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Breast Cancer™ UPDATE

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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2 audio tapes

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Monograph

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How to use this monograph

This is a CME activity that contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form. This monograph contains edited comments, clinical trial schemas, graphics and references, which supplement the audio program and the website, **BreastCancerUpdate.com**, where you will find a full transcription of the audio program and an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**. This regularly updated web site also features an extensive breast cancer bibliography, clinical trial links, a "breast cancer web tour" and excerpts from interviews and meetings catalogued by topic.

Breast Cancer Update: A CME Audio Series and Activity

Statement of Need/Target Audience

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

To bridge the gap between research and patient care, Breast Cancer Update utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists in the formulation of up-to-date clinical management strategies.

Issue 7, 2002 of Breast Cancer Update consists of discussions with four oncology research leaders on a variety of important issues, including the role of trastuzumab in treating HER2-positive metastatic disease, the toxicities of trastuzumab and trastuzumab in combination with other chemotherapeutic regimens, the sequencing of treatment for the elderly patient, current clinical trials for the elderly, adjuvant hormonal therapy and the management of the patient at high risk for breast cancer.

Educational Objectives

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

- Evaluate the survival advantage observed in the trastuzumab pivotal trial in order to determine the importance of considering earlier treatment with trastuzumab in patients with HER2-positive metastatic breast cancer.
- Distinguish among the various approaches to sequencing and combining therapeutic agents in order to define the most efficacious and least toxic treatment regimens for patients with metastatic disease.
- Understand the risks and benefits of combining chemotherapy with trastuzumab in order to select the most effective, least toxic regimens for HER2-positive patients.
- Apply the findings of the 2002 ASCO technology assessment to determine the appropriateness of using aromatase inhibitors as adjuvant therapy for patients with ER/PR receptor–positive breast cancer.
- Identify and manage patients who are at high risk for developing breast cancer using the findings from the 2002 ASCO technology assessment of pharmacologic interventions for breast cancer risk reduction.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Postgraduate Institute for Medicine and NL Communications, Inc. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement

The Postgraduate Institute for Medicine designates this educational activity for a maximum of 3 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

Faculty Disclosure Statements

The Postgraduate Institute for Medicine has a conflict of interest policy that requires course faculty to disclose any real or apparent commercial financial affiliations related to the content of their presentations/materials. It is not assumed that these financial interests or affiliations will have an adverse impact on faculty presentations; they are simply noted in this supplement to fully inform participants. ***Faculty disclosure information can be found on page 37.***

Editor's Note

Are we moving quickly enough?

"I hate breast cancer. In my dark days — which occur perhaps more frequently than I wish – I think about the wonderful people I have treated over the years and how many of them we lost. I hate this disease and a piece of me comes out with every patient with metastatic disease I treat. I'm always hoping and praying for that long duration of remission, but I've been doing this a long time, and I've seen so many good people just have a graceless course. I truly hate breast cancer."

—Hyman B Muss, MD

Every healthcare professional who has witnessed the human havoc of breast cancer has hope that future advances will relegate the disease to the paradigm of pneumococal pneumonia. However, until a "penicillin-like" cure appears, there will be many, many frustrating moments as reflected by Dr Muss.

Occasionally, in interviews for this series, I query research leaders about their coping mechanisms for the frequent heartbreaking moments in breast cancer medicine. Another guest for this issue of Breast Cancer Update, Dr Clifford Hudis, summarized his coping mechanism as "lots of time on the Stairmaster® and participation in clinical research."

After 25 years in oncology and a succession of ASCO meetings that seem to only report baby steps in the overwhelming challenges of this disease, it is easy to feel a sense of disappointment. However, the lead interview of this issue focuses on a patient treated seven years ago by Dr Debu Tripathy. In comparing the therapy this woman received then to how she might be treated today, a somewhat different perspective emerges.

This young woman — presenting with a node-positive, HER2-positive, ER/PR-negative primary tumor — was treated with four cycles of adjuvant AC. Dr Tripathy notes that today this patient would likely be treated with a taxane-containing adjuvant regimen and, perhaps of even greater importance, she would have had the option to enroll in one of a number of major cooperative group trials evaluating trastuzumab in the adjuvant setting.

In fact, when this woman relapsed with metastatic disease in 1996, she was enrolled in the pivotal randomized trial by Slamon et al comparing chemotherapy alone to chemotherapy plus trastuzumab. The rapid pace of clinical research is evident, when one considers that just a few years after this study demonstrated an

advantage to adding trastuzumab in metastatic setting, the NSABP, Intergroup and the newly formed BCIRG all had implemented adjuvant trastuzumab trials.

Dr Tripathy's case highlights another major conceptual development in clinical research in the last few years — specifically, the attention to the impact of post-trial therapy in studies of metastatic disease. This patient actually progressed on the treatment to which she was randomized (paclitaxel alone), as well as the crossover therapy mandated in the study (paclitaxel plus trastuzumab).

However, she subsequently had a remarkable complete response to trastuzumab plus vinorelbine. Dr Tripathy notes the irony in this woman's relatively long survival being the result of third-line therapy initiated after the trial's major randomizations.

In the previous issue of Breast Cancer Update, Dr Joyce O'Shaughnessy commented on the impact of post-trial therapy on the results of the X-T versus T trial that evaluated the biochemically synergistic combination of capecitabine and docetaxel. She noted that while the patients randomized to X-T had longer survival than those who received docetaxel alone, patients who received capecitabine after docetaxel also had excellent outcomes. This brings up the question of what might have been demonstrated with a third arm of capecitabine followed by docetaxel on progression.

Compared to 10-15 years ago, trials in the metastatic setting are currently planned not only to improve treatment options, but perhaps even more importantly, to delineate strategies to be tested in the adjuvant setting. Just as the chemo-trastuzumab approach moved quickly to the earlier disease setting, X-T is now being evaluated in both adjuvant and neoadjuvant trials.

The timetable on moving therapies through the breast cancer continuum is rapidly accelerating. In this issue, Dr Rowan Chlebowski, who authored the first ASCO Technology Assessment on breast cancer chemoprevention, provides insights on the second version of this futuristic document. He notes that, in the last seven years, we have progressed from initial randomized trials of aromatase inhibitors in advanced disease, to studies that will explore this strategy in high-risk women.

Is this coalescence of an integrated breast cancer clinical research strategy a cause for optimism or simply more hype? Having just returned from Oxford, England, where Sir Richard Peto presented preliminary unpublished results from the first international meta-analysis on early endocrine therapy of prostate cancer (about 17 years after a similar analysis in breast cancer), we can at least state that breast cancer is at the vanguard of oncologic research in solid tumors. On the other hand, for physicians like Dr Muss, on the front line of this disease, there unfortunately will be many more dark personal moments before definitive answers are attained.

—Neil Love, MD

Debu Tripathy, MD

Professor of Medicine and Director,
Komen Alliance Breast Cancer Research Center,
University of Texas Southwestern Medical Center

Edited comments by Dr Tripathy

CASE 1:
45-year-old premenopausal woman with recurrent breast cancer who participated in the trastuzumab pivotal trial

History

At initial presentation in 1995, this woman had a 2-centimeter, high-grade, ER/PR-negative, HER2-positive (IHC 3+) tumor and three positive lymph nodes (stage IIB). She was treated with a mastectomy and adjuvant doxorubicin/cyclophosphamide.

Approximately one year after completing adjuvant chemotherapy, she had a chest wall recurrence and pulmonary metastases. She had neglected to come in for follow-up, and the recurrence was fairly extensive over the entire left chest wall, involving the side and extending to the scapula. There were some areas of ulceration anteriorly. She was having a fair amount of discomfort over her chest wall, but she was not having any symptoms from her pulmonary disease.

Follow-up

She enrolled on the randomized trial comparing chemotherapy alone to chemotherapy plus trastuzumab. She was randomized to paclitaxel alone and progressed. Then, she was eligible to cross over to paclitaxel/trastuzumab. However, she did not respond to that combination either.

The pulmonary nodules doubled in size to around four centimeters. Her chest wall disease also expanded to involve the lower aspect of the chest wall and more of the scapular area. She also developed lymphadenopathy in the axillary and supraclavicular areas on the left side.

CASE 1 *(Continued)*

The protocol allowed the chemotherapy regimen to be changed, and then she was treated with vinorelbine/trastuzumab. She had a dramatic response to that regimen and an excellent quality of life. After about two and a half years, she again progressed in the chest wall, lung and also the liver. She ultimately died of hepatic failure about two years ago.

Case discussion

By the time this patient presented with local recurrence, local radiotherapy was not an option. When she was staged, she also had pulmonary metastases. She was clearly a candidate for some form of systemic therapy, and she was eligible for the randomized trial with trastuzumab. Since she had already received doxorubicin, she was randomized between paclitaxel alone and combination paclitaxel/trastuzumab.

We were, of course, discouraged that she did not respond to either paclitaxel alone or — on crossover — to paclitaxel/trastuzumab. Given some of the uncertainty and the lack of options, it was reasonable to try a combination of vinorelbine/trastuzumab. At that time, here was very early data about the synergy with these two agents from Mark Pegram's laboratory.

Part of the reason this case is so memorable is that she had a very dramatic response to vinorelbine/trastuzumab. Her chest wall disease essentially disappeared completely. I have never really seen such a response in someone whose disease was so extensive. She had some residual pinkness to the skin, but really no nodular changes. Her pulmonary nodules did not go away completely, but they regressed by 80% or 90%. She had a major — almost complete — response.

Choice of adjuvant chemotherapy

Currently, I am using four cycles of doxorubicin/cyclophosphamide mostly for patients with negative lymph nodes. If a patient with ER-negative, node-positive disease presented today, I would use adjuvant doxorubicin/cyclophosphamide, followed by paclitaxel.

In patients with ER-positive disease, I think it is reasonable to use paclitaxel. I am, however, concerned about the subanalysis showing a lack of benefit in patients with ER-positive disease. Although the statisticians tell us not to look at that subset, CALGB 9344 had 2,000 ER-positive and 1,000 ER-negative cases. Early data from NSABP B-28 seems to show a trend in the same direction.

Even though I think taxanes are reasonable, and, in fact, they are the control arm of many of the Intergroup studies, for my patients with node-positive, ER-positive disease, I also think it is reasonable to use six cycles of an anthracycline-containing regimen, like FAC or FEC. That is typically what I am using.

Choice of adjuvant hormonal therapy in premenopausal patients

In patients with ER-positive disease and positive lymph nodes, I would use tamoxifen following the adjuvant chemotherapy. In women who are still menstruating, I think the LHRH agonists are reasonable as well, but the value of adding an LHRH agonist to tamoxifen is still questioned. In the large European study, the Zoladex® in Premenopausal Patients (ZIPP) trial, there was a clear advantage with goserelin, but in the subgroup of women on tamoxifen, it was not statistically significant.

A proposed Intergroup study will evaluate chemotherapy followed by tamoxifen, with or without an LHRH agonist, in women who are still menstruating after chemotherapy. Now that the ATAC trial results are available, they are also thinking about evaluating an LHRH agonist plus anastrozole in those women. I would support a trial where the control arm would be tamoxifen and the experimental arms would be an LHRH agonist plus tamoxifen, and an LHRH agonist plus an aromatase inhibitor.

Postmastectomy radiation therapy

Unless a patient has a primary tumor that is more than five centimeters, or with skin involvement or more than four positive lymph nodes, I do not routinely use radiation therapy postmastectomy. It is still unclear whether a positive HER2 status alone would be enough of a risk factor for local recurrence to warrant the use of radiation therapy.

The use of postmastectomy radiation therapy in patients with one to three positive lymph nodes is an area that is under investigation. Patients with one to three positive lymph nodes, and a primary tumor that is less than five centimeters, are the subjects of a randomized trial comparing postmastectomy radiation therapy to observation.

Phase III Randomized Study of Radiotherapy after Mastectomy and Adjuvant Chemotherapy in Women with Stage II Breast Cancer with One to Three Positive Nodes Open Protocol

Protocol ID: ACOSOG-S9927, CAN-NCIC-SWOG-S9927, CLB-49910, E-S9927, GUMC-00223, NCCTG-S9927, NSABP-SWOG-S9927, RTOG-9915, SWOG-S9927

Eligibility	Stage II (T1-2, N1, M0) adenocarcinoma of the breast, primary tumor ≤ 5 cm, 1 to 3 positive axillary lymph nodes and chemotherapy ± hormonal therapy after mastectomy

ARM 1 | Radiotherapy 5 days a week for 5 weeks

ARM 2 | Observation

Patients are followed every 6 months for 2 years and then annually for 15 years.

Source: NCI Physicians Data Query, September 2002.

Responses to second-, third- and fourth-line chemotherapy

I have seen maybe two or three patients with a dramatic response to second-, third- or fourth-line chemotherapy. For example, we start them on capecitabine, and they have a great response — independent of trastuzumab.

I have seen HER2-negative patients progress on doxorubicin and then on paclitaxel, and then have a great response to capecitabine. Even though these patients are not common, we do occasionally encounter patients who respond to their third- or fourth-line chemotherapy much more dramatically than prior agents. We need to develop markers of resistance and sensitivity to therapy, so we can know ahead of time what drugs to use.

Choice of systemic therapy for patients with HER2-positive metastatic disease

In patients with HER2-positive metastatic disease, it is a given that those patients will receive trastuzumab. Whether to add chemotherapy is the question. In the absence of cardiac disease, I would use trastuzumab monotherapy in a patient who is asymptomatic or whose disease was not immediately life-threatening.

An asymptomatic patient with bone-only or soft-tissue disease would be — in my mind — an ideal candidate for trastuzumab monotherapy. In a patient with multiple liver lesions who might get into trouble with a little progression — even though they were asymptomatic — I might consider combination therapy with chemotherapy plus trastuzumab.

For combination therapy, I use a taxane with trastuzumab. Since the data is based on paclitaxel, I tend to use that. There are early trial results from combinations with docetaxel showing response rates from 35% to 60%. Certainly, I think docetaxel is active in combination with trastuzumab.

The group at UCLA strongly believes that the synergy with docetaxel — at least in the laboratory — is greater than with paclitaxel. Therefore, they have designed their trials, both in advanced and early-stage disease, with docetaxel.

The high response rates with the combination of vinorelbine/trastuzumab are encouraging. Soon, we may have reason to use it as first-line therapy. There are proposed trials comparing a taxane to vinorelbine, in combination with trastuzumab, as front-line therapy. Vinorelbine/trastuzumab and paclitaxel/trastuzumab are both very tolerable. Bone marrow toxicity may occur a little earlier with vinorelbine.

Trastuzumab pivotal trial

The primary outcome initially chosen was time to disease progression. Survival, even though it was captured, was not expected to be different. In fact, that is why the crossover was allowed. When the survival difference

emerged, despite the fact that close to 70% of the patients crossed over, it was indeed remarkable.

In retrospect, it would have been interesting to have trastuzumab monotherapy as the third arm of that trial. In fact, such a trial is now being proposed. For example, trastuzumab alone will be compared to trastuzumab plus a taxane. Then, upon progression on trastuzumab alone, there will be a second randomization to either a taxane alone, or a taxane plus trastuzumab. I think that that will be an excellent trial.

Trastuzumab in combination with other agents

Another area of interest is the combination of trastuzumab with other drugs. Some of these combinations are driven by *in vitro* data. The combinations with gemcitabine and the platinums look interesting.

Much of the original preclinical work was done with cisplatin. In fact, an early Phase II study by Mark Pegram demonstrated activity for trastuzumab in combination with cisplatin in very refractory patients. The BCIRG and the group at UCLA are capitalizing on this in their adjuvant trial.

There is also data from a trial in metastatic disease looking at trastuzumab in combination with either carboplatin, or cisplatin along with docetaxel, which found very high response rates.

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

	Number of Subjects	Overall Response Rate
Weekly paclitaxel/trastuzumab		
Fountzilas G. *Ann Oncol* 2001;12:1545-51.	34	62%
Seidman AD. *JCO* 2001;19:2587-95.	50	67%-81%
Paclitaxel/gemcitabine/trastuzumab		
Miller KD. *Oncology (Huntingt)* 2001;15 (2 Suppl 3):38-40.	27	not reported
Docetaxel/trastuzumab		
Burris H. *Sem Oncol* 2001;28;38-44.	16	45%
Uber K. *Proc ASCO* 2001. #1949.	19	63%
Meden H. *Proc ASCO* 2001. #1987.	12	50%
Esteva FJ. *JCO* 2002;20:1800-8.	30	63%
Docetaxel/carboplatin/trastuzumab		
Slamon DJ. *Proc ASCO* 2001. #193.	14	64%
Docetaxel/cisplatin/trastuzumab		
Pienkowski T. *Proc ASCO* 2001. #2030.	34	76%
Weekly vinorelbine/trastuzumab		
Burstein HJ. *Proc ASCO* 2002. #211.	50	64%
Burstein HJ. *JCO* 2001;19:2722-30.	40	75%
Jahanzeb M. *Proc ASCO* 2001. #1986.	20	60%
Liposomal anthracycline/trastuzumab		
Theodoulou M. *Proc ASCO* 2002. #216.	33	58%

Trastuzumab/vinorelbine

Probably the most exciting data is the high degree of activity demonstrated with the trastuzumab/vinorelbine combination. This has been confirmed in a separate trial, but I think it still needs to be confirmed in the large ongoing multicenter trial. Furthermore, I believe there is a trial comparing paclitaxel or docetaxel to vinorelbine in combination with trastuzumab.

Phase III Randomized Study of Trastuzumab (Herceptin) in Combination with Either Vinorelbine or Taxane-Based Chemotherapy in Patients with HER2-Overexpressing Metastatic Breast Cancer Open Protocol

Protocol IDs: DFCI-01087, GSK-2001-P-000473/2

Eligibility | HER2-positive (FISH+ or IHC 3+) invasive stage IV breast cancer

ARM 1 | Trastuzumab + vinorelbine

ARM 2 | Trastuzumab + [paclitaxel or docetaxel]

Courses in both arms repeat every 8 weeks in the absence of disease progression or unacceptable toxicity.

Source: NCI Physician Data Query, September 2002

Neoadjuvant trastuzumab

The neoadjuvant data for trastazumab exemplify a totally different set of circumstances. With chemotherapy alone, clinical response rates are in the 70% to 90% range. It is not surprising then that the trastuzumab combinations show those same response rates. Since the pathologic complete response rate is a surrogate for survival, we are very interested in that.

I support these trials. I do not treat patients outside of a trial with neoadjuvant trastuzumab, but we are certainly going to participate in the CALGB trial with neoadjuvant trastuzumab. That trial is designed to determine the efficacy of dexrazoxane (Zinecard®), trastuzumab in combination with paclitaxel, and one year of trastuzumab following surgery.

First, the patients are randomized to receive doxorubicin/cyclophosphamide, with or without dexrazoxane. This part of the trial will determine whether the introduction of a cardioprotectant can have a long-term effect on controlling cardiotoxicity. In the second phase of the study, the patients will receive paclitaxel/trastuzumab. Then, the patients will have surgery, and they will receive trastuzumab for one year.

Phase III Randomized Study of Doxorubicin and Cyclophosphamide with or vithout Dexrazoxane, Followed By Paclitaxel vith or without Trastuzumab (Herceptin), Followed by Surgery and Radiotherapy vith or without Trastuzumab in Women with HER2+ Stage IIIA or IIIB or Regional Stage IV Breast Cancer Open Protocol

Protocol ID: CLB-49808

Eligibility	HER2-positive (FISH+ or IHC 3+) primary infiltrating adenocarcinoma of the breast (T3, N1, M0 or any T, N2 or N3, M0 or T4, any N, M0, including clinical or pathological inflammatory disease or regional stage IV disease with supra- or infraclavicular lymph nodes as only site of metastasis)
ARM 1	[AC + dexrazoxane] q 3 weeks x 4 → [T + H] q week x 12 → surgery → RT → H q week x 40 weeks
ARM 2	AC q 3 weeks x 4 → [T + H] q week x 12 → surgery → RT → H q week x 40 weeks

Treatment continues in all arms in the absence of distant disease progression.
Hormone receptor-positive patients may receive oral tamoxifen daily for 5 years.
Patients are followed every 6 months for 5 years and then annually for 5 years.

A = doxorubicin; C = cyclophosphamide; T = paclitaxel; H = trastuzumab

Source: CALGB, September 2002

Algorithm for HER2 testing

We assume that the tumors with a 3+ score on immunohistochemistry (IHC) are truly HER2-positive, and we do not test them further. If a tumor has a 2+ score on IHC, we test with fluorescence *in situ* hybridization (FISH). Even in patients with an IHC score of 0 or 1+ and other features of excessively aggressive disease, we may also do a FISH test.

An IHC score of 3+ is pretty reliable, as long as it is done at a laboratory that performs a lot of assays. Both the Intergroup and the NSABP study discovered that smaller community hospitals were overscoring tumors as 3+. Close to 30% of the 3+ scores were downstaged when they were reviewed centrally. These protocols have now been amended to require that the patients wait for final randomization until there is a central review of their HER2 status.

I think the same things apply to FISH testing. Since FISH testing already tends to be done at more centralized laboratories, we have not yet explored the quality control issues. I suspect there will be a proliferation of FISH testing, and the reagents will go out to all the community hospitals. Even though there is probably less room for interobserver variability, the same issues will apply. I hope as the FISH technology disseminates, people will do these quality control-type studies.

At some point, it may be possible that the only test that will be done is FISH. Personally, I believe it to be more accurate and less subject to interobserver variability. I think the cost should be downplayed if it is only a difference of

$100 or $200. However, when trastuzumab is given incorrectly for several months, that involves many thousands of dollars. It behooves us all — even from a cost standpoint — to get the most accurate test up and running.

Schedules of trastuzumab plus weekly taxanes

It was expected that weekly taxanes would be effective with trastuzumab, and, in fact, it was found to be the case. This paves the way for using weekly taxane regimens in the adjuvant setting and also for metastatic disease.

Trastuzumab administered every three weeks

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. 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.

Adjuvant trastuzumab

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 big question. We do not know the answer yet. Therefore, adjuvant trastuzumab is being evaluated in high-risk women with node-positive disease, where 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 (i.e., 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.

Clinical implications of the ATAC trial results

The biggest change in breast cancer has been the advances in hormonal therapy. I was surprised, when the early results from the ATAC trial were reported, that the benefits with anastrozole were evident so early.

I think the data from the ATAC trial is very convincing. It is a huge trial with more than 9,000 patients, and it is very unlikely that the curves will change over time. However, I am not sure what the long-term toxicities will be. The data already suggests that there may be a higher risk of fracture in women on aromatase inhibitors.

Currently, my approach is to use tamoxifen for low-risk patients with node-negative disease. In higher-risk patients (i.e., multiple positive nodes), I could probably make a case that, even with a small risk of osteoporosis, there is more to gain from an aromatase inhibitor. The benefits are proportional to the risks.

The final issue is the risk of tamoxifen. Tamoxifen is generally a safe drug, but in women over the age of 70, there is an excess risk of stroke. I think in women over the age of 70, I am also compelled to consider an aromatase inhibitor. Even in lower-risk women, my threshold for risk goes a little lower in those over the age of 70, mostly because of the risk of stroke.

In premenopausal women with multiple positive nodes, I would consider medical oophorectomy. In those types of patients, it might be reasonable to use an aromatase inhibitor. In premenopausal women with multiple positive nodes who stop menstruating after chemotherapy and have low estradiol levels, I would also consider an aromatase inhibitor.

Interchangeability of the aromatase inhibitors

In the adjuvant setting, I am currently using anastrozole, but I think the aromatase inhibitors are generally equivalent. At least, we have data on anastrozole. Soon, we will have data with some of the other aromatase inhibitors in the adjuvant setting.

Fulvestrant: Sequencing of hormones therapy in metastatic disease

Fulvestrant (Faslodex®) 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 end point, I think we have to look at that information cautiously. Fulvestrant and the aromatase inhibitors, in my mind, really represent equivalent therapeutic choices.

Select publications

The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359:2131–9. **Abstract**

Balducci L et al. **Management of breast cancer in the older woman.** *Cancer Control* 2001;8(5):431-41. **Abstract**

Boyages J et al. **Use of the St Gallen classification for patients with node-negative breast cancer may lead to overuse of adjuvant chemotherapy.** *Br J Surg* 2002;89(6):789-96. **Abstract**

Bundred N, Howell A. **Fulvestrant (Faslodex): Current status in the therapy of breast cancer.** *Expert Rev Anticancer Ther* 2002;2(2):151-60. **Abstract**

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

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Edited comments by Dr Muss

CASE 2: 72-year-old woman with ER+ PR+ HER2+ breast cancer

History

This vigorous, active and very healthy woman presented with a 2-centimeter tumor that was hormone receptor-positive and HER2-positive. Two of 14 lymph nodes were positive. Atorvastatin (Lipitor®) was the only medication she was taking.

Follow-up

She was treated adjuvantly with four courses of doxorubicin/cyclophosphamide followed by anastrozole, which was well tolerated.

Case discussion

I think the mindset that some physicians have is that 70-year-olds are "really old," but a healthy 70-year-old woman can live another 15 years. A patient with several positive nodes has a very high risk of recurrence, and breast cancer may shorten her life.

Selection of adjuvant hormonal therapy

In patients like this one with HER2-positive disease (IHC 3+ or FISH-positive), there are specific reasons to consider an adjuvant aromatase inhibitor. As suggested by the molecular biology and preclinical data, women with HER2-positive disease may have some degree of tamoxifen resistance.

Additionally as patients get older, their risk of vascular disease generally increases. Tamoxifen probably does not substantially increase the risk above baseline, but it is a concern.

A positive HER2 status would lead me to consider an aromatase inhibitor in postmenopausal patients. I would also probably consider the implications on bone and get a baseline bone mineral density.

CASE 2 *(Continued)*

Treatment on relapse

If this patient presented two years later with hip pain, a bone scan that was positive in several areas, normal laboratory values and no evidence of other obvious metastases, I certainly would use another form of endocrine therapy. It would be reasonable to select tamoxifen, because she has not been exposed to it. Even though she has HER2-positive disease and that might make the response rate to tamoxifen lower, I would probably still try it.

Fulvestrant would also be a reasonable alternative. We really do not know about the influence of HER2 status on the response to fulvestrant. Theoretically, it may not be influenced because of fulvestrant's different mechanism of action.

There is preclinical data suggesting that trastuzumab can reverse resistance to endocrine therapy. The CALGB will be conducting a clinical trial in women who develop a recurrence while on adjuvant tamoxifen, or shortly after stopping it. Those women will be randomized to trastuzumab alone or trastuzumab plus tamoxifen. The trial will determine whether tamoxifen resistance can be reversed by trastuzumab. There will also be similar trials with the aromatase inhibitors.

Use of bisphosphonates in patients with metastatic breast cancer

At the initial diagnosis of metastatic disease to the bone, I put patients on a bisphosphonate. These agents are all pretty much equivalent, but I think most of us are using zolendronate because short infusions are preferred over long infusions. There are differences in the potency of the bisphosphonates, but there are no convincing differences in their efficacy when used at the optimal doses.

Second-line therapy for recurrent breast cancer

In the first few months, endocrine therapy can produce a flare in markers, alkaline phosphatase, skin lesions and bone pain. If after six months of tamoxifen, however, this patient was having more hip pain and the bone scan had a few more lesions, I believe I would try further endocrine therapy if the symptoms were modest. Since chemotherapy is palliative, there is no rush to use it.

On the other hand, if the patient had a profound change in tumor biology, multiple new metastases, pain all over and substantial liver involvement, I would probably turn to chemotherapy. In the typical patient, however, the scenario is slower, and there is time to act. Therefore, I would try another endocrine therapy.

Fulvestrant would be a very good choice. One could also try a progestin, but I am impressed by the data comparing fulvestrant to anastrozole in patients who are refractory to tamoxifen. It is fascinating that fulvestrant, which prevents dimerization of the estrogen receptor, attacks the same estrogen receptor that was not effectively using tamoxifen as an antagonist. This means that the cancer is still endocrine-dependent.

Third-line therapy for recurrent breast cancer

If after four to five months of fulvestrant, the patient then developed a few more lesions but was still in pretty good shape, it would be reasonable to consider another aromatase inhibitor, such as exemestane. In a study by Lonning et al, exemestane was effective in women who were refractory to either letrozole or anastrozole.

Fourth-line therapy for recurrent breast cancer

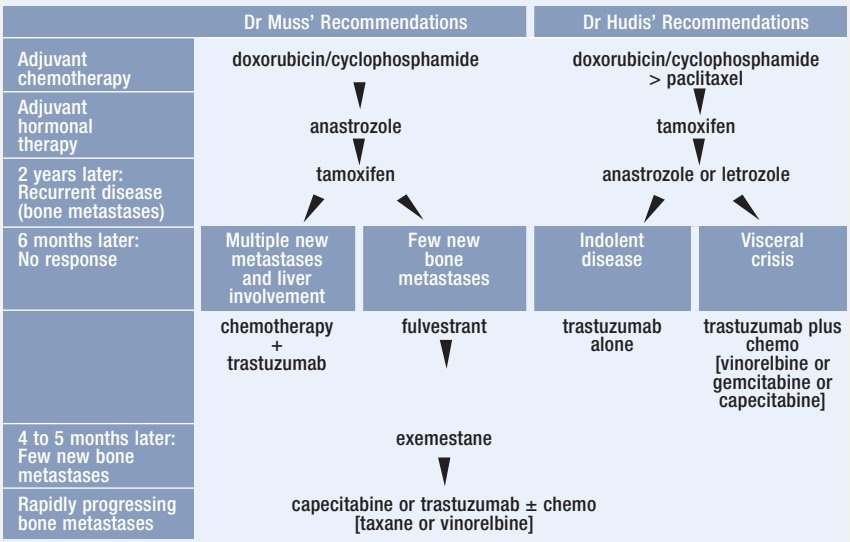
If the patient's bone metastases were rapidly progressing every few months, I think it would be reasonable to next use trastuzumab alone, trastuzumab plus a taxane, or perhaps trastuzumab plus vinorelbine. It would be rational to select a drug like capecitabine as well.

If the patient was not very symptomatic, I suspect there would not be great differences with any of those interventions. The response rates will certainly be higher, I suspect, for trastuzumab plus a taxane than for capecitabine. My personal approach, though, has been to use capecitabine in many of these patients.

If the patient certainly had any major progression, my bias would be to give trastuzumab plus chemotherapy. If the patient were somewhat reluctant about chemotherapy for any reason, single-agent trastuzumab would be an alternative. In Vogel's paper, the time to progression and survival for single-agent trastuzumab was similar to those in the pivotal trial. Although it is not a fair comparison, the numbers look pretty good.

I am sensitive to the data from the trastuzumab pivotal trial, which demonstrated a survival advantage of about five months for trastuzumab plus chemotherapy compared to chemotherapy alone. The pivotal trial was not designed so that trastuzumab was given to all patients second-line after chemotherapy, which would have conclusively proven that there was an advantage to giving trastuzumab plus chemotherapy, together. I suspect I am a "contrarian" here.

Two different treatment approaches for a 72-year-old woman with a 2-cm breast lesion (estrogen receptor-positive and HER2-positive) and 2/14 positive lymph nodes



Fulvestrant versus anastrozole: Conclusions

"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. Most events were mild and the safety profiles were similar. The most frequently reported drug-related AEs were hot flashes, nausea, sweating, headache, and asthenia; all are recognized side effects of endocrine treatments for breast cancer.

Fulvestrant is given as an IM injection once a month. Injection site reactions were uncommon and mild in intensity, with only one reaction leading to a patient withdrawing from treatment, thus demonstrating that the use of the fulvestrant injection is well tolerated.

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

Combined analysis of two studies evaluating fulvestrant (FAS) versus anastrozole (AN) in tamoxifen resistant patients with metastatic disease

". . . all patients were included in a newly developed statistical analysis of DOR, defined for responders as the time from onset of response to disease progression and for non-responders as zero. In this analysis, DOR was significantly greater (ratio of average response durations = 1.30; 95% CI 1.13 to 1.50; p=0.0003) for FAS vs AN. It can therefore be concluded that FAS is at least as effective as AN and provides prolonged DOR in postmenopausal women with ABC."

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

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

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

* In those responding to treatment.

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

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

82-year-old woman with inflammatory breast cancer

I just evaluated an 82-year-old woman with HER2-positive, estrogen receptor-negative inflammatory breast cancer. She was in excellent condition with minimal other medical problems. I treated her very aggressive tumor with a taxane and trastuzumab, which she tolerated superbly and to which she had a fantastic response. Now, I am treating her with trastuzumab every three weeks. Although she is not on a clinical trial, she did have inflammatory breast cancer with some positive nodes after surgery.

There is no evidence to suggest that trastuzumab's tolerability or efficacy is any different in the elderly. I have actually treated several very elderly women with trastuzumab.

Hormonal therapy versus chemotherapy for women with metastatic breast cancer

In metastatic disease, sequential chemotherapy is as good as combination chemotherapy. The majority of studies have shown no improvement in survival for more intense over more modest regimens.

I believe the goal for the patient with metastatic breast cancer is controlling the disease by preventing tumor growth for as long as possible. In patients with mild bone pain, keeping them stable for five years without any tumor shrinkage, and being able to manage their pain with an anti-inflammatory, will maintain their quality of life better than aggressive chemotherapy that may shrink the tumor but cause more toxicity. I believe in sequential therapy, which is associated with less toxicity.

Chemotherapy selection for patients with metastatic breast cancer: Role of capecitabine

In patients with lymphangitic spread or a bilirubin of 3 mg/dL, time is of the essence, and I would select an anthracycline, a taxane or capecitabine/docetaxel. But, those are the minority of patients. The goals of treatment 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 myelo-suppression with capecitabine. If a patient does not have hand-foot syndrome, they will probably tolerate it very well. I think that diarrhea is generally modest, but the hand-foot syndrome can be substantial.

I suspect that the dose in the package insert is too high. Data suggests that doses of 2,000 or perhaps 1,500 mg/m²/day (in two divided doses) for 14 consecutive days are as effective. The incidence of the hand-foot syndrome

declines substantially with these doses, and it becomes necessary to reduce the dose in only about 15% of patients.

Adjuvant chemotherapy for elderly women

In unpublished data from the Oxford 2000 Overview, there were about 1,200 elderly patients (≥70 years old), out of about 200,000, who were randomized to adjuvant chemotherapy or observation. The proportional reduction in the risk of relapse associated with adjuvant chemotherapy was very similar for that group of patients. In fact, it was a bit higher than that for the 60- to 69-year-old group, and similar to that for the 50- to 59-year-old group.

This data suggests that there is no reason that the Overview, which supports the value of adding adjuvant chemotherapy to endocrine therapy, would not apply to older women. The question is, "Is the patient going to live long enough to obtain a benefit?" In the United States, a 70-year-old woman in fair health will live on average to 85 years of age. A 75-year-old woman will also live to about 86 or 87 years of age, and an 80-year-old woman will live an average of another six to eight years. Seventy-year-old patients have a 15-year life span. If they have three or four positive lymph nodes or a very large, high-grade, node-negative tumor and are in reasonable health, breast cancer will be the major problem in their life.

CALGB: Adjuvant trial of capecitabine versus CA/CMF

In my adjuvant trial for elderly (≥ 65 years) women with node-positive breast cancer or high-risk (≥ 3 cm), node-negative breast cancer, patients are randomized to either standard chemotherapy or capecitabine. Because of the controversies about standard therapy, we gave doctors and patients the option of either CMF with an oral cyclophosphamide regimen or AC.

We have a quality-of-life assessment as part of the trial. We are looking at function and comorbidities, a major issue in the management of older women with breast cancer in the adjuvant setting. We are also going to evaluate other issues including the biology of breast cancer and patient compliance. In a companion study with tissue blocks, we will look at HER2 and thymidine phosphorylase, which is related to the effect of capecitabine. This trial in older women may provide clues on how to predict which patients will benefit from what therapies.

CALGB Phase III Single-Agent Adjuvant Chemotherapy Trials

	Randomization Arms		Eligibility
CLB-49907	capecitabine	CMF or AC	Elderly women (≥ 65 years) with operable breast cancer
CLB-40101	paclitaxel	AC	Women with high-risk node-negative breast cancer

Source: NCI Physician's Data Query, September 2002.

The Overview demonstrated that combination chemotherapy was better than single-agent chemotherapy in the adjuvant setting. These results, however, were based on single-agent trials with older drugs like melphalan. In fact, we are resurrecting single-agent chemotherapy in the adjuvant setting through our trial in older women, as well as a large CALGB trial in women with node-negative disease.

CALGB node-negative trial

The CALGB trial in women with node-negative breast cancer will compare weekly paclitaxel with doxorubicin/cyclophosphamide as adjuvant therapy. It has a two-by-two factorial design. Patients randomized to doxorubicin/cyclophosphamide will receive either four or six cycles, and patients randomized to paclitaxel will receive either 12 or 18 weeks of therapy. This study is based on some randomized neoadjuvant trials conducted at MD Anderson, which compared paclitaxel to FAC.

Select publications

Blum JL et al. **Multicenter, Phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients.** *Cancer* 2001;92(7):1759-68. **Abstract**

Dowsett M et al. **HER-2 amplification impedes the antiproliferative effects of hormone therapy in estrogen receptor-positive primary breast cancer.** *Cancer* Res 2001;61(23):8452-8. **Abstract**

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

Lonning PE et al. **Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: A phase II trial.** *J Clin Oncol* 2000;18:2234-44. **Abstract**

Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node-positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study.** *Proc ASCO* 2001;**Abstract 141.**

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

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

Pavlakis N, Stockler M. **Bisphosphonates for breast cancer.** *Cochrane Database Syst Rev* 2002;(1):CD003474. **Abstract**

Pinto AE et al. **C-erbB-2 oncoprotein overexpression identifies a subgroup of estrogen receptor-positive (ER+) breast cancer patients with poor prognosis.** *Ann Oncol* 2001;12(4):525-33. **Abstract**

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

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

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. **Abstract**

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2002 ASCO technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer

Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: Status report 2002.** *J Clin Oncol* 2002;20:3317-27.

In developing these guidelines, our group struggled with issues related to the role the aromatase inhibitors would play. Eric Winer highlighted that in the short run, maybe the most important outcome of the ATAC trial, is that now we have a proven alternative.

In the past, we had some data for toremifene versus tamoxifen, but the ATAC trial shows us that there's a drug that could be better and that certainly appears in many ways to be safer — and specifically safer in terms of toxicities that bother patients.

I have a very informed patient population. My patients come in asking questions, and I like those patients in terms of my own style of practice. It's the one that works for me.

So, I share this information with them, not only for the purpose of education, but also because even if I don't talk about it with them and even if they don't bring it up, it's very likely that after they leave my office in the weeks or months that follow, they're going to hear about this. I'd rather talk about it with them at the beginning.

Key issues addressed by the 2002 ASCO technology assessment on the adjuvant use of aromatase inhibitors

Conclusions
"The panel was influenced by the compelling, extensive, and long-term data available on tamoxifen. Overall, the panel considers the results of the ATAC trial and the extensive supporting data to be very promising but insufficient to change the standard practice at this time (May 2002). A five-year course of adjuvant tamoxifen remains the standard therapy for women with hormone receptor positive breast cancer. The panel recommends that physicians discuss the available information with patients, and, in making a decision, acknowledge that treatment approaches can change over time. Individual health care providers and their patients will need to come to their own conclusions, with careful consideration of all of the available data."

Women who have already started taking adjuvant tamoxifen
In a woman who has already started a course of adjuvant tamoxifen, no data currently supports the substitution of an aromatase inhibitor (A.I.) for tamoxifen. Women experiencing intolerable side effects related to tamoxifen may consider switching to an A.I..

Women who have completed a 5-year course of adjuvant tamoxifen and are disease-free
In a woman who has completed a 5-year course of adjuvant tamoxifen and is disease-free, an A.I. should not be considered unless such therapy is part of a clinical trial.

Premenopausal women
In premenopausal women with functioning ovaries, the A.I.s are contraindicated. In the adjuvant setting, an A.I. in combination with either an LHRH agonist or oophorectomy should not be considered outside the context of a clinical trial.

In women who are premenopausal at diagnosis and experience a disruption in ovarian function from chemotherapy, adjuvant A.I.s should also not be used. There is concern about the use of A.I.s in women with a probability of resuming ovarian function.

Women with HER2-positive breast cancer
HER2 status should not be used in making decisions about adjuvant hormonal therapy.

Women with a relative or absolute contraindication to the initiation of adjuvant tamoxifen
In postmenopausal women with a contraindication to adjuvant tamoxifen, an adjuvant A.I. may be reasonable. Careful consideration should be given to the significance of any relative contraindication compared to the proven benefits of tamoxifen.

Women who develop ER/PR–positive invasive breast cancer while taking either tamoxifen or raloxifene
Postmenopausal women developing ER/PR–positive cancers while taking tamoxifen or raloxifene are considered clinically resistant to these antiestrogenic agents. Therefore, it is reasonable to use an adjuvant A.I..

Duration of therapy with an A.I. in the adjuvant setting
If an A.I. is used as adjuvant therapy, it should be administered for 2 to 3 years based on the ATAC trial results. The issue of duration of therapy should be reassessed when more data becomes available.

Anastrozole versus other A.I.s
In the adjuvant setting, the only available data for the third-generation A.I.s are with anastrozole. Although the A.I.s are closely related, they may have different toxicity profiles. Therefore, anastrozole is the preferred A.I. in the adjuvant setting.

DERIVED FROM: Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: Status report 2002.** *J Clin Oncol* 2002;20:3317-27.

Adjuvant hormonal therapy in women previously taking tamoxifen or raloxifene

This comes at exactly the right time, because we may now have patients who have already taken tamoxifen and/or raloxifene, either for prevention of breast cancer or osteoporosis. A burning question has been: What to do with the breast cancers that develop in those patients, if they are ER-positive? Now we know that those patients can be offered an aromatase inhibitor as adjuvant therapy.

Another issue is the woman who develops a second primary ER-positive breast cancer while on tamoxifen, many physicians would have immediately used an aromatase inhibitor in the past. ATAC provides a little more solid evidence to support that decision.

Adjuvant hormonal therapy in women with contraindications to or intolerable toxicities from tamoxifen

In a patient who has a history of a hypercoagulable state or unacceptable toxicities with tamoxifen, one might consider switching to an aromatase inhibitor. Although, I am not convinced that switching to an aromatase inhibitor will alleviate patients' hot flashes.

In women complaining of weight gain with adjuvant tamoxifen, the first thing we do is counsel them. There is no guarantee that some of those complaints will not continue when the patient switches to an aromatase inhibitor. If, after a long discussion, the patient says they are going to stop taking tamoxifen, I certainly would encourage an aromatase inhibitor.

Adjuvant hormonal therapy in women with HER2-positive breast cancer

I agree with the findings of the ASCO technology assessment guidelines that at present time, HER2 status should not be used to determine adjuvant therapy in early stage breast cancer.

Adjuvant therapy in an elderly patient with a 2-cm tumor (ER-positive, HER2-positive) and two positive lymph nodes (see page 17)

I would treat this type of patient with adjuvant combination chemotherapy and five years of tamoxifen. 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 more involves the physiologic age than the chronologic age. It 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.

Outside of a clinical trial, I would use adjuvant doxorubicin/

cyclophospha-mide followed by paclitaxel (ACT), backing off only if there was a specific toxicity in a particular patient. I am not convinced that ACT is much more toxic than AC. Elderly patients would also be eligible for Hy Muss' trial, comparing single-agent capecitabine to either CMF or AC.

Adjuvant systemic therapy of patients with HER2-positive breast cancer

In patients who also have HER2-positive breast cancer, unless there is a specific contraindication, I would be biased in favor of using an anthracycline. Although many experts believe that HER2 status is not a proven predictive factor for response to chemotherapy, I think there is more than a little evidence to suggest that patients with HER2-positive disease may derive marginal benefit from anthracyclines.

TAC compared to FAC

As demonstrated in Jean Marc Nabholtz's abstract comparing TAC (docetaxel/doxorubicin/cyclophosphamide) to FAC (5-fluorouracil/doxorubicin/cyclophosphamide). Overall, there was a statistically significant improvement in disease-free survival associated with TAC.

Interestingly, it was most striking in the group with one to three positive lymph nodes, and a preplanned subset analysis showed no benefit in the group with four or more positive lymph nodes. The TAC versus FAC trial is another brick in the foundation indicating that there is a small and clinically important advantage to the taxanes. Patients with HER2-positive disease seem to get a marginal benefit from taxanes also.

First-line therapy for recurrent ER-positive, HER2-positive breast cancer (see page 15)

In a patient relapsing two years after adjuvant ACT and while on tamoxifen, with bone-only disease that is easily managed, I would certainly be inclined to try an aromatase inhibitor as my first maneuver. I would use either anastrozole or letrozole.

I would watch the patient closely in that situation. If there were signs of early disease progression, it would not take much to convince me to change direction and think about using trastuzumab.

A two-year time period is the threshold at which point one would be biased in favor of using more hormone therapy. We know that an early relapse on adjuvant tamoxifen does not speak well for subsequent responses to hormone therapy. In some studies, two years has been the cut-off for the likelihood of response to subsequent hormonal treatments.

Second-line therapy for recurrent ER-positive, HER2-positive breast cancer

In a patient not responding to first-line therapy with an aromatase inhibitor, the algorithm is a little different from what it was in the past. There are now three

options.

The first option is to consider yet another hormonal therapy. Since the response to one hormonal therapy, on average, predicts the response to subsequent hormonal therapies, I think that is the option least likely to be successful. The other options include chemotherapy, conventionally, and single-agent trastuzumab, less conventionally.

Choice of therapy for women with indolent disease

Until a few years ago, the only other option would have been chemotherapy. For a patient with what appears to be indolent disease but that is nevertheless progressing, the toxicities of many chemotherapy agents would make me less enthusiastic about this approach. The availability of single-agent trastuzumab changes the playing field. In this type of patient, I would feel most justified in using single-agent trastuzumab.

Randomized trial data clearly shows a time-to-progression and survival advantage for chemotherapy plus trastuzumab, compared to chemotherapy alone, and no data demonstrates that trastuzumab alone is equivalent to trastuzumab plus chemotherapy. There is indirect data, however, suggesting that trastuzumab can be initiated, and if there is disease progression, chemotherapy can subsequently be started while continuing the trastuzumab, without any real loss of apparent benefit.

From Chuck Vogel's data there is good evidence that in patients with HER2-positive (FISH-positive or IHC 3+) metastatic disease, single-agent trastuzumab before chemotherapy is comparable to conventional chemotherapy. That data provides me with the basis for using single-agent trastuzumab.

Choice of therapy for women with visceral crisis

In patients with approaching visceral crisis (i.e., ascites, a pleural effusion, multiple new pulmonary nodules and multiple new liver metastases), I would start chemotherapy plus trastuzumab. If the patient had received adjuvant AC and paclitaxel, in my practice, the patient would be treated with trastuzumab in combination with vinorelbine, gemcitabine or often capecitabine.

These are combinations for which there are no randomized trial data. But the patient is, most likely, refractory to paclitaxel, which would have normally been my first choice. So, I must base my decision on Phase II evidence, and for all those drugs, there is Phase II evidence of safety.

Third-line therapy for recurrent ER-positive, HER2-positive breast cancer

In patients progressing after one year of trastuzumab, I would next turn to chemotherapy. One situation where I would almost always continue trastuzumab would be when I did not think the trial was adequate. For example, in a patient treated with trastuzumab who had progression at week eight, I would be concerned that we did not establish adequate serum levels.

If the patient had not received paclitaxel in the adjuvant setting, I would use paclitaxel. If the patient had received paclitaxel in the adjuvant setting, I would use capecitabine next. The quality-of-life aspects of capecitabine make it a natural choice.

I am biased towards capecitabine because of its oral route, flexible scheduling/dosing and its decidedly different toxicity profile. It does not cause profound neutropenia or alopecia. Commonly, patients who have had adjuvant AC/paclitaxel and develop metastatic disease are disheartened when they are told that they will get alopecia once again. In terms of quality of life, being able to offer a regimen that does not cause alopecia is appealing.

I do not use the package insert dose of capecitabine for any patients initially. For compliance reasons, I think it is easier to recommend a single pill size — 500 milligrams. Typically, I calculate the dose based on a 25% 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 get away with minimal diarrhea and nominal hand-foot syndrome. When we first started using capecitabine, we encountered serious diarrhea. Now that we have made this adjustment, I do not believe we see the same incidence. 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.

HER2-positive, hormone receptor-negative inflammatory breast cancer in an 82-year-old woman (see page 20)

If the patient were healthy enough to have surgery, my inclination would be to use combination chemotherapy (doxorubicin/cyclophosphamide), and if she responds, then treat her with surgery followed by paclitaxel and radiation therapy.

This patient would be also eligible for the CALGB trial evaluating neoadjuvant trastuzumab. That trial involves four cycles of AC, with or without dexrazoxane, and 12 weeks of paclitaxel/trastuzumab followed by surgery and trastuzumab to complete a year. If she were not healthy enough to have surgery, that changes the equation a little for me. Then, I would actually be thinking about trastuzumab for its palliative benefit. I would think of her as a patient with metastatic disease.

Controversy regarding sentinel node examination

Two abstracts presented at ASCO 2002 highlighted this controversy. One, a retrospective analysis of a large data-set suggests that the discovery of any cancer cells (either by IHC or H&E) — regardless of the number — connotes a poor prognosis compared to no cells.

Interestingly, the curves do not appear to diverge until many years — maybe eight or more. If this were the case, it warns us not to be so quick to accept the lack of significance seen with short-term follow-up studies. The limitation to this study is

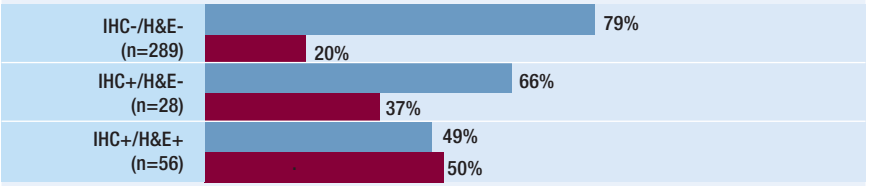
that it was not a sentinel node trial. The patients all had axillary dissections, which were retrospectively analyzed. Since the vast majority of patients on this trial had a single positive node, we think it could correlate to the sentinel node.

On the other hand, the abstract presented immediately afterwards suggested no link between survival and the discovery of epithelial-staining cells in the bone marrow or the sentinel node. The discrepancy highlights that this is still an unanswered question.

In patients with an IHC-positive sentinel node that is H&E negative, it is a tough call. Patients with larger tumors with poor prognostic features will receive treatment anyway. The situations that are the most difficult are the older patient who will be treated with hormonal therapy alone, or the patient with a very small primary tumor for whom presence of nodal involvement would dramatically change the approach.

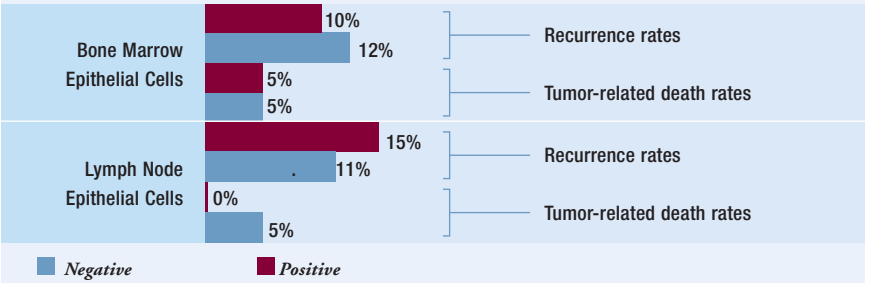
Based on the retrospective data-set from our center — presented at ASCO — I am inclined to think about systemic therapy for those patients. However, I would prefer that those patients enroll on a clinical trial.

Impact of occult micrometastases in the axillary lymph nodes of node-negative women: median follow-up of 17.6 years



Derived from: Tan LK et al. **Occult/micrometastases in axillary lymph nodes of breast cancer patients are significant: A retrospective study with long-term follow-up.** *Proc ASCO* 2002. Abstract 146.

Recurrence rates and tumor-related death rates in 189 women with node-negative breast cancer and single epithelial cells in bone marrow or lymph nodes: median follow-up of 4.2 years



Derived from: Gebauer G et al. *Proc ASCO* 2002. Abstract 147.

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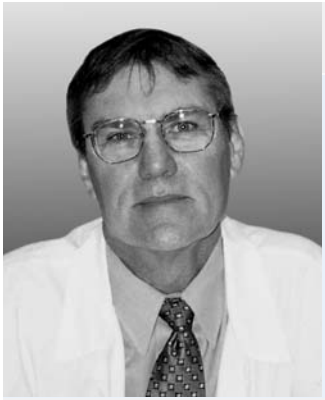

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2002 ASCO technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene and aromatase inhibition

Key Conclusions from the 2002 ASCO Technology Assessment on Pharmacologic Interventions for Breast Cancer Risk Reduction

Tamoxifen

- May be offered to women with a 5-year projected breast cancer risk of ≥ 1.66%.
- Is appropriate for the goal of reducing the short-term risk of developing breast cancer.
- Provides the greatest clinical benefit/risk ratio in:
  - younger (premenopausal) women
  - women without a uterus
  - women at higher breast cancer risk.
- Has not yet demonstrated an overall health benefit or an increase in survival.

Raloxifene

- Is not recommended for the reduction of breast cancer risk.
- Should be reserved to prevent or treat bone loss in postmenopausal women.

Aromatase Inhibitors

- Are not recommended for the reduction of breast cancer risk outside a clinical trial.

Derived from: Chlebowski RT et al. **American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition.** *J Clin Oncol* 2002;20:3328-43. **Abstract**.

Evolution of chemoprevention research

In 1999, there were about 350 events in the NSABP-P1 trial which demonstrated a 50% risk reduction with tamoxifen. At the same time, there were less than 100 events on the European trials which showed almost no effect. Now, results from the International Breast Cancer Intervention Study (IBIS-1) have been published. Additionally, Jack Cuzick's meta-analysis has updated the other two European trials.

In the European studies, risk assessment was completely based on family history. Therefore, they had a different patient population. In the NSABP-P1 and IBIS-1 trials, 17% and 5% of the women, respectively, had LCIS or atypical ductal hyperplasia. In the Royal Marsden trial and the Italian trial, none of the women had those conditions.

IBIS-1 randomized over 7,000 women with an increased breast cancer risk to tamoxifen or placebo. Although 40% of the women were receiving hormone replacement therapy, there still was a 33% statistically significant reduction in breast cancer.

When all of the trials are pooled together, there is an overall 38% reduction in breast cancer risk. There is a statistically significant 50% reduction in the risk of ER/PR receptor-positive breast cancer and a statistically nonsignificant 25% increase in ER/PR receptor-negative breast cancer with tamoxifen. Interestingly, all-cause mortality is the same for women receiving tamoxifen or placebo. However, there may not yet be enough deaths to make a statement about tamoxifen's effect on overall mortality.

The statistically nonsignificant increase in ER/PR receptor-negative breast cancers is an interesting issue. Last year, in the *Journal of the National Cancer Institute*, the Seattle group reported on an epidemiological study suggesting the same thing. One potential explanation is that suppressing the receptor-positive breast cancers leads to a differential increase in ER/PR receptor-negative cancers.

International Breast Cancer Intervention Study (IBIS-1) Main Results: Median Follow-up of 50 Months

	Tamoxifen (n=3,573)	Placebo (n=3,566)	
Total Breast Cancer Cases	69	101	OR = 0.68 (0.50–0.92)
DCIS	5	16	OR = 0.31 (0.12–0.82)
Invasive	64	85	OR = 0.75 (0.54–1.04)
Venous Thromboembolic Events	43	17	P = 0.001

OR = Odds Ratio (95% CI) for tamoxifen versus placebo

Derived from Cuzik J. **First results from the International Breast Cancer Intervention Study (IBIS-1): A randomised prevention trial.** *Lancet* 2002;360:817-24. Abstract.

Clinical implications of chemoprevention trials

The 2002 ASCO technology assessment states that tamoxifen be recommended for the short-term (five-year) reduction of breast cancer risk. The indications for tamoxifen have narrowed, because we are more cognizant of its side effects and the fact that younger women and women without a uterus derive the most benefit.

The patient-care message from the 2002 ASCO technology assessment is that tamoxifen effectively reduces the risk of breast cancer, but women must consider the risks and benefits. I think younger women (under the age of 50) with an increased risk of breast cancer based on family history or several biopsies, will benefit the most. Older women, without a uterus and with a strong family history, may benefit as well. At this point, tamoxifen is for short-term breast cancer risk reduction as opposed to general health benefit.

IBIS-2 chemoprevention trial

The IBIS-2 trial plans to identify a high-risk population based on family history and to randomize them to anastrozole or placebo. There is a more complicated schema for patients with DCIS, in which tamoxifen may be the control arm.

The Study of Tamoxifen and Raloxifene (STAR) trial is ongoing and has recruited over 13,000 of it's target 22,000 patients. The STAR trial does not have a placebo control. However, IBIS-2 is going ahead with a placebo control.

The 58% percent reduction in contralateral breast cancer reported for anastrozole in the ATAC trial suggests that anastrozole may be better than tamoxifen, with a different toxicity profile. Since the effects of tamoxifen on overall health are unknown, it may be appropriate to go forward with the placebo control.

Tamoxifen and the risk of uterine sarcoma

Tamoxifen has an — undeserved — bad reputation. The recent FDA warning about the risk of uterine sarcoma will make that reputation worse. I do not think it changes the risk-benefit ratio, but, it might make women hesitant about taking tamoxifen.

In tracking toxicity reports, the FDA saw a number of uterine sarcomas — a relatively uncommon malignancy. Then, they discovered that, of the tamoxifen-associated endometrial malignancies, approximately 20% were uterine sarcomas. Since this represented a worse-prognosis cancer, they wanted to focus attention on the DCIS and the risk-reduction indication.

Hormonal therapy and cognition

Evidence from preclinical, clinical observational and randomized trials suggests that estrogen may play a role in maintaining cognition in postmenopausal women. There are large-scale randomized trials involving thousands of women that will address this question, but, we do not currently have prospective data.

One of the issues for tamoxifen, since it increases hot flashes by about 20%, is that it crosses the blood-brain barrier and interacts with the central nervous system (CNS). Therefore, tamoxifen could act as an estrogen antagonist in the CNS and be associated with poor cognition. However, that has not been found with the screening questionnaires done in NSABP-P1 and other trials, but, those questionnaires are generally insensitive and not designed to answer that specific question.

Effects of tamoxifen on brain metabolism

To test the hypothesis that tamoxifen might impair cognition, we utilized a very interesting neuroimaging technique — proton magnetic resonance spectroscopy — that can measure the concentrations of biochemical markers associated with brain injury.

We measured myo-inositol levels, which increase in response to brain injury. An increase in myo-inositol levels is predictive of progression in AIDS dementia and Alzheimer's disease and is linearly related with age.

We studied 75 women (≥ 65 years of age) who received hormone replacement therapy for two or more years, tamoxifen for two to five years or no hormonal therapy. We found a time-dependent, statistically significant reduction in myo-inositol levels in women treated with tamoxifen. There was a similar trend in the women treated with estrogen.

These results would lead us to predict that tamoxifen will have a neuroprotective effect in the CNS. Perhaps, tamoxifen is agonistic on this part of the brain, but antagonistic on the part that controls vasomotor symptoms.

The role of lifestyle modifications in breast cancer prevention

Reduction in dietary fat intake

There are over 50,000 women currently randomized to studies evaluating the role of dietary fat intake reduction in primary or secondary breast cancer risk reduction. The Women's Health Initiative (WHI) randomized 47,000 healthy, postmenopausal women to dietary fat intake reduction or observation. A report on all-cause mortality will be available in 2005.

The Women's Intervention Nutrition Study (WINS) has accrued close to 2,400 postmenopausal women who received standard adjuvant chemotherapy. After the women complete their standard interventional therapy, they are randomized to dietary fat intake reduction or observation. We have over 200 events and are due to report in a year or two. The Women's Healthy Eating and Living (WHEL) study has a similar design, and randomizes postmenopausal women up to three years after breast cancer diagnosis.

I think these studies have a good chance of being positive. One of the reasons I am enthusiastic is the attention focused on molecular medicine and biology and the cross-talk between all the receptor pathways. It is easy to see how the insulin-regulatory pathway is going to play a role in this process.

Pam Goodwin reported in the *Journal of Clinical Oncology* a prospective observational study. She found that women with fasting insulin levels in the highest quintile, compared to the lowest, had an eight-fold increased risk of breast cancer recurrence and death. Therefore, insulin itself might be a mitogen. In the nonprotocol setting, I will chat with breast cancer survivors about modifying their dietary fat intake.

Exercise

Observational studies demonstrate that increasing exercise may decrease the chance of breast cancer recurrence. Therefore, there are ongoing pilot studies. There are many potential mechanisms for exercise's antitumor effects, including a change in estrogen levels, insulin-regulatory pathways and COX-2 inhibition.

In noncancer patients, exercise is a great mediator of hot flashes, but, this has not been discussed in the breast cancer setting. There was a report at ASCO 2002 demonstrating that exercise increased bone mineral density in women receiving chemotherapy for breast cancer. There was also another report indicating that a physician's recommendation to exercise resulted in a change in women's intentions to exercise.

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Wysowski DK et al. **Uterine sarcoma associated with tamoxifen use.** *N Engl J Med* 2002;346(23):1832-3. **Abstract**

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals, LP
capecitabine	Xeloda®	Roche Laboratories, Inc.
cyclophosphamide	Cytoxan®, Neosar®	Bristol-Myers Squibb Company, Pharmacia Corporation
dexrazoxane	Zinecard®	Pharmacia Corporation and Upjohn Co.
docetaxel	Taxotere®	Aventis Pharmaceuticals
doxorubicin	Adriamycin®, Rubrex®	Pharmacia Corporation
exemestance	Aromasin®	Pharmacia Corporation
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals, LP
gemcitabine	Gemzar®	Eli Lilly and Co.
imatib mesylate	Gleevec®	Novartis Pharmaceuticals
letrozole	Femara®	Novartis Pharmaceuticals
paclitaxel	Taxol®	Bristol-Myers Squibb Company
raloxifene	Evista®	Eli Lilly and Co.
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
toremifene	Fareston®	Orion Pharmaceuticals
trastuzumab	Herceptin®	Genentech, Inc.
vinorelbine tartrate	Navelbine®	Glaxo Wellcome, Inc.
zolendronate	Zometa®	Novartis Pharmaceuticals

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Post-test

Questions *(please circle answer)*:

1. For the patient who has received adjuvant tamoxifen, at first relapse, fulvestrant was demonstrated in a clnical trial table to be…

a. inferior to anastrozole

b. equivalent or superior to anastrozole

2. True/False: The efficacy and tolerability of trastuzumab has been documented in Phase III trials to be inferior in older women.

3. True/False: The discovery of any epithelial-staining cancer cells in the sentinel node has not been definitively proven to predict survival.

4. The CLB-49808 trial is designed to test the effectiveness of which of the following drugs in protecting against the long-term cardiotoxicity of trastuzumab?

a. Atorvastatin (Lipitor®)

b. Dexrazoxane (Zinecard®)

d. Celecoxib (Celebrex®)

5. The FDA recently released a warning for which of the following tamoxifen-related side effects?

a. uterine sarcoma
b. hot flashes
c. thromboembolic events
d. impaired cognitive function

6. The planned IBIS-2 trial will contain which of the following arms for non-DCIS patients?

a. Tamoxifen c. Placebo e. B and C
b. Anastrozole d. A and B f. All of the above

7. True/False: The trastuzumab pivotal trial in metastatic disease contained a monotherapy arm.

8. According to the 2002 ASCO technology assessment guidelines, HER2 status…

a. should be used to determine adjuvant therapy in early stage breast cancer.

b. should not be used to determine adjuvant therapy in early stage breast cancer.

c. can be used to determine adjuvant therapy in early stage breast cancer, but it is not reliable.

9. According to an ASCO presentation by Nabholtz et al comparing TAC (docetaxel/doxorubicin/cyclophosphamide) to FAC (5-fluorouracil/doxorubicin/cyclophosphamide), in patients with HER2-positive disease, TAC…

a. was slightly inferior to FAC

b. was slightly superior to FAC

c. was equivalent to FAC

10. True/False: A recent prospective observational study presented in the *Journal of Clinical Oncology* found that women with fasting insulin levels in the highest quintile, compared to the lowest, had an eight-fold increased risk of breast cancer recurrence and death.

Post-test Answer Key
1. b, 2. False, 3. True, 4. b, 5. a, 6. E, 7. False, 8. b, 9. b, 10. True

Evaluation Form

02-1125-ES-12 **BCU7 | 2002**

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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Extent to which program activities met the identified objectives
Upon completion of this activity, participants should be able to:

- Evaluate the survival advantage observed in the trastuzumab pivotal trial in order to determine the importance of considering earlier treatment with trastuzumab in patients with HER2-positive metastatic breast cancer 5 4 3 2 1
- Distinguish among the various approaches to sequencing and combining therapeutic agents in order to define the most efficacious and least toxic treatment regimens for patients with metastatic disease 5 4 3 2 1
- Understand the risks and benefits of combining chemotherapy with trastuzumab in order to select the most effective, least toxic regimens for HER2-positive patients ... 5 4 3 2 1
- Apply the findings of the 2002 ASCO technology assessment to determine the appropriateness of using aromatase inhibitors as adjuvant therapy for patients with ER/PR receptor–positive breast cancer 5 4 3 2 1
- Identify and manage patients who are at high risk for developing breast cancer using the findings from the 2002 ASCO technology assessment of pharmacologic interventions for breast cancer risk reduction 5 4 3 2 1

Overall effectiveness of the activity

Objectives were related to overall purpose/goal(s) of activity 5 4 3 2 1
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Will the information presented cause you to make any changes in your practice? ___Yes ___No

If Yes, please describe any change(s) you plan to make in your practice as a result of this activity.

_____

_____

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