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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. The first CD and website also contain PowerPoint® files of the slides located at the end of the monograph.

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 1 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Burstein, Goldhirsch, Yardley and Rivkin 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 towards the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity.

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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:

Harold J Burstein, MD, PhD	Grants/Research Support: Aventis Pharmaceuticals Inc, GlaxoSmithKline, Genentech BioOncology
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Saul E Rivkin, MD	No financial interests or affiliations to disclose

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
bevacizumab	Avastin™	Genentech BioOncology
buserelin	Suprefact®	Various
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
celecoxib	Celebrex®	Pfizer Inc
cyclophosphamide	Cytosan® Neosar®	Bristol-Myers Squibb Company Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin®	Pfizer Inc
epirubicin hydrochloride	Ellence®	Pfizer Inc
epothilone	—	Bristol-Myers Squibb Company
exemestane	Aromasin®	Pfizer Inc
filgrastim	Neupogen®	Amgen
5-fluorouracil,5-FU	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly & Company
goserelin	Zoladex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals Corporation
methotrexate	Various	Various
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pegfilgrastim	Neulasta™	Amgen
rofecoxib	Vioxx®	Merck & Company Inc
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
toremifene citrate	Fareston®	Orion Corp
trastuzumab	Herceptin®	Genentech BioOncology
triptorelin	Various	Various
vinorelbine	Navelbine®	GlaxoSmithKline

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Editor's Note

Frank's mom

Few things are more enjoyable than a good old-fashioned tumor panel brawl, so it was with great pleasure that I was able to ruffle a few feathers during a Meet the Professor session I moderated at the recent Lynn Sage Breast Cancer Symposium.

A community-based oncologist presented a case referred for a second opinion. The patient had relapsed after prior therapy with neoadjuvant trastuzumab in a nonprotocol setting. I asked Dr Stephen Jones to comment on the neoadjuvant trastuzumab, and Steve launched into an extended polemic intended to crush any notion that this treatment strategy was acceptable.

I then called on another panel member, Dr Charles Vogel, my mentor when I was part of the University of Miami Breast Cancer Research Division and the one person in the room I knew would be unfazed by Dr Jones' rather strong opinion.

Sensitive to Steve's visible discomfort and umbrage, Chuck noted very quietly and calmly that, while he generally agreed that nonprotocol neoadjuvant trastuzumab is not appropriate, he had treated two carefully selected patients in his practice with this approach and both women had done extremely well.

What Chuck did not mention, and Steve definitely did not know, was that one of those patients happened to be the mother of our chief audio engineer, Frank Cesarano, who was recording the proceedings of that event.

I first met Frank in 1990 shortly after he graduated from the prestigious University of Miami School of Music. Prior to that time, our group had utilized a host of different freelance audio production engineers. I sought out Frank because a taping in Atlanta had gone terribly awry. Specifically, a fascinating interview with Bernie Fisher had been recorded incorrectly, and the audio was garbled and unintelligible.

Frank informed me that he personally could not fix this priceless educational resource, but he had heard that Gloria Estefan's producer had developed new software that might solve the problem. The next day, we trooped over to the Miami diva's recording studio and, amazingly, the problem was palliated, albeit at an exorbitant price. Frank and I have been working together ever since, and over the years he has played a central role in developing the *Breast Cancer Update* audio series — recording hundreds of my interviews with cancer research leaders.

This endeavor has now branched out into tandem audio series on prostate, colorectal and lung cancer, and in tracking down the very elite investigators in these fields, our partnership has, on occasion, resulted in some rather amusing situations.

For example, in 1999 I secured an interview with an internationally known researcher from the United Kingdom who was presenting an important paper at the San Antonio Breast Cancer Symposium. Like many of my interviewees from “across the pond,” this investigator wished to be recorded very early in the morning due to difficulties coping with jet lag.

When recording at large meetings, we often convert a hotel suite into a mini-studio, and when I opened the door at 5:30 AM to meet this professor, I encountered a profoundly disheveled, bleary-eyed persona whose night out in one of San Antonio’s Mexican cantinas left him — as Saturday Night Live’s Mike Myers would say — without voice.

Having spent two years trying to arrange this recording, and knowing that this research leader might not be back in the United States for some time, I was determined to resuscitate my guest’s voice. Frank had a suggestion, and before long he and I were pushing this doc into the bathroom of the suite, turning on the hot water in the shower to create some ambient steam in the room, and applying impromptu chest physiotherapy. The result was a fascinating but somewhat gravelly interview.

Around that time, Frank’s 72-year-old mother, Mary Cesarano, was diagnosed with extensive but localized, HER2-positive, inflammatory breast cancer. For a number of specific reasons, her treating oncologist, Dr Vogel, decided to forgo his usual approach and utilized six weeks of neoadjuvant trastuzumab and paclitaxel followed by mastectomy, radiation therapy and one year of trastuzumab monotherapy. Today — more than four years later — Mary has no aftereffects of this treatment and remains cancer-free.

Because Frank has been on our team for so long, many of the research leaders interviewed for our series get to know him, and some have learned about his mom’s story. Melody Cobleigh, a pioneer in trastuzumab clinical research, always asks Frank how his mother is doing and smiles broadly when she receives the good news.

Sometimes, when I see Frank huddled over his recording equipment during a research leader’s interview, I wonder what he is thinking, particularly when the topic turns to the management of HER2-positive disease in breast cancer patients.

I especially remember our interview with Dr Dennis Slamon, who humbly and eloquently spoke about how deeply he was moved by the human impact of his work on the lives of women treated



Frank and Mary Cesarano

with trastuzumab. Dr Slamon could not have known that a few feet away was one more family member whose life will never be the same because of this research.

In this issue of *Breast Cancer Update*, Dr Harold Burstein discusses a recent study he published on neoadjuvant trastuzumab, and like many other preoperative approaches, this work is providing very important clues about the mechanisms of action and predictors of response. Until further studies are reported — including findings from the major ongoing adjuvant trials — controversy will continue to exist regarding the role of trastuzumab in locally advanced disease.

Every CME program we produce includes discussion of clinical questions for which suboptimal databases confound the practice of evidence-based decision-making. This edition is no different as Denise Yardley discusses the role of TAC versus dose-dense AC → T adjuvant chemotherapy; Aron Goldhirsch comments on hormone therapy in premenopausal women utilizing ovarian ablation alone or with aromatase inhibitors; and Saul Rivkin presents a controversial perspective on sequential single-agent versus combination chemotherapy for metastatic disease.

Every oncologist has encountered cases with both positive and negative outcomes when interventions utilized stretch the boundary of existing evidence. Mary Cesarano's case typifies a carefully thought-out strategy that worked.

—Neil Love, MD

New Feature for *Breast Cancer Update*: Mini-PowerPoint® Atlas

On page 31 of this issue, we launch this new feature to assist in delivering CME presentations. The PowerPoint® files of these slides are located on the first CD enclosed with the program. Each subsequent issue will include a new set of slides, all of which are also posted for downloading on BreastCancerUpdate.com. The first mini-atlas focuses on the current clinical trials of the International Breast Cancer Study Group (IBCSG), which is chaired by Dr Aron Goldhirsch who is interviewed in this issue.



Edited comments by Dr Burstein

CAN-NCIC-MA17 trial: Efficacy of aromatase inhibitor following five years of adjuvant tamoxifen

Led by the National Cancer Institute of Canada, MA17 randomly assigned over 5,000 postmenopausal women who had received tamoxifen for between four and a half and six years and were free of tumor, to receive letrozole or a placebo. Letrozole reduced the rate of breast cancer events by about 50 percent, including the risk of distant metastases and the risk of ipsilateral or contralateral breast cancer. The differences were so robust after only two and a half years that the study was closed before completing its planned five-year duration (Figure 1.1).

The data are exciting because letrozole has the potential to improve the long-term prognosis for the largest demographic group of patients — postmenopausal women with hormone receptor-positive breast cancer. Historically, these women have been offered five years of tamoxifen; now many such patients should consider taking letrozole after completing that therapy.

It's always exciting to close a study early because of such good news, but follow-up trials are needed to address unanswered questions about the best way to use letrozole in this setting. Also, there are concerns regarding the profound estrogen deprivation effects of aromatase inhibitors, particularly osteoporosis. We can study those issues, and there are interventions, but it means that we have to pause before blindly recommending this therapy to everyone.

Risk of recurrence after adjuvant tamoxifen

A patient's risk of breast cancer recurrence is greatest the first few years after diagnosis; after three or four years it begins to plateau. While this is particularly true for hormone receptor-negative breast cancers, with ER-positive breast cancers the slope is quite gradual. It astonishes me how many late recurrences there can be, but most women in the MA17 trial did very well.

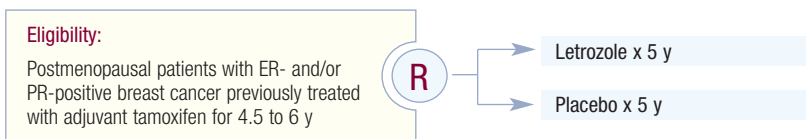
Women with early-stage breast cancer, who are free of recurrence through five years of tamoxifen, have a relatively low risk of recurrence and a good prognosis. In the placebo arm of the trial, the annual risk of a breast cancer event was about two to three percent per year. The absolute benefits of letrozole are relatively modest. In the aggregate, letrozole prevented one breast cancer event per 100 women per year.

Dr Burstein is an Assistant Professor of Medicine of the Harvard Medical School Breast Oncology Center at the Dana-Farber Cancer Institute in Boston, Massachusetts.

In patients with ER-positive disease, the time courses for late recurrences in node-positive and node-negative disease are similar. In MA17, the relative hazard ratio was the same for the benefit of letrozole over placebo in both node-positive and node-negative patients. However, because we presume patients with node-negative disease have a lower residual jeopardy five years out, the absolute benefit of taking letrozole for patients with such a good prognosis is less than if they'd had a lot of positive nodes. Patients with node-positive disease are still at greater residual jeopardy.

Figure 1.1

Phase III Randomized Study of Letrozole versus Placebo in Postmenopausal Women with Primary Breast Cancer Who Have Completed at Least Five Years of Adjuvant Tamoxifen **Closed Protocol**



Accrual: 5,187

Protocol IDs: CAN-NCIC-MA17, CLB-49805, E-JMA17, EORTC-10983, IBCSG-BIG97-01, JRF-Vor-Int-10, NCCTG-CAN-MA17, NCCTG-JMA.17, SWOG-CAN-MA17, SWOG-JMA17

Disease-free survival and recurrences (median follow-up, 2.4 years)

	Letrozole (N=2575)	Placebo (N=2582)	p-value
Estimated 4-year DFS	93%	87%	P < 0.001
Local, metastatic, new contralateral primary	75 (2.9%)	132 (5.1%)	P < 0.00008

SOURCES: 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). **Abstract.**

NCI Physicians Data Query, January 2004

Clinical implications of MA17

The risk reduction seen in MA17 included both distant metastases and second breast cancer events — either in-breast recurrence or secondary contralateral breast cancers. These local regional recurrences constituted a relatively large fraction of all the breast cancer events seen in MA17. For most women who have had one breast cancer, their greatest threat to survival is the breast cancer we already know about, rather than a second breast cancer. For the well-informed patient, the data can be interpreted to offer a secondary benefit — chemoprevention.

The use of aromatase inhibitors in prevention is being explored by a number of investigators. The differences in the ATAC trial are relatively modest, but there

remains a trend favoring the aromatase inhibitor in terms of preventing second in-breast recurrences or contralateral breast cancers. It suggests there are two things going on — continued control of microscopic distant metastases and ongoing improvement in reducing the risk of primary breast cancer.

Time since completion of tamoxifen and aromatase inhibitor

MA17 was open to women who had finished tamoxifen within the past three months, but we have no data for women who have been off tamoxifen for a longer period. In practice, I consider letrozole therapy for patients who have finished their five years of tamoxifen therapy within the past year. Beyond year six, women who have had no recurrences have an additional period of time during which they've done well, and that means their moving-forward risk is even lower than it was before. It's difficult to know whether or not the data apply to them.

The whole issue of the timing, duration and sequencing of antiestrogen strategies is very interesting, and everyone is looking forward to the results of the Breast International Group/Femara®-Tamoxifen (BIG/FEMTA) study. This large European trial has four arms: (1) five years of an aromatase inhibitor, (2) five years of tamoxifen, (3) two years of tamoxifen followed by three years of an aromatase inhibitor, and (4) two years of an aromatase inhibitor followed by three years of tamoxifen (Figure 1.2).

Aromatase inhibition as initial adjuvant therapy

Either tamoxifen or anastrozole are up-front options for postmenopausal women with ER-positive tumors based on the data from one large randomized trial, the ATAC study. I present that data but also review the decades of experience we've had with tamoxifen. I also review the different side-effect profiles of these medications.

In terms of selection of an aromatase inhibitor up front, there is no data at this point for letrozole and exemestane, therefore, I prefer to go with anastrozole if I'm going to use up-front aromatase inhibition.

Ovarian suppression in the treatment of premenopausal women with breast cancer

The IBCSG is coordinating a series of three nested trials: SOFT, PERCHE and TEXT. These trials address what is probably the most important conceptual question in premenopausal breast cancer right now: Beyond tamoxifen, does planned ovarian suppression benefit patients?

In particular, does it benefit women who receive chemotherapy or who don't receive chemotherapy, and if a woman experiences chemotherapy-related amenorrhea, does she still need ovarian suppression? We will probably not have the data for at least five or 10 years, but these are very important trials that offer a wonderful opportunity for community oncologists to participate in answering this critical question.

Currently, I consider ovarian suppression for two groups of patients. The first group includes patients at high risk — multiple positive nodes, very high-risk tumors — and particularly young women, less than 35 or 40 years of age, who may not go into menopause with chemotherapy. The other group includes women who are at the opposite end of the spectrum — very low-risk tumors, smaller tumors, node-negative — for whom the benefits of chemotherapy are very small. In these women, I present ovarian suppression as an option, not necessarily in addition to chemotherapy but perhaps even instead of it.

Figure 1.2

Recent and Ongoing Trials of Sequential Adjuvant Endocrine Therapy

Study	N	Randomization	Status
ABCSG-8	3,500	TAM x 2 y → Anastrozole x 3 y TAM x 2 y → TAM x 3 y	Open
NSABP-B-33	3,000	TAM x 57-66 m → EXE Placebo x 2 y	Temporarily closed
IBCSG-18-98/ EU-99022/ IBCSG 01-98	5,180	TAM x 5 y Letrozole x 5 y TAM x 2 y → Letrozole x 3 y Letrozole x 2 y → TAM x 3 y	Closed
CAN-MA17/ SWOGJMA17/ BIG 97-01/ CLB-49805	4,800	TAM 4.5-6 y → Letrozole Placebo x 5 y	Closed
ICCG 96 BIG 97-02	4,400	TAM x 5 y TAM x 2-3 y → EXE 2-3 y	Closed
ARNO-95	1,059	TAM x 2 y → Anastrozole x 3 y TAM x 2 y → TAM x 3 y	Closed
Italian (ITA)	445	TAM x 2-3 y → Anastrozole x 2-3 y TAM x 2-3 y → TAM x 2-3 y	Closed
GROCTA 4B	380	TAM x 2-3 y → Aminoglutimide x 2-3 y TAM x 2-3 y → TAM x 2-3 y	Closed

TAM = tamoxifen; EXE = exemestane.

SOURCE: NCI Physician Data Query, January 2004. **German Adjuvant Breast Cancer Group Website.**
Boccardo F. Presented at: Nottingham International Breast Cancer Conference, 2003.

Dose-dense adjuvant chemotherapy

The availability of growth factors and better supportive care measures has enabled us to ask very interesting questions about dose schedule and dose intensity. We have to acknowledge the contributions that Larry Norton and his mathematical models have made in this arena.

CALGB-9741 compared the standard three-week schedule of AC followed by paclitaxel to a dose-dense, every-two-week schedule. The study also looked at a question of sequential monotherapy versus concurrent therapy. The analyses suggested that, while there was no clinically important difference between sequential therapy and concurrent therapy, the every-two-week schedule was superior to the every-three-week schedule. If I'm going to give sequential AC and paclitaxel, I give it every two weeks, instead of every three weeks, because of the survival advantage associated with that regimen.

For node-positive patients, I'm most commonly using dose-dense AC followed by paclitaxel. We feel quite comfortable with this regimen.

As a protocol option, we have been exploring dose-dense AC followed by paclitaxel with pegfilgrastim. I would not encourage people to use pegfilgrastim instead of filgrastim outside of a study, although I know it is widely done.

Treatment of patients with metastatic, HER2-positive, ER-positive breast cancer in a nonprotocol setting

In women who have HER2-positive disease and potentially endocrine-sensitive tumors, I start with endocrine therapy for a couple of reasons. First, clearly endocrine therapy can still be effective in HER2-positive breast cancer, and I like to get as much mileage as appropriate from endocrine treatments. There's this myth that these patients don't benefit from endocrine treatment, but that's simply not the case.

Second, the pivotal study from Dennis Slamon, evaluated chemotherapy plus or minus trastuzumab and found that neither estrogen receptor status nor prior endocrine treatment adversely affected response rates or outcomes to combinations of chemotherapy and trastuzumab. I don't believe we burn any bridges by starting with endocrine therapy. When the patient is no longer a candidate for endocrine therapy, I usually introduce chemotherapy. If the tumor is HER2-positive, then I use chemotherapy plus trastuzumab.

Clinical trials of preoperative trastuzumab/chemotherapy in HER2-positive breast cancer

We conducted a pilot program of preoperative trastuzumab and paclitaxel for women with HER2-positive breast cancer. After 12 weeks of preoperative therapy, the patients had surgery and then received four cycles of doxorubicin and cyclophosphamide. There was a very high response, on the order of 70 to 80 percent, with a pathologic complete response rate of approximately 18 to 20 percent. The treatment seemed feasible in that none of the patients developed symptomatic heart failure or other complications.

We followed that study with a trial of preoperative trastuzumab and vinorelbine. Again, we saw very robust response rates and pathologic complete response rates on the same order of magnitude, and subsequent anthracycline-based therapy was found to be feasible following the initial trastuzumab and chemotherapy combination. Preoperative trastuzumab is a fascinating model for exploring how this drug actually works.

We are putting together another pilot combining trastuzumab with one of the platinum drugs and a taxane. While this is not the standard of care for women presenting with Stage III or locally-advanced, HER2-positive disease, we are increasingly considering it as a realistic treatment option for these patients.

Emerging data from the cooperative group trials evaluating changes in LVEF with standard chemotherapy and, in some instances, with trastuzumab-based therapy in the early-stage setting collectively indicate that it's going to be feasible. This does not mean we should be giving trastuzumab to all patients, and we do not do so outside of a clinical trial, but looking ahead a couple of years, I believe we're going to find ways to sequence trastuzumab into adjuvant chemotherapy without prohibitive cardiac toxicity.

First-line therapy for anthracycline-naïve, HER2-positive, metastatic disease

If a woman has a hormone receptor-negative tumor, the only strategy we have is chemotherapy, but if the tumor is HER2-positive, then I give chemotherapy with trastuzumab. Oncologists who prefer to begin with an anthracycline-based regimen as first-line therapy for an HER2-positive tumor presumably do so because of a historic belief that everyone needs an anthracycline up front. I don't believe that's true. Mary Costanza conducted a study for the CALGB at the University of Massachusetts that compared a first-line, anthracycline-based regimen to a nested series of Phase II agents and showed no real difference in survival.

In addition, George Sledge's ECOG trial, probably the best data we have, compared doxorubicin to paclitaxel versus the combination and found no substantial difference in the duration of response or in overall survival for any of those three strategies. We now have a variety of active nonanthracycline-based drugs, and trastuzumab has clearly been shown to improve survival. I think that's the priority, and we should rely on that data rather than falling back on data from the 1970s.

Combination trastuzumab/chemotherapy in the metastatic setting

Several published trials showed the response rate to single-agent trastuzumab is on the order of 30 to 35 percent in patients whose tumors are HER2 3+ by IHC or FISH-positive, so monotherapy is a viable option. However, the response rates to chemotherapy plus trastuzumab are typically twice that, so I usually start with a combination. We've been interested in nontoxic chemotherapy regimens and have done a lot of work with vinorelbine and trastuzumab (Figure 1.3). That combination tends to be well-tolerated, doesn't cause alopecia or nausea, and I find it appealing for patients who don't want more aggressive chemotherapy.

I usually treat with the combination to a point of optimal response and then discontinue the chemotherapy, leaving the patient on trastuzumab. There's no data telling us whether that's good or not, but it spares patients the side effects of chemotherapy, and many women experience extended periods of disease control.

Figure 1.3

Phase II Multicenter Study Evaluating Trastuzumab and Vinorelbine as First-Line Therapy for HER2-Overexpressing Metastatic Breast Cancer **Closed Protocol**

Eligibility:

HER2-positive metastatic breast cancer, measurable disease, baseline ejection fraction $\geq 50\%$

PROTOCOL →

Trastuzumab + vinorelbine

Accrual: 54

Overall response rates (N=54)

Best response	Number of patients	Response rate
Complete response	4	7%
Partial response	33	61%
Stable disease ≥ 6 months	9	17%

SOURCE: Burstein HJ et al. **Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: Multicenter Phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm.**

J Clin Oncol 2003;21(15):2889-95. **Abstract.**

Discontinuing both agents is another viable option, but the patients generally feel they've gotten significant clinical benefit from trastuzumab and, because it's relatively nontoxic and can be offered on an every-three-week treatment schedule, they prefer to continue taking it. Most of my dosing is built around weekly trastuzumab, but if the patient transitions to trastuzumab monotherapy or if we're using an every-three-week chemotherapy cocktail, then I use the every-three-week dosing.

Continuation of trastuzumab beyond disease progression

In patients who experience long periods of disease control with trastuzumab monotherapy and then progress again, restarting them on the original chemotherapy with trastuzumab is very reasonable. If the cancer recurs within a short window, then it's probably time to move on to another chemotherapy agent. I tend to continue the trastuzumab, unless the patient needs an anthracycline or is going on to a protocol that precludes trastuzumab.

This is an area in which we have no data to direct us, so MD Anderson tried to mount a study in which women who progressed on trastuzumab with a taxane would be randomly assigned to vinorelbine with or without trastuzumab. It was a reasonably well-designed study, but there was one major scientific flaw — trastuzumab has a very long half-life, probably three weeks, so there could still be circulating levels of trastuzumab for the first eight to 12 weeks of no trastuzumab treatment, which confounds the endpoint.

The second and more practical problem was that patients were not willing to be randomized — they all wanted to continue taking trastuzumab. That study was closed, but they have tried to reintroduce it through the SWOG. I hope that's successful because it's a very important study.

Oral chemotherapy agents in the treatment of metastatic breast cancer

We continue to be interested in oral chemotherapies in the metastatic setting. They are relatively underexploited in terms of patient convenience and global utilization. Patients like the convenience of oral medicines as long as they don't compromise efficacy, and most of the planet does not have access to sterile IV preparation. We have more and more oral drugs that are efficacious, and it would be marvelous if we could develop effective oral chemotherapy cocktails that could be used in the adjuvant setting.

Capecitabine is a very useful and widely used drug that's FDA-approved for anthracycline- and taxane-pretreated breast cancer, but I believe it's a very reasonable first-line agent. Randomized studies comparing capecitabine to traditional CMF and to paclitaxel as first-line treatment have shown generally equivalent results (Figure 1.4). We are currently conducting a Phase I study evaluating the combination of capecitabine and oral vinorelbine. One of the lessons we've learned is that oral chemotherapy is still chemotherapy; we don't obviate side effects like neutropenia just because it's a pill.

Figure 1.4

Phase II Study Results of Capecitabine Compared to Standard Chemotherapy in Patients with Metastatic Breast Cancer

	O'Shaughnessy et al (n=95)		Talbot et al (n=41)	
Median age	69 years old		52 years old	
Treatment setting	First-line		Anthracycline-pretreated	
Regimen	capecitabine 2510 mg/m ² /day for 2 wk	CMF q 3 wk	capecitabine 2510 mg/m ² /day for 2 wk	paclitaxel 175 mg/m ² q 3 wk
Overall response (95% CI)	30% (19-43%)	16% (5-33%)	36% (17-59%)	26% (9-51%)
Number of complete responses	3	0	3	0
Median time to progression	4.1 mo	3.0 mo	3.0 mo	3.1 mo
Median survival	19.6 mo	17.2 mo	7.6 mo	9.4 mo

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

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

Select publications

Publications discussed by Dr Burstein

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

Boccardo F et al. Sequential tamoxifen and aminoglutethimide versus tamoxifen alone in the adjuvant treatment of postmenopausal breast cancer patients: Results of an Italian cooperative study. *J Clin Oncol* 2001;19(22):4209-15. [Abstract](#).

Bryant J, Wolmark N. Letrozole after tamoxifen for breast cancer—What is the price of success? *N Engl J Med* 2003;349(19):1855-7. No abstract available.

Burstein HJ. Beyond tamoxifen—Extending endocrine treatment for early-stage breast cancer. *N Engl J Med* 2003;349(19):1857-9. No abstract available.

Burstein HJ et al. Preoperative therapy with trastuzumab and paclitaxel followed by sequential adjuvant doxorubicin/cyclophosphamide for HER2-overexpressing stage II or III breast cancer: A pilot study. *J Clin Oncol* 2003;21(1):46-53. [Abstract](#).

Burstein HJ et al. Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: Multicenter Phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm. *J Clin Oncol* 2003;21(15):2889-95. [Abstract](#)

Costanza ME et al. Safety and efficacy of using a single agent or a Phase II agent before instituting standard combination chemotherapy in previously untreated metastatic breast cancer patients: Report of a randomized study—Cancer and Leukemia Group B 8642. *J Clin Oncol* 1999;17(5):1397-406. [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](#)

Harris L et al. Preoperative trastuzumab and vinorelbine (HN) is a highly active, well-tolerated regimen for HER2 3+/FISH+ Stage II/III breast cancer. *Proc ASCO* 2003; [Abstract 86](#).

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

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](#)

Sledge GW et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An Intergroup trial (E1193). *J Clin Oncol* 2003;21(4):588-92. [Abstract](#)

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

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



Edited comments by Dr Goldhirsch

International Breast Cancer Study Group (IBCSG) trials

Because we believe in tailored treatment, our group conducts trials within biologically homogeneous populations. Currently, we have three sets of trials: (1) studies for patients with endocrine-responsive disease, (2) trials for patients with endocrine-unresponsive disease and (3) protocols for patients with local recurrences.

Postmenopausal women with endocrine-responsive breast cancer

We completed accrual to an adjuvant trial (IBCSG-18-98) comparing five years of tamoxifen, five years of letrozole, two years of tamoxifen followed by three years of letrozole, and two years of letrozole followed by three years of tamoxifen in postmenopausal patients with endocrine-responsive disease. This trial accrued 8,028 patients (Slide 13, page 37).

A lifelong treatment strategy for patients with an increased risk of breast cancer recurrence might be reasonable. I think maintaining the cells under control and suppressing new tumors requires a sequential approach that includes endocrine therapy for tumors that are endocrine responsive.

Premenopausal women with endocrine-responsive breast cancer

In premenopausal women with endocrine-responsive disease, we initiated three adjuvant trials in August 2003. The Suppression of Ovarian Function Trial (SOFT), the Tamoxifen and Exemestane Trial (TEXT) and the Premenopausal Endocrine Responsive Chemotherapy Trial (PERCHE).

The SOFT trial will compare tamoxifen alone to ovarian function suppression plus tamoxifen and ovarian function suppression plus exemestane. This trial was designed specifically for oncologists who view tamoxifen as standard therapy (Slide 4, page 33).

The TEXT trial will compare ovarian function suppression plus tamoxifen to ovarian function suppression plus exemestane. These patients may or may not receive chemotherapy (Slide 5, page 33).

Dr Goldhirsch is a Professor at the University of Bern in Switzerland; Chairman of the Scientific Committee of the International Breast Cancer Study Group; Director of the Department of Medicine at the European Institute of Oncology in Milan, Italy; and Head of the Division of Medical Oncology at the Oncology Institute of Southern Switzerland in Lugano, Switzerland.

The PERCHE trial will determine whether adjuvant chemotherapy is necessary. Premenopausal women are randomly assigned to chemotherapy or no chemotherapy (Slide 6, page 34). Adjuvant chemotherapy selection is left entirely up to the investigator, and endocrine therapy consists of ovarian function suppression with tamoxifen or exemestane. Patients may also be randomized to TEXT for endocrine therapy.

Women with a resected locoregional breast cancer recurrence

The Swiss trial comparing adjuvant tamoxifen to observation in patients with endocrine-responsive local recurrences demonstrated an advantage for the patients receiving adjuvant tamoxifen compared to those treated with only local therapy. We are conducting a trial with NSABP to evaluate the benefit of adjuvant chemotherapy in the treatment of patients with local recurrences (Slide 10, page 36).

Patients are randomly assigned to chemotherapy or observation after completing local treatment for the recurrence. Several chemotherapy regimens can be used for a duration of six months. Patients with endocrine-responsive disease will also receive adjuvant endocrine therapy. I think chemotherapy will provide an advantage for patients with endocrine-unresponsive disease.

Women with endocrine-unresponsive disease

In patients with endocrine-unresponsive disease that has HER2-overexpression, the HERA trial will compare one or two years of adjuvant trastuzumab to observation after the completion of adjuvant chemotherapy (Slide 7, page 34; slide 8, page 35). In patients with endocrine-unresponsive and HER2-negative disease, another trial will randomly assign patients after completion of adjuvant chemotherapy to observation or one year of low-dose metronomic cyclophosphamide and methotrexate (Slide 9, page 35). This inexpensive regimen has been proven in two series of patients with advanced disease (Figure 2.1).

Metronomic chemotherapy

Metronomic chemotherapy has some antiangiogenic effects. Bob Kerbel will soon publish new information on the induction of antiangiogenic effects by low-dose chemotherapy. In the *Annals of Oncology* (January 2002), we published the results of a trial with about 60 patients treated with low-dose oral cyclophosphamide and methotrexate. In pretreated patients, the clinical benefit rate was about 30 percent. Two patients with biopsy-proven liver metastases had a complete remission. The patients experienced occasional Grade I leukopenia.

Globalization of breast cancer clinical research

The SOFT, TEXT and PERCHE trials have led to a unification of research efforts. This is the first time that globalization has been recognized as a priority for everyone, and everyone made the jump. This has been quite impressive.

Figure 2.1

Efficacy of Low-Dose Oral Methotrexate and Cyclophosphamide in Women with Metastatic Breast Cancer

Objective response rate	12/63	(19.0%)
Clinical benefit rate	20/63	(31.7%)
Complete response	2/63	(3.1%)
Partial response	10/63	(15.9%)
Stable disease for 24 weeks	8/63	(12.7%)

SOURCE: Colleoni M et al. **Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: Antitumor activity and correlation with vascular endothelial growth factor levels.** *Ann Oncol* 2002;13(1):73-80. [Abstract](#)

Pregnancy in women who have been diagnosed with breast cancer

According to case reports and cohort studies, pregnancy after a diagnosis of breast cancer has been associated with an improved prognosis. Obviously, prospective studies have not been conducted and could only be accomplished through a registry of all pregnancies. The concern about pregnancy leading to a breast cancer recurrence is not substantiated by any data.

Case comment: Nonprotocol management of a 32-year-old woman with resected ER-positive, node-positive breast cancer

A 32-year-old woman has a long life expectancy, and I would recommend a full course of chemotherapy and endocrine therapy for such a patient. I would probably use an LHRH analog plus tamoxifen. In advanced disease, data show an advantage for an LHRH analog plus tamoxifen compared to tamoxifen alone. In the adjuvant setting, Nancy Davidson's data are compelling, although her trial did not have a tamoxifen-alone arm. Additionally, the Austrian trial demonstrated that an LHRH analog plus tamoxifen was much better than chemotherapy.

In a premenopausal woman with low-risk, endocrine-responsive disease, I would consider adjuvant ovarian ablation or suppression plus tamoxifen without chemotherapy. Endocrine-responsive disease is less likely to be of high metastatic potential; therefore, I would prefer endocrine treatment. Thirteen studies have shown this approach to be completely legitimate.

Predicting response to chemotherapy

For a long time it has been speculated that an increased labeling index predicts for response. Mark Lippman was the first person to receive credit for that concept. Data reported in Milan indicate that high proliferation rate, as expressed by Ki-67, predicts for response to chemotherapy. Endocrine unresponsiveness also predicts for response to chemotherapy. For example, women with endocrine-unresponsive disease have a complete remission rate that is four or five times greater than those with endocrine-responsive disease. Attempts are also being made to determine a

gene profile that will predict for response to docetaxel. This should be done, but we are still in the very early stages.

Neoadjuvant therapy

We are evaluating chemotherapy, chemotherapy plus endocrine therapy, and endocrine therapy alone in both premenopausal and postmenopausal women. Our pathology group is conducting a very thorough biological dissection of all features, preoperatively and postoperatively.

We use neoadjuvant endocrine therapy only in a protocol setting, because we are unsure of the duration of exposure required to obtain the maximum effect. With chemotherapy, a response is evident within three months; this is not the case with endocrine treatment. Neoadjuvant endocrine therapy is trickier in terms of obtaining tumor shrinkage in order to obtain breast conservation.

Concomitant versus sequential hormonal therapy and chemotherapy

The most important clinical trial results reported last year were from SWOG-8814, which evaluated the concomitant or sequential use of chemotherapy and tamoxifen. That trial proves that even with a doxorubicin-containing combination, tamoxifen should be administered sequentially. Each therapy reduces the effect of the other. In the retrospective analyses of the trials in which tamoxifen and cytotoxics were combined, the effect was devastating.

Select publications

Publications discussed by Dr Goldhirsch

Albain K et al. Adjuvant chemohormonal therapy for primary breast cancer should be sequential instead of concurrent: Initial results from Intergroup trial 0100 (SWOG-8814). *Proc ASCO* 2002;[Abstract 143](#).

Colleoni M et al. Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: Antitumor activity and correlation with vascular endothelial growth factor levels. *Ann Oncol* 2002;13(1):73-80. [Abstract](#)

Davidson NE et al. Chemohormonal therapy in premenopausal, node-positive, receptor-positive breast cancer: An Eastern Cooperative Oncology Group Phase III Intergroup trial (E5188,INT-0101). *Proc ASCO* 2003;[Abstract 15](#).

Gomez Cuadra MO. 5th Milan Breast Cancer Conference, Milan, Italy, 11-13 June 2003. *Breast Cancer Res* 2003;5(5):276-9. No abstract

Jakesz R et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: Evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer—Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002;20(24):4621-7. [Abstract](#)

Klijn JG et al. Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: A randomized study. *J Natl Cancer Inst* 2000;92(11):903-11. [Abstract](#)

Waeber M et al. Adjuvant therapy after excision and radiation of isolated postmastectomy locoregional breast cancer recurrence: Definitive results of a Phase III randomized trial (SAKK 23/82) comparing tamoxifen with observation. *Ann Oncol* 2003;14(8):1215-21. [Abstract](#)



Edited comments by Dr Yardley

Replacing anthracyclines with taxanes in the adjuvant setting

One of the most interesting questions in adjuvant therapy is: Can a taxane replace an anthracycline? The US Oncology trial presented by Stephen Jones evaluated docetaxel and cyclophosphamide versus doxorubicin/cyclophosphamide. In a population of patients, irrespective of HER2 status, this trial suggests that you don't need anthracyclines (Figure 3.1). The taxanes may really be usurping the role of the anthracyclines.

The BCIRG adjuvant trastuzumab trial also has a novel, nonanthracycline arm — docetaxel/platinum/trastuzumab — in an HER2-positive population. This combination is based on the preclinical *in vitro* data of synergism with these agents.

Figure 3.1

US Oncology Trial 9735: Adjuvant AC x 4 versus Docetaxel/Cyclophosphamide (TC) x 4 in Patients with Stage I-III Operable Breast Cancer*

	AC (60/600 mg/m ² q3w (n=510))	TC (75/600 mg/m ² q3w (n=506))
Relapses	61 (12%)	45 (9%)
Death (all causes)	45 (9%)	38 (7.5%)

Note: No significant differences in DFS or OS.

*Median Follow-up: 43 months

SOURCE: Jones SE et al. **Three year results of a prospective randomized trial of adjuvant chemotherapy for patients (pts) with stage I-III operable, invasive breast cancer comparing 4 courses of doxorubicin/cyclophosphamide (AC) to 4 courses of docetaxel/cyclophosphamide (TC).** *Proc ASCO* 2003;[Abstract 59](#).

Adjuvant chemotherapy in a nonprotocol setting

I do not use four cycles of AC. I will consider CMF in some patients with node-negative disease who are at low risk. I usually use six-cycle anthracycline-based regimens — typically FEC. I'm looking forward to the Canadian MA21 trial data directly comparing a six-cycle anthracycline-based regimen to AC followed by paclitaxel. I think this is the "million-dollar question."

Dr Yardley is the Director of Breast Cancer Research at the Sarah Cannon Cancer Center in Nashville, Tennessee.

Taxanes clearly have benefit in the adjuvant setting, and I typically utilize the six-cycle TAC regimen. The disease-free and overall survival of dose-dense therapy and TAC are equivalent. Growth factor support, used in conjunction with TAC, reduces the rate of febrile neutropenia to that seen in CALGB-9741 (Figure 3.2).

Figure 3.2

Indirect Comparison of Adjuvant Clinical Trial Results in Patients with Node-Positive Breast Cancer: BCIRG-001 (TAC versus FAC) and CALGB-9741 (Dose-dense [DD] versus Conventional Scheduling [CS] Chemotherapy)

	BCIRG-001*		CALGB-9741**	
Number of patients	1,491		2,005	
Median follow-up	55 mo		36 mo	
	Relative reduction TAC/FAC	% Reduction	Relative reduction DD/CS	% Reduction
Disease-free survival	HR = 0.72 $p = 0.001$	28%	RR = 0.74 $p = 0.007$	26%
Overall survival	HR = 0.70 $p = 0.008$	30%	RR = 0.69 $p = 0.014$	31%

*SOURCE: Martin M et al. TAC Improved DFS and OS over FAC in node positive early breast cancer patients, BCIRG-001: 55 months follow-up. *Breast Cancer Res Treat* 2003; **Abstract 43**.

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

Hormonal therapy in postmenopausal women

Counseling postmenopausal patients about adjuvant hormonal therapy requires a lengthy discussion. I refer to studies in the metastatic setting demonstrating a benefit to the aromatase inhibitors over tamoxifen on several endpoints, and I review the ATAC trial results and discuss the risks and benefits of the therapies and the limitations of the data.

Bone density is a big issue for patients. We aim to cure them of their breast cancer but don't want to leave them with a second problem. I monitor bone density very closely in patients on aromatase inhibitors. I also counsel patients about the side effects of tamoxifen, including endometrial cancer and thromboembolic events, especially those with comorbid conditions and a propensity for clotting.

Over the last six months, I estimate 30 to 40 percent of my patients have chosen tamoxifen and 60 to 70 percent chose an aromatase inhibitor. I believe letrozole and anastrozole are probably equivalent, but I typically use anastrozole because the ATAC data is with anastrozole.

With the recent data on tamoxifen followed by the aromatase inhibitors, this discussion is even more complicated. Some patients have misconceptions about switching after two or three years of tamoxifen. Others are relieved to know some data support changing drugs at the end of five years to give them a little bit more protection.

Chemotherapy in elderly women

We have a trial in the elderly looking at intravenous CMF every three weeks versus single-agent docetaxel. The rationale for this was an Australian trial in the metastatic setting of CMF versus paclitaxel, in which paclitaxel was the “winner.” Another elderly trial in the metastatic setting demonstrated weekly docetaxel was very well-tolerated, with less than a one percent rate of febrile neutropenia.

We’ve had some trouble accruing to this trial, largely because the elderly patient population has so many options. They are typically hormone receptor-positive and often have indolent disease. In light of the slow accrual, we are considering closing it and letting the Intergroup trial address the role of chemotherapy in the elderly.

In the adjuvant setting, the Intergroup trial evaluating AC or CMF versus capecitabine is trying to find a more user-friendly regimen for elderly patients. The Intergroup has now built in somewhat closer patient monitoring. In looking at the elderly population, I think capecitabine is a great drug in the metastatic setting, but I believe the doses have to be modified from what is indicated in the standard package insert.

Combination versus single agent-chemotherapy in the metastatic setting

This is a big debate in oncology right now. I use combinations in some patients and single agents in others, and I believe the heterogeneity of the disease warrants that. Dr Sledge’s trial demonstrated the response rate and the time to progression were significantly in favor of the combination regimen, but overall survival was equal to that of single agents with the crossover (Figure 3.3).

I may consider using a combination regimen to control the disease more quickly in very young patients, those with a very short disease-free interval, visceral disease or a large tumor burden. In the chemotherapy-naïve patient, I typically incorporate a taxane up front either as a single agent or in combination — often with a platinum.

I don’t typically combine taxanes with an anthracycline up front. We have a trial of gemcitabine/carboplatin in patients previously treated with a taxane and an anthracycline, trying to use a nontaxane, nonanthracycline regimen in the first-line metastatic setting.

Sequencing of single agents in the metastatic setting is basically a patient-physician decision. I evaluate prior adjuvant therapy, the disease location and the

patient's last regimen. We have data that vinorelbine following a taxane sometimes enhances peripheral neuropathy, so if a taxane was the last sequential single agent they received, I may look at capecitabine, gemcitabine or another agent.

Quality of life issues are also important in choosing the right therapy. Does the patient want to come in for a weekly therapy or might she be a better candidate for capecitabine? For example, someone trying to minimize time away from work may be a good candidate for an oral therapy. I also look at side-effect profiles. For example in a diabetic patient, neuropathy or extra steroid use may come into play.

I don't believe we have data suggesting a certain sequence to which one should adhere. The drug that's given earliest tends to have the highest response rate, and it drops sequentially thereafter.

Figure 3.3

Phase III Trials Comparing Single-Agent and Combination Chemotherapy for Metastatic Breast Cancer

Treatment	XT Trial*		Intergroup Trial E1193**		
	Docetaxel	Capecitabine/ docetaxel	Doxorubicin	Paclitaxel	Doxorubicin/ paclitaxel
Objective response	30%	42%	36% (20% response to crossover)	34% (22% response to crossover)	47%
Median survival	11.5 mo	14.5 mo	19.1 mo	22.5 mo	22.4 mo

*Comparing docetaxel monotherapy and combination capecitabine/docetaxel

**Comparing doxorubicin, paclitaxel and combination doxorubicin/paclitaxel

SOURCES: 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(12):2812-23. [Abstract](#)

Sledge GW et al. **Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An Intergroup trial (E1193).** *J Clin Oncol* 2003;21(4):588-92. [Abstract](#)

Clinical research in targeted therapy

Our center has a very active Phase I program directed by Skip Burris. This is one of the most exciting aspects of practice, because we have very early hands-on experience with many of the novel agents.

An example of one of these agents is a very user-friendly oral drug with minimal side effects. It is a dual tyrosine kinase inhibitor, which blocks the epidermal growth factor receptors I and II. We saw durable responses in a Phase I trial in patients with trastuzumab-refractory malignancy (Figure 3.4). It has now moved into a Phase II trial in metastatic breast cancer with paclitaxel, based on data like

that of trastuzumab, indicating that some targeted agents have higher response rates in combination with chemotherapy. We will also be moving into a Phase III trial in breast cancer patients.

Phase I trials are typically not designed to evaluate response, but to identify the maximum tolerated dose. With some of these targeted agents, you can deliver high doses without encountering toxicity. With agents like capecitabine and docetaxel, we realized we can dose-reduce and maintain the same outcomes. We've done skin biopsies and are evaluating biologic endpoints such as the maximum inhibition of tyrosine kinase and phosphorylation to help determine the dose to use in our subsequent trial.

Figure 3.4

Tolerability of an Oral, Dual Tyrosine Kinase Inhibitor, GW572016, in a Dose-Escalation Study

"A Phase I study of GW572016, an orally active, reversible, dual inhibitor of EGFR/ErbB2 tyrosine kinases, was conducted in a dose-escalation scheme (175 to 1800 mg/day) in patients (pts) with solid tumors. Pts were administered GW572016 on a once daily (qd) schedule with the exception of one cohort administered 900 mg twice a day (bid), and were re-evaluated monthly. ...

"Grade 1-2 rash, diarrhea, nausea, vomiting, constipation, fatigue, and anorexia were the most frequent adverse events in all qd dose cohorts. Grade 3 toxicity was not observed in any of the qd dose cohorts."

SOURCE: Burris HA et al. **A Phase I study of GW572016 in patients with solid tumors.** *Proc ASCO* 2003;[Abstract 994](#).

Case discussion: Novel agents in a heavily pretreated patient

I am taking care of a woman in her thirties who was diagnosed with breast cancer when she was postpartum. She underwent a mastectomy, and her disease recurred in the skin. She also had some clinically positive supraclavicular nodes and a small lung nodule and liver lesion.

Her tumor expressed EGFR type I. When I began seeing her, fatigue was her biggest complaint, but she had no symptoms from the visceral involvement.

Her disease had been heavily pretreated — she had received a prior anthracycline and taxane, epothilone, gemcitabine and capecitabine. She wanted to be treated with a novel agent, and we put her on our trial of the oral dual tyrosine kinase inhibitor.

Her disease initially responded to this agent, and she maintained stable disease for almost a year. Her last scan demonstrated progression in one of the visceral lesions, so we're looking at some other options for her.

I believe she has been able to maintain an upbeat attitude because she has a life outside the hospital as a wife and a mother. It's always discouraging to tell a patient that it's time to think about another treatment because even in this time of novel agents, there are limitations in the drugs available. It is fortunate that there are so many new drugs being investigated and coming to the market, but oncology is a very humbling experience when we realize how little control we often have.

Trastuzumab with or without chemotherapy in the metastatic setting

I use first-line trastuzumab with chemotherapy in patients with HER2-positive disease. Depending on the adjuvant therapy they received and the time since their treatment, I usually use paclitaxel/carboplatin with trastuzumab. We conducted a trial of this regimen on a weekly schedule (Figure 3.5), and it was well-tolerated. Nick Robert's data used an every-three-week schedule, and patients on that study had much more myelosuppression.

In the patient whose disease responds to chemotherapy and trastuzumab, I typically discontinue the chemotherapy when the patient is stable and continue single-agent trastuzumab. You can run into issues regarding how much chemotherapy to give to patients who continue to respond. I typically average about six cycles and then maintenance if there is evidence of response. When they move to trastuzumab alone, I utilize the every-three-week regimen.

Upon progression, I typically change the chemotherapy regimen and continue the trastuzumab, but we don't have randomized trial data to follow. MD Anderson tried to evaluate this with vinorelbine versus vinorelbine/trastuzumab following a taxane, but the trial closed due to poor accrual because patients didn't want to stop the trastuzumab. The little data that's out there suggest a rationale and benefit for continuing the trastuzumab and changing the chemotherapy.

Figure 3.5

Efficacy of First-Line Paclitaxel/Carboplatin/Trastuzumab in Patients with HER2-Overexpressing Metastatic Breast Cancer

	ORR	TTP	Median survival
All (IHC 2+, 3+; n=61)	66%	12 mo	29 mo
FISH+	89%	19 mo	30+ mo*
FISH-	44%	8.5 mo	19 mo

* Median survival not reached at 30 months; ORR = objective response rate; TTP = time-to-progression

SOURCE: Yardley DA et al. Final results of the Minnie Pearl Cancer Research Network first-line trial of weekly paclitaxel/carboplatin/trastuzumab in metastatic breast cancer. *Breast Cancer Res Treat* 2002; [Abstract 439](#).

HER2-positive locally advanced disease

I have not been utilizing trastuzumab up front in patients with locally advanced disease. We are conducting a neoadjuvant trial, and I believe it is an interesting concept. In evaluating the Phase II trials comparing neoadjuvant vinorelbine to vinorelbine/trastuzumab or docetaxel alone to docetaxel/trastuzumab, the pathologic response rates haven't been overwhelmingly different. Trastuzumab is not a high response rate drug, so I'm not sure it's going to be a "big home run" in changing pathologic complete response rates. I'm still awaiting the adjuvant study results.

Hormone therapy versus trastuzumab in ER-positive, HER2-positive disease

The preclinical data combining trastuzumab with hormonal agents is very exciting; however, the hormonal agents alone offer patients good quality of life in terms of being able to take a pill and not being tethered to the doctor's office. I discuss the options with my patients, and more often than not, I give hormonal therapy without encumbering them with IV trastuzumab. I will do this until the clinical trials (Figure 3.6) show that the synergism exists in the clinical setting with the combination of hormones and trastuzumab.

In a woman with rapidly progressing ER-positive disease, I tend to use chemotherapy up front, followed by maintenance with single-agent trastuzumab. Following chemotherapy/trastuzumab I may consider adding hormonal therapy to the trastuzumab maintenance. In this setting, looking at the preclinical data, I lean towards the aromatase inhibitors, although there really hasn't been a definitive trial.

Figure 3.6

Ongoing Clinical Trials Evaluating Trastuzumab in Combination with Hormonal Therapy in Patients with ER/PR-Positive, HER2-Positive Disease

Protocol IDs	Target accrual	Eligibility criteria	Randomization
CWRU-030118, GENENTECH-H2223G, ROCHE-1100, ROCHE-B016216E, ROCHE-B016216	202	Postmenopausal, ER/PR+, HER2+ (IHC 3+ or FISH+) Stage IV	Arm 1: Anastrozole qd + trastuzumab qw Arm 2: Anastrozole qd
NU-01B4, PHARMACIA-NU-01B4	18-60	Postmenopausal, ER/PR+, HER2+ (IHC 3+ or FISH+) Stage IV	Exemestane qd + trastuzumab q3w

SOURCE: NCI Physician Data Query, December 2003.

Activity, tolerability and sequencing of fulvestrant

My patients like fulvestrant because it lets them get on with their activities and maintain their quality of life. In my experience, it has been much more likely to result in stable disease rather than produce measurable responses or complete remissions. However, it has stabilized patients with excellent quality of life for long periods of time without having to change therapy.

It'll be interesting to see the trials that move fulvestrant into the front-line setting. All of the hormonal agents, when they first become available, are used in patients with refractory disease.

Select publications

Publications discussed by Dr Yardley

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](#)

Burris HA et al. A Phase I study of GW572016 in patients with solid tumors. *Proc ASCO* 2003;[Abstract 994](#).

Citron M et al. Superiority of dose-dense (DD) over conventional scheduling (CS) and equivalence of sequential (SC) versus combination adjuvant chemotherapy (CC) for node-positive breast cancer (CALBG 9741, INT C9741). *Breast Cancer Res Treat* 2002;[Abstract 15](#).

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](#)

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](#)

Hainsworth JD et al. Weekly docetaxel in the treatment of elderly patients with advanced breast cancer: A Minnie Pearl Cancer Research Network Phase II trial. *J Clin Oncol* 2001;19(15):3500-5. [Abstract](#)

Jones SE et al. Three year results of a prospective randomized trial of adjuvant chemotherapy for patients (pts) with stage I-III operable, invasive breast cancer comparing 4 courses of doxorubicin/cyclophosphamide (AC) to 4 courses of docetaxel/cyclophosphamide (TC). *Proc ASCO* 2003;[Abstract 59](#).

Martin M et al. TAC Improved DFS and OS over FAC in node positive early breast cancer patients, BCIRG-001: 55 months follow-up. *Breast Cancer Res Treat* 2003;[Abstract 43](#).

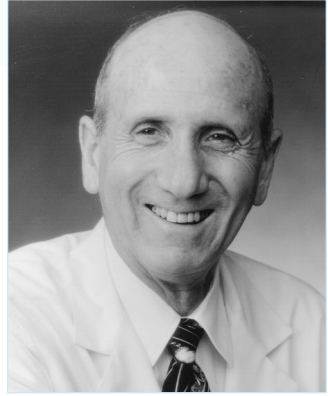
Robert N et al. Phase III comparative study of trastuzumab and paclitaxel with and without carboplatin in patients with HER-2/neu positive advanced breast cancer. *Breast Cancer Res Treat* 2002;[Abstract 35](#).

Sledge GW et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An Intergroup trial (E1193). *J Clin Oncol* 2003;21(4):588-92. [Abstract](#)

Spector N et al. Safety, clinical efficacy, and biologic assessments from EGF10004: A randomized Phase IB study of GW572016 for patients with metastatic carcinomas overexpressing EGFR or erbB2. *Proc ASCO* 2003;[Abstract 772](#).

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

Yardley DA et al. Final results of the Minnie Pearl Cancer Research Network first-line trial of weekly paclitaxel/carboplatin/trastuzumab in metastatic breast cancer. *Breast Cancer Res Treat* 2002;[Abstract 439](#).



Edited comments by Dr Rivkin

Case study:

Patient preference for a nonanthracycline-based regimen

I initially evaluated this highly intelligent 44-year-old school nurse three years ago when she presented after a lumpectomy with an ER-negative, HER2-negative tumor and four positive axillary nodes. I offered her FAC and paclitaxel, and she refused this therapy. She had heard very negative descriptions about the alopecia and cardiotoxic effects of FAC, and she is from a part of Washington state where many people don't believe in chemotherapy. She was also concerned that the therapy would interfere with her job and lifestyle.

She had a great deal of family support for her decision to decline this chemotherapy regimen. She agreed to take CMF but was aware that this therapy might not reduce her risk as much as other regimens. She did well for three years and then developed a lump in her breast, which she detected herself.

Follow-up of patients after treatment of a primary tumor

I believe we should do more intense follow-up in practice — if we detect tumor recurrence earlier, we can do a better job of treating it. This patient didn't come back for regular follow-up, and she skipped several visits, which is not uncommon. I check tumor markers on my patients all the time, but hers were not positive and her liver enzymes were normal.

I do not agree with the ASCO guidelines and the movement away from the concept of early diagnosis of tumor recurrence. I had a patient with one bony metastasis 21 years ago. We gave her CAF chemotherapy and radiation to the lesion, and she is still alive today with no other metastases.

Diagnosis of metastatic disease

It is difficult to evaluate breasts that have undergone radiation, and this patient's breast was indurated from the radiation; however, the lesion on physical exam was between two and four centimeters. Her performance status at that time was 100 percent — in fact, she is an avid kayaker and was completely asymptomatic.

Dr Rivkin is a Medical Oncologist at the Swedish Medical Center Cancer Institute, Principle Investigator of the Southwest Oncology Group, Regional President of PSOC, and Clinical Professor of Medicine at the University of Washington in Seattle, Washington.

We did a complete staging workup, and she had four lesions in the liver. Biopsies indicated ER/PR-negative, HER2-negative breast cancer. She was devastated and saw the end of her life before her. She had good social support from her husband, family and friends. We also have two full-time social workers, a wonderful support group, and our oncology nurses are available to help our patients cope with the emotional aspects of their disease.

Treatment of asymptomatic metastatic disease with combination chemotherapy

At that point, I treated her with weekly chemotherapy with doxorubicin, cyclophosphamide and paclitaxel using growth factor support. She tolerated the therapy well despite hair loss and some anemia. Neuropathy is generally less severe when paclitaxel is given on a weekly schedule as opposed to every three weeks.

I believe patients with Stage IV disease tolerate chemotherapy better than those with Stage II disease because their lives are on the line. While she had previously dreaded losing her hair, nothing bothered her now. She continued to work and she continued to kayak throughout her treatment.

Many physicians would have treated her with sequential single agents, and several studies show that this approach is just as good as combination chemotherapy. I was motivated by her young age and her emotional reaction — I believe she would have balked at a single-agent approach.

She's had more than a 50 to 60 percent response in the breast and still has lesions in the liver. I recently started her on capecitabine. When she progresses, it is going to be tough, but she's optimistic and she's a fighter. Maybe there will be something else out there for her — bevacizumab, gefitinib or maybe a new drug.

Capecitabine: Dosing and scheduling

Capecitabine is an excellent drug and very efficacious. The oral agents are wonderful for cancer patients, and capecitabine has a great reputation in Seattle. My patients say it works, and taking three or four pills per day is pretty easy. I usually dose capecitabine at 1,000 mg/m² twice a day for 14 days and then one week off.

I have a patient with liver metastases who is going on her fourth year on capecitabine. I started her on the full dose, but she actually dose-reduced herself, and she takes it five days in a row every two weeks. Her liver is now disease-free.

It will take us a long time to determine the pharmacokinetics of this drug and how best to deliver it. We have typically given two weeks on, one week off, but why not give continuous low-dose therapy?

Educating patients about potential toxicities with capecitabine

We are very careful and instruct patients to call us at the first sign of diarrhea. The major concern is that patients won't call us. To treat the hand-foot syndrome, we have used celecoxib or rofecoxib and Vitamin B-6 — I don't know if it works or not.

Progress in breast cancer

I like to make sick people well again, and I believe we can help our patients to live longer. We have data in our center demonstrating that our patients do better than the national average. Right now approximately 17 percent of our breast cancer patients have carcinoma *in situ*.

In our early studies, 60 percent of our patients had four or more positive nodes, and 12 to 13 percent of these had 10 or more positive nodes. Currently, in our adjuvant studies, only 20 percent of our patients have four or more positive nodes. We're doing better with adjuvant therapy — the tumors are smaller, the nodes are fewer and hopefully, the drugs are better.

Select publications

Capecitabine

Hudis CA. **Single-agent vs combination therapy in advanced breast cancer: Potential roles of capecitabine.** *Oncology (Huntingt)* 2002;16(10 Suppl 12):13-6. [Abstract](#)

Lauman MK et al. **Effect of pyridoxine on the incidence of palmar plantar erythroderma (PPE) in patients receiving capecitabine.** *Proc ASCO* 2001; [Abstract 1565](#).

Lin EH et al. **Celecoxib attenuated capecitabine induced hand-and-foot syndrome (HFS) and diarrhea and improved time to tumor progression in metastatic colorectal cancer (MCRC).** *Proc ASCO* 2002;[Abstract 2364](#).

Miles D et al. **Combination versus sequential single-agent therapy in metastatic breast cancer.** *Oncologist* 2002;7 Suppl 6:13-9. [Abstract](#)

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(12):2812-23. [Abstract](#)

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

Reichardt P et al. **Multicenter Phase II study of oral capecitabine (Xeloda) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy.** *Ann Oncol* 2003;14(8):1227-33. [Abstract](#)

Seidman AD et al. **Single-agent capecitabine: A reference treatment for taxane-pretreated metastatic breast cancer?** *Oncologist* 2002;7 Suppl 6:20-8. [Abstract](#)

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

Mini-PowerPoint® Atlas: Current clinical trials of the International Breast Cancer Study Group

Editor's Note: This issue marks the launch of this new feature. The PowerPoint® files of the following slides are located on CD 1 and can also be downloaded at

BreastCancerUpdate.com.

Slide 1: IBCSG Open Trials

Slide 2: IBCSG Overview

Slide 3: IBCSG Clinical Trial Design

Slide 4: SOFT: Suppression of Ovarian Function Trial

Slide 5: TEXT: Tamoxifen and Exemestane Trial

Slide 6: PERCHE: Premenopausal Endocrine Responsive Chemotherapy Trial

Slide 7: HERA: Herceptin Adjuvant Trial

Slide 8: HERA: Herceptin Adjuvant Trial

Slide 9: IBCSG 22-00: Low-Dose Cytotoxics as Antiangiogenesis Treatment following Adjuvant Induction Chemotherapy

Slide 10: IBCSG 27-02 (BIG1-02): Chemotherapy versus Observation for Radically Resected Locoregional Relapse

Slide 11: IBCSG 17-98: HABITS — Hormonal Replacement Therapy after Breast Cancer — Is It Safe?

Slide 12: IBCSG 16-98: Exemestane versus Tamoxifen as Adjuvant Therapy

Slide 13: IBCSG 18-98: BIG FEMTA

Slide 1

IBCSG Open Trials

- Adjuvant Endocrine Therapy in Premenopausal Patients (SOFT, TEXT, PERCHE)
- Adjuvant Trastuzumab (HERA)
- Adjuvant Antiangiogenesis with Low-dose Cytotoxics (IBCSG 22-00)
- Chemotherapy after Locoregional Relapse (IBCSG 27-02)
- Safety of Hormone Replacement after Breast Cancer (IBCSG 17-98)

Source: <http://www.ibcsg.org/>

Breast Cancer
UPDATE

IBCSG Overview

- Established as Ludwig Breast Cancer Study Group (1978)
- International Breast Cancer Study Group (IBCSG – 1986)
- Charter member:
Breast International Group (BIG)
- Coordinating Center: Bern, Switzerland
- Statistical and Data Management Centers: USA

Source: <http://www.ibcsg.org/>

IBCSG: Clinical Trial Design

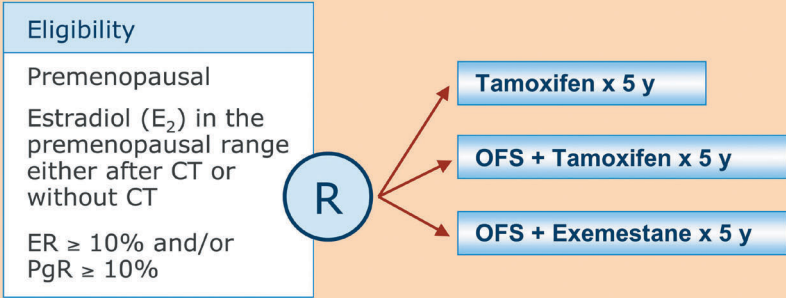
- Based upon biological hypotheses
- Selected for direct impact on patient care
- Whenever possible, trials use 2 x 2 factorial designs
- Trials complement each other, allowing data to be combined

Source: <http://www.ibcsg.org/>

SOFT

Suppression of Ovarian Function Trial

Target accrual: 3,000 patients



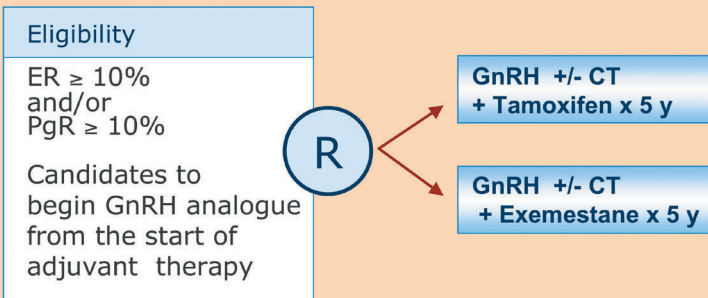
CT = chemotherapy; OFS = ovarian function suppression using triptorelin x 5 years or surgical oophorectomy or ovarian irradiation

Source: <http://www.ibcsg.org/>

TEXT

Tamoxifen and EXemestane Trial

Target accrual: 1,845 patients



CT = chemotherapy; GnRH = triptorelin x 5 years, but oophorectomy or radiation is allowed after 6 months

Source: <http://www.ibcsg.org/>

Slide 6

PERCHE

Premenopausal Endocrine Responsive **CHE**motherapy Trial

Target accrual: 1,750 patients

Eligibility
Premenopausal
ER \geq 10% and/or PgR \geq 10%
Patients for whom CT is considered to be a randomized option (lower risk)



OFS + TEXT or T or E x 5 y

OFS + TEXT or T or E x 5 y
+ any CT

CT = chemotherapy; OFS = ovarian function suppression using triptorelin or surgical oophorectomy or radiation; TEXT = randomized trial comparing tamoxifen versus exemestane

Source: <http://www.ibcsg.org/>



Slide 7

HERA

HERceptin Adjuvant Trial

Target accrual: 3,192 patients

Eligibility
Primary BCA
HER2-positive
Completed CT



No trastuzumab

Trastuzumab q3w x 1 y

Trastuzumab q3w x 2 y

BCA = breast cancer; CT = adjuvant chemotherapy

Source: <http://www.ibcsg.org/>



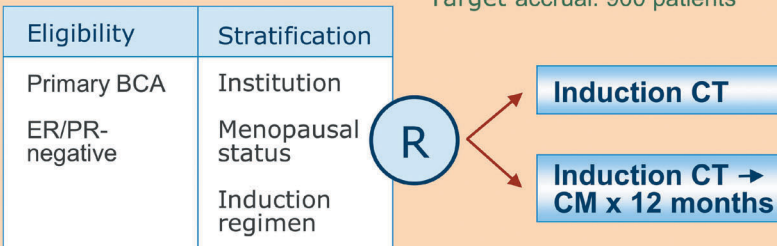
HERA HERceptin Adjuvant Trial

- **Primary Endpoint**
 - Disease-free survival
- **Secondary Objectives**
 - Overall survival, relapse-free survival, distant disease-free survival
 - Incidence of cardiac dysfunction
 - Outcomes of 1 versus 2 years of trastuzumab
 - Safety and tolerability of trastuzumab

Source: NCI Physicians Data Query, January 2004

IBCSG 22-00: Low-Dose Cytotoxics as Antiangiogenesis Treatment following Adjuvant Induction Chemotherapy

Target accrual: 900 patients



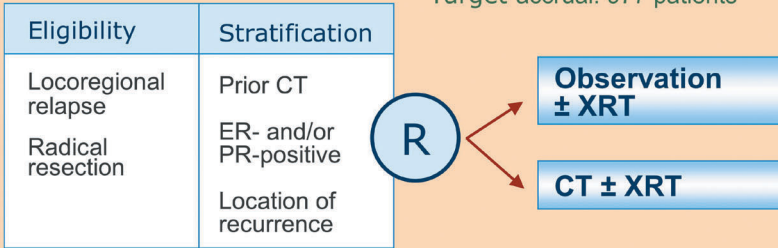
BCA = breast cancer; CM = oral cyclophosphamide and methotrexate;
CT = adjuvant chemotherapy

Source: <http://www.clinicaltrials.gov>, January 2004

Slide 10

IBCSG 27-02 (BIG1-02): Chemotherapy versus Observation for Radically Resected Locoregional Relapse

Target accrual: 977 patients



CT = chemotherapy; XRT = radiation therapy

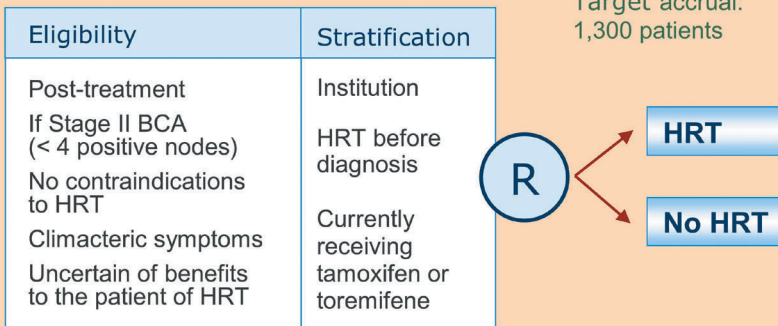
Source: <http://www.ibcsg.org/>

Breast Cancer
UPDATE

Slide 11

IBCSG 17-98: HABITS — Hormonal Replacement Therapy after Breast Cancer — Is It Safe?

Target accrual:
1,300 patients



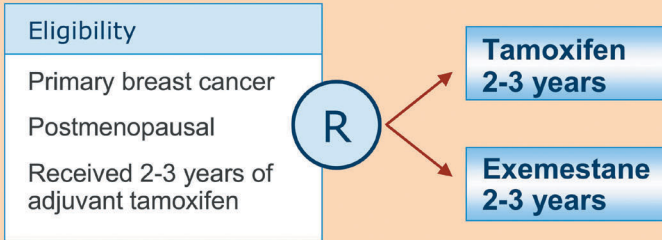
Source: <http://www.ibcsg.org/>

Breast Cancer
UPDATE

Slide 12

IBCSG 16-98: Exemestane versus Tamoxifen as Adjuvant Therapy

Final accrual: 4,484 patients



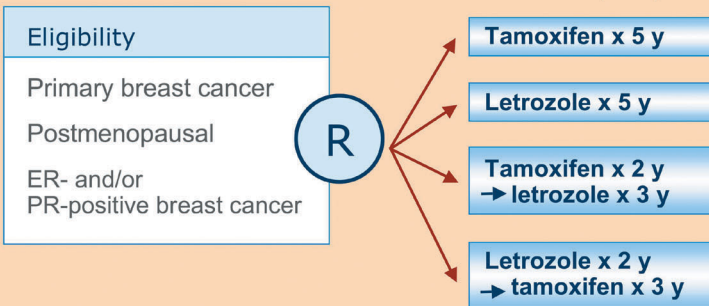
Source: <http://www.ibcsg.org/>

Breast Cancer
UPDATE

Slide 13

IBCSG 18-98 (BIG FEMTA)

Final accrual: 8,028 patients



Source: <http://www.ibcsg.org/>

Breast Cancer
UPDATE

Post-test: Breast Cancer Update, Issue 1, 2004

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

- Which of the following is not one of the randomization arms in the SOFT trial?
 - Tamoxifen
 - Ovarian function suppression plus tamoxifen
 - Exemestane
 - Ovarian function suppression plus exemestane
 - None of the above
- Metronomic chemotherapy is believed to work through an antiangiogenic effect.
 - True
 - False
- MA17, the Phase III study of letrozole versus placebo in postmenopausal women with primary breast cancer who have completed at least five years of adjuvant tamoxifen, was closed early because:
 - The estimated benefit of letrozole was substantially greater than expected
 - The toxicities of letrozole were greater than expected
 - None of the above
- The reduction in the frequency of new primary tumors in the contralateral breast in MA17 was compatible with the reduction in the frequency of contralateral disease among women who received adjuvant tamoxifen therapy in earlier studies.
 - True
 - False
- Randomized studies comparing capecitabine to traditional CMF and to paclitaxel as first-line treatment for advanced/metastatic breast cancer showed generally equivalent efficacy results.
 - True
 - False
- In Dennis Slamon's pivotal trial evaluating chemotherapy plus or minus trastuzumab in the metastatic setting, which of the following adversely affected response rates and outcomes in patients treated with the combination:
 - Estrogen receptor status
 - Prior endocrine therapy
 - None of the above
- Kent Osborne and his colleagues at Baylor demonstrated in *in vitro* models that the inhibition of either EGFR or HER2, using drugs such as gefitinib or trastuzumab, potentiates the effectiveness of agents such as tamoxifen or fulvestrant.
 - True
 - False
- In the pilot program conducted by Dr Burstein and colleagues, preoperative trastuzumab and paclitaxel resulted in a pathologic complete response rate of approximately:
 - < 5 percent
 - 10 percent
 - 20 percent
 - 40 percent
- Several clinical trials in patients with metastatic disease have demonstrated response rates to trastuzumab monotherapy of 30 to 35 percent.
 - True
 - False
- The US Oncology trial reported by Stephen Jones and colleagues, evaluating AC versus docetaxel/cyclophosphamide (TC) in early breast cancer, demonstrated a survival advantage for TC compared to AC.
 - True
 - False

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

Evaluation Form: Breast Cancer Update, Issue 1, 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 NA = 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 intervention 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
Harold J Burstein, MD, PhD	5 4 3 2 1	5 4 3 2 1
Aron Goldhirsch, MD	5 4 3 2 1	5 4 3 2 1
Denise A Yardley, MD	5 4 3 2 1	5 4 3 2 1
Saul E Rivkin, 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 1, 2004

Please Print Clearly

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

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City: _____ State: _____ Zip Code: _____

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

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

Signature: _____

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

____ Yes ____ No

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

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

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

Degree:

MD DO PharmD RN NP PA BS Other _____

To obtain a certificate of completion and receive credit for this activity, please complete the 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.