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Breast Cancer™ UPDATE

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

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Table of Contents

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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 on 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 5 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Hudis, Muss, Abrams and Cobleigh on the integration of emerging clinical research data into the management of breast cancer.

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Jeffrey Abrams, MD

No financial interests or affiliations to disclose

Melody A Cobleigh, MD

Consultant: Genentech BioOncology
Honorarium: Aventis Pharmaceuticals Inc, Genentech BioOncology

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
bevacizumab	Avastin™	Genentech BioOncology
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
clodronate	Not FDA-approved	—
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Rubex®	Bristol-Myers Squibb Company
epirubicin hydrochloride	Ellence®	Pfizer Inc
filgrastim	Neupogen®	Amgen Inc
fluorouracil (5-FU)	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly and Company
letrozole	Femara®	Novartis Pharmaceuticals
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

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Editor's Note

Touchdown

When I sojourned to the University of Miami to begin my internship in 1972, the football team wasn't very good. In fact, lacking strong leadership and community support, the UM Hurricane team was literally on the verge of extinction. However, in 1979 a completely unexpected change in fortune occurred. A man named Howard Schnellenberger took the reins of the program and became head coach. The rest is history as Schnellenberger's vision, leadership and savvy recruiting of talented players like quarterbacks Bernie Kosar and Vinny Testeverde helped elevate the program to the highest level — a national championship — within four years.

People with foresight and the ability to actualize their dreams are essential in every profession. Clinical cancer research is no exception. In this issue of our series, as in most of our programs, you will hear thoughtful, charismatic breast cancer research leaders chat about what's new and exciting in the field. It is these dynamic people and others featured in our programs who are providing the much-needed leadership for breast cancer treatment and research.

Cliff Hudis and Hy Muss have been key members of the CALGB breast cancer committee for many years. Hy was chairman and Cliff is currently co-chair. Two recent trials from this group have permanently changed the face of adjuvant therapy, and dare we say it — the chemotherapy paradigm. CALGB-9344 survived some early criticism aimed primarily at the principal investigator, Craig Henderson, who was recently interviewed for our series. The bottom line is that this study was among the first to alert us to the substantial potential of taxanes in the adjuvant setting.

The follow-up trial, CALGB-9741, can legitimately be described as one of the most important randomized studies ever reported on the treatment of any cancer. With mathematical masterminding by Larry Norton, this trial posed a simple yet critical question: "Can the outcome of adjuvant chemotherapy for breast cancer be improved by simply changing the treatment schedule without altering the agents or doses utilized?" In this case, the question was whether dose-dense AC followed by T given every two weeks with growth factor support would result in fewer recurrences and deaths than an every three-week schedule.

The stunning answer — first delivered at the San Antonio Breast Cancer Symposium in December 2002 — is yes, and while we may not know whether it was the altered schedule of AC or T that was crucial in delivering the benefit, the results of this sentinel trial have everyone's attention.

In this program, Cliff makes a critical related point, and for once I have actually been hearing the mentor (Larry) quoting the mentee (Cliff) during meetings. Specifically, Cliff addresses a recently published *JCO* paper by Gary Lyman (another recent interviewee) documenting frequent dose reductions and delays in the use of adjuvant chemotherapy in community treatment settings in the late 1990s. I personally believe that these types of dose delays are no longer common, but that is a story for another day. (See our recently published periodical *Patterns of Care* for more perspective on the subject.)

Cliff's concept is simple yet easy to overlook, and relates to both CALGB-9741 and Gary's work. If *decreasing* the treatment interval reduces the rates of recurrence and death, might dose reductions and delays *increase* the recurrence rate and mortality? What is important about the provocative patient care implications of this CALGB trial is that the leadership of Cliff, Hy and many others has now provided us with a pristine data set that has the potential to save lives.

Jeff Abrams — also interviewed in this issue — has made a similar impact by making the NCI's Cancer Trials Support Unit (CTSU) a reality that is gaining momentum. By essentially linking the United States cooperative clinical trial groups into one "Intergroup," the CTSU is significantly speeding up trial accrual. Jeff cites the example of the recently reported Canadian MA17 trial demonstrating an advantage to letrozole versus placebo in postmenopausal women completing five years of adjuvant tamoxifen. About 70 percent of the 5,000 women enrolled in this important randomized trial were from the United States and entered through the CTSU mechanism.

I remember hearing quiet grumbling when Jeff started the CTSU some years ago — new procedures, new paperwork, etc. No one is grumbling now, as randomized trials are able to provide us answers quicker than ever.

Melody Cobleigh is another research leader I interviewed for this program. You will always find Melody and her Windy City colleague, Janet Wolter, front and center at any NSABP meeting. I recall running into both of them at the hotel check-in line at the Orlando meeting last year. When I asked them what was new, Melody chirped, "I am trying to get the breast committee to do a trial incorporating trastuzumab plus radiation therapy for DCIS." That got my attention, and we agreed to sit down and talk about this and other new research concepts in a future interview. As always, Melody tells it like it is, and perhaps like it may be in the future. Dynamic people like Cliff, Hy, Jeff and Melody have created and are creating a legacy for the future of breast cancer management.

Twenty-five years after Howard Schnellenberger began loading up the Hurricane football team roster with future NFL stars, the University of Miami continues to perfect its formula for success by constantly bringing in new leaders with new ideas. Twenty-five years from now I hope to write on these pages of the powerful legacy that was being created by today's clinical research leaders who share their hopes and dreams with us in every issue of our series.

— Neil Love, MD
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Clifford A Hudis, MD

EDITED COMMENTS

Practical implications of the MA17 trial

With patients just finishing five years of adjuvant tamoxifen, I always discuss the MA17 data for switching to letrozole, which has demonstrated improvement in disease-free survival.

We don't know how long to give letrozole or what the long-term overall health implications will be. Nor do we know whether it will have an overall survival impact, although my bias is that it will. I was struck by how high the risk of recurrence was in the second five years in the MA17 data. The estimated recurrence rate was 13 percent in patients on placebo and seven percent in patients on letrozole.

This risk of recurrence illustrates why an efficacious therapy after adjuvant tamoxifen is desirable. We don't have subset data to guide us in treating patients with small, node-negative breast cancers. I concede that the predicted benefit for these patients would be small, but we need clinical trials examining these subsets.

Letrozole initiation after prior history of adjuvant tamoxifen

We don't know how long after a patient completes five years of adjuvant tamoxifen it is still beneficial to initiate letrozole. I consider the NSABP-P-1 prevention trial and the patient's risk for recurrence at that point. The P-1 trial showed that if we intervene, we change a woman's hazard rate for breast cancer occurrence, but we don't know at what point the reduction in hazard rate becomes so low it is of marginal value (1.1).

For a patient with a 1.1-centimeter, node-negative breast tumor, intervention might still be beneficial a couple years after finishing tamoxifen, but for a patient with eight positive nodes and a 2.5-centimeter tumor, I would be willing to treat her further out because her hazard rate is probably still relatively high. When the results of the MA17 trial were revealed, the patients on placebo were offered letrozole even though we didn't know whether it would be effective two or three years after tamoxifen.

Dr Hudis is Chief of Breast Cancer Medicine Service for the Solid Tumor Division of Memorial Sloan-Kettering Cancer Center in New York, New York.

1.1 Disease-Free Survival in Postmenopausal Women Randomly Assigned to Letrozole Following Five Years of Adjuvant Tamoxifen

"On the basis of these findings, postmenopausal women with hormone-receptor-positive tumors who have completed about five years of adjuvant tamoxifen therapy should be considered for letrozole treatment. However, our results, which necessitated the discontinuation of the study, leave the optimal duration of treatment undefined and the question of long-term toxicity unanswered. Data from other, ongoing aromatase-inhibitor trials will contribute information regarding toxic effects, but the question of the optimal duration of treatment will not be answered by the current trials. Our study did not address the efficacy of letrozole therapy in women in whom tamoxifen therapy had been discontinued more than three months earlier, but because there was an ongoing reduction in the hazard of recurrence in the letrozole group, the use of the drug in such women should be considered. Consequently, our trial committee has recommended that women in the placebo group in our study discuss their personal risk profile with their oncologist and be considered for letrozole therapy."

SOURCE: 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

Aromatase inhibitors versus tamoxifen in HER2-positive tumors

Retrospective subset analyses of several trials show higher response rates with aromatase inhibitors than with tamoxifen in HER2-positive tumors. This area continues to evolve and I don't believe we have the final answer, but the overarching trend seems clear (1.2).

1.2 Response Rates Following Neoadjuvant Aromatase Inhibitors in Postmenopausal Patients with Locally Advanced ER-Positive Breast Cancer

	Clinical response (CR + PR)		
	All patients	HER2-positive	HER2-negative
Nonrandomized Anastrozole (n=112)*	83.1%	54.6%	95.0%
Randomized Letrozole (n=124)**	60.0%	69.0%	53.0%
Tamoxifen (n=126)**	41.0%	17.0%	40.0%

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

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;19:3808-16. Abstract

CALGB-9741: Dose-dense chemotherapy

Unlike some other trials, analysis of CALGB-9741 was time-driven, not event-driven. I'm glad we didn't have an event trigger because we'd still be waiting for this important data, and results are only relevant for a certain period of time. The study stipulated an analysis at 36 months and, consistent with trends in adjuvant therapy in general and adjuvant therapy trials in particular, the actual number of events at 36 months was far less than expected — 315 events for event-free survival rather than the expected 515 events. The data revealed a statistically significant advantage to every two-week versus every three-week therapy but no difference between sequential versus concurrent AC.

My coauthors and I are confident of our report on CALGB-9741 because of the hazard rates for recurrence. I believe medical oncologists need to pay attention to the risk of recurrence each year. For node-positive breast cancer, the hazard function peaks early, at about two to three years, and then drops off. In this trial, at year four in follow-up we were already well down on the hazard function curve — a bell-shaped curve at the beginning.

The peak incidence of recurrence on a yearly basis had already passed, and seeing an advantage at this point told us that the every two-week therapy would always have an advantage in this trial. That won't change because most of the events have already transpired.

Hazard rates of recurrences

Some criticize the data from CALGB-9741 because the magnitude of benefit over time may not be as large as it is now. That's fair, because it could fluctuate, but the positivity won't go away. We saw the same phenomenon in CALGB-9344 — if you plot the hazard function and compare paclitaxel to no paclitaxel, sometimes the curves are close together and sometimes the curves are further apart, but the aggregate benefit is clear and consistent.

Some physicians thought we got excited too early about the CALGB-9344 data, but I believe they focused on the raw numbers instead of the trend. Similarly, based on the 47-month follow-up of the ATAC trial, we can predict that the five-year disease-free survival will continue to be greater for patients on anastrozole, even though the magnitude may be different. Both ATAC and CALGB-9741 have enough patients and events to be statistically significant, and these hazard rates will not invert in years to come.

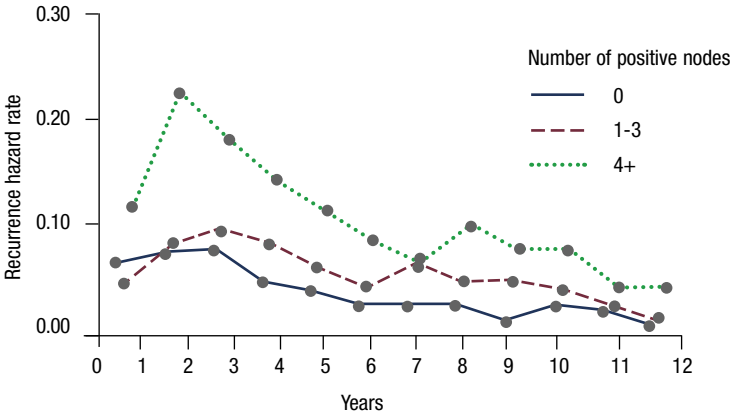
Natural history of recurrences and nodal status

The traditional view has been that node-positive patients have an early spike in recurrence, then after three to five years an inflection in their hazard rate occurs, and then it declines at a constant rate. For node-negative breast cancer, no early peak occurs — just a constant rate of recurrence.

I'm not certain this analysis would be so dichotomous with modern data sets and staging. I believe we need to explore this carefully. I can tell a patient with node-positive disease who is disease-free at 36 months that her chances of recurrence

are lower than any time earlier in her history, but that's all I'm certain of. After five years without recurrence, patients are in a very good prognostic group, and many statisticians would argue that their original nodal status doesn't matter a great deal, but that their risk of recurrence in the second five years is fairly constant (1.3).

1.3 Annual Hazard Rates of Recurrence for Breast Cancer after Primary Therapy



SOURCE: Adapted with permission from Saphner T et al. **Annual hazard rates of recurrence for breast cancer after primary therapy.** *J Clin Oncol* 1996;14(10):2738-46. Abstract

Dose-dense study of FEC

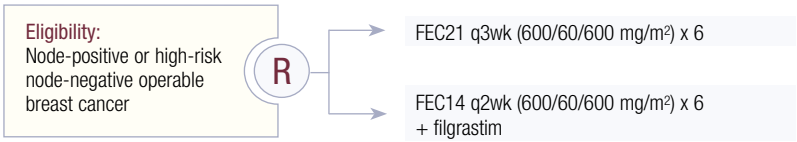
At the 2003 San Antonio Breast Cancer Symposium, Venturini et al presented data from a trial comparing FEC every two weeks versus every three weeks (1.4). It's one of the few studies that, like CALGB-9741, truly tested dose density because every patient received the same doses of the same drugs for the same number of cycles and the only variable was the interval between treatments. I commend Venturini and his colleagues because that approach is the key to demonstrating the value of dose-dense therapy.

We hoped Venturini's trial would confirm CALGB-9741 as a general principle, but their event rate was lower than expected and the study lost its power (1.4). In CALGB-9741, we also had fewer events than expected. Fortunately, our trial was large enough to demonstrate the benefit of dose density at 36 months. They presented the data showing a trend in favor of the dose-dense therapy, stating that while the trial was not positive, the range of possibilities included positivity.

Consistent with CALGB-9741, they were able to show that dose-dense therapy was faster with fewer episodes of febrile neutropenia. Although I was disappointed that their study didn't have the power to confirm the CALGB data, I'm confident that their data was consistent with ours.

1.4 Phase III Adjuvant Trial of Standard versus Accelerated FEC

Protocol ID: GONO-MIG1
Accrual: 1,214 (Closed)



Change in hazard of death with FEC14 compared to FEC21

	FEC14	Hazard ratio (HR)
Overall population	-18%	HR = 0.82 (95% CI = 0.6-1.12), $p = 0.22$
<50 years	-49%	HR = 0.51 (95% CI = 0.27-0.94)
50-59 years	-29%	HR = 0.71 (95% CI = 0.40-1.25)
>60 years	+48%	HR = 1.48 (95% CI = 0.80-2.75)

"Accelerated FEC is a safe and effective regimen in the treatment of early breast cancer. Despite numbers of events preclude drawing any definitive conclusion, in the whole group of patients accelerated FEC seems to be associated with a favorable improvement in survival compared to standard FEC. Particularly in patients aged less than 50 years, in terms of survival a statistically significant advantage of accelerated FEC was observed."

SOURCE: Venturini M et al. **Phase III adjuvant trial comparing standard versus accelerated FEC regimen in early breast cancer patients: Results from GONO — MIG1 study.** *Breast Cancer Res Treat* 2003;**Abstract 12**.

Integrating dose density into new clinical trials

Several trials are now incorporating the every two-week schedule (1.5). At my institution we're evaluating even shorter intervals without compromising dose. In MSKCC-03092, patients receive epirubicin/cyclophosphamide (EC) at 10- or 11-day intervals for four cycles followed by four subsequent cycles of paclitaxel at 10- or 11-day intervals. I'm confident paclitaxel will be tolerable at that schedule, but the practical questions are whether we can use it immediately following EC and whether the anthracycline can be tolerated with such short intervals.

We're also going to study six cycles of EC followed by six cycles of a taxane. That sequence has already been, in a sense, adopted by the Intergroup in SWOG-SO221, which compares every two-week doxorubicin/cyclophosphamide (AC) to a weekly low-dose doxorubicin and daily oral cyclophosphamide.

Both regimens are followed by a taxane, either low-dose weekly or standard every two-week paclitaxel. It's a two-by-two factorial design that doesn't actually test dose density because variations in dose size, number of cycles and the length of treatment intervals are used. Rather, it is testing metronomic chemotherapy to determine the optimal schedule for paclitaxel.

Another important trial using dose-dense chemotherapy is CALGB-40101, which incorporates the every two-week schedule comparing paclitaxel to AC in patients with high-risk, node-negative breast cancer. It also compares four cycles versus six, and although many clinicians think they already know which is better, this is the first point-on testament.

If you accept my premise that the dose density issue is a continuum, it's not so difficult to believe that therapy every two weeks is better than every three weeks. One may question whether it's worth the effort, but because treatment is completed faster and it lowers the risk of neutropenic fever, I believe it's worth it.

1.5 Ongoing Trials Evaluating Dose-Dense Chemotherapy

Protocol ID	Target accrual	Eligibility	Randomization
MSKCC-03092	11-38	Stage I-III or inflammatory	• EC + FIL x 4 → EC + paclitaxel + FIL x 4
SWOG-SO221	4,500	Node-positive or high-risk node-negative	• AC + PEG q2wk x 6 → paclitaxel + PEG q2wk x 6 • AC + FIL qwk x 15 → paclitaxel + PEG q2wk x 6 • AC + PEG q2wk x 6 → paclitaxel qwk x 12 • AC + FIL qwk x 15 → paclitaxel qwk x 12
CALGB-40101	4,646	High-risk node-negative	• AC q2wk x 4] +G-CSF • AC q2wk x 6] +G-CSF • Paclitaxel q2wk x 4] +G-CSF • Paclitaxel q2wk x 6] +G-CSF

FIL = filgrastim, E = epirubicin, PEG = pegfilgrastim, A = doxorubicin, C = cyclophosphamide

SOURCE: NCI Physician Data Query, May 2004.

The impact of dose reductions and delays

A retrospective analysis of CMF from Bonadonna in Milan showed that reductions to below 85 percent of planned dose intensity are detrimental to patient outcome, yet interesting evidence from Germany and the United States shows that oncologists lower and delay dose far more often than anticipated (1.6).

Several factors cause dose reduction and delays. To begin, the use of growth factors represents a financial and technical barrier. Also, we didn't have convincing data that delaying a few days here and there mattered until recently. In addition, toxicities other than myelosuppression, including fatigue, mucositis, diarrhea and nausea, can lead to dose reductions and delays.

Every time we dose-reduce or delay, we may be compromising therapy. Clinicians should ask themselves whether they have evidence that this is safe to do. Right now, they don't. All the evidence we have says that dose reductions and delays are not safe.

1.6 Treatment Delays, Dose Reductions and Reduced Relative Dose Intensity (RDI) in Adjuvant Chemotherapy for Early Stage Breast Cancer (ESBC)

"Given the evidence supporting the importance of maintaining full dose-intensity for best chemotherapy outcomes in ESBC, the data reported here have important implications with respect to the quality of breast cancer care delivered in the community setting. This large, practice-based study demonstrates that both planned and subsequent chemotherapy dose modifications resulting in reduced RDI are frequently implemented despite the risk of compromised outcome. In a subset analysis of the study data by year of treatment (data not shown), the percentage of patients receiving reduced RDI less than 85% was found to fall progressively with increasing year of treatment, from approximately two thirds of patients in the early 1990s to one third in the later 1990s. Although it is encouraging that there were fewer occurrences of reduced RDI among patients treated in more recent years, our results nonetheless demonstrate that a substantial proportion of women receiving adjuvant breast cancer chemotherapy receive less than 85% of the dose-intensity associated with reference standard regimens."

SOURCE: 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** [Citations omitted]

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**.

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**

Bonadonna G et al. **Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up.** *N Engl J Med* 1995;332(14):901-6. **Abstract**

Budman DR et al; The Cancer and Leukemia Group B. **Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer.** *J Natl Cancer Inst* 1998;90(16):1205-11. **Abstract**

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**

Coleman R et al. **Association between prior chemotherapy and the adverse event (AE) profile of adjuvant anastrozole (A) or tamoxifen (T): A retrospective analysis from the ATAC trial.** *Proc ASCO* 2004;**Abstract 767**.

Coombes RC et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. **Abstract**

Distler W et al. **Impact of age on the gynecologic adverse event (AE) profile of anastrozole (A) or tamoxifen (T) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2004;**Abstract 770**.

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;19:3808-16. **Abstract**

Geyer Jr CE et al. **Cardiac safety analysis of the first stage of NSABP B-31, a randomized trial comparing the safety and efficacy of adriamycin and cyclophosphamide (AC) followed by taxol to that of AC followed by taxol plus herceptin in patients (Pts) with operable, node-positive (N+), HER-2 overexpressing breast cancer (HER2+BC).** *Breast Cancer Res Treat* 2003;**Abstract 23**.

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**

Henderson IC et al. **Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (PTS) with node-positive primary breast cancer (BC).** *Proc ASCO* 1998;**Abstract 390**.

Henderson IC et al. **Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.** *J Clin Oncol* 2003;21(6):976-83. **Abstract**

Locker GY et al. **The time course of bone fractures observed in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2003;**Abstract 98**.

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**

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

Sainsbury R et al. **The use of adjuvant chemotherapy in the ATAC trial: Nationality correlates with the use of chemotherapy.** *Proc ASCO* 2004;**Abstract 597**.

Saphner T et al. **Annual hazard rates of recurrence for breast cancer after primary therapy.** *J Clin Oncol* 1996;14:2738-46. **Abstract**

Venturini M et al. **Phase III adjuvant trial comparing standard versus accelerated FEC regimen in early breast cancer patients: Results from GONO — MIG1 study.** *Breast Cancer Res Treat* 2003;**Abstract 12**.

Hyman B Muss, MD

EDITED COMMENTS

Intergroup trial of adjuvant capecitabine in elderly women

CALGB-49907, which is an Intergroup trial also available through the Cancer Trials Support Unit (CTSU) of the NCI, compares capecitabine, an oral 5-FU prodrug, with CA or CMF.

In this trial, for patients randomly assigned to standard therapy (CA or CMF), the physician chooses which of these two regimens to use. The goal is to determine whether capecitabine is equally effective as standard adjuvant therapy.

The women eligible for this trial are 65 years and older with node-positive or high-risk, node-negative breast cancer. Women with ER-positive tumors can receive tamoxifen or anastrozole as their endocrine therapy. So far, the trial is accruing reasonably well.

We are gathering excellent quality-of-life data and collecting adherence data with an electronic pill bottle. We are also evaluating some incredible laboratory science including genes that might tell us about toxicity, such as levels of thymidine phosphorylase, thymidylate synthase and dihydropyrimidine dehydrogenase (DPD). In addition, we'll be storing all the blocks for future work.

We're excited about this study. While it's a little early for me to predict how to compare these regimens, I believe patients may perceive that capecitabine is a little easier to take because it is oral and not associated with alopecia.

Dosing of capecitabine and monitoring for toxicity

In CALGB-49907, capecitabine is given at a dose of 2,000 mg/m^2 per day in divided doses for 14 consecutive days every three weeks for six cycles. We initially escalated the dose to 2,500 mg/m^2, but we elected to reduce it because of severe toxicity. I believe this lower dose is certainly adequate. Rarely can patients tolerate a full dose on a continuous basis as indicated in the package insert.

Two patients out of the first 60 in the trial died, probably as a result of capecitabine toxicity. The first patient had profound DPD deficiency, and within several days of starting capecitabine she developed severe diarrhea and mucositis and was

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admitted with marked pancytopenia. She became septic and died.

The second patient had some modest diarrhea after her sixth course at 2,500 mg/m^2, and unfortunately the clinicians caring for her could not convince her to come into the clinic when she called. Over a period of weeks she became more symptomatic, developed a severe infection and died.

The incidence of DPD deficiency is probably less than one percent. Unfortunately, no reliable test exists to screen for this disease. It is not practical to measure DPD because large quantities of blood are needed. The deficiency is likely a polymorphism in a protein that is present but not functional.

Based on our experience with the DPD-deficient patient, we amended the protocol to identify these patients. We now have women come in between days four and six of the first cycle and again several days later for "mini checks." We do this to make sure we don't miss patients who may have profound toxicity early. These checks will enable us to stop the drug early and avoid serious toxicity.

Our assessment is that capecitabine is a reasonably safe drug, but patients need to be informed. Doctors who don't frequently use capecitabine need to be aware of this early toxicity, and older patients should be contacted and assessed.

Use of capecitabine in the metastatic setting

I treat a majority of patients, old and young, with capecitabine as first-line therapy in the metastatic setting. I find that many patients, especially the elderly, are wary of chemotherapy. Despite all of our wonderful endocrine agents, at some point most women progress and need chemotherapy. Capecitabine is a nice way to initiate a patient into treatment — it is oral, doesn't cause hair loss and is a gentle way to begin chemotherapy. In addition, the response rates are comparable to the response rates of taxanes, gemcitabine and vinorelbine.

I pay close attention to hand-foot symptoms because that can be a difficult problem — especially in the elderly patient. I usually start with a dose somewhat lower than 2,000 mg/m^2, especially with older patients, and then raise it quickly rather than risk that a patient will develop toxicity and decide not to receive any more chemotherapy. Overall, I believe capecitabine is an excellent drug.

Single agents versus combination chemotherapy in the metastatic setting

Based on the best published data, I believe that single-agent sequential therapy is still the best way to manage most patients with metastatic breast cancer. It is less toxic, you're not lowering dose — and perhaps efficacy — below a threshold level, and survival is identical. Additionally, other drugs can be offered later. I believe single-agent sequential therapy is the way to go, and I start with capecitabine first in most patients.

I don't believe vast differences exist with regard to responses and confidence intervals; however, there are exceptions, such as the patient with terrible bone pain or in whom another doubling of their liver or pulmonary metastases will

be catastrophic. Occasionally patients have pleural effusions that are difficult to manage. While achieving a faster response is helpful in these cases, these are the minority of patients.

When I use combinations, I use agents like capecitabine and docetaxel (2.1). In chemotherapy-naïve patients, anthracyclines and taxanes have very high response rates, but in the last several years in my practice I have started with a combination regimen in only about 10 percent of patients.

Breast cancer is not high-grade lymphoma or acute myeloid leukemia. We have time to work with the patients. This is a really tough problem for which all of our therapy is palliative.

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

	XT Trial: Comparing docetaxel monotherapy and combination capecitabine/docetaxel		Intergroup Trial E1193: Comparing doxorubicin, paclitaxel and combination doxorubicin/paclitaxel		
Treatment	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 months	14.5 months	18.9 months	22.2 months	22.0 months

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**

New strategies for adjuvant and neoadjuvant clinical trials

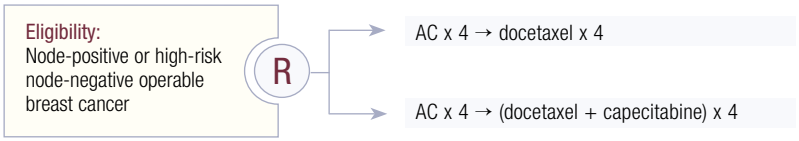
I believe the adjuvant trials studying the combination of capecitabine and docetaxel are wonderful trials to evaluate extremely active drugs in the adjuvant setting (2.2). We have several outstanding agents with high response rates in the metastatic setting, such as capecitabine, vinorelbine and gemcitabine, which haven't been evaluated in the adjuvant setting. I support the strategy of moving these agents into the adjuvant course of treatment.

The neoadjuvant setting is another arena in which I believe we need more research (2.3). It is not uncommon for us to see patients after preoperative therapy and surgery who have seven positive nodes and scattered tumor throughout the breast. We don't know what to do in these cases. Obviously we put patients with ER- or PR-positive tumors on endocrine therapy, but I don't think any of us believes this is going to be a great strategy. I believe exploring agents such as capecitabine in those patients is a great idea.

I also think that some breast cancers have very few cells in cycle kinetically — like low-grade lymphomas. We will never cure these patients with aggressive agents, but perhaps metronomic, low-dose therapy — whether it's weekly taxanes, weekly anthracyclines or capecitabine for a prolonged period of time — would treat that component of cells that aren't cycling. All of these are great options for future studies.

2.2 A Randomized, Open-Label, Multicenter, Phase III Trial Comparing AC Followed by either Docetaxel (T) or Capecitabine Plus Docetaxel (XT) as Adjuvant Therapy for Female Patients with High-Risk Breast Cancer

Protocol ID: US Oncology 01-062
Target Accrual: 1,810 patients (Open)



ER- and/or PR-positive patients receive tamoxifen or anastrozole (postmenopausal only) x 5 years.

SOURCE: Protocol 01-062 synopsis, June 2002. **www.usoncology.com/ourservices/trialdetail.asp?tid=01062**

2.3 Proposed NSABP-B-27 Preoperative Chemotherapy Replacement Trial

AC q3wk ↔ docetaxel q3wk → surgery
AC q3wk ↔ docetaxel/capecitabine q3wk → surgery
AC q3wk ↔ docetaxel/gemcitabine q3wk → surgery

↔ In this proposed 3 x 2 factorial design, some patients will receive AC followed by docetaxel or docetaxel combination regimens; in others, the sequence of administration will be reversed.

SOURCE: NSABP Website, accessed June 16, 2004.

Potential for use of vinorelbine/capecitabine (VINOCAP) combinations

Some excellent Phase I and II abstracts have shown good response rates and modest toxicity with VINOCAP (2.4). I have occasionally used this in patients with metastatic disease who have progressed quickly. This is an example of a combination that would be great to study in large numbers in the adjuvant setting — for example, AC or TAC up front followed by VINOCAP. I believe these are extremely effective combinations when compared to some of the biologic agents, which we're trying to move up front despite having very little efficacy data.

2.4 Phase II Clinical Trials of Vinorelbine and Capecitabine (VINOCAP) Reported in Patients with Metastatic Breast Cancer

Study	No. of patients	Doses of VINOCAP	Objective response CR + PR	SD	Grade III/IV neutropenia	Grade III/IV hand-foot
[1]Ahn Sr, JH et al, 2002	19	25 mg/m^2 2,500 mg/m^2	53%	NR	22%	0%
[2]Ghosn M et al, 2003	30	25 mg/m^2 1,650 mg/m^2	68%	NR	13%	0%
[3]Hess DD et al, 2002*	36	20-25 mg/m^2 800-1,250 mg/m^2	50%	28%	8%	0%
[4]Domenech G et al, 2001	12	18 mg/m^2 2,000 mg/m^2	58%	25%	25%	NR
[5]Gligorov J et al, 2003	16	60 mg/m^2 2,000 mg/m^2	31%	NR	25%	NR
[6]Stuart N et al, 2003	80	25 mg/m^2 2,000 mg/m^2	40%	7%	NR	0%

* Phase I/II dose-finding study
VINOCAP = vinorelbine and capecitabine
SD = stable disease >6 months; NR = not reported

DERIVED FROM: [1]Ahn Sr, JH et al. *Proc ASCO* 2002;**Abstract 2030**. [2]Ghosn M et al. *Proc ASCO* 2003;**Abstract 270**. [3]Hess DD et al. *Proc ASCO* 2002;**Abstract 2915**. [4]Domenech G et al. *Proc ASCO* 2001;**Abstract 1939**. [5]Gligorov J et al. *Proc ASCO* 2003;**Abstract 351**. [6]Stuart N et al. *Proc ASCO* 2003;**Abstract 183**.

Nonprotocol adjuvant management of patients with positive nodes

Right now, I believe that TAC and dose-dense AC followed by T are among the two best choices for adjuvant chemotherapy in node-positive patients. I use more dose-dense therapy, and by limiting anthracyclines to four courses, perhaps we will have somewhat less cardiotoxicity in the long run. I've occasionally observed cardiotoxicity with some of the six-cycle or more anthracycline regimens. This is more of a gut feeling than a scientific observation, and I believe both regimens are excellent.

In terms of quality of life and toxicity, my interpretation is the regimens are not drastically different. You must use growth factors with TAC because the rate of neutropenic fever can be ameliorated with filgrastim or preferably pegfilgrastim.

Surprisingly, patients stay on cycle with the use of growth factors. My experience is that when using growth factors, very few people are neutropenic at the two-week point. Any experienced clinician knows that at some point, with six cycles every three weeks of any therapy without growth factors, a delay will occur. My experience using growth factors with dose-dense therapy or TAC is that you will almost always be there on day 14 or day 21, ready to treat the patient.

Dose reduction and delay

I rarely use non-dose-dense therapy; however, for physicians who do, and have neutropenic patients on the day of planned therapy, I lean towards the use of growth factors rather than dose reduction. A threshold dose probably exists for anthracyclines, and I suspect growth factors are a way of making sure you hit that threshold.

I believe that some physicians "low-ball" patients on the dose of therapy in trying to be "nice" and minimize toxicity. However, if you start at half the dose because you believe the patient is fragile, you're doing the patient a disservice. I think you need to evaluate the data and treat patients according to how they were managed in the protocol.

I think people are becoming more aware that a threshold effect probably occurs — the word gets out. I also believe that growth factors allow people to stay on schedule because you don't see the profound drops in counts and the high rates of neutropenic fever. Hopefully this will translate to better efficacy outcomes in adjuvant therapy in the future.

This also may explain why postmenopausal patients in the Overview appeared to receive half the benefit from chemotherapy that younger patients received. Biologically, I can't understand why that happens, yet it seems consistent over 15 years in the Overview. I suspect a large part may be dosing issues in the older studies that dominate the Overview. Perhaps this will change in future analyses.

Dose-dense therapy or TAC in patients with negative nodes

I believe that using dose-dense therapy or TAC is not outrageous in a very high-risk, node-negative patient. Using one of the prognostic models available, like Peter Ravdin's ADJUVANT! program, some node-negative patients have worse outcomes than node-positive patients. For example, someone with a small ER/PR-positive, low-grade tumor with one positive node has a better prognosis than someone with a 3.5-centimeter, receptor-negative, high-grade tumor with lymphovascular invasion and negative nodes.

I believe it is reasonable to use dose-dense therapy in node-negative patients at high risk. I've done this on occasion, because by using a program like ADJUVANT!, it is clear that the benefit can be very substantial in going from an AC or CMF regimen to a FEC regimen, a TAC regimen or a dose-dense regimen.

Use of fulvestrant in clinical practice

I've used fulvestrant, and my experiences have been good. It's an excellent drug, and we've seen some good responses. Fulvestrant provides an excellent option for patients with slowly progressive metastases, irrespective of site. I use it more in the third-line setting after an aromatase inhibitor in women who progress after adjuvant tamoxifen.

Patients come in every four weeks for an injection. Many of these women are also receiving bisphosphonates, so they come in and we give them their bisphos-

phonate and their fulvestrant injection and check them over. Fulvestrant is very well- tolerated and I can't recall any major side effects. While some patients find the injection a little uncomfortable, most patients tolerate it well and do not get sick — nor do they have to remember to take pills. I haven't found the injection to be a major issue.

Select publications

Ahn Sr, JH et al. **Phase II study of combination chemotherapy of capecitabine and vinorelbine in metastatic breast cancer with previous exposure to anthracycline and taxane: Preliminary results.** *Proc ASCO* 2002;**Abstract 2030**.

Domenech G et al. **Vinorelbine/capecitabine (VINOCAP) combination remission induction therapy for metastatic breast cancer (MBC).** *Proc ASCO* 2001;**Abstract 1939**.

Ghosn M et al. **Final results of a phase II study of vinorelbine in combination with capecitabine as first line chemotherapy for metastatic breast cancer (MBC).** *Proc ASCO* 2003;**Abstract 270**.

Gligorov J et al. **Capecitabine and oral vinorelbine in metastatic breast cancer: Preliminary experience.** *Proc ASCO* 2003;**Abstract 351**.

Hess DD et al. **Phase I-II trial of capecitabine and vinorelbine in elderly patients (pts: > 65y) with metastatic breast cancer (MBC): SAKK 25/99 for the Swiss Group of Clinical Cancer Research, Berne, Switzerland.** *Proc ASCO* 2002;**Abstract 2915**.

Lu Z et al. **Decreased dihydropyrimidine dehydrogenase activity in a population of patients with breast cancer: Implication for 5-fluorouracil-based chemotherapy.** *Clin Cancer Res* 1998;4(2):325-9. **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**

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**

Stuart N et al. **Vinorelbine and capecitabine (VX) for advanced breast cancer — a phase II study showing good activity and potential for further development.** *Proc ASCO* 2003;**Abstract 183**.

Cancer Trials Support Unit

Over the past five years, the Cancer Trials Support Unit (CTSU) (**http://www.ctsu.org/**) has developed a single regulatory support system. Instead of oncologists who belong to multiple cooperative groups having to register and file different applications every year with each group, they register once and each cooperative group utilizes that information. The centralization of that data has been very helpful. Similarly, centralization of all the IRB data on a per-study basis has been very helpful.

This should ease the burden of clinical trial participation on investigators in the community and academic institutions, which was one of our charges five years ago when the Armitage and the Implementation Committees reviewed and made some important recommendations about the NCI clinical trials system.

Our goal is to increase the speed in which we complete important trials. The system can clearly do that, as witnessed by the recent MA17 trial evaluating letrozole after adjuvant tamoxifen. More than 5,000 patients enrolled in the MA17 trial, and although NCI of Canada led that trial, 3,500 of the patients enrolled were from the United States cooperative groups. We completed accrual to that trial in less than four years and had results about one and a half years later. The system does work, and it can rapidly provide answers to important questions.

We want the different cooperative groups to be competitive in coming up with the best trial ideas — that's healthy for the system. On the other hand, as soon as those trials are formulated and made available to doctors and patients, it's very important that they accrue as rapidly as possible. By putting the trials on the CTSU menu, we keep all the advantages of the cooperative groups in terms of their scientific creativity while breaking down the barriers to rapid accrual by allowing cross-group accrual.

Now we've basically made every study an Intergroup study, because any member of one adult cooperative group can participate in other cooperative groups' studies. This becomes important when evaluating the science; as we find molecular signatures and break patients into smaller subsets, more participants

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and sites will be necessary to obtain the numbers required for these subsets. Similarly, to do trials in less common diseases, we need this cross-group participation. In its first two years, the CTSU had a slow take-off, but more recently, accrual has been improving.

Barriers to clinical trial accrual

According to the Harris poll presented by Bob Comis at ASCO some years ago, approximately 60 percent of patients claimed to have never been offered participation in a clinical trial. Clearly, if the doctors don't offer clinical trial participation, we can't even reach first base. Barriers to clinical trial accrual are multifactorial, and the CTSU was designed to attack several of these barriers (3.1).

3.1 CTSU's Objectives

- Increase physician and patient access to Phase III NCI-sponsored clinical trials
- Streamline and standardize trial data collection and reporting
- Reduce regulatory/administrative burden on investigators participating in NCI-sponsored cooperative group clinical trials (Phases 1-3)

SOURCE: Clinical Trials Support Unit Website. Available at: **http://www.ctsu.org/**. Accessed May 20, 2004.

Having the infrastructure support — the research nurse support, the IRB support and the financial support — to actually carry out the research is critical when deciding to participate in clinical trials — especially in community practice. In addition, sometimes randomization can be a problem for some physicians and patients. While not able to handle all those issues, the CTSU was designed to reduce the burden of the regulatory paperwork.

The CTSU is dependent upon Congress for its budget, and we are trying to show data that clinical trial research costs more, on average, than the $2,000 per patient that we typically reimburse for Phase III trials. Hopefully we'll be able to make that case and obtain better reimbursement. One of the other strategies we use is to work closely with industry partners on several important studies. Sometimes they help us supplement the research reimbursement, and some of our trials are reimbursed at higher rates than the government reimbursement rate.

Physicians' perspectives on randomized trials

For many physicians who choose not to participate in clinical trials, randomization is an issue. We, as physicians, feel that we know the right answer, although time and again the trials have shown that we don't know the right answer or that our initial intuition isn't correct. Many physicians like to go with their bias or intuition and don't want to randomly assign patients to therapy. In addition, randomization takes more time on the part of the physician. They must explain the pros and cons, as opposed to just presenting a patient with a definitive treatment plan.

It takes a special type of physician who's willing to put biases aside and take the necessary time to explain why the choice of the therapy will be assigned randomly and why that makes sense in this situation. We always have a harder time when the trial is comparing a treatment to no treatment. The physicians who utilize a particular treatment are biased that the treatment will work. Those trials are quite challenging, especially in radiation oncology.

Clinical research in elderly patients with breast cancer

Elderly patients in this country — including patients with breast cancer — are difficult to enroll into clinical trials. All the barriers in younger people plus the additional barriers of travel, supportive care at home and, perhaps, different approaches to the idea of randomization exist amongst the elderly. We must design the appropriate trials and then educate the doctors and the patients about the need to have these patients participate. In the United States, our population is aging. In coming years, the elderly are going to be the largest number of patients with cancer, and we need evidence-based medicine to treat them properly. If we don't do clinical trials in that group, we won't have that.

CALGB-49907: Adjuvant chemotherapy trial in the elderly

CALGB-49907 is not currently accruing well. Hyman Muss has made some changes to try to make the eligibility a little more streamlined and easier for physicians and patients. Unfortunately, we ran into toxicity problems in two patients in the capecitabine arm. These cases were evaluated by the data monitoring committee, and one case was thought to be related to an enzyme deficiency. The other case was thought to be an unfortunate late toxicity in which the patient didn't contact the physician in a timely fashion.

New rules have been written into the trial to ensure toxicity problems do not occur again. We strongly believe that this trial will address a very good question: How does an oral agent compare to traditional intravenous chemotherapy? In patients with metastatic disease, capecitabine has been shown to be better than CMF, so we might even have an efficacy advantage.

IMPACT trial: Neoadjuvant hormonal therapy

Neoadjuvant chemotherapy and neoadjuvant hormonal therapy offer great potential advantages. If we can find surrogate markers to predict outcome, we can speed up, by many years, the ability to determine which treatments work in the adjuvant setting. The investigators from the IMPACT trial (3.2) — comparing anastrozole, tamoxifen, and anastrozole plus tamoxifen — were trying to make that point. In terms of reducing Ki67, anastrozole was better than tamoxifen, which parallels the ultimate outcome of the ATAC trial.

I don't believe in using a single marker as the only surrogate. However, if we can use a surrogate marker to predict the ultimate outcome and correlate it with survival, then these trials may not need to enroll 3,000 to 5,000 patients. Instead, they can enroll 300 to 400 patients and provide an answer within a year. Now we

need to prove that surrogates correlate with survival, and the IMPACT trial was an interesting first step in that direction.

The IMPACT trial seemed to confirm that the aromatase inhibitors might be better than tamoxifen in patients with HER2-positive disease. It could be that the benefit associated with anastrozole in the ATAC trial was largely due to the population with HER2-positive disease, and tamoxifen and anastrozole may be equally effective in patients who don't overexpress HER2. It's also possible that anastrozole is better even in the patients with HER2-negative disease. I would like to see that analysis of the ATAC trial data.

3.2 Anastrozole (A) versus Tamoxifen (T) versus the Combination (C) as Neoadjuvant Endocrine Therapy for Postmenopausal Patients with Estrogen Receptor-Positive Breast Cancer: The IMPACT Trial (N=330)

	A	T	C
Objective clinical tumor response[1]	37.2%	36.1%	39.4%
Patients who became eligible for breast-conserving surgery after 3 months of treatment[1]	45.7%	22.2%	26.2%
Geometric mean reductions in Ki67 after 2 weeks of treatment[2]	76%	59%	64%

SOURCES: [1]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.**

[2]Dowsett M, Smith I, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;**Abstract 2.**

Impact of CALGB-9741 on ongoing adjuvant trials

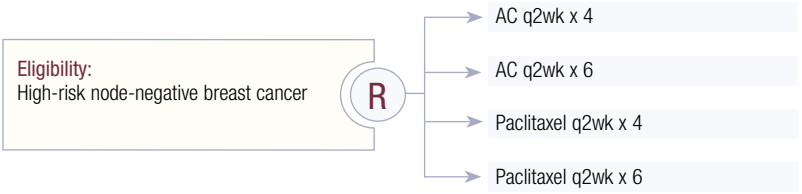
After the presentation of the results from the adjuvant dose-dense trial (CALGB-9741), the cooperative groups had to decide whether they should modify any of the ongoing adjuvant trials using a doxorubicin, cyclophosphamide and taxane combination. With regards to the adjuvant trastuzumab trials, they decided not to modify them because it was not known what the interaction would be between trastuzumab and this altered doxorubicin schedule. However, in the CALGB-led Intergroup trial (CALGB-40101) — comparing AC for four or six cycles to paclitaxel for four or six cycles — in women with node-negative disease, the AC schedule was changed to every two weeks (3.3).

Although we believe CALGB-9741 is a positive study, it is a single positive study. Some do not believe adjuvant dose-dense therapy should become the new standard based on one study, especially when fairly small differences in survival were reported. Therefore, they want another study to test this concept before it becomes a standard approach. I agree, because we have sometimes seen small differences in survival not hold up over time. Personally, I believe the results from

CALGB-9741 will hold up, but it's certainly reasonable to wait for a confirmatory study. The NSABP will try to address this again by comparing dose-dense AC followed by T to ATC in a head-to-head comparison.

3.3 Randomized Phase III Adjuvant Trial of AC versus Paclitaxel

Protocol IDs: CALGB-40101, CTSU
Accrual: 4,646 (Open)



Note: G-CSF is utilized in each arm.

SOURCE: NCI Physician Data Query, June 2004.

Adjuvant bisphosphonates

The largest study conducted to date on this issue was done in Europe and showed a survival benefit for adjuvant clodronate. However, adjuvant bisphosphonates didn't really catch on and become the standard of care because the benefit in reduction of bone metastases did not hold up. We are awaiting the results from NSABP-B-34 before concluding whether adjuvant bisphosphonates have a role as standard therapy. In follow-up to NSABP-B-34, a SWOG-led trial will compare more potent bisphosphonates to clodronate. The bisphosphonates and the aromatase inhibitors make sense as combination therapy because the bisphosphonates prevent osteoporosis. Ongoing trials — both NCI- and pharmaceutical company-sponsored — will determine the efficacy of the bisphosphonates in preventing osteoporosis related to the aromatase inhibitors.

Select Publications

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**

Dowsett M, Smith I, on behalf of the IMPACT Trialists. **Greater Ki67 response after 2 weeks neoadjuvant treatment with anastrozole (A) than with tamoxifen (T) or anastrozole plus tamoxifen (C) in the IMPACT trial: A potential predictor of relapse-free survival.** *Breast Cancer Res Treat* 2003;82(1 Suppl 1);6;**Abstract 2**.

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;82(1 Suppl 1);6;**Abstract 1**.

Melody A Cobleigh, MD

EDITED COMMENTS

Multigene assay for predicting recurrence in patients with node-negative breast cancer

Based on literature review and known prognostic factors in breast cancer, approximately 185 genes were selected for a multigene panel and tested in two data sets: one from Rush-Presbyterian-St Luke's Medical Center and the other from Providence-St Joseph Medical Center. Twenty-one genes appeared to predict for outcome and were then confirmed in a subset of the patients from the NSABP-B-20 tamoxifen-only arm.

NSABP-B-14 tested this multigene panel prospectively in 668 patients with ER-positive, node-negative breast cancer, and the panel predicted recurrence risk far better than age, tumor size or tumor grade. This assay assigns patients a recurrence score from zero to 100 to assist in deciding on treatment alternatives (4.1).

4.1 Ten-Year Distant Recurrence Rate According to Risk Group

Risk group	Percent of patients	10-year distant recurrence rate	95% confidence interval
Low	51%	6.8%	4.0-9.6%
Intermediate	22%	14.3%	8.3-20.3%
High	27%	30.5%	23.6-37.4%

$p < 0.00001$ for comparison between high- and low-risk groups

SOURCE: Paik S. **Development and validation of a multi-gene RT-PCR assay for predicting recurrence in node negative, ER+, tamoxifen-treated breast cancer patients: NSABP studies B-20 and B-14.** Presentation, San Antonio Breast Cancer Symposium, 2003;**Abstract 16**. Available at: **http://www.sabcs.org**. Accessed March 17, 2004.

For example, patients at low risk who have approximately a 6.8 percent recurrence risk after five years of adjuvant tamoxifen would realize perhaps a two percent absolute benefit from chemotherapy, whereas patients at high risk would experi-

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ence a greater reduction. I believe it's going to make difficult decisions like this much easier for patients and physicians.

Currently, I don't press patients with node-negative, ER-positive disease to take chemotherapy because I don't know who really needs it. Rather, I provide the patient with the information and encourage her to discuss it with her family and let me know her decision. In my practice, almost all the young women take chemotherapy, and almost all the elderly women choose not to, but many patients are in the middle.

Clinical impact of dose-dense chemotherapy

I believe the dose-dense approach is an advance in treatment. It's amazing that chemotherapy every two weeks rather than every three weeks can be less toxic, but that's been my experience. Prior to this data, my nonprotocol treatment for patients with node-positive disease consisted of AC times four followed by paclitaxel for four cycles.

With dose-dense therapy, dose delays do not occur, the patients feel fine and are thrilled to finish therapy earlier, and neutropenic fever is rare. The one toxicity that concerns me is neurotoxicity because it's less objective. We can harm patients by continuing paclitaxel when significant neurotoxicity is present.

Proposed NSABP trial of trastuzumab as a radiosensitizer in patients with HER2-positive DCIS

Ductal carcinoma in situ is HER2-positive more frequently than invasive cancers. Theoretically, if we intervene earlier in the pathogenesis of breast cancer, we might be able to prevent HER2-positive breast cancers. Also, in vitro evidence indicates that trastuzumab is a radiosensitizer and a chemosensitizer, so an NSABP study has been proposed in which patients with HER2-positive DCIS will be randomly assigned after lumpectomy to receive radiation with or without concurrent trastuzumab.

While nearly half of ER-negative cases overexpress HER2, only 19 percent of ER-positive cases do so. This proposed trial will evaluate both subsets. Trastuzumab will be administered with one dose at the beginning of radiation and a second dose three weeks later, which should be tolerable based on the ongoing adjuvant trials in which a couple thousand patients have received concurrent trastuzumab and radiotherapy with no safety signals. I'm hopeful we will see fewer ipsilateral recurrences in this trial, and it will be interesting to see whether trastuzumab can prevent HER2-positive DCIS in the contralateral breast.

Clinical trials of adjuvant trastuzumab

Combining the Intergroup and NSABP adjuvant trastuzumab trials is a terrific idea because we'll have data earlier, hopefully within three years. I'll be shocked if the trastuzumab arm doesn't prove to be superior. As for safety, I don't believe trastuzumab causes a marked increase in cardiac toxicity. The three adjuvant trials currently underway are all monitored every six months, and no significant

safety signal has been reported. I don't use adjuvant trastuzumab in a nonprotocol setting. I believe the oncology community has learned from the bone marrow transplant experience.

An interesting paper presented at the 2003 San Antonio Breast Cancer Symposium evaluated neoadjuvant trastuzumab in primary breast cancer. The data indicated that trastuzumab markedly increases the rate of apoptosis, so it appears to cause cell kill rather than to decrease proliferation. It also pointed out that the apoptosis occurs very quickly, so indefinite long-term therapy may not be necessary.

Combination regimens with bevacizumab

A Phase I/II trial at UCLA is evaluating the combination of trastuzumab and bevacizumab, which is a great idea because HER2-positive tumors significantly activate angiogenesis.

The prior trial of capecitabine with or without bevacizumab is negative from a scientific standpoint because the primary endpoint — time to progression — was not met (4.2). However, the response rate was increased. In the preceding Phase I/II study, the response rate for single-agent bevacizumab was approximately nine percent in heavily treated patients, which is similar to what was seen with trastuzumab in heavily pretreated populations.

ECOG-2100, the current Phase III randomized trial of paclitaxel with or without bevacizumab in patients with locally recurrent or metastatic breast cancer, will be the acid test.

4.2 Efficacy and Toxicity of Capecitabine Plus Bevacizumab versus Capecitabine Alone

Efficacy	Capecitabine n=230	Capecitabine + bevacizumab n=232
Objective response rate	19.1%	30.2%
Duration of response	6.7 months	4.96 months
Progression-free survival	4.2 months	4.9 months
Toxicity	**n=215**	**n=229**
Hypertension (grade 3)	0.5%	17.9%
Thromboembolic	5.6%	7.4%
Pulmonary embolism	1.4%	1.3%
Deep vein thrombosis	2.3%	6.1%
Bleeding	11.2%	28.8%
Grade ≥3	1.4%	0.4%
Proteinuria	7.4%	22.3%
Cardiac (grade 3 or 4)	0.9%	3.1%

SOURCE: Miller K. **Phase III trial of capecitabine (Xeloda®) plus bevacizumab (Avastin™) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane.** *Presentation, San Antonio Breast Cancer Symposium*, 2002. *Breast Cancer Res Treat* 2002;**Abstract 36**.

I expect that the trial will be positive, because why would bevacizumab work in colon cancer but not other solid tumors? It's the same target. In my own small cohort of patients, the patients who were randomly assigned to the combination of paclitaxel/bevacizumab appear to be doing very well compared to the patients receiving paclitaxel alone.

Trastuzumab for locally advanced or inflammatory breast cancer

In patients with locally advanced or inflammatory breast cancer, I believe trastuzumab may be appropriate in the nonprotocol setting. These are patients in big trouble, and no prospective randomized trials are currently evaluating this issue. I believe they need trastuzumab, and I give it to them in combination with chemotherapy. I would probably use the weekly regimen of carboplatin/paclitaxel/trastuzumab, and if a patient has had local therapy, I'd use radiation concurrent with trastuzumab and then stop.

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

Approximately 90 percent of my patients with ER-negative, HER2-positive metastatic breast cancer receive single-agent trastuzumab as first-line therapy. If a patient presents with a life-threatening illness or progresses on trastuzumab, I add chemotherapy. In patients who respond and then progress again, I continue trastuzumab indefinitely and change chemotherapy agents as needed.

The trial that documented a survival advantage for chemotherapy plus trastuzumab, compared to chemotherapy alone, was missing a third arm — trastuzumab alone. A concurrent trial evaluated first-line, single-agent trastuzumab in patients with metastatic breast cancer, and the survival curves of that single-arm trial are identical to the combination arm of the randomized trial.

Even when you evaluate variables such as prior use of adjuvant therapy, patient's age or number of metastatic sites, the survival curves are identical. Even though the data supporting single-agent trastuzumab are not from the same randomized trial, I believe it exists in a concurrent fashion.

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

In patients with ER-positive, HER2-positive metastatic breast cancer, I use front-line hormone therapy, assuming they don't present with life-threatening disease. If the patient responds and then progresses, I continue with endocrine therapy.

If she does not respond initially, then I use trastuzumab monotherapy and add chemotherapy when progression occurs. I haven't used trastuzumab and hormonal therapy together because I'm unaware of in vitro models showing a synergy between these two therapies.

When using trastuzumab as monotherapy or in combination with chemotherapy, I use the every three-week schedule. In terms of chemotherapy, when a patient

presents in visceral crisis, I find the weekly carboplatin/paclitaxel/trastuzumab combination is extremely well-tolerated and very active. I use either vinorelbine/trastuzumab or weekly carboplatin/paclitaxel/trastuzumab.

Capecitabine in the metastatic setting

In metastatic disease, I believe sequential single-agent chemotherapy is a gentler approach than combination therapy with equivalent survival. Capecitabine is probably my favorite drug in this setting because it's oral, very active and extremely well-tolerated as long as patients are properly educated about side effects. I prefer capecitabine before an anthracycline or a taxane in a patient who hasn't received either one.

As for dosing, I start with full-dose capecitabine — 2,500 mg/m^2 rounded down to the nearest 500 milligrams (for 14 days followed by seven days off therapy). I participated in the capecitabine with or without bevacizumab trial in which the FDA mandated starting with the full dose, and I learned that some patients tolerate very large doses of capecitabine. My nurse practitioner is meticulous in educating patients to stop as soon as they begin experiencing side effects. Many patients require a dose reduction, but they need not become extremely ill before we do so.

Select Publications

Claus EB et al. **Pathobiologic findings in DCIS of the breast: Morphologic features, angiogenesis, HER-2/neu and hormone receptors.** *Exp Mol Pathol* 2001;70(3):303-16. **Abstract**

Cobleigh MA et al. **Tumor gene expression predicts distant disease-free survival (DDFS) in breast cancer patients with 10 or more positive nodes: High throughput RT-PCR assay of paraffin-embedded tumor tissues.** *Proc ASCO* 2003;**Abstract 3415**.

Esteban J et al. **Tumor gene expression and prognosis in breast cancer: Multi-gene RT-PCR assay of paraffin-embedded tissue.** *Proc ASCO* 2003;**Abstract 3416**.

Hoque A et al. **HER-2/neu gene amplification in ductal carcinoma in situ of the breast.** *Cancer Epidemiol Biomarkers Prev* 2002;11(6):587-90. **Abstract**

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

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**

Paik S et al. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients — NSABP studies B-20 and B-14.** *Breast Cancer Res Treat* 2003;82(Suppl 1):10;**Abstract 16**.

Parton M et al. **High incidence of HER2 positivity in inflammatory breast cancer.** *Breast* 2004;13(2):97-103. **Abstract**

Tripathy D et al. **Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression.** *J Clin Oncol* 2004;22(6):1063-70. **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**

PowerPoint Atlas: Cancer Trials Support Unit (CTSU)

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: Cumulative accrual and sites by year

Slide 2: Cumulative accruing sites by type

Slide 3: CTSU protocol history

Slide 4: Cumulative accrual by multi-modality group

Slide 5: Cumulative accrual by disease type

Slide 6: Cumulative accrual by lead group

Slide 7: Cumulative enrollments by group

Slide 8: Cumulative accrual group credited by multi-modality group

Slide 9: Cumulative accrual by protocol

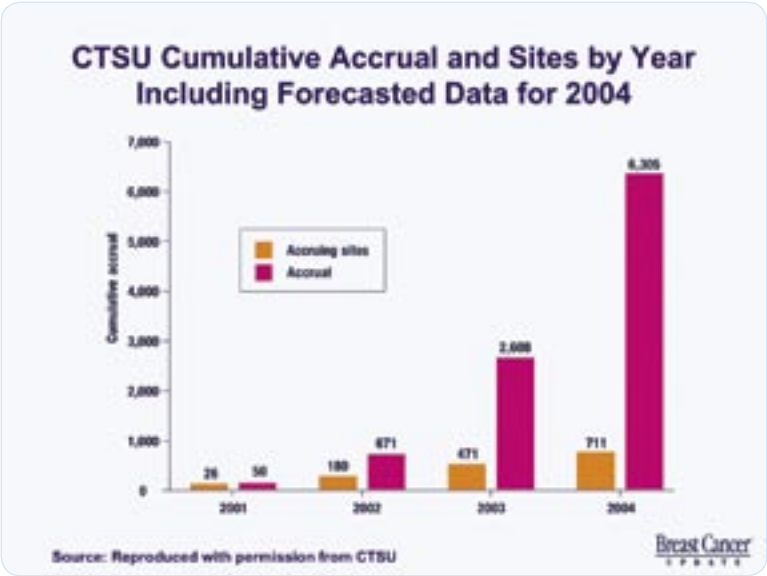
Slide 10: Cumulative accrual for new protocols

Slide 11: Monthly accrual forecast for 2004

Slide 12: CTSU 12-month accrual summary

Slide 13: Local IRB/facilitated review utilization

Slide 1



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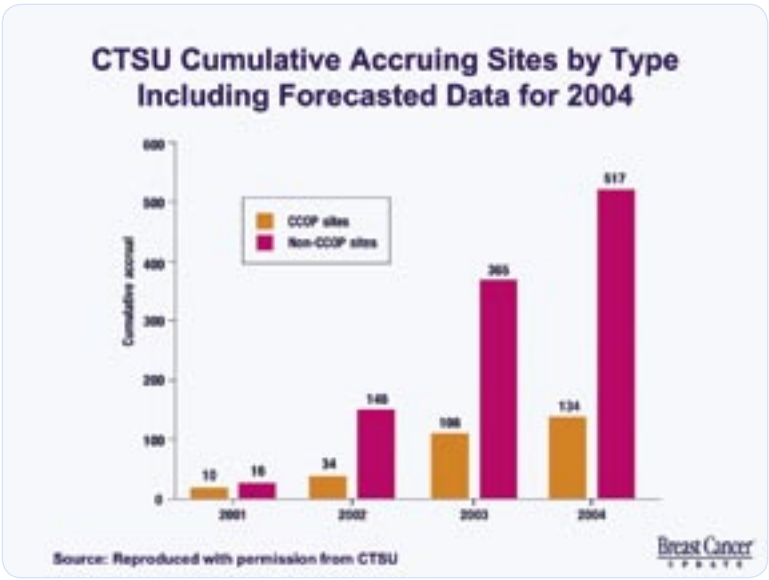

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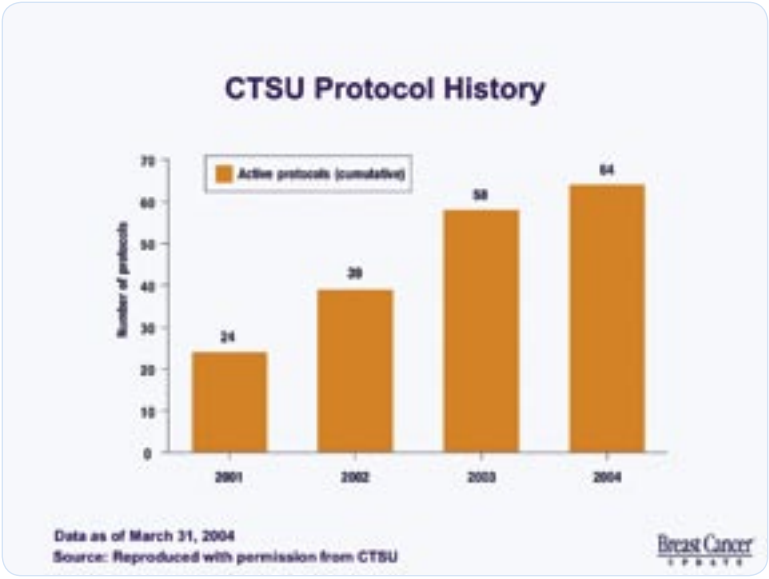

Slide 4

CTSU Cumulative Accrual by Lead Group

	2001	2002	2003	2004
NCIC-CTG	2	13	415	668
NSABP	4	222	735	894
NCCTG	0	1	6	11
CALGB	10	72	484	693
ECOG	15	228	634	833
SWOG	11	80	176	228

Data as of March 31, 2004
Source: Reproduced with permission from CTSU

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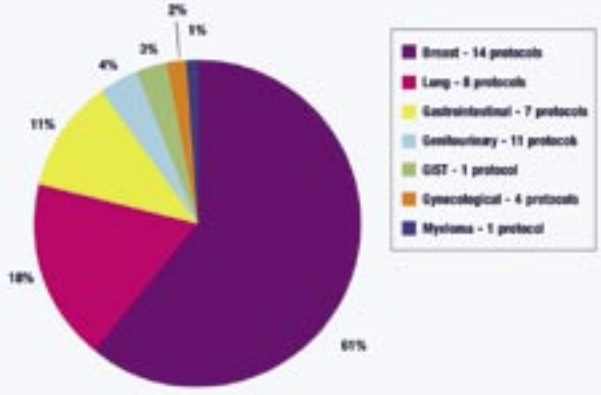
Slide 5

CTSU Accrual by Disease Type



Data as of March 31, 2004
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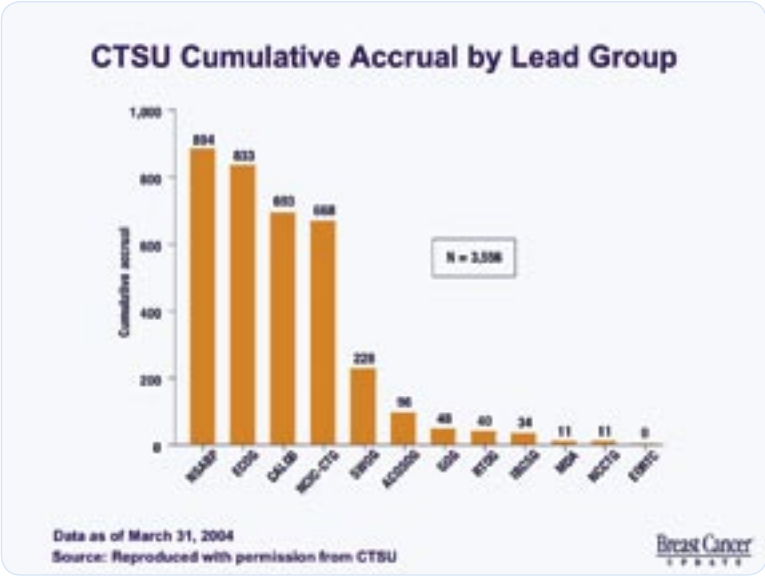
Slide 6



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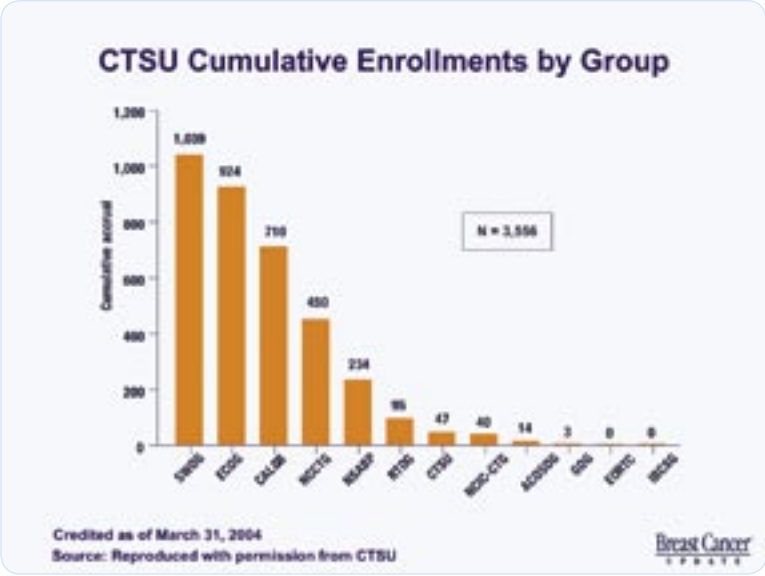

Slide 8

CTSU Cumulative Accrual Group Credited By Cooperative Group

	2001	2002	2003	2004
NCIC-CTG	0	4	29	40
CTSU	0	1	33	47
NSABP	4	30	164	234
NCCTG	9	48	288	450
CALGB	13	251	578	710
ECOG	15	167	704	924
SWOG	8	158	723	1039

Data as of March 31, 2004
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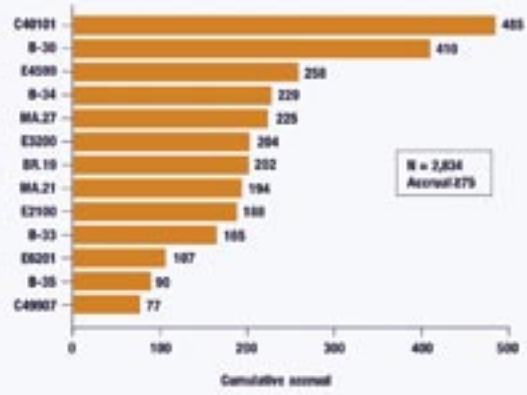
Slide 9

CTSU Cumulative Accrual by Protocol



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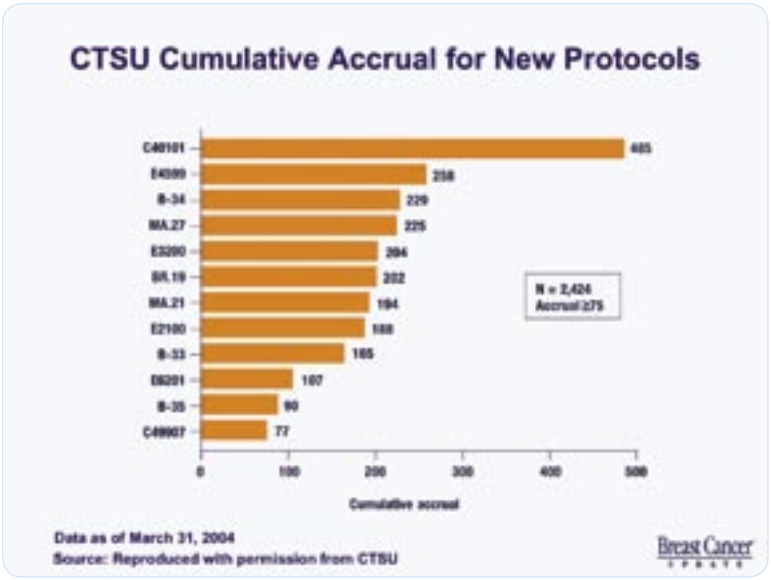
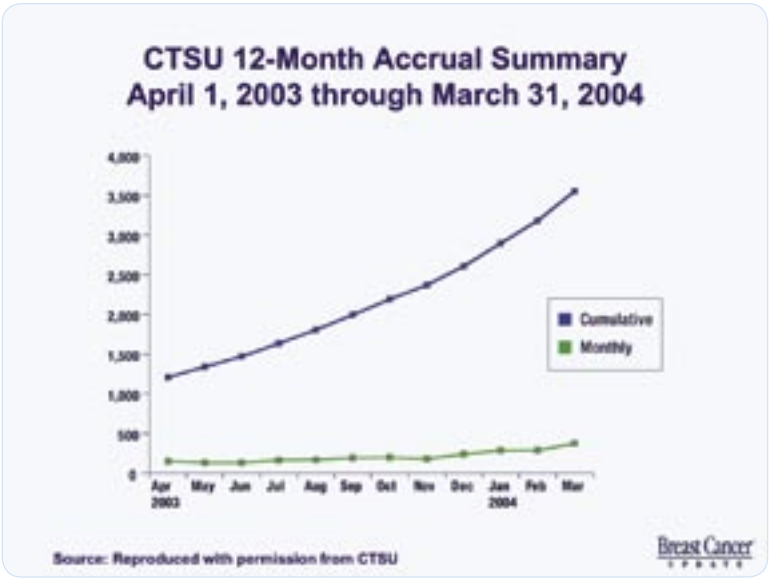
Slide 10

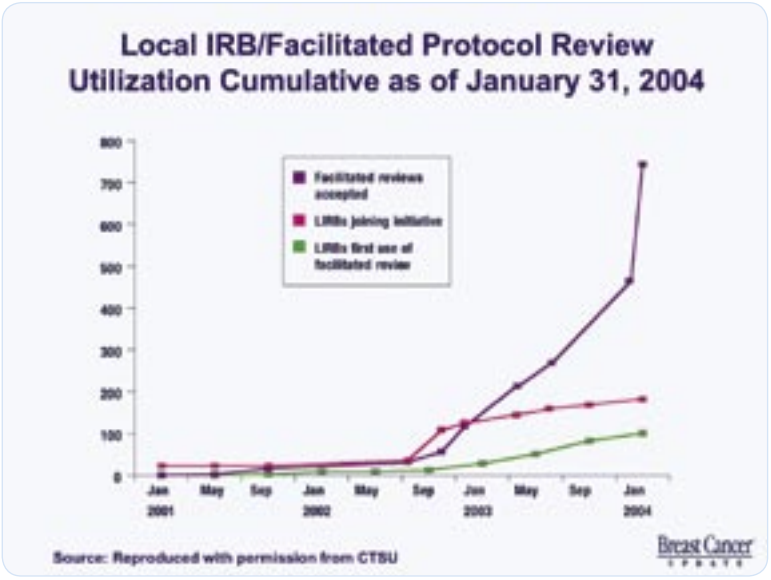


Slide 11

Slide 12



Slide 13



Post-test:
Breast Cancer Update — Issue 5, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Dihydropyrimidine dehydrogenase (DPD) deficiency occurs in about _____ of patients.**
   a. One percent
   b. 15 percent
   c. 20 percent
   d. 50 percent

2. **Intergroup trial E-1193, comparing combination versus sequential chemotherapy, demonstrated a(n):**
   a. Survival advantage for sequential single-agent chemotherapy
   b. Survival advantage for combination chemotherapy
   c. Equivalent survival for single-agent versus combination chemotherapy
   d. Objective response advantage but equivalent survival with combination chemotherapy versus single-agent chemotherapy

3. **Data from retrospective and subset analyses of several trials show higher response rates with aromatase inhibitors than with tamoxifen in HER2-positive tumors.**
   a. True
   b. False

4. **In the Italian Tamoxifen Arimidex® trial, patients who switched to anastrozole experienced:**
   a. A decreased risk of relapse
   b. A statistically nonsignificant improvement in overall survival
   c. Both of the above
   d. None of the above

5. **CALGB-9741 demonstrated a statistically significant disease-free and overall survival advantage to every two-week versus every three-week therapy.**
   a. True
   b. False

6. **The CTSU's objectives are to:**
   a. Increase physician and patient access to NCI-sponsored clinical trials
   b. Streamline and standardize trial data collection and reporting
   c. Reduce regulatory/administrative burden on investigators participating in NCI-sponsored cooperative group clinical trials (Phases I-III)
   d. All of the above
   e. None of the above

7. **CALGB-49907 is an adjuvant trial in elderly women comparing capecitabine to which of the following:**
   a. CMF
   b. AC
   c. Paclitaxel
   d. Both a and b
   e. All of the above

8. **The IMPACT trial compared which of the following neoadjuvant hormonal therapies:**
   a. Anastrozole
   b. Tamoxifen
   c. Anastrozole plus tamoxifen
   d. All of the above
   e. None of the above

9. **The survival curve from Charles Vogel's trial of single-agent trastuzumab in women with previously untreated metastatic breast cancer was similar to the survival curve for the combination arm in the trial comparing chemotherapy plus trastuzumab versus chemotherapy alone.**
   a. True
   b. False

10. **CALGB-40101 evaluates every two-week AC versus every two-week paclitaxel, both regimens for either four or six cycles in high-risk, node-negative patients.**
    a. True
    b. False

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

Evaluation Form:
Breast Cancer Update — Issue 5, 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 on breast cancer treatment. . . . . 5 4 3 2 1 N/A
- 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 N/A
- 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 N/A
- 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 N/A
- 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 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- 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 N/A

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Clifford A Hudis, MD	5 4 3 2 1	5 4 3 2 1
Hyman B Muss, MD	5 4 3 2 1	5 4 3 2 1
Jeffrey Abrams, MD	5 4 3 2 1	5 4 3 2 1
Melody A Cobleigh, MD	5 4 3 2 1	5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

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

Evaluation Form:
Breast Cancer Update — Issue 5, 2004

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

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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 .....

FOLLOW-UP

As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey.

☐ No, I'm not interested in participating in a follow-up survey.

Additional comments about this activity:

.....

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Breast Cancer™ UPDATE

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Breast Cancer™
UPDATE

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