BCU | 2003 VOL 2 | ISSUE 1

Breast Cancer™ UPDATE

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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2 Audio Tapes

2 Audio CDs

Monograph

CME Certified

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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 CD or tape, 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 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 website 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.

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 patients with HER2-positive breast cancer.
- Develop a management strategy for women with ER-positive and -negative breast cancers in the adjuvant, neoadjuvant and metastatic settings.
- Counsel postmenopausal patients with ER-positive tumors about the risks and benefits of aromatase inhibitors in the adjuvant setting.
- Evaluate the relevance of emerging clinical trial data on dose-dense adjuvant chemotherapy.

Issue 1, 2003 of Breast Cancer Update consists of discussions with three research leaders on a variety of important topics including aromatase inhibitors in the adjuvant setting, dose-dense chemotherapy, ovarian ablation and the use of capecitabine.

Specific learning objectives for Issue 1

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

- Describe the rationale for and results of clinical research on dose-dense adjuvant chemotherapy.
- Counsel and make recommendations for individual ER-positive, postmenopausal patients regarding the use of adjuvant aromatase inhibitors.
- Discuss the ongoing / planned clinical trials of capecitabine in the adjuvant and neoadjuvant settings.
- Describe the clinical implications of research on combinations of chemotherapy with trastuzumab in women with HER2-positive metastatic disease.

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.

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

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Faculty financial interests or affiliations

Larry Norton, MD
No financial interests to disclose

Gabriel N Hortobagyi, MD
Consultant: Genentech, Inc.
Honoraria: AstraZeneca Pharmaceuticals, LP, Genentech, Inc., Pharmacia Corporation

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Grants/Research Support: Aventis Pharmaceuticals
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Occasional speaker: AstraZeneca Pharmaceuticals, LP

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Armidex®	AstraZeneca Pharmaceuticals, LP
capecitabine	Xeloda®	Roche Laboratories, Inc.
carboplatin	Paraplatin®	Bristol-Meyers Squibb Company
cisplatin	Platinol-AQ®	Bristol-Meyers Squibb Company
cyclophosphamide	Cytoxan®, Neosar®	Bristol-Meyers Squibb Company, Pharmacia Corporation
docetaxel	Taxotere®	Aventis Pharmaceuticals
doxorubicin	Adriamycin®, Rubrex®	Pharmacia Corporation
5-fluorouracil, 5-FU	-	Various manufacturers
filgrastim	Neupogen®	Amgen, Inc.
exemestane phosphate	Aromasin®	Pharmacia Corporation
goserelin	Zoladex®	AstraZeneca Pharmaceuticals, LP
letrozole	Femara®	Novartis Pharmaceuticals
paclitaxel	Taxol®	Bristol-Meyers Squibb Company
pegfilgrastim	Neulasta®	Amgen, Inc.
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
trastuzumab	Herceptin®	Genentech, Inc.

Editor's Note

The Process Works

"CALGB 9741 is a clear example of the process working. You have a theoretical idea; you generate laboratory experiments; you generate clinical experiments and then you obtain buy-in from clinical investigators to test the idea. In fact, this is the first major cooperative group randomized trial chaired by a community-based oncologist — Marc Citron. The entire scientific process had buy-in across the board, and it showed that the system works. In many ways, the presentation of the data and the publication of the paper are just the beginning. We have to see how the clinical and research communities react to the data. But when you open up the pages and you see who's alive and who's dead, and see that there are women who are alive because of this process who otherwise would have died, it makes me glad I'm in this field. It's a very exciting, gratifying result."

— Larry Norton, MD

Every September, breast cancer aficionados — hoping to obtain an early peek at the next "hot story" in clinical research — eagerly anticipate the arrival of the San Antonio Breast Cancer Symposium agenda. By the time my copy appeared, Rick Kaderman, our vice president of Scientific Affairs, had already placed a very prominent highlight mark on the session scheduled for 9:00 AM, Thursday, December 12. The profoundly intriguing title of the presentation to be delivered by Marc Citron was "Superiority of dose-dense over conventional scheduling and equivalence of sequential vs. combination adjuvant chemotherapy for node-positive breast cancer (CALGB 9741, INT C9741)."

Like Rick, I was very eager to learn more about the results of this study, but I was also well aware that the abstract for this tantalizing report would not be available until shortly before the meeting. In late October, I ran into Cliff Hudis, one of the authors of the paper and a frequent guest on our series. I thought this might be my opportunity to obtain an inside track on some of the details of the data. However, no amount of cajoling would loosen Cliff's lips. How much of an advantage would the dose-dense approach convey? Would there be an overall survival benefit? As I pondered these and other questions, my curiosity was piqued even more by Cliff's broad smile and strong encouragement to attend the session. I sensed that this might be the chemotherapeutic equivalent to last year's ATAC trial results, which permanently changed the adjuvant endocrine therapy landscape.

Knowing that any discussion with CALGB investigators would be embargoed until the abstract was posted on the San Antonio website shortly before the meeting, I arranged a November interview with the individual whose perspective on this trial most aroused my interest. Larry Norton has spent the last 25 years espousing a mathematical approach to the war on cancer, and his fervor and commitment to the Norton-Simon hypothesis has always evoked my admiration, particularly since, until now, there has been little phase III clinical trial confirmation of this principle.

In a 1994 interview for this series, Larry predicted that his mathematical model would someday be tested in a large-scale, randomized breast cancer trial. It was quite clear at that point that he expected the results to confirm his long-held speculation that inhibiting tumor regrowth between chemotherapy treatment cycles played a key role in the effectiveness of a chemotherapeutic regimen. CALGB 9741 was launched in 1997. The trial had a crisp, highly targeted, two-by-two factorial design (Figure 1) and because the agents and doses in the three arms were identical, the study addressed Norton's dose-dense theory head on.

Figure 1: CALGB Trial 9741

2x2 Factorial Design	Q 2 wk + filgrastim	Q 3 wk
Sequential A➜T➜C	24 weeks of therapy	36 weeks of therapy
Concurrent AC➜T	16 weeks of therapy	24 weeks of therapy

DERIVED FROM : Presentation, M Citron, San Antonio Breast Cancer Symposium 2002.

I was a bit nervous when I arrived at Larry's cozy corner office at Memorial Sloan Kettering on November 18, as I was not 100 percent certain that the abstract had already been released. We both immediately logged on to the San Antonio website and, thankfully, the abstract was there in all its glory — a 26 percent relative reduction in relapse rate and 31 percent relative reduction in mortality with the dose-dense strategy. These findings were particularly noteworthy because of the reduced toxicity in these randomization arms. While Larry quipped "This is one of the first regimens where there's nothing not to love about it, " he was also typically cautious in predicting how the data would impact patient care and the design of future clinical trials.

A few weeks later, Marc Citron presented these historic findings to a packed San Antonio lecture hall. I interviewed Dr Citron later that day, and his thoughtful views will be presented in our next issue of Breast Cancer Update. As part of our annual San Antonio Breast Cancer Symposium "interview blitz," I also chatted with 14 other researchers at all hours of the day and night during the meeting. Like last year's ATAC extravaganza, there were a multitude of opinions. However, there was a uniform perspective among these researchers that the CALGB findings provide important proof of a principle that, at the very least, will now require routine discussion of the results with patients contemplating adjuvant chemotherapy.

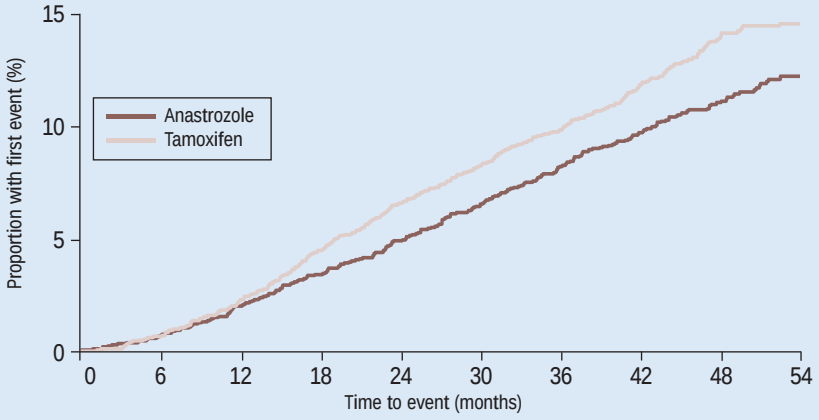
One of the most rewarding aspects of producing the Breast Cancer Update series has been the opportunity to participate in documenting the evolution of clinical research. While large phase III adjuvant trials like CALGB 9741 and ATAC have been at the focal point of progress in reducing breast cancer mortality, these studies have, at times, also been quite maddening in their very gradual evolution.

When I interviewed Michael Baum last year about ATAC, he commented on the frequent "periods of uncertainty in the evolution of science and medicine." Many of the questions posed by investigators last year about ATAC were answered at this year's meeting, where 14 more months of follow-up demonstrated that the disease-free survival curves of the anastrozole and tamoxifen arms are continuing to diverge (Figure 2). Most of the researchers I interviewed now agree with the viewpoint Gabe Hortobagyi has been expressing since the first presentation of ATAC — anastrozole is a rational, and in many cases, preferable endocrine approach for postmenopausal women with ER-positive breast cancer. It will be interesting to see whether clinicians repeat the ATAC experience and have a similarly cautious initial response to the CALGB data, particularly since a survival benefit is being reported with the dose-dense strategy.

Twenty-five years ago, a group of 100 researchers gathered for the first San Antonio Breast Cancer Symposium. That same year, at the National Cancer Institute, the remitting course of a patient with Hodgkin's disease treated with MOPP caused a "light bulb to go off" in Larry Norton's head. The carefully planned scientific process that followed this observation culminated in a startling presentation that has not only provided a new treatment option for women, but has also confirmed that the clinical trial process truly works.

—Neil Love, MD

Figure 2: Probability of first event in receptor-positive population



DERIVED FROM: Presentation, A Buzdar, San Antonio Breast Cancer Symposium 2002. Reproduced with permission.

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Edited comments by Dr Norton

Evolution of the Norton-Simon Hypothesis

The study design of CALGB 9741 was based on rigorous mathematical modeling, which generated clinical trial data and then generated this experiment. This study had a 25-year history, starting with a clinical observation, which led to a theory, which led to experiments to refine the model, which generated new experiments and eventually led to these results.

The original clinical observation was a patient I saw with Hodgkin's disease when I was a clinical associate at the National Cancer Institute. He finished six cycles of MOPP chemotherapy and did very well for over a year, but relapsed in the same sites with the exact same histology approximately 17 months later. We put him back on MOPP chemotherapy, and again he had a spectacular response. We saw growth, regression and regrowth.

My background was in mathematics, and I worked with Richard Simon from the National Cancer Institute to graph this out and try to fit curves to it. But when we tried to fit the existing models to the data on this particular patient, it just didn't work.

Mathematical models for tumor growth

We looked at the Skipper-Schabel model, which says that exponential growth is constant log growth, and exponential regression translates to constant log kill. If a tumor doubles in a certain period of time, it will double in that period of time no matter how big it is. If it shrinks by half over a period of time in response to therapy, it will always shrink by half. Gompertzian growth is exponential growth with a constant exponential regression.

The question was how the Skipper-Schabel model applied to Gompertzian growth. It was very clear looking at this patient's record that his response was not log kill. It turned out to be simple — if the tumor grew in a Gompertzian fashion, it would regress in a Gompertzian fashion.

When I graphed it, this patient fit so perfectly that I could accurately predict when he would go in complete remission. As long as you have homogeneity in response to therapy, the model worked very well. This led to a series of laboratory experiments and clinical trials. Using this model, deviations from Gompertzian growth are due to drug resistance — the emergence of different clones with different growth kinetics and responses to therapy.

Dose-dense therapy targets inhibition of regrowth

A paper in *Seminars in Oncology* in the mid-1980s indicated that the primary problem in Gompertzian growth is not cell kill, but rather regrowth between cycles. While therapy gets us closer to the cure limits, you have to get below a small number of cells to prevent regrowth, and you regrow faster away from that limit. There's a rebound effect, and the key is to inhibit that regrowth.

One of the simplest ways to address regrowth is to move the doses of therapy close enough together to have less regrowth between cycles. This is extremely powerful in Gompertzian kinetics, as long as you can drive the tumor toward that cure limit. In the adjuvant setting, when you're probably close to the cure limit, you can have dramatic benefits by giving the doses closer together in time.

The Gompertzian model and tumor regrowth

"In the Gompertzian model, smaller tumors grow faster, so tumor regrowth between treatment cycles is more rapid when cell kill is greatest. Reducing the time available for tumor regrowth (increasing dose density), which is now possible through the use of colony-stimulating factors to hasten hematopoietic recovery, may have a greater impact on clinical outcome than dose escalation. Sequential schedules allow optimal doses to be used in dose-dense cycles."

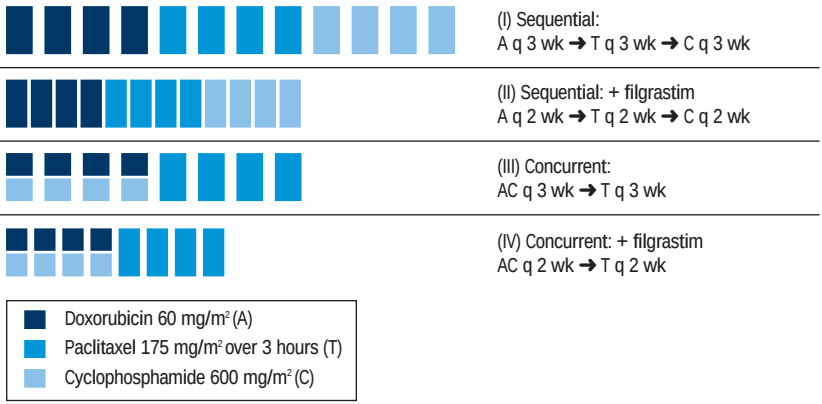
EXCERPTED FROM: Norton L. **Evolving concepts in the systemic drug therapy of breast cancer.** *Semin Onc* 1997;24(4 Suppl 10):S10-3-S10-10. **Abstract.**

CALGB 9741: Phase III study of dose-dense and sequential adjuvant chemotherapy

This study was designed with input from all members of the breast Intergroup and coordinated by the CALGB. It had a two-by-two factorial design. The two parameters were dose-density — giving drugs every two weeks instead of every three weeks using G-CSF — and combination versus sequential therapy. The doses were the same optimal doses derived from previous clinical trial experience. The only difference was the schedules.

PHASE III RANDOMIZED STUDY OF SEQUENTIAL CHEMOTHERAPY USING DOXORUBICIN, PACLITAXEL, AND CYCLOPHOSPHAMIDE OR CONCURRENT DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL AT 14- AND 21-DAY INTERVALS IN WOMEN WITH NODE-POSITIVE STAGE II OR IIIA BREAST CANCER **Closed Protocol**
Protocol IDs: CLB-9741, E-C9741, NCCTG-C9741, SWOG-C9741
Projected Accrual: 2,000 patients

Eligibility: Operable, stage II or IIIA adenocarcinoma of the breast (T0-3, N1-2, and M0) surgically treated by either a modified radical mastectomy or a lumpectomy plus axillary node dissection



SOURCE: NCI Physician Data Query, December 2002 and adapted from presentation, M Citron, San Antonio Breast Cancer Symposium 2002.

Improved survival with less toxicity with dose-dense chemotherapy

The study demonstrates a considerable advantage to dose density in disease-free survival — the primary endpoint of the study — and overall survival. There was an approximate 31 percent reduction in the annual odds of death with the dose-dense therapy.

This benefit was not at the cost of increased toxicity. In fact, the dose-dense regimens were less toxic than the conventional regimens, particularly in terms of neutropenia. In every important parameter except for anemia, dose-dense therapy was superior in terms of toxicity. Sequential dose-dense therapy eliminated the anemia while maintaining preservation of efficacy.

This is one of the first regimens I've seen where there's nothing "not to love." It's more efficacious, less toxic and over more quickly. The incidence of longer-term effects, so far, is the same as we would expect from the drugs without dose density. In retrospect, it is logical — you're giving G-CSF for neutropenia, getting the drugs in more quickly, leaving less time to develop other toxicities and obtaining more efficacy because more drug is given over a shorter period of time.

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)

SOURCE: 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 (CALBG 9741, INT C9741).** *Breast Cancer Res Treat* 2002;**Abstract 15.**

The importance of hematopoetic support during dose-dense therapy

One key factor in the dose-dense approach is the use of granulocyte colony-stimulating factors. Some form of granulocyte stimulation is absolutely essential, and this trial utilized filgrastim on days 3-10.

Monica Fornier, Cliff Hudis and colleagues are planning a study to look at the longer-acting formulation — pegfilgrastim. We have every reason to believe this agent will be both very effective and more convenient for the patient. Once we have the feasibility data, which should be fairly soon, I think the longer-acting formulation could be utilized for regimens like this.

Clinical applicability of dose-dense adjuvant chemotherapy

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

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

Optimal dosing and scheduling in dose-dense chemotherapy

I am concerned physicians will be enthralled with the idea of giving the doses closer together and reduce the doses in order to accomplish that. This may or may not work, depending on the cell kill per dose. I would rather use 60 mg / m^2 of doxorubicin as often as possible than go down to 30 or 40 mg / m^2 of doxorubicin to give it more often.

The doses selected for this trial were based on previous studies. CALGB 9344 demonstrated that doses greater than 60 mg/m^2 of doxorubicin do not convey any advantage, and that the addition of paclitaxel made an important difference, especially in the subset of patients with estrogen receptor-negative tumors.

Another CALGB study of patients with stage IV advanced disease by Eric Winer showed that doses of paclitaxel higher than 175 mg/m^2 were associated with more toxicity and no significant advantage. The NSABP also did a series of excellent randomized trials, which showed that the efficacy of cyclophosphamide was capped at the dose of 600 mg/m^2.

Trials determining optimal dose of agents in CALGB 9741

Trial	Agent and doses studied	Results
NSABP B-22	Cyclophosphamide • 600 mg/m^2/w x 4 • 1200 mg/m^2/w x 2 • 1200 mg/m^2/w x 4	No significant differences in DFS or OS between groups. Increased grade 4 toxicity with higher dose.
NSABP B-25	Cyclophosphamide • 1200 mg/m^2/w x 4 • 2400 mg/m^2/w x 2 • 2400 mg/m^2/w x 4	Intensifying and increasing dose 2 to 4 times the standard (600mg/m^2) did not improve outcome.
CALGB 9342	Paclitaxel • 175 mg/m^2 q 3 w • 210 mg/m^2 q 3 w • 250 mg/m^2 q 3 w	Higher doses did not improve response rate or survival, but led to greater toxicity.
CALGB 9344	Doxorubicin • 60 mg/m^2 q 3 w x 4 • 75 mg/m^2 q 3 w x 4 • 90 mg/m^2 q 3 w x 4	No significant differences in DFS or OS related to dose.

DFS = disease free survival; OS = overall survival

SOURCES:

Fisher B et al. **Further evaluation of intensified and increased total dose of cyclophosphamide for the treatment of primary breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-25.** *J Clin Onol* 1999;17(11):3374-88.**Abstract**

Winer E et al. **Failure of higher dose paclitaxel to improve outcome in patients with metastatic cancer – Results from CALGB 9342.** *Proc ASCO* 1998;**Abstract.**

Henderson IC et al. **Improved disease-free (DFS) and overall survival (OS) from the addition of sequential Paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (PTS) with node-positive primary breast cancer (BC).** *Proc ASCO* 1998;**Abstract.**

We chose the every two-week schedule for trial CALGB 9741 out of convenience. There's no real reason it has to be two weeks. In fact, with G-CSF, most patients are ready to be treated after 10 or 11 days. If changing from 21 days to 14 days results in a one-third reduction in mortality, then going from 14 days to 10 days may result in a further reduction in mortality. These are the kinds of regimens that we need to start testing prospectively in clinical trials.

Dose and schedule of adjuvant paclitaxel

The issue of weekly dosing of taxanes — specifically paclitaxel — is an open question. Weekly administration certainly reduces toxicity and seems to preserve response rate. The CALGB is accruing patients to a study comparing weekly versus every three-week paclitaxel. This trial is also asking questions about trastuzumab use in the setting of metastatic breast cancer. While this is a very important trial, the weekly paclitaxel is being given at a compromised dose. It uses 80 mg/m^2 per week, which adds up to a high cumulative dose, but we don't know the dose-response curve for paclitaxel at that level. It's possible that 175 mg/m^2 every two weeks is more effective in cell kill than 80 mg/m^2 every week.

You can give more than 80 mg/m^2 per week of paclitaxel for a few cycles, but then you see significant toxicity, particularly neurotoxicity. There are interesting agents being investigated in terms of their ability to ameliorate the neurotoxicity of paclitaxel enough to give a higher dose every week. It may even be possible to approach the every two-week dose on a weekly basis by using G-CSF.

PHASE III RANDOMIZED STUDY OF PACLITAXEL VIA ONE HOUR INFUSION EVERY WEEK VERSUS THREE HOUR INFUSION EVERY 3 WEEKS WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN) IN PATIENTS WITH INOPERABLE, RECURRENT, OR METASTATIC BREAST CANCER WITH OR WITHOUT OVEREXPRESSION OF HER2-NEU **Open Protocol**

Protocol ID: CLB-9840, CTSU
Projected Accrual: 580 patients within 3 years

Eligibility	Inoperable, recurrent or metastatic breast cancer with known HER2 status and LVEF at least 45%. Patients are stratified according to prior chemotherapy for metastatic disease and HER2 status.

Group A: HER2-negative

ARM 1	Paclitaxel q 3 w
ARM 2	Paclitaxel q w
ARM 3	Paclitaxel q 3 w + trastuzumab q w
ARM 4	Paclitaxel q w + trastuzumab q w

Group B: HER2-positive

ARM 5	Paclitaxel q 3 w + trastuzumab q w
ARM 6	Paclitaxel q w + trastuzumab q w

Both groups: Courses repeat in the absence of disease progression or unacceptable toxicity.
Quality of life is assessed at baseline and then at 3, 6 and 9 months.

Study Contact:
Andrew D Seidman, Chair. Tel: 212-636-5875

SOURCE : NCI Physician Data Query, December 2002

Trastuzumab as first-line therapy in metastatic disease

The pivotal trial of trastuzumab clearly showed a survival advantage to trastuzumab combined with chemotherapy — either AC or paclitaxel. AC/trastuzumab led to a higher-than-expected — and higher-than-acceptable — incidence of cardiotoxicity, so doxorubicin is not widely used with trastuzumab. Paclitaxel with trastuzumab in the HER2-positive situation clearly results in a survival advantage, and it does not make sense to deny patients that survival advantage.

We still don't know how long to continue trastuzumab after disease progression, and there is a current MD Anderson trial evaluating this. The clinical trial community needs to address this issue.

Phase III trial of trastuzumab and paclitaxel with or without carboplatin in advanced breast cancer

Platinums are active agents, and there is evidence of benefit in combining them with trastuzumab. Nicholas Robert is reporting an important phase III study comparing trastuzumab and paclitaxel with and without carboplatin in patients with HER2-positive advanced breast cancer. The addition of carboplatin increased the response rate and the duration of response. I think it is important to find out whether these agents need to be combined to obtain the desired result, or whether they can be given sequentially.

Phase III study comparing trastuzumab and paclitaxel with and without carboplatin in patients with HER2/neu-positive, advanced breast cancer

Eligibility	HER2-positive, metastatic breast cancer patients with no prior chemotherapy for metastatic disease
ARM 1	H q week + T q 3 weeks
ARM 2	H q week + TC q 3 weeks

Study Results

Parameters	HTC Regimen	HT Regimen	P Value
Response Rate (RR)	57%	38%	P < 0.01
RR in HER2 IHC 3+	67%	37%	P = <0.01
Time to progression (TTP)	13 months	7 months	P = 0.002
TTP in HER2 IHC 3+	17 months	9 months	P = 0.004

HTC = trastuzumab, paclitaxel, carboplatin; HT = trastuzumab, paclitaxel

SOURCE: Robert N et al. **Phase III study comparing trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 35.**

Advantages of capecitabine in the management of metastatic disease

Capecitabine is an excellent agent. From a cell kinetics perspective, it achieves very high intracellular levels of 5-fluorouracil, so dose is not compromised. Oral administration is a significant advantage. Patients with disease progression on hormonal therapy who are not psychologically ready for intravenous therapy can go from their hormone pill to capecitabine without a big transition. It is oral and can be administered frequently, giving a high-dose bolus of 5-fluorouracil. Patients do not have a lot of toxicity if the dose is monitored carefully.

We give capecitabine two weeks on followed by one week off, but this may not be the optimal schedule. Many of us have talked for years about exploring other schedules of administration, and I would like to see more innovative schedules of capecitabine tested in clinical trials. A higher dose given weekly or every five or ten days would give the patient a very high dose of 5-fluorouracil. I'm not sure we have achieved the optimal schedule for this important active agent.

Capecitabine plus docetaxel as combination therapy

Capecitabine and docetaxel are both very active agents. In advanced disease, when we're dealing with heterogeneous drug sensitivity, studying the drugs together makes a lot of sense. A higher percentage of patients may respond to therapy with improved duration of disease control because some patients will benefit who wouldn't have before.

I've treated some patients with stage IV disease who responded brilliantly to docetaxel but did not respond well to capecitabine. Others respond to capecitabine, but not to docetaxel.

If a given patient has a largely capecitabine-sensitive tumor, I'd be better off treating with capecitabine than with the capecitabine / docetaxel combination. If response is my primary goal, and I don't know whether the tumor is responsive to capecitabine, I'm better off giving the combination more.

However, I don't know what happens if I treat with docetaxel, and switch to capecitabine if I don't see an early response. This is somewhat different from the common clinical practice of treating for a long time before switching. I think we wait too long before changing therapies in general, because we actually wait for tumor regrowth. Even if we obtain a good response to one drug, we wait for tumor regrowth before we switch, and we probably should do this sooner.

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

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

Select Publications

Dose-dense chemotherapy regimens

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 (CALBG 9741, INT C9741).** *Breast Cancer Res Treat* 2002; **Abstract 15.**

De Giorgi U et al. **High-dose epirubicin, preceded by dexrazoxane, given in combination with paclitaxel and filgrastim provide a safe and effective mobilization regimen to support three courses of high-dose dense chemotherapy in patients with stage II-III breast cancer.** *Proc ASCO* 2002; **Abstract 1680.**

Eggemann H et al. **Sequential dose-dense epirubicin/paclitaxel (E-T) with G-CSF support compared to standard EC – T (epirubicin/cyclophosphamide followed by paclitaxel) for patients with operable breast cancer and 1-3 positive lymph nodes-first toxicity analysis.** *Breast Cancer Res Treat* 2002; **Abstract 646.**

Ellis GK et al. **Dose-dense anthracycline-based chemotherapy for node-positive breast cancer.** *J Clin Oncol* 2002;20(17):3637-43. **Abstract**

Emens LA et al. **A phase I toxicity and feasibility trial of sequential dose-dense induction chemotherapy with doxorubicin, paclitaxel, and 5-fluorouracil followed by high dose consolidation for high-risk primary breast cancer.** *Breast Cancer Res Treat* 2002;76(2):145-56. **Abstract**

Euler U et al. **Dose and time intensified epirubicin/cyclophosphamide (EC) as preoperative treatment in locally advanced breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 154.**

Fornier MN et al. **Doxorubicin followed by sequential paclitaxel and cyclophosphamide versus concurrent paclitaxel and cyclophosphamide: 5-year results of a phase II randomized trial of adjuvant dose-dense chemotherapy for women with node-positive breast carcinoma.** *Clin Cancer Res* 2001;7(12):3934-41. **Abstract**

Fountzilas G et al. **Dose-dense sequential chemotherapy with epirubicin and paclitaxel versus the combination, as first-line chemotherapy, in advanced breast cancer: A randomized study conducted by the Hellenic Cooperative Oncology Group.** *J Clin Oncol* 2001;19(8):2232-9. **Abstract**

Jackisch C et al. **Primary endpoint analysis of the Geparduo-study - Preoperative chemotherapy (PCT) comparing dose-dense versus sequential adriamycin/docetaxel combination in operable breast cancer (T2-3, N0-2,M0).** *Breast Cancer Res Treat* 2002; **Abstract 152.**

Jackisch C et al. **Dose-dense biweekly doxorubicin/docetaxel versus sequential neoadjuvant chemotherapy with doxorubicin/cyclophosphamide/docetaxel in operable breast cancer: Second interim analysis.** *Clin Breast Cancer* 2002;3(4):276-80. **Abstract**

Norton L. **Theoretical concepts and the emerging role of taxanes in adjuvant therapy.** *Oncologist* 2001;6 Suppl 3:30-5. **Abstract**

Paciucci PA et al. **Neo-adjuvant therapy with dose-dense docetaxel (DTX) plus short-term G-CSF support for locally advanced breast cancer (LABC).** *Proc ASCO* 2002; **Abstract 1943.**

Razis E et al. **Dose-dense sequential chemotherapy with epirubicin and paclitaxel in advanced breast cancer.** *Cancer Invest* 2001;19(2):137-44. **Abstract**

Rodriguez CA et al. **Dose-dense docetaxel and mitoxantrone as first line chemotherapy for metastatic breast cancer (MBC).** *Proc ASCO* 2002; **Abstract 1938.**

Untch M et al. **Dose-dense sequential epirubicin-paclitaxel as preoperative treatment of breast cancer: Results of a randomised AGO study.** *Proc ASCO* 2002; **Abstract 133.**

van Rossum CK et al. **Dose intensification of epirubicin and paclitaxel with G-CSF support for patients with metastatic breast cancer: A randomized phase II study of dose-dense and dose-escalated chemotherapy.** *Proc ASCO* 2002; **Abstract 2040.**

von Minckwitz G et al. **Dose-dense versus sequential adriamcycin / docetaxel combination as preoperative chemotherapy (pCHT) in operable breast cancer (T2-3, N0-2,M0) - Primary endpoint analysis of the GEPARDUO-study.** *Proc ASCO* 2002; **Abstract 168.**

Hematopoetic growth factors

Anderlini P, Champlin R. **Use of filgrastim for stem cell mobilisation and transplantation in high-dose cancer chemotherapy.** *Drugs* 2002;62(Suppl 1):79-88. **Abstract**

Crawford J. **Pegfilgrastim administered once per cycle reduces incidence of chemotherapy-induced neutropenia.** *Drugs* 2002;62(Suppl 1):89-98. **Abstract**

Curran MP, Goa KL. **Pegfilgrastim.** *Drugs* 2002;62(8):1207-13; discussion 1214-5. **Abstract**

Ellis GK et al. **Dose-dense anthracycline-based chemotherapy for node-positive breast cancer.** *J Clin Oncol* 2002;20(17):3637-43. **Abstract**

Frasci G. **Treatment of breast cancer with chemotherapy in combination with filgrastim: Approaches to improving therapeutic outcome.** *Drugs* 2002;62 Suppl 1:17-31. **Abstract**

Holmes FA et al. **Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer.** *J Clin Oncol* 2002;20(3):727-31. **Abstract**

Holmes FA et al. **Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: A multicenter dose-finding study in women with breast cancer.** *Ann Oncol* 2002;13(6):903-9. **Abstract**

Molineux G. **Pegylation: engineering improved pharmaceuticals for enhanced therapy.** *Cancer Treat Rev* 2002;28(Suppl A):13-6. **Abstract**

Nabholtz JM et al. **Phase III Trial Comparing Granulocyte Colony-Stimulating Factor to Leridistim in the Prevention of Neutropenic Complications in Breast Cancer Patients Treated with Docetaxel/ Doxorubicin/Cyclophosphamide: Results of the BCIRG 004 Trial.** *Clin Breast Cancer* 2002;3(4):268-75. **Abstract**

Shogan JE et al. **A single dose of pegfilgrastim reduces the incidence of febrile neutropenia in various risk strata compared with daily filgrastim following myelosuppressive chemotherapy.** *Breast Cancer Res Treat* 2002; **Abstract 536.**

Shogan JE et al. **Pegfilgrastim shows safety and efficacy similar to filgrastim in elderly patients with breast cancer.** *Proc ASCO* 2002; **Abstract 260.**

Siena S et al. **A single dose of pegfilgrastim per chemotherapy cycle allows most patients to receive an average relative dose intensity (ARDI) ≥ 85%.** *Breast Cancer Res Treat* 2002; **Abstract 535.**

Valley AW. **New treatment options for managing chemotherapy-induced neutropenia.** *Am J Health Syst Pharm* 2002;59(15 Suppl 4):S11-7. **Abstract**

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Edited comments by Dr Hortobagyi

Implications of the ATAC trial in clinical practice

The results of the ATAC trial are quite compelling. Even if you assume for the sake of argument that the curves will come together with further follow-up, the safety profile of anastrozole is still clearly better than tamoxifen. I cannot prevent endometrial cancer short of removing the uterus, but I can prevent or treat osteoporosis and fractures. Since the safety profile of anastrozole is better than tamoxifen and it is therapeutically superior, I have a problem not offering anastrozole to my postmenopausal patients — not as a neutral choice but as a better choice. I do discuss with my patients the enormous amount of clinical experience we have with tamoxifen, but if my sister developed breast cancer today, I would certainly recommend anastrozole as opposed to tamoxifen.

Hazard ratios of anastrozole compared to tamoxifen in updated efficacy results of the ATAC trial (median follow-up of 47 months, 1373 events)

	Study population	Hormone receptor-positive subgroup
Probability of first event	HR = 0.86 (95% CI 0.76-0.99) p = 0.030	HR = 0.82 (95% CI 0.70-0.96) p = 0.014
Probability of recurrence	HR = 0.83 (95% CI 0.71-0.96) p = 0.015	HR = 0.78 (95% CI 0.65-0.93) p = 0.007
Incidence of new contralateral breast primaries	OR = 0.62 (95% CI 0.38-1.02) p = 0.062	OR = 0.56 (95% CI 0.32-0.98) p = 0.042

HR = Hazard ratio; OR = Odds ratio

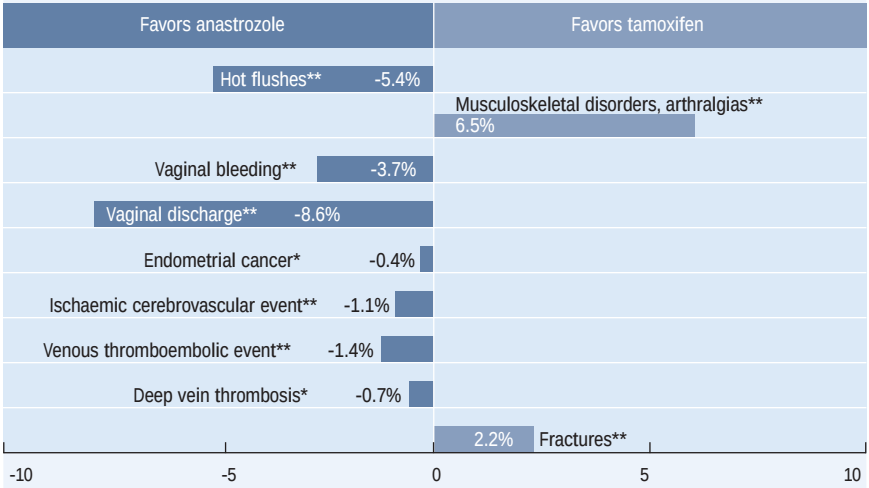
DERIVED FROM: Buzdar A et al. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer — Updated efficacy results based on a median follow-up of 47 months.** *Breast Cancer Res Treat* 2002; **Abstract 13.**

Updated 47-month follow-up of the ATAC trial

"With increased follow-up, AN continues to show superior efficacy to TAM, these benefits being most apparent in the clinically relevant hormone receptor-positive population. These results confirm that the benefits observed with AN are likely to be maintained over the long-term. A safety update has confirmed the findings of the main analysis…"

SOURCE : Buzdar A et al. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer — Updated efficacy results based on a median follow-up of 47 months.** *Breast Cancer Res Treat* 2002; **Abstract 13.**

Significant differences in pre-defined adverse events



Difference between anastrozole and tamoxifen adverse events (%)

*** p < 0.05, ** p < 0.01**

DERIVED FROM: **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(9324):2131-9. **Abstract**

Use of other aromatase inhibitors in the adjuvant setting

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

Making clinical decisions in the face of uncertainty

Oncology is one of the classic specialties in which uncertainty is a way of life because of progress and constant change. It is important for our professional organizations to have consensus at various points in the evolution of a particular treatment. Having said that, those guidelines and consensus statements tend to be relatively conservative. Most of the time that is perfectly appropriate, but physicians will have to make individual decisions based on interactions with patients. Some of those decisions will follow guidelines, while others will not.

There are situations where departing from a guideline is clearly wrong. For instance, there is widespread acceptance that aromatase inhibitors should not be used in premenopausal women. Departing from the guidelines in that setting is clearly inappropriate because you would actually reject scientific evidence as the basis for your decisions. But, in situations where there are data and evidence to support various options, there is nothing wrong with deviating from a consensus statement as long as it is appropriate for that specific patient.

Recommending adjuvant anastrozole based on early trial results

There is no comparable trial in the history of medical oncology or breast cancer, and there is no other tumor type with so many well-planned clinical trials conducted. We are in a leadership position in oncology, and we can't advocate doing the best trials and then ignore the results of those trials. Every single trial we do brings with it some of the unknown.

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

We have very compelling data about anastrozole from the ATAC trial, in terms of its therapeutic and safety profile superiority. I would be doing a disservice to my patients who are candidates for adjuvant aromatase inhibitor therapy by not presenting the data. I also present tamoxifen as an option, but in the last six months I would say that 60 percent of my postmenopausal patients chose anastrozole rather than tamoxifen. There is no right or wrong decision, but for me, there are compelling data to prefer anastrozole.

Incorporating early research results into practice

I was actually one of the individuals who initially fought against the use of adjuvant tamoxifen — especially in premenopausal women — in the 1980s. Up until the early 1990s, in our own clinical trials at MD Anderson, we did not include endocrine therapy in the adjuvant treatment of premenopausal women. We learn from history that we probably fail to understand the impact of emerging data on the lives of women. Coming from that background, my

flexibility in accepting the new and relatively early data of the ATAC trial is more significant to me. If I had understood the deep implications of what tamoxifen could do in terms of saving lives in the early 1980s, I could probably have modified many of our own activities and policies during the subsequent ten years.

There are situations in which one needs to be much more conservative. I was much more cautious in the high-dose chemotherapy area, because there was much to lose. However, the safety issues of high-dose chemotherapy in the 1980s and of aromatase inhibitors in the 21st century are so enormously different that we cannot even compare them.

Providing patients with treatment options and recommendations

One of our major goals is to fully educate our patients by giving them relevant, accurate and complete information, so that they understand their prognosis, treatment options and the benefit-to-risk ratio they will face with each of those options. But we can't stop there. We also need to make a recommendation after that education. Obviously this recommendation will incorporate our biases and prejudices, but we are better qualified — even with those biases and prejudices — than a patient who just had "oncology 101" during the previous 20-30 minutes. I feel very strongly about that.

Over the past 30 years in medicine, we have moved from a paternalistic approach to the other extreme. Many of my colleagues try to be so neutral that they do not make a recommendation. The burden of decision-making has been removed completely from the physician, who is best qualified to make that choice or recommendation, to the patient, who sometimes is — but most of the times is not — in the best position to make that choice without guidance. I understand and agree that patients need to have autonomy. We clearly have the obligation to inform them fully, but I think we need to go beyond that. We have to get to know our patients and understand their motivations, their understanding of risks and benefits, their definition of therapeutic gain and their acceptable level of risks and side effects. As physicians, we need to help them make a decision. To abrogate that responsibility is an unfortunate — and I hope temporary — trend in the medical profession.

Adjuvant randomized clinical trials of trastuzumab

There is a substantial body of data suggesting that while there is a slight excess in cardiac events with trastuzumab and anthracycline-based chemotherapy in the adjuvant setting, it is unlikely to affect survival in any major way.

We have elected to support the BCIRG adjuvant trial, but the NCCTG and NSABP trials are equally worthwhile. All three will contribute to our understanding of how best to incorporate trastuzumab in the adjuvant setting. While it is reasonable to ask whether we can derive the same amount of benefit from trastuzumab with a non-anthracycline-containing regimen as with an anthracycline-containing regimen, the bulk of the data from retrospective

analyses of many of our previous trials points to the importance of anthracyclines precisely in HER2-positive patients.

I think it is shortsighted to abandon anthracyclines on the basis of a potential risk for toxicity. The history of oncology is full of toxic agents that were almost discarded until someone found a way to administer them safely. That is true for anthracyclines, cisplatin, alkylating agents and taxanes. We should not be surprised that these drugs have toxicity, but we should not discard them lightly. We should learn to use them safely through clinical trials, and there are many ways to address this issue of developing the safest and most effective combination with trastuzumab.

PHASE III RANDOMIZED STUDY OF ADJUVANT DOXORUBICIN, CYCLOPHOSPHAMIDE, AND DOCETAXEL WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN®) VERSUS TRASTUZUMAB, DOCETAXEL, AND EITHER CARBOPLATIN OR CISPLATIN IN WOMEN WITH HER2-NEU-EXPRESSING NODE-POSITIVE OR HIGH-RISK NODE-NEGATIVE OPERABLE BREAST CANCER **Open Protocol**

Protocol ID: BCIRG-006
Projected Accrual: 3,150 patients

Eligibility	Node-positive or high-risk node-negative, HER2-overexpressing (FISH-positive) breast cancer

ARM 1	AC x 4 ➜ docetaxel x 4
ARM 2	AC x 4 ➜ docetaxel x 4 + H (qw x 12 weeks) ➜ H (qw x 40 weeks)
ARM 3	(Docetaxel + C) x 6 + H (qw x 18 weeks) ➜ H (qw x 34 weeks)

C = cisplatin or carboplatin; H = trastuzumab

Study Contact:
Linnea Chap, Chair. Tel: 310-829-5471
Jonsson Comprehensive Cancer Center, UCLA

SOURCE: NCI Physician Data Query, December 2002

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
Projected Accrual: 1,000-2,700 patients

Eligibility	HER2-positive, node-positive breast cancer

ARM 1	AC x 4 ➜ paclitaxel x 4
ARM 2	AC x 4 ➜ paclitaxel x 4 + H qw x 1 year

H = trastuzumab
All ER/PR-positive patients receive tamoxifen x 5 years. Lumpectomy patients undergo radiotherapy at completion of chemotherapy and concurrent with trastuzumab.

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

SOURCE: NCI Physician Data Query, December 2002

PHASE III RANDOMIZED STUDY OF DOXORUBICIN PLUS CYCLOPHOSPHAMIDE FOLLOWED BY PACLITAXEL WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN®) IN WOMEN WITH HER2-OVEREXPRESSING NODE-POSITIVE BREAST CANCER **Open Protocol**

Protocol ID: NCCTG-N9831, CLB-49909, E-N9831, SWOG-N9831
Projected Accrual: 3,000 patients (1,000 per treatment arm)

Eligibility	Node-positive, HER2-overexpressing breast cancer

ARM 1	AC x 4 ➜ T qw x 12
ARM 2	AC x 4 ➜ T qw x 12 ➜ H qw x 52
ARM 3	AC x 4 ➜ (T + H) qw x 12 ➜ H qw x 40

T = paclitaxel; H = trastuzumab
All ER/PR-positive patients receive tamoxifen or an aromatase inhibitor x 5 years.
Patients may undergo radiotherapy at the completion of paclitaxel.

Study Contacts:
Peter A Kaufman, Chair. Tel: 603-650-6700, Cancer and Leukemia Group B
Nancy E Davidson, Chair. Tel: 410-955-8489, Eastern Cooperative Oncology Group
Edith A Perez, Chair. Tel: 904-953-6832, North Central Cancer Treatment Group
Silvana Martino, Chair. Tel: 310-998-3961, Southwest Oncology Group

SOURCE: NCI Physician Data Query, December 2002

PHASE III RANDOMIZED STUDY OF TRASTUZUMAB (HERCEPTIN) IN WOMEN WITH HER2-POSITIVE PRIMARY BREAST CANCER **Open Protocol**

Protocol IDs: BIG-01-01, EORTC-10011, "HERA"

Projected Accrual: 3,192 patients

Eligibility	Node-negative or -positive, HER2-positive breast cancer previously treated with at least 3 months or 4 courses of approved neoadjuvant or adjuvant chemotherapy with or without radiotherapy

ARM 1	H q3w x 1 year
ARM 2	H q3w x 2 years
ARM 3	No H

H = trastuzumab

Study Contacts:
Martine J Piccart-Gebhart, Chair. Tel: 32-2-5413206
Breast International Group

Robert E Coleman, Chair. Tel: 114 226 5213
EORTC Breast Cancer Group

SOURCE: NCI Physician Data Query, December 2002

Clinical trials of trastuzumab combinations in the metastatic setting

Protocol IDs	Eligibility Criteria	Randomization Arms
CWRU-030118, GENENTECH-H2223G, ROCHE-1100, ROCHE-B016216C, ROCHE-BO16216	Postmenopausal, ER/PR+, HER2+ (IHC 3+ or FISH-positive) metastatic disease	Arm 1: Anastrozole qd + trastuzumab qw Arm 2: Anastrozole qd
BCIRG-007, GENENTECH-UCLA-0109024, NCI-G02-2116, ROCHE-UCLA-0109024, UCLA-0109024	Stage IIIB or IV, HER2-positive breast cancer	Arm 1: [(T+C) q3w + H qw] x 8, then H q3w Arm 2: (T q3w + H qw) x 8, then H q3w
EU-99028, SWS-SAKK-22/99	HER2-overexpressing metastatic breast cancer	Arm 1: H qw until DP, then [H qw + (paclitaxel qw x 3, followed by 1 w rest)] Arm 2: [H qw + (paclitaxel qw x 3, followed by 1 w rest)]
CLB-9840, CTSU	Inoperable, recurrent or metastatic breast cancer with measurable disease and known HER2 status	HER2 non-overexpressing Arm 1: paclitaxel q3w Arm 2: paclitaxel qw Arm 3: paclitaxel q3w + H qw Arm 4: paclitaxel qw + H qw HER2 overexpressing Arm 1: paclitaxel q3w + H qw Arm 2: paclitaxel qw + H qw
DFCI-01087, GSK-2001-P-000473/2	HER2+ metastatic breast cancer (IHC 3+ but FISH- are ineligible)	Arm 1: (H + vinorelbine) qw x 8 w Arm 2: H qw x 8 w + (paclitaxel qw x 8 w OR docetaxel on w 1, 2, 3, 5, 6 and 7)

H = trastuzumab; T = docetaxel; C = cisplatin or carboplatin; DP = disease progression

SOURCE: NCI Physician Data Query, December 2002

Dosing and scheduling of chemotherapy

The expression "where there's smoke, there's fire" applies to an issue we have been studying for decades — chemotherapy dose and schedule. We learned the hard way with high-dose chemotherapy and bone marrow transplantation, but I think there is room to test various parts of that hypothesis. Several interesting trials are exploring the question of dose-density versus dose-escalation or a bolus of single agents versus combination chemotherapy.

Metronomic chemotherapy was resuscitated in the process of developing angiogenesis inhibitors. A number of investigators found that fairly traditional chemotherapeutic agents have an antiangiogenic effect and substantial antitumor activity when given chronically in low doses as opposed to intermittently at high doses.

The experience with taxanes and fluoropyrimidines highlights the importance of scheduling. It is quite likely that the doses and schedules initially approved for both taxanes might not be optimal, and there may be other less accepted or unexplored schedules that might lead us to better administration of these drugs.

Capecitabine: A targeted chemotherapy

Capecitabine is a fascinating agent, which in addition to teaching us more about the fluoropyrimidines in general, brought out the targeted aspect of chemotherapy. Conceptually, capecitabine is a hybrid of a traditional cytotoxic agent and a targeted agent activated on site. This is an absolutely fascinating observation, not dissimilar to the aromatase inhibitors, which also utilize the mechanism of targeting an area rich in the enzyme relevant to the intervention. We have a lot more to explore in this area.

Enzymatic activation of capecitabine

"Capecitabine is not intrinsically cytotoxic, and requires conversion to 5-FU via a three-step enzymatic cascade . . . The final conversion step, which results in the generation of 5-FU, is mediated by thymidine phosphorylase (TP), an enzyme with significantly higher activity in tumor tissue than normal tissue . . . TP expression correlates with fast malignant growth, aggressive invasion potential, and poor patient prognosis. TP activation may, therefore, enable capecitabine to specifically target aggressive cells. In addition, the crucial role of TP in the activation of capecitabine provides a clear rationale for combining capecitabine with other antitumor agents that further upregulate TP in tumor tissue..."

EXCERPTED FROM : Seidman AD, *Aapro M. Oncologist* 2002;7(Suppl 6):1-3.

Neoadjuvant trial of capecitabine-docetaxel

As a group, we reached the consensus that for patients whom we are reasonably certain will receive chemotherapy, we prefer to administer all chemotherapy before surgery. In a recent neoadjuvant study, we found that 12 cycles of weekly paclitaxel were better than four cycles of three-weekly paclitaxel followed by four cycles of FAC.

Phase III randomized trial of weekly versus three-weekly neoadjuvant paclitaxel followed by FAC: Pathological complete response rates (pCR)

	Node-positive		Node-negative	
	Weekly (n=50)	Q 3 Week (n=51)	Weekly (n=68)	Q 3 Week (n=67)
pCR	14 (28%)	7 (14%)	20 (29%)	9 (13%)

SOURCE: Green MC et al. **Weekly (wkly) paclitaxel (P) followed by FAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC — Final results of a prospective phase III randomized trial.** *Proc ASCO* 2002; **Abstract 135.**

We recently activated a trial of neoadjuvant docetaxel and capecitabine. This trial will compare four cycles of the capecitabine-docetaxel regimen to 12 weekly cycles of paclitaxel, with both arms then receiving four cycles of FEC. We feel that we are building upon the best arm of a previous regimen while also exploring the interaction between capecitabine and docetaxel.

MD ANDERSON NEOADJUVANT TRIAL OF WEEKLY PACLITAXEL VERSUS CAPECITABINE-DOCETAXEL FOLLOWED BY FEC AND LOCAL THERAPY

Eligibility	Stage IIA-IIIA breast cancer
ARM 1	paclitaxel qw x 12 ➜ FEC x 4 ➜ local therapy (surgery or RT)
ARM 2	(capecitabine + docetaxel) x 4 ➜ FEC x 4 ➜ local therapy (surgery or RT)

Note: ER/PR-positive patients will receive endocrine therapy after completion of local therapy.

DERIVED FROM: Livingston R. **Current and planned trials with capecitabine in adjuvant/neoadjuvant therapy of breast cancer.** *Oncology* (suppl) 2002;16(10):29-32.

Neoadjuvant chemotherapy in women who may be node-negative

I am comfortable offering neoadjuvant chemotherapy to women who may be node-negative, because in the past 30 years we have learned that most things in breast cancer are not black and white, but rather gradations or trends. Nothing at this point tells me that node-negative breast cancer is different from node-positive breast cancer with one positive node. If it is appropriate to use a taxane in the adjuvant setting for a 2.5 cm breast cancer with a single positive node containing a 7 mm metastatic deposit, I don't see a major biological difference for that same primary without that metastatic deposit in a single node.

I probably would not use a taxane off-protocol in a patient with a 1.2 cm node-negative primary, but this too is an evolving area. The initial trials of taxanes were done in node-positive breast cancer, but we are in the process of testing them in node-negative disease. The question will be how to select those patients who should receive everything, those who shouldn't receive anything, and how to define the grades in between.

For the trials we are conducting now, we do fine needle aspiration of palpable nodes prior to preoperative chemotherapy, so that we know if there is a node containing malignant cells. But, if I have a patient with a well-defined 3 cm breast cancer, I'm going to give chemotherapy whether she has positive nodes or not. Her risk of recurrence is very similar to that of someone with node-positive breast cancer.

Chemotherapy in premenopausal women: Benefits of ovarian ablation

Ovarian ablation with chemotherapy is an area we have not explored adequately. It is certainly apparent that for premenopausal, estrogen receptor-positive patients, ovarian suppression is beneficial. The evolving LHRH analog data suggest that ovarian suppression or ablation need not be permanent. Even temporary suppression has a substantial therapeutic benefit, although we do not know the optimal duration of suppression.

If we accept that this is the case, it is important to develop cytotoxic regimens that do not cause permanent ovarian ablation. Since we backed off six cycles of cyclophosphamide to four cycles of FEC plus a similar duration of a taxane, our preliminary observation is that fewer patients undergo permanent cessation of menses. So, the incorporation of a taxane might have other circumstantial benefits in terms of fertility as well as the major therapeutic goal.

Evolution of breast cancer treatment

Those who don't know history are condemned to repeat it. For example, it is fascinating to see the evolution of the St Gallen consensus statements over time. At one point, we essentially said that node-negative patients should not receive adjuvant systemic therapy, but for the most recent one, we did not exclude anyone with invasive breast cancer. Our interventions haven't changed much during that time, but what has evolved is our understanding of the risks and benefits of treatment and what our patients are willing to accept and, in fact, request. All of this is in constant evolution, and what is absolutely true today may not be absolute tomorrow, and what is totally contraindicated today might become standard of care in just a few years.

Select Publications

Use of aromatase inhibitors in the adjuvant setting

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(9324):2131-9. **Abstract**

Pharmacokinetics of anastrozole and tamoxifen alone, and in combination, during adjuvant endocrine therapy for early breast cancer in postmenopausal women: A sub-protocol of the 'Arimidex and Tamoxifen Alone or in Combination' (ATAC) trial. *Br J Cancer* 2001;85(3):317-24. **Abstract**

Baum M. **The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal patients: Factors influencing the success of patient recruitment.** *Eur J Cancer* 2002;38(15):1984. **Abstract**

Baum M. **A vision for the future?** *Br J Cancer* 2001;85 Suppl 2:15-8. **Abstract**

Bianco AR. **ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial — Anastrozole is superior to tamoxifen as adjuvant treatment in postmenopausal women with early breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 632.**

Buzdar A. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer — Updated efficacy results based on a median follow-up of 47 months.** *Breast Cancer Res Treat* 2002; **Abstract 13.**

Buzdar AU. **New generation aromatase inhibitors — From the advanced to the adjuvant setting.** *Breast Cancer Res Treat* 2002;75 Suppl 1:S13-7; discussion S33-5. **Abstract**

Buzdar AU. **Anastrozole (Arimidex) — An aromatase inhibitor for the adjuvant setting?** *Br J Cancer* 2001;85 Suppl 2:6-10. **Abstract**

Goss PE. **Preliminary data from ongoing adjuvant aromatase inhibitor trials.** *Clin Cancer Res* 2001;7(12 Suppl):4397s-4401s; discussion 4411s-4412s. **Abstract**

Jones SE. **Antiaromatase agents: Evolving role in adjuvant therapy.** *Clin Breast Cancer* 2002;3(1):33-42. **Abstract**

Mokbel K. **The evolving role of aromatase inhibitors in breast cancer.** *Int J Clin Oncol* 2002;7(5):279-83. **Abstract**

Ragaz J. **Adjuvant trials of aromatase inhibitors: Determining the future landscape of adjuvant endocrine therapy.** *J Steroid Biochem Mol Biol* 2001;79(1-5):133-41. **Abstract**

Sainsbury R. **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.**

Wellington K, Faulds DM. **Anastrozole in early breast cancer**. *Drugs* 2002;62(17):2485-92. **Abstract**

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(15):3317-27. **Abstract**

Adjuvant chemotherapy for patients with node-negative breast cancer

Aapro MS. **Adjuvant therapy of primary breast cancer: A review of key findings from the 7th International Conference, St. Gallen, February 2001.** *Oncologist* 2001;6(4):376-85. **Abstract**

Abrams JS. **Adjuvant therapy for breast cancer — Results from the USA consensus conference.** *Breast Cancer* 2001;8(4):298-304. **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**

Buchholz TA et al. **Impact of systemic treatment on local control for patients with lymph node-negative breast cancer treated with breast-conservation therapy.** *J Clin Oncol* 2001;19(8):2240-6. **Abstract**

Fisher B et al. **Prognosis and treatment of patients with breast tumors of one centimeter or less and negative axillary lymph nodes.** *J Natl Cancer Inst* 2001;93(2):112-20. **Abstract**

Fisher B et al. **Findings from recent National Surgical Adjuvant Breast and Bowel Project adjuvant studies in stage I breast cancer.** *J Natl Cancer Inst Monogr* 2001;(30):62-6. **Abstract**

Fisher B et al. **Tamoxifen and chemotherapy for axillary node-negative, estrogen receptor-negative breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-23.** *J Clin Oncol* 2001;19(4):931-42. **Abstract**

Joly F et al. **Long-term quality of life in premenopausal women with node-negative localized breast cancer treated with or without adjuvant chemotherapy.** *Br J Cancer* 2000;83(5):577-82. **Abstract**

Jones SE et al. **Adjuvant chemotherapy with doxorubicin and cyclophosphamide in women with rapidly proliferating node-negative breast cancer.** *Clin Breast Cancer* 2002;3(2):147-52. **Abstract**

Morrow M, Krontiras H. **Who should not receive chemotherapy? Data from American databases and trials.** *J Natl Cancer Inst Monogr* 2001;(30):109-13. **Abstract**

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Edited comments by Dr Davidson

Dr Davidson's Case Presentation:

The patient is a 37-year-old premenopausal, nulliparous woman with a 2.1 cm ER-positive, HER2-positive (IHC 3+) infiltrating ductal carcinoma. She had 3 positive axillary lymph nodes. The patient underwent a modified radical mastectomy with TRAM reconstruction. She received AC ➜ docetaxel chemotherapy followed by tamoxifen and postmastectomy radiation therapy. This case was presented to a group of physicians at a Breast Cancer Update case-based panel meeting at the 3rd annual Lynn Sage Breast Cancer symposium on November 1, 2002. Below are the electronic keypad audience responses to management questions about this case.

Would you recommend regional radiation therapy?

Yes	41%
No	59%

Which adjuvant chemotherapy would you recommend?

AC-paclitaxel	29%	AC-docetaxel	24%
TAC x 6	16%	Other	31%

Scenario 1: The patient receives chemotherapy and is still menstruating after therapy. Which endocrine therapy would you recommend?

Tamoxifen	37%
Tamoxifen + LHRH agonist	34%
Anastrozole*	11%
Anastrozole + LHRH agonist	8%
Other	10%

Scenario 2: The patient receives chemotherapy and stops menstruating after therapy. Which endocrine therapy would you recommend?

Tamoxifen	90%
Anastrozole	10%

Scenario 3: The patient receives chemotherapy and stops menstruating after therapy. She had a car accident 2 years ago, and was later treated for a deep venous thrombosis. Which endocrine therapy would you reccomend?

Tamoxifen	38%
Anastrozole	30%
Other	18%
None	14%

**As per package insert, anastrozole should not be used in an actively menstruating woman.*

Postmastectomy radiation therapy in women with one to three positive nodes

I usually have my node-positive, post-mastectomy patients evaluated by a radiation oncologist to discuss the pros and cons of radiation. If they have four or more nodes, I recommend radiation pretty highly, and if they're node-negative I'm pretty much against it. In my experience, younger women with greater numbers of positive lymph nodes are more likely to opt for radiation.

Radiation therapy decisions are also often influenced by the type of reconstruction that a woman has had. Women with implant reconstruction are sometimes not quite as enthusiastic about radiation because of the potential deleterious cosmetic effects.

Nonprotocol use of AC-docetaxel

We participate in the NSABP B-30 trial, which involves AC followed by docetaxel as its standard arm. In a nontrial setting, I would frequently think about using the standard arm. For example, if I was discussing NSABP B-30 with a patient, when we come back to a discussion of standard therapy outside of the trial, we would talk about the standard arm of this trial.

I would tell her about our uncertainty with regard to the taxanes. Sometimes in a nonprotocol setting, we go in with the notion that the patient is going to take the AC, we'll see how it is going and then she'll come back and tell me how she feels about taking the taxane. I have not been a big fan of six cycles of TAC or FEC, but I know that many physicians are.

PHASE III RANDOMIZED STUDY OF ADJUVANT DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY DOCETAXEL VERSUS DOXORUBICIN AND DOCETAXEL VERSUS DOXORUBICIN, DOCETAXEL, AND CYCLOPHOSPHAMIDE IN WOMEN WITH BREAST CANCER AND POSITIVE AXILLARY LYMPH NODES

Open Protocol

Protocol ID: CTSU, NSABP B-30
Projected Accrual: 4,000 eligible patients

Eligibility	Node-positive primary breast cancer

ARM 1	AC x 4 → T x 4
ARM 2	AT x 4
ARM 3	ACT x 4

A = doxorubicin, C = cyclophosphamide, T = docetaxel

Patients in all arms who are ER-positive and/or PR-positive receive tamoxifen daily for 5 years. Patients ≥ age 50 may also receive tamoxifen at the discretion of their physician if they are ER-negative, PR-negative, or ER/PR unknown. Patients are followed every 6 months for 5 years and then annually thereafter.

Study Contact:
Sandra M Swain, Chair Ph: 301-451-6882
National Surgical Adjuvant Breast and Bowel Project

SOURCE: NCI Physician Data Query, December 2002

Docetaxel versus paclitaxel in the adjuvant setting

Some physicians are more interested in docetaxel than paclitaxel for several reasons. One is the enthusiasm about the preoperative docetaxel results from NSABP B-27. The second reason is that some people have looked at the BCIRG trial of TAC versus FAC as an endorsement of docetaxel.

I think that we're doing an awful lot of early reporting. The TAC results are interesting, but I want to see more follow-up. I actually thought TAC would make a lot of headway in the community, but — at least where I live — it doesn't seem to have made a big impact.

I'm most impressed that people are taking the subset analysis from that trial very seriously. I've had people call me, reluctant to use TAC in a patient with six positive lymph nodes, because in that trial the advantage was only seen in the women with one to three positive nodes. I'm impressed with how evidence-based many of the physicians that I have spoken to are in making therapeutic decisions.

ADJUVANT TAC VERSUS FAC
Disease-free survival (DFS) and overall survival for 1,491 patients after a median follow-up of 33 months (TAC: n=745; FAC: n=746)

ARM 1	TAC (docetaxel, doxorubicin, cyclophosphamide 75/50/500 mg/m^2) q3w x 6
ARM 2	FAC (5-fluorouracil, doxorubicin, cyclophosphamide 500/50/500 mg/m^2) q3w x 6

	Risk Ratio TAC/FAC	Absolute Reduction %	P Value
DFS	0.68	8%	0.0011
by nodal status			
1-3	0.50	11%	0.0002
4+	0.86	2%	0.33
by receptor status			
HR-	0.62	—	0.005
HR+	0.68	—	0.02
Overall Survival	0.76	5%	0.11
by nodal status			
1-3	0.46	7%	0.006
4+	1.08	2%	0.75

HR+ = ER- and/or PR-positive tumors

SOURCE : 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.** *ASCO* 2002; **Slide Presentation.**

Non-anthracycline containing regimens

We all feel reasonably confident that anthracycline-containing regimens are probably slightly better than non-anthracycline-containing regimens; however, I am still a fan of CMF in patients who have cardiotoxicity issues. If you look at the differences — for example a CAF versus CMF trial that we did through the Intergroup — the absolute difference in benefit was actually very small. Some patients may not find that worthwhile when considering the tradeoff in terms of the cardiotoxicity concerns.

Effect of HER2 and nodal status on choice of chemotherapy

I have not routinely used HER2 status to make chemotherapy decisions. I do tell patients that there is some belief that HER2 positivity might drive one to think harder about an anthracycline-containing regimen. This finding, however, isn't true across all studies, and we know from our adjuvant trastuzumab trials that we're not very good at measuring HER2 status.

There has been as much as a 25-30 percent discordance rate between local and central laboratory testing. This makes me very nervous about putting a lot of emphasis on a study if I'm not completely confident about the quality of the data.

If a patient had 15 positive nodes, I would probably think even harder about any regimen that involves six months of therapy and not so hard about four cycles of AC. I would also be thinking very hard about her endocrine therapy. With regard to adjuvant trastuzumab, I am a purist on this issue and a big believer in the randomized trials — I have not given any adjuvant trastuzumab outside the context of a clinical trial.

Ovarian suppression in ER-positive, premenopausal women

Many younger women are still menstruating after the completion of chemotherapy. Several years ago, I would only have discussed tamoxifen, but presently I do actually discuss the uncertainty about ovarian suppression strategies. I usually recommend tamoxifen, and if a patient feels strongly, sometimes she'll also undergo ovarian suppression.

In higher-risk women, I would consider it more strongly. Based on a very small retrospective subset analysis, women with 10 or more positive lymph nodes were the ones who seemed to get a fair amount of benefit from the combined endocrine therapy. The caveat here is that even in our seemingly large trial that, that group is only 100 women — a very small subset to base a lot on.

Impact of HER2 status on choice of endocrine therapy

There is a belief that perhaps aromatase inhibitors are more effective than tamoxifen in ER-positive, postmenopausal women whose tumors overexpress HER2. This is based, in part, on Matt Ellis' preoperative study. There is really no equivalent data in premenopausal women.

Richard Love did a trial in Vietnam of premenopausal women where the standard of care was no adjuvant therapy, and the experimental arm was oophorectomy and tamoxifen. He found that there was no impact of HER2 status on response to endocrine therapy. Combined endocrine therapy was effective regardless of HER2 status. I don't think HER2 status should have any influence on the approach to adjuvant endocrine therapy.

If a premenopausal woman stops menstruating after the completion of chemotherapy, I would be oriented towards tamoxifen, but I would have a discussion about tamoxifen versus anastrozole. Many of my very sophisticated patients would want to talk about the impact of HER2 status in that setting, and I've had a couple who decided to go on anastrozole because of their belief that tamoxifen may not be as good in that subset of ER-positive, HER2-positive women.

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

Marker Status	Letrozole		Tamoxifen		P Value
	No. of Responders/Total	%	No. of Responders/Total	%	
ErbB-1/2 positive	15/17	88	4/19	21	.0004
ErbB-1/2 negative	55/101	54	42/100	42	.0780

DERIVED FROM: 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**

Endocrine therapy in a woman with history of a deep vein thrombosis

In a postmenopausal woman who has had a deep vein thrombosis in the past several years, I would move to an aromatase inhibitor without thinking very hard about it. If she had stopped menstruating after chemotherapy, I would probably consider her postmenopausal.

It's a little tougher in premenopausal women, and I would think more about an ovarian suppression strategy as my only strategy. Ovarian ablation or suppression as an alternative to tamoxifen in premenopausal patients was endorsed by the 2000 NIH consensus conference.

Intergroup Trial 0101

The design of this trial was CAF chemotherapy versus CAF chemotherapy followed by five years of goserelin versus CAF chemotherapy followed by five years of goserelin and tamoxifen. There is no impact on disease-free survival in the overall population with the addition of goserelin, but there is a trend to suggest that the younger patients may benefit.

Although it seemed like such a large clinical trial at the time it was initiated, 1,500 women doesn't have the power to reveal a significant difference even in those younger women and even with all this follow-up.

We don't have any new data over the last year on this question. We have a lot of re-examination of old data. My synopsis is that in ER-positive, premenopausal women, tamoxifen is a good drug. Ovarian suppression or ablation is also beneficial, but we are having a difficult time figuring out how to integrate them.

PHASE III RANDOMIZED COMPARISON OF ADJUVANT THERAPIES IN PREMENOPAUSAL WOMEN WITH RESECTED NODE-POSITIVE HORMONE RECEPTOR-POSITIVE ADENOCARCINOMA OF THE BREAST

Closed Protocol

Protocol IDs: INT-0101, CLB-9192, EST-5188, SWOG-8851
Projected Accrual: 1,500 eligible patients

Eligibility	Premenopausal, node-positive, hormone receptor-positive patients within 12 weeks of surgery, who received no prior endocrine or chemotherapy

ARM 1	Surgery ➜ CAF
ARM 2	Surgery ➜ CAF ➜ Z x 5 years
ARM 3	Surgery ➜ CAF ➜ ZT x 5 years

CAF = cyclophosphamide, doxorubicin, fluorouracil; Z = goserelin; T = tamoxifen

Patients who have had less than a total masectomy receive radiotherapy on Regimen A beginning either prior to initiation of chemotherapy or within 4 weeks after completion of chemotherapy.

SOURCE: NCI Physician Data Query, December 2002

INT-0101 trial results: 7.4 years follow-up

	DFS	Survival	DFS (Patients under age 40)
CAF	58%	77%	49%
CAF ➜ goserelin	64%	78%	59%
CAF ➜ goserelin, tamoxifen	73%	80%	69%

DERIVED FROM: Presentation, NE Davidson, San Antonio Breast Cancer Symposium, 2001.

The one new trial that I've seen over the last year is the Austrian trial published in the last couple of months comparing CMF chemotherapy to ovarian suppression with tamoxifen in premenopausal estrogen receptor-positive women. They suggested that the outcome was slightly better with the combined endocrine therapy.

The difficulty with that trial is that the women who took chemotherapy didn't take tamoxifen because it was not the standard of care when the trial was launched. Today we think of that as a pretty profound deficit with that study and related studies. So we need to come together to investigate this further. There is a trio of trials that we are trying to launch worldwide to look at issues of ovarian suppression in young women.

Combining LHRH agonists and aromatase inhibitors in premenopausal women

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

Assessment of menopausal status in ER-positive patients and choice of endocrine therapy

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

I approach premenopausal women with metastatic disease who become clinically menopausal after receiving chemotherapy as postmenopausal. I have been using first-line aromatase inhibitors in these women for several reasons. First, I'm impressed by the trial data comparing them to tamoxifen as first-line therapy. Second, many of those women have already been exposed to or are on tamoxifen at the time of their relapse.

I start with either letrozole or anastrozole, and I can't tell you why sometimes I choose one over the other. I generally do not use exemestane as my first choice. If the person has a good response to their first aromatase inhibitor, I am hoping to capitalize on the work from Per Lonning suggesting that women who have been exposed to the nonsteroidal aromatase inhibitors can have a 20 percent clinical benefit with exemestane.

SOFT: Ovarian ablation with tamoxifen or an aromatase inhibitor

The adjuvant ovarian suppression trial that I am most enthusiastic about is SOFT — Suppression of Ovarian Function Trial. Premenopausal, ER-positive

women who may or may not have received chemotherapy will be randomized to tamoxifen for five years, ovarian suppression / ablation plus tamoxifen, or ovarian suppression / ablation plus an aromatase inhibitor. This very interesting trial will help us address several issues. Does ovarian ablation or suppression add to tamoxifen? And if this is an important strategy, is it better to use tamoxifen or an aromatase inhibitor in those suppressed women?

This trial is an international collaboration, put together by the International Breast Cancer Study Group (IBCSG). The US cooperative groups have signed on to it, and it is winding its way through the approval process in the United States right now. I think it will be launched within the next year.

IBCSG SOFT TRIAL: SUPPRESSION OF OVARIAN FUNCTION TRIAL

Eligibility	Premenopausal, ER+ or PR+ women
ARM 1	Tamoxifen
ARM 2	Ovarian suppression + tamoxifen
ARM 3	Ovarian suppression + exemestane

SOURCE: Winer EP et al. **ASCO Technology Assessment: Aromatase inhibitors as adjuvant therapy for women with hormone receptor positive breast cancer.** *J Clin Oncol* 2002;20:3317-3327. Appendix 1. Selected adjuvant breast cancer trials with third-generation aromatase inhibitors

Other trials of aromatase inhibitors with ovarian suppression

There are two other studies of aromatase inhibitors with ovarian suppression. One is built on the premise — which is pretty popular in Europe — that since we know ovarian suppression is important, some investigators would be unenthusiastic about a trial that didn't involve ovarian suppression. For those investigators, the trial would be ovarian suppression with tamoxifen or ovarian suppression with an aromatase inhibitor.

The other trial asks the question, "If you do ovarian suppression with either tamoxifen or an aromatase inhibitor, do you really need chemotherapy?" This trial randomizes to chemotherapy or not, plus endocrine therapy.

I believe that will be a tough concept to sell in the United States, but it may have some enthusiasts abroad. I personally think randomized trials that involve two very different treatments, chemotherapy or not, will be a little more difficult to conceptualize.

These trials were put together by the International Breast Cancer Study Group. They have been looked at by the US cooperative groups, and different groups will decide whether or not to endorse each trial. Subgroups may decide that they are not as enthusiastic about one design or another, and that they want to put all their effort into one. My personal preference is the SOFT trial, because I think it addresses the issues of interest to many US investigators.

IBCSG TEXT TRIAL: TAMOXIFEN AND EXEMESTANE TRIAL

Eligibility	Premenopausal, ER+ or PR+ women
ARM 1	Ovarian suppression + exemestane
ARM 2	Ovarian suppression + tamoxifen

SOURCE: Winer EP et al. **ASCO Technology Assessment: Aromatase inhibitors as adjuvant therapy for women with hormone receptor positive breast cancer.** *J Clin Oncol* 2002;20:3317-3327. Appendix 1. Selected adjuvant breast cancer trials with third-generation aromatase inhibitors

Counseling postmenopausal women on adjuvant endocrine therapy: Tamoxifen versus aromatase inhibitors

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

Many patients know a lot about tamoxifen. They know that it has a long track record, and they're pretty comfortable with that. However, it's always stunning to me as an oncologist how much bad press tamoxifen has received, for practically the least toxic drug I can prescribe. It amazes me how many people will go through six months of chemotherapy without batting an eyelash, yet come in very concerned about the long-term consequences of tamoxifen.

The majority of my patients are going on tamoxifen right now, but I think the sands are shifting. At the beginning, everybody sort of sat tight, but since the FDA approval, I've seen more women who are open to anastrozole by the time they come to see me. When I do use an aromatase inhibitor in the adjuvant setting, I only use anastrozole. I'm a purist on that. The one trial we have adjuvant data from utilized anastrozole, so I want to do it exactly as we did in that trial.

Use of bisphosophonates in the adjuvant setting

There is a trial in Austria randomizing premenopausal, ER-positive patients to various endocrine therapies with a second randomization to different schedules of zoledronate. Their long-term goal is not only impact on bone density, but also on breast cancer recurrence, based on all these conflicting results with clodronate.

In my practice, I usually watch bone mineral densities, and if they get down to a range I'm unhappy with, I use one of the oral bisphosphonates. I still use a lot of adjuvant tamoxifen, and for premenopausal women that is a pretty good bone drug. They may not need anything in addition until they come off of tamoxifen. I haven't used a lot of adjuvant aromatase inhibitors, but I think this is where it might turn out to be an issue in the future.

Approach to chemotherapy in younger versus older women with metastatic disease

My philosophy in treating older versus younger women with chemotherapy is basically the same, but sometimes the patient choices are different. Many times in metastatic disease, we use all of the available therapies, so what we're really deciding on is the order — what to start with. Many patients make that decision based on their personal values. I find many of my older patients are attracted to capecitabine because it is an oral agent. Some of my younger patients think of intravenous therapy as more aggressive, and they prefer that strategy. But, this perception is people's gut reaction rather than being reality-based.

Capecitabine in the metastatic setting

I am a big fan of capecitabine. Maybe it comes from being a "hormonal-therapy person" preferring pills to begin with, because I use it a lot for salvage chemotherapy in women who've already had an anthracycline and taxane for metastatic disease. In oncology, we tend to remember our successes, but I have seen several very impressive responses with capecitabine in pretty dire circumstances. I have had women on it for a considerable period of time with relatively good quality of life. My personal best was somebody who was on capecitabine for several years.

Combination versus sequential therapy in the metastatic setting

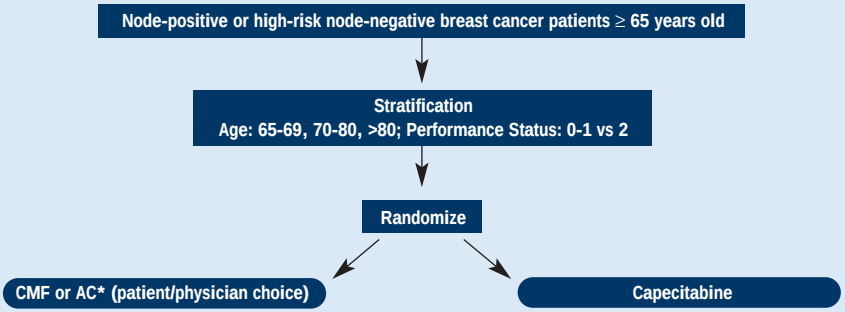
ECOG-1193 trial compared doxorubicin followed by paclitaxel at disease progression versus paclitaxel followed by doxorubicin at disease progression versus the combination. There is no question that the response rate was higher with the combination, but at the end of the day, survival was identical in the three arms. This says to me that how you package those drugs is probably not as important as long as people are exposed to both of them in the metastatic setting.

I am philosophically more inclined toward sequential single-agent therapy in metastatic breast cancer. However, I'm fascinated by the capecitabine / docetaxel trial. Most of the women on that trial who took docetaxel alone did not get exposure to capecitabine, and I suspect that if there had been a crossover arm, the survival would not have been much different. Having said that, I am an enthusiast about the adjuvant and neoadjuvant trials looking at the combination of capecitabine / docetaxel.

Adjuvant capecitabine trial in elderly women

I would probably be willing to put women of any age on this trial, but I think the trial focuses on elderly patients for two reasons. One is that the elderly are a research focus of Hyman Muss, the principal investigator of the trial. The other is that he thought oral therapy, which is a little less intrusive, might be more in keeping with the lifestyle issues faced by the elderly patient.

CALGB 49907: A randomized trial of adjuvant chemotherapy with standard regimens (CMF or AC) versus capecitabine in women 65 years and older with node-positive or high-risk node-negative breast cancer



*** Patients whose LVEF is not within lower limits of normal must receive CMF, not AC.**
All ER+ or PR+ patients receive tamoxifen x 5 years.

SOURCE: CALGB 49907 Protocol.

We haven't had a lot of single-agent adjuvant therapy for quite some time, so that always gives people pause. We are revisiting whether some of our newer single agents — when given optimally — might be every bit as good as some of our combination therapies.

In the Intergroup, we are about to launch a trial in node-negative patients that is a two-by-two design involving either four or six cycles of AC versus 12 or 18 weeks of paclitaxel. The question is whether or not you can preserve the benefits of adjuvant chemotherapy with a better toxicity profile, particularly the concern about longer-term cardiotoxicity.

People were impressed by the preclinical and early clinical information, which suggested that weekly taxanes may be better than an every three-week schedule. I am interested to see whether 18 weeks of paclitaxel is the kind of therapy that you can just breeze through. It may not be quite as simple as we think.

Select Publications

Adjuvant endocrine therapy in premenopausal patients

Aebi S et al. **Is chemotherapy alone adequate for young women with oestrogen-receptor-positive breast cancer?** *Lancet* 2000;355(9218):1869-74. **Abstract**

Baum M et al. **Management of premenopausal women with early breast cancer: Is there a role for goserelin?** *Proc ASCO* 2001; **Abstract 103.**

Boccardo F et al. **Cyclophosphamide, methotrexate, and fluorouracil versus tamoxifen plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: Results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial.** *J Clin Oncol* 2000;18:2718-27. **Abstract**

Celio L et al. **Premenopausal breast cancer patients treated with a gonadotropin-releasing hormone analog alone or in combination with an aromatase inhibitor: A comparative endocrine study.** *Anticancer Res* 1999;19:2261-8. **Abstract**

Cheung KL et al. **The combined use of goserelin and anastrozole as second line endocrine therapy in premenopausal women with advanced breast cancer - A study of its clinical and endocrine effects.** *Proc ASCO* 2001; **Abstract 1937.**

Colleoni M et al. **Early start of adjuvant chemotherapy may improve treatment outcome for premenopausal breast cancer patients with tumors not expressing estrogen receptors. The International Breast Cancer Study Group.** *J Clin Oncol* 2000;18(3):584-90. **Abstract**

Davidson N et al. **Effect of chemohormonal therapy in pre-menopausal, node (+), receptor (+) breast cancer: An Eastern Cooperative Oncology Group phase III Intergroup trial (E5188, INT-0101).** *Proc ASCO* 1999; **Abstract 249A, 67A.**

Dowsett M et al. **Vorozole results in greater estrogen suppression than formestane in postmenopausal women and when added to goserelin in premenopausal women with advanced breast cancer.** *Breast Cancer Res Treat* 1999;56:25-34. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Ovarian ablation for early breast cancer.** *Cochrane Database Syst Rev* 2000;CD000485. **Abstract**

Early Breast Cancer Trialists' Collaborative Group. **Ovarian ablation in early breast cancer: Overview of the randomised trials.** *Lancet* 1996;348:1189-96. **Abstract**

Ejlertsen B et al. **Comparable effect of ovarian ablation (OA) and CMF chemotherapy in premenopausal hormone receptor positive breast cancer patients (PRP).** *Proc ASCO* 1999.

Forward D et al. **Combined use of goserelin (Zoladex) and anastrozole (Arimidex) in premenopausal women with metastatic breast cancer (MBC).** *Proc ASCO* 2000; **Abstract 582.**

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.**

Goldhirsch A et al. **Adjuvant therapy for very young women with breast cancer: Need for tailored treatments.** *J Natl Cancer Inst Monogr* 2001;(30):44-51. **Abstract 582.**

Goss PE, Strasser K. **Aromatase inhibitors in the treatment and prevention of breast cancer.** *J Clin Oncol* 2001;19:881-94. **Abstract**

Hoffken K, Kath R. **The role of LH-RH analogues in the adjuvant and palliative treatment of breast cancer.** *Recent Results Cancer Res* 2000;153:61-70. **Abstract**

Houghton J et al. **The ZIPP trial of adjuvant Zoladex in premenopausal patients with early breast cancer: An update at five years.** *Proc ASCO* 2000; **Abstract 359.**

Jakesz R. **Comparison of adjuvant therapy with tamoxifen and goserelin vs. CMF in premenopausal stage I and II hormone-responsive breast cancer patients: Four-year results of Austrian Breast Cancer Study Group (ABCSG) Trial 5.** *Proc ASCO* 1999; **Abstract 250.**

Jakesz R et al. **Chemotherapy versus hormonal adjuvant treatment in premenopausal patients with breast cancer.** *Eur J Cancer* 2002;38(3):327-32. **Abstract**

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):4628-35. **Abstract.**

Jonat W et al. **Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: The Zoladex Early Breast Cancer Research Association Study.** *J Clin Oncol* 2002;20(24):4621-7. **Abstract.**

Kaufmann M et al. **Updated survival results from the Zebra trial.** *Breast Cancer Res Treat* 2002; **Abstract 254.**

Klijn JG et al. **Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: A meta-analysis of four randomized trials.** *J Clin Oncol* 2001;19:343-53. **Abstract**

Love RR et al. **Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer.** *J Clin Oncol* 2002;20(10):2559-66. **Abstract**

Michaud LB, Buzdar AU. **Complete estrogen blockade for the treatment of metastatic and early stage breast cancer.** *Drugs Aging* 2000;16:261-71. **Abstract**

Michaud LB et al. **Combination endocrine therapy in the management of breast cancer.** *Oncologist* 2001;6(6):538-46. **Abstract**

Milla-Santos A et al. **A randomized trial of goserelin (Zoladex™) + tamoxifen versus goserelin + anastrozole (Arimidex™)) in pre/perimenopausal patients with hormone dependent advanced breast cancer.** *Breast Cancer Res Treat* 2002; **Abstract 289.**

Muss HB. **Factors used to select adjuvant therapy of breast cancer in the United States: an overview of age, race, and socioeconomic status.** *J Natl Cancer Inst Monogr* 2001;(30):52-5. **Abstract 289.**

Parulekar W et al. **Incidence and prognostic impact of amenorrhea during adjuvant therapy in high risk premenopausal breast cancer patients: Analysis of a National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) phase III study.** *Proc ASCO* 2001; **Abstract 97.**

Recchia F et al. **Goserelin as ovarian protection in the adjuvant treatment of premenopausal breast cancer: A phase II pilot study.** *Anticancer Drugs* 2002;13(4):417-24. **Abstract.**

Sayer HG et al. **Bone mineral density in premenopausal patients in a randomized trial of adjuvant endocrine therapy (ZIPP-TRIAL).** *Proc ASCO* 2001; **Abstract 96.**

Sverrisdottir A et al. **Premenopausal breast cancer: Chemotherapy and endocrine therapy.** *Drugs* 2002;62(14):2025-38. **Abstract.**

Post-test

Questions *(please circle answer)*:

1. The three-year results of CALGB 9741 show dose-dense therapy to be superior to conventional scheduling in which of the following parameters?

A. Improved disease-free survival
B. Improved overall survival
C. Reduced incidence of grade 4 neutropenia
D. All of the above

2. CALGB clinical trial experience has shown the dose of doxorubicin is capped in efficacy at which of the following levels?

A. 60 mg/m^2
B. 75 mg/m^2
C. 90 mg/m^2
D. 175 mg/m^2

3. Gompertzian growth is exponential growth with a constant exponential regression.

A. True
B. False

4. Which of the following statements is true about the 47-month updated results of the ATAC trial?

A. The disease-free survival continues to be greater with anastrozole than with tamoxifen.
B. The time to recurrence continues to be greater with anastrozole than with tamoxifen.
C. The reduction in contralateral breast cancers continues to be greater with anastrozole than with tamoxifen.
D. All of the above
E. None of the above

5. Dr Hortobagyi believes that oncologists should present all of the information to patients but not make treatment recommendations or bias patients with their opinions.

A. True
B. False

6. In the phase III study comparing trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu-positive, advanced breast cancer, the addition of carboplatin did not improve response rates or time to progression.

A. True
B. False

7. A preoperative study by Matt Ellis demonstrated that letrozole was more effective than tamoxifen in HER2-positive, ER-positive, postmenopausal women.

A. True
B. False

Questions *(please circle answer)*:

8. Which of the following is not a randomization arm of the SOFT trial?

A. Tamoxifen
B. Aromatase inhibitor
C. Ovarian suppression + tamoxifen
D. Ovarian suppression + aromatase inhibitor

9. Which of the following agents should not be used in actively menstruating women?

A. Tamoxifen
B. Anastrozole
C. Goserelin acetate
D. Trastuzumab
E. None of the above

10. Which of the following is not being evaluated in the adjuvant setting?

A. Trastuzumab
B. Capecitabine
C. Aromatase inhibitors and ovarian suppression
D. All of the above are being evaluated in the adjuvant setting

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: Postgraduate Institute for Medicine, P. O. Box 260620, Littleton, CO 80163-0620, FAX (303) 790-4876.

Evaluation Form

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Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

Postgraduate Institute for Medicine (PIM) respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. Please note, a certificate of completion is issued only upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:
5 = *Outstanding* 4 = *Good* 3 = *Satisfactory* 2 = *Fair* 1 = *Poor*

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

- Describe the rationale for and results of clinical research on dose-dense chemotherapy. 5 4 3 2 1
- Counsel and make recommendations to postmenopausal patients regarding the use of adjuvant aromatase inhibitors. 5 4 3 2 1
- Discuss the ongoing/planned clinical trials of capecitabine in the adjuvant and neoadjuvant settings. 5 4 3 2 1
- Describe the clinical implications of research on combinations of chemotherapy with trastuzumab in women with HER2-positive metastatic disease. 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.

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

Degree:

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

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This program was supported by educational grants from AstraZeneca Pharmaceuticals, LP; Genentech, Inc.; Roche Laboratories, Inc.; and Amgen, Inc.

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