen for a year or two, I would still consider switching to "delayed adjuvant" therapy with letrozole.

— J Michael Dixon, MD

In selecting an aromatase inhibitor, I consider the clinical setting and generally choose the agent that was studied in that setting. That was simple when we had data from just the ATAC, IES and MA17 trials. I would select anastrozole for up-front therapy, exemestane after two or three years and letrozole after five years of tamoxifen.

Of course, that was just an artifact of

the way the studies were designed and reported, and now we have other trials with data on different products in different settings, including the BIG-01-98 and ARNO trials. The data from these trials are incredibly similar to the data from the initial studies, so it may be a class effect and it may not matter which agent we choose.

— Harold J Burstein MD, PhD

At the two-year point, switching either to exemestane or anastrozole is an option, but I prefer exemestane, because the exemestane study is the most mature with the longest follow-up and a near survival difference.

For a patient who has received five years of tamoxifen, letrozole is the only drug studied, and I use it in women with node-positive and high-risk, node-negative disease, but I think the MA17 data has become a little fuzzier at this point in time because no survival difference was seen in women with node-negative disease.

With seven studies of adjuvant aromatase inhibitors, I believe oncologists will start mixing and matching, thinking there is a class effect and that these agents are all the same. I'm not sure that's necessarily true, and I still try to follow the data. However, if someone

FIGURE 25

Endocrine Therapy after Five Years of Tamoxifen

- 65-year-old woman in average health who has completed 5 years of tamoxifen
- 1.2-centimeter, Grade II tumor
- ER-positive, HER2-negative
- 3 positive nodes

How would you manage this patient's therapy at the following three time points?

	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	0%	0%	0%	0%	0%	0%
Start anastrozole	3%	16%	3%	14%	0%	4%
Start letrozole	97%	77%	84%	58%	40%	19%
Start exemestane	0%	1%	3%	0%	0%	0%
Use no further hormonal therapy	0%	6%	10%	28%	60%	77%

has intolerance to one of the aromatase inhibitors, I feel pretty comfortable switching them to another that they can tolerate.

— Stephen E Jones, MD

Based on the recent letrozole and exemestane data, the issue arises whether we should switch women to an aromatase inhibitor after either two to three years or four to five years of tamoxifen. At this point, the survival data is somewhat limited, but the disease-free survival data certainly favors that type of approach. The unknown, of course, is that neither of those large randomized trials had a control arm with an aromatase inhibitor alone. Therefore, I believe the question of whether tamoxifen adds anything to an aromatase inhibitor remains outstanding.

Nonetheless, if a woman who has started on tamoxifen gets into trouble, I don't hesitate to switch her over to an aromatase inhibitor unless there is an absolute contraindication. Even when women do fine on tamoxifen, after the second or third year, I will have a discussion with them to see whether they have an interest in switching over. I don't force that approach on them because these patients certainly could finish up five

years of tamoxifen, and by that time, we can anticipate having further discussion.

— Gary Lyman, MD, MPH

The data presented at ASCO and San Antonio support the concept that switching to an aromatase inhibitor rather than continuing tamoxifen is beneficial. I switch to either exemestane or anastrozole. I don't see any difference between the two when looking at the data. I would also consider switching to an aromatase inhibitor at one or four years of tamoxifen.

In terms of what to do at five years, I don't have a clear rule as to recommending post-tamoxifen letrozole.

— Generosa Grana, MD

If a patient has completed five years of adjuvant tamoxifen, I pull out the calculator and inform the patient what to expect from their breast cancer in the next 10 years, with and without letrozole. Then I discuss the pros and cons of therapy, and it's pretty easy to come to a decision.

I suspect most of these patients in my practice will opt for continued therapy, but it's somewhat age-dependent. We have some bright, "salt-of-the-earth" type

women here in the Midwest and they may be 78 years old and say, "Look, nobody's going to live forever — and I don't have a lot of funds, so let's not do it." I feel quite comfortable with that decision if there are a lot of competing causes of mortality, and it doesn't mean you can't always start an aromatase inhibitor if the patient develops recurrent disease.

— Charles L Loprinzi, MD

ER testing

We generally count any staining as ER-positive, but our pathologists will note if it is a low positive. You worry whenever you see low positives that the patient is not going to receive the same benefit as someone who has a high positive, even though it's not very well data-driven.

I will offer hormonal therapies to patients with low positive tumors, but will feel less comfortable with that as a mainstay, depending on the risk. Certainly, I'd be more inclined to add chemotherapy to hormonal therapy for a patient with node-positive disease or even one with node-negative disease if she had a big enough tumor or other high-risk features.

— Ann Partridge, MD

FIGURE 26

Determination of Estrogen Receptor Status

How do you define ER positivity?

Any staining	50%	24%
Staining above lab cut-off	47%	70%
Staining above individual cut-off value you determine	3%	6%

FIGURE 27

Monitoring and Maintaining Bone Density

In your postmenopausal patients receiving adjuvant aromatase inhibitors, do you routinely evaluate bone density?

Yes	97%	80%
No	3%	20%

In your postmenopausal patients receiving adjuvant aromatase inhibitors, do you generally use prophylactic bisphosphonates?

Yes	20%	39%
No	80%	61%

I rely on my pathology department to determine ER positivity, and I am willing to accept any ER positivity as positive, although I'm much more concerned with an ER positivity at one to five percent. At those levels I'm more likely to favor chemotherapy in addition to hormonal therapy.

— *Generosa Grana, MD*

Our institution pretty much still is basing our assessment on IHC assays. I don't have a firm threshold for treatment, but certainly anything under 10 percent is negative as far as I'm concerned.

Even for a patient with 10 to 30 percent cells staining positive, I will tell them, "You're technically positive, but I don't think I would rely on hormonal therapy alone, if there's any level of risk for the future."

There has been data, some of which was presented at San Antonio, clearly suggesting that perhaps we should take another look at quantitative ER and PR, particularly with regard to the rela-

tive value of the aromatase inhibitors compared to a SERM. We're not at that point at our institution, but I think if the data matures and suggests a benefit from quantitative measurements, we'll probably go back to either doing that or reporting both and discussing them with the patient.

— *Gary Lyman, MD, MPH*

Most pathology laboratories have their own criteria for defining ER positivity and, to varying degrees, may differentiate percentages. Most of them are using immunohistochemical stains nowadays, and, one to 10 percent is considered weakly positive. Greater than 10 percent staining at our institution is considered positive.

There's more and more information coming out to suggest that the degree of positivity may be important. This information seems like it has gone back and forth over the last 10 years. But effort has gone on to see if we can more routinely get different classifications of

positivity, from 10 percent on up to near 100 percent.

There's never an absolute in this business. Administering treatments such as hormonal therapy depend on a number of factors, including clinical presentation, but over 10 percent of cells staining is positive. If I have a patient with metastatic disease that's lung-only, the ER is weakly positive and there's no burning need for chemotherapy, it may well be reasonable to use hormone therapy. So I believe there are degrees of comfort in decision-making.

— *Charles L Loprinzi, MD*

Bone density monitoring and the aromatase inhibitors

I will generally steer a woman towards tamoxifen who comes to me with well-advanced bone demineralization, osteopenia or frank osteoporosis. However, for a woman without major problems, I will order a baseline bone density evaluation either before or within the first several months of starting her on an aromatase inhibitor. I then repeat those studies on an annual basis.

I do not use bisphosphonates for every woman I start on an aromatase inhibitor. The data clearly shows that most women don't need them and using them will add to the cost, morbidity, number of the visits and need for additional medication.

If clinically relevant changes begin to occur, I will discuss with the patient whether or not to add a bisphosphonate to try to stabilize or reverse some of the effects, or to make a change in the hormonal regimen.

— *Gary Lyman, MD, MPH*

Well before I used adjuvant aromatase inhibitors, I have taken it as my responsibility to monitor bone density. I have a much younger population of breast cancer patients who have been put through early menopause with chemotherapy. So ever since I started practice, it was my routine to make that part of my checklist with each follow-up.

FIGURE 28

Vasomotor Symptoms and Tamoxifen

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

Mean	30%	26%
------	-----	-----

FIGURE 29

Tamoxifen and Weight Gain

Do you believe that tamoxifen can cause weight gain?

Yes	40%	77%
No	50%	22%
Not sure	10%	1%

FIGURE 30

Tamoxifen and Weight Gain

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

Mean	27%	20%
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I truly haven't changed my practice with the use of AIs. All women who are postmenopausal at the end of their primary treatment receive a DEXA scan. Most commonly, I repeat the scan every two years, but in patients with low bone density, I'll do it after a year or so.

I'm not prophylactically starting patients on bisphosphonates if they're on an aromatase inhibitor, because not all women need it. I'm starting it if the bone density drops.

— Julie Gralow, MD

One of the major side effects of aromatase inhibitors is accelerated osteoporosis and risk of osteoporotic fracture; however, two important points need to be made. First, the risk of osteoporotic fractures is approximately 0.5 to one fracture per hundred women per year, which is roughly the difference in disease-free survival that most of the studies also show.

Secondly, we don't know what the

impact of these drugs will be on the bones 15 years from now. We have limited data for three to five years of follow-up in all these trials, and, for the most part, it's reasonably reassuring. However, remember that women who go through menopause in their early fifties lose a lot of bone rapidly, but they don't develop osteoporosis or osteoporotic fractures until their seventies. We have no data on what will happen 10 years after a 57-year-old woman begins taking an aromatase inhibitor, and we have to be respectful of that lack of data.

When I treat a women with aromatase inhibitors, I generally order a baseline bone mineral density study within the first two months of initiating therapy and then repeat it a year or two later. As for treatment, I follow the standard WHO guidelines as to when to begin therapy for osteoporosis, and osteopenia, and I generally use an oral bisphosphonate.

— Harold J Burstein MD, PhD

Tolerability and adherence with tamoxifen

Based on clinical trial data and my own experience, I believe there are fewer side effects with the aromatase inhibitors than tamoxifen. Certainly there is less concern about uterine and thromboembolic complications, and I have found that there are usually fewer complaints about hot flashes or the severity of the hot flashes from women on anastrozole. Approximately 10 percent of women will have enough difficulty from their hot flashes or other symptoms that they will not want to continue tamoxifen; however, the majority of women still do very well on it.

— Gary Lyman, MD, MPH

Adherence is such a complex thing, and it's going to become increasingly important in oncology because of the greater use of oral drugs. I did a study using an insurance and pharmacy database from New Jersey and Pennsylvania, looking at adherence with tamoxifen. The database predominantly contained patients who were on Medicare or Medicaid, so the old and the poor.

Adherence was actually better for women who were taking tamoxifen in their first year than most other chronic therapies. For most chronic therapies for conditions such as heart disease and hypertension, people take approximately 50 percent of their drug.

In our study, we found that overall adherence was a little over 80 percent, but that a substantial proportion, nearly 25 percent of our patients, took less than 80 percent per year. Some of this had to do with side effects, but the literature on adherence in oncology is kind of all over the place. Even with severe side effects, some people adhere while with minimal side effects others don't.

— Ann Partridge, MD

Systemic therapy for DCIS

We do not assess hormone receptor status for every patient with DCIS, but this is an evolving area. Generally, when a woman with a high-grade DCIS is

FIGURE 31

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	83%	58%
Occasionally	10%	25%
Never	7%	17%

FIGURE 32

Endocrine Therapy for DCIS

About what percentage of your patients with DCIS receive tamoxifen?

Percent who receive tamoxifen	46%	71%
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FIGURE 33

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	63%	40%
Have used an aromatase inhibitor in a patient with DCIS	0%	5%
Have used an aromatase inhibitor in a patient with DCIS but only in patients who have problems with or contraindications to tamoxifen	37%	55%

referred to me, I do try to obtain receptor status, and, if the receptors are positive, I will initiate a discussion about the potential benefit of tamoxifen in terms of delaying or preventing local recurrence with hormonal therapy.

Certainly, the ATAC trial and other data clearly shows that SERMs are not the only hormonal agents that reduce the risk of contralateral disease or second malignancies. Aromatase inhibitors do that and probably do it a bit better than tamoxifen. So if a woman with a high-grade DCIS is concerned about a local-regional recurrence or needing a full mastectomy, I will discuss the data and the possibility of starting adjuvant hormonal therapy. Outside of that type of situation, I don't use it routinely unless a woman is interested in chemoprevention.

— Gary Lyman, MD, MPH

DCIS is so stressful for patients, and these women have high levels of anxiety. In terms of systemic treatment, the only option available at this time is tamoxifen, based on the best data available from NSABP-B-24. I generally go through that with patients. If a person's had a mastectomy, then all they're doing is preventing a recurrence in their contralateral breast with tamoxifen. There really is no data that tamoxifen prevents systemic recurrences, because they are so rare. It probably does in a few people, but that's not the main reason to be treated. I usually talk to patients about it as a more local issue, because for the vast majority of women, their greatest risk is their local risk. So if they've had a mastectomy, I say, "Sure, you can take tamoxifen for that two-percent benefit in terms of prevention, but it also carries risks with it."

I check hormone receptor status and would not discuss tamoxifen with someone with hormone receptor-negative DCIS. The data reveals that it's not helpful, based on the subset from B-24. I do talk to a lot of women about tamoxifen, and I'd say about 50 to 60 percent of the patients I offer it to decide to take it.

Currently, the aromatase inhibitors are being studied for DCIS, but no data is available yet. Do I think it's probably going to show a benefit? Sure, but I wouldn't use them until the studies report a benefit.

— Ann Partridge, MD

For the DCIS population and those who come in with ductal hyperplasia with atypia, I do have a discussion about chemoprevention and will try to present all the issues, both pro and con. Since there is limited data at this point in terms of the aromatase inhibitors for chemoprevention, unless a woman has a contraindication or intolerance to a SERM, I would not use an aromatase inhibitor at this point. Do I think it's going to prove effective in that role? Probably. But for a woman who hasn't been treated for an invasive cancer, I'm much less willing to gamble with her bones than I would be for a woman who's at risk for recurrence of a true invasive breast cancer.

— Gary Lyman, MD, MPH

I use tamoxifen for patients who want endocrine therapy for DCIS. Based on data from the adjuvant setting, the NSABP is conducting a large trial to determine if there is a role for aromatase inhibitors in the treatment of DCIS, which I believe is a very reasonable study. The good news for patients with DCIS is that most women do very well. With the current surgical and radiation therapy techniques, the risk of recurrence is only five to 10 percent, and we can more or less cut that in half with tamoxifen. The challenge is, "Can we do much better than that?"

— Harold J Burstein MD, PhD

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EDITOR'S COMMENT

Selection of chemotherapy for metastatic disease is clearly related to prior adjuvant treatment and to the patient's age and performance status. Breast cancer specialists (BCS) more commonly use capecitabine and less commonly use docetaxel than community-based oncologists (CBO). In patients with symptomatic metastatic disease — particularly those who received prior anthracycline and taxane therapy — capecitabine and docetaxel is a preferred combination for all oncologists.

Nanoparticle paclitaxel became available just prior to the BCS survey. At the time of the survey, there was minimal clinical experience with this agent. However, based on available clinical data, BCS believe that this agent has a superior therapeutic ratio compared to docetaxel and cremophor-formulated paclitaxel.

FIGURE 34

Clinical Use of Serum Tumor Markers

How frequently do you use tumor markers in breast cancer patients with...

	Metastatic disease		Postadjuvant therapy (node-positive)	
	Breast Cancer Specialists	General Oncologists	Breast Cancer Specialists	General Oncologists
Commonly	63%	64%	23%	48%
Occasionally	20%	18%	10%	12%
Rarely	10%	8%	17%	16%
Never	7%	10%	50%	24%

Clinical use of tumor markers

I've found tumor markers to be helpful in cases where patients have metastatic disease that's not readily monitored, easily palpable or visible on chest x-ray. I'll often order markers on patients who require a bone scan, CT or MRI on a regular basis. This allows me to monitor their response to therapy a little more closely.

Obviously, if the markers are climbing in the face of therapy, then I'll step back and do the scans and try to see what's going on in more detail. Using markers allows me, on a treatment-by-treatment basis, to have a reasonably good idea of whether the patient's responding or progressing in between scans.

However, I try to discourage them in settings where I feel that they will not really help me with clinical monitoring.

I have to admit that I have had my arm twisted by patients, as most of us have, to do markers, even after informing them that they are not standard of care or recommended by most professional groups. Patients come in with a high level of anxiety, and I think you have to weigh the patient's psychology in your decision to do this.

For a patient with metastatic disease who is absolutely, over-the-barrel anxious and can't be convinced that markers aren't going to add to her care, I'm willing to do a set of them. If the marker is elevated and I've opened Pandora's box, then I am obligated at some interval to re-check them.

— Gary Lyman, MD, MPH

The ASCO guidelines do not recommend tumor markers in women with

node-positive disease after adjuvant therapy. While the use of markers can lead to an earlier diagnosis of metastatic disease, that doesn't improve survival, which is why the guidelines don't support their use.

However, patients often request them — especially women with high-risk disease — and I believe there is variability in their use in community practices.

— Joanne L Blum, MD

I am a true proponent of clinical observation, and I don't use tumor markers, except in patients who have metastatic disease. In node-negative, node-positive or locally advanced disease, I find that tumor markers give patients and physicians false reassurance.

When markers start to rise, there is alarm, often long before you can find evidence of disease recurrence on imaging studies. If the patient very badly wants tumor markers and they're willing to run

■ BREAST CANCER SPECIALISTS □ GENERAL ONCOLOGISTS

FIGURE 35

Chemotherapy for Asymptomatic Patients with Metastases: No Prior Chemotherapy

- ER-negative, HER2-negative
- No prior systemic therapy
- Rising tumor markers, **asymptomatic** bone mets

What is your usual 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	
Docetaxel	3%	16%	11%	16%	3%	16%	14%	17%	0%	10%	7%	15%
Paclitaxel	21%	17%	28%	9%	21%	18%	21%	8%	14%	19%	21%	8%
Capecitabine	42%	12%	28%	17%	42%	14%	28%	19%	59%	27%	24%	26%
Gemcitabine	0%	0%	3%	16%	0%	0%	3%	18%	0%	4%	10%	15%
Vinorelbine	0%	0%	14%	16%	0%	0%	18%	16%	3%	5%	21%	15%
Capecitabine + docetaxel	0%	6%	3%	5%	0%	4%	3%	4%	0%	1%	0%	2%
Carboplatin + taxane	3%	4%	0%	5%	3%	4%	0%	5%	0%	1%	0%	1%
AC	14%	15%	0%	8%	14%	15%	0%	5%	0%	6%	7%	2%
A + C + docetaxel	0%	14%	0%	0%	0%	13%	0%	0%	0%	3%	0%	0%
Other	10%	8%	6%	5%	10%	10%	6%	5%	10%	6%	3%	3%
No chemotherapy	7%	8%	7%	3%	7%	6%	7%	3%	14%	18%	7%	13%

the risk, then we do tumor markers. And we'll follow tumor markers every four to six months.

— Generosa Grana, MD

We don't use tumor markers to screen for metastatic cancer after adjuvant treatment. We give patients the ASCO guidelines about the follow-up of patients with early-stage breast cancer and explain that tumor markers really add nothing to their follow-up. Fewer and fewer patients are asking us to look at tumor markers, but when they do, I always tell them, "If you want me to do it, we'll do it."

If a patient has a symptom that we think might be metastatic breast cancer, we might order tumor markers, but we generally use them only if a woman has metastatic breast cancer to help us monitor response to therapy.

— Anne Moore, MD

When sequencing single agents, the agent I use depends on which drugs the patient has already received. For example, if a patient with minimal visceral disease has already been exposed to an anthracycline, experienced a long disease-free interval and received hormonal therapy for her metastatic disease, I would consider capecitabine for front-line chemotherapy. I might also consider a weekly taxane first-line.

In an older patient who doesn't want intravenous chemotherapy and doesn't want to lose her hair, I'll certainly consider capecitabine up front, even though it was originally FDA-approved for the anthracycline- and taxane-refractory population.

Capecitabine clearly has activity, is well tolerated and can be used for a long time. In addition, it's a good transitional agent to use when a patient is being

switched from hormonal therapy to chemotherapy — it's oral and patients don't have to come to the office for treatments. However, I might also use a weekly taxane first-line.

Second-line, I generally use either gemcitabine or vinorelbine. The sequence varies, and it often comes down to patient preference. Neither of those drugs causes alopecia, nor does doxorubicin HCL liposome injection. In multiple-line therapy, each of these agents has equivalent single-agent activity, and I don't believe the sequence makes any difference in terms of survival. I believe survival of patients with indolent disease is determined by the biology of their disease, not by which agent we select for second-, third-, fourth- or fifth-line therapy.

— Joanne L Blum, MD

FIGURE 36

Chemotherapy for Symptomatic Patients with Metastases: No Prior Chemotherapy

- ER-negative, HER2-negative
- No prior systemic therapy
- Bone and lung mets, **very symptomatic**

What is your usual 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	
Docetaxel	3%	4%	3%	15%	7%	7%	3%	15%	7%	15%	0%	18%
Paclitaxel	14%	2%	11%	8%	14%	3%	11%	10%	17%	15%	18%	8%
Capecitabine	3%	0%	31%	9%	3%	0%	31%	11%	28%	12%	28%	20%
Gemcitabine	0%	0%	3%	13%	0%	0%	3%	15%	0%	4%	7%	17%
Vinorelbine	0%	0%	11%	8%	0%	0%	11%	10%	7%	5%	7%	23%
Capecitabine + docetaxel	18%	15%	11%	9%	14%	14%	11%	5%	7%	12%	0%	4%
Carboplatin + taxane	14%	16%	3%	12%	14%	17%	3%	8%	3%	12%	7%	0%
AC	18%	23%	17%	8%	18%	22%	17%	9%	14%	15%	10%	3%
A + C + docetaxel	3%	30%	3%	1%	3%	27%	3%	1%	3%	6%	3%	0%
Other	27%	10%	7%	17%	27%	10%	7%	16%	14%	4%	17%	6%
No chemotherapy	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	3%	1%

Sequencing of chemotherapy in patients with metastatic disease

There is no set pattern for how to approach chemotherapy for patients with ER-negative, HER2-negative metastatic disease.

In the past, we saw patients who were chemotherapy-naïve, but we almost never do these days. Having “grown up” with and been involved in many different studies, I would probably still use AC in a patient who did not receive adjuvant chemotherapy — assuming she was otherwise healthy with no heart disease.

If she had a response, at some point, I’d stop the doxorubicin and give CMF until the disease progressed.

I would then go on to use paclitaxel, which I feel is probably somewhat better tolerated than docetaxel for very long-

term use. If the patient is sicker and needs a more rapid response, I would probably choose docetaxel.

Generally, I would then go to capecitabine. In older women or in those who are very concerned with hair loss, you could certainly make a good argument for starting with capecitabine. It’s a very active drug, as long as the right dose is utilized.

Somewhere along the line, I would also use vinorelbine, gemcitabine and — while I haven’t used it — irinotecan would be on the list now, because it has activity. Liposomal doxorubicin is also an option. We’ve done some studies with this agent, which is always sort of “looking for a home.” You’re going to end up using most of these drugs at one time or another in the treatment of metastatic disease.

In patients who have received adju-

vant AC or AC and a taxane, I would start further along in the sequence. If they’ve had AC → paclitaxel, then I might use docetaxel, and then go on to the other agents.

— Stephen E Jones, MD

Sequential single agents versus combination chemotherapy

The vast majority of the time, I use single agents in sequence because they are better tolerated. In a younger patient with fairly aggressive disease who wants to be more aggressive with her treatment, with a likelihood of having a somewhat higher response and possibly a survival advantage, and who is less concerned about the toxicity and side effects, I would certainly consider capecitabine/docetaxel.

I was involved in that study, and this

FIGURE 37

Chemotherapy for Asymptomatic Patients with Metastases: Prior AC → Paclitaxel

- ER-negative, HER2-negative
- Adjuvant AC → paclitaxel 2 years ago
- Rising tumor markers, asymptomatic bone mets

What is your usual 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	
Docetaxel	0%	29%	14%	14%	0%	29%	14%	14%	0%	15%	3%	12%
Paclitaxel	3%	8%	10%	4%	3%	8%	10%	4%	3%	6%	7%	3%
Capecitabine	84%	18%	0%	20%	88%	20%	0%	19%	81%	36%	7%	25%
Gemcitabine	0%	8%	24%	25%	0%	9%	21%	26%	0%	8%	28%	25%
Vinorelbine	0%	8%	39%	14%	0%	7%	45%	18%	3%	11%	42%	18%
Capecitabine + docetaxel	7%	11%	0%	3%	3%	9%	0%	2%	3%	3%	0%	2%
Carboplatin + taxane	0%	6%	0%	4%	0%	6%	0%	3%	0%	1%	0%	0%
Other	3%	5%	10%	12%	3%	5%	7%	10%	3%	3%	3%	1%
No chemotherapy	3%	7%	3%	4%	3%	7%	3%	4%	7%	17%	10%	14%

is a very active but fairly toxic regimen. Paclitaxel/carboplatin is pretty well tolerated, particularly on the weekly schedule. But for the most part, I use single agents.

— Stephen E Jones, MD

My standard first-line chemotherapy in a nonprotocol situation has been capecitabine. I've been impressed by that drug.

Most people have some hormone receptor positivity, and it's a nice switch to go from hormone pills to chemotherapy pills, as long as you watch the dose and watch for the hand-foot syndrome and diarrhea and have them discontinue therapy if they experience those toxicities before it gets too bad.

I do not use the package insert dose of capecitabine. I use 2,000 mg/m² per day or 1,000 mg/m² BID. The question arises: Do you escalate the dose? If they've had a nice response and they're tolerating it well, I might maintain the

dose or, occasionally, if they're in really good shape and have no toxicity at all, I'll go up a bit higher.

— Charles L Loprinzi, MD

We almost always use sequential single-agent therapy unless the patient is highly symptomatic. We like to start with the oral chemotherapy capecitabine. It's a very effective drug and patients who have been through adjuvant therapy prefer not to lose their hair or go back on an intravenous regimen.

— Anne Moore, MD

Effects of age on treatment

I try not to let age affect me with regard to treatment recommendations, because the issue is not so much age as it is comorbidities. The data is very solid on this, not only with regard to the benefit of chemotherapy, but also, to a large extent, the toxicity from chemotherapy.

Older women tend to have more complications with any kind of treatment

— surgery, radiation or chemotherapy — and may need more aggressive supportive care, particularly with regard to bone marrow function.

However, with appropriate supportive care, these women will respond just as well and the durations of response will be at least as long, if not longer. The toxicities will be manageable and generally not life threatening. So until we are talking about the extremes of age, the issue is more comorbidities.

If a woman has several comorbidities — diabetes, congestive heart failure, a previous stroke and so forth — that woman is at increased risk regardless of her age, and in that case age is just one more comorbidity to add to the bundle. So the bottom line for an otherwise healthy, active older woman who doesn't have major comorbidities is to treat her exactly as I would a younger patient with the same menopausal status.

With elderly patients, you get into issues of limited life expectancy and,

FIGURE 38

Chemotherapy for Symptomatic Patients with Metastases: Prior AC → Paclitaxel

- ER-negative, HER2-negative
- Adjuvant AC → paclitaxel 2 years ago
- Bone and lung mets, very symptomatic

What is your usual 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	
Docetaxel	3%	9%	3%	5%	3%	10%	7%	5%	0%	18%	7%	8%
Paclitaxel	0%	1%	0%	0%	0%	1%	0%	1%	0%	7%	3%	1%
Capecitabine	27%	1%	23%	16%	30%	1%	27%	17%	56%	17%	17%	29%
Gemcitabine	0%	6%	27%	29%	0%	6%	23%	31%	0%	15%	27%	29%
Vinorelbine	0%	0%	27%	22%	0%	0%	26%	21%	7%	8%	27%	22%
Capecitabine + docetaxel	47%	41%	0%	9%	41%	41%	0%	7%	17%	17%	0%	4%
Carboplatin + taxane	10%	24%	0%	2%	13%	24%	0%	4%	7%	9%	0%	0%
Other	13%	18%	20%	17%	13%	17%	17%	14%	13%	9%	16%	6%
No chemotherapy	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	3%	1%

particularly if they're asymptomatic, that they're much more likely to die of other problems related to aging. Why add another toxicity, visits to the hospital and a lot of expense, some of which is going to come out of their pocket? For a woman who comes in with symptomatic breast cancer that we would otherwise feel urgently needed to be treated, I will treat. Unless the comorbidities are so imposing and forbidding, I will treat her and use aggressive supportive care to get her through it. She deserves the same opportunity for disease control and longevity as a younger patient.

— Gary Lyman, MD, MPH

My choice of chemotherapy is not determined by the patient's age, but rather the patients' overall health and any comorbid conditions. A 75-year-old person with no comorbid health problems can tolerate chemotherapy almost as well as a much younger patient. On the other hand, if an elderly patient has significant comor-

bid health problems, that will impact my selection of therapy.

Renal function is an important consideration, and drugs often have to be adjusted accordingly. The dose of capecitabine has to be adjusted for renal function, particularly in the elderly, and hepatic function is critical when considering a taxane or drugs like vinorelbine.

Transportation can also be an issue in selecting therapies. Some patients who live far away or don't have transportation on a weekly basis may need to receive treatment every three weeks instead. In such cases, transportation may influence the treatment schedule as opposed to which agent is selected.

— Joanne L Blum, MD

Use of nanoparticle paclitaxel

I believe many physicians will now at least consider using nanoparticle paclitaxel where they are currently using paclitaxel. While it does result in neurotoxicity, it is generally very well tolerated with

fewer side effects, doesn't require special tubing or premedication and is a relatively short infusion compared to standard paclitaxel. We have some data on the weekly schedule, which is also very well tolerated.

I believe many of us will probably use nanoparticle paclitaxel in place of paclitaxel in the palliative setting, where it was studied. It has not been compared to docetaxel. So if your choice is docetaxel, because you want to be a little more aggressive to get somebody into remission or whatever the particular reason you're picking docetaxel, I wouldn't substitute nanoparticle paclitaxel because we do not have data.

— Stephen E Jones, MD

Most of my experience with nanoparticle paclitaxel has been on protocol; we've presented data on two cohorts of patients. At ASCO 2004, we presented data on 106 patients with taxane-refractory disease who received 100 mg/m²

FIGURE 39

Chemotherapy for Asymptomatic Patients with Metastases: Prior AC

- *ER-negative, HER2-negative*
- **Adjuvant AC 2 years ago**
- *Rising tumor markers, asymptomatic bone mets*

What is your usual 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	
Docetaxel	10%	30%	3%	10%	10%	30%	3%	12%	3%	18%	3%	15%
Paclitaxel	25%	28%	22%	9%	21%	29%	29%	8%	24%	22%	21%	9%
Capecitabine	42%	6%	42%	26%	46%	7%	35%	28%	46%	28%	39%	29%
Gemcitabine	0%	0%	10%	24%	0%	0%	10%	22%	0%	6%	10%	20%
Vinorelbine	0%	2%	14%	15%	0%	2%	14%	12%	3%	5%	14%	14%
Capecitabine + docetaxel	3%	11%	3%	5%	3%	11%	3%	4%	0%	1%	3%	2%
Carboplatin + taxane	3%	7%	0%	2%	3%	6%	0%	4%	0%	1%	0%	0%
Other	10%	9%	3%	6%	10%	7%	3%	7%	10%	2%	0%	1%
No chemotherapy	7%	7%	3%	3%	7%	8%	3%	3%	14%	17%	10%	10%

weekly, three weeks on, one week off. We saw a stable disease rate of 15 percent and a response rate of 15 percent, with very acceptable tolerability and safety data. At San Antonio, we presented the second phase of the study with 75 patients who received 125 mg/m² weekly, three weeks on, one week off. The data was comparable in efficacy and tolerability, although there was a little more sensory neuropathy with the higher dose. Edith Perez will be presenting survival data from her Phase III at the 2005 Miami meeting.

Nanoparticle paclitaxel received FDA approval in January 2005, and I've just started a few patients on it, so I can't speak to responses in patients off protocol. The data demonstrated that nanoparticle paclitaxel is a superior drug compared to paclitaxel. It's safer and patients don't experience hypersensitivity reactions. I believe it will eventually replace paclitaxel. From a taxane-refractory perspective, it clearly has benefit.

Nanoparticle paclitaxel is current-

ly being studied in combination with other agents. We don't have any safety data yet on it in combination, although we probably can extrapolate from our experience with paclitaxel. In addition, we can examine our taxane-refractory nanoparticle paclitaxel data.

Memorial Sloan-Kettering has an active study evaluating nanoparticle paclitaxel combined with trastuzumab and carboplatin, and Edith Perez has a study examining capecitabine and nanoparticle paclitaxel, but to date no data has been presented or published on combination therapy with this agent.

Other trials are underway as well, evaluating different doses and different schedules with nanoparticle paclitaxel. We're also moving it to the adjuvant setting, and we're planning a large clinical trial with dose-dense nanoparticle paclitaxel. It'll also be studied in other tumors, and we'll learn the role of this new agent in medical oncology. I believe it's an improvement in treatment because the drug has proven to be beneficial,

patients do not have to take steroids and they don't run the risk of hypersensitivity reactions.

— Joanne L Blum, MD

The pivotal trial of nanoparticle paclitaxel in anthracycline-pretreated patients showed it to be as efficacious as docetaxel in terms of response rates. The Phase III trial demonstrated superior efficacy of nanoparticle paclitaxel 260 mg/m² over paclitaxel 175 mg/m² in terms of response rate and time to progression.

I believe in the next few years 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/m² for three weeks, followed by one week off, as in Joanne Blum's study.

I have treated several patients with this agent and found it to be extremely well tolerated, particularly at the 100mg/m² dose. I don't premedicate patients

FIGURE 40

Chemotherapy for Symptomatic Patients with Metastases: Prior AC

- *ER-negative, HER2-negative*
- **Adjuvant AC 2 years ago**
- *Bone and lung mets, very symptomatic*

What is your usual 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	
Docetaxel	7%	12%	10%	9%	7%	13%	10%	7%	10%	21%	11%	14%
Paclitaxel	14%	9%	0%	5%	17%	9%	0%	4%	18%	22%	3%	2%
Capecitabine	7%	1%	39%	15%	7%	1%	42%	14%	25%	14%	46%	32%
Gemcitabine	0%	0%	18%	25%	0%	0%	14%	30%	0%	8%	10%	25%
Vinorelbine	0%	0%	14%	21%	0%	0%	14%	20%	3%	4%	15%	21%
Capecitabine + docetaxel	31%	28%	3%	11%	31%	32%	3%	10%	14%	14%	0%	1%
Carboplatin + taxane	24%	34%	3%	4%	21%	30%	3%	5%	10%	14%	3%	0%
AC + docetaxel	0%	5%	3%	0%	0%	3%	3%	0%	0%	0%	3%	0%
Other	17%	10%	10%	10%	17%	11%	11%	10%	20%	2%	6%	4%
No chemotherapy	0%	1%	0%	0%	0%	1%	0%	0%	0%	1%	3%	1%

receiving nanoparticle paclitaxel, because patients do not have problems with hypersensitivity reactions. I find weekly dexamethasone is not well tolerated by patients — it tires them and has a crash effect. Avoiding premedication may be one of the reasons we don't see significant side effects with the nanoparticle paclitaxel.

— Joyce O'Shaughnessy, MD

Nanoparticle paclitaxel is an exciting drug. It's a product of good pre-clinical work. Now we have a solid Phase III study and two very interesting Phase II studies. I have looked at the data very carefully and discussed it with investigators, and I'm very enthusiastic about helping with future development of this drug and introducing it into our clinical practice.

In the past, in a nonprotocol setting for a patient who is taxane-naïve, we have been using paclitaxel and, on some occa-

sions, docetaxel once every three weeks. But currently, nanoparticle paclitaxel really has to be considered.

The challenge is that we don't have comparative trials right now of nanoparticle paclitaxel every three weeks versus paclitaxel weekly or of nanoparticle paclitaxel every three weeks versus docetaxel every three weeks. We have different studies showing efficacy, but we lack these head-to-head comparisons of what we think might be the two best approaches with the older taxanes versus nanoparticle paclitaxel.

In this setting, tolerability is paramount to me. Based on the randomized Phase III trial that has been reported, nanoparticle paclitaxel really has a lot of advantages. I'm hesitant to say it is the only taxane I'm going to use, because I think we need more studies. But I don't think we should wait completely and not use the drug for five years. We really need to start discussing the availability

of these agents with all of our patients with metastatic breast cancer.

The nonprotocol situation, patients who have received prior taxane therapy are the perfect patient population to consider for nanoparticle paclitaxel, again, based on the Phase II studies that have been reported to date.

The natural question is: What about the adjuvant setting? It's very tempting to think about moving nanoparticle paclitaxel into the adjuvant setting, but it's a pity that we don't have any data. I hope there will be clinical trials to further explore the optimal way to use this agent. Our cooperative group has not started any trials with nanoparticle paclitaxel in the adjuvant setting, but I'm aware that other groups are developing trials at this time, and I am very supportive of those ideas.

— Edith A Perez, MD

We look forward to nanoparticle

FIGURE 41

Use of Nanoparticle Paclitaxel

** Have you used nanoparticle paclitaxel? Please include on or off protocol use.*

Percent of breast cancer specialists responding yes	33%
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** Note that nanoparticle paclitaxel was not FDA approved at the time of the general oncologist survey.*

FIGURE 42

*** Impression of Nanoparticle Paclitaxel Compared to Paclitaxel and Docetaxel**

What is your impression of the side effects and tolerability of nanoparticle paclitaxel compared to paclitaxel?

Nanoparticle paclitaxel significantly better than paclitaxel	24%
Nanoparticle paclitaxel somewhat better than paclitaxel	55%
Nanoparticle paclitaxel equal to paclitaxel	21%
Nanoparticle paclitaxel somewhat worse than paclitaxel	0%
Nanoparticle paclitaxel significantly worse than paclitaxel	0%

What is your impression of the efficacy/antitumor effect of nanoparticle paclitaxel compared to paclitaxel?

Nanoparticle paclitaxel significantly better than paclitaxel	13%
Nanoparticle paclitaxel somewhat better than paclitaxel	50%
Nanoparticle paclitaxel equal to paclitaxel	37%
Nanoparticle paclitaxel somewhat worse than paclitaxel	0%
Nanoparticle paclitaxel significantly worse than paclitaxel	0%

What is your impression of the side effects and tolerability of nanoparticle paclitaxel compared to docetaxel?

Nanoparticle paclitaxel significantly better than docetaxel	30%
Nanoparticle paclitaxel somewhat better than docetaxel	63%
Nanoparticle paclitaxel equal to docetaxel	7%
Nanoparticle paclitaxel somewhat worse than docetaxel	0%
Nanoparticle paclitaxel significantly worse than docetaxel	0%

What is your impression of the efficacy/antitumor effect of nanoparticle paclitaxel compared to docetaxel?

Nanoparticle paclitaxel significantly better than docetaxel	0%
Nanoparticle paclitaxel somewhat better than docetaxel	24%
Nanoparticle paclitaxel equal to docetaxel	68%
Nanoparticle paclitaxel somewhat worse than docetaxel	8%
Nanoparticle paclitaxel significantly worse than docetaxel	0%

** Note that nanoparticle paclitaxel was not FDA approved at the time of the general oncologist survey.*

paclitaxel. The advantages are the short infusion time and lack of allergic response. We have no experience yet, but in metastatic disease, as soon as it's really available, I believe we'll be using it.

I also believe the oncology community will embrace it, because we can take a patient who currently spends up to three or four hours of infusion time and administer something that takes a half an hour. That's very appealing, not only for the patient, but for the doctors who are trying to get patients in and out.

I wouldn't use it now in the adjuvant setting without data, but I would certainly enter a patient into any available trials.

— Anne Moore, MD

I am thinking of integrating nanoparticle paclitaxel into my practice. I actually treated my first patient with it recently. She had a very poor performance status, had not received chemotherapy and was very symptomatic from her disease. My thinking was to use single-agent paclitaxel or docetaxel, and I chose to use single-agent nanoparticle paclitaxel given on a weekly schedule, because I think the data is very good and the toxicity manageable.

I think that the general oncology community will rapidly accept this agent for a variety of reasons. First, it can be given every three weeks or weekly and the data is good for both. Number two, I think the toxicity profile is favorable. The neuropathy is reversible, the infusion is briefer and there are none of the allergic reactions to the cremophor — all of which are appealing when considering utilizing it.

I am looking forward to those trials that will address the use of nanoparticle paclitaxel in the adjuvant setting, because ultimately we have a drug that appears to be more active than paclitaxel, which has been our mainstay taxane in that setting, and it would be interesting to think that this would give us additional benefit.

— Generosa Grana, MD

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EDITOR'S COMMENT

The rapid, recent acceptance of aromatase inhibitors as adjuvant therapy for postmenopausal women with receptor-positive tumors also means that a new subset of patients will be presenting with recurrent disease with this prior therapy. Both researchers and community oncologists are choosing between tamoxifen, exemestane and fulvestrant in this situation. Overall, there is considerable heterogeneity in virtually all clinical situations where endocrine therapy is used for metastatic disease, reflecting uncertainty about the optimal sequence of agents.

FIGURE 43

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	59%	38%	14%	7%	17%	16%	7%	8%
Letrozole	3%	16%	17%	9%	7%	6%	3%	8%
Exemestane	17%	22%	21%	31%	35%	17%	18%	8%
Fulvestrant	21%	22%	41%	43%	34%	23%	3%	7%
Megestrol acetate	0%	1%	0%	6%	0%	20%	59%	26%
High-dose estrogen	0%	0%	7%	0%	7%	2%	7%	6%
Other	0%	1%	0%	0%	0%	2%	0%	4%
No endocrine therapy	0%	0%	0%	4%	0%	14%	3%	33%

Endocrine therapy for patients presenting de novo with metastatic disease

My goal is to keep a woman on hormonal therapy as long as possible, because quality of life is clearly superior to what it is with chemotherapy. If the patient is hormone therapy naïve, I tend to begin with an aromatase inhibitor, either anastrozole or letrozole. At the time of progression, I often go to tamoxifen and then sequence in exemestane and fulvestrant. If the patient has had tamoxifen, then I go with my nonsteroidal aromatase inhibitor, and then either sequence in fulvestrant or exemestane.

We are participating in several trials that are looking at a loading dose of fulvestrant versus the standard monthly dose. I think it'll be very interesting to see whether that drug will act differently

as the dosing schedule is altered.

— *Generosa Grana, MD*

We rarely see patients present de novo with metastatic disease. If such a patient does present and they are postmenopausal with ER/PR-positive disease, then I use an aromatase inhibitor based on the current data of increased efficacy when compared with tamoxifen.

— *Joanne L Blum, MD*

Endocrine therapy for postmenopausal women after adjuvant tamoxifen

Generally, patients are either going to relapse on tamoxifen or after adjuvant tamoxifen. In that setting as well as in the fulvestrant versus anastrozole clinical trials, there is evidence that a proportion of women have a longer response

to fulvestrant than to anastrozole when given right after tamoxifen. I have had patients with very long responses to fulvestrant.

I prefer fulvestrant to an aromatase inhibitor after tamoxifen, because approximately 20 percent of patients have very long responses with it in this setting. However, 99 percent of oncologists will choose an aromatase inhibitor after tamoxifen. Fulvestrant is generally being used as third-line.

Despite Trials 20 and 21, most physicians start with anastrozole rather than fulvestrant because of the way the data have been presented. The North American trial data indicates that there was a longer duration of response with fulvestrant; however, the vast majority of oncologists believe fulvestrant and anastrozole are equivalent agents.

For the last decade, most oncologists

FIGURE 44

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?** (check one in each column)*

	1st-line		2nd-line		3rd-line		4th-line	
Tamoxifen	0%	2%	20%	3%	23%	3%	21%	9%
Anastrozole	24%	44%	0%	6%	0%	1%	0%	2%
Letrozole	70%	49%	0%	11%	0%	4%	7%	5%
Exemestane	0%	3%	27%	38%	27%	34%	31%	5%
Fulvestrant	3%	2%	50%	38%	40%	39%	7%	13%
Megestrol acetate	0%	0%	0%	2%	7%	9%	20%	37%
High-dose estrogen	0%	0%	3%	0%	3%	3%	7%	5%
Anastrozole, exemestane or letrozole	3%	—	—	—	—	—	—	—
Other	0%	0%	0%	0%	0%	1%	0%	2%
No endocrine therapy	0%	0%	0%	2%	0%	6%	7%	22%

FIGURE 45

Sequencing Endocrine Therapy in Hormonal Therapy-Naïve Patients with Metastases

*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	3%	19%	60%	27%	13%	8%	17%	13%
Anastrozole	20%	42%	3%	13%	0%	5%	0%	0%
Letrozole	74%	36%	0%	13%	0%	8%	3%	3%
Exemestane	0%	3%	17%	27%	30%	23%	30%	16%
Fulvestrant	0%	0%	17%	18%	54%	48%	30%	26%
Megestrol acetate	0%	0%	0%	0%	0%	4%	10%	24%
High-dose estrogen	0%	0%	3%	0%	3%	1%	7%	2%
Anastrozole, exemestane or letrozole	3%	—	—	—	—	—	—	—
Other	0%	0%	0%	1%	0%	0%	0%	2%
No endocrine therapy	0%	0%	0%	1%	0%	3%	3%	14%

have started patients on an aromatase inhibitor — which works. It is hard to argue with something that works. Furthermore, the dose and schedule of fulvestrant is not fully worked out and is under investigation. In fact, some of the

current trials of fulvestrant involve three different dosing schedules.

Deciding between fulvestrant and an aromatase inhibitor is also a financial issue. Exemestane, which has 20 percent activity third line, is probably fairly

equivalent to fulvestrant. But if a patient doesn't have prescription drug coverage, a monthly injection of fulvestrant might be more economically appealing than paying \$200 to \$250 for the aromatase inhibitor.

FIGURE 46

Hormonal Therapy after Progression on Adjuvant Tamoxifen: Asymptomatic Patients

- ER-positive, HER2-negative
- On adjuvant tamoxifen x 4 years
- **Rising tumor markers, asymptomatic bone mets**

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 57				Age 75			
	1st-line		2nd-line		1st-line		2nd-line	
Anastrozole	14%	46%	0%	9%	14%	45%	0%	8%
Exemestane	0%	7%	24%	30%	0%	6%	24%	28%
Letrozole	73%	37%	3%	7%	70%	39%	7%	6%
Fulvestrant	3%	4%	63%	47%	3%	6%	55%	51%
Other	7%	4%	3%	4%	6%	2%	7%	4%
No endocrine therapy	3%	2%	7%	3%	7%	2%	7%	3%

So in selecting an endocrine agent for a postmenopausal patient, I generally start with fulvestrant and then switch to letrozole or exemestane. From there, I continue to utilize every available endocrine agent until I'm absolutely convinced that the disease is hormone-resistant and there is no further benefit to endocrine therapy.

— Stephen E Jones, MD

Endocrine therapy for postmenopausal women after adjuvant anastrozole

Previously, patients received tamoxifen in the adjuvant setting, so we would use an aromatase inhibitor front-line in the metastatic setting. Fulvestrant was used second-line, or we could use megestrol acetate, but for many women fulvestrant has a more convenient side effect profile.

Now that more women receive aromatase inhibitors in the adjuvant setting, we're using tamoxifen or fulvestrant as first-line treatment in the metastatic setting.

While I do use fulvestrant, I confess that because of the convenience of oral hormonal therapies, I generally use an aromatase inhibitor or tamoxifen before

fulvestrant, but fulvestrant is clearly a reasonable drug to utilize in this setting.

— Harold J Burstein MD, PhD

We are just beginning to see patients who have been treated with two or three years of adjuvant anastrozole and then relapsed. Currently, there is very little data on treatment options in this setting. It's kind of a "dealer's choice" because there are no hard-and-fast rules.

There are multiple options including fulvestrant, exemestane and even tamoxifen — if the patient hasn't seen it — because it's obviously still a very useful drug. So the sequence is going to be all over the map for most folks.

— Stephen E Jones, MD

In a patient who has completed five years of adjuvant anastrozole, I use exemestane or fulvestrant. In my experience, patients tolerate the fulvestrant injections just fine. We have randomized data comparing fulvestrant versus anastrozole in patients who have already received tamoxifen, but the optimal sequence for using fulvestrant is still undetermined.

In choosing between exemestane and fulvestrant, I ask my patients whether they prefer an injection or a pill. If they have transportation problems, then I use

an oral agent. However, for the Medicare population, these drugs are very expensive. If the patient does not have adequate insurance coverage and can't afford them, then a monthly injection may be better. Compliance is also an issue to be considered when choosing between a daily oral agent and a monthly injection.

— Joanne L Blum, MD

I think fulvestrant is a great alternative for patients with hormone receptor-positive metastatic breast cancer. Personally, I tend to use it as second- or third-line hormonal treatment. Not that I know that it's worse or better than the other drugs, but more because it came last.

— Ann Partridge, MD

Most clinicians consider fulvestrant a third-line therapy for patients who have failed tamoxifen and an aromatase inhibitor; however, clinical trials have shown fulvestrant is equivalent to anastrozole after tamoxifen failure. In a recently published European study comparing front-line fulvestrant versus tamoxifen, I did not view fulvestrant as inferior.

In addition, a Phase III study is underway comparing fulvestrant to exemestane for second-line therapy. I do use third-line fulvestrant, but I will use it first-line,

FIGURE 47

Approach to Therapy in Symptomatic Patients with ER-Positive Disease

- ER-positive, HER2-negative
- On adjuvant tamoxifen x 4 years
- **Bone and lung mets, symptomatic**

Which general approach to therapy would you take in selecting treatment for each of these patients?

	Age 40 (premenopausal)		Age 57		Age 75	
Chemotherapy alone	0%	26%	0%	18%	0%	12%
Chemotherapy until disease stabilization, then hormone therapy "maintenance"	67%	71%	67%	76%	27%	61%
Hormone therapy alone	33%	3%	33%	6%	73%	27%

FIGURE 48

Hormonal Therapy after Progression on Adjuvant Tamoxifen: Symptomatic Patients

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 57				Age 75			
	1st-line		2nd-line		1st-line		2nd-line	
Anastrozole	18%	45%	3%	2%	21%	45%	3%	4%
Exemestane	0%	5%	28%	38%	0%	7%	32%	32%
Letrozole	71%	46%	3%	6%	70%	42%	3%	8%
Fulvestrant	4%	3%	52%	49%	3%	5%	56%	52%
Anastrozole, exemestane or letrozole	—	—	—	—	3%	—	—	—
Other	0%	3%	3%	4%	0%	1%	3%	3%
No endocrine therapy	7%	0%	11%	1%	3%	0%	3%	1%

particularly in women who can't afford an aromatase inhibitor. In addition, I would estimate that approximately 40 percent of my patients prefer a monthly injection to taking a pill every day.

— Adam M Brufsky, MD, PhD

Use of fulvestrant in premenopausal women

I only utilize fulvestrant in premenopausal patients in conjunction with ovarian suppression. Particularly in the metastatic setting, we find that many patients will opt for an oophorectomy after ovarian suppression, and then we can treat

them as postmenopausal.

— Stephen E Jones, MD

Management of symptomatic patients with ER-positive disease

Managing patients with ER-positive metastatic disease really depends on the symptoms. If the patient just has bone disease, I'm very likely to go with hormonal therapy, period, and control the bone pain. On the other hand, if she has extensive liver or lung metastases, I'm likely to use chemotherapy until disease

stabilization and then bring the patient back to an aromatase inhibitor.

— Generosa Grana, MD

For a patient who has a pretty good amount of disease, chemotherapy is reasonable to recommend. The question comes up: Do you use chemotherapy alone in that scenario or do you combine it with hormonal therapy?

I think you have two opposing thought processes here. One is, if you go back to the olden days, 15 or 20 years ago, when they were looking at chemohormonal therapy versus chemotherapy or hormone therapy alone, the end result of

FIGURE 49

Hormonal Therapy after Progression on Anastrozole: Asymptomatic Patients

- ER-positive, HER2-negative
- On adjuvant anastrozole x 4 years
- Rising tumor markers, asymptomatic bone mets

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 57				Age 75			
	1st-line		2nd-line		1st-line		2nd-line	
Exemestane	14%	31%	35%	22%	14%	35%	38%	18%
Letrozole	0%	13%	0%	2%	0%	13%	0%	5%
Tamoxifen	55%	28%	10%	7%	52%	26%	10%	6%
Fulvestrant	28%	22%	52%	55%	31%	22%	52%	59%
Other	0%	5%	3%	7%	0%	3%	0%	5%
No endocrine therapy	3%	1%	0%	7%	3%	1%	0%	7%

using them together versus playing them out made no difference in survival.

But there was a higher response rate if you used them both together. So from that scenario, if you really need to get a response, going with chemotherapy combined with hormonal therapy makes sense. However, if you take into account Kathy Albain’s adjuvant data reporting that it’s best to give tamoxifen after the CAF, you could decide to separate the chemotherapy and the hormonal therapy.

I am not opposed to using them both together and would tend to do so. I would give the chemotherapy for two-six cycles, depending on how things were going and then stop it and stay with the hormonal therapy alone.

— Charles L Loprinzi, MD

Side effects and tolerability of fulvestrant

We have not had any problems administering fulvestrant injections. The newer double-doses being investigated for loading doses will require injecting five milliliters in each buttock, which may be an issue. It is a slow injection and the nurses just have to take their time. Most

patients really don’t have any problem.

The side-effect profile of fulvestrant is very benign — few menopausal symptoms and less chance of arthralgias than with aromatase inhibitors. Unlike tamoxifen, fulvestrant is not associated with a higher rate of thromboembolic side effects.

— Stephen E Jones, MD

I haven’t seen too many complaints with fulvestrant, but quite frankly most of these patients have been through so much by the time they get to fulvestrant, they’re not big complainers. They’re usually happy to be off chemotherapy. I know fulvestrant can cause hot flashes and menopausal symptoms, but I haven’t seen a whole lot of that. I have not used fulvestrant in a first-line setting yet.

— Ann Partridge, MD

My patients have tolerated the fulvestrant injections beautifully. They like the fact that they’re coming to the office only once a month. I keep asking them if they’re having significant injection site reactions, and I have not had any significant complaints.

Even the women who are on the loading dose, where they get two injections

as part of a study, really have not had significant complaints.

— Generosa Grana, MD

Oral versus parenteral endocrine therapy for metastatic disease

I believe most patients, if they think the impact is same in terms of controlling their cancer and producing a response, will almost always opt for a pill. There are some specific ancillary situations where I think parenteral therapy has additional advantages to a woman who is paying for her pills out of pocket and doesn’t have to pay for an injection, one who has real compliance issues or one who can’t get back and forth for to the pharmacy to get refills.

However, if I mention that there are oral agents available, women will almost always jump at that opportunity. If they don’t tolerate the oral agents or the disease progresses, certainly, I will consider falling back on parenteral therapy, but up front, I generally go to an oral agent as my first hormonal manipulation in the metastatic setting.

— Gary Lyman, MD, MPH

FIGURE 50

Approach to Therapy in Symptomatic ER-Positive Metastatic Disease

- ER-positive, HER2-negative
- On adjuvant anastrozole x 4 years
- Bone and lung mets, very symptomatic

Which general approach to therapy would you take in selecting treatment for each of these patients?

	Age 57		Age 75	
Chemotherapy alone	10%	18%	7%	11%
Chemotherapy until disease stabilization, then hormone therapy "maintenance"	73%	80%	55%	74%
Hormone therapy alone	17%	2%	38%	15%

FIGURE 51

Hormonal Therapy after Progression on Anastrozole: Symptomatic Patients

If you would use endocrine therapy for the previous case, 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 57				Age 75			
	1st-line		2nd-line		1st-line		2nd-line	
Anastrozole	0%	5%	0%	1%	0%	7%	0%	1%
Exemestane	10%	30%	28%	27%	10%	28%	31%	21%
Letrozole	3%	12%	0%	4%	3%	12%	0%	10%
Tamoxifen	52%	26%	3%	11%	52%	24%	3%	11%
Fulvestrant	25%	27%	52%	47%	28%	29%	52%	47%
Other	0%	0%	3%	5%	0%	0%	3%	5%
No endocrine therapy	10%	0%	14%	5%	7%	0%	11%	5%

FIGURE 52

Patients Preferences for Oral versus Parenteral Therapy

What percentage of your postmenopausal 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	21%	34%
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I give my patients the option usually for second-line therapy and most of them to date prefer a pill to an injection, although some people clearly prefer a shot. I had one woman with whom I was actually going to use adjuvant fulvestrant, because she refused any therapy and I

thought she might think about an injection. I was at a loss for what to do with her because she said she'd never take a pill. I think it's an effective drug that has a lot of potential as an alternative or as another option down the line.

— Ann Partridge, MD

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EDITOR'S COMMENT

Breast cancer specialists (BCS) are much more likely to use trastuzumab without chemotherapy for patients with asymptomatic metastatic disease. BCS combine paclitaxel with trastuzumab more commonly than community-based oncologists (CBO), who more often combine docetaxel with trastuzumab. Both BCS and CBO routinely continue trastuzumab on disease progression, substituting a different cytotoxic agent. BCS have more commonly utilized trastuzumab as adjuvant therapy, but only for a median of three patients.

FIGURE 53

Interpretation of HER2 Test Results

How would you interpret the following IHC results?

	IHC 3+		IHC 2+		IHC 1+	
HER2-positive	87%	78%	0%	4%	0%	0%
HER2-positive only with FISH confirmation	13%	22%	100%	96%	23%	48%
HER2-negative	0%	0%	0%	0%	77%	52%

FIGURE 54

Treatment for De Novo ER-Negative, HER2-Positive Metastatic Disease

How would you generally treat a woman presenting de novo with ER-negative, HER2-positive metastatic disease?

Regimen	Asymptomatic bone mets		Asymptomatic liver mets		Moderate pain/ bone mets		Very symptomatic visceral mets	
	77%	21%	30%	2%	10%	0%	0%	0%
Trastuzumab (H) only	77%	21%	30%	2%	10%	0%	0%	0%
H + Chemotherapy	23%	67%	70%	90%	90%	94%	100%	94%
Chemotherapy alone	0%	12%	0%	8%	0%	6%	0%	6%

Algorithm for HER2 testing

At our institution, we perform IHC testing to assess a tumor's HER2-status initially. Those that are zero or 1+ are considered negative, and 3+ scores are considered positive. Tumors that are 2+ by IHC are tested further by FISH. This algorithm is endorsed by the College of American Pathologists.

Most of the literature reports that errors in HER2-testing are seen in the tumors that are 2+ by IHC and principally in centers that perform a small number of tests. We have published our pathology results at the Harvard Cancer

Center and we have a greater than 90 percent positive and negative predictive value.

With this algorithm, the possibility exists that patients with scores at either end of the spectrum will be under- or overtreated. There probably are a few cases in the zero to 1+ category that are truly HER2-positive by gene amplification. Likewise, probably a couple of percentage of patients whose tumors are 3+ by IHC are really FISH negative, and they may not receive much benefit from trastuzumab, although they might — that has not been studied extensively.

Testing the HER2-status by IHC or FISH is a challenge for many pathology centers, especially small centers that perform a relatively low volume of tests. We have learned from the HER2 story that if we are going to base treatments on the biology of a disease, then we need accurate interpretation of the biology by pathologists. As a result, HER2-testing has improved in the past few years and the pathology community deserves tremendous credit for this. Pathologists recognize the limitations of IHC and, if they see a small volume of cases, they send them elsewhere. In addition, IHC 2+ cases and suspicious cases are re-tested with FISH.

I am far more concerned today with

■ BREAST CANCER SPECIALISTS □ GENERAL ONCOLOGISTS

FIGURE 55

Chemotherapy Regimens Used with Trastuzumab*Which chemotherapies do you generally utilize with trastuzumab?*

	1st-line		2nd-line		3rd-line	
Docetaxel	14%	40%	3%	26%	7%	10%
Paclitaxel	38%	24%	10%	6%	0%	2%
Carboplatin/docetaxel	10%	8%	0%	16%	3%	5%
Carboplatin/paclitaxel	21%	6%	11%	4%	7%	4%
Vinorelbine	17%	14%	70%	34%	10%	33%
Gemcitabine	0%	6%	3%	4%	53%	22%
Other/none	0%	2%	3%	10%	20%	24%

FIGURE 56

Combination of Trastuzumab with Endocrine Therapy or Capecitabine*For patients with metastases, have you utilized trastuzumab combined with...*

	Yes		Number of patients (mean)	
Endocrine therapy	73%	60%	15	10
Capecitabine	63%	52%	15	8

the accuracy of estrogen-receptor testing than HER2 testing. We don't have the same level of quality control in ER-testing, and accuracy is critical when considering endocrine therapy in the adjuvant setting.

— Harold J Burstein MD, PhD

My standard algorithm is to consider tumor specimens that are IHC 0 or 1+ as HER2-negative. There are exceptions to the rules. If the disease is behaving in a particularly malignant fashion, I may want to have FISH testing performed, but that's not my general practice.

If the tumor is 3+, then I'd be comfortable with calling that positive, and if it's 2+, then I'll go ahead and order FISH testing.

— Charles L Loprinzi, MD

In a patient for whom I'm considering trastuzumab, I use FISH testing

— I believe that's the gold standard. For a patient whose tumor is cold negative or in a tumor that is 3+, we probably don't need FISH. However, results of 1+ and 2+ are indeterminate, and FISH is required. Thirty-five percent of 2+ tumors are FISH-positive. In addition, published data suggests significant observer variability from pathologist to pathologist.

— Joanne L Blum, MD

We use IHC, and generally, if the tumors are 1+ or 3+, we do not request FISH — with some exceptions. In general, they test or recommend FISH for 2+ specimens, if clinically indicated. Most of us do not order FISH for tumors that are 1+ or 3+, unless it doesn't make sense or feel completely in sync.

For example, if you have a low-grade lobular carcinoma that is 3+, we'll generally ask for a FISH because you don't

see that very often. Likewise, if it's a high-grade, nasty looking cancer and it's 1+, we might consider FISH just to make sure. But most of the cases that we feel compelled to FISH are those read as 2+.

— Ann Partridge, MD

Approach to HER2-positive disease

In selecting first-line therapy for patients with HER2-positive metastatic disease, I consider the pace of the disease and the patient's desires. If a patient can tolerate chemotherapy and has substantial disease in the liver or lungs, I use docetaxel/carboplatin/trastuzumab. In an older woman or a frail patient or a woman who doesn't want to lose her hair, I select vinorelbine/trastuzumab.

If the patient has ER- and PR-negative disease with only bone or maybe a few soft-tissue metastases, I use trastuzumab alone. In Vogel's data, approximately 25 to 35 percent of women with metastatic, FISH-positive disease responded to single-agent trastuzumab.

I've also used a combination of capecitabine and trastuzumab in the first-line metastatic setting in select cases. For example, in patients with very high bilirubin levels, I find it difficult to give a taxane or anthracycline. However, an abstract presented at ASCO several

FIGURE 57

Trastuzumab Use in Asymptomatic Patients

- ER-negative, **HER2-positive**
- **No prior systemic therapy**
- **Rising tumor markers, asymptomatic bone mets**

What is your usual 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	
Chemotherapy (C) alone	0%	7%	3%	17%	0%	6%	3%	17%	0%	8%	3%	18%
Trastuzumab (T) alone	71%	19%	7%	3%	74%	20%	7%	3%	74%	23%	7%	10%
Trastuzumab + C	29%	70%	90%	77%	26%	71%	90%	77%	23%	61%	87%	68%
T + docetaxel	3%	14%	13%	17%	3%	15%	10%	15%	0%	11%	7%	8%
T + paclitaxel	13%	15%	37%	9%	10%	16%	40%	8%	10%	18%	37%	11%
T + capecitabine	0%	3%	3%	5%	0%	3%	3%	5%	3%	9%	7%	8%
T + gemcitabine	0%	1%	0%	10%	0%	1%	3%	12%	0%	5%	10%	10%
T + vinorelbine	3%	9%	37%	23%	7%	9%	34%	25%	7%	11%	26%	27%
T + carboplatin + taxane	7%	15%	0%	7%	3%	15%	0%	6%	3%	5%	0%	3%
T + AC	3%	6%	0%	0%	3%	6%	0%	0%	0%	2%	0%	1%
T + other	0%	7%	0%	6%	0%	6%	0%	6%	0%	0%	0%	0%
No therapy	0%	4%	0%	3%	0%	3%	0%	3%	3%	8%	3%	4%

Continuation of Trastuzumab after Disease Progression

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

	Age 40 (premenopausal)		Age 57		Age 75	
Percent continuing trastuzumab upon disease progression	93%	84%	93%	85%	83%	83%

years ago showed it was safe to use lower-dose capecitabine in these patients. In vitro data from Slamon and Pegram showed that perhaps these drugs were additive and many clinicians, I believe, overinterpreted that data and felt capecitabine shouldn't be combined with trastuzumab. I don't necessarily agree and a number of clinicians, including myself, have had some success with this combination.

— Adam M Brufsky, MD, PhD

I use trastuzumab-based therapy in every patient with HER2-positive metastatic disease by FISH. And I tend to confirm my HER2-positivity by FISH. Only in the patient who is completely asymptomatic with low volume disease do I give trastuzumab alone. The majority of my patients receive trastuzumab with chemotherapy.

— Generosa Grana, MD

If a symptomatic patient presents with

de novo ER-negative, HER-2-positive metastatic disease in the bone and lung, I use combination chemotherapy with trastuzumab up front — typically a taxane, carboplatin and trastuzumab.

If she had previously received adjuvant AC, the taxane, carboplatin and trastuzumab combination would, again, be excellent. Capecitabine combined with vinorelbine and trastuzumab would be another interesting combination for such a patient.

FIGURE 58

Trastuzumab Use in Symptomatic Patients

- ER-negative, **HER2-positive**
- **No prior systemic therapy**
- **Bone and lung metastases, symptomatic**

What is your usual 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	
Chemotherapy (C) alone	0%	7%	3%	11%	0%	7%	3%	11%	0%	9%	3%	13%
Trastuzumab (T) alone	0%	1%	0%	0%	0%	1%	0%	1%	7%	3%	0%	5%
Trastuzumab + C	100%	92%	97%	89%	100%	92%	97%	88%	93%	88%	97%	82%
<i>T + docetaxel</i>	10%	11%	7%	5%	10%	12%	7%	4%	10%	21%	7%	7%
<i>T + paclitaxel</i>	27%	9%	3%	4%	27%	10%	7%	5%	36%	22%	17%	5%
<i>T + capecitabine</i>	0%	0%	7%	2%	0%	0%	3%	2%	7%	2%	7%	8%
<i>T + gemcitabine</i>	0%	0%	7%	16%	0%	0%	10%	17%	3%	2%	13%	19%
<i>T + vinorelbine</i>	3%	1%	67%	43%	7%	1%	60%	40%	20%	12%	47%	38%
<i>T + capecitabine + docetaxel</i>	3%	6%	3%	5%	3%	6%	7%	4%	0%	5%	3%	1%
<i>T + carboplatin + taxane</i>	54%	49%	0%	7%	50%	46%	0%	6%	17%	16%	0%	1%
<i>T + AC</i>	0%	5%	0%	1%	3%	5%	0%	2%	0%	3%	0%	1%
<i>T + AC + docetaxel</i>	3%	5%	0%	0%	0%	5%	0%	0%	0%	0%	0%	0%
<i>T + other</i>	0%	6%	3%	6%	0%	7%	3%	8%	0%	5%	3%	2%

Continuation of Trastuzumab after Disease Progression

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

	Age 40 (premenopausal)		Age 57		Age 75	
Percent continuing trastuzumab upon disease progression	93%	90%	93%	90%	90%	91%

For an asymptomatic patient with bone metastases, I have used trastuzumab combined with capecitabine with good results. The other option would be a drug like vinorelbine with trastuzumab or a taxane with trastuzumab, depending on what she previously received.

If a patient is completely asymp-

tomatic, one could use single-agent trastuzumab; however, it's very rare for a patient with bone metastases to be without symptoms. Generally these patients are experiencing pain.

— Joanne L Blum, MD

For symptomatic or asymptomatic

patients with HER2-positive disease, you might try trastuzumab alone, but the studies revealing a survival benefit with trastuzumab and chemotherapy are pretty compelling, and rarely do you see survival benefits in the metastatic setting. So I usually try to use chemotherapy with trastuzumab in those patients,

FIGURE 59

Trastuzumab Use in Asymptomatic Patients

- ER-negative, HER2-positive
- Adjuvant AC 2 years ago
- Rising tumor markers, asymptomatic bone mets

What is your usual 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	
Chemotherapy (C) alone	0%	10%	3%	15%	0%	10%	3%	14%	0%	11%	3%	14%
Trastuzumab (T) alone	73%	17%	3%	1%	77%	17%	3%	2%	77%	25%	3%	9%
Trastuzumab + C	27%	69%	94%	81%	23%	69%	94%	81%	20%	56%	91%	72%
T + docetaxel	7%	17%	7%	11%	7%	16%	7%	10%	0%	11%	7%	12%
T + paclitaxel	7%	21%	43%	10%	3%	22%	46%	9%	3%	18%	42%	9%
T + capecitabine	3%	3%	3%	6%	3%	4%	3%	7%	7%	6%	7%	8%
T + gemcitabine	0%	0%	3%	15%	0%	0%	3%	13%	0%	3%	11%	12%
T + vinorelbine	3%	6%	35%	26%	7%	6%	35%	29%	7%	13%	24%	29%
T + carboplatin + taxane	7%	20%	3%	4%	3%	19%	0%	5%	3%	4%	0%	2%
T + other	0%	2%	0%	9%	0%	2%	0%	8%	0%	1%	0%	0%
No therapy	0%	4%	0%	3%	0%	4%	0%	3%	3%	8%	3%	5%

Continuation of Trastuzumab after Progression

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

	Age 40 (premenopausal)		Age 57		Age 75	
	Percent continuing trastuzumab upon disease progression	93%	94%	93%	95%	83%

regardless of symptomatology.

I'll usually try something gentle, such as vinorelbine/trastuzumab. This regimen is very well tolerated — patients don't even lose their hair. If someone needs a quick response and they're chemotherapy- or taxane-naïve, I believe paclitaxel/carboplatin/trastuzumab is a very effective regimen.

We have a neoadjuvant study ongoing that randomly assigns women to vinorelbine/trastuzumab or paclitaxel/carboplatin/trastuzumab. We don't know

which one's more effective. They're both good regimens. Certainly, vinorelbine/trastuzumab is more tolerable and I would take it any day over TCH. So when all things are equal, I lean towards that just because it's less of a quality-of-life burden.

— Ann Partridge, MD

For symptomatic patients with ER-negative, HER-2-positive metastatic disease, I offer trastuzumab and chemotherapy, based on the two studies that compared

chemotherapy alone versus chemotherapy plus trastuzumab.

Trastuzumab clearly improves survival, and it's a very important drug for these women. My chemotherapy choice is based on a variety of factors such as side effects. Obviously, I avoid using anthracyclines at the same time as trastuzumab. I commonly use drugs like paclitaxel or vinorelbine — drugs that have been studied and widely reported on in combination with trastuzumab.

— Harold J Burstein MD, PhD

FIGURE 60

Trastuzumab Use in Symptomatic Patients

- ER-negative, **HER2-positive**
- **Adjuvant AC 2 years ago**
- **Bone and lung mets, very symptomatic**

What is your usual 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	
Chemotherapy (C) alone	0%	4%	3%	11%	0%	4%	3%	12%	0%	5%	3%	13%
Trastuzumab (T) alone	0%	2%	0%	1%	0%	3%	0%	1%	0%	6%	0%	6%
Trastuzumab + C	100%	94%	97%	88%	100%	93%	97%	87%	100%	88%	94%	81%
T + docetaxel	13%	14%	7%	3%	13%	14%	3%	3%	7%	21%	7%	6%
T + paclitaxel	20%	13%	0%	4%	20%	15%	0%	4%	27%	23%	14%	6%
T + capecitabine	0%	0%	3%	4%	0%	0%	3%	6%	7%	4%	3%	7%
T + gemcitabine	0%	0%	7%	18%	0%	0%	10%	16%	3%	1%	10%	19%
T + vinorelbine	0%	3%	74%	46%	0%	3%	75%	46%	17%	15%	54%	40%
T + capecitabine + docetaxel	3%	6%	3%	6%	3%	6%	3%	5%	3%	6%	3%	0%
T + carboplatin + taxane	64%	55%	0%	1%	64%	51%	0%	1%	36%	16%	0%	0%
T + other	0%	3%	3%	6%	0%	4%	3%	6%	0%	2%	3%	3%
No therapy	0%	0%	0%	0%	0%	0%	0%	0%	0%	1%	3%	0%

Continuation of Trastuzumab after Progression

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

	Age 40 (premenopausal)		Age 57		Age 75	
Percent continuing trastuzumab upon disease progression	93%	93%	93%	92%	90%	93%

You can break patients down into two groups: those with relatively indolent versus very symptomatic recurrence. In the former, I'm a big fan of trastuzumab monotherapy up front. Why cause more toxicity than is necessary?

If monotherapy doesn't go well, I'll add in chemotherapy — paclitaxel, vinorelbine or the carboplatin/paclitaxel regimen. I had a patient with a fabulous response who is out now to about five

years with widespread metastatic disease and doing great, so I'm influenced a bit by that experience.

— Charles L Loprinzi, MD

We certainly incorporate trastuzumab in the first-line treatment of metastatic HER2-positive breast cancer. I generally use a taxane — it's approved with paclitaxel, but we certainly have good data with docetaxel and frankly, most

other drugs that I would want to use in the metastatic setting. There is synergy between trastuzumab and many chemotherapy agents, so with trastuzumab, there's even more incentive to be giving combination therapy.

If I have a patient with HER2-positive, ER-negative disease that is not life-threatening, depending on their situation, if they're asymptomatic and have a couple of bone mets, for example, I have

FIGURE 61

Cardiac Monitoring and Trastuzumab

Do you routinely monitor cardiac functioning in your patients receiving trastuzumab?

No	17%	40%
Yes	83%	60%
<i>For those answering "yes," which test(s) do you use?</i>		
MUGA-scan only	81%	82%
Other	19%	18%
<i>For those answering "yes," how often do you assess cardiac functioning?</i>		
Every 2-3 months	15%	42%
Every > 3-6 months	62%	38%
Other	23%	20%

FIGURE 62

Cardiac Functioning and Trastuzumab

Have you discontinued trastuzumab because of abnormal cardiac function tests in a patient who was clinically asymptomatic?

No	27%	40%
Yes	73%	60%
<i>For those answering "yes," in how many patients?</i>		
Mean	5 patients	2 patients
<i>Have you discontinued trastuzumab because of clinically abnormal cardiac function?</i>		
No	33%	68%
Yes	67%	32%
<i>For those answering "yes," in how many patients?</i>		
Mean	4 patients	2 patients

used single-agent trastuzumab.

— Julie Gralow, MD

Clinical trials of trastuzumab with vinorelbine

We've conducted several Phase II trials, including one at Dana-Farber, in which patients received trastuzumab

plus vinorelbine as second- or third-line treatment for metastatic breast cancer. Because of the activity seen, it was moved to first-line where we saw very encouraging response rates on the order of 75 percent with very reasonable time to progression, certainly consistent with other reports of trastuzumab and chemotherapy.

To confirm the data, we then conducted a multi-center Phase II trial, with 17 centers and approximately 50 to 60 patients. Again the response rate was on the order of 70 percent, so we believe this is a very reasonable and active regimen for patients. Since so many patients have received anthracyclines and taxanes in the adjuvant setting, it's a nice regimen to offer them. Obviously, there are many other regimens that we could use with trastuzumab, this is one we just happen to like.

We conducted a randomized Phase II trial, known as the TRAVIOTA trial, for patients receiving first-line chemotherapy for HER2-positive metastatic breast cancer. All the patients received trastuzumab, and they were randomly assigned to also receive either vinorelbine or a weekly taxane — paclitaxel or docetaxel. Unfortunately, we accrued only approximately 85 patients — far short of our original goal. We are analyzing the data this spring and hope to have the data available around the time of ASCO.

— Harold J Burstein MD, PhD

Trastuzumab scheduling

I generally schedule trastuzumab to accommodate the patient's chemotherapy schedule. If the patient is receiving weekly chemotherapy, I use weekly trastuzumab. If the chemotherapy schedule is every three weeks, I am comfortable using trastuzumab that way as well.

For many of my patients with a great response to trastuzumab plus chemotherapy, I administer the chemotherapy for many months and when they seem to have reached an optimal response point or plateau, I discontinue the chemotherapy and continue with trastuzumab alone. At that point, I often switch patients on weekly trastuzumab to an every three-week schedule, because it's more convenient for the patient.

— Harold J Burstein MD, PhD

I don't see any difference between the weekly and three-weekly schedules of trastuzumab. If patients are receiv-

FIGURE 63

Trastuzumab in the Adjuvant Setting

- Woman in average health
- 1.2-centimeter, Grade II tumor
- ER-positive, HER2-negative
- 3 positive nodes

Would you utilize adjuvant trastuzumab for this patient?

	35 years old		65 years old		75 years old	
Yes, off protocol	0%	6%	0%	4%	0%	5%
Yes, clinical trial	90%	75%	90%	70%	76%	51%
No	10%	19%	10%	26%	24%	44%

FIGURE 64

Clinical Use of Adjuvant Trastuzumab

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	73%	82%
Yes	27%	18%

FIGURE 65

Use of Adjuvant Trastuzumab

Have you ever utilized nonprotocol adjuvant trastuzumab?

No	57%	82%
Yes	43%	18%

For those answering “yes,” in how many patients?

Median	2 patients	3 patients
--------	------------	------------

ing weekly vinorelbine, then they’ll receive trastuzumab. If they’re receiving every three-week chemotherapy or trastuzumab monotherapy, I’ll utilize the three-weekly schedule.

— Charles L Loprinzi, MD

Continuation of trastuzumab after progression

The duration of trastuzumab in metastatic disease has not been studied in a randomized trial, so we are conducting

an observational study of 400 patients in approximately 50 centers, and every three months we’re recording each patient’s treatment. I expect we’ll find that about 35 percent of clinicians don’t continue trastuzumab after progression. Many believe that progression with a chemotherapy-trastuzumab regimen indicates resistance to trastuzumab, but I don’t agree.

I believe it is beneficial to continue trastuzumab beyond an initial progression, but I don’t know for how many

progressions it continues to be advantageous. In our retrospective analysis of approximately 200 patients who received front-line trastuzumab, those who continued on trastuzumab seemed to have a small benefit, at least in time to progression, compared to those who did not. A retrospective study from the Hellenic Cooperative Oncology Group demonstrated time to progression intervals of three to four months with third- and fourth-line trastuzumab plus chemotherapy.

— Adam M Brufsky, MD, PhD

Monitoring for cardiotoxicity with trastuzumab

After the initial experience with significant cardiotoxicity in patients on a combination of trastuzumab and anthracyclines, everybody stopped using trastuzumab in combination with anthracyclines, and most of the cardiotoxicity problem went away. For other chemotherapy regimens, whether it’s taxanes or vinorelbine or others, the cardiac toxicity rate is not zero, but it’s considerably less than five percent.

Generally, I order a MUGA or LVEF when I start the trastuzumab and then repeat it approximately roughly four months later. We studied this strategy prospectively in one of our vinorelbine/trastuzumab trials and showed that none of the patients who had well-preserved LVEF at 16 weeks on therapy

developed a significant decline in LVEF. I also check it again when I switch from one trastuzumab-based regimen to another and whenever I'm discontinuing trastuzumab and reintroducing an anthracycline.

The good news is that we believe by avoiding the combination of anthracyclines and trastuzumab, we've managed to avoid most of the problem. However, we have to remain respectful of the drug.

The NSABP adjuvant trial data showed a cardiac toxicity rate of approximately four percent in patients who received AC followed by paclitaxel and trastuzumab, versus approximately one percent in patients who did not receive trastuzumab.

I believe this will probably not prohibit the development of trastuzumab in the adjuvant setting, but it is a reminder that it's not totally benign and should not be used as adjuvant therapy off protocol until we have the clinical data that it is useful in that setting.

— *Harold J Burstein MD, PhD*

I monitor MUGA scans in my patients on trastuzumab every three months continuously for cardiac toxicity. I believe we need data long-term to tell us whether there's a point at which to stop monitoring, where you don't see any continued risk.

— *Generosa Grana, MD*

I always do a baseline MUGA scan to assess baseline left ventricular ejection fraction. But from there on, in the metastatic setting, if the patient doesn't have a lot of risk factors for heart disease, I don't regularly monitor asymptomatic patients without major cardiac risk factors.

I don't routinely evaluate ejection fractions in asymptomatic patients, because if the patient has a drop in ejection fraction but is asymptomatic, it isn't going to influence my treatment. I'm not going to stop a drug that the patient's doing well on. I'm not recommending that my colleagues and my referring physicians do that, but that's just my practice management style.

I have had patients whose ejection

fraction has dropped, but at the first sign of symptoms, I'll repeat the MUGA and hold the drug until the heart failure is treated.

— *Julie Gralow, MD*

Endocrine therapy with trastuzumab

In my patients with ER-positive, HER2-positive metastatic disease, I tend to combine an aromatase inhibitor and trastuzumab. However, I am perfectly honest with patients that I don't know whether this approach gives us additional benefit above and beyond what they could achieve with an aromatase inhibitor alone.

— *Generosa Grana, MD*

It's very frustrating that we don't have a lot of data on the hormonal agents with trastuzumab, but there's clearly nothing preclinically or, to date, clinically, that would suggest any negative interaction. If anything, given the ER and HER2 signaling pathways, you would hypothesize potential synergy between a hormonal agent and trastuzumab. In my patients with hormone receptor-positive patients, I want to avoid chemotherapy for as long as possible, and I'll generally start with a hormonal agent.

Frankly, although this is where there's a difference between the art of medicine and the science of medicine, I will start trastuzumab at the same time as the hormonal therapy, looking for the best blockage of signaling in my breast cancer patients. That's different than some of my colleagues, and it's not pure. It doesn't have the good clinical trials behind it, but I do think that it's kind of hitting two pathways at once and it makes sense to me to try to combine both of these targeted therapies.

— *Julie Gralow, MD*

Use of adjuvant trastuzumab

I hope that the adjuvant trials will be positive in the future, but in the adjuvant setting right now, I have a strong bias against the nonprotocol use of trastuzumab. If my patients went on

the adjuvant trial, I use the rationale that they would be randomly assigned to potentially not receive trastuzumab — a one-third chance of that for the current NSABP trial.

I also take comfort that the NSABP trial has 3,000 patients enrolled, and they're out to two or three years. There's a data monitoring committee watching that trial very closely, and the tendency these days is, if the curves have split and there's clearly an advantage, a public announcement is made. That gives me some comfort.

Ten years ago, I was pretty sure that high-dose chemotherapy with bone marrow transplant would have beaten standard chemotherapy, and in fact, it didn't. So given all that information, my bias is not to use adjuvant trastuzumab.

Inflammatory breast cancer is an active disease, with the cancer clearly present, and there's no clinical protocol evaluating the role of trastuzumab in these patients. I believe most of us would consider it reasonable to utilize trastuzumab in those patients with HER2-positive inflammatory tumors.

— *Charles L Loprinzi, MD*

Off protocol, I use adjuvant trastuzumab in patients with locally advanced and inflammatory disease. These are women whose disease is inoperable at presentation, who have large, bulky tumors or inflammatory disease.

In these cases, I utilize four to six months of trastuzumab-based chemotherapy, send them to surgery if the disease becomes surgically resectable, and then continue chemotherapy plus trastuzumab. Ultimately, these women receive a year plus of trastuzumab. I am not using trastuzumab-based therapy based on node-positivity alone.

— *Generosa Grana, MD*

I think — especially based on presentations of some neoadjuvant data now — we're probably going to see that trastuzumab is a useful drug in the adjuvant setting. The first interim analyses are going to occur for most of the four international adjuvant trastuzumab trials within the next year. And if there

is a marked difference between the arms, we may see reporting of at least one of these trials within the next year. If the difference is small, we'll have to wait for more events to occur.

— Julie Gralow, MD

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Patterns of Care

in Medical Oncology

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This program is supported by education grants from Abraxis Oncology, AstraZeneca Pharmaceuticals LP and Genentech BioOncology.

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This program is supported by education grants from
Abraxis Oncology, AstraZeneca Pharmaceuticals LP
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Last review date: April 2005
Release date: April 2005
Expiration date: April 2006
Estimated time to complete: 2.25 hours