

Breast Cancer™

U P D A T E

Conversations with Oncology Research Leaders
Bridging the Gap between Research and Patient Care

EDITOR

Neil Love, MD

FACULTY

Larry Norton, MD

Martine Piccart, MD, PhD

C Kent Osborne, MD

Maria Theodoulou, MD

CME
Certified

Table of Contents

2	CME Information
4	Editor's Note: Dr Piccart's mother
7	Martine Piccart, MD, PhD Head of Chemotherapy Department, Jules Bordet Institute Chairwoman of the Breast International Group Brussels, Belgium
	Larry Norton, MD Deputy Physician-in-Chief Director, Breast Cancer Programs Norna S Sarofim Chair in Clinical Oncology Memorial Sloan-Kettering Cancer Center New York, New York
13	Martine Piccart, MD, PhD
18	C Kent Osborne, MD Director, Breast Center Professor of Medicine and Molecular and Cellular Biology Baylor College of Medicine Houston, Texas
25	Maria Theodoulou, MD Associate Attending Physician Memorial Hospital for Cancer & Allied Diseases New York, New York
31	PowerPoint Atlas: HER2 and Adjuvant Trastuzumab
38	Post-test
39	Evaluation

HOW TO USE THIS MONOGRAPH

This CME activity 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 located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. BreastCancerUpdate.com includes 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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment.
- Develop and explain a management strategy for treatment of ER-positive and ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the relevance to patients considering adjuvant chemotherapy regimens.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Discuss the risks and benefits of endocrine intervention with women with DCIS and those at high risk of developing breast cancer.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of Issue 4 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Piccart, Norton, Osborne and Theodoulou on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3.25 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

FACULTY DISCLOSURES

As a provider accredited by the ACCME, it is the policy of Research To Practice to require the disclosure of any significant financial interest or any other relationship the sponsor or faculty members have with the manufacturer(s) of any commercial product(s) discussed in an educational presentation. The presenting faculty reported the following:

Martine Piccart, MD, PhD

Grants/Research Support: Aventis Pharmaceuticals Inc, Novartis Pharmaceuticals, Ortho Biotech Products LP
 Consultant: AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals Inc, Bristol-Myers Squibb Company, GlaxoSmithKline, Novartis Pharmaceuticals

C Kent Osborne, MD

Grants/Research Support: AstraZeneca Pharmaceuticals LP, Merck and Company Inc
 Consultant: AstraZeneca Pharmaceuticals LP, Novartis Pharmaceuticals, Pfizer Inc
 Honorarium: Pfizer Inc

Larry Norton, MD

No financial interests or affiliations to disclose

Maria Theodoulou, MD

Grants/Research Support: Elan Corporation, Roche Laboratories Inc
 Honorarium: Bristol-Myers Squibb Company, Eli Lilly and Company, Genentech BioOncology, Roche Laboratories Inc

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
aminoglutethimide	Cytadren®	Novartis Pharmaceuticals
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cyclophosphamide	Cytosan® Neosar®	Bristol-Myers Squibb Company Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Various	Various
epirubicin hydrochloride	Ellence®	Pfizer Inc
exemestane	Aromasin®	Pfizer Inc
filgrastim	Neupogen®	Amgen Inc
5-fluorouracil (5-FU)	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly and Company
goserelin acetate	Zoladex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals
liposomal doxorubicin	Doxil®	Ortho Biotech Products LP
methotrexate	Various	Various
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pegfilgrastim	Neulasta®	Amgen Inc
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech BioOncology
vinorelbine	Navelbine®	GlaxoSmithKline

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.



Editor's Note

Dr Piccart's mother

In 1990, I was honored to receive an invitation to Oxford University to attend and observe the second meeting of the Early Breast Cancer Trialists' Collaborative Group. The renowned research leaders who comprised this esteemed group had been invited by Richard Peto to hear the initial results of the second breast cancer overview. Peto has always been a bit of a maverick — he reminds me of the smart kid in school who diverts attention away from his intelligence and ability by getting into trouble. A perfect example of this mischievous inclination was our accommodations in Oxford. Peto had arranged for all the trialists — a group well-accustomed to high-end hotels — to stay in the Oxford dorms.

Similarly, he also sent out a questionnaire prior to the meeting asking everyone to predict what the data would demonstrate. During the two-day meeting he put up transparencies (he still doesn't like slides or PowerPoint) of these predictions, which he then gleefully destroyed one point at a time with his data. During the meeting, I met Peto and asked if he would allow me to interview him on his next trip "across the pond."

Some time after that, I noted that Sir Richard (actually, knighthood had not yet been bestowed) was giving the kick-off lecture at the New York Metropolitan Breast Cancer Group annual meeting. I inquired about an interview and Peto agreed to be recorded after his talk. For the New York recording — and all subsequent interviews he has done for this series — Peto refused an honorarium, but I also learned he would not specifically commit to when, where and even if we would definitely do the interview. I flew my production crew to New York, reserved a meeting room and set up a mini-recording studio anyhow.

Immediately after his lecture — which exceeded the allotted time limit by 30 minutes and might have gone longer were it not for moderator Larry Norton almost dragging Peto off the stage — I approached Sir Richard, who was chatting with Larry near the podium. Peto was up for the interview; however, he indicated that he would rather do it right there at the podium area. As our production people scrambled to get things set up, on an impulse, I asked Larry to join the recording session.

What followed was one of the most electrifying moments of my career. I felt like a high school basketball player shooting hoops with Michael Jordan and Shaquille O'Neal. For years, Larry would tell me that many people would approach him

and comment on the exceptional quality of the program. It has been 14 years since that once-in-a-lifetime interview.

At the 2004 Miami Breast Cancer Conference, a similar unplanned and memorable event occurred. For quite some time I have been trying to interview Martine Piccart. We finally managed to arrange an appointment just after she completed her last lecture at the meeting and just before she was to return to Belgium. As Dr Piccart and I headed toward the interview room, we happened to pass Larry who was also in town serving as part of the conference faculty. Larry always arranges very tight flight schedules, and we had previously made the decision to delay our annual interview until ASCO where we would have more time together.

As we exchanged pleasantries, Larry mentioned that his flight was delayed and asked if I wanted to chat. Remembering the prior Peto-Norton extravaganza, I made the instantaneous decision to set up “round two,” this time with Larry and Martine. The result — in this issue — was no less interesting than the interview with the original duo.

After Larry buzzed out to the airport, I continued chatting with Dr Piccart. Toward the end of the interview I decided to ask one of the questions that I love to ask pioneers in the field. I inquired why she entered the field of breast oncology. To my surprise, she told me that more than 20 years ago her mother was diagnosed with multiple node-positive breast cancer and received CMF for a year and then tamoxifen for 10 years. Miraculously, the tumor never recurred. But unfortunately, endometrial cancer was later diagnosed — perhaps as a consequence of the tamoxifen — and currently Martine’s mother is being treated with an adjuvant aromatase inhibitor for a second primary tumor.

Listening to this story, and seeing the pain on Dr Piccart’s face as she described the long year her mom spent on CMF, I thought about the ebb and flow of breast cancer research since finishing my fellowship in 1977. At that point, endocrine therapy was the “kinder, gentler” palliative therapy for metastatic disease. Most oncologists assumed it would never have an impact in the adjuvant setting, let alone for women at increased risk.

In 1985, Peto and the overview crushed that assumption, but the evidence of endometrial cancer that emerged in 1992 tempered our enthusiasm. By 2001 a new alternative was appearing — aromatase inhibitors (AIs) — in the form of ATAC and anastrozole. And a bit more than two years later, we are now also seeing evidence of the superiority of AIs after two and five years of tamoxifen.

In a 2001 San Antonio lecture right after Mike Baum presented the ATAC results, Craig Jordan quipped during a presentation, “Tamoxifen — the gold standard of breast cancer therapy... until yesterday.” This prescient remark points directly to the fact that a new adjuvant player had started to make its way through the trials and tribulations of reaching acceptability.

Will this life cycle of a targeted treatment that starts out as palliative therapy for advanced disease and ends up having a dramatic impact on survival as adjuvant therapy — exemplified in the story of Dr Piccart’s mother and the AIs — be

repeated in breast cancer? Many observers believe that this can and will happen and that the leading candidate is trastuzumab. Maria Theodoulou comments in this edition on several major large adjuvant trials in women with HER2-positive tumors. The hope and expectation we all share is that these studies will demonstrate the same kind of meaningful impact that has already been shown with endocrine interventions in women with ER-positive tumors.

The excitement about HER2-positive disease management is also evident in Dr Piccart's discussion of women with liver-only metastases. She has referred a number of these patients for hepatic resection after significant treatment responses to trastuzumab. She also notes the increasing number of patients who have excellent peripheral disease control but CNS disease progression, and she speculates that this will be an important feature to analyze in the emerging adjuvant trastuzumab trial results.

Also in this program, Kent Osborne discusses the evolving research from his lab and others on the interconnection between pathways for HER2 and estrogen receptors. He suggests that a useful strategy to evaluate in clinical trials would be combining interventions that affect both systems. A number of ongoing and proposed studies are investigating this strategy, including an ECOG study combining trastuzumab and anastrozole.

As these and other critical research questions are addressed in ongoing clinical trials, physicians and patients must make difficult decisions in many situations for which suboptimal trial data exist. In 1982, the physician treating Dr Piccart's mother — facing the grim prognosis of a woman with eight positive axillary nodes — took a leap of faith with his patient and her daughter, and utilized a treatment strategy that was unproven at that time. Every oncologist considers and balances similar anecdotal success stories with unsuccessful cases as they make the next generation of challenging decisions.

— Neil Love, MD

NLove@ResearchToPractice.net

SWOG-S0221: Comparing different schedules of adjuvant AC and paclitaxel

This Intergroup trial (Figure 1.1) will compare a regimen of oral cyclophosphamide and a weekly anthracycline to the dose-dense every two-week doxorubicin and cyclophosphamide (AC) regimen used in CALGB-9741. It will also compare dose-dense every two-week to weekly paclitaxel.

Frankly, I don't know which regimens will be better, and I have pure equipoise on this particular study. The trial is not as clean a comparison as the one in CALGB-9741, in which all the doses were kept exactly the same and only the schedule was varied.

For the dose-dense regimens, the additional expense associated with filgrastim and pegfilgrastim is a real and very important concern.

Larry Norton, MD

SWOG-S0221 is an important study, particularly with regard to the best way to administer paclitaxel. Weekly paclitaxel is a potentially interesting regimen, and it's logical to compare it to a dose-dense regimen that is probably more expensive.

On the other hand, weekly paclitaxel will require weekly visits to the hospital, which might not be easy. In the meantime, ECOG-1199 will provide a head-to-head comparison of every three-week paclitaxel, every three-week docetaxel, weekly paclitaxel and weekly docetaxel (Figure 1.2).

Martine Piccart, MD, PhD



Dr Piccart is the Head of the Chemotherapy Department at the Jules Bordet Institute and Chairwoman of the Breast International Group in Brussels, Belgium.

Dr Norton is Deputy Physician-in-Chief and Director of Breast Cancer Programs and Norma S Sarofim Chair in Clinical Oncology at the Memorial Sloan-Kettering Cancer Center in New York, New York.

Utilization of dose-dense taxanes

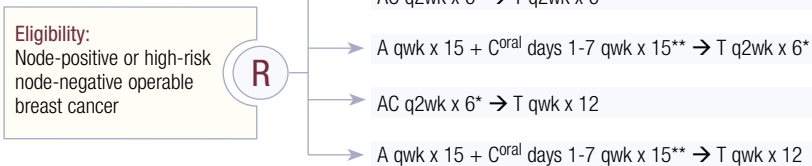
Except for cost issues, no reason exists to not use paclitaxel in a dose-dense fashion. We do not yet know how docetaxel should be administered, and it should be studied as an every two-week regimen. I've heard doctors state that they don't want to use a more aggressive dose-dense regimen unless the patients are at very high risk. Frankly, the dose-dense regimen is less toxic, more effective and faster. If CALGB-9741 had demonstrated that the regimens had equal efficacy, there would be real arguments for using a dose-dense regimen just from the toxicity point of view.

Larry Norton, MD

Figure 1.1

Phase III Randomized Study of Four Schedules of Adjuvant AC and Paclitaxel

Protocol ID: SWOG-S0221
Target Accrual: 4,500 (Open)



*Patients receive pegfilgrastim on day 2; **Patients receive filgrastim days 2-7
C^{oral} = oral cyclophosphamide; T = paclitaxel

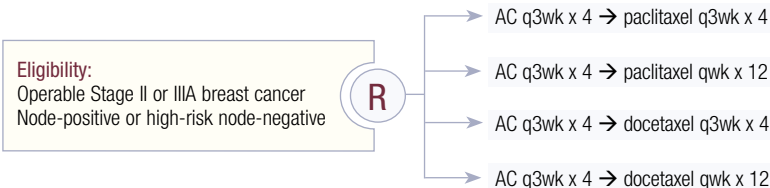
Study Contact:
Southwest Oncology Group, G Thomas Budd, MD, Study Coordinator
Tel: 216-444-6480

SOURCE: NCI Physician Data Query, April 2004.

Figure 1.2

Phase III Randomized Study of Doxorubicin and Cyclophosphamide Followed by Paclitaxel or Docetaxel

Protocol IDs: ECOG-1199, CALGB-49906, NCCTG-E1199, SWOG-E1199
Accrual: 5,000 (Closed)



SOURCE: NCI Physician Data Query, April 2004.

A few years ago we piloted a trial of every two-week docetaxel. It was too toxic, and the patients experienced very serious skin problems and mucositis. I don't believe docetaxel will be a good drug to use every two weeks. It is very effective when used every three weeks, and I don't think it will be more effective when administered weekly. I believe the comparison should be between the every three-week docetaxel and dose-dense paclitaxel.

Martine Piccart, MD, PhD

Utilization of dose-dense AC in patients with node-negative disease

As a result of CALGB-9741, the adjuvant trial CALGB-40101 in patients with node-negative disease was amended to use every two-week AC. The proof of greater efficacy with less toxicity was the major consideration in that protocol amendment. In terms of the science, I think it's reasonable to use every two-week AC without a taxane in a nonprotocol setting. I would hypothesize that patients with negative nodes or a low volume of disease may benefit even more.

From years of trials and the worldwide overview pioneered by Richard Peto, we've learned that if something works in patients with node-negative disease, it will work in patients with node-positive disease and vice versa. I don't think it's necessary to show that dose-dense therapy is going to work in patients with node-negative disease.

It is a question of the risk of relapse for the patient. A patient with a six-centimeter, poorly differentiated primary tumor and negative nodes has an enormous risk of relapse, and that patient should benefit as much as a patient with a smaller primary tumor and a few positive nodes.

Aside from any issues of efficacy, the dose-dense approach offers considerable advantages in terms of completing therapy earlier. We offer our patients a choice. We say, "Let's start dose-dense therapy and see how you do. If you really hate it and you need an extra week, we can always delay things." I've not had a single person who wanted a delay. They just want to complete therapy.

Larry Norton, MD

Those of us who have been following the developments in the mathematical model really believe that CALGB-9741 is a positive trial because it addresses this mathematical concept. Others are more skeptical and believe the difference is due to the paclitaxel schedule. We don't have a clear answer.

Ideally, we should evaluate whether the anthracycline or the taxane must be administered in a dose-dense manner. We don't have time to answer these questions, as too many other important questions need to be addressed. However, I believe it's reasonable to use dose-dense AC. In Europe it's not possible to use dose-dense chemotherapy because of financial issues.

Martine Piccart, MD, PhD

Neoadjuvant trial of dose-dense therapy

In Europe we compared preoperative every two-week epirubicin and cyclophosphamide (EC) administered with filgrastim over three months to the Canadian CEF regimen administered over six months in patients with locally advanced tumors. The trial enrolled about 400 patients; hence, it was underpowered and we didn't observe a difference. Interestingly, every two-week EC was nice in the sense that the chemotherapy was completed in three months instead of six months. I don't believe we are harming women with this regimen, and I have no problem with the choice of this particular schedule.

Martine Piccart, MD, PhD

The mathematical model predicts that dose-dense therapy is not better in terms of response in the preoperative setting because of the large tumor volume. We learned from Gompertzian growth that faster regrowth occurs with more regression. Negative data in the preoperative setting corroborate this particular view. Hence, dose density is not going to play a role in that setting.

Larry Norton, MD

Molecular determinants of Gompertzian growth

We're close to finding the molecular determinants of Gompertzian growth (i.e., which systems are deranged in neoplasia). For many centuries, cancer was thought of as a disease of increased proliferation. In fact, when pathologists see many cells on a slide, they label it as hyperproliferative. In reality, all they can say is that it's very dense and there are many cells. The presence of many cells may mean proliferation, a reduction in cell loss, apoptosis or senescence. The cells may have accumulated over a long period of time, and they are not necessarily rapidly dividing.

Now, molecular tools are available to assess and describe which genes are associated with proliferation, apoptosis, senescence, the geometry of the tumor or the spatial arrangement of the cells. All of those factors are clearly related to the Gompertzian phenomenon. This exciting era in breast cancer clinical research will tie together molecular analyses and well-designed clinical trials so that we understand the biology and the intervention, and then link them together.

Larry Norton, MD

We have a trial that is still in the planning stages in which molecular biological factors will be evaluated prospectively in patients receiving different treatment schedules. We will repeat CALGB-9741 while building into the trial one or two biological hypotheses. The first hypothesis is that highly proliferating tumors are going to derive a huge benefit from dose-dense therapy. The second hypothesis is that a dose-dense strategy is most effective in tumors that are completely lacking all receptors (i.e., ER-negative, PR-negative), for which chemotherapy is the only treatment option. Some of those tumors are very aggressive and highly proliferating.

Martine Piccart, MD, PhD

Incidence of dose reductions and delays in adjuvant chemotherapy

Gary Lyman conducted a nationwide survey of community-based oncology practices to determine the incidence of dose reductions and delays in patients receiving adjuvant chemotherapy. It's really very scary now that we have the dose-dense data.

If changing therapy from every three weeks to every two weeks can reduce the annual odds of death by 31 percent, I shudder to think what going from three to four or five weeks will do in terms of impairing our ability to cure the cancer. Also, with the anthracyclines, the optimal dose seems to be 60 mg/m² — higher doses don't provide any benefit, but lower doses rapidly reduce efficacy. I'm worried about dose modifications and schedule changes.

Larry Norton, MD

Use of adjuvant aromatase inhibitors in postmenopausal women

We're closer to being able to make a statement about the use of up-front adjuvant aromatase inhibitors in postmenopausal women. I still believe, however, that it is a tad premature. We still don't know about the aromatase inhibitors' long-term efficacy and toxicity profiles.

Solid data indicate that patients benefit for more than a decade after two to five years of adjuvant tamoxifen, but we don't have comparable data for the aromatase inhibitors. I wouldn't fault a physician for using an adjuvant aromatase inhibitor as front-line therapy; the ATAC trial data indicate that is a reasonable alternative. But in the absence of a survival difference, which is important, it would not be wrong to start with tamoxifen.

Interesting studies are looking at the sequential use of selective estrogen-receptor modulators (SERMs) and aromatase inhibitors. Good biological reasons suggest that it may make sense to set up the tumor with a SERM first, before using an aromatase inhibitor. The data from Italy about the sequential use of a SERM and an aromatase inhibitor is provocative. In the next six to nine months, as we see more data, we'll be in a better position to make a definitive statement.

A sequential strategy would provide the opportunity to improve bone mineral density in patients with osteopenia or osteoporosis, which can be treated aggressively during the period of time the patient is receiving a SERM. I believe bone mineral density will be a big issue in this patient population because chemotherapy induces premature menopause in younger women. We're going to have a gargantuan population of cured individuals who will have problems with fractures, which in some cases can be life-threatening. We must work hard to maintain bone mineral density.

Larry Norton, MD

I agree with Larry. In the future, we may find out that we need to start with an aromatase inhibitor in some of these endocrine-responsive tumors that have other elements of aggressiveness, like HER2 overexpression. For other tumors, a sequential strategy (e.g., two to three years of tamoxifen followed by three to

four years of an aromatase inhibitor) may be preferred. A differential strategy according to the tumor's molecular markers would not surprise me.

Martine Piccart, MD, PhD

Select Publications

Baum M et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses.** *Cancer* 2003;98(9):1802-10. [Abstract](#)

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1);[Abstract 3](#).

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](#)

Gnant M et al. **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (\pm zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: results of a randomized multicenter trial.** *Breast Can Res Treat* 2002;76(Suppl 1):31;[Abstract 12](#).

Lear-Kaul KC et al. **Her-2/neu status in breast cancer metastases to the central nervous system.** *Arch Pathol Lab Med* 2003;127(11):1451-7. [Abstract](#)

Leyland-Jones B et al. **Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel.** *J Clin Oncol* 2003;21(21):3965-71. [Abstract](#)

Lindrud S et al. **Central nervous system progression during systemic response to trastuzumab, humanized anti-HER-2/neu antibody, plus paclitaxel in a woman with refractory metastatic breast cancer.** *Breast J* 2003;9(2):116-9. [Abstract](#)

Lower EE et al. **Increased rate of brain metastasis with trastuzumab therapy not associated with impaired survival.** *Clin Breast Cancer* 2003;4(2):114-9. [Abstract](#)

Lyman GH et al. **Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices.** *J Clin Oncol* 2003;21(24):4524-31. [Abstract](#)

Osoba D et al. **Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer.** *J Clin Oncol* 2002;20(14):3106-13. [Abstract](#)

Pestalozzi BC, Brignoli S. **Trastuzumab in CSF.** *J Clin Oncol* 2000;18(11):2349-51. No abstract available

Shmueli E et al. **Central nervous system progression among patients with metastatic breast cancer responding to trastuzumab treatment.** *Eur J Cancer* 2004;40(3):379-82. [Abstract](#)

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

Therasse P et al, on behalf of the European Organization for Research and Treatment of Cancer. **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](#)

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

Selecting systemic therapy for patients with an initial relapse

I look at the characteristics of the primary tumor, the duration of the disease-free interval, the sites of the metastases and whether they are symptomatic or life-threatening.

If I am confident there is a reasonable chance that the woman will respond to endocrine therapy, it will be my first choice. I keep women on endocrine therapy as long as possible.

The best way to sequence hormonal agents is not yet known. However, strong evidence from several Phase III trials suggests that an aromatase inhibitor is superior to tamoxifen in postmenopausal women. No reason exists to not use an aromatase inhibitor initially in those women. Ongoing trials will determine the optimal therapy for women with disease that progresses on an aromatase inhibitor.



Role of fulvestrant in patients with disease that progresses on adjuvant tamoxifen

I'm still using an aromatase inhibitor as my first choice. Fulvestrant is a rational choice for patients who have been treated with an aromatase inhibitor and have disease progression. Since the estrogen receptor is still present and possibly hyperactive in these situations, it makes sense to use fulvestrant, which destroys the estrogen receptor. I believe that in the trials comparing fulvestrant to other drugs, fulvestrant will be superior.

In Belgium, fulvestrant is not registered for use, but we are able to obtain the drug on a compassionate-use basis. We have had a very good experience in terms of long-term disease stabilization rather than true objective response. We have been using fulvestrant in women who have received several lines of endocrine therapy.

This experience is encouraging and clearly demonstrates that fulvestrant has the potential to offer some activity, even after two to three lines of prior therapy. We have seen very long-lasting disease stabilization with this extremely well-tolerated agent.

Dr Piccart is the Head of the Chemotherapy Department at the Jules Bordet Institute and Chairwoman of the Breast International Group in Brussels, Belgium.

Resection of liver-only metastases in patients with HER2-positive, ER-negative disease

We need to approach patients who have HER2-positive, ER-negative disease with a different mindset. Sometimes women with HER2-overexpressing breast cancer and liver metastases have a dramatic response to a taxane and trastuzumab. After a while, the taxane must be discontinued because of toxicity, but trastuzumab is continued. If the disease is still controlled at that time, the woman will probably be a long-term survivor.

In these situations I consider whether a surgeon should try to remove the remaining metastatic lesions in the liver. Ideally, we should conduct a randomized trial to prove that this strategy will improve survival. However, I have done it in a few select cases — very young women who were willing to fight as much as possible. We discuss that there is no proof that resection of the liver metastases will improve their survival, and I don't propose this approach with only three to four months of treatment. Initially, I observe the quality of the response. I begin to consider this potential strategy when the woman is nine to 10 months from treatment initiation, doing well and has negative imaging studies.

Brain metastases in patients treated with trastuzumab

Approximately one-third of women who are responding to trastuzumab develop brain metastases. A few of my patients with brain metastases have died even though they had a complete remission in the liver. We need to develop clinical trials to address this problem, and I'm hoping that we can find something better than prophylactic cranial irradiation (PCI).

Perhaps it would be best to conduct a study with PCI when we are able to predict which women are at high risk for developing brain metastases. Maybe genetic profiling could help us, and we need to start investigating potential molecular markers that might indicate a higher risk of developing this complication.

Since these are patients in whom the disease is responding beautifully in other sites, it's obvious there is a problem with trastuzumab entering the blood-brain barrier (Figure 2.1). It is possible that the adjuvant trastuzumab trials may demonstrate an improvement in distant disease-free and overall survival but an increased risk of brain metastases. We are going to evaluate that very carefully in the large European adjuvant trastuzumab trial. Brain metastases may also be a problem with the taxanes.

Trastuzumab alone or in combination with chemotherapy

I use trastuzumab alone in a minority of patients — elderly women or young women who are not willing to undergo another course of chemotherapy. Otherwise, I prefer a combined strategy. In patients who have had a prior response to chemotherapy and trastuzumab and are now receiving trastuzumab alone but have disease progression, I don't stop trastuzumab; instead I reintroduce chemotherapy for three to four months. I have seen nice responses in those situations. If

the treatment-free interval was long, I might use the initial chemotherapy. If the treatment-free interval was six months or less, I would select a different agent.

We have strong data supporting the use of taxanes in combination with trastuzumab. A recent trial comparing docetaxel with or without trastuzumab had striking results favoring the combination (Figure 2.2). I believe it is a good regimen to choose. If I were to use paclitaxel, I would administer it weekly with trastuzumab. The trials comparing vinorelbine and paclitaxel are interesting. I have seen impressive anecdotal responses to vinorelbine plus trastuzumab.

Figure 2.1

Serum versus CSF Levels of Trastuzumab

“It is unknown whether and to what extent trastuzumab can cross the blood-brain barrier. Therefore, we measured CSF and concomitant serum levels of trastuzumab in a 62-year-old patient with meningeal carcinomatosis treated with weekly intravenous trastuzumab....

“A few hours after trastuzumab infusion, serum levels achieved were as expected in the range of 10,000 to 100,000 ng/mL. Concomitant CSF levels were 300-fold lower. Despite a possibly leakier blood-brain barrier in this patient with meningeal carcinomatosis, only minimal amounts of trastuzumab penetrated the CSF. Therefore, it is unlikely that intravenous trastuzumab would be useful to treat meningeal or cerebral disease of breast cancer.”

SOURCE: Pestalozzi BC, Brignoli S. *J Clin Oncol* 2000;18(11):2350-1. No abstract available

Figure 2.2

Phase II Randomized Trial of Docetaxel with or without Trastuzumab as First-Line Therapy in Women (N=188) with HER2-positive Metastatic Breast Cancer

	Docetaxel + trastuzumab	Docetaxel alone*	p-value
Overall response rate	61%	36%	0.001
Median survival	27.7 months	18.3 months	Not reported
Median time to progression	10.6 months	6.1 months	0.0001
Median duration of response	8.3 months	4.2 months	Not reported
Febrile neutropenia	23%	17%	Not reported

*44 percent of the patients treated with docetaxel alone crossed over to receive trastuzumab

SOURCE: Extra JM et al. **First-line trastuzumab (Herceptin®) plus docetaxel versus docetaxel alone in women with HER2-positive metastatic breast cancer (MBC): results from a randomised phase II trial (M77001).** *Breast Cancer Res Treat* 2003;82(Suppl):47:Abstract 217.

Scheduling of trastuzumab

Good data about the every three-week trastuzumab schedule do not exist. A Phase II trial with about 100 patients demonstrated a response rate for every three-week trastuzumab that was similar to the response rate with a weekly schedule. I'm still a little uncomfortable because I do not believe that either of the schedules is the right one, and there could potentially be a better schedule.

Our Canadian colleagues have been evaluating a higher loading dose administered up front. Since I'm still uncomfortable with the question of optimal schedule in a woman at high risk who needs a rapid response, I start with a weekly schedule and then switch to an every three-week schedule as soon as I know she's responding. This is a very conservative approach, and I am not saying I am right. It's just the way I do it (Figure 2.3).

Figure 2.3

Scheduling of Trastuzumab

What schedule of trastuzumab do you generally use?

Weekly	Every three weeks
88%	12%

SOURCE: National Patterns of Care Survey of Medical Oncologists, 2004.

Nonprotocol management of patients with HER2-negative, ER-negative metastatic disease

These patients can only benefit from chemotherapy. I use combination chemotherapy when I need a quick response and sequential single agents when I don't. In a patient who has recently received adjuvant AC and a taxane and has relapsed, I would probably use capecitabine 2,100 mg/m², two weeks on and one week off, as my first choice for a sequential single agent.

Interestingly, an ongoing EORTC trial (EORTC-10001) is comparing capecitabine and vinorelbine in these women. We don't know which drug is better in this situation, but women tend to like an oral drug and many would choose capecitabine. In a woman who has received prior adjuvant ACT and is ill with metastatic disease, I like to use vinorelbine and capecitabine or vinorelbine and 5-FU regimens, which are quite effective and relatively well-tolerated.

Select publications

Bendell JC et al. **Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma.** *Cancer* 2003;97(12):2972-7. [Abstract](#)

Esteva FJ et al. **Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002 1;20(7):1800-8. [Abstract](#)

- Extra JM et al. **First-line trastuzumab (Herceptin®) plus docetaxel versus docetaxel alone in women with HER2-positive metastatic breast cancer (MBC): results from a randomised phase II trial (M77001).** *Breast Cancer Res Treat* 2003;82(Suppl):47; [Abstract 217](#).
- Lear-Kaul KC et al. **Her-2/neu status in breast cancer metastases to the central nervous system.** *Arch Pathol Lab Med* 2003;127(11):1451-7. [Abstract](#)
- Leyland-Jones B et al. **Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel.** *J Clin Oncol* 2003;21(21):3965-71. [Abstract](#)
- Lindrud S et al. **Central nervous system progression during systemic response to trastuzumab, humanized anti-HER-2/neu antibody, plus paclitaxel in a woman with refractory metastatic breast cancer.** *Breast J* 2003;9(2):116-9. [Abstract](#)
- Lower EE et al. **Increased rate of brain metastasis with trastuzumab therapy not associated with impaired survival.** *Clin Breast Cancer* 2003;4(2):114-9. [Abstract](#)
- Montemurro F et al. **A phase II study of three-weekly docetaxel and weekly trastuzumab in HER2-overexpressing advanced breast cancer.** *Oncology* 2004;66(1):38-45. [Abstract](#)
- Osoba D et al. **Effects on quality of life of combined trastuzumab and chemotherapy in women with metastatic breast cancer.** *J Clin Oncol* 2002;20(14):3106-13. [Abstract](#)
- Pestalozzi BC, Brignoli S. **Trastuzumab in CSE.** *J Clin Oncol* 2000;18(11):2349-51. No abstract available
- Robert N et al. **Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive breast cancer.** *Breast Cancer Res Treat* 2002;76(Suppl):37; [Abstract 35](#).
- Shmueli E et al. **Central nervous system progression among patients with metastatic breast cancer responding to trastuzumab treatment.** *Eur J Cancer* 2004;40(3):379-82. [Abstract](#)
- Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-92. [Abstract](#)
- Tedesco KL et al. **Docetaxel combined with trastuzumab is an active regimen in HER-2 3+ overexpressing and fluorescent in situ hybridization-positive metastatic breast cancer: A multi-institutional phase II trial.** *J Clin Oncol* 2004 5;22(6):1071-7. [Abstract](#)
- Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26. [Abstract](#)

CAN-NCIC-MA17 trial of letrozole versus placebo after five years of adjuvant tamoxifen

We know from previous studies that continuing adjuvant tamoxifen beyond five years is not beneficial and, according to one study, might even be deleterious. MA17 randomly assigned patients who had completed five years of tamoxifen to five years of letrozole or a placebo.

The trial was stopped early because the estimated benefit of letrozole was substantially greater than expected — unblinding revealed a 40 percent reduction in recurrences in the patients on letrozole.

Today, many women diagnosed with breast cancer receive adjuvant aromatase inhibitors. But for the thousands currently on adjuvant tamoxifen, the results of MA17 are applicable. Women with very low-risk disease may not derive enough benefit from an additional five years of hormonal therapy to make it worthwhile, but for women at higher risk, switching to an aromatase inhibitor is a reasonable alternative and I offer it to my patients.

MA17 limited enrollment to patients who had completed tamoxifen within the past three months, but I'm comfortable extending that to six months or even 12 months for patients at very high risk.

Estrogen deprivation in HER2-positive, ER-positive breast cancer

As predicted based on model systems, estrogen deprivation has been shown to be beneficial in HER2-positive, ER-positive tumors. Even though such tumors have numerous estrogen receptors in the membrane and nucleus, and high growth factor signaling, if the estrogen receptors are not activated with a ligand such as tamoxifen or estrogen, neither of these pathways are activated.

A few years ago people doubted the results of Matt Ellis' study in which letrozole produced a much higher response rate than tamoxifen in patients with HER2-positive disease because the study involved a small number of patients. However, Mitch Dowsett's IMPACT trial has shown that another aromatase inhibitor



— anastrozole — is also much better than tamoxifen in these patients. In practice, when HER2 is overexpressed, estrogen deprivation may be a better choice than tamoxifen — either an oophorectomy in younger women or an aromatase inhibitor in older women.

Tamoxifen resistance and the conversion of tumors from HER2-negative to HER2-positive

We have laboratory and clinical data suggesting that tamoxifen can convert a tumor from HER2-negative to HER2-positive (Figure 3.1). In an in vivo model using a cell line with low EGFR and HER2, we've shown that initially, tamoxifen has antiestrogenic activity on the tumor. However, after three or four months tamoxifen resistance develops, and tamoxifen acquires the ability to stimulate the tumor.

Figure 3.1

Changes in Estrogen Receptor and HER2 Status in Tamoxifen-Relapsed Breast Cancer

"Of the 29 ER+ patients 5 (17%) became ER- at R. Three patients were HER2+ PT and remained so at R, but another 3 that were HER2- PT became HER2+ at R, 2 of these remaining ER+. ...

"The data indicate that tamoxifen-relapsed breast cancer varies substantially from PT: decreases in ER+ and increases in HER2+ status occur; tumors that are ER+/HER2+ at relapse express high levels of p-P38. Since HER2 and P38 signaling can activate ER and enhance tamoxifen agonist activity inhibition of these pathways is a strategy worth exploring."

R = relapse; PT = pretreatment

SOURCE: Dowsett M et al. **Molecular changes in tamoxifen-relapsed breast cancer: Relationship between ER, HER2 and P38-MAP-kinase.** *Proc ASCO 2003;Abstract 7.*

At three or four months, increased EGF and HER2 receptors are on the cell membrane. Blocking those can prevent the development of tamoxifen resistance. A tyrosine kinase inhibitor like gefitinib, trastuzumab or both can be used to inhibit the EGFR/HER2 pathway. The combination is superior because each drug inhibits the growth factor pathway in a different way.

Clinical data demonstrating the conversion of tumors from HER2-negative to HER-2 positive is limited because it requires serial biopsies. We collaborated on a study with Mitch Dowsett in which we had biopsies from 37 patients taken just before tamoxifen use, with subsequent biopsies taken at the time of tamoxifen resistance. We found three cases that were initially HER2-negative but converted to positive at the time of tamoxifen resistance. Two of those were actually gene-amplified.

We need to confirm that with a larger data set, but it may be that in some patients, EGFR and HER2 are upregulated at the time of tamoxifen resistance. From a practical perspective, patients with HER2-negative tumors who progress on tamoxifen should be retested because if the metastases are positive, trastuzumab may be indicated.

As we develop more targeted therapies, we'll need to perform more biopsies in the metastatic setting to identify changes in the tumor profile in order to select the appropriate therapy. EGFR and HER2 can go up in a small proportion, estrogen receptor goes away in 15 to 20 percent, and there may be other potentially targeted molecules that can change over time.

Mechanism of action of fulvestrant

Fulvestrant degrades the estrogen receptor — it's a complete antagonist on the nuclear receptors, and studies suggest it is also an antagonist on the membrane receptors. This may explain why HER2-overexpressing tumors respond well to fulvestrant in cultured model systems and in vivo models. Hypothetically, fulvestrant in the HER2-overexpressing tumor blocks the cross-talk by eliminating the estrogen receptor; thus the estrogen receptor can't activate the growth factor pathway. We don't have clinical data to confirm this, but we expect that in patients with ER-positive, HER2-positive tumors, fulvestrant might be more effective than tamoxifen.

Prolonged duration of response with fulvestrant

In animal models comparing fulvestrant to tamoxifen, fulvestrant substantially prolonged the time it took for the development of resistance. However, at the current dose we have not yet seen that translate into a longer duration of response in clinical trials. On the other hand, in the two trials of second-line fulvestrant versus anastrozole, the duration of response with fulvestrant was significantly longer in one of the trials — 19 months versus 11 months — and the combined analysis showed a longer duration of remission in patients treated with fulvestrant (Figure 3.2). Although clinical data suggest that long remissions can be seen with fulvestrant, I believe we haven't had enough studies with fulvestrant and we don't know the optimal dose.

Efficacy of fulvestrant in the metastatic setting

In patients progressing on tamoxifen, tamoxifen binds the estrogen receptors and may actually stimulate growth of the tumor — it certainly is no longer inhibiting it. Treating these patients with an aromatase inhibitor will be ineffective until all the tamoxifen is gone, which takes a couple of months.

Fulvestrant, on the other hand, competes with tamoxifen for binding, thus the response may be quicker with fulvestrant than with an aromatase inhibitor in that setting.

Figure 3.2

Efficacy of Fulvestrant Compared to Anastrozole in Postmenopausal Women with Advanced Breast Cancer Progressing on Prior Endocrine Therapy: Combined Analysis of Two Multicenter Trials

	Fulvestrant (n=428)	Anastrozole (n=423)
Complete response	4.7%	2.6%
Partial response	14.5%	13.9%
Objective response rate	19.2%	16.5%
Clinical benefit*	43.5%	40.9%
Disease progression	50.2%	52.2%
Median time to disease progression	5.5 months	4.1 months
Median duration of response in those responding	16.7 months	13.7 months

*Clinical benefit = complete response + partial response + stable disease \geq 24 weeks

SOURCE: Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38. [Abstract](#)

We expected fulvestrant to be superior to tamoxifen, but in the first-line setting it proved to be similar, not better. That's peculiar because second-line trials show fulvestrant to be equal to or better than aromatase inhibitors, and aromatase inhibitors have been shown to be superior to tamoxifen.

It may be that we're just not dosing fulvestrant correctly. We know from the randomized trial that half of the currently recommended dose is insufficient, and we know it takes three to six treatments to achieve steady state blood levels with fulvestrant, so perhaps a higher dose or a loading dose (or both) is required. These options are being investigated (Figure 3.3).

Adjuvant trastuzumab

I'm optimistic that trastuzumab will be effective in targeting HER2-overexpressing tumors in the adjuvant setting. With tamoxifen, our first targeted therapy, we saw a 30 percent response rate and 20 percent stable disease rate in patients with ER-positive metastatic disease. When used for five years in the adjuvant setting, however, it reduced the recurrence rate by almost half. In HER2-positive metastatic disease, approximately 25 percent of patients experience remission with trastuzumab monotherapy, but what if trastuzumab offers an advantage similar to that of tamoxifen in the adjuvant setting?

Figure 3.3

Ongoing Clinical Trials of Fulvestrant

Study	Trial design	Dosing/scheduling of fulvestrant	Targeted accrual
NCCTG-N0032	Phase II trial of fulvestrant in postmenopausal women after progression on an aromatase inhibitor ± tamoxifen	250 mg monthly	80
SAKK	Phase II trial of fulvestrant in postmenopausal women after progression on tamoxifen and a nonsteroidal aromatase inhibitor	250 mg monthly	93
EFFECT	Double-blind, placebo-controlled Phase III trial of fulvestrant vs exemestane in postmenopausal women after progression on a nonsteroidal aromatase inhibitor	500 mg day 0, 250 mg days 14, 28 and then monthly	660
SOFEA	Phase III trial of fulvestrant vs fulvestrant + anastrozole vs exemestane in postmenopausal women with ER- and/or PgR-positive breast cancer who progressed on anastrozole or letrozole	250 mg monthly	750
SWOG-S0226	Phase III trial of anastrozole vs fulvestrant in postmenopausal women with ER- and/or PgR-positive advanced breast cancer	250 mg monthly	690
FACT	Phase III trial of anastrozole + fulvestrant vs anastrozole in postmenopausal women with ER- and/or PgR-positive metastatic breast cancer or premenopausal women on goserelin	500 mg day 0, 250 mg days 14, 28 and then monthly	558
ECOG-4101	Phase II trial of fulvestrant + gefitinib vs anastrozole + gefitinib in postmenopausal women with ER- and/or PgR-positive metastatic breast cancer	250 mg monthly	204

SOURCE: Sahmoud T. **Clinical trial designs for further development of fulvestrant (Faslodex®)**. Poster, Lynn Sage Breast Cancer Symposium, September 2003.

It’s clear that when you’re treating widespread metastatic disease, all of these therapies, particularly chemotherapy and targeted therapies, have a much greater effect on micrometastases than macrometastases. We’ll know more in a year or two when we begin receiving data from the current adjuvant trastuzumab trials (Figure 3.4).

Neoadjuvant trastuzumab monotherapy

Jenny Chang, a member of our group, presented a study of neoadjuvant trastuzumab given weekly for three weeks to women with HER2-overexpressing tumors. Within three weeks, 26 percent of the patients already had a partial remission, and all of the patients had some reduction in tumor size. I think these targeted therapies will be much more effective early on in the tumor’s life than in treating widespread metastatic disease. And it may turn out that we’ll see definite activity of these agents, even with just a few weeks of treatment.

The study had only 27 patients and the objective was to learn about predictors of trastuzumab activity, what targets are being blocked by trastuzumab and so forth. But, to our surprise, within three weeks we saw these responses. The median reduction in tumor volume was 20 percent.

Figure 3.4

Clinical Trials of Adjuvant Trastuzumab

"The testing of trastuzumab in the adjuvant setting is currently in progress, given the demonstration of survival benefit with trastuzumab and chemotherapy in advanced-stage disease, and the observation of poorer outcomes in patients with HER2-positive breast cancer. There are currently four major phase III multicenter trials that in total will randomize approximately 12,000 patients to regimens with or without trastuzumab. ..."

"The major endpoints of these trials include overall and disease-free survival. The further investigation of the cardiac safety of trastuzumab in relation to the anthracyclines is also an important component in these studies."

SOURCE: Tan AR, Swain SM. **Ongoing adjuvant trials with trastuzumab in breast cancer.** *Semin Onc* 2003;30(suppl 16):54-64. [Abstract](#)

Now we're beginning to think that maybe we should do a trial of longer-term treatment. What if we treated for six weeks rather than three? Maybe the majority of the patients would already have a partial remission. Plus, we learned that trastuzumab induces apoptosis and doesn't seem to have much of an impact on cell proliferation, which was shown in vitro (Figure 3.5).

Figure 3.5

Induction of Apoptosis with Neoadjuvant Trastuzumab

"Contrary to in vitro data, human breast cancer specimens obtained from this prospective in vivo study demonstrate for the first time that trastuzumab induces apoptosis but does not affect cell cycle kinetics in the primary breast cancers of women receiving neoadjuvant treatment. This data suggests that trastuzumab would not likely antagonize the effects of chemotherapy by reducing the proliferation rate, which might be of concern with other growth factor inhibitors. In addition, since trastuzumab results in tumor cell death, shorter treatment durations rather than indefinite long-term treatment should be investigated."

SOURCE: Chang JC et al. **Induction of apoptosis without change in cell proliferation in primary breast cancers with neoadjuvant trastuzumab.** *Breast Cancer Res Treat* 2003;[Abstract 24](#).

But tumor cells growing on glass in vitro don't mimic the in vivo situation very well. You can obtain some clues but — unlike receptor tyrosine kinase inhibitors like gefitinib, which inhibit cell proliferation — trastuzumab seems to work by apoptosis, at least in this one study. It induces apoptosis within a week of treatment.

Obviously, it was a small study with a very short duration, but we learned a great deal about trastuzumab. We saw apoptosis and rapid reductions in tumor size in some patients, and none of the patients progressed during that three-week period. People had thought, based on other trials, that trastuzumab would downregulate and degrade HER2, but we didn't observe a change in the HER2 level during that period of time.

A great deal of interesting biologic information was derived from this small study that will help plan subsequent neoadjuvant studies to determine how these drugs should be used.

Select Publications

Baum M et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses.** *Cancer* 2003;98(9):1802-10. [Abstract](#)

Bharwani L et al. **Inhibiting the EGFR/HER2 pathway with gefitinib and/or trastuzumab restores tamoxifen sensitivity in HER2-overexpressing tumors.** *Breast Cancer Res Treat* 2003;[Abstract 25](#).

Boccardo F et al. **Anastrozole appears to be superior to tamoxifen in women already receiving adjuvant tamoxifen treatment.** *Breast Cancer Res Treat* 2003;82(Suppl 1);[Abstract 3](#).

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (arimidex, tamoxifen, alone or in combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;[Abstract 4](#).

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](#)

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802. [Abstract](#)

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

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial.** *J Clin Oncol* 2002;20(16):3386-95. [Abstract](#)

Osborne CK et al. **Role of the estrogen receptor coactivator AIB1 (SRC-3) and HER2/neu in tamoxifen resistance in breast cancer.** *J Natl Cancer Inst* 2003;95(5):353-61. [Abstract](#)

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38. [Abstract](#)

Smith I, Dowsett M, on behalf of the IMPACT Trialists. **Comparison of anastrozole vs tamoxifen alone and in combination as neoadjuvant treatment of estrogen receptor-positive (ER+) operable breast cancer in postmenopausal women: the IMPACT trial.** *Breast Cancer Res Treat* 2003;[Abstract 1](#).

CALGB-49907: Capecitabine versus CA/CMF in the elderly

This trial evaluates whether there is equivalence between the standard chemotherapy regimens of AC or CMF versus oral capecitabine, and how these regimens impact survival in elderly women, for whom we have very little trial data.

In addition to the more familiar ER, PR and HER2 markers, we are looking at some interesting predictive and prognostic markers and other biological markers. We are also examining how these drugs are processed in the elderly population.

The data from the metastatic setting provided the rationale for selecting capecitabine for this trial. In addition to the convenience of an oral regimen, the trials comparing capecitabine to single-agent paclitaxel and to CMF demonstrated benefits from capecitabine in time to progression. However, capecitabine is not a benign drug, so we are closely monitoring patients.

Originally, the dosing for capecitabine started at 2,000 mg/m² per day in divided doses, two weeks on and one week off for four cycles, and could be increased to the 2,500 mg/m² level described in the package insert. However, two deaths have occurred during the trial, one of which was consistent with a DPD deficiency. This patient became myelosuppressed and septic within just a few days of receiving her first cycle. The second patient, who had tolerated most of her treatments very well, was dose-escalated and ultimately developed toxicities and died. As a result, the trial was amended, and capecitabine dosing is now capped at 2,000 mg/m².

Choice of single-agent versus combination chemotherapy in patients with HER2-negative, ER-negative disease

My approach in selecting single-agent versus combination chemotherapy really depends on whether a patient presents with visceral crisis and a heavy burden of disease. I tend to use capecitabine/docetaxel combination therapy in patients with visceral crises. I don't want to wait two or three months to see what kind of response the patient will have with single-agent therapy (Figure 4.1). I'm



Figure 4.1

Benefit of Combination Therapy in Patients with Significant Tumor Burden

“The early separation of the survival curves suggests that the combination therapy prevented early deaths in a subset of patients, the majority of whom had heavily pretreated disease and significant tumor burden in this trial. . . .

“In addition, it should be taken into account that after failure of study chemotherapy in the current trial, only 60% to 70% of patients received further cytotoxic therapy. Therefore, 30% to 40% of patients did not have the opportunity to benefit from subsequent chemotherapy administered sequentially.”

EXCERPT FROM: O’Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results.** *J Clin Oncol* 2002;20:2812-23. **Abstract**

impressed by the fast responses with the combinations.

If, on the other hand, I have an asymptomatic patient with low-burden disease, I will stretch my single-agent therapy in a sequential fashion for as long as I can. The sequence will depend upon the treatment goals I have established with the patient, what toxicity profile the patient is willing to undertake and the disease-free interval from the most recent chemotherapy. If, for example, a patient relapses within six months of receiving AC followed by docetaxel, I would opt for a non-taxane-containing regimen.

In stable patients I would probably use capecitabine because of its oral administration and excellent response profile. In patients who progress on capecitabine, I would look at other single agents, such as vinorelbine or gemcitabine, with the order depending on what side effects patients were willing to tolerate.

In patients presenting *de novo* with HER2-negative metastatic disease, I will opt for capecitabine/docetaxel, depending on their burden of disease. If I want a quick response, I’ll use anthracyclines up front, knowing that I have a finite window of opportunity for treatment. In patients with ER-negative disease I generally prefer drugs that I’ll be able to use long-term.

Clinical trial evaluating nonpegylated liposomal doxorubicin plus trastuzumab

The pivotal trial of chemotherapy and trastuzumab demonstrated a 27 percent overall and 16 percent symptomatic cardiac dysfunction rate, but the trial also demonstrated survival benefits in the anthracycline/trastuzumab arm. This inspired us to find a safer way to bring this class of agents back into the clinical setting with trastuzumab. We are particularly motivated because trastuzumab is now being evaluated in the adjuvant setting, and we’d like to identify a cardiac-safe regimen for potentially curable patients.

Gerald Batist looked at this issue in a trial of liposomal versus conventional doxorubicin plus cyclophosphamide, which demonstrated equivalent time to progression in both arms and a cardiac safety advantage in the liposomal arm. We participated in a cardiac safety trial of nonpegylated liposomal doxorubicin in combination with trastuzumab.

We studied 37 women with this drug combination and saw that only two patients actually had cardiac toxicity. One patient was asymptomatic but was withdrawn because of a drop in LVEF; the other patient had symptomatic cardiac disease. The low rate of nonhematologic toxicity was wonderful, but the real surprise in the trial was the 58 percent overall response rate and a clinical benefit of 79 percent.

These exciting results may encourage further study of liposomal doxorubicin in combination with trastuzumab. Jose Baselga, for instance, is leading a European team of investigators in studying the metastatic application of this drug combination with a taxane in patients with HER2-positive disease.

Treatment of HER2-positive, anthracycline-naïve patients with metastatic disease

I'll treat these patients with trastuzumab plus vinorelbine or a taxane, or use a triplet such as carboplatin/paclitaxel/trastuzumab, depending upon the patient's tolerance for side effects. Of course, it would be ideal to enroll patients in a clinical trial with trastuzumab and liposomal doxorubicin. I withhold anthracyclines until later.

Trastuzumab monotherapy is also a reasonable option for patients with small-volume, HER2-positive disease who are not open to the idea of chemotherapy. Chuck Vogel demonstrated a 47 percent clinical benefit with trastuzumab monotherapy in chemotherapy-naïve patients with measurable metastatic disease (Figure 4.2). I tend to use trastuzumab with chemotherapy up front and then apply trastuzumab alone as maintenance treatment.

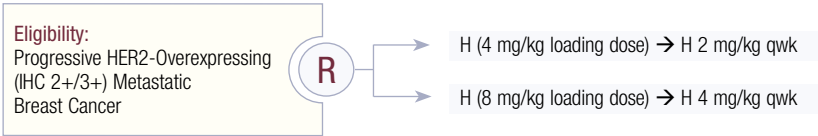
Choice of chemotherapy in combination with trastuzumab for metastatic disease

I have been using carboplatin/docetaxel/trastuzumab frequently, especially in patients with bulky disease and visceral crises. My choice of which chemotherapeutic agent to use is guided by the toxicities a patient is willing to tolerate. A woman with newly diagnosed metastatic disease may feel absolutely violated by the idea of hair loss with the use of a weekly taxane. I also like the vinorelbine/trastuzumab combination. It's well-tolerated and generates good responses.

Once a patient reaches an optimal response on combination therapy, I discontinue the chemotherapy and maintain them on trastuzumab almost indefinitely. Some of my patients have been on monotherapy for three or four years, if only to avoid the possibility of upregulating proliferative mechanisms when trastuzumab is stopped.

Figure 4.2

Randomized Study of Standard versus Higher-Dose Trastuzumab Monotherapy as First-Line Therapy in Women with HER2-Overexpressing Metastatic Breast Cancer



H = trastuzumab

Response, clinical benefit and survival with first-line trastuzumab

Subset	Objective response	Clinical benefit*	Median duration of survival
All Patients	29/111 (26%)	42/111 (38%)	24 months
ER-positive	12/52 (23%)	19/52 (36%)	–
ER-negative	16/54 (30%)	21/54 (39%)	–
IHC 3+	29/84 (35%)	40/84 (48%)	–
IHC 2+	0/27 (0%)	2/27 (7%)	–
FISH-positive	27/79 (34%)	38/79 (48%)	–
FISH-negative	2/29 (7%)	3/29 (10%)	–

*Clinical benefit = complete, partial or minor response or stable disease greater than 6 months

Note: There was no evidence of a dose-response relationship for response, survival or adverse events.

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

If patients progress on maintenance trastuzumab, I go back to the original chemotherapy/trastuzumab regimen and often I've regained a response. If I do not regain a response, I quickly switch to a different chemotherapy after eight to 10 weeks. Even when I switch chemotherapies, I continue the trastuzumab as long as I'm getting a response from the new chemotherapy.

If a patient progresses rapidly after introducing a new chemotherapy agent, it becomes apparent that trastuzumab is no longer effective. At this point, I stop the antibody and look for available clinical trials or introduce conventional anthracyclines in patients who have never had them. If a patient has tried the conventional anthracyclines, I use weekly anthracyclines.

Algorithm for HER2 testing

A forthcoming publication will provide the results of an analysis of tissue samples we conducted at Memorial Sloan-Kettering. We evaluated almost 3,000 surgical specimens. Of those samples that received a zero grading by good pathologists and a good reference lab with large volume experience, using the HercepTest®, we

tried to determine how many were actually FISH-amplified. We found that one in 100 of our specimens was FISH-amplified, despite having tested zero by IHC.

Our analysis also demonstrated that some IHC 1+ samples were FISH-amplified. We know that approximately 10 percent of 1+ patients will show FISH-amplification. Although in most clinical settings an IHC of zero to 1+ is deemed negative for HER2, we occasionally encounter a patient who is FISH-amplified (Figure 4.3).

A retrospective analysis of 500 paraffin blocks demonstrated that patients who scored zero or 1+ were FISH-amplified three and seven percent of the time, respectively. In patients who were IHC 2+, 25 percent were FISH-amplified. IHC 3+ cases correlated with FISH over 90 percent of the time.

Clearly, there remains a gray area surrounding IHC scores of 1+ and zero. This has a huge impact in the metastatic setting. You may treat a patient with a non-trastuzumab-containing regimen who is refractory to chemotherapy and not responding to hormonal therapy the way in which you would expect most metastatic breast cancers to respond. In patients who have a short disease-free survival and present with metastatic disease fairly quickly after adjuvant treatment for node-negative disease, I often go back and check for gene amplification with FISH.

Figure 4.3

Defining HER2 Positivity

How do you interpret the following lab results?

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

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

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

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

SOURCE: National Patterns of Care Survey of Medical Oncologists, 2003.

CALGB-9741: Dose-dense versus conventionally scheduled chemotherapy

The dose-dense study recently reported by Marc Citron was very interesting. It attempted to answer the question of how to apply mathematical modeling in our efforts to circumvent chemotherapy resistance in the adjuvant setting, while simultaneously optimizing survival.

Specifically, the study examined chemotherapy regimens given every 14 days with growth factor support, as opposed to the conventional 21-day cycle. What I found most impressive was the safety data that showed the very minimal toxicities associated with the dose-dense therapy. Whether the survival curves continue to separate remains to be seen.

Although confirmatory trials are needed to determine the potency of this regimen, dose density might prove to be the way to treat patients in whom cell mutation is a concern. Could we be over-treating patients with this regimen? Perhaps, but given the safety data so far reported, I'm very enthusiastic about using dose-dense chemotherapy and would be comfortable with that "over-treatment" in a node-positive patient.

Select Publications

Batist G et al. **Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer.** *J Clin Oncol* 2001;19:1444-54. [Abstract](#)

Citron M 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;21:1431-9. [Abstract](#)

O'Shaughnessy J. **Capecitabine and docetaxel in advanced breast cancer: analyses of a phase III comparative trial.** *Oncology* 2002;16(10 Suppl 12):17-22. [Abstract](#)

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

Theodoulou M et al. **TLC D99 and Herceptin is safe in advanced breast cancer: final cardiac safety and efficacy analysis.** *ASCO Annual Meeting* 2002;[Abstract 216](#).

Trigo J et al. **Cardiac safety and activity of a phase I study of 3-weekly myocet in combination with weekly herceptin and paclitaxel in HER2-positive locally advanced or metastatic breast cancer.** *ASCO Annual Meeting* 2002;[Abstract 242](#).

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

PowerPoint Atlas: HER2 and Adjuvant Trastuzumab

Editor's Note: The PowerPoint files of the following slides are located on CD 1 and can also be downloaded at BreastCancerUpdate.com.

Slide 1: HercepTest® 3+ tumor cell staining

Slide 2: HercepTest® 3+ tumor cell staining in lymphatic vessels

Slide 3: HercepTest® 2+ tumor cell staining

Slide 4: HercepTest® 2+ tumor cell staining

Slide 5: Very weak HER2 expression (HercepTest® 1+) with incomplete membrane staining

Slide 6: HER2 gene amplified via FISH

Slide 7: HER2 gene amplified via FISH viewed by confocal laser microscopy

Slide 8: In situ hybridization with a chromogenic tag (CISH)

Slide 9: Randomized clinical trials of adjuvant trastuzumab

Slide 10: Intergroup comparison of local and central HercepTest®

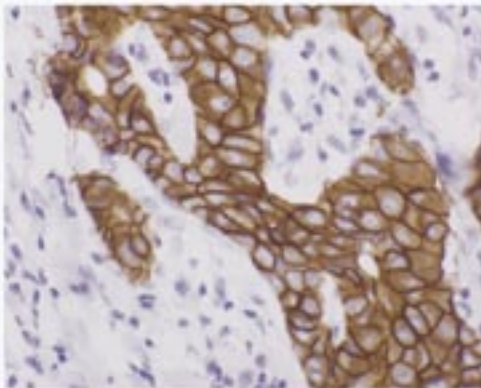
Slide 11: Intergroup comparison of local HER2 testing and central FISH

Slide 12: Intergroup comparison of central HercepTest® and FISH

Slide 13: NSABP-B-31 comparison of local IHC 3+ and central HER2 testing

Slide 1

HercepTest® 3+: Tumor Cells with HER2 Protein on Cytoplasmic Membranes

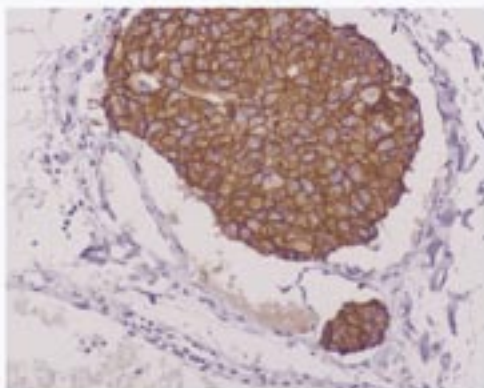


Courtesy of Mehrdad Nadji, MD, University of Miami School of Medicine

Breast Cancer
UPDATE

Slide 2

**HercepTest® 3+: Tumor Cells in Lymphatic
Vessels in Inflammatory IDC**

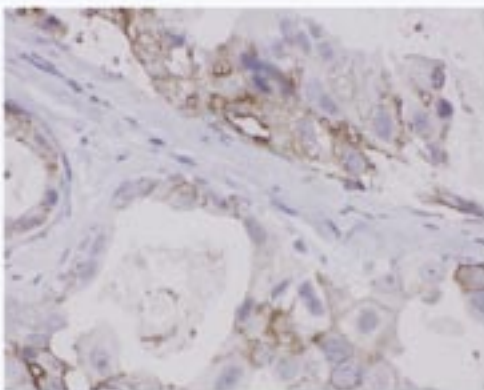


Courtesy of Mehrdad Nadji, MD, University of Miami School of Medicine

Breast Cancer
EPSTE

Slide 3

**HercepTest® 2+ with HER2 Overexpression
in Most but Not All Tumor Cells**

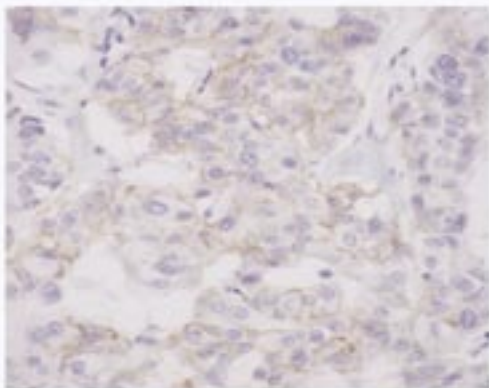


Courtesy of Mehrdad Nadji, MD, University of Miami School of Medicine

Breast Cancer
EPSTE

Slide 4

**HercepTest® 2+ with Weaker Staining in
Some but Not All Tumor Cells**

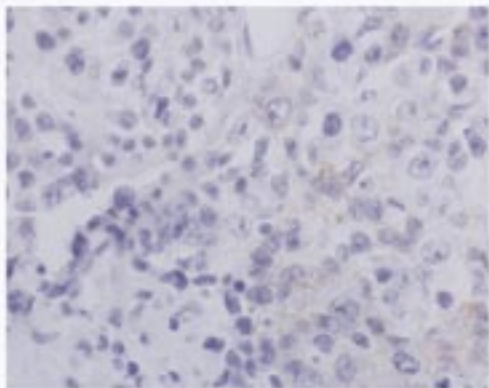


Courtesy of Mehrdad Nadji, MD, University of Miami School of Medicine

Breast Cancer
STATS

Slide 5

**Very Weak HER2 Expression (HercepTest® 1+) in
Few Cells and Incomplete Membrane Staining**

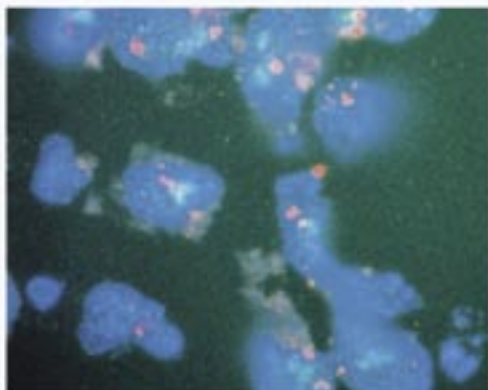


Courtesy of Mehrdad Nadji, MD, University of Miami School of Medicine

Breast Cancer
STATS

Slide 6

HER2 Gene Amplified via FISH with Red Dots as a Marker for Chromosome 17

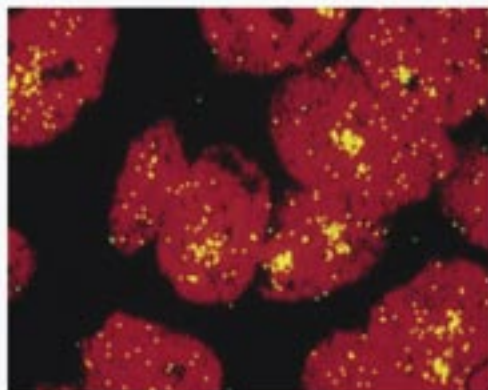


Courtesy of Mehrdad Nadj, MD, University of Miami School of Medicine

Breast Cancer
EPHAPS

Slide 7

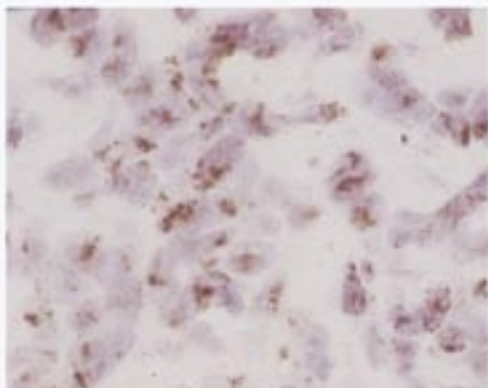
HER2 Gene Amplified by FISH Seen as Yellow Dots as Viewed by Confocal Laser Microscopy



Courtesy of Mehrdad Nadj, MD, University of Miami School of Medicine

Breast Cancer
EPHAPS

In Situ Hybridization with a Chromogenic Tag (CISH): HER2 Gene Seen as Brown Granules



Courtesy of Mehrdad Nadji, MD, University of Miami School of Medicine

Breast Cancer
EPHAPS

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 qwk x 1 year
Intergroup N9831 (3,300 patients)	Node + IHC 3+ or FISH+	AC x 4 → paclitaxel qwk x 12 AC x 4 → paclitaxel qwk x 12 → H qwk x 1 year AC x 4 → (paclitaxel + H) qwk x 12 H qwk x 40 wks
BCIRG-006 (3,150 patients)	Node + FISH+	AC x 4 → docetaxel x 4 AC x 4 → docetaxel x 4 + H (qwk x 12 wks) → H (qwk x 40 wks) (Docetaxel + C) x 6 + H (qwk x 18 wks) → H (qwk x 34 wks)
BIG-01-01 HERA (4,482 patients)	Node + and - IHC 3+ or FISH+	H q3w x 1 year H q3w x 2 years No H

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

Source: NCJ Physician Data Query, April 2004.

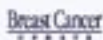
Breast Cancer
EPHAPS

Slide 10

Comparison of Local HER2 Testing Performed for Study Entry into N9831 and Central HercepTest™

	Central HercepTest™ Score				Total
	3+	2+	1+	0	
Local HER2 Testing					
IHC-positive (3+)	81	12	9	8	110
FISH-positive	7	0	1	1	9
Total	88	12	10	9	119

Source: Roche PC et al. *J Natl Cancer Inst* 2002;94(11):855-7.

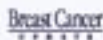


Slide 11

Comparison of Local HER2 Testing Performed for Study Entry into N9831 and Central FISH

	Central FISH Result		Total
	Not amplified	Amplified	
Local HER2 Testing			
IHC-positive (3+)	37	73	110
FISH-positive	3	6	9
Total	40	79	119

Source: Roche PC et al. *J Natl Cancer Inst* 2002;94(11):855-7.

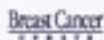


Slide 12

Comparison of Central FISH and Central HercepTest™ in N9831

	Central HercepTest™ Score				Total
	3+	2+	1+	0	
Central Vysis® FISH					
Not amplified	9	12	10	9	40
Amplified	79	0	0	0	79
Total	88	12	10	9	119

Source: Roche PC et al. *J Natl Cancer Inst* 2002;94(11):855-7.



Slide 13

NSABP-B-31: Central Laboratory Testing of Specimens Scored as IHC 3+ by Community Laboratories

Central Laboratory's Results	Percent of Cases (n=104)
Strongly positive (3+) by the HercepTest™ assay	79%
Positive for gene amplification by the PathVysion™ FISH assay	79%
Neither strongly positive (3+) by the HercepTest™ assay nor positive for gene amplification	18%

Palk S et al. *J Natl Cancer Inst* 2002;94(11):852-4.



QUESTIONS (PLEASE CIRCLE ANSWER):

1. The Intergroup trial SWOG-S0221 will compare two schedules of adjuvant AC and two schedules of paclitaxel.
 - a. True
 - b. False
2. Adjuvant dose-dense therapy offers which of the following advantages:
 - a. Greater efficacy
 - b. Less toxicity
 - c. Shorter duration of therapy
 - d. All of the above
 - e. None of the above
3. In the adjuvant setting, current clinical trials are evaluating the sequential use of SERMs and aromatase inhibitors.
 - a. True
 - b. False
4. In postmenopausal women with metastatic breast cancer, Phase III trial data suggest that tamoxifen is superior to aromatase inhibitors.
 - a. True
 - b. False
5. Close to 80 percent of women who are responding to trastuzumab develop brain metastases.
 - a. True
 - b. False
6. A recent trial found docetaxel plus trastuzumab to be superior to docetaxel alone in patients with HER2-positive metastatic breast cancer.
 - a. True
 - b. False
7. The MA17 study of letrozole versus placebo in postmenopausal women who have completed at least five years of adjuvant tamoxifen was closed early because:
 - a. The estimated benefit of letrozole was substantially greater than expected
 - b. The toxicities of letrozole were greater than expected
 - c. None of the above
8. In the Italian Tamoxifen Anastrozole (ITA) trial in which patients were switched after two or three years of adjuvant tamoxifen to two or three years of anastrozole, no advantage was seen with anastrozole.
 - a. True
 - b. False
9. Combined analysis of two trials comparing fulvestrant to anastrozole in postmenopausal patients with metastatic disease demonstrated:
 - a. Longer duration of response favoring fulvestrant
 - b. Longer duration of response favoring anastrozole
 - c. Equivalent duration of response for fulvestrant and anastrozole
10. The pivotal trial of chemotherapy and trastuzumab demonstrated the following overall rate of cardiac dysfunction in the anthracycline/cyclophosphamide/trastuzumab arm:
 - a. 16 percent
 - b. 27 percent
 - c. 37 percent
11. The CALGB-9741 study demonstrated significantly higher toxicity in the dose-dense chemotherapy arm versus the conventional chemotherapy arm.
 - a. True
 - b. False

Evaluation Form:

Breast Cancer Update — Issue 4, 2004

Research To Practice 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 your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor N A = not applicable to this issue of *BCU*

GLOBAL LEARNING OBJECTIVES

To what extent does this issue of *BCU* address the following global learning objectives?

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment. 5 4 3 2 1 NA
- Develop and explain a management strategy for treatment of ER-positive and ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings. 5 4 3 2 1 NA
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. 5 4 3 2 1 NA
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. 5 4 3 2 1 NA
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the relevance to patients considering adjuvant chemotherapy regimens. 5 4 3 2 1 NA
- Counsel appropriately selected patients about the availability of ongoing clinical trials. 5 4 3 2 1 NA
- Discuss the risks and benefits of endocrine intervention with women with DCIS and those at high risk of developing breast cancer. 5 4 3 2 1 NA

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Martine Piccart, MD, PhD	5 4 3 2 1	5 4 3 2 1
Larry Norton, MD	5 4 3 2 1	5 4 3 2 1
C Kent Osborne, MD	5 4 3 2 1	5 4 3 2 1
Maria Theodoulou, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Evaluation Form:

Breast Cancer Update — Issue 4, 2004

Please Print Clearly

Name: Specialty:

ME No.: Last 4 Digits of SSN (required):

Street Address: Box/Suite:

City, State, Zip:

Telephone: Fax:

E-Mail:

Research To Practice designates this educational activity for a maximum of 3.25 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

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

Signature: Date:

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 PharmD NP BS
 DO RN PA Other

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.

Breast Cancer™

U P D A T E

<i>EDITOR</i>	Neil Love, MD
<i>ASSOCIATE EDITORS</i>	Michelle Paley, MD Richard Kaderman, PhD
<i>WRITERS</i>	Lilliam Sklaver Poltorack, PharmD Sally Bogert, RNC, WHCNP Douglas Paley Margaret Peng Nelson Vega
<i>CME DIRECTOR</i>	Michelle Paley, MD
<i>ART DIRECTOR</i>	Albert Rosado
<i>SENIOR DESIGNER</i>	Tamara Dabney
<i>GRAPHIC DESIGNER</i>	Ben Belin
<i>PRODUCTION EDITOR</i>	Aura Herrmann
<i>ASSOCIATE PRODUCTION EDITOR</i>	Alexis Oneca
<i>COPY EDITORS</i>	Sandy Allen Pat Morrissey/Havlin
<i>AUDIO PRODUCTION</i>	Frank Cesarano
<i>TECHNICAL SERVICES</i>	Arly Ledezma
<i>WEB DESIGN</i>	John Ribeiro
<i>PRODUCTION COORDINATOR</i>	Cheryl Dominguez
<i>EDITORIAL ASSISTANTS</i>	Vanessa Dominguez Patricia McWhorter Arai Peñaite Raquel Segura Tere Sosa Arlene Thorstensen Melissa Vives
<i>CONTACT INFORMATION</i>	Neil Love, MD Research To Practice One Biscayne Tower 2 South Biscayne Boulevard, Suite 3600 Miami, FL 33131 Fax: (305) 377-9998 Email: NLove@researchtopractice.net
<i>FOR CME INFORMATION</i>	Margaret Peng, CME Administrator Email: MPeng@researchtopractice.net

Copyright © 2004 Research To Practice. All rights reserved.

This program is supported by education grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Roche Laboratories Inc and Amgen Inc.

The audio tapes, compact discs, Internet content and accompanying printed material are protected by copyright. No part of this program may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording or utilizing any information storage and retrieval system, without written permission from the copyright owner.

The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantor.

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management.

Any procedures, medications or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's product information and comparison with recommendations of other authorities.

Breast Cancer™

U P D A T E

Copyright © 2004 Research To Practice.

This program is supported by education grants from AstraZeneca Pharmaceuticals LP, Genentech BioOncology, Roche Laboratories Inc and Amgen Inc.



Sponsored by Research To Practice.

This activity has been planned and produced in accordance with the ACCME Essential Areas and Policies.

Last review date: May 2004

Release date: May 2004

Expiration date: May 2005

Estimated time to complete: 3.25 hours