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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 on pages 38-40 or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program and the website, **BreastCancerUpdate.com**, where you will find 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**.

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 uses 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.

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment.
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer patients in your practice.
- Develop and explain a management strategy for treatment of ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Develop and explain a management strategy for treatment of ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Counsel ER-positive, postmenopausal patients about the risks and benefits of aromatase inhibitors in the adjuvant setting.
- Evaluate the emerging data on dose-dense chemotherapy and explain its relevance to patients.

Issue 4, 2003, of Breast Cancer Update consists of discussions with four research leaders on a variety of important topics including neoadjuvant endocrine therapy, adjuvant trastuzumab clinical trials, ovarian ablation and aromatase inhibitors in premenopausal women and the impact of clinical research on breast cancer treatment paradigms.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 4

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

- Consider the use of neoadjuvant endocrine therapy in patients with locally advanced, ER-positive breast cancer.
- Evaluate the data on carboplatin/paclitaxel/trastuzumab, and consider utilizing this regimen in women with HER2-positive metastatic disease.
- Describe planned and ongoing clinical trials utilizing capecitabine combinations in the metastatic setting.
- Consider the potential benefit of zoledronic acid and goserelin in combination with tamoxifen or anastrozole when treating women with these agents.

ACCREDITATION STATEMENT

NL Communications is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

NL Communications, Inc designates this educational activity for a maximum of 3.25 category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity.

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J Michael Dixon, MD, FRCS	**Grants/Research Support:** AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals Corporation, Pharmacia Corporation
Edith Perez, MD	**Grants/Research Support:** Bristol-Myers Squibb Company, Aventis Pharmaceuticals Inc, Pharmacia Corporation
Bernard Fisher, MD	**Grants/Research Support:** No financial interests or affiliations to disclose.
Michael F Gnant, MD	**Grants/Research Support:** Novartis Pharmaceuticals Corporation, Aventis Pharmaceuticals, AstraZeneca Pharmaceuticals LP **Consultant:** AstraZeneca Pharmaceuticals LP

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin hydrochloride	Adriamycin®	Pfizer Inc
doxorubicin HCL liposome injection	Doxil®	Ortho Biotech Products LP
epirubicin hydrochloride	Ellence®	Pfizer Inc
erlotinib (OSI-774)	Tarceva™	Genentech Inc, OSI Pharmaceuticals, Hoffman-LaRoche Ltd
estradiol	Various	Various
exemestane	Aromasin®	Pfizer Inc
fluorouracil, 5FU	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly & Company
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
goserelin	Zoladex®	AstraZeneca Pharmaceuticals LP
irinotecan	Camptosar®	Pfizer Inc
letrozole	Femara®	Novartis Pharmaceuticals Corporation
methotrexate	Various	Various
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pegfilgrastim	Neulasta®	Amgen Inc.
prednisolone	Various	Various
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech Inc
vinorelbine	Navelbine®	GlaxoSmithKline
zoledronic acid/zoledronate	Zometa®	Novartis Pharmaceuticals Corporation

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Editor's Note

Research to Practice

In our 1988 inaugural issue of *Breast Cancer Update*, Dr Bernard Fisher was the first research leader interviewed. At that time, a National Cancer Institute "Clinical Alert" had just been mailed to every oncologist in the United States. The "Clinical Alert" released data from several major randomized clinical trials that evaluated adjuvant systemic therapy in breast cancer patients with node-negative disease. The NCI — then under the direction of another one of our interviewees, Vincent DeVita — reasoned that these groundbreaking clinical trial data were critical to the management of a large number of women and that the usual peer-review process should be circumvented to provide clinicians immediate access to these results.

Two of the studies that were part of the NCI's Clinical Alert were NSABP trials, and Dr Fisher seemed the logical person to query about the daily practice implications of these groundbreaking results. Armed with a list of case scenarios to present for feedback, my enthusiasm was immediately crushed when Dr Fisher replied, "Patients should be entered into clinical trials. It's not the role of the clinical researcher to interpret data or tell people how to practice."

In the first few years of this audio series, Dr Fisher's opinion was shared by a number of investigators interviewed. Gradually, the pendulum shifted and I began to identify researchers who were willing to discuss their own management strategies for patients in a nonprotocol setting. Today, almost all of our interviews include these highly valued insights and experiences.

The *Breast Cancer Update* team has also been very interested in how community-based oncologists manage their patients. In 1995, we began using electronic keypad polling at meetings and national telephone surveys to assess oncologists' practice patterns. Our current approach to continuing medical education involves the integration of data about the practice patterns of research leaders and community-based oncologists into all of our programs.

In that regard, the enclosed supplement to this issue includes dozens of keypad-polling questions posed at the recent Miami Breast Cancer Conference. We have supplemented these data with research results and ongoing clinical trial designs, in order to create a snapshot of how recent research findings are being integrated into clinical practice.

For this issue, Dr Fisher again joins us to share his views on where we are at the moment in clinical research and where we might likely be headed in the next decade. No one has done more to help breast cancer patients than Dr Fisher, and it is always an honor to speak with this legendary leader. As usual, he

"didn't know what he had to say that people would want to hear about," but, of course, he provides a fascinating commentary on chemoprevention, preoperative chemotherapy, breast-conserving surgery and other major paradigm shifts that he engineered. True to form, he still avoids interpreting research data from a patient-care perspective.

Elsewhere in this issue several of our guests are more willing to talk about their current practice strategies. Mike Dixon discusses his use of aromatase inhibitors in the neoadjuvant and adjuvant setting, Edith Perez provides insight about her use of trastuzumab in metastatic disease, and Michael Gnant is very candid in his review of therapy for premenopausal women with estrogen receptor-positive cancers.

During a recent "Meet the Professor" session in Dallas, community-based medical oncologist, Barry Brooks — while presenting a particularly difficult case from his practice — made the following comment, which framed a pivotal message from our audio series:

"Medical oncologists are a modern day manifestation of the myth of Prometheus — chained to the rock, and every day, the big predatory bird comes and eats away part of him, and then overnight he regrows, the next day to be partially consumed again. Your *Breast Cancer Update* series is very helpful because you are able to discern that no one knows how to take care of some of these patients. And it gives oncologists comfort that we're all in the same large boat, even though it may be somewhat painful from time to time."

Every day, oncologists likes Drs Dixon, Perez and Gnant, who devote their careers to breast cancer research, education and patient care, encounter clinical situations that have no perfect solutions. We are fortunate that these research leaders and many others are willing to share their perspectives and experiences on these challenging situations.

—Neil Love, MD

National Cancer Institute: Clinical alert from the National Cancer Institute. *Breast Cancer Res Treat* 1988;12:3-5. **Abstract**

NIH Consensus Conference: Treatment of early-stage breast cancer. *JAMA* 1991;265:391-95. **Abstract**

DeVita VT Jr, Hubbard SM. **NCI's breast cancer clinical alert: Rationale and results.** *Resid Staff Physician* 1989;35(8):49-55. **Abstract**

Fisher B et al. **A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen receptor-negative tumors.** *N Engl J Med* 1989;320:473–8. **Abstract**

Fisher B et al. **A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen receptor-positive tumors.** *N Engl J Med* 1989;320:479–84. **Abstract**

Johnson TP et al. **Effect of a National Cancer Institute Clinical Alert on breast cancer practice patterns.** *J Clin Oncol* 1994;12(9):1783-8. **Abstract**

Mansour EG et al. **Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer. An intergroup study.** *N Engl J Med* 1989;320:485–90. **Abstract**

Mariotto A et al. **Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999.** *J Natl Cancer Inst* 2002;94:1626-34. **Abstract**

Spratt JS, Greenberg RA. **Validity of the clinical alert on breast cancer.** *Am J Surg* 1990;159(2):195-8. **Abstract**

J Michael Dixon, MD, FRCS

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Edited comments by Dr Dixon

Neoadjuvant anastrozole trial

Several years ago, we conducted a trial using three months of neoadjuvant anastrozole in 23 postmenopausal women with estrogen receptor-positive breast cancer. Interestingly, 22 of those patients continued on adjuvant anastrozole after the trial ended. It has now been four years since these patients started on adjuvant anastrozole, so we have a reasonable follow-up period from which to gather additional data.

We evaluated whether the response rate to anastrozole was dependent on the initial tumor's HER2 status. It was a small study with only 23 patients, but we obtained reasonable material from 22. We found that six patients had tumors with a 3+ score for HER2 protein overexpression, and all six responded clinically to anastrozole. All six of the patients' tumors decreased in size by more than 50 percent in bidimensional area, thereby fulfilling the criteria for a partial response with only a three-month treatment period.

This supports previous evidence that the aromatase inhibitors are effective for patients with HER2 3+ tumors, and it's the first data showing that anastrozole is effective in this group. A slightly lower response rate was seen in patients with tumors that were not HER2 3+, but there was no statistically significant difference between response rates. When we looked at the percentage reduction in tumor volume, there was a trend for the HER2 3+ tumors to shrink more than the tumors that were HER2-negative. This fits in with the data suggesting a better response rate with the aromatase inhibitors in patients with HER2 3+ tumors.

It also contrasts with the data presented by Matt Ellis last year at San Antonio, in which patients with HER2 3+ tumors did not have a consistent reduction in proliferation when treated with neoadjuvant tamoxifen. We, too, have evaluated tamoxifen in the neoadjuvant setting, and found the same results as Matt Ellis — HER2 3+ tumors don't have a consistent change in proliferation with tamoxifen.

Clinical response rate and reduction in proliferation associated with neoadjuvant anastrozole in postmenopausal women with estrogen receptor-rich breast cancer

		PROLIFERATION (MEDIAN Ki67)	
HercepTest™ score	Clinical response rate*	Pre-anastrozole	Post-anastrozole
0/1+(n=16)	94%	23.5	5
3+(n=6)	100%	22.5	7.5

*Complete or partial response

SOURCE: Dixon JM et al. **Anastrozole demonstrates clinical and biological effectiveness in erbB2 ER-positive breast cancers.** *Breast Cancer Res Treat* 2002. **Abstract 263.**

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

	Letrozole		Tamoxifen		
Marker status	Responders	%	Responders	%	*p* value
ErbB-1/2 positive	15/17	88	4/19	21	.0004
ErbB-1/2 negative	55/101	54	42/100	42	.0780

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

All of the tumors — HER2-positive and negative — also demonstrated a reduction in proliferation over the three-month neoadjuvant period. The order of reduction in proliferation was the same for the tumors that were HER2-positive and negative.

Proliferation decreases within a few days of starting anastrozole, and this opens up a new avenue for treatment. The idea is — if you see a postmenopausal woman with breast cancer, you don't really have to worry about the date of surgery, because you can put her on anastrozole and know that by the time you operate, her tumor will be biologically different.

The IMPACT trial of neoadjuvant anastrozole

The neoadjuvant anastrozole study, known as the IMPACT trial, has finished recruiting 330 patients who were randomized to anastrozole alone, anastrozole and tamoxifen or tamoxifen alone. From this study, we should be able to determine whether there are any differences in response rates to these agents in patients with HER2-positive tumors. We will also be able to evaluate biological end points, and that should tell us a little bit more about the interaction between anastrozole and HER2.

The IMPACT trial will tell us a lot about how these drugs work, and I think it is a very important study. I'm pleased we have completed it. The results, however, won't be available until the middle of next year.

After surgery, if the patient had responded to the three months of neoadjuvant endocrine therapy, they continued on the same medication and remained blinded. There are some patients still on the combination. If the patient did not respond, then they were unblinded and put on the other agent.

IMPACT Trial: A Randomized Double-Blind Trial of Preoperative Tamoxifen, Anastrozole or the Combination in Postmenopausal Breast Cancer Patients **Closed Protocol**

Eligibility: Postmenopausal, ER/PR-positive: T2 (≥ 2 cm). T3, T4b NO-2, MO

ARM 1: Tamoxifen x 3 months → Surgery
ARM 2: Anastrozole x 3 months → Surgery
ARM 3: Anastrozole + tamoxifen x 3 months → Surgery

DERIVED FROM: Boeddinghaus I et al. **Neoadjuvant Arimidex or tamoxifen, alone or combined, for breast cancer (IMPACT): PgR-related reductions in proliferation marker Ki67.** *Proc Asco* 2000:**Abstract 360**.

Biologic effects of the tamoxifen and anastrozole combination

We don't know what happens in the tumor when we give both anastrozole and tamoxifen, but we could guess. I think it will be like the effects of tamoxifen. Many of us thought that the combination was never going to work anyway, because when you reduce estrogen levels with anastrozole, tamoxifen acts like a partial estrogen agonist. I don't think there was ever any good scientific rationale to the combination.

It's interesting to speculate about what will be seen inside the tumor with the combination. The good news is that we have sequential biopsies and we will be able to look at which genes are switched on or off by the three treatments in the IMPACT trial. That will give us real insight into how the combination arm works.

Resistance to tamoxifen in patients with HER2-positive cancer

I think resistance occurs because tamoxifen's mode of action is through the HER2 pathway, whereas anastrozole works independently of HER2. That may be too simple. In the series of patients on the IMPACT trial, and others we're treating with aromatase inhibitors, we will be able to look at more details, because we have fresh tissue before diagnosis, during treatment and after treatment.

I'm using micro-array techniques and proteomics, and we are about to see — in great detail — how these drugs interact. The simplistic way we now look at how these drugs work will be overshadowed by what we learn from these studies.

Selection of patients for neoadjuvant endocrine therapy

Patients who express the most estrogen receptor (ER) will have the greatest reductions in tumor volume with neoadjuvant endocrine therapy. We only treat patients with Allred scores of 6, 7 or 8.

The Allred score is a composite of the percentage of cells that stained and the intensity of their staining. The percentage of cells staining is classified from 0 through 5, and the intensity of cells staining is rated as 1, 2 or 3. Then if you add, for example, 5 and 3 together, you have an Allred score of 8. In order to initiate therapy, the cutoff we use for positivity would be over one-third of the cells staining strongly or over two-thirds staining moderately.

Allred score for ER status (0-8)*

% Staining score	Proportion of positive staining cells	Intensity score	Average intensity of positively stained cells
0	none	0	none
1	< 1/100	1	weak
2	1/100 to 1/10	2	intermediate
3	1/10 to 1/3	3	strong
4	1/3 to 2/3		
5	> 2/3		

*Allred Score = % Staining score + Intensity score

DERIVED FROM: Harvey JM et al. **Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer**. *J Clin Oncol* 1999;17(5):1474-81. **Abstract**

Fortunately, the majority of postmenopausal women are strongly ER-positive, and these are the women most likely to benefit. Their median reduction in tumor volume with three months of neoadjuvant anastrozole therapy is over 80 percent. Not only does a large part of the tumor disappear within that three-month period, but the nature of the tumor also changes — there is reduced cellularity and proliferation.

If you select patients for treatment carefully, the response rates to neoadjuvant endocrine therapy are very high. In a poster we presented at the San Antonio Breast Cancer Symposium, the response rate to anastrozole in that group of patients was 80 percent and they had a greater than 50 percent reduction in a bidimensional area with three months of neoadjuvant therapy. We were able to convert two-thirds of the patients requiring mastectomy to breast-conserving surgery.

Underutilization of neoadjuvant endocrine therapy

I believe neoadjuvant endocrine therapy is underutilized. It is valuable in some patients, particularly the elderly, and the biggest increase in breast cancer incidence over the next decade will be in older patients. Currently, 40 percent of women with breast cancer are over 70 years of age, and that is likely to go up to nearly 50 percent over the next decade. These are women whom you wouldn't necessarily want to give neoadjuvant chemotherapy. We have very good drugs, such as the aromatase inhibitors, that produce consistently high response rates and reductions in tumor volume.

Selecting an agent for neoadjuvant endocrine therapy

The problem with putting a newly diagnosed patient on tamoxifen is that it takes two to three weeks for the levels to accumulate in the blood. Additionally, the rate of deep venous thrombosis (DVT) and pulmonary embolus increases immediately before surgery. For these reasons, I do not find preoperative tamoxifen particularly attractive. Anastrozole doesn't appear to increase the risk of DVT or pulmonary embolus; hence, it is a more attractive agent to use before surgery.

Preoperative anastrozole is also more appealing because it affects the basic biology of the tumor. There's always been a fear that surgery might spread breast cancer. I believe this is theoretical, rather than practical. Nonetheless, the cancer cells are less likely to implant if one operates on a tumor under the influence of a drug that turns off proliferation.

Predicting the efficacy of neoadjuvant endocrine therapy

I believe that over the next several years, the neoadjuvant model, by which one can access the tumor on numerous occasions during the three months of therapy, will provide very valuable data about how these drugs work. We also hope to be able to identify — within a few days of starting a drug — whether the patients will derive a long-term beneficial response.

Within 24 hours of starting these drugs, changes occur within the tumor. The aim of our new work is to develop a series of markers to allow us to predict within two weeks of starting a drug, such as anastrozole, whether the patient will derive long-term benefit. We're able to correlate these changes at two weeks with the response at three months.

Eventually this might allow us to diagnose a patient, start them on a drug and operate on them. Then, by looking at the tumor at the time of surgery, we may be able to determine whether that drug had the expected effect and should be continued long-term. Our hope is to develop some simple tests to allow us to look at an individual patient and say, "Yes, this patient should be treated with this drug," or "This patient had the changes that we would hope would predict long-term benefit."

Estrogen receptor-directed, primary systemic therapy compared to conventional therapy in operable breast cancer

At the San Antonio Breast Cancer Symposium, we presented long-term follow-up data on patients randomized to conventional therapy (mastectomy followed by appropriate adjuvant therapy) or neoadjuvant therapy selected on the basis of the patients' estrogen receptor status. Premenopausal patients with estrogen receptor-positive cancers were randomized to neoadjuvant therapy with goserelin. Most postmenopausal women with estrogen receptor-positive cancers were randomized to neoadjuvant therapy with tamoxifen, although some received aromatase inhibitors.

This trial, which involved a relatively small number of patients, offered no evidence that patients receiving neoadjuvant therapy did worse and a slight suggestion that they actually did better. There was no difference between the patients who received neoadjuvant endocrine therapy and neoadjuvant chemotherapy. Although the number of patients involved is not sufficient for us to draw any definite conclusions, it's an interesting study.

Randomized Trial Comparing Estrogen Receptor (ER)-Directed, Primary Systemic Therapy to Conventional Therapy in Operable Breast Cancer **Closed Protocol**

ARM 1: Primary Systemic Therapy directed by ER x 3 months*
- ER+ and postmenopausal → tamoxifen
- ER+ and premenopausal → goserelin
- ER- → CAP every 3 weeks x 4

ARM 2: Conventional Therapy
- Surgery ± Radiation → Premenopausal and node+ → CMF x 6
- All others → tamoxifen daily x 5 years

C = cyclophosphamide, A = doxorubicin, P = prednisolone, M = methotrexate, F = fluorouracil
*Patients progressing on hormonal therapy switched to chemotherapy.

Six-year disease-free and overall survival for primary systemic therapy directed by estrogen receptor status compared to conventional therapy for patients who have relapsed at a median follow-up of 8 years.

	Primary systemic therapy directed by ER (n=40)		Conventional therapy (n=47)	
	Node-negative	Node-positive	Node-negative	Node-positive
Disease-free survival	83%	50%	64%	42%
Overall survival	85%	50%	70%	45%

DERIVED FROM: Cameron DA et al. **Oestrogen receptor-directed, primary systemic therapy: A randomised trial compared with conventional therapy in operable breast cancer.** *Breast Cancer Res Treat* 2002. **Abstract 157.**

Integrating adjuvant anastrozole into clinical practice

The ATAC data are very impressive for adjuvant anastrozole. To some extent, I think we expected the separation in the curves to increase, as they did. The bone data was a concern but I don't think it will be too much of an issue because studies show that use of bisphosphonates can avoid this problem.

The reduction in vaginal bleeding, vaginal discharge, hot flushes and endometrial cancer associated with anastrozole was much more impressive. I believe that the overall benefits are much greater with aromatase inhibitors in postmenopausal women with estrogen receptor-positive tumors.

If one looks at the differences between an anthracycline-containing regimen and CMF, the benefits are quite modest. In the ATAC trial, the benefits are actually greater, yet, throughout the world, anthracyclines are now first-line therapy for patients with breast cancer. We've not yet jumped to using an aromatase inhibitor as first-line therapy; however, I don't think this is very far off.

Interchangeability of the aromatase inhibitors in the adjuvant setting

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 has 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.

Tolerability of anastrozole versus tamoxifen

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."

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.

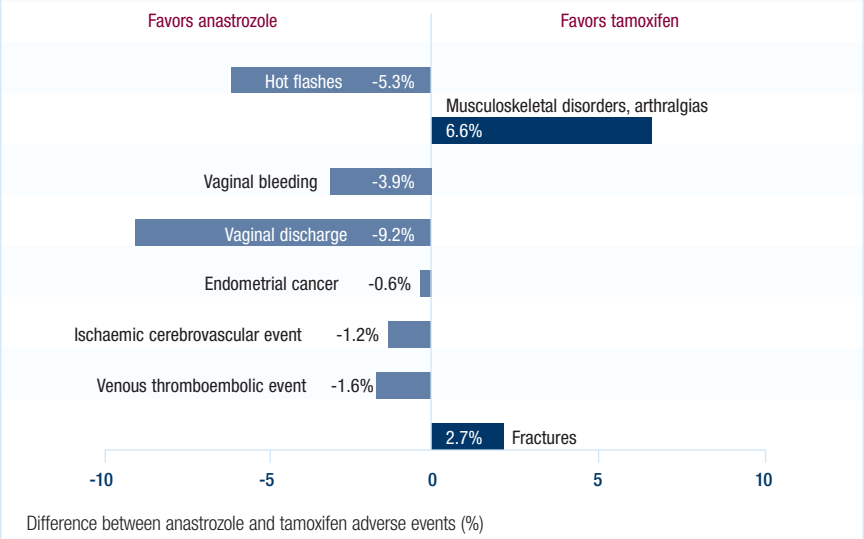
With tamoxifen, some women are disabled by vaginal discharge. This is particularly true of women with any degree of prolapse, who have a constant leak. For a few women, it affects their quality of life to a major degree. In the metastatic setting, there was virtually no vaginal discharge associated with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

Differences in adverse effects between tamoxifen and anastrozole

". . . in comparison with tamoxifen alone, anastrozole was associated with significant reductions in hot flushes, vaginal discharge, vaginal bleeding, ischaemic cerebrovascular events, venous thromboembolic events (including deep-vein thromboses), and endometrial cancer. By contrast, musculoskeletal disorders and fractures were significantly more common with anastrozole than with tamoxifen."

SOURCE: ATAC 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 randomized trial.** *Lancet* 2002;359:2131-39. **Abstract**

Significant differences in predefined adverse events in the ATAC trial



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

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.

IBIS-II trial

IBIS-II, a prevention trial, will compare anastrozole to placebo in women at high risk of developing breast cancer. In the UK, tamoxifen as prevention has not caught on because it has a high rate of morbidity. The IBIS-I study showed a very minimal effect for tamoxifen with considerable morbidity. Anastrozole looks like a better agent for prevention than tamoxifen, so I agree with the direct comparison to placebo.

Based on the ATAC trial data, I would expect anastrozole to dramatically decrease the number of breast cancers that develop. I think anastrozole should be superior to tamoxifen in that setting.

An IBIS-II subprotocol will also evaluate the effects of anastrozole on bone density. The trial is randomizing patients into three groups: (1) high risk for osteoporosis (evidence of osteopenia on DEXA scans), (2) intermediate risk for osteoporosis, and (3) low risk for osteoporosis (bones are very dense). The patients at high risk will receive bisphosphonates, the patients at intermediate

risk will be randomized to bisphosphonates and the patients at low risk will receive anastrozole alone without being randomized to bisphosphonates.

IBIS-II: International Breast Cancer intervention Study-II **Open Protocol**

Eligibility: Postmenopausal women with increased breast cancer risk

ARM 1: Anastrozole x 5 years
ARM 2: Placebo qd x 5 years

SOURCE: Jack Cuzick, PhD, Personal Communication, November 2002.

Select publications

Neoadjuvant endocrine therapy

Boeddinghaus I et al. **Neoadjuvant Arimidex or tamoxifen, alone or combined, for breast cancer (IMPACT): PgR related reductions in proliferation marker KI67.** *Proc Am Soc Clin Oncol* 2000. **Abstract 360.**

Cameron DA et al. **Oestrogen receptor directed primary systemic therapy: A randomised trial compared with conventional therapy in operable breast cancer.** *Breast Cancer Res Treat* 2002. **Abstract 157.**

Dixon JM et al. **Anastrozole demonstrates clinical and biological effectiveness in erbB2 ER-positive breast cancers.** *Breast Cancer Res Treat* 2002. **Abstract 263.**

Dixon JM et al. **Neoadjuvant letrozole: The Edinburgh experience.** *Breast Cancer Res Treat* 2002;**Abstract 264.**

Dixon JM et al. **Neoadjuvant endocrine therapy of breast cancer: A surgical perspective.** *Eur J Cancer* 2002;38(17):2214-21. **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**

Ellis MJ et al. **Letrozole (Femara®) is a more effective antiproliferative agent than tamoxifen irrespective of ErbB1 and/or ErbB2 positive status: Evidence from a phase III randomized trial of neoadjuvant endocrine therapy for postmenopausal women with estrogen receptor positive primary breast cancer.** *Breast Cancer Res Treat* 2001. **Abstract 10.**

Ellis MJ. **Neoadjuvant endocrine therapy for breast cancer: Medical perspectives.** *Clin Cancer Res* 2001;7(12 Suppl):4388s-91s. **Abstract**

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

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Edith Perez, MD

Professor of Medicine
Mayo Medical School
Chair, NCCTG Breast Cancer Committee

Edited comments by Dr Perez

NCCTG-983252: Randomized Phase II trial comparing two schedules of paclitaxel, carboplatin and trastuzumab

We compared a weekly schedule to a once-every-three-week schedule of paclitaxel, carboplatin and trastuzumab in patients with HER2-positive metastatic breast cancer. Tolerability was much better for the weekly schedule. Although I thought this would be the case, I was surprised how great the tolerability was for the weekly regimen. Essentially, there was no significant toxicity and the activity was very high.

Our trial fits in very well following Nick Robert's data demonstrating the benefits of adding carboplatin to paclitaxel and trastuzumab, administered once every three weeks.

We will present our results at ASCO 2003. The target accrual for our study was 92 patients, and we will report data on approximately 75 percent of these patients. Because we found the weekly schedule to be better tolerated, after a certain number of patients enrolled, we actually closed the once-every-three-week arm and continued accrual only to the weekly regimen.

For the weekly schedule, we administered paclitaxel three out of four weeks. I believe it is critically important to take that fourth week off of chemotherapy to really optimize tolerability.

In both arms, we administered the chemotherapy concurrently with trastuzumab for the first six months. Then at the six-month point, we discontinued the chemotherapy and continued trastuzumab alone — trying to maximize the activity of the interaction of the three drugs while ameliorating long-term toxicities.

Phase II Study of Paclitaxel, Carboplatin and Trastuzumab as First-Line Chemotherapy in Women with Overexpressed HER2, Metastatic Breast Cancer **Open Protocol**

Protocol ID: NCCTG-983252

Projected Accrual: 36-92 women

Eligibility: Women with metastatic HER2-positive (IHC 3+ or FISH +) breast cancer

ARM 1: [Paclitaxel + carboplatin + trastuzumab] every 3 weeks x 8 → trastuzumab every 3 weeks until disease progression

ARM 2: [Paclitaxel + carboplatin + trastuzumab] every week for 3 out of 4 weeks x 6 → trastuzumab every 3 weeks until disease progression

Study Contact:
Edith Perez, Chair, Tel: 507-284-2111
North Central Cancer Treatment Group

SOURCE: NCI Physician Data Query, April 2003.

NCCTG-N9932: Phase II docetaxel and carboplatin trial

We submitted to ASCO 2003 the results from our Phase II trial evaluating docetaxel and carboplatin, administered every three weeks, as first-line therapy in patients with metastatic breast cancer. There were various reasons for conducting this trial. First was the activity of docetaxel. Second was the desire to test the other taxane, and we were the first cooperative group in the United States to test paclitaxel and carboplatin. Third were data from the UCLA group and the BCIRG evaluating docetaxel, carboplatin and trastuzumab, but there was no solid data for the chemotherapy alone.

Treatment was continued until progression or toxicity. The study demonstrated that the activity was very comparable to the activity for paclitaxel and carboplatin. Slightly more myelosuppression occurred because we did not use prophylactic growth factor support — although it was allowed. There was very little peripheral neuropathy.

Phase II Study of Docetaxel and Carboplatin as First-Line Therapy in Patients with Metastatic Adenocarcinoma of the Breast **Closed Protocol**

Protocol ID: NCCTG-N9932

Projected Accrual: 55 women

Eligibility: Women with metastatic breast cancer

Treatment: [docetaxel + carboplatin] every 3 weeks x 4

SOURCE: NCI Physician Data Query, April 2003.

Clinical trials of epidermal growth factor receptor (EGFR) inhibitors

We are developing new trials to address the issue of anti-EGFR therapy in patients with metastatic disease. There has been some preclinical, initial Phase I and Phase

II data demonstrating that there is indeed activity for these drugs. We are going to conduct a trial evaluating gemcitabine in combination with OSI-774, also known as erlotinib, in patients with refractory breast cancer.

Within the NCCTG and the rest of the breast Intergroup, we are also developing a large first-line trial, which will take a few months to be activated, exploring gefitinib (Iressa®). We plan to manage patients initially with chemotherapy consisting of docetaxel and capecitabine. Patients who have at least disease stabilization will be randomized to receive gefitinib or placebo. We are exploring the potential for this targeted therapy to maintain the response seen with initial chemotherapy.

Recently, we've seen some exciting results in terms of survival with the docetaxel/capecitabine combination, and we are actually planning to utilize a slightly modified schedule from the one published by Dr O'Shaughnessy. Although this regimen is very appealing, the issue of toxicity has prevented many physicians from incorporating it into their practices. Since that initial study, other analyses have documented that we can start with lower doses of the chemotherapy drugs. That is why we want to incorporate the combination in this new clinical trial.

Trial of Gefitinib after Capecitabine/Docetaxel in Patients with Metastatic Disease (Planned Protocol)

All patients will receive chemotherapy with capecitabine/docetaxel.
Patients with stable disease or response randomized to:

ARM 1: gefitinib
ARM 2: placebo

SOURCE: Edith Perez, personal communication, March 2003.

Sequential single-agent versus combination chemotherapy in metastatic disease

I'm really happy Dr Sledge published the data from ECOG-1193, because I believe it will dispel a number of myths. For example, there is a myth that combination chemotherapy is more toxic and leads to a worse quality of life than single-agent chemotherapy.

In patients eligible to receive first-line chemotherapy for metastatic breast cancer, ECOG-1193 demonstrated that the combination of paclitaxel concurrent with doxorubicin led to a better response rate and time to progression with a similar quality of life and survival compared to a sequential taxane and anthracycline regimen. This study supports the use of combination therapy, because those patients had a higher possibility of responding and living longer without disease progression and without an adverse effect on quality of life.

In my practice, if a patient has a good performance status and symptoms from the malignancy, it makes sense to ameliorate the symptoms from the tumor as soon as possible, while really paying attention to tolerability. That's where there

is a big difference between using good combination chemotherapy and high-dose chemotherapy with transplant, because the latter approach led to high response rates with significant toxicity.

I believe single-agent chemotherapy is also a very good option for the patient who is relatively asymptomatic and doesn't have rapid disease progression or visceral crisis. It's not that I use combination chemotherapy for all patients or that I insist on single-agent sequential therapy; however, we are planning to do a study to address this in patients with refractory disease.

Combining capecitabine and irinotecan in patients with metastatic breast cancer

We conducted a large, multi-institutional, community-based, randomized Phase II trial that clearly demonstrated the activity of irinotecan. In a subset of patients with prior exposure to both anthracyclines and taxanes, the response rate for weekly irinotecan was 27 percent.

We plan to build on these data and the experiences with capecitabine in the advanced breast cancer setting. We don't yet know anything about the combination of capecitabine and irinotecan in patients with breast cancer, but that's one of the arms we will use in our Phase III trial. We will randomize patients with disease that is refractory to anthracyclines and taxanes to combination or sequential therapy with capecitabine and irinotecan. We will focus on time to progression as the main endpoint, while evaluating quality of life.

I feel that the gastrointestinal toxicity may be somewhat lower with irinotecan in breast cancer patients compared to colorectal cancer patients. There are several reasons for that: (1) patients with colorectal cancer — at least most of the time — have had surgery on the gastrointestinal tract and that may have an impact on irinotecan's tolerability, and (2) in the colorectal trials, irinotecan is typically combined with 5-fluorouracil, which can also enhance toxicity. We are taking a different approach in the breast cancer trials by evaluating irinotecan alone or in combination with capecitabine.

Fulvestrant in the metastatic setting

We have had an interest in fulvestrant at the Mayo Clinic and in the NCCTG for many years. We participated in one of the pivotal trials conducted in the United States, which was eventually published by Dr Osborne in the *Journal of Clinical Oncology*.

Fulvestrant is a very well-tolerated drug. It provides an alternative to oral therapy, which could be very important for patients who have difficulty remembering to take tablets on a daily basis or patients who do not have prescription coverage for oral medications.

In patients with estrogen receptor-positive metastatic breast cancer who have had prior exposure to tamoxifen and aromatase inhibitors, we have been conducting a Phase II trial, through the NCCTG, evaluating the activity and

tolerability of fulvestrant. Our accrual is going very well. Activity has been clearly demonstrated, and we have not had any problems with hot flashes.

Data was presented at the San Antonio Breast Cancer Symposium by another group demonstrating the feasibility and activity of fulvestrant after aromatase inhibitors. Hopefully, this larger clinical trial will corroborate the activity of fulvestrant in this patient population.

Phase II Study of Fulvestrant in Women with Metastatic Breast Cancer Who Have Failed Aromatase Inhibitor Therapy **Open Protocol**

Protocol ID: NCCTG-N0032
Projected Accrual: 41-94 women

Eligibility: Women with progressive local-regional or metastatic breast cancer whose disease has progressed after a prior third-generation aromatase inhibitor

Treatment: Fulvestrant IM q 28 days until disease progression or unacceptable toxicity

Study Contact:
James N Ingle, Chair, Tel: 507-284-2111
North Central Cancer Treatment Group

SOURCE: NCI Physician Data Query, April 2003.

First-line therapy for patients with HER2-positive metastatic breast cancer

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.

Continuing trastuzumab after disease progression

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.

NCCTG-N9831 adjuvant trastuzumab trial

N9831 is a randomized Phase III clinical trial building on several issues: (1) the relative importance of anthracyclines in the adjuvant management of patients with HER2-positive breast cancer, (2) the value of taxanes in patients eligible to receive adjuvant therapy, (3) the specific value of taxanes for patients with

HER2-positive breast cancer, and (4) the value of weekly paclitaxel therapy for patients with breast cancer.

We were comforted by the data presented from CALGB-9741. That trial administered dose-dense chemotherapy with growth factor support once every two weeks, and in our trial we are using an even more dose-dense approach by administering paclitaxel on a weekly basis. The AC in our trial is still being given once every three weeks. Although we thought about potentially changing it to once every two weeks, we are not going to for several reasons.

First, we hypothesized that the advantage seen in CALGB-9741 may be due to the paclitaxel schedule. This theory is partially based on Marjorie Green's data at MD Anderson, which evaluated the benefit of giving weekly paclitaxel compared to once every three weeks in the neoadjuvant setting. Additionally, we have data regarding the cardiac safety of AC administered once every three weeks followed by paclitaxel with or without trastuzumab. We didn't want to introduce another factor that could impact on cardiac toxicity.

Right now we feel very comfortable with the schedule. We know patients in both the control or investigational arms are receiving dose-dense paclitaxel, which we think is perhaps the most important aspect of dose-dense treatment.

Phase III Randomized Study of Doxorubicin plus Cyclophosphamide followed by Paclitaxel with or without Trastuzumab in Women with HER2-Overexpressing, Node-Positive Breast Cancer **Open Protocol**

Protocol ID: NCCTG-N9831, CLB-49909, E-N9831, SWOG-N9831, GUMC-00224

Projected Accrual: 3,000 women

Eligibility: Women with HER2-positive (IHC 3+ or FISH +), operable (T1-3, pN1-2, M0) breast cancer

ARM 1: AC q 3 weeks x 4 → paclitaxel q week x 12
ARM 2: AC q 3 weeks x 4 → paclitaxel q week x 12 → trastuzumab q week x 52
ARM 3: AC q 3 weeks x 4 → [paclitaxel + trastuzumab] q week x 12 → trastuzumab q week x 40

AC = doxorubicin and cyclophosphamide

All postmenopausal ER- or PR-positive patients receive oral tamoxifen or an aromatase inhibitor once daily for 5 years beginning no later than 5 weeks after the last dose of paclitaxel.

Study Contact:

Edith Perez, Chair, Tel: 507-284-2111, North Central Cancer Treatment Group	Nancy E Davidson, Chair, Tel: 410-955-8489, Eastern Cooperative Oncology Group	Peter A Kaufman, Chair, Tel: 603-650-6700, 1-800-639-6918, Cancer and Leukemia Group B	Silvana Martino, Chair, Tel: 310-998-3961, Southwest Oncology Group

SOURCE: NCI Physician Database Query, April 2003.

Cardiotoxicity in the NCCTG-N9831 adjuvant trastuzumab trial

In January 2002, we received notification of a few patients who developed congestive heart failure on NCCTG-N9831. Since we did not know if it was a

real problem or if we just happened to have a few cases at the same time, we decided to temporarily halt accrual to the third arm of the trial — AC followed by paclitaxel and concurrent trastuzumab — until we had more time to do two things.

First, we had to evaluate the clinical course of those few patients who developed congestive heart failure. Second, we had to analyze the data based on all of the more than 700 patients enrolled up to that point. Eventually, we found that there were just a few patients who had developed congestive heart failure and that the patients who developed congestive heart failure had prompt improvements in their clinical symptoms with medication.

We submitted this information to our independent data monitoring committee. Since the cases of congestive heart failure were below the threshold we had established in the protocol in June 2002, it was recommended that we reopen accrual to this third arm of the trial. We meet with our cardiologists on a monthly basis to look at all of the data from this study. We have very good compliance with the cardiac testing we recommend as part of this clinical study.

Based on data in the metastatic setting, trastuzumab is associated with congestive heart failure. In the adjuvant setting, it is going to be a matter of assuring that the incidence of congestive heart failure is low and working on potential predictors of congestive heart failure. There are trials being devised to address this issue. We are looking at hypertension, the patient's age and radiation therapy to the left chest as being predictors of cardiotoxicity. We are also doing quality control to avoid enhancing the potential cardiotoxicity of trastuzumab.

Theoretically, it makes sense that trastuzumab will have a role in the adjuvant setting. But first, we need to finish the clinical trials to prove that point. Then we will have to look at ways to ameliorate cardiotoxicity, even if it's only a few percentage points.

Ejection fraction assessment in the NCCTG-N9831 adjuvant trastuzumab trial

We perform very thorough analyses of ejection fractions as part of NCCTG-N9831, and we have submitted the data to the ASCO 2003 meeting. The specific data we will present are based on the evaluations of ejection fraction after AC chemotherapy. We have a lot of clinical experience with AC, but there's a scarcity of data regarding its effect on ejection fraction. We found that AC, at a cumulative dose of 240 mg/m^2, had a zero incidence of congestive heart failure, but there were decreases in ejection fraction. These decreases in ejection fraction tended to be transient.

Our opinion is that ejection fraction may be an interesting marker, but we don't know if frequent measurements are good in terms of predicting who will develop congestive heart failure. At this time, I cannot comment on the effect of trastuzumab on ejection fraction.

Adjuvant trastuzumab use in and out of the clinical trial setting

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.

We have several clinical protocols available. 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 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. The 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.

Phase III Randomized Study of Doxorubicin and Cyclophosphamide followed by Paclitaxel with or without Trastuzumab (Herceptin) in Women with Node-Positive Breast Cancer that Overexpresses HER2 **Open Protocol**

Protocol ID: NSABP-B-31

Eligibility: HER2-positive adenocarcinoma with > 1 positive lymph node

ARM 1: AC x 4 → T x 4
ARM 2: AC x 4 → T x 4 + H (qw x 52 weeks)

AC=doxorubicin/cyclophosphamide; T=paclitaxel; H=trastuzumab

ER/PR-positive patients receive tamoxifen for 5 years begining within 3-12 weeks after the last dose of chemotherapy. Patients who have received prior chemopreventive tamoxifen may be treated with additional tamoxifen at investigator's discretion. Anastrozole may be substituted for tamoxifen for postmenopausal patients at the investigator's discretion.

Study Contact:
Edward Romond, MD, Chair, Tel: 859-323-8043
National Surgical Adjuvant Breast and Bowel Project

SOURCE: NCI Physician Database Query, May 2003.

Nonprotocol management of patients with node-positive breast cancer

The management of patients with node-positive breast cancer has become more complex in the last year, and we now have several very good regimens. However, we don't have proof that any one of these regimens is absolutely better than another. The options today include the FEC regimen, which is not commonly used in the United States, TAC regimen and sequential AC followed by paclitaxel or docetaxel.

If I'm going to use AC followed by a taxane, I tend to use the dose-dense regimen published in the *Journal of Clinical Oncology* based on CALGB-9741, or I may still use AC once every three weeks followed by weekly paclitaxel. If I were to use docetaxel, then I would use AC once every three weeks followed by docetaxel once every three weeks, because of docetaxel's tolerability when administered once every three weeks compared to weekly. When I use the AC every-two-week regimen, I use pegfilgrastim rather than filgrastim. While we do not have data on that, I believe it is much more convenient for patients, and we have incorporated it into our clinical practice.

Three-year Results of CALGB-9741, a Phase III Randomized Study Comparing Dose-dense versus Conventional Scheduling and Sequential versus Combination Adjuvant Chemotherapy for Node-positive Breast Cancer

Parameters	Dose-dense scheduling	Conventional scheduling	*p* value
Disease-free survival	85%	81%	RR = 0.74 ($p = 0.007$)
Overall survival	92%	90%	RR = 0.69 ($p = 0.014$)

DERIVED FROM: Citron M et al. **Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) vs. combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALGB-9741. INT C9741).** *Breast Cancer Res Treat* 2002. **Abstract 15.**

Select publications

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Perey L et al. **Fulvestrant ('Faslodex') as hormonal treatment in postmenopausal patients with advanced breast cancer progressing after treatment with tamoxifen and aromatase inhibitors.** *Breast Cancer Res Treat* 2002; **Abstract 49.**

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Nicholson RI et al. **Modulation of epidermal growth factor receptor in endocrine-resistant, estrogen receptor-positive breast cancer.** *Ann N Y Acad Sci* 2002;963:104-15. **Abstract**

Normanno N et al. **Cooperative inhibitory effect of ZD1839 (Iressa) in combination with trastuzumab (Herceptin) on human breast cancer cell growth.** *Ann Oncol* 2002;13(1):65-72. **Abstract**

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Slichenmyer WJ, Fry DW. **Anticancer therapy targeting the erbB family of receptor tyrosine kinases.** *Semin Oncol* 2001;28(5 Suppl 16):67-79. **Abstract**

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Bernard Fisher, MD

Distinguished Service Professor
University of Pittsburgh
Past Chairman and Scientific Director
National Surgical Adjuvant Breast and Bowel Project (NSABP)

Edited comments by Dr Fisher

Preoperative systemic therapy

Most of the early NSABP trials — the so-called "paradigm-shifting" trials — arose from research in my laboratory. We evaluated what we now call translational research — transferring laboratory research data into clinical practice.

The concept of preoperative chemotherapy started in my laboratory in the 1980s. Animal studies showed that the tumor kinetics are different when you remove the tumor compared to treating it before surgery with radiation therapy, tamoxifen or cytotoxic agents. These observations resulted in the concept of preoperative systemic therapy.

The NSABP-B-18 trial was the first well-designed, randomized clinical trial that evaluated the importance of the timing of chemotherapy. Early studies of preoperative chemotherapy suggested that it doesn't really matter whether you initiate therapy before or after surgery in terms of distant disease-free and overall survival.

However, the use of preoperative therapy may be of value as a biological tool. The most important issue is whether or not you can use preoperative therapy as a surrogate for determining who will benefit from systemic therapy. Essentially, the question is, "Can we determine, based on how patients respond to therapy in the first 63 days, who will benefit in terms of disease-free and overall survival?"

The next question to be addressed is, "Would more effective tumor reduction translate into more complete responders, and, if so, would that therapy be more likely to have a beneficial effect on distant disease?" If not, then use of some other systemic therapy should be considered.

Biologic tumor markers and neoadjuvant therapy

"Clinical and pathological response are, at best, crude and late indicators of overall outcome. The key potential of neoadjuvant therapy is to identify and validate biological markers during therapy that may predict early for long-term outcome. These may be biomarkers that are predictive of overall response, predictive of chemoresistance or predictive of response to particular agents. Breast cancer presents an ideal model for this research because of the ease of access to tumour tissue by fine-needle or core biopsy. Several biological markers have been studied in this setting including proliferation with Ki-67, apoptosis, proliferating fraction, ER, PgR, c-erbB2, bcl-2 and p53."

SOURCE: Shannon C, Smith I. **Is there still a role for neoadjuvant therapy in breast cancer?** *Crit Rev Oncol/Hematol* 2003;45:77-90. **Abstract**

Mastectomy versus breast-conserving surgery

One of my agendas associated with preoperative chemotherapy was to eliminate the need for most mastectomies by the year 2000. Mastectomy should not be used as a primary locoregional therapeutic approach in most patients. If a patient has a tumor too large to perform a lumpectomy, then that patient should receive preoperative chemotherapy before considering mastectomy. Some patients may still require mastectomy, but currently we are seeing complete clinical disappearance of tumors in 50 to 60 percent of patients. This improvement in our approach to breast cancer is another step that we've taken in going from radical to modified to simple mastectomy, to quadrantectomy to lumpectomy and finally to preoperative reduction allowing for lumpectomy.

A commentary on the 20-year trial results of mastectomy versus breast-conserving surgery

"What proportion of women with breast cancer should receive breast-conserving therapy? The answer depends on the particular population of women, but a reasonable goal is that every woman should be informed of the availability of breast-conserving therapy and of the suitability of the procedure in her particular case. In a study of 231 women with breast cancer who were seen for a second opinion between 1996 and 1999, Clauson et al reported that 29 percent of the women had been offered only the option of a mastectomy during the initial consultation... .

"Efforts to expand eligibility for breast-conserving therapy and to reduce the associated morbidity are well under way. Preoperative chemotherapy and endocrine therapy have been shown to be safe and effective ways to shrink tumors that are too large for a lumpectomy with a good cosmetic result. Accelerated fractionation schedules and brachytherapy are being studied as alternatives to six weeks of external-beam irradiation. However, if we do not apply what we have learned from the pioneering work of Fisher and Veronesi and their colleagues to the treatment of the women with breast cancer we see today, we will have made little or no progress over the past 20 years in the search for a rational approach to the local treatment of breast cancer. It is time to declare the case against breast-conserving therapy closed and focus our efforts on new strategies for the prevention and cure of breast cancer."

SOURCE: Morrow M. **Rational local therapy for breast cancer.** *N Engl J Med* 2002;347(16):1270-71.

Chemoprevention of breast cancer

NSABP-P-1 demonstrated a proof of principle. Tamoxifen prevented the clinical expression of breast cancers in about 50 percent of women at high risk. Epidemiologists question whether this is true prevention or whether we're simply treating early at the level of phenotypic expression. That's possible, but I'm certain that there will be other candidates for prevention, such as the aromatase inhibitors. These agents have less toxicity, which will make them ideal agents for testing in the prevention setting. As the mechanisms for detecting breast cancer improve, we are going to detect more lesions that are "preventable." The prognosis for these women is so good that we don't see why we should treat them. However, in the prevention mode we are treating these women and are very happy to reduce their risk of breast cancer by 50 percent. We are in a conundrum, "Should we treat them or not?"

Future outlook for breast cancer research

Undoubtedly, molecular genetics will contribute to the treatment of breast cancer, but I don't yet know how it will play out. Somebody, somewhere must seize this information and put it into a testable hypothesis. The better the hypothesis, the more likely it will yield positive results. One of the big challenges for the future is how to test these hypotheses. Whether or not our present day clinical trial mechanism will be adequate is open to speculation.

Our best chance to make a major impact on breast cancer is to allow people the freedom to become involved in research. We need totally dedicated, committed individuals who are zealots about the research agenda that they want to push forward. I don't believe this kind of change will take place through consensus meetings and expert panels.

Select publications

Preoperative (neoadjuvant) systemic therapy

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Edited comments by Dr Gnant

ABCSG-12: Adjuvant anastrozole or tamoxifen in combination with goserelin (± zoledronic acid) for hormone receptor-positive, premenopausal breast cancer

Trial background and rationale

We have conducted trials with premenopausal breast cancer patients with endocrine-responsive disease for more than 10 years, attempting to optimize treatment, particularly without the use of cytotoxic chemotherapy. In ABCSG-05, we showed that the chemical ovariectomy with goserelin plus tamoxifen was equivalent or actually better than the standard CMF. So, in Austria, we have come to a consensus that this hormonal therapy is appropriate for premenopausal women with low- and intermediate-risk, hormone-responsive breast cancer.

We feel the effect of cytotoxic chemotherapy in these patients is more an endocrine effect, and we can show that those patients who experience

Randomized Adjuvant Trial of Tamoxifen and Goserelin versus Cyclophosphamide, Methotrexate and Fluorouracil in Premenopausal Patients **Closed Protocol**

Protocol ID: ABCSG-05
Projected Accrual: 1,034 patients

Eligibility: Patients with Stage I or II ER-/PR-positive breast cancer

ARM 1: Surgery (+RT) → Goserelin q 28 d x 3 years + Tamoxifen x 5 years
ARM 2: Surgery (+RT) → CMF on days 1, 8 q28d x 6

SOURCE: Presentation, M Gnant, 2002 San Antonio Breast Cancer Symposium;
Jakesz R et al. **Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: Evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer – Austrian Breast and Colorectal Cancer Study Group Trial 5.** *J Clin Oncol* 2002; 20(24):4621-27 **Abstract**

amenorrhea during chemotherapy do much better than those that don't. So at least part — maybe 70 or 80 percent — of the benefit of chemotherapy is actually an endocrine effect, rather than a direct cytotoxic effect.

ABCSG-05 Trial Results: 5-year follow-up

	Goserelin + Tamoxifen (n=511)	CMF (n=523)	*p* Value (Breslow)
Breast cancer-specific deaths	41 (8%)	51 (10%)	0.900
Relapses	88 (17%)	109 (21%)	0.0176
Local recurrences	24 (5%)	42 (8%)	0.0029
Cancer of opposite breast	3 (1%)	12 (3%)	0.0001

DERIVED FROM: Jakesz R et al. **Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: Evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer – Austrian Breast and Colorectal Cancer Study Group Trial 5.** *J Clin Oncol* 2002; 20(24):4621-27 **Abstract**

This treatment approach is not as popular in the U.S. as it is in Europe, partially because the history of the endocrine treatment is not as extensive in the U.S. While medical oncologists in the U.S. are beginning to prescribe combinations of goserelin with other agents, cytotoxic chemotherapy remains the standard.

Given the results of ABCSG-05, the next logical step was to determine how to improve on the combination of goserelin/tamoxifen. It has been demonstrated several times that the aromatase inhibitors anastrozole and letrozole decrease serum estradiol levels in women even more effectively than tamoxifen, so ABCSG-12 was designed to compare the combination goserelin/tamoxifen to goserelin/anastrozole.

Anastrozole or Tamoxifen in Combination with Goserelin (± Zoledronic Acid) as Adjuvant Treatment for Hormone Receptor-positive Premenopausal Breast Cancer **Open Protocol**

Protocol ID: ABCSG-12
Projected Accrual: 1,250 patients

Eligibility: Premenopausal women with Stage I/II, ER+/PR+ breast cancer, <10 positive lymph nodes

ARM 1: Surgery → goserelin + tamoxifen
ARM 2: Surgery → goserelin + tamoxifen + zoledronic acid
ARM 3: Surgery → goserelin + anastrozole
ARM 4: Surgery → goserelin + anastrozole + zoledronic acid

SOURCE: Presentation, M Gnant, 2002 San Antonio Breast Cancer Symposium

Trial design

The ABCSG-12 trial has four arms comparing goserelin/tamoxifen to goserelin/anastrozole with or without zoledronic acid. We included zoledronic

acid because it's the most potent bisphosphonate pharmacokinetically and we were concerned about the risk of osteoporosis with the aromatase inhibitors. Chemotherapy is only permitted as neoadjuvant therapy. No postoperative chemotherapy is allowed.

We did not include a tamoxifen-only arm because we tried to build upon our own results with goserelin/tamoxifen, which is now a national standard in Austria. I also believe tamoxifen-only treatment in premenopausal women is debatable because there is reasonable evidence you need to include some cytotoxic treatment.

Rationale and dosing for zoledronic acid

We still do not know whether bisphosphonates can impact survival, but the claim that they reduce bone metastasis is logical. If you can impact osteoclast function, then you might in some way delay or inhibit bone metastasis. In addition, zoledronic acid has exhibited antitumor functions, specifically antiangiogenic and apoptosis-inducing effects in animal models.

We began our trial with a dose of eight milligrams of the agent every month, higher than what is used in osteoporosis — hoping to see a survival benefit. However, alarming information about renal toxicity with the drug came out after the trial opened, so we decided to go back to the recommended antiosteoporosis dose.

Although safety is the most important directive you can use as a study group, this was probably a missed research opportunity. When we analyzed the serum creatinine levels of the 100 patients who received the higher dose — and we have more than a thousand such measurements — there was never even a slight increase in serum creatinine.

The alarming toxicity data came from heavily pre-treated myeloma patients — some of whom had impaired renal function before they ever began zoledronic acid. We are treating younger breast cancer patients who usually have perfect renal function, so I believe it would have been a safe approach. Clearly, we had to put safety first and reduce the dose to four milligrams every six months.

The dose of zoledronic acid used in animal models where antitumor mechanisms were seen would translate to a 32-milligram dose in humans, which is currently considered unsafe. However, I have heard that there are Phase I and II trials in myeloma patients with even higher doses administered more slowly. It's believed that if you increase the infusion time to two or three hours, the kidneys are pharmacokinetically able to handle the higher doses, but I haven't seen any written or published data on that.

Interim bone mineral density results

The early results of ABCSG-12 demonstrate that the combination of goserelin/anastrozole, and goserelin/tamoxifen to a lesser degree, leads to significant deterioration in bone mineral density in premenopausal women and

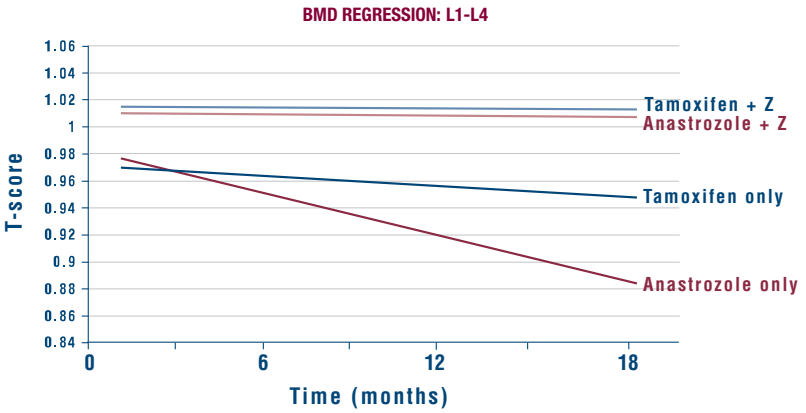
that this can be completely counteracted by zoledronic acid. Even though tamoxifen has an agonistic effect on bone, when combined with the more potent agent, goserelin, it results in a net reduction in bone density. The bone deterioration is more pronounced with anastrozole/goserelin, but there is not a significant difference at this time. The main message is that zoledronic acid was able to completely prevent bone loss, regardless of which hormone combination the patients received.

While the trial is ongoing, we decided we needed to present the bone mineral density results after the interim analysis. We wanted to inform physicians and patients about the effects on bone and give them the opportunity to do something to counteract these, if necessary.

The decrease in bone mineral density is about 10 percent — osteopenic rather than osteoporotic — so treatment is not mandatory. However, patients can take precautions such as exercise and vitamin substitution.

Also, we are observing a strong correlation between age, baseline bone mineral density and changes in bone mineral density. In younger patients, if you decrease the estradiol with goserelin/anastrozole to almost undetectable levels, they suffer a more pronounced deterioration in bone mineral density than the perimenopausal patients. Younger patients on anastrozole or tamoxifen may be at higher risk, although we have never seen a patient with a T-score change of more than minus 2.5, in whom bisphosphonate treatment would be mandatory.

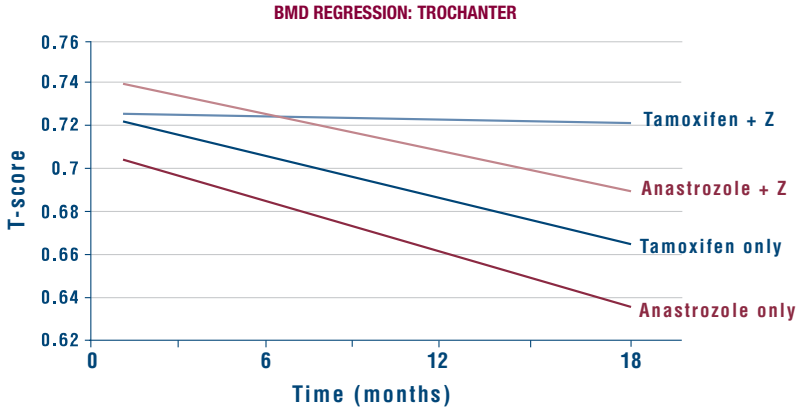
Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronic acid) as adjuvant treatment for hormone receptor-positive, premenopausal breast cancer: Results of a randomized multicenter trial (ABCSG-12).



Z = Zoledronic Acid

SOURCE: Presentation, M Gnant, 2002 San Antonio Breast Cancer Symposium

Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronic acid) as adjuvant treatment for hormone receptor-positive, premenopausal breast cancer: Results of a randomized multicenter trial (ABCSG-12).



Z = Zoledronic Acid

SOURCE: Presentation, M Gnant, 2002 San Antonio Breast Cancer Symposium

Anticipated long-term results

One problem with this study is that the event rate is lower than we expected. In 15 years of designing and conducting clinical trials, it has always been my experience that we overestimate the event rate. This is good for patients, but not for the trial. I expect that next year we'll have to consider increasing the sample size, basing it on the actual event rate in the first two years, rather than on our pretrial projections.

I suspect that we will not see a survival benefit for the bisphosphonates at our current dose of zoledronic acid; however, we may see a slight survival advantage for the anastrozole combination, based on the ATAC data. Goserelin renders all the patients postmenopausal, and I don't know of any reason women who become postmenopausal as a result of therapy would respond differently than those who become postmenopausal naturally.

Breast-conserving surgery

At our institution, we have a 75 to 80 percent breast conservation rate. In reviewing six of our clinical trials, we found the rate was as high as 82 percent in premenopausal patients with T1 tumors. With extensive use of preoperative chemotherapy and improved operative techniques, I believe mastectomy should become an obsolete surgical procedure.

Significant variance exists in breast conservation rates from country to country. Some of that is a cultural difference in the surgeon's approach to patients, and

some of that variance has to do with the availability of radiotherapy resources. In countries outside the western world, this is a major problem.

From the patient's point of view, it is very important that we have the resources available to facilitate breast conservation everywhere in the world. In the year 2003, I feel it's unacceptable for any patient not to be offered a reasonable choice of organ conservation in all surgical oncology indications, whether it's breast, rectal or other cancers.

Significant increase in breast conservation in trials conducted by the Austrian Breast & Colorectal Cancer Study Group: Three time periods from 1984 to 1997

Subgroup	1984-1990	1991-1993	1994-1997	*p* value
Premenopausal node-positive overall	27.2%	50.8%	73.2%	$p \leq 0.001$
Premenopausal node-positive, T1	33.7%	60.0%	81.8%	$p \leq 0.001$
Premenopausal node-positive, T2	22.9%	42.8%	63.2%	$p \leq 0.001$

DERIVED FROM: Jakesz R et al. **Significant increase in breast conservation in 16 years of trials conducted by the Austrian Breast & Colorectal Cancer Study Group.** *Ann Surg* 2003:237(4):556-64. **Abstract**

Neoadjuvant hormonal therapy and disease progression

I do not routinely use preoperative hormonal therapy outside of clinical trials. To me, the problem with the neoadjuvant endocrine treatment is that you have a certain rate of nonresponders, which we don't have with cytotoxic chemotherapy. For example, in our neoadjuvant trial, ABCSG-14, comparing three versus six cycles of epirubicin and docetaxel, we have a 70 to 80 percent response rate, probably a 15 to 25 percent complete pathological remission rate, and no progressive disease.

Disease progression during neoadjuvant therapy is a big problem. Patients are eager to have their lump removed, and while they may be willing to undergo neoadjuvant therapy to increase their likelihood of breast conservation, if you use endocrine therapy you have to tell them there's a 10 percent chance the lump will actually grow. I believe we should continue to test this therapy in clinical trials on cohorts of patients not suitable for cytotoxic chemotherapy.

Sentinel node: A standard of practice

We are not involved in sentinel node trials because this procedure is already the standard of care in Austria. One of the advantages of being in a small country with a well-functioning network of breast centers is that you can quickly translate an experimental procedure into daily practice. A set of guidelines was established, teaching courses were offered, institutions exchanged surgeons and sentinel node biopsy became a standard in the country.

Research in radiotherapy

We are conducting a trial randomizing patients with low risk after breast

conservation to radiation or no radiation. Patients must be over age 60, node-negative, on endocrine therapy and have a tumor size less than 3 centimeters. We have shown in retrospective studies that these patients have a local recurrence rate of only about two percent, so we need to determine if there's a subset of patients who do not need adjuvant radiation after breast conservation. This study will require a large number of patients and a long follow-up to determine equivalence of these two approaches.

We also have two Austrian institutions exploring intraoperative radiotherapy (IRT). It's very compelling to substitute this for five weeks of treatment, but from what I know about the concept of fractions, the rationale for this approach may be debatable. Also, in all the trials that I'm aware of, IRT is being used in patients at very low risk, and these are patients who probably do not need radiation whatsoever.

Future of research in breast cancer treatment and prevention

I believe future research will focus on defining subgroups of women with low- and intermediate-risk disease and finding appropriate treatments. One of the problems at this point is that progress may be made in smaller increments and may cost more. It may be easier and cheaper to increase an effect from 50 to 70 percent, than to increase it from 70 to 75 percent.

In the population at high risk, efforts to maximize dosing and then rescue patients, as with stem cell transplantation, have failed overall. It's probably a qualitative effect, rather than a quantitative effect, in that tumor cells vary in their response to different treatments. I believe researching areas such as growth factors and tyrosine kinase treatment will be important.

A promising trend in research is the emerging chip technology. This allows researchers to target specific mutations present in each cancer, which will hopefully lead to the development of tailored, more effective treatments, especially in the population at high risk. Chip technology may also be used in prevention by helping us understand the transition from atypical ductal hyperplasia to cancer, how invasion occurs and determining which women — other than BRCA carriers — are at high-risk for developing breast cancer. Once we identify these patients, we can intervene with endocrine treatment for prevention.

Patient benefits from participation in clinical trials

We have demonstrated that patients gain individual benefits from participating in clinical research trials. We did a retrospective analysis, presented at ASCO in 2000, comparing 5,700 patients in clinical trials with 2,000 patients with similar risk treated by a so-called standard treatment. These were all primary breast cancer patients and there was almost a 10 percent survival difference in favor of the patients on trials.

Clearly there is a problem with the standard of treatment patients receive outside clinical trials. In our analysis, we were able to look at the treatment

received by the patients not in trials, and about 90 percent of these patients received therapies we would consider suboptimal. Clinical trials are designed to ensure that patients receive optimal therapy. I see 500 breast cancer patients a year, and by treating patients within a clinical trial, I have all kinds of assistance — checklists, monitors, data verifications — to prevent me from forgetting something.

An additional explanation for the survival benefit of clinical trial participation is that, through required visits and tests, we pick up other medical problems that can be remedied. While a patient's risk reduction is about 40 percent after ten years, only 20 percent comes from breast cancer-related survival. The other 20 percent is related to other causes of death. I know a prospective randomized comparison of regular follow-up versus symptom-oriented follow-up doesn't show any survival difference, but personally I don't agree with that data.

When we treat patients within clinical trials, we not only help that individual patient, but we also help the next generation of patients and I believe that this is the most important task right now.

Impact of participation in randomized clinical trials on survival of women with early-stage breast cancer – An analysis of 7,985 patients.

	Patients participating n=5,532	Patients not participating n=2,453	*p*
Overall survival – 5-yr	84%	78%	
Overall survival – 10-yr	69%	64%	$p < 0.00001$
Median survival time	187.5 months	152.8 months	
Relapse-free survival – 5-yr	74%	70%	
Relapse-free survival – 10-yr	58%	55%	$p = 0.0001$

In the Cox model, participation in randomized trials independently reduced the odds for dying from the disease: RR 0.63; 95% CI: 0.553-0.723; $p < 0.0001$.

DERIVED FROM: Gnant M. **Impact of participation in randomized clinical trials on survival of women with early-stage breast cancer – An analysis of 7,985 patients.** *Proc ASCO* 2000:**Abstract 287.**

Select publications

Publications discussed by Dr Gnant

Gnant M. **Impact of participation in randomized clinical trials on survival of women with early-stage breast cancer – An analysis of 7,985 patients.** *Proc ASCO* 2000:**Abstract 287.**

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

Jakesz R et al. **Significant increase in breast conservation in 16 years of trials conducted by the Austrian Breast & Colorectal Cancer Study Group.** *Ann Surg* 2003:237(4):556-64. **Abstract**

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Post-test: Breast Cancer Update, Issue 4, 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. Patients with HER2 3+ tumors have better response rates with aromatase inhibitors than with tamoxifen.
a. True
b. False

2. Neoadjuvant endocrine therapy has which of the following effects on tumors, which are strongly ER-positive:
a. Reduction in tumor size
b. Reduction in cellularity
c. Reduction in proliferation
d. All of the above

3. Letrozole and exemestane have been thoroughly tested in the adjuvant setting and are considered equivalent to anastrozole.
a. True
b. False

4. In NCCTG-983252, comparing a weekly to a once-every-three-week schedule of paclitaxel, carboplatin and trastuzumab, which of the following was seen?
a. Tolerability was better for the weekly schedule
b. Tolerability was better for the once-every-three-week schedule
c. Tolerability was equal for both schedules

5. In patients eligible to receive first-line chemotherapy for metastatic breast cancer, E-1193 demonstrated that the combination of paclitaxel concurrent with doxorubicin led to a better response rate and time to progression with a similar quality of life and survival compared to a sequential taxane and anthracycline regimen.
a. True
b. False

6. Frequent measurements of ejection fraction can predict patients who will develop congestive heart failure on trastuzumab.
a. True
b. False

7. When using dose-dense AC followed by paclitaxel in patients with node-positive breast cancer, based on results of CALGB-9741, Dr Perez utilizes pegfilgrastim for growth factor support.
a. True
b. False

8. The NCCTG is planning a trial of docetaxel and capecitabine followed by gefitinib (Iressa®) in patients with metastatic breast cancer.
a. True
b. False

9. NSABP-P-1 demonstrated tamoxifen prevented the clinical expression of breast cancers in about 50 percent of women at high risk.
a. True
b. False

10. The interim analysis of ABCSG-12, goserelin/tamoxifen versus goserelin/anastrozole ± zoledronic acid, showed that zoledronic acid:
a. Increased the loss of bone mineral density
b. Had no effect on bone mineral density
c. Reduced bone mineral density loss with goserelin/anastrozole, but not with goserelin/tamoxifen
d. Completely prevented bone loss, regardless of which hormone combination the patient received

11. According to Dr Gnant, the variance in breast conservation rates from country to country are related to
a. Cultural differences in the surgeon's approach to the patient
b. Availability of radiotherapy resources
c. Number of practicing surgeons
d. a & b

Post-test Answer Key: 1a, 2d, 3b, 4a, 5a, 6b, 7a, 8a, 9a, 10d, 11d

Evaluation Form: Breast Cancer Update, Issue 4, 2003

NL Communications respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please complete this evaluation form. A certificate of completion is issued only upon receipt of our completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = *Outstanding* 4 = *Good* 3 = *Satisfactory* 2 = *Fair* 1 = *Poor*

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment 5 4 3 2 1
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer patients in your practice 5 4 3 2 1
- Develop and explain a management strategy for treatment of ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings 5 4 3 2 1
- Develop and explain a management strategy for treatment of ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings 5 4 3 2 1
- Counsel ER-positive, postmenopausal patients about the risks and benefits of aromatase inhibitors in the adjuvant setting 5 4 3 2 1
- Evaluate the emerging data on dose-dense chemotherapy and explain its relevance to patients 5 4 3 2 1

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 4

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

- Consider the use of neoadjuvant endocrine therapy in patients with locally advanced, ER-positive breast cancer 5 4 3 2 1
- Evaluate the data on carboplatin/paclitaxel/trastuzumab, and consider utilizing this regimen in women with HER2-positive metastatic disease 5 4 3 2 1
- Describe planned and ongoing clinical trials utilizing capecitabine combinations in the metastatic setting 5 4 3 2 1
- Consider the potential benefit of zoledronic acid and goserelin in combination with tamoxifen or anastrozole when treating women with these agents 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
J Michael Dixon, MD, FRCS	5 4 3 2 1	5 4 3 2 1
Edith Perez, MD	5 4 3 2 1	5 4 3 2 1
Bernard Fisher, MD	5 4 3 2 1	5 4 3 2 1
Michael F Gnant, MD	5 4 3 2 1	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

Evaluation Form: Breast Cancer Update, Issue 4, 2003

Please Print Clearly

Name: _____

Specialty: _____ ME#: _____ SS#: _____

Street Address: _____ Box/Suite: _____

City: _____ State: _____ Zip Code: _____

Phone Number: _____ Fax Number: _____Email: _____

I certify my actual time spent to complete this educational activity to be ___ hour(s).

Signature: _____

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.

_____

_____

What other topics would you like to see addressed in future educational programs?

_____

_____

What other faculty would you like to hear interviewed in future educational programs?

_____

_____

Degree:

☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ BS ☐ Other _____

To obtain a certificate of completion and receive credit for this activity, please complete the exam, fill out the evaluation form and mail or fax both to: NL Communications, Inc., 400 SE Second Avenue, Suite 401, Miami, FL 33131-2117, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.