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HOW TO USE THIS MONOGRAPH

This is a CME activity that contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form on pages 38-40 or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program and the website, **BreastCancerUpdate.com**, where you will find an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**.

Breast Cancer Update: A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well-informed of these advances. To bridge the gap between research and patient care, *Breast Cancer Update* uses one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists in the formulation of up-to-date clinical management strategies.

GLOBAL LEARNING OBJECTIVES

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

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

Issue 5, 2003, of *Breast Cancer Update* consists of discussions with four research leaders on a variety of important topics including chemotherapy and hormonal therapy in combination with trastuzumab in the metastatic setting, management of HER2-negative patients with metastatic disease, dose-dense scheduling of adjuvant therapy, use of adjuvant aromatase inhibitors, overcoming resistance to endocrine therapy and ongoing clinical trials in breast cancer.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 5

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

- Evaluate novel data regarding dose-dense scheduling of chemotherapy and the use of aromatase inhibitors for adjuvant therapy.
- Learn potential strategies to overcome acquired resistance to endocrine therapy.
- Develop awareness of the efficacy and tolerability data from clinical trials of trastuzumab in combination with platinum agents/chemotherapy and ongoing clinical trials with trastuzumab in order to counsel appropriately selected patients.
- Consider a spectrum of perspectives in the management strategies for patients with ER-negative, HER2-negative, metastatic breast cancer.

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Mark D Pegram, MD	**Consultant:** Aventis Pharmaceuticals Inc, Genentech Inc, ChromaVision Medical Systems, Inc
Paul E Goss, MD, PhD, FRCP(CA), FRCP(UK)	**Grants/Research Support/Speakers' Bureau:** Novartis Pharmaceuticals Corporation, Schering Plough Corporation, Pharmacia Corporation, Pfizer Inc, Biomedicine
Kathleen I Pritchard, MD	**Grants/Research Support/Speakers' Bureau/Consultant:** AstraZeneca Pharmaceuticals LP, Pharmacia Corporation
Generosa Grana, MD	**Speakers' Bureau:** AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals Inc

Pharmaceutical agents discussed in this program

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

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Editor's Note

The "Kaplan Regimen"

Our Continuing Medical Education (CME) group focuses on emerging clinical research data and the perspectives of clinical investigators. We also know that the viewpoints of community-based physicians are another valuable resource for our work. To that end, we gather data about decision-making by community-based physicians via national telephone surveys and editorial working group meetings.

A recent *Breast Cancer Update* working group meeting in New York was very informative. As part of that platform, the 35 participating medical oncologists submitted four cases from their practices that we evaluated beforehand, and in some cases, discussed with the working group. Dr Barry Kaplan, an oncologist from Queens, submitted a particularly provocative case. This premenopausal woman, in her late 30s, presented with primary breast cancer and multiple bone metastases. The patient's tumor was ER/PR-positive and HER2-positive, and the patient — who was very well-versed about her prognosis and usual therapeutic options — pressed Dr Kaplan for the most intense treatment regimen that would be rational.

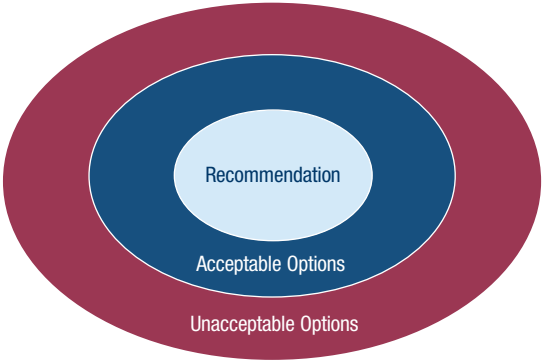
After reviewing a variety of options, Dr Kaplan, with strong support and agreement from the patient, utilized a combination of docetaxel, capecitabine, an LHRH agonist, anastrozole, trastuzumab, and a bisphosphonate. Our two faculty members for this part of the meeting — Drs Hy Muss and Eric Winer — seemed to blanch at the concluding Powerpoint comment from Dr Kaplan's case write-up: "I think this was a good choice for this woman; do you?" I asked the group, knowing there would be a variety of responses.

Dr Kaplan, a regular listener of our series, is well-aware that most research leaders — including Drs Muss and Winer — espouse a sequential, single-agent approach to the treatment of metastatic breast cancer. Certainly, this "shotgun" approach of chemotherapy, endocrine treatment and biologic therapy was very atypical in Dr Kaplan's practice. While one might argue that there is no evidence to support this approach, it is also clear that a randomized, postprogression, crossover trial of the "Kaplan Regimen" would encounter significant accrual challenges if eligibility were restricted to young, premenopausal women with ER/PR-positive, HER2-positive breast cancer.

This case sparked a lively, although not totally conclusive, discussion. While it was clear that most attendees would not have utilized the "Kaplan Regimen," I found a new appreciation for the depth and complexity of evidence-based oncology. In that regard, our CME group developed a new simplified graphical model for clinical decision-making (Figure 1). For any given situation, treatments in the "blue" area represent accepted standards of care based on credible clinical research results. In metastatic breast cancer, there are the multiple treatment options in this category,

and the light "blue" area depicts the therapy an individual oncologist might recommend. The treatments in the "red" area are critical from a CME perspective in that these types of options are not supported by research evidence, although they might move into the "blue" area as clinical trial data evolve.

Figure 1
Treatment Options



The lead interview in this issue of *Breast Cancer Update* provides a perfect example of how this model can be applied. Dr Mark Pegram comments on adjuvant systemic therapy options for the patient with ER-negative, HER2-positive breast cancer. Dr Pegram describes his enthusiasm for the ongoing BCIRG-006 adjuvant trastuzumab trial, but he clearly believes that the nonprotocol use of adjuvant trastuzumab should be in the "red" area (Figure 1).

On the other hand, as first-line therapy for patients with ER-negative, HER2-positive metastatic disease, Dr Pegram believes that trastuzumab either alone or in combination with chemotherapy are the two main options in the "blue" area, and he disagrees with the small number of physicians utilizing chemotherapy without trastuzumab.

While one can argue that palliative situations like metastatic breast cancer must be managed with empathetic creativity, there are many effective therapies that can minimize morbidity and prolong survival. Do you believe the "Kaplan Regimen" has merit in a nonprotocol setting? Have you ever utilized such a strategy? Or is it a choice that belongs in the "red zone"? Kindly email your input on these and any other challenging questions in your practice to NLove@med.miami.edu.

—Neil Love, MD

Mark D Pegram, MD

Associate Professor of Medicine
David Geffen School of Medicine at UCLA

Director, Women's Cancer Program
UCLA/Jonsson Comprehensive Cancer Center

Edited comments by Dr Pegram

Early Phase I experience with trastuzumab/cisplatin in metastatic disease

One important case we have followed is a patient in her mid-50s, who was diagnosed with metastatic breast cancer about 10 years ago. She had multiple pulmonary nodules and a supraclavicular lymph node, which was biopsied and confirmed that she had distant metastases. At the time, HER2 testing was in its infancy, and there were no commercially available tests. An IHC assay was run in Dennis Slamon's laboratory, and the tumor was scored as IHC 3+.

Consequently, the patient was offered participation in one of the early Phase I trastuzumab clinical trials, evaluating a combination of chemotherapy plus trastuzumab. The combination she received was trastuzumab/cisplatin. After receiving a few cycles of cisplatin and maybe 18 or 20 weeks of trastuzumab, she had a complete clinical remission. Back in those days, Phase I trials came to an end, and she went off study.

That was more than 10 years ago. She is alive and well and in complete remission to this day. We all have miraculous patients like this who do particularly well. Is this just an interesting anecdote or is this patient trying to tell us something about the biology of breast cancer? In particular, the interaction between the platinums and trastuzumab is something we have been studying in our laboratory at UCLA for quite some time. We would like to think that the synergy between these two agents explains this patient's particularly good outcome.

Phase III randomized trial of trastuzumab/paclitaxel with or without carboplatin

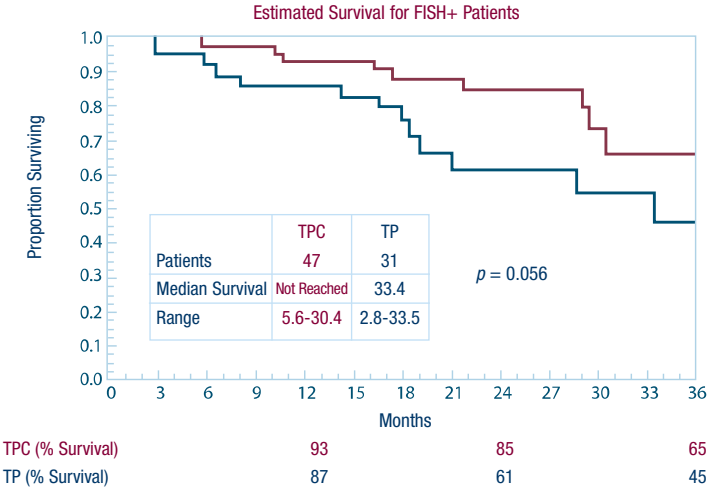
The *in vitro* synergy between the platinums and trastuzumab has recently been put to the test. At the San Antonio Breast Cancer Symposium, Dr Nicholas Robert presented the results from a study that randomized patients with HER2-

positive metastatic disease to receive trastuzumab/paclitaxel or trastuzumab/paclitaxel/carboplatin.

The results were remarkable. In the patients who received carboplatin in addition to trastuzumab/paclitaxel, the response rates and the time to progression were significantly improved.

Since FISH status was analyzed retrospectively and not all of the patients have had their tumors tested by FISH, preliminary data revealed a trend in the FISH-positive patients towards prolonged survival with the addition of carboplatin to trastuzumab/paclitaxel. This is very provocative data suggesting that addition of carboplatin might improve the survival of patients with HER2-positive metastatic breast cancer.

Phase III Comparative Study of Trastuzumab and Paclitaxel with and without Carboplatin in Patients with HER2/Neu-Positive Advanced Breast Cancer



TPC = trastuzumab/paclitaxel/carboplatin

TP = trastuzumab/paclitaxel

SOURCE: Nicholas Robert, Presentation, 2002 San Antonio Breast Cancer Symposium

Trastuzumab/platinum/taxane regimens

At UCLA, we have an ongoing confirmatory trial comparing trastuzumab/docetaxel to trastuzumab/docetaxel/carboplatin. The trial is based on data we generated at UCLA showing that the synergy between trastuzumab and docetaxel appears to be better than the synergy between trastuzumab and paclitaxel. Therefore, patients at UCLA are encouraged to consider enrolling in that clinical trial.

Phase III Randomized Study of Docetaxel and Trastuzumab (Herceptin) with or without Carboplatin in Women with HER2-Positive Stage IIIb or IV Breast Cancer **Open Protocol**

Protocol IDs: UCLA-0109024, BCIRG-007, ROCHE-UCLA-0109024, GENENTECH-UCLA-0109024, NCI-G02-2116
Projected Accrual: 444 patients (222 per treatment arm)

Eligibility: 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

T = docetaxel; C = carboplatin; H = trastuzumab

Study Contacts:

Linnea Chap, MD, Protocol Chair, Tel: 310-829-5471, Jonsson Comprehensive Cancer Center, UCLA	Dennis J Slamon, MD, PhD, Tel: 310-825-5193, Jonsson Comprehensive Cancer Center, UCLA	Jean Marc Nabholtz, MD, Tel: 310-825-5687, Jonsson Comprehensive Cancer Center, UCLA	John Crown, MD, Tel: 011-353-1-269-5033, St. Vincent's University Hospital

SOURCE: NCI Physician Data Query, June 2003.

If, however, patients decline participation or don't meet the strict eligibility criteria but might still benefit, we have in some instances treated them off protocol with a triple-drug regimen. We have had encouraging results even off protocol, and our colleagues in the community are also seeing good success off protocol.

There is also a neoadjuvant trial evaluating a trastuzumab/platinum/taxane regimen. At the last couple of ASCO meetings, Judith Hurley has reported preliminary data showing particularly high pathologic complete response rates in patients treated with neoadjuvant trastuzumab/docetaxel/cisplatin.

Even off protocol, I think this regimen is a consideration. As oncologists, we are very comfortable using taxane/platinum combinations. We're very comfortable with the types of side effects encountered, particularly cytopenias. We saw significant cytopenias with these trastuzumab/platinum/taxane regimens, more so than with just trastuzumab/taxane, but they were certainly manageable. In Robert's study, the incidence of febrile neutropenia was four percent in one of the arms and five percent in the other arm, but there were no statistically significant differences.

First-line therapy for patients with HER2-positive metastatic disease

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

BCIRG-006 adjuvant trastuzumab trial

BCIRG-006 is a multinational, randomized, controlled trial for patients with FISH-positive, early stage breast cancer — either node-positive or high-risk, node-negative disease. Patients are randomized to one of three different treatment arms: AC followed by docetaxel, AC followed by docetaxel/trastuzumab with trastuzumab continued for a total of one year, and trastuzumab/docetaxel with either carboplatin or cisplatin.

For the first time in a large randomized adjuvant study, a nonanthracycline-containing synergistic combination will be put to the test in a very carefully selected patient population. All of the patients must have FISH-positive disease, therefore, I think the trial will define the standard of care for the adjuvant treatment of patients with HER2-positive breast cancer.

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
UCLA/Jonsson Comprehensive Cancer Center

SOURCE: NCI Physician Data Query, June 2003.

BCIRG-006 is accruing well ahead of schedule. In fact, more than 1,500 of the anticipated 3,150 patients have been accrued to the trial so far. It will likely be the first adjuvant trastuzumab trial to complete accrual. It is anticipated that the accrual will be closed at the end of 2003 or early first quarter 2004.

The other important component of this trial is safety. There is a data safety monitoring committee and a specific cardiac safety monitoring committee. They are monitoring all of the treatment arms in real time, and they have predefined trigger points that call for an interruption in the protocol if there are any flags for cardiotoxicity in the AC followed by trastuzumab/docetaxel arm.

In fact, the study was designed in such a way that the arm can drop out. If we encounter cardiotoxicity problems, we would still have a two-arm study — one arm with conventional chemotherapy and the other arm with trastuzumab/platinum/taxane.

It doesn't appear that cardiac safety is going to be a big issue in the adjuvant trastuzumab trials. Although there was a scare some months ago with the Intergroup trial and one arm was closed temporarily, that arm has reopened and the most recent update, presented by Dr Edith Perez, reveals that the incidence of depressed ejection fractions is the same in all of the arms of the Intergroup trial.

Adjuvant trastuzumab in the nonprotocol setting

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

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

Influence of trastuzumab therapy on tumor HER2 status

We don't really know what happens to a patient's HER2 status after they have been treated with trastuzumab. In the metastatic setting, some case series of pre- and post-treatment biopsies have been reported with conflicting results. Because most of the trastuzumab trials have been conducted in patients with metastatic disease, in whom it is difficult to obtain biopsies, there is no good database of pre- and post-treatment tumor tissues.

When HER2 gene amplification occurs, it appears to be a very stable event. Several studies have shown good concordance between the HER2 status in the primary tumor and the metastases. Given that level of concordance and the presumed genetic stability for HER2 amplification, I would be very surprised if trastuzumab could change HER2 gene amplification.

I suspect that if one rebiopsied a patient with residual tumor after trastuzumab therapy, one would find the HER2 gene still amplified. I would expect that the tumor's genotype would probably not be changed whether the cancer was responding or resistant to trastuzumab. It's just mind-boggling that we haven't done that yet. We need to do a better job of obtaining tissue for laboratory analysis.

Trials combining trastuzumab with hormonal therapy

In preclinical models, we observed greater efficacy for tamoxifen plus trastuzumab and fulvestrant plus trastuzumab compared to each drug alone. The more we can do to constrain potential mechanisms of escape for the cancer cell, the better. If HER2 is a potential mechanism of escape from hormone sensitivity, then targeting both at the same time could work.

A number of ongoing trials are evaluating these combinations, and based on our preclinical data at UCLA, we think they might work. However, due to the inverse correlation between HER2 and ER, accrual to these studies has been difficult.

Clinical Trials Combining Trastuzumab Plus Hormonal Therapy for Patients with ER/PR-positive, HER2-positive, Metastatic and/or Locally Advanced Breast Cancer

Chair	Trial setting	Menopausal status	Projected accrual	Treatment arms
J Mortimer	Phase III	pre/post	280	trastuzumab + tamoxifen trastuzumab
B Langer	Phase II/III	post	202	trastuzumab+ anastrozole anastrozole
R O'Regan	Phase II	post	18-60	trastuzumab + exemestane

SOURCE: NCI Physician Data Query, June 2003

Fulvestrant in clinical practice

I've been pleased with fulvestrant and have not found the need to deviate from the package insert recommendations. In my experience, patient tolerance has been excellent with very few complaints about side effects. We're using fulvestrant in patients who have already had prior hormonal therapies, so perhaps they don't mention side effects because they are already used to the hormone withdrawal side effects.

I've certainly not had the occasion to stop fulvestrant in any patient because of toxicity. Compliance is very good, and the injection really isn't an issue. These are highly motivated patients with a devastating disease, so they do not object to receiving an injection. I am using two 2.5 cc injections.

Potential synergy between fulvestrant and trastuzumab

HER2 does two different things to the estrogen receptor (ER). First, it decreases ER expression so there's less ER in a patient with HER2-positive disease. Even if the tumor is ER-positive, it is less positive than a tumor from a patient with HER2-negative disease. Second, through cross talk between the signal transduction pathways for HER2 and ER, there is phosphorylation of the ER that may alter the biology of the receptor and result in an activated species.

For that reason, it would be nice to eliminate the ER in a HER2-driven tumor. Fulvestrant, given its mechanism of action, provides a particularly attractive way to deal with the ER in a patient with HER2-positive disease. It's an ideal model that works in preclinical xenograph models.

Trials combining trastuzumab with biologic agents

Erlotinib

We are especially interested in moving forward with biologic combinations. In fact, we have a couple of open trials at UCLA evaluating combinations of

biologics. Dr Carolyn Britten is conducting a Phase I/II clinical trial with trastuzumab in combination with erlotinib, a small molecule inhibitor of the epidermal growth factor receptor (EGFR/HER1).

In this instance, we're studying whether inhibiting HER1 and HER2 simultaneously might be better than just HER2 blockade alone. This may potentially allow fewer avenues of escape for the cancer cells. We hope this will be another improvement in the treatment of HER2, positive disease.

Bevacizumab

Based on measurements from our laboratory showing a strong correlation between HER2 and expression of the vascular endothelial growth factor (VEGF), a Phase I trial just opened at UCLA. A very strong concordance between HER2 and VEGF in primary breast cancer has been confirmed by other groups. Linderholm et al presented data at ASCO demonstrating the same thing in a very large data set. We've just completed a study involving about 612 patients with primary breast cancers showing this type of correlation.

Part of the pathophysiology behind HER2-driven disease may be regulation of the angiogenic switch. If we could address both of those problems, maybe we would see improved therapeutic efficacy. We've applied this theory in animal models using a combination of trastuzumab and the humanized anti-VEGF antibody, bevacizumab. In those studies, the combination had better results against murine tumor xenographs.

Based on these pilot data, we have a new Phase I trial that will be escalating the bevacizumab dose and using the standard FDA-approved dose of trastuzumab. When we complete the Phase I trial, it is designed to roll over into a formal Phase II trial to accrue more safety and efficacy data.

Treatment options for patients with ER-negative, HER2-negative, metastatic disease

This is a difficult subject, because it involves the controversy over combination chemotherapy and monotherapy. For the first time, the FDA has approved a combination chemotherapy regimen for metastatic disease, the docetaxel/capecitabine combination.

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

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

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

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

Transition from hormonal therapy to chemotherapy

The transition from hormonal therapy to chemotherapy in metastatic disease maybe a little bit easier with capecitabine than with other agents. In patients with low-volume disease and no life-threatening metastases, capecitabine is an attractive option. We have used it in elderly patients in whom pulling out the "big gun" intravenous drugs is a bit more problematic.

On the other hand, in patients who have marked progression, rising liver function tests and symptomatic pulmonary metastases, combination chemotherapy — like capecitabine/docetaxel — becomes more of a consideration.

Phase III trial comparing capecitabine with or without bevacizumab

It's interesting how the trial was viewed. It was touted as being a negative study, which it was, since it failed to meet its primary endpoint. However, when looking at a dataset, it's very important to see if there are any positive signals.

The response rate for the capecitabine/bevacizumab arm was significantly higher than for the capecitabine-alone arm. There must be some explanation for that, because there was a blinded response evaluation committee. One potential explanation is that the bevacizumab had a beneficial effect.

We might have missed a significant improvement in time to progression by virtue of the fact that these were heavily pretreated patients. Historically, there aren't many drugs that have been shown to improve time to progression after anthracycline and taxane failure. This is a really difficult patient population.

ECOG-E-2100: Phase III trial comparing paclitaxel with or without bevacizumab

ECOG is conducting a large randomized trial comparing paclitaxel with or without bevacizumab as first-line therapy for patients with metastatic disease. I believe that there's still hope for bevacizumab in metastatic breast cancer. Until I see the frontline trial, I'm not going to walk away from the concept of targeting VEGF with bevacizumab.

Our data demonstrates a correlation between HER2 and VEGF. The patients with the highest probability of responding to VEGF-directed therapy are the HER2-positive patients. A limitation of the ECOG trial is that patients with very high levels of VEGF might not be accrued to that trial.

Phase III Randomized Study of Paclitaxel with or without Bevacizumab in Patients with Locally Recurrent or Metastatic Breast Cancer Open Protocol

Protocol IDs: E-2100, CTSU

Projected Accrual: 316 - 650 patients

Eligibility: Locally recurrent disease not amenable to resection with curative intent or metastatic disease

ARM 1: Paclitaxel qw x 3 + bevacizumab q2w

ARM 2: Paclitaxel qw x 3

Treatment repeats in both arms every 4 wks for 18 courses in the absence of disease progression or unacceptable toxicity.

Study Contacts:

Kathy Miller, MD, Protocol Chair, Tel: 317-274-0920, Eastern Cooperative Oncology Group

Edith A Perez, MD, Protocol Chair, Tel: 507-284-2111, North Central Cancer Treatment Group

Tamara Shenkier, MD, Protocol Chair, Tel: 604-877-6000, NCIC-Clinical Trials Group

Melody A Cobleigh, MD, Protocol Chair, Tel: 312-942-3240, National Surgical Adjuvant Breast and Bowel Project

SOURCE: NCI Physician Data Query, June 2003.

Use of adjuvant dose-dense chemotherapy schedules

The new CALGB-9741 dataset are very provocative. The results must be explained, and they cannot be dismissed. Clearly, there was a statistically significant benefit for dose-dense chemotherapy compared to an every-three-week schedule. Based on this interim analysis, the cooperative groups have decided to move to a dose-dense approach in their future and, in some cases, ongoing studies.

I would like to see confirmation in other clinical trials, and confirmatory trials are in progress, so we will have that data in the future. Off protocol, should we be taking this approach into consideration for the treatment of our patients? It is an attractive option for a patient with a high risk of recurrence (i.e., Stage II disease).

I have used the dose-dense approach in some patients, and I have tweaked the regimens a bit in some cases. For example, I have given four cycles of the anthracycline-containing combination with growth factor support and then used weekly taxanes without growth factor support in patients in whom growth factor use was an issue or in an elderly patient whom I didn't want to have as much risk of neutropenia. Weekly taxanes are still a dose-dense regimen. In some instances, I've used the every-two-week schedule all the way through.

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 **Closed Protocol**

Protocol IDs: CLB-9741, E-C9741, NCCTG-C9741, SWOG-C9741

ARM 1: A q 3 wk x 4 → T q 3 wk x 4 → C q 3 wk x 4
ARM 2: A q 2 wk x 4 → T q 2 wk x 4 → C q 2 wk x 4*
ARM 3: AC q 3 wk x 4 → T q 3 wk x 4
ARM 4: AC q 2 wk x 4 → T q 2 wk x 4*

*Filgrastim (G-CSF) is administered on days 3-10 after each dose of doxorubicin, paclitaxel and cyclophosphamide.

A = doxorubicin; T = paclitaxel; C = cyclophosphamide

Parameters	Dose-dense Scheduling	Conventional Scheduling	*p* Value
Disease-free survival	85%	81%	RR = 0.74 ($p = 0.010$)
Overall survival	92%	90%	RR = 0.69 ($p = 0.013$)

SOURCE: Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003; 21(8):1431-9. **Abstract**

Publications discussed by Dr Pegram

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. **Abstract**

Hurley J et al. **Neoadjuvant herceptin/taxotere/cisplatin in the treatment of locally advanced and inflammatory breast cancer.** *Proc Am Soc Clin Oncol* 2002:**Abstract 196**.

Konecny G et al. **Quantitative association between HER-2/neu and steroid hormone receptors in hormone receptor-positive primary breast cancer.** *J Natl Cancer Inst* 2003;95(2):142-53.

Miller KD et al. **Phase III trial of capecitabine (Xeloda®) plus bevacizumab (Avastin™) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane.** *Breast Cancer Res Treat* 2002;76 (Suppl 1); **Abstract 36**.

Pegram MD et al. **Trastuzumab and chemotherapeutics: Drug interactions and synergies.** *Semin Oncol* 2000;27(6 Suppl 11):21-5; discussion 92-100. **Abstract**

Pegram MD et al. **Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment.** *J Clin Oncol* 1998;16(8):2659-71. **Abstract**

Pegram MD and Slamon DJ. **Combination therapy with trastuzumab (Herceptin) and cisplatin for chemoresistant metastatic breast cancer: Evidence for receptor-enhanced chemosensitivity.** *Semin Oncol* 1999;26(4 Suppl 12):89-95. **Abstract**

Robert N et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer.** *Breast Cancer Res Treat* 2002; 76 (Suppl 1); **Abstract 35**.

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *New England Journal of Medicine* 2001; 344:783-92. **Abstract**

Platinum compounds in breast cancer

Ligibel JA and Winer EP. **Trastuzumab/chemotherapy combinations in metastatic breast cancer.** *Semin Oncol* 2002;29(3 Suppl 11):38-43. **Abstract**

Martin M. **Platinum compounds in the treatment of advanced breast cancer.** *Clin Breast Cancer* 2001;2(3):190-208; discussion 209. **Abstract**

Nabholtz JM et al. **HER2-positive breast cancer: Update on Breast Cancer International Research Group trials.** *Clin Breast Cancer* 2002;3 (Suppl 2):75-9. **Abstract**

Nabholtz JM et al. **Docetaxel in the treatment of breast cancer: An update on recent studies.** *Semin Oncol* 2002;29(3 Suppl 12):28-34. **Abstract**

Spigel DR and Burstein HJ. **HER2 overexpressing metastatic breast cancer.** *Curr Treat Options Onco.* 2002;3(2):163-74. **Abstract**

Bevacizumab

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Burstein HJ et al. **Phase II trial of the anti-VEGF antibody bevacizumab in combination with vinorelbine for refractory advanced breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 446**.

Gray R et al. **The safety of adding angiogenesis inhibition into treatment for colorectal, breast, and lung cancer: The Eastern Cooperative Oncology Group's (ECOG) experience with bevacizumab (anti-VEGF).** *Proc ASCO* 2003;**Abstract 825**.

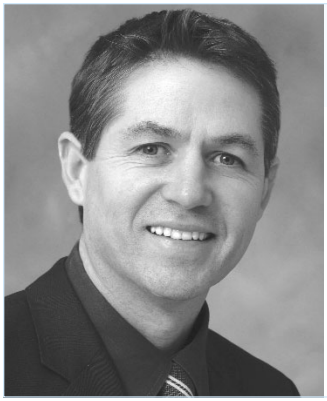
Hillan KJ et al. **The role of VEGF expression in response to bevacizumab plus capecitabine in metastatic breast cancer (MBC).** *Proc ASCO* 2003;**Abstract 766**.

Ferrara N. **Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: Therapeutic implications.** *Semin Oncol* 2002;29(6 Suppl 16):10-4. **Abstract**

Jain RK. **Tumor angiogenesis and accessibility: role of vascular endothelial growth factor.** *Semin Oncol* 2002;29(6 Suppl 16):3-9. **Abstract**

Miller KD et al. **Phase III trial of capecitabine (Xeloda®) plus bevacizumab (Avastin™) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane.** *Breast Cancer Res Treat* 2002;**Abstract 36**.

Rosen LS. **Clinical experience with angiogenesis signaling inhibitors: Focus on vascular endothelial growth factor (VEGF) blockers.** *Cancer Control* 2002;9(2 Suppl):36-44. **Abstract**



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Edited comments by Dr Goss

Development of resistance to endocrine therapy

There are two types of resistance to endocrine therapy in invasive breast cancer — *de novo* resistance and acquired resistance. We're only beginning to understand *de novo* resistance. Kent Osborne and his colleagues presented their ongoing research on HER2 overexpression, showing that through HER2, the mitogen activated protein (MAP) kinase pathways increase, and through MAP kinase, a number of receptors are phosphorylated.

Growth stimulation occurs through MAP kinase independently, but, in addition, MAP kinase seems to alter the estrogen receptor, making it more sensitive to both circulating estrogen and to the agonistic effects of tamoxifen. In a neoadjuvant study, Matt Ellis and his colleagues showed that patients who have HER2-positive, estrogen receptor-positive tumors are *de novo* resistant to tamoxifen but are sensitive to aromatase inhibitors. It's probably partly through the MAP kinase pathway.

Data from SWOG Study of ErbB-2 Amplification, ErbB-1 Expression and Tamoxifen Response in ER-positive Metastatic Breast Cancer

	ErbB-2 unamplified	ErbB-2 amplified	ErbB-1 negative	ErbB-1 positive
Response (CR+PR+SD)	56%	47%	58%	36%
Time to treatment failure	7 months	5 months	8	4
Median survival overall	31 months	25 months	31	24

CR = complete response; PR = partial response; SD = stable disease > 6 months

SOURCE: Arpino G et al. **ErbB-2 amplification, ErbB-1 expression and tamoxifen response in ER-positive metastatic breast cancer: A SWOG study.** *Breast Cancer Res Treat* 2002:**Abstract 232.**

Development of aromatase overexpression

Endocrine resistance may occur in a number of ways. One is through estrogen receptor mutation at the breast cancer cell level and another is through the sensitivity of the cell to the estrogen content in and around the tumor cell. If one thinks about estrogen arriving at the breast cancer cell, there's collaboration between the epithelial cell and the peritumoral stromal cells. Aromatase is functional in the peritumoral and the tumor cells, and it recruits the help of adjacent cells to create an autocrine loop of estrogen production. That loop has been shown to happen by estrogen deprivation and specifically through aromatase inhibitor therapies.

In cell culture you can evoke aromatase overexpression by long-term estrogen deprivation (LTED). The LTED cells will try to overcome the inhibition and upregulate aromatase. The same thing is true if you use aromatase inhibition *in vivo* in animal models. Tumor cells can also make substances that create alternative promoters of the aromatase gene. The aromatase gene is supposed to use specific promoters in the breast, and under influence of these substances, the ovarian promoter, for example, can be de-silenced, and the gene starts to function as it does in the ovary and drive aromatase production.

A phenomenon of aromatase overexpression in the face of aromatase inhibition and estrogen deprivation potentially occurs in the tumor and peritumoral cells. Couple that with a MAP kinase pathway being overexpressed, and you have increased sensitivity of the receptor resulting in exquisite sensitivity to estrogen and to the agonistic effects of any of the SERMs.

Optimal duration of adjuvant aromatase therapy

We've learned that prolonged therapy with tamoxifen may lead to a form of tamoxifen-acquired resistance, but we don't yet know if this occurs with aromatase inhibitors. We also don't know the correct duration of therapy with aromatase inhibitors. One clue might be the number of patients who relapse during therapy; another might be seeing what happens to patients at the cessation of adjuvant aromatase inhibitor therapy. That's an unknown entity at this point, and we don't yet have data from ATAC or any other aromatase trial to tell us what's going to happen.

For years, investigators have talked about designing trials in which one switches back and forth between anti- and pro-estrogenic therapies to see if one could confound the cell. It has been shown that physiologic levels of estrogen can destroy tamoxifen-sensitive cells. Theoretically, the same thing could happen with aromatase inhibitors. If you supersensitize cells to estrogen and then increase the concentration of estrogen, it might be cytocidal, or cytostatic. Therefore, re-introducing estrogen therapy after aromatase inhibitors might work — and it might be effective at lower doses than previously used.

Utilization of agents to reverse resistance to aromatase inhibitors

It's possible that prolonged aromatase inhibitor therapy alone will control most tumors, or we might find a point at which we need to introduce a resistance reverser. With *de novo* resistance, we might need to couple the inhibitor with a reverser from the beginning. Gefitinib (Iressa®) is an obvious reverser — it blocks the EGF receptor tyrosine kinase and it appears to reverse the acquired estrogen deprivation resistance that occurs — so an obvious combination would be an aromatase inhibitor with gefitinib. Whether they would be given in sequence or together from the beginning will have to be studied in clinical trials.

Currently there are no adjuvant trials evaluating that combination, but there are metastatic trials with gefitinib plus an aromatase inhibitor. There are also trials being designed in which patients failing on an aromatase inhibitor are either switched to gefitinib or continued on the aromatase inhibitor plus gefitinib.

Phase II Trials of Gefitinib (Iressa®) Plus an Aromatase Inhibitor (AI) in Patients with Estrogen Receptor-positive, Metastatic Breast Cancer

Study	Entry	Intervention	Target accrual	Status
E-4101	Recurrent/metastatic disease, no prior AI therapy	Anastrozole + gefitinib Fulvestrant + gefitinib	148	Approved, not yet active
CTRC-IDD-0219	Locally advanced or metastatic disease, progression after > 2 months AI therapy	Anastrozole → anastrozole + gefitinib	36-78	Active

SOURCE: NCI Physician Data Query, May 2003.

Intrabreast estrogen levels and the development of breast cancer

Aromatase activity probably occurs within the breast. For reasons that are unclear to me, in postmenopausal women the breast increases its estrogen production. It might just be because the estrogen levels fall; however, there is almost parity in intrabreast estrogen concentrations in pre- and postmenopausal women, which is extraordinary when you think of the reduction in plasma estrogen levels in postmenopausal women.

I believe women at risk for breast cancer have over-estrogenized breasts. It might be because there's receptor quirkiness or some coactivator milieu — I don't know why, and I'm not saying it's the only mechanism of breast cancer development, but I truly believe that breast cancer is usually caused by over-estrogenecity of the breast. I think it's like a subtle and slow poison that builds year after year.

There is marked ratio of intrabreast to peripheral levels of estrogen. It has been suggested that a very low dose of an aromatase inhibitor may shut off the intrabreast aromatase production sufficiently to tone down the estrogen level. Even a slight reduction in estrogen could translate into a profound reduction of

risk. We may not need to obliterate estrogen; rather we may just need to tone it down more specifically in the breasts.

Modulating the aromatase gene to reduce estrogen production in the breast

The HER2, COX-2 and aromatase are on a hierarchical pathway, and they actually drive each other. In my opinion, you could shut the pathway down at any one of those levels.

The COX-2 pathway is of specific interest to us. It's induced by the presence of ductal carcinoma *in situ* and by invasive cancer. COX-2, through prostaglandin E-2 and modulated through cyclic AMP, upregulates the aromatase gene and causes estrogen production. In the preinvasive lesion, one thing that could be exploited is that as the cells start progressing to DCIS, the COX-2 pathway starts to increase breast production of estrogen. This could be toned down with COX-2 inhibition. I think celecoxib alone could be an intrabreast cancer drug, and indeed the epidemiologic data supports that.

In the hormone-dependent rat model, celecoxib acts against estrogen receptor-positive breast cancer. In cultured cells, it acts against estrogen receptor-negative breast cancer cells, causing a dose-dependent reduction in proliferation. In the rat mammary model, it has synergy with exemestane. Celecoxib has the potential to help exemestane knock out ER-positive lesions and to impact ER-negative lesions independently by blocking the COX-2 pathway.

A Phase III chemoprevention trial of exemestane and celecoxib

The NCIC of Canada will launch a worldwide prevention trial comparing placebo versus exemestane versus exemestane plus celecoxib. One rationale is that we think there is a higher proportion of hormone-dependent lesions in the preinvasive disease setting than in the invasive disease setting, so we believe antihormone therapy will have its greatest impact in prevention.

There were several reasons for incorporating a placebo arm, including that it's easier to show true efficacy and toxicity of a compound against a placebo and that the sample size of the study is much smaller. In addition, the meta-analysis of tamoxifen, particularly in elderly women, suggests no net health benefit. Dr Jack Cuzick has applied those data to the ASCO Technology Assessment, and the expert panel recommended a placebo for future breast cancer prevention trials.

Side effects of aromatase inhibitors: Implications for prevention

Considerably fewer vasomotor symptoms and problems with weight gain are associated with aromatase inhibitors than with tamoxifen. While these are anecdotal observations, I have seen these differences in my own practice so often that I'm fairly certain they will prove to be true.

Perfectly healthy women considering prevention have a different level of motivation and tolerance of side effects than breast cancer patients who have been thrust into menopause by chemotherapy. The aromatase inhibitors are very well-tolerated and very safe, and I think healthy women with even the slightest motivation to reduce their breast cancer risk will find them acceptable.

Impact of the ATAC data on clinical practice

I was taken aback by the ASCO Technology Assessment. I agree with their points, but I think the onus on the regulators wasn't to see if anastrozole was better than tamoxifen, but only to see if it was worse. It's almost inconceivable that it could turn out to be worse.

Now, with 13 more months of follow-up, I believe the data is going to change people's viewpoints. My personal take on the ATAC presentation in 2001 was that we should switch from tamoxifen to anastrozole for adjuvant therapy. The curves were convincing, and the trend is likely to increase with time.

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

Hormonal therapy after failure on adjuvant anastrozole

Selection of a hormonal therapy after a patient relapses on anastrozole is a problem. Tamoxifen or fulvestrant could be highly effective, but if the MAP kinase pathway is overdriven from the aromatase inhibition, tamoxifen might act more as an agonist, and fulvestrant might be a better choice. To my knowledge, in terms of ATAC or other patients who have relapsed on an adjuvant aromatase inhibitor, there haven't been any data presented yet addressing this issue.

Benefits of bisphosphonate therapy

The impact of adjuvant aromatase inhibitors on bone will be offset by bisphosphonate therapy. Hopefully, in the case of exemestane, it won't even be an issue. Bisphosphonates cause osteoclast apoptosis and inhibit osteoclast activity, so they should be able to counteract the estrogen depletion effects of aromatase inhibitors. Estrogen deprivation increases bone re-absorption, whereas bisphosphonates decrease it. Some data suggest bisphosphonates have an antimetastatic effect, so they may be more than just a salvage therapy for the aromatase inhibitors; they may also be an anticancer therapy.

Phase III Trials of Adjuvant Clodronate (1600 mg PO qd) for Early Stage Breast Cancer

Author	Reduction in skeletal mets	Reduction in nonskeletal mets	Survival in clodronate arm
Diel et al	Yes	Yes	Increased
Powles et al	Yes during Rx only	No	Increased
Saarto et al	No	No	Decreased

DERIVED FROM:

Diel I et al. **Reduction in new metastases in breast cancer with adjuvant clodronate treatment.** *N Engl J Medical* 1998;339(6): 357-363. **Abstract**

Powles TJ et al. **A randomized placebo controlled trial to evaluate the effect of the bisphosphonate, Clodronate, on the incidence of metastases and mortality in patients with primary operable breast cancer.** *Breast Cancer Research Treat* 2001; **Abstract 1**

Saarto T et al. **Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial.** *J Clin Oncol* 2001;19 (1): 10-17. **Abstract**

Effect of estrogen levels on women's health

I am very interested in how closely a woman's health is related to a small range of estrogen. The slope of the postmenopausal estrogen range is a very small curve and is tightly related to breast cancer risk, osteoporosis and probably cardiovascular risk.

My personal feeling is that healthy postmenopausal women without breast cancer need their estrogen level "customized." We can tone it up with HRT, but now we have a subtle way of toning it down. We have tried the two extremes — blockbuster ablation or massive replacement — but we haven't tried zoning in on a middle range. I'm 100 percent convinced that in the next 10 to 15 years we will develop an understanding of women's estrogen levels and their impact on health.

Select publications

Publications discussed by Dr Goss

Arpino G et al. **ErbB-2 amplification, ErbB-1 expression and tamoxifen response in ER-positive metastatic breast cancer; A SWOG study.** *Breast Cancer Res Treat* 2002:**Abstract 232.**

Dirix LY et al. **Open-label, multi-center, controlled study of exemestane (E-Aromasin®) with or without celecoxib (Cx - Celebrex®) in postmenopausal women with advanced breast cancer (ABC) progressed on tamoxifen (T).** *Breast Cancer Res Treat* 2002:**Abstract 269.**

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**

Shou J et al. **Blockade of the estrogen receptor/growth factor cross-talk implicated in breast cancer tamoxifen resistance using a selective EGFR TK inhibitor.** *Breast Cancer Res Treat* 2002:**Abstract 246.**

Siris E et al. **Effects of raloxifene on fracture severity in postmenopausal women with osteoporosis: Results from the MORE study.** *Osteoporos Int* 2002:13;907-13. **Abstract**

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Edited comments by Dr Pritchard

ATAC trial data update: 47-month follow-up

It shouldn't have come as a surprise that anastrozole was better than tamoxifen in the adjuvant setting, given what we know from metastatic disease. This year's updated results are important — it's reassuring to see the efficacy of anastrozole holding up with little change in the toxicity profile. I expect we'll have survival data in a year or so, and if that is significant, I think practice patterns will change quickly.

The unanswered questions that trouble me about anastrozole are: Why are we giving it for five years? Is it because giving tamoxifen for five years seemed to be best? Is three years better? Is seven years better? These questions don't suggest anastrozole is an unacceptable alternative. We just seem to know less about it and its long-term side effects.

I use anastrozole in the adjuvant setting primarily for patients who can't or won't take tamoxifen, such as patients with a history of thrombophlebitis. Physicians in Canada use anastrozole as an alternative, rather than the standard, but patients are well-informed, and they ask about it. When I discuss the possible complications of tamoxifen, I tell my patients about anastrozole.

CALGB-9741: Dose-dense adjuvant chemotherapy

The data from CALGB-9741 is interesting. This trial had a two-by-two design, and one could argue whether you should look at the four individual blocks separately, or whether you can just interpret it as a two-by-two trial. The investigators' interpretation is that the dose-dense approach is better than a standard approach.

We use doxorubicin/cyclophosphamide/paclitaxel as a standard regimen in clinical trials and in practice, so we'd be interested in knowing whether that combination is significantly better given in a dose-dense fashion. I don't know if this study is powered to show that. The other question is whether the

sequential therapy, given in a dose-dense fashion, is as good as any of the other three cells. If it is, that regimen may be the least toxic and that would be interesting to know.

Some people believe that these particular regimens should now be given in a dose-dense fashion. Some even believe that every regimen should be given in a dose-dense manner, and I think that's wrong. It's very intriguing that there may be a better approach, but it's too early for me to change my practice. I'd like to see more data on the individual cells. Some data from other investigators support dose density, but other results do not, so it's not clear to me whether we have enough data to support this approach.

Canadian study of neoadjuvant CEF versus dose-intensified EC

We are about to publish the results of a study comparing dose-intensive EC to CEF in locally advanced breast cancer in the *Journal of Clinical Oncology*. This was a large study of about 440 patients that we conducted with the EORTC and the Swiss group. We found that the dose-intensive EC was virtually the same as CEF. Patients in the dose-intensive EC arm were given G-CSF, and we saw less febrile neutropenia in that group but higher rates of thrombocytopenia and anemia, so it is a bit of a trade-off.

This isn't a real dose-dense study because the drugs in the two arms aren't the same. It's more of a dose-intensive regimen because we gave the epirubicin and cyclophosphamide in half the time in the EC arm, and it was not superior. The curves separated somewhat, but there was never a significant difference between the two arms.

Canadian adjuvant trial comparing intensive CEF versus standard CMF in premenopausal patients with node-positive disease

At the 2002 San Antonio meeting, we presented data from our CMF versus dose-intensive CEF trial with a nine-year median follow-up. We designed the trial with a dose-intensive regimen to use as much anthracycline as we could. We used epirubicin in that arm because it is less cardiotoxic, and we matched the drug schedules in both arms.

We published the data in 1998 with five-year median follow-up. At that point, the data showed that the CEF was superior for disease-free and overall survival, and it remains superior at this much longer follow-up. We've looked at all the long-term side effects. We saw five cases of acute leukemia in the CEF arm versus one case in the CMF arm and four cases of congestive heart failure in the CEF arm versus one case in the CMF arm. So while there are some serious long-term toxicities, the rates are very low.

Phase III Adjuvant Chemotherapy with Intensive CEF (CTX/EPI/5-FU) versus Standard CMF (CTX/MTX/5-FU) in Premenopausal Patients with Carcinoma of the Breast with Positive Axillary Nodes **Closed Protocol**

Protocol IDs: CAN-NCIC-MA5, NCI-V90-0027

Total Number of Patients Accrued: 710 patients

Eligibility: Premenopausal women with node-positive breast cancer

ARM 1: (Cyclophosphamide 75 mg/m^2 d 1-14) + (epirubicin 60 mg/m^2 d 1, 8) + (fluorouracil 500 mg/m^2 d 1, 8)

ARM 2: (Cyclophosphamide 100 mg/m^2 d 1-14) + (methotrexate 40 mg/m^2 d 1, 8) + (fluorouracil 600 mg/m^2 d 1, 8)

Patients who underwent less than a total mastectomy received radiotherapy.

SOURCE:

NCI Physician Data Query, May 2003.

Pritchard KI et al. **A randomized trial comparing CEF to CMF in premenopausal women with node-positive breast cancer: Update of NCIC CTG MA.5.** *Breast Cancer Res Treat* 2002:**Abstract 17.**

CAN-NCIC-MA5 : A Randomized Trial Comparing CEF to CMF in Premenopausal Women with Node-positive Breast Cancer

Median follow-up	5-year follow-up 59 months		10-year follow-up 106 months	
	CMF	CEF	CMF	CEF
5-year relapse-free survival rates	53%	63%	—	—
10-year disease-free survival rates	—	—	45%	52%
5-year actuarial survival rates	70%	77%	—	—
10-year overall survival	—	—	58%	62%
Acute leukemia (# of cases)	0	5	1	5
Congestive heart failure (# of cases)	1	0	1	4

DERIVED FROM:

Levine MN et al. **Randomized trial of intensive cyclophosphamide, epirubicin and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group.** *J Clin Oncol* 1998;16(8):2651-8. **Abstract**

Pritchard KI et al. **A randomized trial comparing CEF to CMF in premenopausal women with node-positive breast cancer: Update of NCIC CTG MA.5.** *Breast Cancer Res Treat* 2002:**Abstract 17.**

CAN-NCIC-MA21 dose-dense chemotherapy adjuvant trial

We are conducting a trial that many Americans are participating in, comparing CEF versus dose-dense EC plus G-CSF followed by paclitaxel versus AC followed by paclitaxel, which was one of the comparative arms of CALGB-9741. This may give us a lot of cross-reference points to compare all of these regimens.

In Canada we continue to use CEF as one of our standard arms, but we chose EC in this trial instead because it can be given in a 12-week schedule and we wanted to sequence paclitaxel with what we were already doing. In addition, our previous trial had already shown the EC and CEF regimens to be equivalent. We added erythropoietin to the EC arm to prevent the anemia and sequenced the paclitaxel after it, which resulted in a six-month regimen.

Phase III Randomized Study of Adjuvant Cyclophosphamide, Epirubicin and Fluorouracil versus Cyclophosphamide, Epirubicin, Filgrastim (G-CSF) and Epoetin Alfa Followed by Paclitaxel versus Cyclophosphamide and Doxorubicin Followed by Paclitaxel in Premenopausal or Early Postmenopausal Women with Previously Resected Node-positive or High-risk Node-negative Stage I-IIIA Breast Cancer Open Protocol

Protocol IDs: AMGEN-CAN-NCIC-MA21, BMS-CAN-NCIC-MA21, CAN-NCIC-MA21, JANSSEN-CAN-NCIC-MA21, NCCTG-CAN-NCIC-MA21, P-UPJOHN-CAN-NCIC-MA21
Projected Accrual: 1,500 patients

Eligibility: Node-positive or high-risk node-negative breast cancer

ARM 1: [(Epirubicin + fluorouracil d 1-8) + cyclophosphamide d 1-14] q 4w x 6
ARM 2: [(Epirubicin + cyclophosphamide d 1) + filgrastim d 2-13 + epoetin alfa SC q wk] q 2 w x 6 → (paclitaxel d 1 + filgrastim d 2-13 + epoetin alfa SC q wk) q 3 w x 4
ARM 3: Doxorubicin + cyclophosphamide q 3 w x 4 → paclitaxel q 3 w x 4

Study Contacts:
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SOURCE: NCI Physician Data Query, May 2003.

Management of the patient with metastatic breast cancer

I manage patients with metastatic disease palliatively. I don't mean palliative as in end-of-life, because we have more effective treatments, and I believe these patients are living longer. I try to treat them as gently as possible for as long as I can, and I use hormones, hormones and more hormones.

I also use bisphosphonates in any patient with bone disease. I think these agents have made a huge difference in quality of life for these patients. I no longer see patients with multiple fractures and terrible bone problems. Nor do I see hypercalcemia as often as I once did. The bisphosphonates have been a great boon for patients in the metastatic setting.

Chemotherapy in the metastatic setting

We seem to be giving more and more lines of chemotherapy to patients with metastatic disease. We see good responses to first-line and second-line therapy, so we try third- and fourth-line treatments. Although we all seem to keep giving it, I wonder whether it's worth it. It would be nice to have more approaches with less toxicity.

I don't use the same doses of agents in the metastatic setting that I use in the adjuvant setting, and I don't use colony-stimulating factors as much in this setting, because I'm treating for palliation. I reduce doses by a quarter or a third and simply treat patients more gently. For example, with capecitabine, the dose-limiting toxicity is usually hand-foot syndrome. But this agent works great if you start out at 75 percent of the full dose. My theory is that if I hospitalize patients as a result of toxicities, it may be two weeks or a month out of their life, and who knows how much more time they have.

Capecitabine/docetaxel in the metastatic and adjuvant settings

When Dr Joyce O'Shaughnessy presented the positive data from the capecitabine/docetaxel trial in the metastatic setting, I was surprised by the results. Many of us thought there would be no significant difference. We had compared doxorubicin with and without vinorelbine and didn't see a significant difference, so we expected to see the same results with this study. The data is exciting and I think it warrants examination in the adjuvant setting. If we can treat these patients for three to six months and have them be well for five or ten years, that's worth studying.

Efficacy of XT vs T in Patients with Anthracycline-pretreated Metastatic Breast Cancer

	Capecitabine/Docetaxel (XT) n=255	Docetaxel (T) n=256	*p* value
Median time to progression	6.1 months [95% CI: 5.4-6.5]	4.2 months [95% CI:3.4-4.5]	log rank $p = 0.0001$
Objective tumor reponse	42% [95% CI:36-48]	30% [95% CI:24-36]	$p = 0.006$
Stable disease	38% [95% CI:32-44]	44% [95% CI:38-50]	
Median survival	14.5 months [95% CI:12.3-16.3]	11.5 months [95% CI:9.8-12.7]	log rank $p = 0.0126$

DERIVED FROM: O'Shaughnessy J et al. **Superior survival with capecitabine and docetaxel combination chemotherapy in anthracycline-pretreated patients with advanced breast cancer.** *J Clin Oncol* 2002;20:2812–2823. **Abstract**

Management of patients with ER-negative, HER2-negative metastatic breast cancer

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

Progress in the management of breast cancer

We've made significant progress overall in terms of breast cancer screening and adjuvant therapy. We're seeing smaller cancers and earlier cancers. We are also seeing fewer cancers that turn into metastatic disease, or if they do, it takes longer. I believe that a large part of this progress in adjuvant therapy can be attributed to the use of hormonal therapy, primarily tamoxifen, as opposed to chemotherapy, although I think we've made progress in both areas.

We've also certainly seen improvement in the quality of life of patients with metastatic disease, and some of that is from unexpected places like the bisphosphonates. We have seen very radical operations disappear. As much progress as we have seen in the management of breast cancer, we could still stand to see more. While I think we'll be using some of the same modalities, I believe that we are headed towards gene arrays and targeted therapy.

Select Publications

Publications discussed by Dr Pritchard

Levine MN et al. **Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group.** *J Clin Oncol* 1998;16(8):2651-8. **Abstract**

Pritchard KI et al. **A randomized trial comparing CEF to CMF in premenopausal women with node-positive breast cancer: Update of NCIC CTG MA.5.** *Breast Cancer Res Treat* 2002:**Abstract 17**.

Therasse P et al. **Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: An EORTC-NCIC-SAKK multicenter study.** *J Clin Oncol* 2003;21(5):843-50. **Abstract**

Therasse P et al. **Neo-adjuvant dose intensive chemotherapy in locally advanced breast cancer (LABC): An EORTC---NCIC---SAKK randomized phase III study comparing FEC (5FU, epirubicin, cyclophosphamide) vs high dose intensity EC + G-CSF (filgrastim).** *Proc ASCO* 1998:**Abstract**.

Trudeau ME. **Optimizing adjuvant breast cancer chemotherapy: Rationale for the MA.21 study.** *Oncology (Huntingt)* 2001;15(5 Suppl 7):7-13. **Abstract**

Induction chemotherapy for locally advanced breast cancer

Ahlgren J et al. **Phase II study of epirubicin, cisplatin and capecitabine as neo-adjuvant chemotherapy in women with locally advanced or inflammatory breast cancer.** *Proc ASCO* 2003;**Abstract 107.**

Alkhatib F et al. **Docetaxel and epirubicin as neoadjuvant chemotherapy in patients with locally advanced breast cancer.** *Proc ASCO* 2002:**Abstract 2068**.

Baltali E et al. **Neoadjuvant chemotherapy with taxotere-epirubicin-5-fluorouracil (TEF) in local-regionally advanced breast cancer: A preliminary report.** *Tumori* 2002;88(6):474-7. **Abstract**

Braud AC et al. **Combination of vinorelbine, epirubicin, and cyclophosphamide as neoadjuvant chemotherapy for locally advanced breast cancer: Phase II study.** *Am J Clin Oncol* 2002;25(3):303-7. **Abstract**

Chow LW et al. **Neoadjuvant celecoxib and 5-fluorouracil/epirubicin/cyclophosphamide (FEC) for the treatment of locally advanced breast cancer (LABC).** *Proc ASCO* 2003;**Abstract 327.**

Davidson N et al. **Improved outcome following treatment with sequential primary chemotherapy Doxorubicin (A) cyclophosphamide (C)x4 and paclitaxel (P) x4 compared to AC x6 for locally advanced breast cancer (LABC).** *Proc ASCO* 2003;**Abstract 353.**

de Matteis A et al. **Docetaxel plus epidoxorubicin as neoadjuvant treatment in patients with large operable or locally advanced carcinoma of the breast: A single-center, phase II study.** *Cancer* 2002;94(4):895-901. **Abstract**

Ezzat A et al. **Dose dense neoadjuvant sequential chemotherapy in the management of locally advanced breast cancer: A phase II study.** *Proc ASCO* 2003;**Abstract 202.**

Ezzat AA et al. **High complete pathological response in locally advanced breast cancer using paclitaxel and cisplatin.** *Breast Cancer Res Treat* 2000;62(3):237-44. **Abstract**

Fornasiero A et al. **Neoadjuvant moderately high-dose chemotherapy with rh-G-CSF in locally advanced breast carcinoma.** *Tumori* 2001;87(4):223-8. **Abstract**

Gajdos C et al. **Relationship of clinical and pathologic response to neoadjuvant chemotherapy and outcome of locally advanced breast cancer.** *J Surg Oncol* 2002;80(1):4-11. **Abstract**

Gogas H et al. **Neoadjuvant chemotherapy with a combination of pegylated liposomal doxorubicin (Caelyx) and paclitaxel in locally advanced breast cancer: A phase II study by the Hellenic Cooperative Oncology Group.** *Ann Oncol* 2002;13(11):1737-42. **Abstract**

Ikeda T et al. **The role of neoadjuvant chemotherapy for breast cancer treatment.** *Breast Cancer* 2002;9(1):8-14. **Abstract**

Lara F et al. **High pathological complete response (PCR) after neoadjuvant chemotherapy with doxorubicin and docetaxel in locally advanced breast cancer.** *Proc ASCO* 2000:**Abstract 492**.

Maldonado D et al. **Neoadjuvant chemotherapy with fluorouracil-epirubicin-cyclophosphamide (FEC) and GM-CSF every 14 days in locoregionally advanced breast cancer (LABC): Preliminary report.** *Proc ASCO* 2000:**Abstract 486**.

Malhotra V et al. **Neoadjuvant and adjuvant chemotherapy (CT) with doxorubicin and docetaxel (DD) with surgery and radiation in locally advanced breast cancer.** *Proc ASCO* 2001:**Abstract 1771**.

Milla-Santos A et al. **Anastrozole is an effective neoadjuvant therapy for patients with hormone-dependent, locally-advanced breast cancer irrespective of cerbB2.** *Proc ASCO* 2003;**Abstract 154.**

Morrell L et al. **MVAC as neoadjuvant therapy in locally advanced and inflammatory breast cancer: Ten year update.** *Proc ASCO* 2003;**Abstract 244.**

Ozmen V et al. **Inflammatory breast cancer: Results of anthracycline-based neoadjuvant chemotherapy.** *Breast J* 2003;9(2):79-85. **Abstract**

Paciucci PA et al. **Neo-adjuvant therapy with dose-dense docetaxel plus short-term filgrastim rescue for locally advanced breast cancer.** *Anticancer Drugs* 2002;13(8):791-5. **Abstract**

Petruzelka LB et al. **Neoadjuvant chemotherapy with vinorelbine and epirubicine in locally advanced breast cancer (LABC): Preliminary report.** *Proc ASCO* 2001:**Abstract 1898**.

Puglisi F et al. **Phase II trial of neoadjuvant chemotherapy with doxorubicin and cyclophosphamide followed by docetaxel in stage II-III breast cancer.** *Proc ASCO* 2002:**Abstract 1993**.

Shannon C, Smith I. **Is there still a role for neoadjuvant therapy in breast cancer?** *Crit Rev Oncol Hematol* 2003;45(1):77-90. **Abstract**

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Edited comments by Dr Grana

Clinical impact of CALGB-9741: Dose-dense versus conventional scheduling

The data from CALGB-9741 was the first instance in a long time that we saw an impact of altering dose and dose density. We've been so disillusioned by the high-dose therapy concept that this was refreshing. The data looked very promising. The disease-free survival data was impressive. The overall survival data was less impressive. I think oncologists are uncertain of how they will translate the data into practice.

When this type of data is presented, it's our responsibility to discuss it with patients and consider what the patients themselves have to say about it. Some patients are very educated and do a lot of research in preparation for their treatment selection and participate in decision-making.

I'd be very comfortable using the dose-dense regimen. We enrolled patients in that trial. I will present this data much as I present the data on AC/paclitaxel from the two studies that have been done. I will then offer it as an option, but I have some caveats and I'll share those caveats with the patient. Patients have to understand that I don't believe this data has the maturity I'd like to see.

Most of us are creatures of habit and we've become very accustomed to the every-three-week regimen — the AC x 4/taxane. I'm also somewhat concerned about the increased toxicity, although the study did not show an enormous increase. Most of us have an inherent fear that as we're changing doses we'll have enhanced hematologic toxicity. Introduction of a G-CSF is not going to be an issue, except that many of us are now in the habit of using pegfilgrastim, which is used on an every-three-week schedule. The question is: Can it safely be used at two-week intervals?

Management of patients with ER-negative, node-positive breast cancer

Currently, I'm using AC x 4 followed by docetaxel x 4. Both the sequential and concurrent dose-dense regimens are also reasonable options. I find that the sequential regimen is easier in terms of logistical planning, and that's probably what I would recommend to the patient. I also discuss data regarding AC/paclitaxel, TAC/FAC and participating in ongoing trials.

Neoadjuvant clinical trial of capecitabine/docetaxel

I'm very enthusiastic about the neoadjuvant capecitabine/docetaxel trial. The neoadjuvant approach is exciting in that it allows you to see the effects of your therapy and what you can achieve in terms of pathologic complete response. We need to improve on what's been accomplished previously. AC/docetaxel has only achieved a 25 percent pathologic complete response. Clearly, there's a lot of room for improvement. The addition of capecitabine in that setting is a wonderful approach, and I'm looking forward to the initiation of the NSABP trial to help answer that question.

NSABP Trial of Preoperative Doxorubicin/Cyclophosphamide (AC) Followed by Docetaxel versus Preoperative AC Followed by Capecitabine and Docetaxel (XT) **Proposed Protocol**

ARM 1: AC x 4 → docetaxel x 4 → surgery
ARM 2: AC x 4 → docetaxel/capecitabine → surgery

SOURCE: Eleftherios Mamounas, Personal Communication, November 2002

CALGB-49907: Phase III trial of chemotherapy in the elderly

I am participating in Hyman Muss' study, CALGB-49907, evaluating capecitabine versus AC or CMF in elderly patients. The concept of altering chemotherapy for the elderly is very important and timely. It's time that we look at patients and other factors in their lives, rather than treat everybody in the same mode. The data evaluating capecitabine versus CMF in metastatic disease showed equal effectiveness, so it is a timely study to be doing.

Single-agent capecitabine will not necessarily be easier to tolerate than CMF, but it avoids some of the issues with the intravenous use of drugs and the frequency of visits to the office. Some of the other toxicities associated with capecitabine may make it a little bit harder than CMF.

Capecitabine/docetaxel in the management of patients with metastatic disease

I use the capecitabine/docetaxel regimen for a select group of women with metastatic disease — those with more extensive disease and with a better

performance status. The regimen produces good results but may have significant toxicity, especially at the doses that were initially presented.

I tend to start at 1250 mg/m^2 twice a day for 14 days followed by seven days off as the regular approach. If you select your patient population appropriately, it's tolerable. The hand-foot syndrome is manageable with appropriate dose reductions when it occurs. The hardest symptom complex that I encounter with that regimen is the GI toxicity. It's more difficult to manage and less amenable to improvement with dose reductions.

Use of single-agent capecitabine in the metastatic setting

I've had good results using capecitabine monotherapy. Like vinorelbine, I use it in patients who do not have life-threatening disease and are better candidates for single-agent therapy. I tend to use capecitabine preferentially, because the single-agent data with vinorelbine has not been particularly impressive.

Translation of the 47-month update of the ATAC trial data to clinical practice

I was very excited to see the initial presentation of the ATAC trial data, because the results were very believable. I went home and began discussing it with my patients. These women needed to be informed about the data, because they were going to hear about it in the media. I also wanted to reassure them that, if they were on tamoxifen, they should continue on tamoxifen.

In newly diagnosed patients, I had in-depth discussions. We talked about the limitations and the strengths of the trial, and the majority of patients with whom I discussed it as a viable option felt very comfortable using anastrozole. I have used anastrozole in a large number of patients. Now, we have 47 months of follow-up and the early data holds. If anything, the data looks more promising, so it gives us even more confidence in the selection of this agent.

Use of bisphosphonates in patients on aromatase inhibitors

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

Osteoporosis and osteoporotic risks are a significant factor for many of these women in the long term. They are not going to receive hormone replacement therapy, so that is a factor. I have changed my practice over the last year in how I approach bone disease. In the past, I felt very comfortable with tamoxifen. I monitored bone mineral densities, but I was comfortable with maintaining women with osteopenia on tamoxifen in addition to recommending more exercise and calcium supplements.

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

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

Managing patients with osteoporosis on bisphosphonates

My most significant concern is with patients in their early 50s with ER/PR-positive tumors with five or six positive lymph nodes and osteoporosis despite being on alendronate.

The choices are easy in terms of chemotherapy, because these are women whom I will encourage a six-month chemotherapy regimen — AC/paclitaxel or AC/docetaxel. The biggest dilemma in that woman is the choice of tamoxifen or anastrozole, knowing that she's already osteoporotic and has already received a bisphosphonate. It really has to be shared decision-making in deciding which hormonal agent to use. My philosophy has been — from the first presentation of the ATAC data — to present the risks and benefits, discuss the patient's concerns and then make a decision.

Other aromatase inhibitors in the adjuvant and metastatic settings

In the adjuvant setting, I only use anastrozole, because it is the only aromatase inhibitor for which we have data. We can postulate that all three aromatase inhibitors will be active and have similar toxicity, but we don't know that.

In the metastatic setting, letrozole and anastrozole appear to be very similar in both effectiveness and toxicity. Exemestane has really not been well-evaluated, but I would wager that the results will be similar. In the metastatic setting, I don't have much of a preference for one aromatase inhibitor versus another. There's been a lot of speculation that letrozole may lead to some amount of adrenal insufficiency. I'm not sure whether that will be true. Exemestane may have a superior safety profile in terms of bone, but we should think about its potential steroidal effects.

We need the adjuvant studies with large numbers of patients to address that issue. We're not going to get that answer from the metastatic studies, because there have been too few patients.

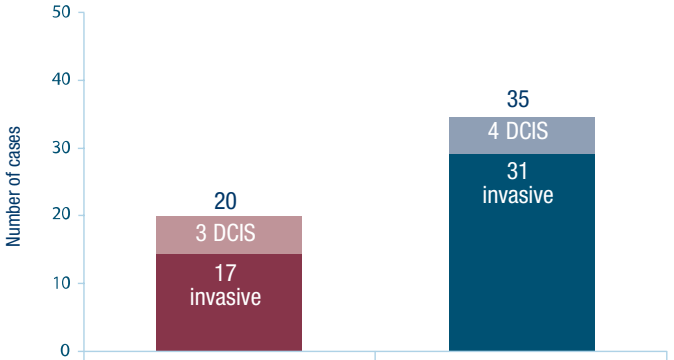
Potential for aromatase inhibitor use for risk reduction

If we look at the ATAC data, the improvement in terms of contralateral breast cancer risk is impressive. It is over 50 percent better than what we have achieved with tamoxifen. If the prevention trials with the aromatase inhibitors are positive, then the discussion will be easier than it ever was for us with

tamoxifen, because tamoxifen was virgin territory. We had to begin with no understanding about chemoprevention. There was a whole process of educating physicians and patients, and that has been done.

The major obstacle for the use of tamoxifen in women at high risk is their fear of endometrial cancer and thrombosis. Some women are concerned about hot flashes and the quality of life issues, but I think when you eliminate those fears, it'll be much easier to convince women to utilize a chemoprevention strategy.

ATAC Trial 47-month Follow-up: Incidence of New (Contralateral) Breast Primaries in Receptor-positive Population



	OR	95% CI	*p* value
AN vs TAM	0.56	0.32-0.98	0.042

SOURCE: Aman Buzdar, Presentation, 2002 San Antonio Breast Cancer Symposium.

Clinical trials of adjuvant trastuzumab

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

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

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

Randomized Clinical Trials of Adjuvant Trastuzumab

Trial (Target Accrual)	Eligibility	Randomization
NSABP B-31 (2,700 patients)	Node + IHC 3+ or FISH+	AC x 4 → paclitaxel x 4 AC x 4 → paclitaxel x 4 + H qw x 1 year
Intergroup N9831 (3,300 patients)	Node + IHC 3+ or FISH+	AC x 4 → paclitaxel qw x 12 AC x 4 → paclitaxel qw x 12 → H qw x 1 year AC x 4 → (paclitaxel + H) qw x 12 → H qw x 40
BCIRG-006 (3,150 patients)	Node + FISH+	AC x 4 → docetaxel x 4 AC x 4 → docetaxel x 4 + H (qw x 12 weeks) → H (qw x 40 weeks) (Docetaxel + C) x 6 + H (qw x 18 weeks) → H (qw x 34 weeks)
BIG-01-01 HERA* (3,192 patients)	Node + and - IHC 3+ or FISH+	H q3w x 1 year H q3w x 2 years No H

*Post-chemohormonal therapy randomization

H = trastuzumab; C = cisplatin or carboplatin; AC = doxorubicin + cyclophosphamide

SOURCE: NCI Physician Data Query, May 2003; Piccart MJ et al. **Herceptin for the treatment of breast cancer: What we know — and what we have yet to learn.** *CancerFutures* 2002;1:73-9. **Abstract**

Management of the chemotherapy-naïve patient with HER2-positive metastatic breast cancer

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

Managing patients with HER2-positive, locally advanced or inflammatory disease

The most difficult patients to manage are those with locally advanced, inflammatory or even locally metastatic disease — the woman with massive tumor in the chest wall, supraclavicular nodes and axillary nodes who has HER2-positive disease. You can treat that woman with trastuzumab/vinorelbine. The biggest dilemma is: How long do you treat, and at what point do you stop chemotherapy and just continue with trastuzumab? Also, at what point do you stop trastuzumab?

I gave one patient vinorelbine and trastuzumab for about 10 months. She had a fantastic response and went to surgery. At the time of surgery, she had microscopic disease in the breast. I continued the vinorelbine and trastuzumab for another four to six months, and then gave her six months of trastuzumab. It's totally empiric. I think you could also easily make an argument that this patient should stay on lifelong trastuzumab.

Select publications

Use of bisphosphonates in breast cancer

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Lipton A. **Bisphosphonates and metastatic breast carcinoma.** *Cancer* 2003;97(3 Suppl):848-53. **Abstract**

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Mohla S et al. **Third North American Symposium on Skeletal Complications of Malignancy: summary of the scientific sessions.** *Cancer* 2003;97(3 Suppl):719-25. **Abstract**

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Post-test: Breast Cancer Update, Issue 5, 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. A Phase III trial that compared trastuzumab/paclitaxel (TH) to trastuzumab/paclitaxel/carboplatin (THC) demonstrated:

a. Significantly improved response rates and time to progression with THC
b. Significantly improved response rates but no change in time to progression with THC
c. Equivalent response rate and time to progression

2.The only FDA-approved chemotherapy combination regimen for metastatic breast cancer is:

a. Doxorubicin/docetaxel
b. Doxorubicin/paclitaxel
c. Docetaxel/capecitabine
d. Paclitaxel/capecitabine

3. As pre-invasive disease progresses from atypical hyperplasia to DCIS, overexpression occurs in which of the following pathways?

a. HER2
b. COX-2
c. Estrogen receptor
d. All of the above

4. Patients who have HER2-positive, ER/PR-positive tumors are *de novo* resistant to tamoxifen but sensitive to aromatase inhibitors.

a. True
b. False

5. In CALGB-9741, compared to conventional scheduling, adjuvant dose-dense chemotherapy resulted in improved disease-free and overall survival.

a. True
b. False

6. According to data presented by Dr Gnant, what effect did zoledronate have on bone loss associated with hormonal therapy in postmenopausal patients?

a. Reversed bone loss
b. Increased bone loss
c. Had no impact on bone loss

7. In the ATAC trial, there were 40 to 50 percent fewer invasive and noninvasive contralateral breast cancers in patients receiving anastrozole compared to tamoxifen.

a. True
b. False

8. There is a positive correlation between HER2 and VEGF expression.

a. True
b. False

9. Tyrosine kinase inhibitors, such as gefitinib, may be capable of reversing resistance to endocrine therapy.

a. True
b. False

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

Evaluation Form: Breast Cancer Update, Issue 5, 2003

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

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

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

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 5

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

- Evaluate novel data regarding dose-dense scheduling of chemotherapy and the use of aromatase inhibitors for adjuvant therapy 5 4 3 2 1
- Learn potential strategies to overcome acquired resistance to endocrine therapy. . 5 4 3 2 1
- Develop awareness of the efficacy and tolerability data from clinical trials of trastuzumab in combination with platinum agents/chemotherapy and ongoing clinical trials with trastuzumab in order to counsel appropriately selected patients 5 4 3 2 1
- Consider a spectrum of perspectives in the management strategies for patients with ER-negative, HER2-negative metastatic breast cancer 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Mark D Pegram, MD	5 4 3 2 1	5 4 3 2 1
Paul E Goss, MD, PhD, FRCP(CA), FRCP(UK)	5 4 3 2 1	5 4 3 2 1
Kathleen I Pritchard, MD	5 4 3 2 1	5 4 3 2 1
Generosa Grana, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Evaluation Form: Breast Cancer Update, Issue 5, 2003

Please Print Clearly

Name: _____

Specialty: _____ ME#: _____ Last 4 digits of SS# (required): _____

Street Address: _____ Box/Suite: _____

City: _____ State: _____ Zip Code: _____

Phone Number: _____ Fax Number: _____Email: _____

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Signature: _____

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

___Yes ___No

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

_____

_____

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

_____

_____

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

_____

_____

Degree:

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

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