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Note: All quotations from research leaders are excerpted from prior CME activities. Affiliations and financial disclosures can be found at: www.BreastCancerUpdate.com.

Editor's Note

Doing the Math

This special supplement to *Breast Cancer Update* is part of a long-term project by our education group and reports the results of a national telephone survey, that we initiated in May and June of this year, of 120 randomly selected medical oncologists.

This is the second consecutive year that we have conducted such a survey and participating physicians received a modest honorarium for reviewing a series of clinical case scenarios and describing what they would likely recommend to patients in these situations. These data, along with many other sources of information on the patterns of oncology care, are carefully considered when we plan our continuing medical education (CME) programs.

It is interesting to note that while many resources have been expended to evaluate new treatment interventions, there has been a relatively minimal investment in determining how these advances are implemented in practice. Our efforts in this regard have suggested a number of conclusions specifically related to medical oncology:

1. **Information transfer can be very rapid, but also may be incomplete:**

   For example, our survey demonstrates that six months after Dr Craig Allred's fascinating presentation at the San Antonio Breast Cancer Symposium in December 2002, on the relationship between estrogen receptor (ER) assay results and benefit from tamoxifen in women with ductal carcinoma *in situ* (DCIS), most oncologists are now considering ER results in patients with DCIS (see second figure on page 9).

   On the other hand, Dr Allred also noted that many tumors are being incorrectly identified by pathology laboratories as ER-negative, and that virtually any evidence of ER protein should lead clinicians to consider endocrine treatment. Our survey suggests that this information is not being utilized, and leads us to believe that some women who would benefit from hormonal therapy are not receiving it.

2. **Oncologists employ multiple information sources to keep up-to-date on emerging research results (see page 3):**

   A recent working-group meeting with 43 community-based medical oncologists demonstrated the utilization of a variety of tools that supplement the "gold standard" of peer-reviewed journal articles. Our audio series has achieved its measure of success, largely because physicians can "multitask" and become updated while driving their automobiles.

3. Research leaders' opinions are a major impetus for altering treatment patterns:

Another source of patterns of care data that we actively utilize to plan our CME activities is audience keypad responses from meetings such as our Miami Breast Cancer Conference. At the 2001 Miami meeting, our group identified a treatment pattern that seemed to conflict with available clinical research data. About 25 percent of physicians indicated that their first-line therapy for women with HER2-positive, ER-negative metastases was chemotherapy without trastuzumab. On many of our subsequent CME programs, we queried research leaders on this issue. There was essentially universal agreement that the pivotal trial data from Slamon et al, demonstrating a survival benefit for adding trastuzumab to chemotherapy, strongly supported this combined approach. Our current survey now demonstrates a marked decrease in the number of physicians who use chemotherapy alone in this situation (see page 36).

4. Physicians are proactive about involving patients in challenging treatment decisions:

The use of anastrozole versus tamoxifen in adjuvant therapy of postmenopausal patients is an example of how oncologists are presenting multiple options to patients when research data does not clarify an optimal choice (see page 14). Many practicing oncologists tell us that patients frequently arrive with Internet-based printouts and related questions, and the "web-savvy" patient has likely contributed to a shift toward greater patient involvement.

We view CME as a critical component in the clinical research continuum, and while clinicians and patients look forward to major advances in future outcomes for cancer therapies, it is essential that we do whatever possible to ensure that modest recent advances are effectively translated into options for our patients.

—Neil Love, MD

How do you stay up-to-date on breast cancer?*
(Participants chose multiple items)

	Percent of oncologists
Journals	100%
Scientific meetings	91%
Speaking with colleagues	88%
Audio: *Breast Cancer Update*	74%
Tumor boards	69%
Internet	61%
Print monographs	52%
Dinner meetings	47%
Weekly conferences/ grand rounds	47%
Pharmaceutical sales representatives	36%
Newspapers/lay press	27%

**Breast Cancer Update* Working Group of 43 oncologists. May 2003.

Survey Results

Impact of Tumor Size and Nodal Status on Choice of Adjuvant Therapy

65-year-old woman with ER-positive, HER2-negative IDC: Which adjuvant therapy would you recommend?

Clinical situation	Chemotherapy alone	Chemotherapy plus endocrine therapy	Endocrine therapy alone	No therapy
2.2-cm, 10 positive nodes	15%	78%	7%	—
2.2-cm, negative nodes	5%	75%	15%	5%
0.8-cm, negative nodes	—	8%	89%	3%

Editor's Note

Chemotherapy plus endocrine treatment are standard in postmenopausal women with node-positive and higher-risk, node-negative, ER-positive tumors. There is a marked shift to endocrine therapy alone for women with tumors at less than a 10 percent risk for recurrence.

Research Leader Commentary*

A patient with an 8-millimeter, node-negative, ER-positive cancer has an extremely good prognosis and is unlikely to achieve much benefit from chemotherapy — particularly when they are in an age group in which the benefits from chemotherapy are very small. This is an appropriate situation to discuss adjuvant endocrine therapy, but in this setting I would consider it optional. It would not be optional, however, with a 1.5-centimeter tumor — in which case I more strongly recommend endocrine therapy.

— Monica Morrow, MD

The implication for tailored treatment advice today depends on the degree of certainty that either modality alone will be sufficient for an individual patient. At one extreme, patients with both receptors absent can only be treated effectively with chemotherapy. The addition of endocrine agents in this population is at best useless and may be actively harmful either by the direct toxicity of the endocrine agent or by interference with cytotoxics. At the other extreme, some patients may have such strong receptor expression, that the probability of control with endocrine therapy alone, is considered sufficiently high that no cytotoxic treatment is required, especially among patients with low risk for recurrence.

Between these extremes, there is a gradation in level of uncertainty that endocrine therapy alone will be sufficient. In this in-between group, measures of absolute risk (e.g., increased nodal involvement), and factors that might predict resistance to tamoxifen (HER2 overexpression) are relative (although imprecise) indications for the addition of cytotoxic therapy. For patients in lower risk groups such as postmenopausal patients in NSABP Trial B-20 and IBCSG Trial IX, and premenopausal patients in IBCSG Trial 11 — endocrine therapy alone may suffice.

— Goldhirsch A et al. J Clin Oncol 2003;21(17):1-9.

*Unless otherwise noted, comments are edited from prior CME activities.

Impact of Tumor Size and Nodal Status on Choice of Adjuvant Chemotherapy

65-year-old woman with ER-positive, HER2-negative IDC: Would you recommend adjuvant chemotherapy?

Tumor status	Oncologists recommending chemotherapy
2.2-cm, 10 positive nodes	93%
2.2-cm, negative nodes	80%
0.8-cm, negative nodes	8%

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

Chemo	2.2-cm, 10 positive nodes	2.2-cm, negative nodes
AC-docetaxel	40%	6%
AC-paclitaxel	34%	3%
AC	16%	61%
CMF	—	24%
FAC/FEC	8%	3%
Other	2%	3%

Editor's Note

Taxane-containing chemotherapy combinations with anthracyclines have become standard for women with node-positive tumors, but are utilized far less frequently with node-negative tumors.

Research Leader Commentary

The increased risk of relapse and death associated with tumor metastasis to the ipsilateral axilla has in the past significantly influenced the choice of treatment…. Even with endocrine-responsive disease, the higher risk of relapse and the presence of endocrine-resistant clones within the tumor, in general, have been taken as indications for the inclusion of cytotoxic chemotherapy in the treatment regimen… . Treatment with four courses of doxorubicin and cyclophosphamide was shown to be equivalent to six courses of classical CMF. Several regimens and schedules, such as Canadian cyclophosphamide, epirubicin, and fluorouracil (Canadian CEF); the cyclophosphamide, doxorubicin,and fluorouracil (CAF) regimen; dose-dense administration of doxorubicin, paclitaxel, and cyclophosphamide; and also to some extent, tailored fluorouracil, epirubicin, and cyclophosphamide (FEC), and docetaxel, doxorubicin, and cyclophosphamide (TAC) have been shown in comparative trials to yield superior results, though at the cost of greater complexity, economic cost, or toxicity. These more effective regimens may be preferred in patients at higher risk.

— Goldhirsch A et al. J Clin Oncol 2003;21(17):1-9.

Impact of Age on Use of Adjuvant Chemotherapy

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

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

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

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

Editor's Note

In a woman with multiple positive nodes, an anthracyline-taxane combination is frequently utilized, even in older women.

Research Leader Commentary

The age cut-off at which I would not recommend adjuvant chemotherapy depends on what the patient looks like. That is obviously not true in the extreme; I cannot imagine a situation in which I would give adjuvant chemotherapy to a 98-year-old woman. This decision also requires a very informed discussion with the patient about the risks and benefits of therapy. I can imagine treating patients into their eighties with adjuvant chemotherapy, but I would certainly be less likely to do so as they get older. Elderly patients would also be eligible for the trial that Hy Muss is leading, comparing single-agent capecitabine to either CMF or AC.

— Clifford A Hudis, MD

For the 60- to 70-year-old patient with an ER-positive breast cancer, I would discuss the very modest benefits of chemotherapy. If a patient chooses chemotherapy, then I would support that as a reasonable option, but would not recommend it. These women should receive hormonal therapy. If a tumor is predominantly hormone-sensitive, then the added benefit from chemotherapy is going to be very small. Additionally, we know that the older the woman, the smaller the benefit from chemotherapy. In postmenopausal women, the effect from chemotherapy on survival is about one-half to one-third of the effect in premenopausal women. If you include older women who have ER-positive tumors, the effect from chemotherapy is even less.

— I Craig Henderson, MD

Clinical Use of Dose-Dense Adjuvant Chemotherapy

Have you used dose-dense chemotherapy with growth factor support in the adjuvant setting outside the context of a clinical trial?

Yes	30%
No	70%

Of physicians answering yes: In how many patients have you used adjuvant dose-dense chemotherapy?

Mean	11 patients

Editor's Note

Only a few months after the initial presentation in San Antonio by Dr Marc Citron, of the first results of CALGB-9741, about one-third of oncologists have utilized adjuvant dose-dense chemotherapy in a nonprotocol setting.

Research Leader Commentary

Dose-dense adjuvant chemotherapy in a nonprotocol setting is a reasonable option. The CALGB-9741 trial accrued over 2,000 patients and shows improved efficacy, decreased death rates and reduced toxicity; therefore, there's no reason not to use dose-dense therapy at this time.

I believe in dose-dense therapy because I've seen its evolution in the laboratory and the clinic for 25 years, and it has a solid basis. However, no individual can stand up and say this is the new standard of care. We have to see how people are going to utilize this in the community. I would not be shocked to find this approach widely accepted and used, but whether it becomes a new standard of care needs to be defined by the community.

— Larry Norton, MD

For oncologists involved in clinical research, the message is, that choice of which chemotherapy drugs to use is not the only way forward: The schedule of drug administration is an important variable, in addition to the timing and duration of chemotherapy, which might also play a role, but have been poorly investigated to date. Now it is our task to confirm these data independently with a much larger trial that will allow identification of subgroups that derive substantial benefit from the dose-densification approach.

On the basis of a single trial of 2,000 women, it would not be wise for clinicians in practice to routinely adopt accelerated chemotherapy for all patients with high-risk breast cancer. Nevertheless, while waiting for the confirmatory evidence, the individualized use of these dose-dense regimens as given in INT-9741 for high-risk women — particularly for those who cannot count on beneficial effects of adjuvant endocrine therapy — is not unreasonable, provided that the women are informed about the uncertainties regarding the risk/benefit ratio of dose-dense therapies. A last, but certainly no less important message, is that it might be dangerous and harmful to extrapolate the results of INT-9741 to other drugs or combinations.

— Piccart MJ. J Clin Oncol 2003;21(8):1425-8.

Use of Dose-Dense Adjuvant Chemotherapy in Patients With High-Risk Disease

Women with 2.2-cm, ER-positive, HER2-negative IDC and 10 positive nodes: If you recommend adjuvant chemotherapy, would you recommend a dose-dense (q 2 week) regimen with growth factor support?

Patient age	Fraction of oncologists recommending
33-year-old	46%
43-year-old	45%
55-year-old	28%
65-year-old	29%
77-year-old	15%

Editor's Note

Physicians report that they are much more likely to consider dose-dense treatment in younger patients, although there is no research evidence that the benefit-to-risk ratio differs with patient age.

Research Leader Commentary

Dose-dense therapy is definitely a therapeutic option for patients with high-risk breast cancer at this time. It is not the standard of care, but is an alternative to discuss with patients at risk for relapse. In my older patients, who may not be able to tolerate combination treatment, I use sequential ATC, and I think we'll find sequential, dose-dense ATC will be well-tolerated by the elderly.

I always present patients with options, and I like to hear what they have to say. In general, patients want the treatment with the most potential for cure. Many also want to receive the treatment quickly — in fact, that's one of the most common reasons patients express for wanting dose-dense therapy. I was initially embargoed from revealing the results of CALGB-9741, but now I discuss it with patients. I give them my take on the literature and my recommendation.

Most oncologists like to see five years of follow-up in an adjuvant study. I find that when I talk to physicians about emerging trends, I can generally divide the reactions into thirds. One-third embrace it, a second-third are not sure and the remaining third are definitely against it. I've been surprised how positively dose-dense therapy has been received. As I talk to physicians, I find they are often already using or at least considering it. This approach appears to be more widely accepted than I had expected at this time.

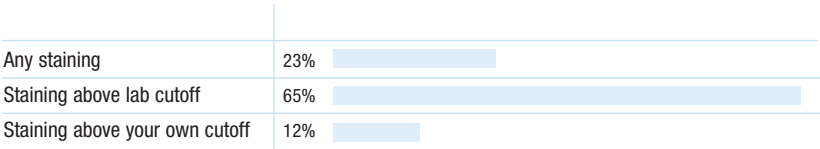
— Marc Citron, MD

In the nonprotocol setting, I feel obligated to discuss the results from CALGB-9741 with patients who have positive nodes. After discussing the fact that these were very early results, but perhaps relevant to a particular patient's care, I have treated some patients at high risk with this dose-dense regimen. I also discuss standard treatment options, including the combination of doxorubicin and cyclophosphamide followed by a taxane, and I discuss CAF-type regimens.

— G Thomas Budd, MD

Determining Estrogen Receptor Status

How do you define ER-positivity?



Do you generally request ER status for DCIS?

Editor's Note

The presentation by Allred at the 2002 San Antonio meeting on the correlation of ER results and benefit of tamoxifen in DCIS has led to a rapid shift in clinical practice, but clinicians continue to rely on pathology laboratories to define ER-positivity in spite of data demonstrating that this approach often excludes patients who can benefit from hormonal therapy.

Research Leader Commentary

There is variation in defining ER-positivity in Europe and across the United States. I agree with Kent Osborne that this variation is extraordinarily disturbing — particularly as our hormonal therapies continue to improve. My feeling is that if there is any receptor present in a tumor, it should be considered positive. Clearly, we can miss a very low positive result quite easily, and the result may be that patients who should receive adjuvant endocrine therapy are not receiving it. We need to get this assay correct for every woman.

— Anthony Howell, BSc, MBBS, MSc, FRCP

With minimal training, pathologists in our laboratory were in agreement on discriminating positive from negative tumors in 99% of cases. The optimal cut point in our study was a total IHC score of greater than 2, meaning that even patients whose tumors scored 3 (corresponding to as few as 1% to 10% weakly positive cells) had a significantly improved response, compared with those who had lower scores....

…Many hospital and commercial laboratories have converted to assessing ER status exclusively by IHC on archival tissue. They use diverse methodologies, and most have arbitrarily chosen 10% or even 20% positive tumor cells as their cutoff for defining ER positivity, potentially denying a substantial number of patients the benefits of adjuvant hormone therapy.

— Harvey JM et al. J Clin Oncol 1999;17:1474-81.

Endocrine Therapy of DCIS

What percentage of your patients with DCIS receive tamoxifen?

Receive tamoxifen	66%
Do not receive tamoxifen	34%

What results would you expect from a trial comparing tamoxifen to anastrozole in postmenopausal women with DCIS?

Regarding Toxicity	2002	2003
Less toxicity with anastrozole	55%	80%
No significant difference	45%	20%
Regarding Efficacy		
Greater benefits with anastrozole	65%	60%
No significant difference	35%	40%

Editor's Note

Currently, most patients with DCIS are treated with tamoxifen, and many clinicians are optimistic that ongoing randomized trials comparing anastrozole to tamoxifen will eventually result in a positive benefit-to-risk ratio for anastrozole. Most research leaders agree that anastrozole should not be used in patients with DCIS at the present time.

Research Leader Commentary

It is clear that DCIS is a highly curable disease from which almost no one should die. If tamoxifen and radiation therapy can reduce the incidence of future invasive cancer to less than two percent, can we achieve even better results with another agent, such as anastrozole?

I think it is worthwhile to test anastrozole to see if the small amount of undesired recurrent cancers can be negated. The question becomes: Will anastrozole be any better than tamoxifen and at what risk?

NASBP-B-35 is a large study of 3,000 patients, and it will go on for the next five years. It is restricted to postmenopausal patients with DCIS who have ER-positive tumors. Studies in the advanced and adjuvant invasive settings found that anastrozole was at least as good as tamoxifen and perhaps superior. Also, the toxicity was less worrisome — anastrozole doesn't cause uterine cancer or thromboembolism. The issues with anastrozole are that it can't be used in premenopausal women and that it may cause osteoporosis.

— Richard Margolese, MD

Impact of ATAC Trial Results on Choice of Adjuvant Endocrine Therapy

What percentage of your postmenopausal patients receiving adjuvant endocrine therapy receive each of the following agents?

	Mean
Tamoxifen	59%
Anastrozole	35%
Other aromatase inhibitor	6%

Editor's Note

Less than two years after the initial presentation of the ATAC trial results, anastrozole is now a common option presented to postmenopausal women with ER-positive tumors.

Research Leader Commentary

The new ATAC trial data gives me comfort and a sense of vindication that we waited a year before starting to make therapeutic recommendations. Last year, I publicly supported the ASCO Technology Assessment. Last year, I needed persuasion to use adjuvant anastrozole. It was a nice option if tamoxifen could not be tolerated or was contraindicated.

This year, however, with the updated efficacy and safety data, my position has changed. Now, my default therapy for ER-positive postmenopausal women is anastrozole unless contraindicated. We have another year of follow-up in the ATAC trial, and I am impressed by the separation of the curves. The safety update is also comforting. The fracture rate isn't racing away, the relative risks are stable and the other safety profile issues strongly continue to favor anastrozole.

— Michael Baum, ChM, FRCS

Currently, I uniformly recommend anastrozole to my patients at high risk for recurrence. I also use anastrozole in patients who are experiencing problems with tamoxifen — severe hot flashes, weight gain or issues related to their uterine status. Occasionally, I have had patients on anastrozole who switched to tamoxifen because of arthralgias. Tamoxifen is still a reasonable choice in an older patient with a low risk of recurrence. I have not switched a patient who was doing well on tamoxifen to anastrozole. I also have not used the other aromatase inhibitors outside of a clinical trial, because the data is with anastrozole.

— Nicholas J Robert, MD

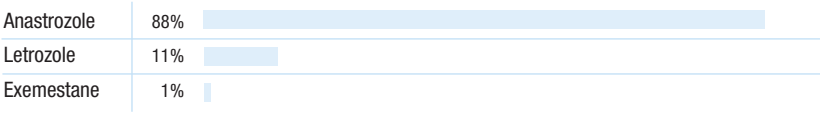
My personal take on the ATAC presentation in 2001 was that we should switch from tamoxifen to anastrozole for adjuvant therapy. The curves were convincing, and the trend is likely to increase with time.

When selecting an aromatase inhibitor, clinically, it makes sense to use anastrozole because we have the data to support it. From a research perspective, it's probable that other compounds will yield the same or even better results. Medical-legally, it would be difficult to defend the choice of another aromatase inhibitor for which there is no data over anastrozole in the clinical setting.

— Paul E Goss, MD, PhD, FRCP(CA), FRCP(UK)

Use of Other Aromatase Inhibitors in the Adjuvant Setting

When you use aromatase inhibitors in the adjuvant setting, which agent do you generally use?



Editor's Note

Although many research leaders are optimistic that future clinical trials will demonstrate benefits for other aromatase inhibitors other than anastrozole in the adjuvant setting, most clinicians utilize only anastrozole for nonprotocol adjuvant therapy.

Research Leader Commentary

Bill Miller and Per Lonning warn us not to make assumptions about the efficacy and tolerability of the three aromatase inhibitors because there are very subtle differences between them. We cannot extrapolate from ATAC to exemestane because there may be differences in efficacy and tolerability between the steroidal and nonsteroidal agents. Exemestane is a permanent antiaromatase with weak androgenic effects.

Letrozole and anastrozole are nonsteroidal aromatase inhibitors, but letrozole appears to produce a slightly greater reduction in aromatase. While one might predict this would cause greater efficacy, the tiny trickle of estrogen left by anastrozole may be important for tolerability. We cannot assume a class effect — we must do the trials.

— Michael Baum, ChM, FRCS

I do not use aromatase inhibitors other than anastrozole in the adjuvant setting because there are no data. While we have to extrapolate in a number of situations, I do not see an advantage of the other aromatase inhibitors from the existing data. It is possible that some time in the future, someone will show a distinct advantage of one of these other agents, but at this point, the data were generated with anastrozole, so I use anastrozole.

— Gabriel N Hortobagyi, MD

There are no data for letrozole or exemestane in the adjuvant setting. Anastrozole is the only drug that's been tested in that setting, and I believe it is the drug we should use.

Each of the aromatase inhibitors is slightly different, and they have slightly different effects on circulating estrogen levels. Exemestane may have some androgenic activity, which may have some beneficial effects, but it may have some negative effects as well. It may have some better bone effects, but it may cause a bit more weight gain. We don't know at the moment.

We probably need some direct comparative data of the side-effect profiles of the different drugs. I suspect it might come down to which is the most tolerable, since they're all effective. Anastrozole has a head start because it has a better side-effect profile than tamoxifen, and we always thought tamoxifen was a pretty safe drug. Until we have data comparing the different drugs, we have to use the drug that has been tested in this setting.

— J Michael Dixon, MD, FRCS

Tolerability of Tamoxifen

What percent of your patients has difficulty tolerating tamoxifen?

Difficulty tolerating tamoxifen	19%
No difficulty tolerating tamoxifen	81%

In the adjuvant setting, how many postmenopausal patients have you switched from tamoxifen to an aromatase inhibitor because the patient had difficulty tolerating tamoxifen?

Mean	11 patients

Editor's Note

While most research leaders have not advocated routinely switching from adjuvant tamoxifen to aromatase inhibitors, a significant number of patients have difficulty tolerating tamoxifen, and these women may be candidates to switch therapy.

Research Leader Commentary

Vasomotor symptoms are a real problem for women taking tamoxifen. A number of our patients have had to stop tamoxifen because their quality of life was so poor. The long-term prognosis is excellent for many women on adjuvant hormonal therapy; therefore, it's not a great idea to give them a drug that makes them feel worse.

With tamoxifen, some women are also disabled by vaginal discharge. This is particularly true of women with any degree of prolapse who have a constant leak. For a few women, it affects their quality of life to a major degree. In the metastatic setting, there was virtually no vaginal discharge associated with the aromatase inhibitors, and it has not been a problem in the adjuvant setting.

A large percentage of women on tamoxifen complain of weight gain, while anastrozole doesn't seem to cause weight gain. The art of medicine is to find agents that suit the patient and minimize the side effects. Anastrozole offers us another option. Tolerability of anastrozole is excellent in the group of patients we've treated, who tend to be a bit older. The patients come in and say, "How do I know I'm on a drug? Because I don't feel any different. I don't have any side effects."

— J Michael Dixon, MD, FRCS

The biggest problem with tamoxifen is not the risk of thromboembolism or uterine cancer, but managing uterine bleeding. Any woman who has uterine bleeding on tamoxifen goes through a panoply of tests, which causes a great deal of anxiety. A large percentage of women, sometime during their five years of therapy, undergo a gynecologic procedure.

This is what's really unacceptable about tamoxifen. We overinvestigate some of these symptoms. This may be due to our medical-legal milieu, but it contributes to a miserable lifestyle and a lot of anxiety for women on tamoxifen in the adjuvant and preventative settings.

— Gershon Locker, MD

Counseling Postmenopausal Women About Adjuvant Endocrine Therapy Options

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

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

Editor's Note

Most clinicians in practice discuss both tamoxifen and aromatase inhibitors as treatment options for postmenopausal patients being considered for adjuvant endocrine therapy.

Research Leader Commentary

In counseling postmenopausal women about adjuvant endocrine therapy, it's a lot longer discussion now than in the past, because I feel obligated to discuss the ATAC trial in some detail and talk with people about their preferences. Some women are pretty clear that they want anastrozole, and I am comfortable prescribing it to them. Obviously, if a woman has contraindications to tamoxifen, it's a pretty easy decision.

— Nancy Davidson, MD

Over the past 30 years in medicine, we have moved from a paternalistic approach to the other extreme. Many of my colleagues try to be so neutral that they do not make a recommendation. I understand and agree that patients need to have autonomy. We clearly have the obligation to inform them fully, but I think we need to go beyond that. We have to get to know our patients and understand their motivations, their understanding of risks and benefits, their definition of therapeutic gain and their acceptable level of risks and side effects. As physicians, we need to help them make a decision.

Since the safety profile of anastrozole is better than tamoxifen and it is therapeutically superior, I have a problem not offering anastrozole to my postmenopausal patients — not as a neutral choice but as a better choice. I discuss with my patients the enormous amount of clinical experience we have with tamoxifen, but if my sister developed breast cancer today, I would certainly recommend anastrozole as opposed to tamoxifen.

— Gabriel N Hortobagyi, MD

Adjuvant Endocrine Therapy in Premenopausal Women

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

	33-year-old (premenopausal, menstruating after chemotherapy)	43-year-old (premenopausal to start, but stops menstruating after chemo and has postmenopausal estradiol and FSH/LH levels)
Tamoxifen	69%	67%
Anastrozole	6%	27%
Tamoxifen + GnRH agonist	14%	3%
GnRH agonist alone	8%	—
Anastrozole + GnRH agonist	3%	—
Letrozole	—	3%

Editor's Note

Tamoxifen is still considered standard endocrine therapy for premenopausal patients, but anastrozole is also considered an option in patients who become postmenopausal after receiving adjuvant chemotherapy.

Research Leader Commentary

The Early Breast Cancer Trialists' Collaborative Group Overview results indicated a beneficial effect of ovarian ablation. This treatment significantly improved long-term survival for women younger than 50 years of age, at least in the absence of chemotherapy. Long-term side effects, mainly for young women, are still a significant issue when this treatment is offered especially because the safety of treatments for menopausal symptoms is unknown. For premenopausal women with endocrine-responsive disease, ovarian function suppression (goserelin) with or without tamoxifen appeared to be at least as effective as CMF chemotherapy alone, and information is available that the addition of tamoxifen to goserelin is more effective than goserelin alone, at least in the presence of chemotherapy.

— *Goldhirsch A et al. J Clin Oncol 2003;21(17):1-9.*

In terms of determining whether a woman is pre- or postmenopausal, I usually just assess patients clinically, not by testing with blood work. If their menstrual periods go away, usually I'm already giving tamoxifen if the patient is ER-positive, so I don't actually need to know her menopausal status to approach that. If we were routinely using anastrozole in postmenopausal women — and we are in that transition time right now — then we might have to work a little harder to make sure they truly are postmenopausal. The other issue is that women can become transiently postmenopausal and have recovery of ovarian function at a later date.

— *Nancy Davidson, MD*

Aromatase Inhibitors in Premenopausal Women

Have you prescribed aromatase inhibitors in the adjuvant setting for premenopausal women?

No	75%
Yes, alone	5%
Yes, with ovarian suppression	18%
Yes, both (alone and with ovarian ablation)	2%

Have you prescribed aromatase inhibitors in the metastatic setting for premenopausal women?

No	55%
Yes, alone	15%
Yes, with ovarian suppression	25%
Yes, both (alone and with ovarian ablation)	5%

Editor's Note

Aromatase inhibitors should only be given to premenopausal women in combination with ovarian suppression or ablation, and this strategy is utilized by some clinicians, both in the adjuvant and advanced disease settings.

Research Leader Commentary

I'm very enthusiastic about the research strategy of looking at LHRH agonists with aromatase inhibitors. Extrapolating from the early data in postmenopausal breast cancer, which suggested that anastrozole may have superior efficacy compared to tamoxifen, this also seems like a rational strategy to transfer to premenopausal women. The two issues are whether or not it is actually going to be efficacious, and what is the cost in terms of side effects. I wouldn't utilize this strategy outside the context of a clinical trial.

The adjuvant ovarian suppression trial that I am most enthusiastic about is the Suppression of Ovarian Function Trial (SOFT). Premenopausal, ER-positive women who may or may not have received chemotherapy will be randomized to tamoxifen for five years, ovarian suppression/ablation plus tamoxifen, or ovarian suppression/ablation plus an aromatase inhibitor. This very interesting trial will help us address several issues. Does ovarian ablation or suppression add to tamoxifen? And if this is an important strategy, is it better to use tamoxifen or an aromatase inhibitor in those women with suppression.

— Nancy Davidson, MD

Impact of Age on Choice of Adjuvant Endocrine Therapy

Postmenopausal women with 2.2-cm, ER-positive, HER2-negative IDC and 10 positive nodes: If you recommend adjuvant endocrine therapy, which agent would you select?

Patient age	Tamoxifen	Anastrozole	Other Aromatase Inhibitor
55	43%	51%	6%
65	35%	59%	6%
77	43%	49%	8%

Editor's Note

Although some research leaders have suggested that anastrozole may be particularly advantageous in older women who are at greater risk for cardiovascular disease, no clear age relationship was noted in this survey.

Research Leader Commentary

Tamoxifen is generally a safe drug, but in women over the age of 70, there is an excess baseline risk of stroke and I strongly consider an aromatase inhibitor. Even in lower-risk women, my threshold for an aromatase inhibitor goes a little lower in those over the age of 70, mostly because of the risk of stroke.

— Debu Tripathy, MD

In many cases, anastrozole has a better side-effect profile than tamoxifen. Although, there were more fractures in the patients on anastrozole, there were less thromboembolic events, hot flashes and endometrial cancers. In addition, while some of tamoxifen's side effects are manageable, they are usually not preventable.

In contrast, anastrozole's main side effect — bone fractures — can potentially be prevented with bisphosphonates, calcium supplements or exercise. Some clinicians would rather take the risk to gain better efficacy, and they may elect to start patients on a bisphosphonate to hopefully prevent bone mineral density loss. The large number of patients in the ATAC trial gives us confidence that there are not any serious but uncommon side effects associated with anastrozole.

— John F Robertson, MD, FRCS

An important consideration, especially in the adjuvant breast cancer setting where drugs will be prescribed for long periods of time, is the side-effect profile of the drug... .The findings from the advanced-disease setting with respect to thromboembolic events, vaginal bleeding, and arthralgia were confirmed in this trial after long-term treatment. Among the predetermined adverse events analysed, in comparison with tamoxifen, treatment with anastrozole led to significantly fewer episodes of hot flushes, vaginal discharge, vaginal bleeding, endometrial cancer, strokes and thromboembolic disease (including thrombophlebitis and deep venous thromboembolic events).

— ATAC Trialists' Group. Lancet 2002;359(9324):2131-9.

Impact of Tumor Size and Nodal Status on Choice of Adjuvant Endocrine Therapy

65-year-old woman with ER-positive, HER2-negative IDC: If you recommend adjuvant endocrine therapy, which agent would you recommend?

Tumor characteristics	Tamoxifen	Anastrozole	Other Aromatase Inhibitor
2.2-cm, 10 positive nodes	35%	59%	6%
2.2-cm, negative nodes	47%	45%	8%
0.8-cm, negative nodes	54%	38%	8%

Editor's Note

Use of anastrozole increases with the risk of relapse, perhaps reflecting the demonstration of reduction in recurrence rate noted in the ATAC trial.

Research Leader Commentary

Until the update presented in 2002, I had not changed my clinical practice based on the early ATAC results. I was waiting to see more data and whether or not the curves were coming together. However, at 47 months, the divergence of the curves shows a three percent advantage for anastrozole. There will not be three percent events in either arm over the next year; therefore, the anastrozole advantage will continue to be the same or greater in the next year.

I will now tell patients that there are two options. One option, tamoxifen, seems less efficacious in the short-term, but we know its short- and long-term toxicities. With anastrozole, the time to relapse is substantially improved at the four-year point, but we really don't have any long-term safety or efficacy data. The FDA did, however, find adequate evidence to allow approval of the drug in the adjuvant setting. There is a risk with either therapy, and some patients will want the new therapy which has the potential to be better.

— Peter Ravdin, MD, PhD

When I heard the ATAC trial data last year, I was impressed. It's a large trial of more than 9,000 patients, and the disease-free survival benefit with anastrozole was credible. It was interesting that the combination didn't work, but anastrozole certainly appeared superior to tamoxifen.

The results of the 47-month update show continued improvement in disease-free survival with actual improvement in the hazard rate with time, which provides even more support for the use of anastrozole in the adjuvant setting.

— Nicholas J Robert, MD

Change in Adjuvant Endocrine Therapy Use Since 2002

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

	2002	2003
Tamoxifen	63%	35%
Anastrozole	31%	59%
Other Aromatase Inhibitor	6%	6%

Editor's Note

There has been a significant shift in the last year toward use of anastrozole in high-risk situations, perhaps reflecting the encouraging 47-month ATAC trial follow-up presented in San Antonio in December 2002.

Research Leader Commentary

The ASCO technology assessment that does not support the use of adjuvant anastrozole outside a clinical trial is based on fear of the unknown in the face of the single largest clinical trial ever conducted in the adjuvant setting. We have no comparable trial in the history of medical oncology or breast cancer, and there is no other tumor type with so many well-planned clinical trials conducted.

We are in a leadership position in oncology, and we can't advocate doing the best trials and then ignore the results of those trials. Every single trial we do brings with it some of the unknown.

We began using tamoxifen well before we had a five-year follow-up. I remember when Michael Baum presented the early data from the NATO trial in 1982. It had less than two years of follow-up, and he was already publicly talking about the advantages of adjuvant tamoxifen — and the NATO trial pales in size and design in comparison to the ATAC trial.

We have very compelling data about anastrozole from the ATAC trial, in terms of its therapeutic and safety profile superiority. I would be doing a disservice to my patients who are candidates for adjuvant anti-aromatase therapy by not presenting the data.

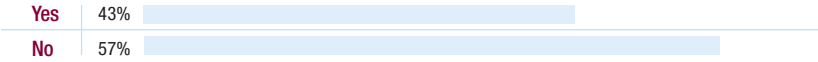
I also present tamoxifen as an option. About 60 percent of my postmenopausal patients chose anastrozole rather than tamoxifen. There is no right or wrong decision, but for me, there are compelling data to prefer one versus the other.

— *Gabriel N Hortobagyi, MD*

Bone Density in Patients on Adjuvant Aromatase Inhibitors

Do you routinely evaluate bone density in your patients on adjuvant aromatase inhibitors?

Do you use bisphosphonates preventively in your patients on adjuvant aromatase inhibitors?



Editor's Note

Most clinicians are evaluating bone density in women receiving aromatase inhibitors in the adjuvant setting, and bisphosphonates are commonly used preventively.

Research Leader Commentary

Loss of bone mineral density with anastrozole can be monitored. We don't withhold chemotherapy because we are worried about the white cell count — we give it, but we monitor the white cell count. Osteopenia is not a dramatic crisis like neutropenia. I would check bone mineral density at diagnosis, upon initiation of anastrozole and annually thereafter. I would intervene with a bisphosphonate if it started to fall. The one adverse effect favoring tamoxifen over anastrozole can be managed.

— Michael Baum, ChM, FRCS

The data presented by Dr Gnant in San Antonio, demonstrating that zoledronate reversed the bone loss associated with hormonal therapy in premenopausal patients treated with an LHRH agonist and anastrozole, was very interesting. Bone is my major concern when I'm considering anastrozole in the adjuvant setting, because many of these women have small cancers and, in reality, have an excellent prognosis.

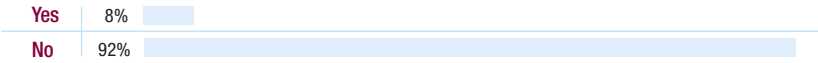
I obtain bone mineral density at the initiation of an aromatase inhibitor. If patients have good bone mineral density, I urge exercise and calcium. If they have osteopenia, I initiate bisphosphonates. If they have osteoporosis, I think long and hard about whether that patient might be better served with tamoxifen.

We fear bone loss today, but if the bisphosphonate studies demonstrate that they will decrease metastatic risk, then bisphosphonates will become commonplace in the treatment of early stage breast cancer.

— Generosa Grana, MD

Adjuvant Trastuzumab Outside the Clinical Trial Setting

65-year-old woman with 2.2-cm, ER-positive, HER2-positive IDC and 10 positive nodes: Would you recommend adjuvant trastuzumab?



Editor's Note

Trastuzumab is currently being studied in a number of key Phase III adjuvant trials, but most clinicians do not use this therapy outside a protocol setting, even in patients at very high risk.

Research Leader Commentary

I have not used adjuvant trastuzumab in a nonprotocol setting. Our experience with bone marrow transplantation taught us that we could not always trust our preconceived notions about what would work. We need to answer the questions regarding adjuvant trastuzumab quickly, so I have only been entering patients — even those with high-risk, 10 or more positive nodes or inflammatory disease — in clinical trials.

— Melody A Cobleigh, MD

Whether it makes sense to use adjuvant trastuzumab in a woman whose odds of dying from breast cancer are less than the odds of dying from atherosclerotic heart disease is a major research question. We do not know the answer yet. Therefore, adjuvant trastuzumab is being evaluated in women with high-risk, node-positive disease, in whom the potential benefits might be at least proportionally larger.

It may be reasonable to use adjuvant trastuzumab off-protocol for a young woman with multiple (e.g., 15) positive nodes and HER2-positive disease, or for a young woman with HER2-positive, inflammatory breast cancer. Although I personally have not done that, I think it is sound medical judgment as long as the patient is informed of the potential toxicities.

— Debu Tripathy, MD

In the nonprotocol adjuvant setting, it's hard to know the right thing to do. I've evaluated patients with high-risk disease — 10 or more positive nodes — in whom I've considered adjuvant trastuzumab therapy off protocol.

I don't want to say that this is something that is widely done at our center — it's infrequent and uncommon. However, the prospects for a patient with that type of disease are really unacceptable. If you consider that trastuzumab prolongs survival in patients with metastatic disease, biologically there are probably many similarities between high-risk Stage II and advanced disease. Therefore, that would be an interesting patient population to study, and off protocol we have considered such patients for adjuvant trastuzumab therapy.

— Mark D Pegram, MD

With regard to adjuvant trastuzumab, I am a purist on this issue and a big believer in the randomized trials — I have not given any adjuvant trastuzumab outside the context of a clinical trial.

— Nancy Davidson, MD

Adjuvant Trastuzumab Outside the Clinical Trial Setting

Have you ever used trastuzumab in the adjuvant setting outside the context of a clinical trial?

Yes	18%
No	82%

In how many patients have you used adjuvant trastuzumab?

Mean	7 patients

Editor's Note

A minority of clinicians have utilized adjuvant trastuzumab outside a protocol setting in select patients, although most research leaders do not support that practice.

Research Leader Commentary

If someone uses trastuzumab outside of the clinical trial setting, they're essentially shooting in the dark. We do not yet understand the duration of therapy, the schedule to be used in combination with chemotherapy and the potential risks or benefits the patients may derive.

There are several clinical protocols available including our Intergroup trial. I hope that every woman diagnosed with breast cancer tells her physician, "If I have this bad prognosis, I want to participate in the clinical trial that will help answer the question."

The NSABP is also conducting a very good adjuvant trial, also based on solid scientific principles. The NSABP trial has two arms — AC followed by paclitaxel, and AC followed by paclitaxel concurrent with trastuzumab for three months, followed by trastuzumab alone. Our NCCTG trial has three arms. NSABP-B-31 is using paclitaxel once every three weeks, as in CALGB-9344, while N9831 is utilizing weekly paclitaxel.

— Edith Perez, MD

The ongoing clinical trials of trastuzumab in the adjuvant, locally advanced and inflammatory settings are likely to give us a lot of information in the next few years. If the data in patients with local disease shows the same results as in the metastatic setting for trastuzumab, it will be an exciting day.

The research question that has to be answered is: How do we use it appropriately? Do we use AC followed by paclitaxel and concurrent trastuzumab, or should we be using a nonanthracycline-containing regimen to avoid cardiac toxicity? Those two questions are going to be very important to address in clinical trials.

I have not been using trastuzumab in the adjuvant setting but have used it for locally advanced and inflammatory disease. I'm selective in choosing patients for whom I'll use it. Often, it will be the patient who did not respond well to AC or had very aggressive disease.

— Generosa Grana, MD

Clinical Use of Tumor Markers

Do you use tumor markers for follow-up in the following situations?

	Node-positive primary disease	Metastatic disease
Never	15%	10%
Rarely	12%	10%
Occasionally	20%	10%
Commonly	53%	70%

Editor's Note

Although screening with tumor markers is not considered standard of care, many clinicians utilize this approach in high-risk adjuvant and metastatic settings.

Research Leader Commentary

I don't know of any reason to use markers, because it's not clear that initiating therapy based on marker elevations helps patients' outcomes in the long term.

I don't want to be absolute about it. The fact of the matter is that I actually have this discussion with patients. I tend to sway them away from using markers, but I do tell them that there are very rare potential scenarios in which one, in retrospect, might say, "I wish I'd used a marker." For example, in a patient who develops a fairly rapid complication, such as a tumor-related brachial plexus problem, and by the time you start them on chemotherapy you cannot alleviate symptoms. You might have saved, or at least delayed, the onset of that problem.

The risk of using tumor markers is that we might overreact. We take a patient who perhaps didn't need to be exposed to the side effects of chemotherapy for quite some time, and expose them much earlier because of elevated serum markers, but we don't affect their overall clinical course or their survival. The serum marker problem can cut both ways in terms of helping you or hurting you.

— Debu Tripathy, MD

In general, I think we wait too long before changing therapies, because we actually wait for tumor regrowth. Even if we obtain a good response to one drug, we wait for tumor regrowth before we switch and we probably should switch sooner.

I think this is one of the key things we have to start looking at in terms of clinical trials and monitoring patients. PET scanning and tumor markers might be very useful in this regard. It might be more advantageous to change therapies when the tumor markers rise than when there's imaging evidence of disease progression.

Earlier diagnosis of metastatic disease may make a significant difference if your therapy is effective. At Memorial Sloan-Kettering Cancer Center we have a tumor vaccine protocol for patients with rising markers without clinical evidence of disease. This is where vaccines may make a difference.

— Larry Norton, MD

Patient Perspectives on Therapy in the Metastatic Setting

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

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

In what percentage of your patients with metastatic disease is alopecia a major concern with chemotherapy?

Major concern	34%
Not a major concern	66%

In what percentage of your patients with metastatic disease is having intravenous chemotherapy as opposed to oral therapy a major concern?

Major concern	17%
Not a major concern	83%

Editor's Note

Clinicians perceive that most women with metastatic breast cancer are concerned about both tumor control and minimizing treatment morbidity.

Research Leader Commentary

Patients who relapse after adjuvant therapy are scared to death, and most of them are still in the "fight mode" at that point. If a patient wants the most effective therapy, I will recommend combination chemotherapy. However, many older women with very indolent disease who have undergone treatment for a long time consider their quality of life to be very important. For these patients, being treated with a very effective pill like capecitabine is attractive.

Capecitabine monotherapy is a very reasonable option for metastatic breast cancer. We did a small, randomized Phase II trial comparing intravenous CMF and full-dose capecitabine as front-line therapy in elderly patients. The response rate with capecitabine was 30 percent compared to 16 percent with intravenous CMF.

In a randomized Phase II trial of anthracycline-pretreated patients, comparing paclitaxel to capecitabine, the response with the capecitabine was 36 percent compared to 26 percent with paclitaxel. The confidence intervals were widely overlapping, so we couldn't conclude that capecitabine is superior, but what we can say from these two studies is that it's certainly unlikely that capecitabine is worse than CMF or paclitaxel.

— Joyce O'Shaughnessy, MD

Combination Versus Sequential Chemotherapy in the Metastatic Setting

Would you generally use combination or sequential single-agent chemotherapy in women in their 50s with ER/PR-negative, HER2-negative breast cancer in each of the following metastatic situations?

Clinical situation	Combination	Sequential single agents
Asymptomatic patients with bone metastases	23%	77%
Asymptomatic patients with several small lung metastases	30%	70%
Asymptomatic patients with several small hepatic metastases	38%	62%
Patients with moderate pain requiring oral narcotics with bone metastases	50%	50%
Very symptomatic patients with visceral metastases	85%	15%

Editor's Note

Single-agent chemotherapy is the most common approach to asymptomatic patients with metastatic disease, but combination therapy is more commonly utilized in symptomatic patients.

Research Leader Commentary

ECOG-1193 compared doxorubicin (A) to paclitaxel (T) — with a crossover at progression — to the combination (AT). There was no difference in survival, and patients treated with AT have a worse quality of life than those treated with sequential single-agent therapy. I do not use combination chemotherapy in the metastatic setting, except in patients with life-threatening disease. If the patient has not had an anthracycline or taxane recently, I would probably use AT. Capecitabine/docetaxel is another option for patients who have recently progressed on an anthracycline.

— Melody A Cobleigh, MD

The ECOG-1193 trial compared doxorubicin followed by paclitaxel at disease progression to paclitaxel followed by doxorubicin at disease progression to the combination. While the response rate was higher with the combination, survival was identical in the three arms. I am philosophically more inclined toward sequential single-agent therapy in metastatic breast cancer. However, I'm fascinated by the capecitabine/docetaxel trial.

Most of the women on that trial who took docetaxel alone did not get exposure to capecitabine, and I suspect that if there had been a crossover arm, the survival would not have been much different. Having said that, I am an enthusiast about the adjuvant and neoadjuvant trials looking at the combination of capecitabine/docetaxel.

— Nancy Davidson, MD

Chemotherapy Combinations in Metastatic Disease

Patient has ER/PR-negative, HER2-negative metastatic disease: When you use combination chemotherapy in these women, what combinations do you generally use?

	Adjuvant chemotherapy		
Agents	**No prior therapy**	**AC-paclitaxel two years ago**	**AC two years ago**
Capecitabine/docetaxel	16%	64%	61%
AC	29%	—	—
FAC/FEC	26%	6%	3%
AT (either taxane)	16%	3%	6%
Platinum agent/docetaxel	3%	9%	9%
Capecitabine/paclitaxel	—	3%	6%
Other	10%	15%	15%

Editor's Note

Capecitabine combined with docetaxel is the most common chemotherapy combination utilized in patients with prior adjuvant chemotherapy.

Research Leader Commentary

Putting the clinical trial data together, the evidence that combination treatment is inherently superior to sequential treatment is not strong. The evidence favouring combination therapy is best for paclitaxel with trastuzumab and docetaxel with capecitabine. In both cases, the agents combined are distinct in their mode of action and may demonstrate genuine synergy… perhaps, the most provocative comparison is with another study investigating the addition of an active drug, vinorelbine, to standard single-agent treatment with doxorubicin. In this trial, the combination of doxorubicin and vinorelbine was more toxic and there was no improvement in the response rate or time to progression with the allocated therapy. Likewise, when paclitaxel was compared with cyclophosphamide as a partner for doxorubicin, increased toxicity and a consequent loss of delivered doxorubicin dose intensity resulted in there being no impact on the response rate or other measures of efficacy. Clearly, simply combining cytotoxics with proven single-agent activity does not necessarily lead to improvement even in terms of response rate.

— Wright TL et al. Eur J Cancer 2002;38:1957-60.

I believe that in patients with relatively asymptomatic indolent disease, it is very reasonable to give docetaxel and capecitabine sequentially. Conversely, there is a subgroup of patients with more aggressive, symptomatic disease who will not have the opportunity to receive sequential therapy. For these patients, the capecitabine/docetaxel combination may be preferred. There is also a hypothesis that a trial comparing capecitabine/docetaxel to docetaxel followed by capecitabine would still result in a survival advantage for the combination. The combination has a very clear biochemical and preclinical synergy, is quite different from most other doublets. Docetaxel upregulates thymidine phosphorylase, which leads to the enhanced conversion of the capecitabine prodrug to 5-FU at the tumor site.

— Joyce O'Shaughnessy, MD

Sequencing of Single Agents in Chemotherapy-Naïve Patients With Metastatic Disease

Postmenopausal women with ER/PR-negative, HER2-negative metastatic disease who received no prior chemotherapy: What sequence of sequential single-agent chemotherapy do you typically use?

Agent	1st line	2nd line	3rd line
Docetaxel	58%	28%	5%
Doxorubicin	30%	23%	8%
Paclitaxel	10%	18%	—
Capecitabine	2%	17%	38%
Vinorelbine	—	7%	20%
Gemcitabine	—	5%	25%
Cyclophosphamide	—	2%	2%
None	—	—	2%

Editor's Note

Taxanes and anthracyclines are the most common single agents utilized in women with no prior chemotherapy. Capecitabine is the most common third-line agent.

Research Leader Commentary

In the metastatic setting, I generally treat ER-negative patients with an anthracycline-containing regimen first and a taxane or taxane-containing regimen second. I use capecitabine in patients who are relatively asymptomatic and want something milder or prefer oral therapy. Otherwise, I tend to use this agent in the third-line setting. Many of our patients have failed adjuvant anthracyclines, so it's usually a choice of either a taxane-containing regimen or something a bit milder. We use a lot of capecitabine and vinorelbine, but we don't know how their response rates compare to anthracyclines or taxanes. My guess is that it doesn't make a lot of difference.

— Kathleen I Pritchard, MD

What you do early in their treatment may never be reflected in a survival advantage, because they have many other opportunities for treatment down the line.

In a chemotherapy-naïve patient with metastatic disease, I generally use docetaxel/capecitabine (XT). There is no evidence that you harm the patient in any way if you give an anthracycline after a taxane. I eventually use an anthracycline, but I just don't feel compelled to use it up front. The decision whether to use a single-agent taxane or single-agent capecitabine or the combination for front-line therapy depends on factors such as the patient's presentation and the extent of her disease.

As we get into later-line therapy, when patients become more symptomatic, more heavily tumor-burdened and their life expectancy is shortening, I think a very reasonable argument can be made for better palliation and maybe even better survival with a well-tolerated combination regimen.

— Joyce O'Shaughnessy, MD

Sequencing of Single Agents in Metastatic Disease after Adjuvant AC

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

Agent	1st line	2nd line	3rd line
Docetaxel	65%	30%	3%
Paclitaxel	20%	2%	2%
Capecitabine	8%	33%	23%
Vinorelbine	—	20%	33%
Gemcitabine	2%	8%	35%
Doxorubicin	5%	5%	2%
Cyclophosphamide	—	—	2%
Platinum	—	2%	—

Editor's Note

For patients with prior AC chemotherapy, taxanes and capecitabine are the next agents commonly utilized.

Research Leader Commentary

The goals of treatment in the metastatic setting are disease control — providing symptoms are modest — and quality of life. I use a lot of single-agent capecitabine. In two small randomized Phase II trials, which should really not be compared, the response rates are similar to CMF or paclitaxel. Additionally, capecitabine is an oral agent, and it does not cause hair loss. Many patients have had prior adjuvant chemotherapy, and they may have had bad experiences from previous hair loss. Capecitabine is an extremely well-tolerated drug. It is rare to see myelosuppression with capecitabine and the diarrhea is generally modest. If a patient does not have hand-foot syndrome, they will probably tolerate it very well.

— Hyman B Muss, MD

After 20 years of a relative drought in drug development, we have witnessed the approval of ten new agents for the treatment of MBC in the last eight years. Several of these agents changed the natural history of advanced breast cancer and replaced older agents that we had used for decades. The role of chemotherapy for the palliative treatment of patients with hormone-insensitive (estrogen receptor/progesterone receptor [ER/PR]-negative) or hormonal therapy-refractory MBC is well established. The most important cytotoxic agents employed between the 1970s and the mid-1990s were the anthracyclines (doxorubicin and epirubicin). Anthracycline-containing regimens were proven superior to regimens that did not include anthracyclines in randomized clinical trials. Therefore, for two decades, anthracycline therapy was the backbone of palliative regimens for patients with MBC. However, within the past decade, three new cytotoxic agents (paclitaxel, docetaxel and capecitabine) were approved for the treatment of MBC. All three agents improved the overall survival (OS) of patients with MBC in well-designed controlled clinical trials.

— Valero V et al. J Clin Oncol 2003;21(6):959-62.

Sequencing of Single Agents in Metastatic Disease After Adjuvant AC-Paclitaxel

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

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

Editor's Note

For patients with prior AC→T chemotherapy, docetaxel and capecitabine are the next agents commonly utilized.

Research Leader Commentary

Based on cross-trial comparisons of Phase II data, many single agents have very similar response rates and times to progression. Given the relative equivalence of capecitabine, vinorelbine and gemcitabine in patients who have failed a taxane and an anthracycline, I make decisions based on convenience and toxicity.

If patients have not been treated with an anthracycline or a taxane, I start with those first. But many of the patients with metastatic disease whom we're seeing now have already failed an anthracycline or a taxane in the adjuvant setting, and we have to consider moving on to different classes, especially if they've relapsed quickly.

If they've had a long disease-free interval, then we treat them with either a taxane or anthracycline. However, in the taxane and anthracycline failures, capecitabine really is a strong consideration because of its convenience for the patient.

—Mark D Pegram, MD

Few patients present *de novo* with MBC, and the great majority of patients who later develop MBC are now receiving anthracycline-based adjuvant therapy. In fact, paclitaxel is approved by the United States Food and Drug Administration for adjuvant chemotherapy of primary breast cancer, so many patients with lymph node-positive breast cancer also receive a taxane following (or in combination with) anthracycline-based adjuvant chemotherapy. Therefore, fewer patients will be candidates for anthracycline/taxane combinations in the metastatic setting.

— Valero V et al. J Clin Oncol 2003;21(6):959-62.

First-Line Chemotherapy for Asymptomatic Bone Metastases

Patient treated two years ago with adjuvant AC chemotherapy for ER-negative, HER2-negative IDC, now with rising tumor markers and asymptomatic bone metastases: Would you recommend chemotherapy?

	57-year-old	75-year-old
Percent recommending chemotherapy	85%	70%

If you would recommend chemotherapy, which agent would you choose?

	57-year-old	75-year-old
Docetaxel	58%	43%
Capecitabine	15%	36%
Vinorelbine	3%	14%
Paclitaxel	9%	—
Other	15%	7%

Editor's Note

Patients with asymptomatic bone metastases following adjuvant AC chemotherapy are likely to be treated with chemotherapy either a taxane or capecitabine.

Research Leader Commentary

Whenever possible, I like to observe patients with hormone receptor-negative, HER2-negative minimal disease as opposed to starting cytotoxic chemotherapy, because I'm really not convinced that the early institution of cytotoxic chemotherapy leads to a survival advantage.

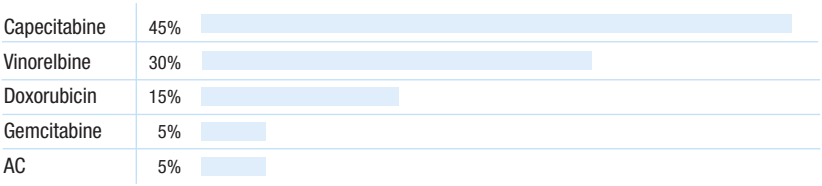
It is likely to impact negatively on quality of life. On the other hand, the vast majority of women, once they know they have metastatic disease, are not going to accept the concept of observation.

When it comes to cytotoxic chemotherapy, my choice would not necessarily be an anthracycline and probably not even a taxane. I'm impressed with the tolerability of — and response — to single-agent therapy with capecitabine, vinorelbine, liposomal doxorubicin or gemcitabine. CMF is also a well-tolerated regimen. Another regimen that we use is a combination of mitoxantrone, 5-FU and leucovorin.

— Charles L Vogel, MD, FACP

Second-Line Chemotherapy After Docetaxel

57-year-old woman treated two years ago with adjuvant AC chemotherapy for ER-negative, HER2-negative IDC, now with rising tumor markers and asymptomatic bone metastases, treated with first-line docetaxel: What would you recommend if the disease progressed on docetaxel?



Editor's Note

Capecitabine is the most likely agent used after progression on a taxane in this situation.

Research Leader Commentary

Kathy Miller presented a case at a seminar recently in which the patient progressed shortly after receiving adjuvant ACT. When the members of the audience were asked what agent they would use next, the most common answer was capecitabine alone. I was surprised by that because the acceptance of capecitabine was slow in the beginning.

I attribute this slow acceptance to two factors. First, capecitabine was approved at too high a dose, so many physicians had an unfavorable first experience using it. Second, capecitabine is the first drug I can think of that was approved before there were any publications in the literature.

Physician acceptance has grown as lower doses have been tried and patients' tolerance has improved. In addition, articles have suggested a relatively high response rate with capecitabine as first-line therapy and in combination therapy, particularly with docetaxel.

— Peter Ravdin, MD, PhD

In hormone-refractory disease, patients will be on chemotherapy indefinitely. We have to consider their lifestyle, figure out what's important to them and be able to accommodate their needs, consistent with good medical practice. Patients must consider the schedule, how frequently they need to come to the clinic and the toxicities of the particular agents.

It's hard to say that any individual single agent is the gold standard. We have the taxanes and the anthracyclines, but the newer agents, such as capecitabine, are also perfectly reasonable to use as front-line agents. In some patients, I would see no problem in doing that. I'm not sure that the sequence in which we use agents makes a difference; therefore, we tend to use the agent with the least toxicity or the toxicity profile most consistent with the patient's needs.

— G Thomas Budd, MD

First-Line Chemotherapy for Symptomatic Metastatic Disease

Patient was treated two years ago with adjuvant AC chemotherapy for ER-negative, HER2-negative IDC, and is now very symptomatic with bone and lung metastases: Which chemotherapy would you recommend?

	57-year-old	75-year-old
Capecitabine/docetaxel	40%	28%
Docetaxel	35%	45%
Paclitaxel	5%	8%
Platinum + taxane	10%	5%
Capecitabine	—	8%
Other	10%	6%

Editor's Note

In this situation, with a symptomatic patient, clinicians are inclined to use a taxane alone or combined with capecitabine.

Research Leader Commentary

Treatment for patients with ER-negative, HER2-negative, metastatic disease is a difficult subject, because it involves the controversy over combination chemotherapy and monotherapy. For the first time, the FDA has approved a combination chemotherapy regimen for metastatic disease, the docetaxel/capecitabine combination.

In appropriate cases, I think that combinations like this can't be overlooked. In my practice, I've moved towards combination chemotherapy for patients with potentially life-threatening metastatic disease; otherwise, the off-protocol treatment for patients with ER-negative, HER2-negative disease involves sequential single-agent regimens.

— Mark D Pegram, MD

I use the capecitabine/docetaxel regimen for a select group of women with metastatic disease — those with more extensive disease and with a better performance status. The regimen produces good results but may have significant toxicity, especially at the doses that were initially presented. I tend to start capecitabine at 1,250 mg/m^2 twice a day for 14 days, followed by seven days off as the regular approach. If you select your patient population appropriately, it's tolerable. The hand-foot syndrome is manageable with appropriate dose reductions when it occurs. The hardest symptom complex that I encounter with that regimen is the GI toxicity. It's more difficult to manage and less amenable to improvement with dose reductions.

— Generosa Grana, MD

Dosing and Scheduling of Capecitabine

Which of the following dosing schedules for capecitabine do you generally use?

1,250 mg/m^2 BID, two weeks on, one week off	18%
1,000 mg/m^2 BID, two weeks on, one week off	68%
750 mg/m^2 BID, two weeks on, one week off	7%
Other	7%

What percent of your patients on capecitabine develop side effects requiring intervention, including dose reduction?

Require intervention	40%
Do not require intervention	60%

Editor's Note

Most clinicians utilize a dose of capecitabine less than that noted in the package insert, but many patients require further dose reduction.

Research Leader Commentary

I do not use the package insert dose of capecitabine for any patients initially. Typically, I calculate the dose based on a 25 percent reduction from the package insert dose — about 1,000 mg/m^2 twice a day for 14 days. Going into the second cycle, I often escalate the dose a bit, maybe by one pill a day, for patients without any toxicity.

I think that with this adjusted-dose approach, most patients experience minimal diarrhea and nominal hand-foot syndrome. Certainly, we do not have the same trouble having patients continue on the drug that we did at the very beginning with the full doses. In terms of the hand-foot syndrome, we tend to dose capecitabine to the point where the hands are a little bit red.

— Clifford A Hudis, MD

We do not start capecitabine at the FDA-approved dose. We typically use capecitabine at 2,000 mg/m^2 per day (total daily dose) divided in two daily doses for two weeks on and one week off. Most women tolerate that dose well for several cycles. The development of the hand-foot syndrome is a problem that ultimately may require either a dose reduction or prolongation of the one-week interval off therapy to two or sometimes even three weeks.

— Robert W Carlson, MD

Dosing and Scheduling of Capecitabine

55-year-old asymptomatic woman with lung metastases was started on capecitabine 1,000 mg/m^2 BID (two weeks on, one week off).

After three cycles, there is no change in the lesions and no side effects of therapy. Which of the following would you generally do?

Continue therapy at the same dose	58%
Increase the dose to 1,250 mg/m^2 BID	23%
Continue capecitabine, add another agent	2%
Stop capecitabine, switch therapy	17%

After three cycles, there is an objective response in her lung lesions, but the patient complains of mild pain and redness in her hands and feet. Which of the following would you generally do?

Continue therapy at the same dose	45%
Reduce dose	30%
Change schedule to 2 weeks off therapy	18%
Stop capecitabine, switch therapy	3%
Switch therapy	4%

Editor's Note

Most clinicians do not dose-escalate capecitabine in a stable patient, but will reduce the dose in the presence of even minimal hand-foot syndrome.

Research Leader Commentary

I suspect that the dose in the package insert is too high. Data suggest that doses of 2,000 or perhaps 1,500 mg/m^2 per day (in two divided doses) for 14 consecutive days, followed by 7 days of rest, are as effective. The incidence of hand-foot syndrome declines substantially with these doses, and it becomes necessary to reduce the dose in only about 15 percent of patients.

— Hyman B Muss, MD

Defining HER2-Positivity

How do you interpret the following lab results?

	IHC 3+	IHC 2+	IHC 1+
HER2-positive	75%	5%	—
HER2-positive only with FISH confirmation	25%	95%	55%
HER2-negative	—	—	45%

How often do you obtain FISH to determine a tumor's HER2 status?

Always	35%
Commonly	38%
Occasionally	27%
Rarely	—
Have not done it	—

Editor's Note

FISH is commonly utilized to confirm HER2 status in tumors that are IHC 2+, and some clinicians utilized this assay for all HER2 testing.

Research Leader Commentary

If one wants to know whether a patient has the HER2 alteration, one should always do FISH testing — not do a default IHC and only do a FISH if they are 2+. Using that algorithm, patients without the HER2 alteration will be treated with trastuzumab, and other patients with the HER2 alteration may not be treated. The BCIRG trial we are conducting was designed with FISH as the only criteria for assessing HER2 status.

Every breast cancer patient should have her HER2 status assessed by FISH testing. We do not use or recommend IHC. I think the day is coming when FISH will be the only HER2-status test used in the community, and I hope it will be sooner, rather than later.

— Dennis J Slamon, MD, PhD

Patients with tumors that score 2+ on immunohistochemistry (IHC) are frequently found to be HER2-negative when tested by fluorescence *in situ* hybridization (FISH). In those patients, I routinely have their tumors retested by FISH. On the other hand, I do not obtain a FISH analysis for patients whose tumors score 3+ on IHC from a laboratory where I trust the pathologist.

Since HER2-positive breast cancer has a fairly specific phenotype (i.e., steroid receptor-negative, younger age, early relapse), I will retest those types of patients by FISH if I have a two- to three-year-old IHC score of 0 or 1+. If the patient's tumor is IHC-negative and FISH-positive, I will treat her with trastuzumab despite the fact that we do not have clinical data for that group of patients. Tumors that are FISH-positive are likely to have ample amounts of HER2 receptors on their cell surface.

— George W Sledge, Jr, MD

Trastuzumab With or Without Chemotherapy in HER2-Positive Metastatic Disease

What therapy would you generally use in women in their 50s with ER/PR-negative, HER2-positive metastatic breast cancer in each of the following situations?

Clinical situation	Trastuzumab alone	Trastuzumab + chemotherapy	Chemotherapy alone
Asymptomatic patients with bone mets	49%	38%	13%
Asymptomatic patients with liver mets	10%	82%	8%
Patients with bone mets and moderate pain requiring oral narcotics	15%	75%	10%
Very symptomatic patients with visceral mets	0%	93%	7%

Editor's Note

Trastuzumab monotherapy is commonly utilized in patients with asymptomatic metastases, but combinations with chemotherapy are standard in most other first-line situations.

Research Leader Commentary

All things being equal and the patient being capable, I opt for the most optimum interactive combination of carboplatin, paclitaxel and trastuzumab (CTH). Trastuzumab can, however, be combined with vinorelbine, capecitabine or gemcitabine. In terms of the response rate, trastuzumab monotherapy is inferior, but the survival data looks comparable to that with the trastuzumab/chemotherapy combination. Therefore, I am quite comfortable in a patient who cannot tolerate or does not want chemotherapy to offer trastuzumab monotherapy. It is not, however, my usual recommendation, which is to exploit any potential synergies. HER2-positive breast cancer is very aggressive, and we want to take our best shot at the disease.

— Dennis J Slamon, MD, PhD

In patients with rapidly progressing, life-threatening, HER2-positive, ER-negative metastatic breast cancer, I use trastuzumab in combination with either paclitaxel or vinorelbine in women who have not previously received a taxane. Otherwise, I use trastuzumab monotherapy. The disease characteristics of the patients in Chuck Vogel's front-line trastuzumab trial are very similar to those in the pivotal trial of trastuzumab with or without chemotherapy. Both of those trials demonstrated similar time to tumor progression. That is not a direct comparison, but the model that we have always used in breast cancer is that we cannot cure metastatic disease. Therefore, we use the treatment that will be most likely to put the patient in remission with the fewest side effects. Clearly, single-agent trastuzumab is a more benign treatment than trastuzumab plus chemotherapy.

We do not yet have prospective, randomized trial data that demonstrate a survival advantage for single-agent trastuzumab. However, if a patient responds to trastuzumab, it will be evident very quickly, often within a couple of weeks. If she progresses, you can always add chemotherapy.

— Melody A Cobleigh, MD

Trastuzumab Combinations: Choice of Regimen

Have you used the CTH (carboplatin, paclitaxel, trastuzumab) combination in women with HER2-positive metastatic disease?

Have you used trastuzumab and capecitabine simultaneously in women with HER2-positive metastatic disease?

Have you used trastuzumab in combination with endocrine therapy?

Editor's Note

Many clinicians have utilized the CTH combination. This regimen, presented by Dr Nicholas J Robert at the 2002 San Antonio meeting, was reported to increase response rate and time to progression compared to trastuzumab/paclitaxel.

Research Leader Commentary

In the US Oncology study of trastuzumab/paclitaxel with or without carboplatin, patients with HER2-positive metastatic disease were randomized to receive trastuzumab/paclitaxel, the successful arm of the pivotal trial, or that combination plus carboplatin. The addition of carboplatin improved both the response rate and time to progression. We looked at survival, although it was early to do so as over 120 patients are still alive. The preliminary analysis shows a trend for improvement with the three-drug regimen. In the IHC 3+ patients, we saw an improvement in survival, with a *P*-value of 0.06 approaching 0.05, and patients with the FISH-positive population showed a similar trend. It will be important to see if the survival advantage persists.

The trastuzumab/paclitaxel/carboplatin regimen was well-tolerated. The only significant difference in toxicity was increased myelosuppression, which we expected to see from adding carboplatin. However, there were no significant differences in terms of serious complications, such as infectious complications, significant neutropenia or fever. Other toxicities, such as neuropathy, allergic responses, nausea and arthralgias, were comparable in both arms.

— Nicholas J Robert, MD

Trastuzumab with Chemotherapy: Choice of Regimen

What chemotherapy regimens do you generally use in combination with trastuzumab?

Regimen	1st line	2nd line
Docetaxel	33%	23%
Paclitaxel	28%	12%
Vinorelbine	22%	28%
Carboplatin/taxane	5%	15%
Capecitabine	—	15%
Other	12%	7%

Editor's Note

Both docetaxel and paclitaxel are the most common chemotherapeutic agents combined with trastuzumab, but vinorelbine is also commonly utilized.

Research Leader Commentary

We now have two well-conducted, Phase III randomized clinical trials comparing the efficacy of a taxane in combination with trastuzumab to a taxane alone. The combination demonstrates an improvement in response rate, time to progression and survival.

In patients with HER2-positive metastatic breast cancer, my first-line recommendation would be a taxane and trastuzumab. Based on the Robert data, I may add carboplatin. I would not use doxorubicin-based chemotherapy as first-line therapy.

— Edith Perez, MD

Published data in the *New England Journal of Medicine* show that trastuzumab-based chemotherapy combinations prolong survival. How many drugs have been shown to improve survival in patients with metastatic breast cancer? Anthracyclines, for example, have not. The meta-analysis of the anthracycline studies in metastatic disease failed to document a survival advantage with any statistical confidence. It is really hard to dismiss that data and not use trastuzumab as first-line therapy for patients with metastatic disease.

— Mark D Pegram, MD

Preclinical studies demonstrated that trastuzumab in combination with certain chemotherapeutic agents worked better than trastuzumab alone. The drugs commonly used to treat breast cancer — doxorubicin, paclitaxel, gemcitabine, methotrexate, vincristine and vinblastine — tended to be additive with trastuzumab, and 5-FU was less than additive.

The platinum salts — cisplatin and carboplatin — appeared to be the most synergistic. After the platinum salts came docetaxel, etoposide, vinorelbine and then the alkylating agents, like cyclophosphamide.

— Dennis J Slamon, MD, PhD

Management of HER2-Positive Metastatic Disease: Effect of Symptomatology and Sites of Disease

57-year-old woman, treated two years ago with adjuvant CMF chemotherapy for ER-negative, HER2-positive (by FISH) IDC: What treatment would you recommend?

Agent	Rising tumor markers, asymptomatic bone mets	Liver and lung mets, very symptomatic
Trastuzumab plus chemotherapy	59%	85%
Trastuzumab alone	30%	—
Chemotherapy alone	11%	15%
None	7%	—

Editor's Note

The survival advantage reported in combining trastuzumab plus paclitaxel has resulted in this combination being commonly utilized in patients with metastatic disease.

Research Leader Commentary

I use single-agent trastuzumab in a similar manner as hormonal therapy. There are subsets of women with HER2-positive disease who don't have horribly aggressive metastatic breast cancer. In those relatively asymptomatic patients who do not have visceral crisis or rapidly progressive disease and are not incapacitated by symptoms, I have no problem at all starting them on first-line, single-agent trastuzumab. However, the patients must be fully informed that they may be giving away something in terms of response rate, based on an analysis of cross trial comparisons with the combination regimens.

— *Charles L Vogel, MD, FACP*

The results of this trial indicate that trastuzumab is active as a single agent and produces durable objective responses in women with HER2-overexpressing breast cancer who have not previously received chemotherapy for their metastatic disease... .These findings are noteworthy in view of the poor prognosis in this population. In addition, patients had lung or liver metastases (67%) because of the requirement for bidimensionally measurable disease.

Furthermore, most patients had received adjuvant chemotherapy (68%), which included an anthracycline (50%) or high-dose therapy with stem-cell rescue (12%)…these results suggest that patients do not incur a major survival disadvantage if they receive trastuzumab alone as first-line therapy for metastatic disease.

…The present results (the preliminary findings of which were originally published in abstract form) have led to randomized clinical trials designed to additionally assess the optimal clinical use of trastuzumab as first-line treatment of patients with metastatic breast cancer. These trials will provide important information regarding the sequence of therapies that provides maximal efficacy and preserves the QOL. In conclusion, single-agent trastuzumab is an active and well tolerated option for first-line treatment of women who have metastatic breast cancer with HER2 overexpression by IHC or with gene amplification by FISH.

— *Vogel CL. J Clin Oncol 2002;20:719-26.*

Management of HER2-Positive Metastatic Disease: Influence of Prior Chemotherapy

57-year-old woman, treated two years ago for ER-negative, HER2-positive (by FISH) IDC: Presents with rising tumor markers and asymptomatic bone metastases. When using trastuzumab with chemotherapy, which agent(s) would you recommend?

	Adjuvant chemotherapy		
Agent	**CMF**	**AC**	**AC-paclitaxel**
Docetaxel	40%	36%	25%
Paclitaxel	25%	23%	5%
Vinorelbine	15%	18%	40%
Platinum/taxane	15%	18%	20%
Other	5%	5%	10%

Editor's Note

In patients with prior AC→T, vinorelbine is the most common chemotherapy agent combined with trastuzumab as first-line therapy.

Research Leader Commentary

The *in vitro* synergy between the platinums and trastuzumab has recently been put to the test. At the San Antonio Breast Cancer Symposium, Dr Nicholas Robert presented the results from a study that randomized patients with HER2-positive metastatic disease to receive trastuzumab/paclitaxel or trastuzumab/paclitaxel/carboplatin. The results were remarkable. In the patients who received carboplatin in addition to trastuzumab/paclitaxel, the response rates and the time to progression were significantly improved.

— Mark D Pegram, MD

In patients with metastatic disease who have not previously received chemotherapy, I utilize trastuzumab in combination with chemotherapy. I'm very impressed by the vinorelbine/trastuzumab data. I find it to be a particularly easy regimen with little toxicity and great effectiveness.

— Generosa Grana, MD

We wondered why there was a difference between paclitaxel and docetaxel since they both hit the same targets. We learned that trastuzumab binds to the HER2 receptor and changes signaling so that there is a transient decrease in DNA repair. The platinum salts work by damaging DNA in a specific way, which is reparable by DNA repair mechanisms that are shut down significantly by trastuzumab. Docetaxel appears to be significantly superior to paclitaxel in the ability to induce programmed cell death. When trastuzumab and docetaxel are used together, the ability to induce programmed cell death is increased significantly. We do not see the same thing with paclitaxel.

— Dennis J Slamon, MD, PhD

Management of HER2-Positive Metastatic Disease: Impact of Age

Patient treated two years ago with adjuvant CMF chemotherapy for ER-negative, HER2-positive (by FISH) IDC, now with rising tumor markers and asymptomatic bone metastases: Which treatment would you recommend?

Agent	57-year-old	75-year-old
Trastuzumab plus chemotherapy	55%	40%
Trastuzumab alone	27%	35%
Chemotherapy alone	11%	12%
None	7%	13%

Editor's Note

Trastuzumab plus chemotherapy is the most common treatment in asymptomatic elderly women with metastatic disease.

Research Leader Commentary

The decision to use trastuzumab sequentially versus concomitantly with chemotherapy is based on issues such as extent of metastatic disease and the time between diagnosis and progression. In a younger, relatively asymptomatic patient with bone metastases and a good performance status, I don't think there is compelling evidence to use both chemotherapy and trastuzumab initially. There is no randomized trial comparing sequential versus concomitant therapy in such a patient, but in other settings comparing sequential versus concomitant therapy with chemotherapy, concomitant therapy doesn't do any better in terms of survival.

Certainly there are patients with metastatic disease in whom you feel chemotherapy is indicated, such as patients with significant visceral or life-threatening disease. Given the positive results of the trials in which trastuzumab was added to chemotherapy — improved response rate, time to progression and survival — my approach has been to give trastuzumab with the chemotherapy.

—Nicholas J Robert, MD

I routinely use trastuzumab as part of my first-line therapy for patients with HER2-positive metastatic breast cancer. Whether to use trastuzumab alone or in combination with chemotherapy is a separate question. In patients with impaired performance status, it would be reasonable and appropriate to give trastuzumab alone.

My sense is that the majority of community oncologists are using trastuzumab in combination with chemotherapy as first-line therapy for HER2-positive metastatic breast cancer. Over the last couple of years, there has been a trend to use trastuzumab earlier in the metastatic setting.

— George W Sledge Jr, MD

Continuation of Trastuzumab Upon Disease Progression

57-year-old woman, treated two years ago for ER-negative, HER2-positive (by FISH) IDC, treated with trastuzumab (with or without chemotherapy) for rising tumor markers and asymptomatic bone metastases: Upon disease progression, would you continue or stop the trastuzumab?

	Adjuvant chemotherapy		
	CMF	AC	AC-paclitaxel
Continue trastuzumab	54%	55%	58%
Stop trastuzumab	46%	45%	42%

Editor's Note

Trastuzumab is commonly continued in the presence of disease progression in the hope of synergy with additional chemotherapy agents.

Research Leader Commentary

No data currently address the optimal duration of trastuzumab therapy. Based on preclinical data, our approach is to continue trastuzumab after the patient has progressed on her first trastuzumab/chemotherapy regimen and to add a different chemotherapeutic agent or I generally use a second synergistic agent like vinorelbine. In the future, we will probably be switching to a different biologic therapy. If the patient is progressing rapidly on her second regimen of trastuzumab and chemotherapy, my own approach is to stop the trastuzumab. If the patient has a slow progression of her disease, I continue the trastuzumab. It is a matter of clinical judgment in the absence of clinical data.

— Dennis J Slamon, MD, PhD

No data exist to guide us in what to do after a patient progresses while receiving trastuzumab and chemotherapy. The trastuzumab story has consistently shown that the laboratory models predict what happens in the clinic. The laboratory models demonstrate that trastuzumab, when combined with most chemotherapeutic agents, is more effective than when a chemotherapeutic agent is used alone. Until I see a trial that shows this is not true, I will continue trastuzumab indefinitely along with the chemotherapy.

— Melody A Cobleigh, MD

On a daily basis, we are presented with patients with metastatic disease who have progressed on trastuzumab. There are no data to guide us in managing these patients. I will usually continue trastuzumab and add another chemotherapy agent. Trastuzumab is very well-tolerated, and you are not really causing harm to the patient by continuing it.

— Joyce O'Shaughnessy, MD

In my standard practice for HER2-positive metastatic disease, I use trastuzumab until disease progression or toxicity. The question of whether trastuzumab should be continued after disease progression is one we are wrestling with on a day-to-day basis. No one knows the answer.

— Edith Perez, MD

Scheduling of Trastuzumab

What schedule of trastuzumab do you generally use?

Weekly	80%
Every 3 weeks	13%
Other	7%

Editor's Note

Most clinicians utilize a weekly schedule of trastuzumab in spite of encouraging evidence that treatment might be effective when given every three weeks.

Research Leader Commentary

Trastuzumab administered at longer intervals (every three weeks) and at three times the dose is being investigated. Brian Leyland-Jones presented data on paclitaxel with trastuzumab given every three weeks that demonstrated the trough did not go below the desirable level. In fact, the overall area under the curve and the peak concentration are higher without any additional toxicity. This may allow for the convenience of every-three-week administration.

I still, however, use weekly trastuzumab. I want a little more toxicity data using it every three weeks. For many drugs, it is the peak level that actually mediates toxicity. That may not be the case with trastuzumab, but I would like a little longer follow-up, especially for cardiotoxicity.

— Debu Tripathy, MD

We, like many others, have been compelled to switch to triple-dose trastuzumab administered every three weeks. When we discuss Dr Brian Leyland-Jones' results from his pharmacokinetic studies with the triple-dose, every-three-week schedule with our patients, many opt for it and so far, we have not had any problems with that schedule.

At this point, however, we really do not have comparative data from large randomized trials. Many of the cooperative group studies evaluating trastuzumab are adopting the every-three-week, triple-dose schedule. In the BCIRG adjuvant trastuzumab trial, trastuzumab will be given following chemotherapy on an every-three-week schedule. Over the next couple of years, hundreds of patients will be treated with the every-three-week schedule and safety data will be collected.

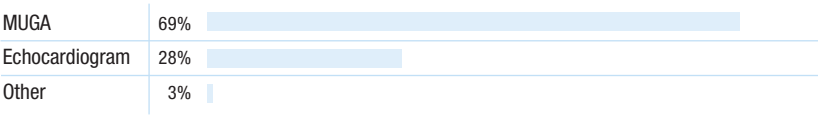
From a theoretical point of view, I am not concerned about efficacy. The peak trastuzumab blood levels are actually higher on the every-three-week schedule. Since there is actually more trastuzumab on board, if anything, there could be greater efficacy. I do not believe that will necessarily be the case, but certainly there is no theoretical reason to expect a decrease in efficacy.

— Mark D Pegram, MD

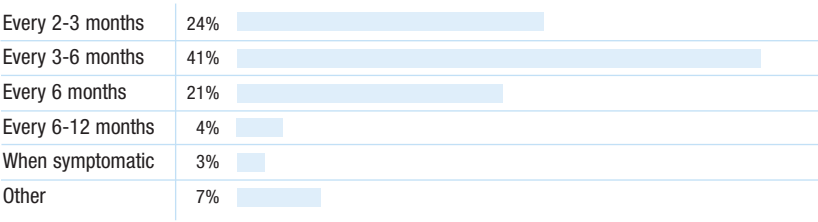
Cardiac Monitoring in Patients on Trastuzumab

Do you routinely monitor cardiac function in your patients on trastuzumab?

What test(s) do you use to monitor cardiac function?



At what frequency do you test to monitor cardiac functioning?



Editor's Note

Most clinicians utilize routine cardiac monitoring in women treated with trastuzumab.

Research Leader Commentary

Risk factors for trastuzumab-associated CD [cardiac dysfunction] are poorly delineated. Only age was associated with increased risk, and only in the AC substratum. A better understanding of risk factors is needed. Multigated blood pool imaging of the heart (MUGA scanning) is currently recommended for baseline assessment and on-treatment evaluation of trastuzumab-treated patients. MUGA scanning seems unable to identify early evidence of CD, and once impaired systolic function is detected by MUGA, significant cardiac damage has already occurred. It would be optimal to have a sensitive, noninvasive test to detect minor cardiac damage in time for an intervention to preserve the myocardium. Troponin-T16 and pro-BNP17 levels are being examined in clinical trials to define their utility in detecting early myocardial damage. In addition, echocardiography is being compared with MUGA scanning to determine if this modality might be more sensitive to changes associated with trastuzumab exposure.

— Seidman A et al. J Clin Oncol 2002;20:1215-21.

Impact of Trastuzumab on Cardiac Function

Have you ever stopped trastuzumab because of abnormal cardiac function tests in women who had no clinical signs of cardiac dysfunction?

Have you ever stopped trastuzumab because of abnormal cardiac function clinically?

Editor's Note

Many clinicians have discontinued trastuzumab because of evidence of cardiac dysfunction on screening tests or clinical findings.

Research Leader Commentary

The most troubling adverse effect of trastuzumab was cardiac dysfunction, a complication that had not been anticipated on the basis of the results of preclinical or early clinical studies. We found that concurrent treatment with an anthracycline, cyclophosphamide and trastuzumab significantly increased the risk of cardiac dysfunction, as compared with treatment with only an anthracycline and cyclophosphamide. A smaller increase in risk also occurred with treatment with paclitaxel and trastuzumab, as compared with treatment with paclitaxel alone, but all these patients had previously received an anthracycline...

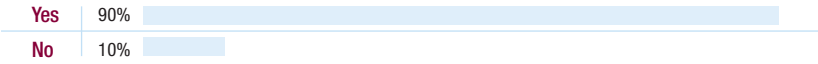
Trastuzumab was discontinued because of cardiac dysfunction in 18 of 235 patients (8 percent) overall, and most of these patients received an anthracycline, cyclophosphamide and trastuzumab. Continued use of trastuzumab did not cause further cardiac deterioration in most patients, and cardiac function improved in 75 percent of patients after the initiation of standard medical care. Among 81 patients who were assigned to receive an anthracycline and cyclophosphamide alone and who later received trastuzumab in an open-label fashion, clinically significant cardiac dysfunction developed in 7 (9 percent). The only significant risk factor associated with cardiac dysfunction was older age. The mechanism of the cardiotoxicity of trastuzumab is unknown.

Given the extremely poor prognosis of patients with HER2-positive metastatic breast cancer, the cardiotoxicity of trastuzumab must be weighed against its potential clinical benefit. We recommend a cautious approach to the use of trastuzumab in patients who have previously received anthracyclines and in those who are currently receiving anthracyclines.

— Slamon DJ et al. N Engl J Med 2001;344(11):783-92.

Use and Tolerability of Fulvestrant

Have you used fulvestrant?



What percentage of your patients receiving fulvestrant reported difficulty tolerating the injection?

Mean	3%

83% of physicians stated that none of their patients receiving fulvestrant reported difficulty tolerating the injection.

What percentage of your patients receiving fulvestrant reported significant side effects?

Mean	3%

78% of physicians stated that none of their patients receiving fulvestrant reported significant side effects.

Editor's Note

Most clinicians have utilized fulvestrant and few report significant side effects with this agent.

Research Leader Commentary

I've used a fair amount of fulvestrant, and I find that it's well-tolerated. Patients don't have any problem coming in once a month for their intramuscular injections. In terms of efficacy, we've had patients experience stabilization of disease for six months. What is nice about fulvestrant is that it offers another option, especially for the patient who may be experiencing difficulty tolerating her current endocrine therapy.

— Nicholas J Robert, MD

I've been pleased with fulvestrant. In my experience, patient tolerance has been excellent with very few complaints about side effects. I've certainly not had the occasion to stop fulvestrant in any patient because of toxicity. Compliance is very good, and the injection really isn't an issue. These are highly motivated patients with a devastating disease, so they do not object to receiving an injection. I am using two 2.5 cc injections.

— Mark D Pegram, MD

First-Line Endocrine Therapy for ER-Positive Metastatic Disease

What is your typical first-line hormonal therapy in postmenopausal women with ER-positive metastatic disease?

	Adjuvant endocrine therapy		
Agent	**No adjuvant endocrine therapy**	**Completed adjuvant tamoxifen 4 years ago**	**Relapsed on anastrozole**
Anastrozole	38%	50%	5%
Letrozole	32%	42%	7%
Tamoxifen	30%	8%	42%
Fulvestrant	—	—	28%
Exemestane	—	—	18%

Editor's Note

Aromatase inhibitors and tamoxifen are common first-line choices for endocrine therapy in postmenopausal women with metastatic disease, but fulvestrant is a common choice for women progressing on adjuvant aromatase inhibitors.

Research Leader Commentary

Selection of a hormonal therapy after a patient relapses on anastrozole is a problem. Tamoxifen or fulvestrant could be highly effective, but if the MAP kinase pathway is overdriven from the aromatase inhibition, tamoxifen might act more as an agonist, and fulvestrant might be a better choice. To my knowledge, in terms of ATAC or other patients who have relapsed on an adjuvant aromatase inhibitor, no data has yet been presented addressing this issue.

— Paul E Goss, MD, PhD, FRCP(CA), FRCP(UK)

The early reports of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial suggest that anastrozole is superior to tamoxifen in the adjuvant treatment of postmenopausal women with invasive breast cancer, and so the increasing use of anastrozole in the adjuvant treatment of postmenopausal breast cancer is a likely result of the ATAC trial. This will require further modification to identify the options for optimal sequential hormonal therapy for those women who experience recurrent disease following anastrozole therapy.

— Carlson RW. Breast Cancer Res Treat 2002;75:S27–S32.

Sequencing of Endocrine Therapy in Endocrine-Naïve Patients With Metastatic Disease

What sequence of hormonal therapy do you typically use in postmenopausal women with metastases who did not receive adjuvant endocrine therapy?

Agent	1st line	2nd line	3rd line	4th line
Anastrozole	38%	28%	5%	—
Tamoxifen	30%	37%	12%	7%
Letrozole	32%	12%	5%	2%
Fulvestrant	—	8%	38%	28%
Exemestane	—	15%	33%	18%
Megestrol acetate	—	—	7%	23%
Other	—	—	—	7%
None	—	—	—	15%

Editor's Note

Fulvestrant is now the most common third-line choice for hormonal therapy in postmenopausal women.

Research Leader Commentary

We now have several options for endocrine therapy. The issues are how, when and in what order we should use these agents. As they are making it to the clinic, I get phone calls from my colleagues asking, "What order do I use these in?" I do not think we know the answer. The challenge for the cooperative groups and pharmaceutical companies is to conduct trials evaluating sequential and combination endocrine therapies.

I believe we will find that different subgroups of patients will respond differently to individual endocrine therapies. Just as we use ER status to decide who will receive endocrine therapy, in the future we may use the progesterone receptor, HER1, 2, 3 and 4, or some of the coactivators and corepressors. These markers may indicate which patients should receive tamoxifen, an aromatase inhibitor or fulvestrant. We are a long way away, but I think we will see it happen.

— Daniel F Hayes, MD

Postmenopausal women with hormone-sensitive disease also have a variety of available hormone therapy options. While tamoxifen remains a reasonable first-line therapy, there is increasing evidence that the non-steroidal AIs anastrozole and letrozole are superior to tamoxifen as first-line therapy.

Fulvestrant is a promising second-line therapy in postmenopausal women initially treated with tamoxifen, and in this setting fulvestrant is at least as effective as anastrozole. The role of fulvestrant in the treatment of breast cancer in postmenopausal women progressing on first-line AI therapy has not been defined. Based upon available data, tamoxifen or possibly fulvestrant are reasonable second-line options. Trials examining activity of fulvestrant in this clinical setting are currently ongoing. As third-line therapy, patients should receive either fulvestrant if treated with second-line tamoxifen, or megestrol acetate if treated with second line fulvestrant. Lastly, if fourth-line therapy is necessary, patients should receive a hormonal agent they have not previously received.

— Carlson RW. Breast Cancer Res Treat 2002;75:S27–S32.

Sequencing of Endocrine Therapy After Tamoxifen in Patients With Metastatic Disease

In postmenopausal women with metastases who did not receive adjuvant endocrine therapy, which agents do you generally use after first-line tamoxifen?

Agent	2nd line	3rd line	4th line
Anastrozole	67%	17%	—
Letrozole	25%	17%	—
Exemestane	—	33%	42%
Fulvestrant	8%	25%	25%
Megestrol acetate	—	8%	—
Aminoglutethimide	—	—	8%
Goserelin	—	—	8%
None	—	—	17%

Editor's Note

Aromatase inhibitors are the most common choice for hormonal therapy in postmenopausal women progressing on tamoxifen.

Research Leader Commentary

These data demonstrate that fulvestrant is the first antiestrogen to show comparable efficacy to anastrozole in the second-line treatment of advanced breast cancer. These data also confirm previous findings of the phase II study that a pure antiestrogen is effective in tamoxifen-resistant patients... . Overall, both treatments were well tolerated, with the percentage of patients experiencing adverse effects (AE) being similar and few patients withdrawing because of AEs... .Taken overall, these data demonstrate that fulvestrant is as effective as anastrozole, with similar tolerability and QOL effects. Fulvestrant should offer clinicians a new option for the treatment of postmenopausal women with advanced breast cancer whose disease progresses after tamoxifen treatment.

— Howell A et al. J Clin Oncol 2002;20:3396-403.

When a hormone-dependent cancer becomes resistant to a SERM, we are not sure of the exact resistance mechanism. One possibility is that cells begin to upregulate HER2, an epidermal growth factor receptor, resulting in constitutive phosphorylation, dimerization and activation of the estrogen receptor. Then, the ligand has no effect, because the estrogen receptor is already activated.

Another resistance mechanism might be the mutation of the estrogen receptor so it becomes hypersensitive to individual ligands. If that is the case, ligand-based therapy (i.e., the SERMs) might suddenly start acting like estrogen; whereas, ligand-annihilating or ligand-depleting therapy (i.e., oophorectomy, LHRH agonists and the aromatase inhibitors) might still be effective. Even with the upregulated HER2 hypothesis, it is possible that phosphorylation makes the receptor hypersensitive to the ligand. In that case again, ligand depletion might be ideal. Fulvestrant, on the other hand, is a ligand that binds to the estrogen receptor and prevents downstream signaling. There is a constant turnover in the estrogen receptor, but the receptor is completely inactivated by fulvestrant because it cannot dimerize.

— Daniel F Hayes, MD

Sequencing of Endocrine Therapy After Anastrozole in Patients With Metastatic Disease

In postmenopausal women with metastases who did not receive adjuvant endocrine therapy, which agents do you generally use after first-line anastrozole?

Agent	2nd line	3rd line	4th line
Tamoxifen	67%	13%	7%
Fulvestrant	—	47%	27%
Exemestane	20%	33%	13%
Letrozole	13%	—	7%
Megestrol acetate	—	7%	26%
Testolactone	—	—	7%
None	—	—	13%

Editor's Note

Tamoxifen is the next most preferred therapy in women progressing on anastrozole, and fulvestrant is the next agent utilized.

Research Leader Commentary

Fulvestrant creates a dilemma in that the pivotal trials were conducted in tamoxifen-refractory patients. Fulvestrant will be used in patients after an aromatase inhibitor, and there is no data on the efficacy of fulvestrant given after an aromatase inhibitor. How effective fulvestrant will be in women who have progressed on an aromatase inhibitor is the key question that needs to be answered.

Biologically speaking, fulvestrant removes the estrogen receptor. It is an estrogen-receptor downregulator. Once fulvestrant complexes with the estrogen receptor, the receptor is actually degraded. In contrast, the estrogen receptor and tamoxifen complex is translocated to the nucleus. The aromatase inhibitors basically remove estrogen, and fulvestrant removes the estrogen receptor; therefore, nothing goes to the nucleus with either an aromatase inhibitor or fulvestrant.

In a woman who has relapsed on adjuvant tamoxifen and has never received an aromatase inhibitor, I would generally use an aromatase inhibitor. In this type of situation, fulvestrant was found to be roughly equivalent to an aromatase inhibitor, and the American trial suggested that the time to disease progression might actually be a little bit longer for fulvestrant. Since that was not the primary endpoint, I think we have to look at that information cautiously. Fulvestrant and the aromatase inhibitors, in my mind, really represent equivalent therapeutic choices.

— Debu Tripathy, MD

Sequencing of Endocrine Therapy After Letrozole in Patients With Metastatic Disease

In postmenopausal women with metastases who did not receive adjuvant endocrine therapy, which agents do you generally use after first-line letrozole?

Agent	2nd line	3rd line	4th line
Tamoxifen	39%	23%	15%
Anastrozole	23%	—	—
Exemestane	23%	31%	—
Fulvestrant	15%	38%	31%
Megestrol acetate	—	8%	39%
None	—	—	15%

Editor's Note

In women progressing on letrozole, a second aromatase inhibitor and tamoxifen are commonly utilized.

Research Leader Commentary

In postmenopausal women, I tend to use fulvestrant following an aromatase inhibitor. That is generally my practice, although we really are lacking data in that situation. There are some Phase II studies and anecdotal reports, however, I believe that there are Phase III trials that are being launched comparing fulvestrant to a steroidal aromatase inhibitor.

In my mind, aromatase inhibitors are the treatment of choice as front-line therapy, based on the bulk of evidence in the majority of postmenopausal women who have received adjuvant tamoxifen. Fulvestrant is certainly an alternative because it was shown to be at least equivalent to anastrozole. From a practical point of view, I tend to use the oral agents initially and then go to fulvestrant as a second-line treatment.

In my experience, fulvestrant is well tolerated. Many of these patients receive a bisphosphonate on a monthly basis anyway, so it really doesn't involve an additional trip to the clinic. The injections tend to be well tolerated, and most patients have not complained about hot flashes. I have seen results that are consistent with what I would expect for an active hormonal agent in that patient population.

— G Thomas Budd, MD

There has been interest in the possibility that resistance to the nonsteroidal AIs would not confer cross-resistance to the steroidal AIs, and vice versa. The absence of cross-resistance would therefore extend the clinical utility of the two AI classes, allowing them to be used in sequential endocrine programs.

Lønning et al. examined the activity of the steroidal AI exemestane in patients with advanced metastatic breast cancer who had initially been treated with either aminoglutethimide or one of the new nonsteroidal AIs. The analysis demonstrated that exemestane was well tolerated and retained antitumor activity in women who had progressed on nonsteroidal AIs, suggesting that it may have a role in second- or third-line therapy after the nonsteroidal AIs.

— Carlson RW. Breast Cancer Res Treat 2002;75:S27-S32.

Endocrine Therapy in Patients With Tumor Recurrence After Receiving Adjuvant Tamoxifen

What sequence of hormonal therapy do you typically use in postmenopausal women with metastases who completed adjuvant tamoxifen four years ago?

Agent	1st line	2nd line	3rd line	4th line
Anastrozole	50%	15%	—	2%
Fulvestrant	—	33%	35%	15%
Letrozole	43%	10%	—	2%
Exemestane	—	33%	40%	5%
Tamoxifen	7%	7%	7%	8%
Megestrol acetate	—	2%	13%	25%
Other	—	—	—	8%
None	—	—	5%	35%

Editor's Note

Patients with prior treatment with adjuvant tamoxifen are commonly treated with aromatase inhibitors and fulvestrant.

Research Leader Commentary

The most recent entrant into the new pantheon of drugs for the treatment of breast cancer is the pure antiestrogen fulvestrant…Fulvestrant downregulates and degrades the estrogen receptor, causes a reduction in progesterone receptor, and has only estrogen antagonistic effects. This is in contrast to tamoxifen, which has partial agonist effects, and the aromatase inhibitors, which reduce the estrogen available to the cancer cell. Both of these trials enrolled women who had previously received endocrine therapy, primarily tamoxifen, in either the adjuvant or metastatic setting and whose disease had progressed while they were receiving or after they had completed the therapy.

Many of the patients were known to have responded and then progressed. Fulvestrant was at least as effective as the comparator, anastrozole and response durations may have been longer. Preclinical data suggest that fulvestrant may be more effective than tamoxifen, and it might work in patients who are initially resistant to tamoxifen. It is possible that combinations of fulvestrant and aromatase inhibitors will be effective, in contrast to the outcome of the ATAC trial, where there was no advantage to combining tamoxifen and anastrozole.

— *Henderson IC. J Clin Oncol, 2002;20(16):3365-68.*

Endocrine Therapy in Patients With Tumor Recurrence on Adjuvant Anastrozole

What sequence of hormonal therapy do you typically use in postmenopausal women with metastases who relapse while receiving adjuvant anastrozole?

Agent	1st line	2nd line	3rd line	4th line
Tamoxifen	43%	15%	—	2%
Fulvestrant	28%	43%	12%	3%
Exemestane	17%	18%	18%	8%
Letrozole	7%	7%	2%	5%
Anastrozole	5%	5%	—	2%
Megestrol acetate	—	7%	33%	3%
Aminoglutethimide	—	—	2%	—
Androgen therapy	—	—	—	10%
High-dose estrogen	—	—	—	2%
None	—	5%	33%	65%

Editor's Note

Patients relapsing on adjuvant anastrozole commonly receive tamoxifen and fulvestrant as additional therapies.

Research Leader Commentary

Fulvestrant is a highly potent, estrogen receptor downregulator, which is equivalent as second-line therapy to our best drugs — the aromatase inhibitors. We now have another best drug. Now, women and physicians have a choice between treatments that are clearly equivalent.

New therapies for advanced breast cancer are useful, because we give endocrine agents sequentially. I believe that the first-line treatment for advanced disease in postmenopausal women — even those who have not had adjuvant tamoxifen — is an aromatase inhibitor. At the moment, I see fulvestrant being used after aromatase inhibitors in women who have not received an aromatase inhibitor in the adjuvant setting. It probably does not matter in which order you give them, but we have more data on aromatase inhibitors than fulvestrant.

There is a biological reason why fulvestrant might be better than anastrozole. Anastrozole lowers the serum estradiol levels, but there is still some estradiol present that could potentially stimulate the tumor. Fulvestrant blocks the receptor continuously, thereby preventing stimulation by circulating estradiol.

I do not believe that the fulvestrant injection is a problem. There have not been major problems with injection site reactions. In fact, it could be seen as an advantage in that women would not have to take pills every day. I do not think women mind an injection if they are receiving an active compound.

— Anthony Howell, BSc, MBBS, MSc, FRCP

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