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Breast Cancer™ UPDATE

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

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FACULTY INTERVIEWS

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GRAND ROUNDS SLIDE PRESENTATION

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CME Certified

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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 8 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Budd, Buzdar, Ellis and Budman on the integration of emerging clinical research data into the management of breast cancer.

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Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
alendronate sodium	Fosamax®	Merck and Company Inc
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
bleomycin	Various	Various
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
celecoxib	Celebrex®	Pfizer Inc
cetuximab	Erbitux™	ImClone Systems
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan® Neosar®	Bristol-Myers Squibb Company Pfizer Inc
dacarbazine	Various	Various
dexrazoxane	Zinecard®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin® Rubex®	Pfizer Inc Bristol-Myers Squibb Company
epirubicin hydrochloride	Ellence®	Pfizer Inc
etoposide	VePesid® Toposar®	Bristol-Myers Squibb Company Pfizer Inc
exemestane	Aromasin®	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
mitomycin	Mutamycin® Mytozytrex®	Bristol-Myers Squibb Company Supergen
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pegfilgrastim	Neulasta®	Amgen Inc
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
thiotepa	Various	Various
trastuzumab	Herceptin®	Genentech BioOncology
vinblastine	Velban®	Eli Lilly and Company
vincristine sulfate	Vincasar®	Teva Pharmaceuticals LTD
vindesine	Various	Various
vinorelbine	Navelbine®	GlaxoSmithKline
warfarin	Various	Various

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Editor's Note

Aman

Some time ago, during the first week of my junior year as an undergraduate at Johns Hopkins, a buddy classmate of mine dragged me to an advanced philosophy course hoping that I would sign up for the semester.

At the time I was a highly motivated premed student with a hot grade point average that promised multiple options for medical school acceptance. The last thing my precious report card needed was a "C" in a four-and-a-half-credit philosophy course.

My schoolmate (affectionately known as "Face" for his less than perfect visage) assured me that if I listened to Dr Mandelbaum for 10 minutes I would be hooked. Sure enough, within the first hour I was mesmerized by Dr M's fascinating stories of old-time philosophers, and I recklessly signed on.

Miraculously, I received an "A" in this very challenging course, mainly as a result of Dr M's unique ability to hold my interest. It was quite some time before I encountered another storyteller of similar prowess — this time at a riverside San Antonio cantina where I found myself across the table from Dr Aman Buzdar. Silently consuming chips and salsa, I listened intently to this very humble and extremely intelligent man.

As I would learn during the course of many interviews over the years, Aman likes to talk as fast as his brain works. Every now and then I have to stop during an audiorecording and ask him to think back to that day we chatted at a more leisurely pace along the San Antonio riverside. In this issue of our series, he slows down enough to tell one of the most controversial clinical oncology tales of this or any other year.

Aman, Gabe Hortobagyi, Eva Singletary and others in the MD Anderson breast cancer group have been very much on the neoadjuvant systemic therapy clinical research bandwagon for many years. In fact, a prior MD Anderson study helped demonstrate the important schedule dependence of paclitaxel, and their ongoing neoadjuvant trial compares FEC → paclitaxel to FEC → capecitabine/docetaxel.

The XT regimen is also being evaluated in a US Oncology adjuvant trial and, while no results are yet available from either of these important studies, the MD Anderson trial is of great interest not only in terms of response rates but also intratumoral tissue assays.

Based on research in metastatic disease by Joyce O'Shaughnessy and colleagues, many would expect that the FEC-capecitabine/docetaxel regimen would produce greater tumor response than FEC-docetaxel. It will be interesting to see how this stacks up against FEC-paclitaxel, but rumor has it that the line in Vegas is favoring XT.

One trial for which results are currently available is the MD Anderson neoadjuvant trastuzumab trial. Aman recently presented this now widely and enthusiastically debated initial yet final data analysis at ASCO in June. The trial focused on women with HER2-positive tumors who received neoadjuvant paclitaxel → FEC alone or with trastuzumab. Due to markedly superior pathologic complete response rates in the trastuzumab-containing arm, the data safety and monitoring committee stopped the trial very early in its course, and at several recent conferences I have found that nothing sparks more spirited debate than these controversial findings.

Aman as usual is unflappable, and on this program he calmly states his case as to why the trial was implemented, why it needed to be stopped early, why it requires and will result in more research, and why this now is a reasonable nonprotocol option to discuss with patients. I can't help but imagine how amusing it would be to have Aman, Mark Pegram (see our next issue) and Cliff Hudis in the same room, and let the boys duke it out over these questions.

Dr Buzdar's propensity to tell it like it is takes me back to another interview I conducted with him right before he was to present the 47-month follow-up data on the paradigm-breaking (don't you hate that phrase) ATAC trial. Everyone at that San Antonio meeting was greatly anticipating the presentation and as we sat down to start the interview, Aman flipped open his computer and quickly reviewed for me what was clearly very encouraging data.

When we finished, he handed me a CD of his presentation, and I felt like a newspaper reporter getting the early scoop on an important story. Listening to him present these data to a packed San Antonio auditorium just hours later, I felt a bit tingly knowing what 7,000 other attendees were about to discover — adjuvant aromatase inhibitors are here to stay.

Of all the key ATAC investigators, Aman was perhaps the first to tell me that that these findings should change standard of care, and, of course, this has come to pass. It should not be too much of a surprise that Aman is ahead of his time as he is by far the most proficient user of PDA cell phone devices that I know. I am still amazed that he was able to edit a PowerPoint presentation on his cell phone at a recent panel discussion in front of my disbelieving eyes.

It's a pleasure to bring extraordinary people such as Aman, Tom Budd and Matt Ellis to you. Like Dr Mandelbaum, these research leaders hold our interest, make complex subjects understandable and provide invaluable perspectives on the management of breast cancer.

— Neil Love, MD
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G Thomas Budd, MD

EDITED COMMENTS

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

At the 2003 San Antonio Breast Cancer Symposium, Dr Soon Paik presented validation data from NSABP-B-14 demonstrating that a new multigene RT-PCR assay could identify gene expression profiles predictive of recurrence in patients with node-negative, ER-positive breast cancer who previously received adjuvant tamoxifen.

On multivariate analysis, this assay was a significantly more powerful predictor than other conventional clinical features. On the other hand, at the same meeting, Dr Esteva presented data from an MD Anderson trial in which the same assay did not fare so well. Esteva's data examined a more diverse group of patients who had not received any adjuvant therapy (1.1).

I find the Paik NSABP data compelling. It has the advantages of being a multicenter trial conducted throughout the United States in both academic centers and community oncology practices, and the blocks were collected prospectively over a defined treatment period.

The data demonstrate the value of this assay in patients treated with tamoxifen. Presumably these data can be generalized to patients treated with aromatase inhibitors; however, that has not been demonstrated.

The Program for the Assessment of Clinical Cancer Tests (PACCT) is planning to study this new technology. The simplest way to validate it would be to study it prospectively, but that would take years to accomplish and by the time the study was completed, newer technology would be available.

Another possibility is to prospectively study whether this, or a similar assay, can be used to select patients at low risk who can be spared chemotherapy, or patients at high risk who need intensive chemotherapy. Clearly, multiple approaches need to be considered, and the final trial design is still being developed.

Dr Budd is Director of Medical Oncology in the Breast Cancer Program and Director of the Cancer Center Chemoprevention Program at The Cleveland Clinic Foundation's Hematology and Medical Oncology/Taussing Cancer Center in Cleveland, Ohio.

1.1 Comparison of Two Studies Evaluating Multigene RT-PCR Assay for Predicting Recurrence in Patients with Node-Negative Breast Cancer

10-year distant recurrence-free survival	NSABP-B-14[1]	MD Anderson[2]
Hazard ratio (95% CI) *p*-value	3.21 (2.23 - 4.61) <0.00001	0.99* (0.98 - 1.00) 0.10
Number of evaluable patients	668	149
Estrogen receptor status	Positive	Positive and negative
Adjuvant therapy	Tamoxifen	None
Study location	Multicenter	Single institution

CI = confidence interval

* No significant correlation with distant recurrence-free survival

SOURCES: [1] 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**.

[2] Esteva FJ. **Multi-gene RT-PCR assay for predicting recurrence in node-negative breast cancer patients that did not receive adjuvant tamoxifen nor chemotherapy.** Presentation. San Antonio Breast Cancer Symposium, 2003.

SWOG-S0221: Dose-dense versus continuous adjuvant chemotherapy

In SWOG-S0221, AC is administered in either an every two-week dose-dense manner with pegfilgrastim versus what might be described as a metronomic schedule with filgrastim. Both schedules are then followed by paclitaxel (1.2). We chose six cycles of AC and paclitaxel in the control arms for several reasons. First, by imposing similar durations of treatment in all arms, we avoid wondering later whether an inferior outcome in any arm reflected the duration of treatment.

In addition, some data suggest six cycles is superior, although this is still controversial. An Austrian trial presented at ASCO in 2004 compared three cycles to six cycles of preoperative epirubicin/docetaxel, and the six-cycle schedule was more efficacious (1.3). Older trials with CMF have had mixed results — some show equivalence while others show six cycles might be better.

In the SWOG study arms, weekly doxorubicin and daily cyclophosphamide are given for 15 weeks. In preclinical models examining the antiangiogenic effects of chemotherapy, it appears that frequent administration of low-dose chemotherapy may be superior to the maximum tolerated dose (MTD) model.

In addition, this more continuous schedule may provide a good chemotherapy base upon which to add other antiangiogenic approaches. Evidence indicates that with the MTD schedule, a burst of vasculogenesis occurs between cycles and possibly hematopoietic growth factors augment that, but it is unclear whether that occurs with weekly doxorubicin and daily cyclophosphamide.

1.2 Phase III Trial of Continuous Schedule AC + G versus the Every Two-Week Schedule of AC Followed by Paclitaxel Given Either Every Two Weeks or Weekly for 12 Weeks as Postoperative Adjuvant Therapy in Node-Positive or High-Risk Node-Negative Breast Cancer

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

Eligibility:
Stage I - III invasive breast cancer, node-positive or high-risk node-negative, with no prior cytotoxic chemotherapy or radiation therapy.

R

- AC q2wk + PEG-G x 6 cycles → T q2wk + PEG-G x 6
- Continuous AC + G x 15 weeks → T q2wk + PEG-G x 6
- AC q2wk + PEG-G x 6 cycles → T qwk x 12
- Continuous AC + G x 15 weeks → T qwk x 12

G = filgrastim; T = paclitaxel; PEG-G = pegfilgrastim;
Continuous AC = weekly doxorubicin + daily, oral cyclophosphamide

Southwest Oncology Group Study Coordinators:
G Thomas Budd, MD — Tel: 216-444-6480
Halle CF Moore, MD — Tel: 216-444-2644

SOURCE: NCI Physician Data Query, October 2004.

1.3 ABCSG-14: Efficacy Data from a Phase III Trial Comparing Three versus Six Cycles of Neoadjuvant Epirubicin/Docetaxel + G-CSF

	3 cycles (n=143)	6 cycles (n=145)	*p*-value
pCR	11 (7.7%)	27 (18.6%)	0.0045
Node-negative	59 (42.8%)	77 (56.6%)	0.02
Breast-conserving surgery	93 (66.9%)	104 (75.9%)	0.1

pCR = pathological complete response

SOURCE: Steger GG et al. **6 vs. 3 cycles of epirubicin/docetaxel + G-CSF in operable breast cancer: Results of ABCSG-14.** *Proc ASCO* 2004;Abstract 553.

Dose-dense chemotherapy

When I use adjuvant AC followed by paclitaxel, I employ a dose-dense schedule because dose density has been demonstrated to be superior; however, the clinicians not employing dose density may feel it needs further follow-up (1.4). In examining the data from CALGB-9741, it is possible that the benefits of dose density pertain only to the paclitaxel treatment, and it may not be advantageous for the anthracycline-based portion of the regimen.

Data shows that paclitaxel given more frequently than every three weeks is superior, whereas the GONO-MIG1 trial, which compared six cycles of 5-FU/epirubicin/cyclophosphamide given every two weeks versus every three weeks, failed to demonstrate a convincing difference between those two schedules.

Intergroup trial of chemotherapy in patients with node-negative tumors

In this current design, dose-dense doxorubicin/cyclophosphamide is given every two weeks for either four or six cycles, and this is compared to dose-dense paclitaxel given every two weeks for four or six cycles. This a very clean study that will help look at this issue of six versus four cycles and will directly compare an anthracycline and a taxane.

Moreover, it dovetails very nicely with SO221 that uses six cycles of dose-dense doxorubicin/cyclophosphamide and six cycles of dose-dense paclitaxel in the control arms.

1.4 Dose-Dense Adjuvant Chemotherapy

Have you used dose-dense adjuvant chemotherapy outside a protocol setting?	
No	36%
Yes	64%
If "yes," when did you first use it?	
1-2 years ago	53%
<6 months ago	47%
If "yes," in about how many patients?	
1-10 patients	59%
11-20 patients	28%
>20 patients	13%

SOURCE: National Survey of Medical Oncologists, 2004.

Pegfilgrastim in dose-dense adjuvant chemotherapy

No major problems have been reported using pegfilgrastim in dose-dense AC → T, and we are using it in SWOG-S0221 in the every two-week arms because of the ease of administration. Pegfilgrastim has been used in patients with lymphoma receiving CHOP every two weeks and patients with Hodgkin's disease using doxorubicin, bleomycin, vinblastine and dacarbazine every two weeks, so I believe we have sufficient data to justify its use, at least in the anthracycline phase of the trial.

When using pegfilgrastim with AC followed by paclitaxel, patients may present for paclitaxel treatment with relatively high white counts; however, I have found that simply proceeding with therapy and continuing pegfilgrastim has been safe and well tolerated.

NSABP-B-38: Adjuvant chemotherapy

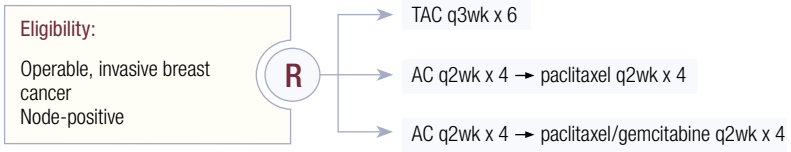
NSABP's pending study, B-38, proposes to compare the two optimal anthracycline/taxane regimens with a new combination in the paclitaxel phase (1.5). It's

a good trial design because in addition to determining whether one of the two standard combinations is superior, it examines an agent new to the adjuvant setting — gemcitabine.

At ASCO, Kathy Albain reported on a trial that showed an advantage for gemcitabine/paclitaxel versus paclitaxel alone in patients with metastatic disease. While the every two-week schedule is a bit of a leap, it was necessary to make it comparable to the dose-dense paclitaxel schedule.

1.5 Phase III Adjuvant Trial Comparing Three Chemotherapy Regimens: TAC; Dose-Dense (DD) AC Followed by DD Paclitaxel; DD AC Followed by Paclitaxel/ Gemcitabine

Protocol ID: NSABP-B-38 (Pending)
Target Accrual: 4800



All arms are followed by 5 years of hormonal therapy in patients with ER/PR-positive tumors
TAC = docetaxel/doxorubicin/cyclophosphamide; AC = doxorubicin/cyclophosphamide

SOURCE: Protocol summaries. NSABP Group Meeting, June 2004.

Combination versus single-agent chemotherapy for metastatic disease

In the metastatic setting, I generally use sequential single agents rather than combination therapy, except in situations in which an early response is vital, such as lymphangitic pulmonary disease. The sequence I utilize depends on the patient's prior therapy, comorbid conditions and lifestyle, so it's extremely variable. I usually use a taxane, which reflects the fact that most of the patients who are relapsing now have not previously been treated with a taxane.

I believe docetaxel is superior to paclitaxel, so for a younger or more seriously ill patient, I tend to use docetaxel every three weeks. In an older patient, I prefer weekly paclitaxel. If a patient has received a taxane and progresses, I generally use capecitabine, starting at two grams per meter squared per day for two weeks, then one week off. Some patients do fine, but some develop a toxicity during the second week, so I shorten the duration of treatment with subsequent cycles.

I have also become more liberal with combination therapy and if a patient is quite ill, I generally use capecitabine/docetaxel. Paclitaxel/gemcitabine is less toxic; however, in examining the various trials, it appears capecitabine/docetaxel may be superior in terms of survival.

Docetaxel has a survival advantage over paclitaxel; paclitaxel plus gemcitabine has a survival advantage over paclitaxel alone; and docetaxel plus capecitabine

has been shown to be superior to docetaxel. Obviously, it's an indirect comparison, but in my experience, the majority of patients I have treated with capecitabine/docetaxel have benefited, although they have also experienced significant toxicity.

Adjuvant therapy for postmenopausal women with ER-positive tumors

In this setting, aromatase inhibitors are superior to tamoxifen. The ATAC trial demonstrated a reduced recurrence rate and event rate with aromatase inhibitors. Various other trials switching at two or three years also showed aromatase inhibitors to be superior.

Some argue that starting adjuvant hormonal therapy with tamoxifen is superior biologically; however, if you start with tamoxifen to set the tumor up for aromatase inhibition and estrogen withdrawal, a patient who may not have relapsed on an aromatase inhibitor may relapse while on tamoxifen.

I believe that aromatase inhibitors should be used initially in most patients. I use anastrozole because that has been studied, but as more trials mature, I suspect we'll find any one of these agents can be used up front. I'm relatively certain they will all prove to be superior to tamoxifen.

Fulvestrant in the metastatic setting

SWOG is conducting a trial in metastatic disease comparing anastrozole alone to anastrozole plus fulvestrant. Preclinical rationale supports this and if an advantage is seen with the combination, then it would be logical to study it in the adjuvant setting. Clearly fulvestrant does not have the estrogenic effects of tamoxifen. It appears to be equivalent to anastrozole but it may be less appealing to study in the adjuvant setting because it involves a monthly injection.

Select publications

Albain S et al. **Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival.** *Proc ASCO* 2004;**Abstract 510**.

Esteva FJ et al. **Multi-gene RT-PCR assay for predicting recurrence in node negative breast cancer patients - M. D. Anderson Clinical Validation Study.** *Breast Cancer Res Treat* 2003;82(Suppl 1):10;**Abstract 17**.

Jones SE et al. **Randomized trial comparing docetaxel and paclitaxel in patients with metastatic breast cancer.** *Breast Cancer Res Treat* 2003;82(Suppl 1):10;**Abstract 10**.

Kaur H, Budd GT. **Metronomic therapy for breast cancer.** *Curr Oncol Rep* 2004;6(1):49-52. **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**.

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**

Steger G et al. **6 vs. 3 Cycles of epirubicin/docetaxel + G-CSF in operable breast cancer: Results of ABCSG-14.** *Proc ASCO* 2004;**Abstract 553**.

MD Anderson trial neoadjuvant/ adjuvant chemotherapy trial

We currently have a trial evaluating the role of capecitabine/docetaxel in the adjuvant and neoadjuvant settings. All patients entering the trial with intact primary tumors are randomly assigned to receive either FEC → paclitaxel or FEC → capecitabine/docetaxel in the neoadjuvant setting. Patients who have previously undergone surgery receive the same randomized treatment, but they receive it in the adjuvant setting.

The control arm is very similar to the control arm we used in our neoadjuvant trastuzumab study. The only difference is that we are using weekly versus every three-week paclitaxel for 12 weeks. The final endpoint will combine the neoadjuvant and adjuvant subgroup data, and evaluate disease-free and overall survival. The neoadjuvant group has an advantage in that we will be able to find the clinical complete remission rate, the pathological complete remission rate and a number of other endpoints.

We currently have more than 200 patients enrolled in the study. In the first cohort, we gave a somewhat higher dose of capecitabine and saw an increase in morbidity. We reduced the dose of capecitabine and, with the use of this attenuated dose, we are seeing more acceptable toxicity.

Now the big question remains: What is the long-term and short-term efficacy? The data are continuously being monitored but we really won't have any information until we have enough patients in the neoadjuvant setting to determine whether the regimens are similar or one is better than the other.

MD Anderson neoadjuvant trial of trastuzumab

At MD Anderson we believe that if a patient with an intact primary tumor is going to need systemic chemotherapy, unless the tumor is small, it is better for them to receive it in the neoadjuvant setting where we can tell whether the treatment is having an impact on the disease or if it is just causing toxicity. A few years ago we launched a study designed to accrue 164 patients with HER2-positive disease and intact primary tumors.

Dr Buzdar is a Professor of Medicine and Deputy Chairman of the Department of Breast Medical Oncology at the University of Texas MD Anderson Cancer Center in Houston, Texas.

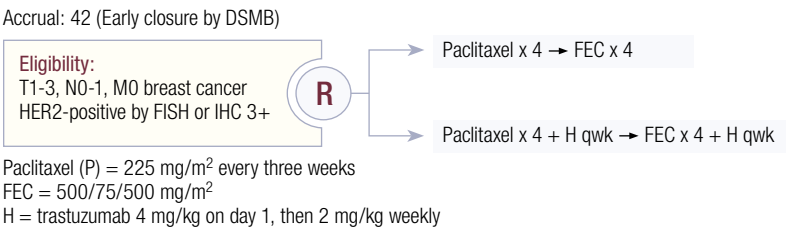
All of the patients enrolled in the trial received four courses of every three-week paclitaxel followed by 12 weeks of FEC (2.1). We used epirubicin instead of doxorubicin because it has a better cardiac safety profile. One half of these patients also received weekly trastuzumab for 24 weeks. Every patient had a baseline cardiac scan and then repeat scans at 12 and 24 weeks.

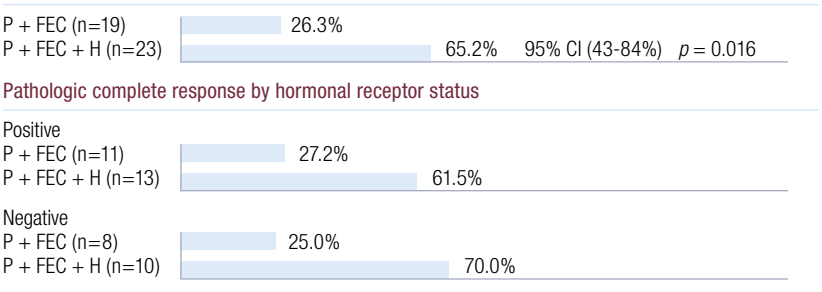
In our previous experience with this chemotherapeutic regimen, about 21 percent of unselected patients had pathological complete remissions. Pathological complete remission is defined as having no tumor left in the breast or in the lymph nodes after therapy. We were hoping that the addition of trastuzumab to chemotherapy would elevate the pathological complete response rate from 21 percent to 41 percent — a 20 percent improvement.

The trial was interesting because we knew what the pathological outcome was as soon as the patient completed surgery. As soon as we had results from 34 patients, we were able to see that 65 percent of the patients in the trastuzumab arm had no tumor whereas only 25 percent of the patients who received chemotherapy alone were tumor free. This was much higher than we had anticipated or hoped for. The clinical response rate was even more striking, as 87 percent of the patients had clinical complete remission in the trastuzumab arm compared to about 50 percent in the chemotherapy-alone arm.

We discussed these data with our institutional Data Monitoring Committee, which looked at them independently and came to the conclusion that the

2.1 Phase III Study of Neoadjuvant Therapy with Anthracycline-Containing Chemotherapy and Paclitaxel with or without Trastuzumab in Patients with HER2-Positive Breast Cancer





SOURCE: Buzdar A. Presentation. ASCO, 2004;**Abstract 520**.

findings were so striking that even if we continued the trial to reach accrual, the results would be similar. Thus the trial was stopped early.

Cardiac safety in neoadjuvant trastuzumab study

Anthracycline-based regimens are the best combination chemotherapies we know. They also have significant synergy with trastuzumab in the metastatic setting. For these reasons, we wanted to test an anthracycline/trastuzumab combination in the neoadjuvant setting; however, the question has always been the cardiac safety data.

We debated the design of a trial that would allow us to accomplish this goal, and the conclusion we came to was to use a safer anthracycline and to use it at a limited dose. All patients in this trial received 75 mg/m^2 of epirubicin in each of four cycles. No patients in the trial had any type of clinical cardiac dysfunction.

We observed a slightly increased incidence of reduced ejection fractions in patients enrolled in the trastuzumab arm compared to the patients in the chemotherapy-alone arm. All of these changes were observed on cardiac scan. What was also surprising was that in almost all of the patients who had drops in their cardiac ejection fractions, the LVEFs returned to normal after therapy was completed.

We also measured troponin T levels in all patients enrolled in the trial. A recent paper in the *New England Journal of Medicine* reports on patients being treated with doxorubicin for leukemia (2.2). In that trial, troponin T levels were evaluated for patients receiving doxorubicin alone and doxorubicin with dexrazoxane to see whether that agent can protect cardiac function.

2.2 Troponin T as a Marker of Myocardial Injury

"Troponins are sensitive and specific markers of myocardial injury. In the absence of injury, troponin levels are usually below the limit of detection of current analytical methods. Low-level elevations have significant prognostic value in patients with unstable angina and myocardial infarction but without ST-segment elevation, since those with baseline cardiac troponin T levels between 0.01 and 0.05 ng per milliliter are at higher risk for death and myocardial infarction at one and six months than are patients with levels below 0.01 ng per milliliter. We have previously demonstrated that low-level elevations of cardiac troponin T induced by doxorubicin are associated with histologic evidence of myocardial injury and are clinically meaningful. ...

"We used cardiac troponin T instead of echocardiographic measurements as an indicator of myocardial injury because of the poor sensitivity and specificity of echocardiography in identifying subclinical abnormalities of left ventricular structure and function in children with cancer who are receiving doxorubicin. Our results suggest that echocardiographic measurements are not valid surrogates for subclinical myocardial injury in this setting. …" [Citations omitted]

SOURCE: Lipshultz SE et al. **The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia.** *N Engl J Med* 2004;351(2):145-53. **Abstract**

Patients receiving dexrazoxane in addition to their chemotherapy had many fewer elevations in their troponin T levels than those receiving doxorubicin alone. The troponin T test is a very sensitive test that can predict whether an anthracycline is causing myocardial damage or not. In all of our patients, with the exception of one on the trastuzumab arm, troponin T remained normal throughout the trial (2.3).

2.3 MD Anderson Neoadjuvant Study: Cardiac Safety Data

Events	P → FEC (n=19)	P → FEC + H (n=23)
CHF	0	0
> 10% decrease in ejection fraction	5	7
Decrease on paclitaxel	0	4
Decrease on FEC	5	3
Improvement in LVEF on follow-up	2	3
Abnormal Troponin T	0	1

SOURCE: Buzdar A. Presentation. ASCO, 2004;**Abstract 520**.

Nonprotocol use of neoadjuvant and adjuvant trastuzumab

Before this data was available, we did not offer neoadjuvant trastuzumab to any patient outside the context of a clinical trial. However, now that the data is in the public domain, I think it is our responsibility to share the information and discuss the issue with our patients. As long as the patient and the physician understand that uncertainties exist regarding the data, the cardiac safety and the long-term outcome, I believe it is a reasonable approach.

At our institution, based on the recommendation of the Data Monitoring Committee, we stopped the control arm of the study. Currently, all patients are being offered chemotherapy with trastuzumab in the neoadjuvant setting. We want to expand our experience, determine whether this data is reproducible and acquire long-term safety data.

On the other hand, if a woman with high-risk node-positive disease comes to MD Anderson seeking adjuvant trastuzumab, our group is divided on the issue. Some physicians within our group believe that a woman at high risk should be offered this therapy in the neoadjuvant or adjuvant setting, whereas others want to be conservative and not offer it.

My experience is that patients who have four or more positive nodes tend to not do well, especially if they have HER2-positive disease. I think we have to discuss these options and let the patients know about these treatments because "the genie is out of the bottle." After appropriate discussion, if the patient agrees and accepts the uncertainties and the limitations of the available data, I am inclined to offer this therapy.

ATAC trial update

As we speak, the ATAC data is being collected and analyzed. As per the protocol, the results will be made public in December 2004. I anticipate that we will have updated survival and efficacy data with a median follow-up of roughly six years, but I have no idea what the data will show. However, even if no statistically significant survival advantage exists up to that point, we still cannot ignore the disease-free survival advantage and the major safety advantages over tamoxifen.

Two key safety issues must be kept in mind with tamoxifen. One is thromboembolic complications, which are unpredictable, and the other is uterine cancer. We also have to recognize that a handful of women in the prevention trial also developed uterine sarcoma. Just the other day I was searching the literature on PubMed and came across a host of cases reporting uterine sarcoma in women who have been treated with tamoxifen.

Side effects are experienced by all patients treated with tamoxifen, whereas safety advantages for anastrozole are here to stay. I think we cannot ignore the fact that anastrozole is a safer drug and overall has a better therapeutic index than tamoxifen.

Role of aromatase inhibitors in clinical practice

I think it is human nature, especially within the academic community, to be cautious when you only have the results of a single study; however, when additional studies confirm those findings, people are much more willing to accept the data. The data from MA17, Intergroup Exemestane Study and an Italian study have a very consistent message — it doesn't matter when you use an aromatase inhibitor, it will result in fewer side effects and a prolongation of disease-free survival, which I believe will eventually translate into a survival advantage. The data now clearly demonstrate that you can change the natural history of breast cancer by offering aromatase inhibitors in various patient populations.

Adjuvant bisphophonates to offset aromatase-inhibitor-related bone loss

I am always surprised by the number of patients whom I expect to have normal bone density but are found to be osteopenic or osteoporotic. In a number of these patients, I have started an aromatase inhibitor and also given them a bisphosphonate. On some occasions, within six months to a year, I have seen positive changes in bone density.

I believe bisphosphonates are effective in preventing, reversing and improving bone loss in osteopenic or osteoporotic patients, and that is why I do not make treatment decisions based on a patient's bone health. If a patient has a risk of recurrence, I believe we should offer them better therapy and use other effective therapies with established value to manage osteopenia or osteoporosis.

In patients who are osteopenic or osteoporotic, I often use alendronate and can tell you from my own experience that several months down the line, a number of these patients will actually have improvements in their bone density in spite of being on an aromatase inhibitor.

Select publications

Baum M et al; The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group. **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;**Abstract 3**.

Buzdar AU et al. **Significantly higher pathological complete remission (PCR) rate following neoadjuvant therapy with trastuzumab (H), paclitaxel (P), and anthracycline-containing chemotherapy (CT): Initial results of a randomized trial in operable breast cancer (BC) with HER/2 positive disease.** *Proc ASCO* 2004;**Abstract 520**.

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**.

Geyer CE Jr 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**.

Gnant M et al. **Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronate) as adjuvant treatment for hormone receptor-positive premenopausal breast cancer: Results of a randomized multicenter trial.** *Breast Cancer Res Treat* 2002;**Abstract 12**.

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**

Lipshultz SE et al. **The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia.** *N Engl J Med* 2004;351(2):145-53. **Abstract**

Marty M et al. **Pooled analysis of six trials of trastuzumab (Herceptin): Exploratory analysis of changes in left ventricular ejection fraction (LVEF) as a surrogate for clinical cardiac events.** *Breast Cancer Res Treat* 2003;**Abstract 218**.

Perez EA et al. **N98-32-52: Efficacy and tolerability of two schedules of paclitaxel, carboplatin and trastuzumab in women with HER2 positive metastatic breast cancer: A North Central Cancer Treatment Group randomized phase II trial.** *Breast Cancer Res Treat* 2003;**Abstract 216**.

Matthew J Ellis, MB, PhD, FRCP

EDITED COMMENTS

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

Previously, gene expression profiling required frozen material; however, perhaps less than one percent of breast cancers are stored in that fashion. A breakthrough came when it was discovered that the RNA wasn't missing in a paraffin block, it was just fragmented. As a result of this discovery and other new technologies, a multigene assay was developed that is predictive of breast cancer recurrence despite adjuvant tamoxifen therapy. This assay was validated in the NSABP studies B-20 and B-14.

As a result, we now have a predictor that scores a woman's risk of relapse between one and 100. Apparently, it is as powerful as tumor grade in predictive ability, but the assay is reproducible and grade is not. At first glance the ability to score a patient's risk appears advantageous. On reflection, however, we know that each individual really has either a zero or a 100 percent risk — either they don't relapse or they do.

The ideal predictor would be a black-and-white test that tells us which patients will relapse. This would be particularly useful when treating healthy, postmenopausal patients with node-negative, ER-positive breast cancer, in whom we're considering adjuvant chemotherapy. Currently we administer a good deal of random therapy, which is expensive and results in unnecessary treatments and toxicities.

We need individualized management strategies that target the tumor's biology and the patient's risk. I've recently been involved with the Program for the Assessment of Clinical Cancer Tests, and we are working on a variety of approaches to prospectively test the new risk predictors. We are planning to conduct a large national trial in which we will use an initial version of a gene-based classifier to group participants.

The trial design may be that patients at low risk will receive no adjuvant therapy, patients at high risk will receive adjuvant chemotherapy, and the patients in

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the gray area of risk will be randomly assigned to chemotherapy or no chemotherapy. We would then have a molecular snapshot of all the patients so that we could study the failures and build in new genes and new models to move closer to the optimal, black-and-white predictive version.

Tamoxifen versus aromatase inhibitors in the adjuvant setting

When the initial ATAC results were presented, I felt very positive regarding the data. This trial provided early evidence that aromatase inhibitors are more effective than tamoxifen. In addition, the aromatase inhibitors did not cause the serious, albeit not very common, toxicities of tamoxifen — namely endometrial cancer and stroke. Weighing the risks and benefits of these two therapies is what motivates me to prescribe aromatase inhibitors for adjuvant therapy in postmenopausal women with ER-positive breast cancer.

Some clinicians continue to argue that tamoxifen is the standard of care, given the amount of data and length of follow-up we have with that agent, and I respect that opinion. In addition, the effectiveness of aromatase inhibitors in the late adjuvant setting could strengthen the argument to begin endocrine therapy with tamoxifen. However, that argument focuses on patients who made it to five years without a relapse, whereas the ATAC data focuses on the first five years, so I continue to favor the aromatase inhibitors.

I certainly understand the viewpoint of the ASCO Technology Assessment. There's a genuine concern that if we proclaim that we have the final answer in the debate between tamoxifen and aromatase inhibitors in the adjuvant setting, it could kill some very important clinical trials. It's better to acknowledge that it's an ongoing open question. While I believe that is reasonable, making such a statement in a large forum where you need to respect many opinions is much different than making a treatment decision for the patient sitting in front of you.

Initially I individualized first-line adjuvant endocrine therapy based on patient variables, but that changed as the cumulative data were reported. Now I generally prescribe aromatase inhibitors for all eligible postmenopausal patients up front. As for which aromatase inhibitor to use, I believe most clinicians treat according to the available data, and that's appropriate. At initial diagnosis, I prescribe anastrozole (3.1).

3.1 Use of Adjuvant Aromatase Inhibitors

When you use an aromatase inhibitor as initial adjuvant therapy, what percentage of this use is for each of the following agents?

Anastrozole	84%
Letrozole	14%
Exemestane	2%

SOURCE: National Survey of Medical Oncologists, 2004.

Endocrine therapy after five years of adjuvant tamoxifen

Whether to continue adjuvant hormonal therapy after five years of tamoxifen is a risk-based decision. While a patient with node-positive disease may benefit significantly, in a patient with node-negative disease and a tumor less than one centimeter in size, the relapse rate might only be a few percent — and reducing that risk with letrozole might not be a meaningful exercise.

The relapse data indicate that approximately half of the relapses occur before five years and the remaining 50 percent occur after five years. If a patient has a 20 percent risk at baseline and doesn't relapse in the first five years, then at five years her relapse rate is 10 percent. In such a patient, letrozole may have a 40 percent effect in reducing the relapse rate, so the absolute benefit is approximately four percent.

That is similar to the effect we expect from adjuvant chemotherapy in patients at low risk, so I believe it's a reasonable therapy. Also, the risks associated with letrozole in this setting appear to be modest, so it makes sense even for relatively low-risk patients. However, there are certainly patients in whom it makes no sense — perhaps patients with a relapse risk rate of five percent or less after five years.

As for the patient who completed her five years of adjuvant tamoxifen therapy a year or more ago, the risk of recurrence is fairly evenly spread over the next 10-year period. If she hasn't relapsed already, you can do a back-of-an-envelope calculation to determine her residual risk.

Then the question is whether the late introduction of further adjuvant hormonal therapy would be helpful. We don't really know. One could consider the patients who crossed over in the MA17 trial versus those who didn't to gain a sense of whether it's helpful, but that's not randomized and may not be valid.

Neoadjuvant trials comparing tamoxifen and aromatase inhibitors

We conducted a neoadjuvant trial comparing letrozole to tamoxifen in postmenopausal women with ER-positive breast cancer. It was similar to the IMPACT trial in that they both compared tamoxifen and an aromatase inhibitor, and both trials are showing aromatase inhibitors to be clinically advantageous in favorably impacting the rates of breast-conserving surgery (3.2). The IMPACT trial studied anastrozole versus tamoxifen.

Also, our trial required that all patients be ineligible for breast-conserving surgery, so the tumors were large and the responses were easy to measure. However, the IMPACT trial enrolled some patients with smaller tumors, and when a tumor shrinks from two centimeters to one centimeter, clinically it's difficult to be certain you're truly measuring response. That might explain why the IMPACT study did not show much difference in clinical response between the arms.

In addition, the IMPACT trial had three arms — anastrozole, tamoxifen, and anastrozole plus tamoxifen — whereas our trial had only two arms, so their

trial wasn't as well powered to show a difference between just tamoxifen and an aromatase inhibitor. Mitch Dowsett examined proliferation at the cellular level in the IMPACT trial and reported that the proliferation changes appeared to be more profound in tumors treated with anastrozole than in tumors treated with tamoxifen.

We're moving ahead with an ACOSOG neoadjuvant study comparing exemestane with or without celecoxib in postmenopausal women with ER-positive, Stage II/III breast cancer who are ineligible for breast-conserving surgery or whose tumors are inoperable. In the United Kingdom, Mike Dixon is the principal investigator for a trial comparing neoadjuvant letrozole and anastrozole. I believe it's important to compare the various aromatase inhibitors because ultimately these agents will be off patent and inexpensive. Knowing which is the most efficacious will be important.

3.2 Efficacy Data from Clinical Trials Comparing Tamoxifen to an Aromatase Inhibitor in the Neoadjuvant Setting

Parameter	Letrozole vs tamoxifen*		Anastrozole vs tamoxifen vs the combination**		
	Letrozole[1]	Tamoxifen[1]	Anastrozole[2]	Tamoxifen[3]	Anastrozole + tamoxifen[4]
Overall response: Clinical	60%	41%	37%	36%	39%
Overall response: Ultrasound	39%	29%	24%	20%	28%
Rate of breast-conserving surgery[5]	48%	36%	46%	22%	26%

[1] All patients had ER/PR-positive tumors
[2] 98% of patients had ER-positive tumors
[3] 99% patients had ER-positive tumors
[4] 96% patients had ER-positive tumors
[5] Includes only patients requiring mastectomy at study entry

SOURCES: * Ellis MJ et al. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial.** *J Clin Oncol* 2001;19(18):3808-16. **Abstract**

** Smith I. **A multicentre double-blind placebo-controlled trial comparing neoadjuvant anastrozole with tamoxifen or the combination.** Presentation. San Antonio Breast Cancer Symposium, 2003;**Abstract 1**.

Select publications

The ATAC Trialists' Group. **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**

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**.

Grand Rounds

Adjuvant Chemotherapy in the Elderly — Current Options and Research Protocols

Daniel R Budman, MD
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New York University
North Shore University Hospital

4.1

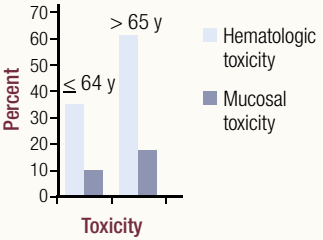
Concerns about Adjuvant Therapy in the Elderly

1. Toxicity
2. Efficacy
3. Feasibility
4. Limited numbers enrolled to date in Phase III trials

4.2

Age and Toxicity in the Elderly: IBCSG VII

- Postmenopausal: tamoxifen vs tamoxifen + classical CMF (x 3)
- CMF more toxic over age 65; less drug delivered
- 5-y DFS in elderly 61% vs 63% for entire cohort



SOURCE: Crivellari D et al. *J Clin Oncol* 2000;18:1412-22. **Abstract**

SLIDES 4.1 , 4.2 Data from the International Breast Cancer Study Group, published in the *Journal of Clinical Oncology*, evaluate the toxicity of chemotherapy in elderly patients. In postmenopausal patients, the initial focus was to look at endocrine therapy versus chemoendocrine therapy — tamoxifen versus tamoxifen plus classical CMF.

CMF was more toxic in the older age group, in terms of both hematologic and mucosal toxicity, and less drug was delivered. A lot of agents have a threshold effect, and if we cut the dose, we're diminishing efficacy with most of the drugs we use. This led the CALGB Breast Committee to consider what should be done with the elderly patient population.

4.3

CALGB Trial 49907

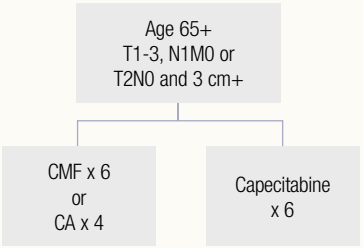
A randomized trial of adjuvant chemotherapy with standard regimens – CMF or CA versus capecitabine in women 65 years and older with early stage breast cancer

Objectives

- Primary: Relapse-free survival
- Secondary:
  - Overall survival
  - Toxicities
  - Quality of life
  - Comorbidity and functional status
  - Adherence to capecitabine

4.4

CALGB Trial 49907: Adjuvant Chemotherapy in the Elderly



Tamoxifen or aromatase inhibitor for 5 years if ER- or PR-positive;
CMF = NCI; CA = 600/60 m^2
Quality-of-life and comorbidity assessments part of trial.
1,800 patients to be randomly assigned.

4.5

CALGB Trial 49907: Dosing CMF and CA

- CMF: Oral regimen 100/40/600 mg/m^2 x 6 cycles
- CA: 600/60 mg/m^2 x 4 cycles (NSABP)
- Capecitabine 2,000 mg/m^2/d (in 2 doses) x 14 followed by 7d off x 6 cycles

SLIDES 4.3 - 4.5 CALGB trial 49907 asks, Can we offer benefit to elderly patients with some of the newer chemotherapy agents? We have numerous agents available. As patients get older, they have comorbid conditions and can't as easily get back and forth to the office for treatment. Ideally, it would be nice to have an oral agent. This trial was discussed by the CALGB Breast Committee for some time and

was felt to have merit. Hyman Muss advocated for this trial and initially met a lot of resistance because people asked, "How can you not give IV chemotherapy?"

The reason is because oral agents are active, and we're looking for efficacy in the adjuvant setting. This study is ongoing and is available through the CTSU or the Cooperative Group mechanism. It's basically doctor's choice — CMF or AC versus capecitabine — for women who are older than 65 years of age and have operable breast cancer.

The objectives are what one would expect: prevent relapse, extend overall survival and avoid toxicity. Quality of life, comorbidities and functional status are important secondary objectives.

Patients with operable disease are randomly assigned to six cycles of classical CMF with all the toxicities or classical AC or capecitabine for six cycles, given on days one through 14 on an every 21-day schedule. Obviously, patients who have hormone receptor-positive disease receive tamoxifen or an aromatase inhibitor.

4.6

Comparing Capecitabine to IV Therapy

- Oral agent
- Targets tumor tissue (potential therapeutic index gain)
- Known efficacy in metastatic setting
- Known toxicity: No cardiac damage
- Major drug interaction is with warfarin
- Potential better quality of life
- Less reliance on caregiver

SLIDE 4.6 Why would the CALGB want to conduct this trial? Capecitabine has the advantage of oral administration and it targets tumor tissue. My major interest has been clinical pharmacology and drug development for the last 15 years, and this is an interesting drug because it's changing the way we think in oncology.

We are trying to target tissue and diminish toxicity rather than just using an active drug. Capecitabine has known efficacy and doesn't cause cardiac damage, which is a major issue as patients get older. The only major drug interaction is with warfarin.

4.7

Targeted Directed Therapy to Enhance Antitumor Efficacy (Therapeutic Index)

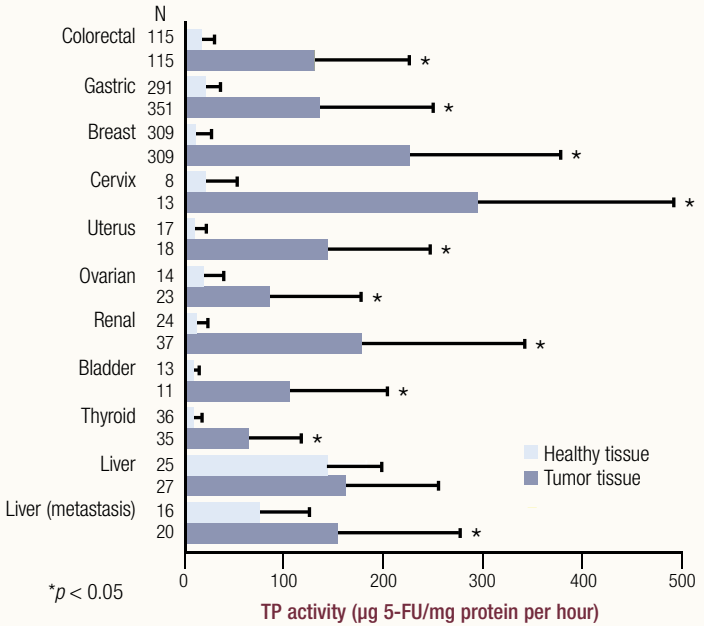
- Inhibit critical protein/enzyme needed by the tumor and not required by normal tissue (problem of redundancy of pathways)
- Use a unique characteristic of the tumor to increase level of cytotoxicity in the tumor compared to normal host tissue

Examples of targeting

1. HER2/neu protein is overexpressed in 1/3 of breast cancers
   - Trastuzumab (antibody to protein)
   - Tyrosine kinase inhibitors (in development)
2. Upregulation of a critical enzyme in the tumor
   - Thymidine phosphorylase is overexpressed in many tumors (40% of breast cancer lesions by IHC)
   - Capecitabine requires thymidine phosphorylase for activation, and the active metabolite then concentrates in tumors

4.8

Enhanced Thymidine Phosphorylase Expression in Human Malignant Tissue Compared to Benign Tissue

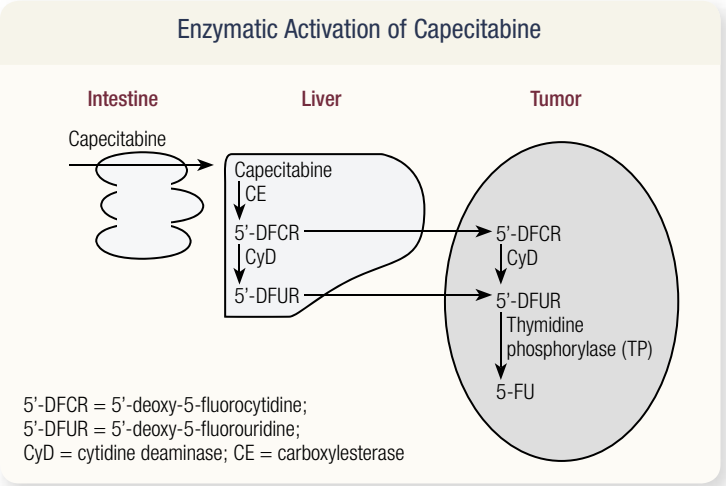


SOURCE: Reprint from Miwa M et al. **Design of a Novel Oral Fluoropyrimidine Carbamate, Capecitabine, which Generates 5-Fluorouracil Selectively in Tumours by Enzymes Concentrated in Human Liver and Cancer Tissue.** *Eur J Cancer* 1998;34(8):1274-81, with permission from Elsevier. **Abstract**

SLIDE 4.7 We also have issues of redundancy of pathways, or you can try to use the unique characteristic of the tumor itself. Other examples of targeted therapy include trastuzumab in patients with HER2-positive disease and the tyrosine kinase inhibitors that are being developed. Capecitabine was particularly attractive to us when we first started working with the drug. The enzyme thymidine phosphorylase, also known as platelet-derived growth factor, is overexpressed in 40 percent of breast cancers, so it's a marker for aggressiveness and it's a marker for some diseases, including breast cancer. Thymidine phosphorylase is necessary to activate capecitabine into the active metabolite, so it's a method of targeting the tumor.

SLIDE 4.8 This slide demonstrates work that has evaluated thymidine phosphorylase in a variety of tumors, and in the majority of tumors, it's overexpressed compared to healthy, normal tissue.

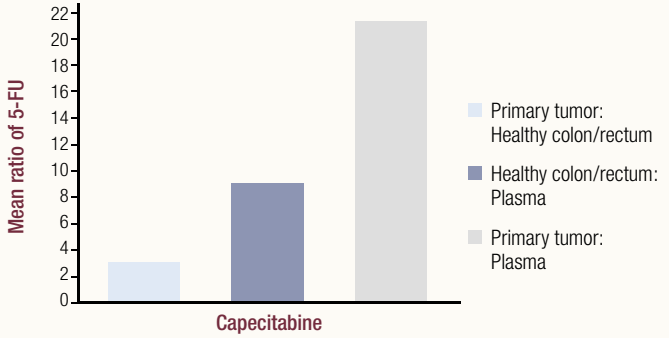
4.9



SLIDE 4.9 The mechanism of action of capecitabine is based on a drug called DFUR, which was developed in Japan. The problem with DFUR was that thymidine phosphorylase was in the gut, so if you took it in oral form you would get diarrhea. The chemists were very clever and put substitutions on it so it would not be activated in the gut — it has to be activated in the liver. It is then transferred to the tumor, where it undergoes metabolism from 5'-DFUR to 5-FU and concentrates in the tumor.

4.10

Mean Ratios of 5-FU Concentrations Following Administration of Capecitabine in Humans – Tumor Targeting



SOURCE: Schüller J et al. *Cancer Chemother Pharmacol* 2000;45:291-7. **Abstract**

SLIDE 4.10 How do we know capecitabine increases the concentration of 5-FU in the tumor? Data have primarily been collected in colorectal cancer. Patients who were treated with a laparotomy were given capecitabine; then biopsies of the tumor and normal tissue were performed and concentrations of 5-FU were measured. A three-fold greater concentration of active metabolite was present in the tumor compared to the surrounding normal tissue, indicating that capecitabine does, indeed, target the tumor.

4.11

Capecitabine Pivotal Breast Trial

- Metastatic breast cancer
- Disease progression on paclitaxel
- 91% previously received doxorubicin
- Third or fourth treatment for many patients
- 2,510 mg/m^2 per day po days 1-14 q3wk
  - Given in two divided doses

SOURCE: Blum JL et al. *J Clin Oncol* 1999;17:(2)485-93. **Abstract**

SLIDE 4.11 This led to a pivotal breast trial led by Joanne Blum in patients with metastatic breast cancer who progressed on paclitaxel. Most of them were previously treated with anthracyclines, and many underwent two or three different treatments. They were administered a dose of capecitabine that I think is a little too high — 2,510 mg/m^2 given in two divided doses on days one through 14 every three weeks.

4.12

Capecitabine Pivotal Trial in Metastatic Disease

Number of patients	162
CR + PR	2% + 18% = 20%
Stable disease	40%
Median time to progression	3-4 months
Median duration of response	7.9 months
Median survival	12.6 months

Number of prior therapies NOT related to response

SOURCE: Blum JL et al. *J Clin Oncol* 1999;17:485-93. **Abstract**

SLIDE 4.12 In these heavily pretreated patients, capecitabine resulted in a 20 percent response rate and increased disease stability.

4.13

Efficacy of Capecitabine in Taxane-Pretreated MBC: Summary of Trial Experience

Number of patients treated	Tumor response (%)	Median response duration (months)	Median time to progression (months)	Median survival (months)
n=162[1]	20	7.9	3.0	12.6
n=74[2]	26	8.3	3.2	12.2
n=136[3]	15	7.5	3.5	10.1
n=32[4]	41	N/A	—	—
n=34[5]	27	N/R	N/A	N/A

N/A = not available; N/R = not reached

SOURCES: [1] Blum JL et al. *J Clin Oncol* 1999;17:485–93. **Abstract** [2] Blum JL et al. *Cancer* 2001;92:1759-68. **Abstract** [3] Reichardt P et al. *Ann Oncol* 2003;14:1227-33. **Abstract** [4] Cervantes G et al. *Proc Am Soc Clin Oncol* 2000;19:121a;**Abstract 469**. [5] Wong Z et al. *Proc Am Soc Clin Oncol* 2000;19:120a;**Abstract 466**.

SLIDE 4.13 The efficacy of capecitabine has been confirmed in a variety of other studies. We have several hundred patients with taxane-pretreated metastatic disease who had demonstrable benefit from capecitabine. The CALGB Breast Committee considered it necessary to show that, if we're going to randomly assign patients to another drug, capecitabine is a reasonable choice.

4.14

Rationale: Capecitabine to be Compared to Combination Treatment in the Adjuvant Setting

- Randomized Phase II study of capecitabine versus CMF as first-line chemotherapy for breast cancer in women aged 55 years or older
  - RR 30% vs 16%; TTP 132 days versus 94 days[1]
- Randomized Phase II study of capecitabine versus paclitaxel in breast cancer patients who failed previous anthracycline therapy
  - RR 36% vs 26%; TTP 3 months versus 3.1 months[2]

SOURCES: [1] O'Shaughnessy et al. *Annal Oncol* 2001;12(9): 1247-54. **Abstract**
[2] Talbot DC et al. *Br J Cancer* 2002;86(9):1367-72. **Abstract**

SLIDE 4.14 With which agents should capecitabine be compared? An underpowered randomized Phase II trial compared capecitabine to CMF. An equivalence study would require thousands of patients, but the efficacy seems to be in the same ballpark. If anything, capecitabine may be slightly better than CMF or paclitaxel administered every three weeks.

4.15

Capecitabine versus CMF or Paclitaxel

	Capecitabine vs CMF	Capecitabine vs paclitaxel
No. of patients	95	41
CR + PR	30% vs 16%	36% vs 26%
TTP – months	4.1 vs 3.0	3.0 vs 3.1
OS – months	21.6 vs 17.2	7.6 vs 9.4
Comment	No chemo for metastases	Anthracycline refractory

SOURCE: Blum JL. *Oncologist* 2001;6:56-64. **Abstract**

SLIDE 4.15 This is the same data presented a different way. In both small Phase II studies, the response rate was 30 percent or more and the time to progression also was similar.

Additional ways exist to exploit tumor targeting

4.16

Potential Role of Combination Therapy

- Upregulation of thymidine phosphorylase (TP) in tumor compared to normal tissue leads to generation of more cytotoxic metabolites in the tumor
- Many agents upregulate TP
- These agents may also be cytotoxic to the tumor
  - Potential of synergistic effects without increased toxicity
  - Potential of converting lesions with borderline TP into sensitive tumors

SLIDE 4.16 With combination chemotherapy, if one could enhance the target, then obviously you would expect more antitumor activity. Many cytotoxic agents actually enhance and upregulate thymidine phosphorylase. These agents can also be cytotoxic, so you can potentially achieve a synergistic effect and upregulation of TP.

4.17

A Single Agent May Offer the Same Survival as a Combination

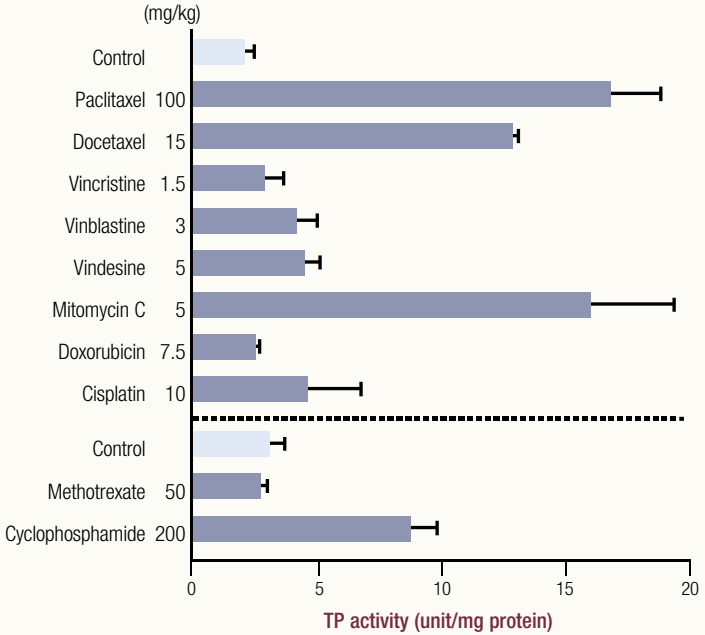
Effect of an active single agent versus combination therapy in earlier disease.

SOURCE: Sledge GW at al. *J Clin Oncol* 2003;21:588-92. **Abstract**

SLIDE 4.17 Andy Seidman's data and the ECOG Trial 1193 chaired by George Sledge suggest that using drugs in sequence in metastatic breast cancer may be just as good as combination therapy.

4.18

TP Upregulation in Tumor Xenografts: Effect of Various Cytotoxics



Gemcitabine and vinorelbine also upregulate TP.

SOURCE: With permission from Ishitsuka H. **Capecitabine: preclinical pharmacology studies.** Kluwer Academic Publishers. *Investigational New Drugs* 2000;18:343-54. **Abstract**

SLIDE 4.18 Preclinical data demonstrate that a variety of drugs — particularly the taxanes and cyclophosphamide — can upregulate thymidine phosphorylase.

4.19

Additional Molecular Benefit of Capecitabine: Downregulation of Tumor Bcl-2 and Bcl-2/Bax

- Bcl-2 (death suppressor) and Bax (death effectors) are apoptotic regulatory factors
- Capecitabine reduced expression levels of Bcl-2/Bax ratio in breast cancer xenografts

– Breast cancer xenograft	– Bcl-2/Bax ratio reduction
– MX-1	– 1/7th
– MAXF-401	– 1/20th

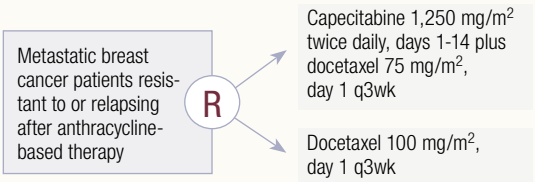
- Capecitabine may enhance the efficacy of docetaxel by accelerating its apoptotic activity.

SOURCE: Fujimoto-Ouchi K et al. *Proc AACR* 2001;**Abstract 463**.

SLIDE 4.19 Another issue that's come out more recently is that capecitabine is not 5-FU. In contrast to 5-FU, capecitabine seems to affect tumor Bcl-2 and Bcl-2/Bax combinations, so capecitabine becomes even more intriguing.

4.20

Capecitabine/Docetaxel (XT) versus Docetaxel: Phase III Study Design



- Patients responding or with stable disease after six weeks of treatment continued until disease progression or unacceptable toxicity
- Primary objective: To demonstrate superior TTP

SOURCE: O'Shaughnessy J et al. *J Clin Oncol* 2002;20(12):2812-23. **Abstract**

SLIDES 4.20 In preclinical work, capecitabine doesn't look like 5-FU. If you use a combination of docetaxel and capecitabine a marked antitumor effect can be achieved, which is not seen with 5-FU.

This preclinical data led Joyce O'Shaughnessy to perform a Phase III clinical trial comparing the combination of capecitabine and docetaxel (XT) to docetaxel alone in heavily pretreated patients with metastatic breast cancer.

4.21

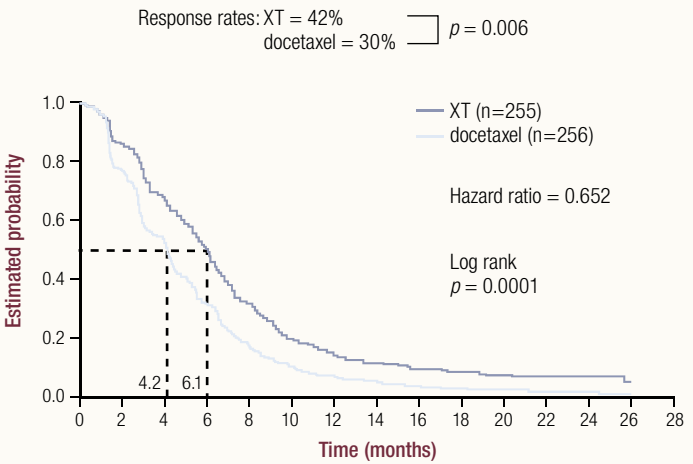
XT: Overall Tumor Response

	Capecitabine/ docetaxel (n=255)	Docetaxel (n=256)	
PR + CR (%)	42	30	$p = 0.006$
95% CI	36-48	24-36	
Stable disease (%)	38	44	
95% CI	32-44	38-50	

SOURCE: O'Shaughnessy J et al. *J Clin Oncol* 2002;20(12):2812-23. **Abstract**

4.22

Capecitabine/Docetaxel (XT): Superior Response Rate and TTP



SOURCE: 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. Reprinted with permission from the American Society of Clinical Oncology. **Abstract**

SLIDES 4.21, 4.22 The response rate was higher with the combination, and this is where the study becomes interesting.

The capecitabine/docetaxel combination had an early benefit for response rate and survival. Relative to the combination, an early and marked drop-off occurred with single-agent docetaxel at 100 mg/m^2, which is a good treatment. This suggests that we really have to think about categorizing patients according to high risk and low risk. In a patient at high risk with a lot of visceral disease, many oncologists will utilize combination chemotherapy, but for a patient at low risk, we will consider sequential single agents.

4.23

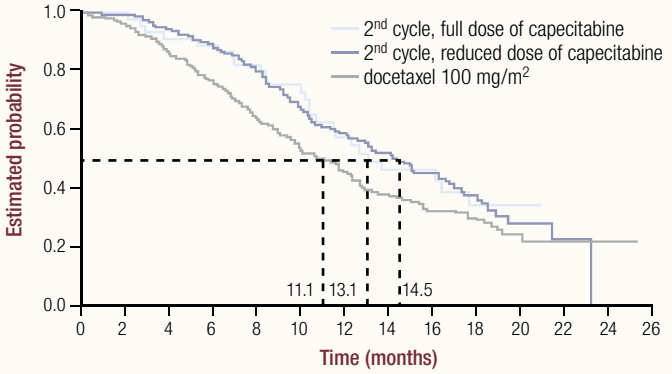
Impact of Dose Modification on Efficacy

Hazard ratio for time to tumor progression for patients with vs without dose reduction

	XT		Docetaxel	
	Any dose reduction	Reduction to 50%	Any dose reduction	Reduction to 50%
Hazard ratio	0.84	1.14	0.99	1.91 (95% CI 1.00-3.66)
p-value	ns	ns	ns	0.0499

4.24

Capecitabine Dose Reduction*: Impact on Survival – No Loss in Efficacy



*After the first treatment cycle

SOURCE: With permission from O'Shaughnessy J. **Capecitabine and docetaxel in advanced breast cancer: Analysis of a Phase III comparative trial.** *Oncology* 2002;16(10 Suppl):17-22. **Abstract**

SLIDES 4.23, 4.24 Currently, US Oncology is evaluating the capecitabine/docetaxel combination in the adjuvant setting.

For most of the drugs we've utilized, the "mantra" in oncology has been to "push the drug to the conventional limit." If capecitabine concentrates in the tumor, we don't have to push it hard. Unfortunately, the only information available from previous studies is that we don't have a good dose-response curve. Again, this is retrospective data from the XT study.

If the docetaxel dose in the XT arm is reduced by 50 percent, a significant decrease in antitumor activity occurs. This has also been

demonstrated in prospective studies in which docetaxel 100 mg/m^2 was better than 60 mg/m^2 and 75 mg/m^2, so docetaxel has a deep dose-response curve.

In comparison, if capecitabine is dose-reduced to 50 percent, no loss of efficacy is observed. The ability of capecitabine to concentrate in the tumor could explain this flat dose-response curve with capecitabine and may allow us to use doses that are not particularly toxic.

This graphically demonstrates that capecitabine dose-reduction did not diminish the survival benefit in the XT study.

4.25

First-Line, Post-Study Chemotherapy in the XT Trial: Single-Agent Capecitabine versus All Other Chemotherapies after Progression on Single-Agent Docetaxel

Chemotherapy	Median survival	Hazard ratio
Capecitabine	21.0 months (95% CI 15.6-27.6)	0.50 (p = 0.0046)
All other chemotherapies	12.3 months (95% CI 10.5-14.0)	

SOURCE: Miles D et al. Poster. 24th Annual San Antonio Breast Cancer Symposium, 2001;**Abstract 287**.

SLIDE 4.25 What happens to patients who progress while receiving docetaxel? Can we salvage them with another agent? Indeed, patients can be salvaged. Unfortunately, the XT trial did not have a mandated crossover, but crossing over to capecitabine after failing docetaxel can extend the life of some of these patients, suggesting that some patients should be treated with single-agent therapy.

What about using combinations of targeted agents?

4.26

Trastuzumab and Chemotherapy *In Vitro* Activity: Median Effect Analysis

Synergistic (CI < 1)		Additive (CI = 1)	
Vinorelbine	0.24	Doxorubicin	0.88
Docetaxel/carboplatin	0.09	Paclitaxel	0.91
Docetaxel	0.30	Epirubicin	0.88
Etoposide	0.54	Vinblastine	1.09
Cyclophosphamide	0.38		
Thiotepa	0.67	Antagonistic (CI > 1)	
Cisplatin	0.56	Methotrexate	1.36
Liposomal doxorubicin	0.70	Fluorouracil	2.87
		Gemcitabine	1.44

CI = Combination Index

This can be cell-line specific

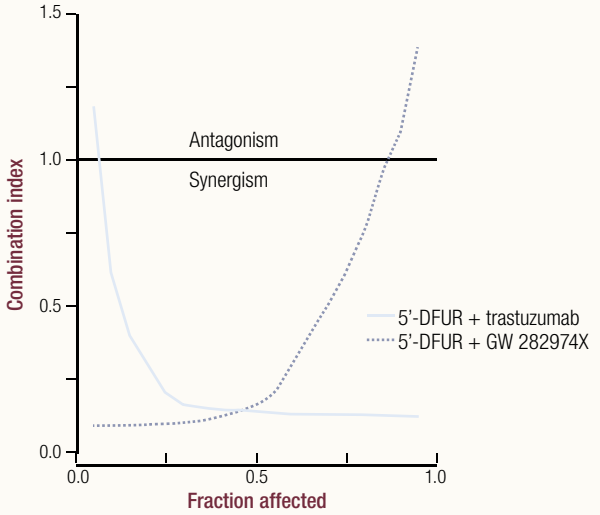
SOURCES: Pegram M et al. *Oncogene* 1999;18:2241-51. **Abstract** Pietras M et al. *Oncogene* 1998;17:2235-49. **Abstract** Pegram M et al. *J Natl Cancer Inst* 2004;96(10):739-49. **Abstract** Konecny GE et al. *Breast Cancer Res Treat* 1999;57:114. **Abstract**

SLIDE 4.26 Mark Pegram and the group at UCLA, as well as other investigators have utilized an evaluative *in vitro* approach called median effect analysis, whereby tissue culture is evaluated for synergism or antagonism. Median effect analysis doesn't inform us about the therapeutic index but it tells us whether or not the drugs are antagonistic. If the drugs are antagonistic, should we be administering them in combination?

Controversy always exists with models. This data depicts trastuzumab in combination with various agents in a cell line that overexpresses HER2. This data was the basis for combining the platinums and taxanes with trastuzumab. In this case, the fluoropyrimidines were antagonistic, but one of the difficulties with this type of model system is it can be cell-line specific.

4.27

EGFR 1, 2 Inhibition and 5'DFUR in MCF7/adr Cell Lines



SOURCE: With permission from Budman DR. Presentation. *Breast Cancer Update* Working Group, May 2004.

SLIDE 4.27 At the 2002 San Antonio Breast Cancer Symposium, we presented data evaluating the metabolite of capecitabine, 5'DFUR, with either a dual kinase inhibitor GW 282974X (provided by GlaxoSmithKline) or trastuzumab using the median effect *in vitro* assay technique. We continued these studies and will submit the full manuscript for publication shortly. Depending upon the breast cancer cell line studied, 5'DFUR combined with trastuzumab could demonstrate either synergistic or antagonistic cytotoxic effects. The results of this assay are shown graphically in the slide in which a multiply-resistant breast cancer cell was studied *in vitro* with the drug combinations. Combination Index values less than 1 are synergistic and fraction affected indicates the degree of cytotoxicity induced by the combination of drugs at various concentrations.

The model is most accurate at a fraction affected value of 0.5. For this cell line under the culture conditions we employed, the combination of 5'DFUR with trastuzumab is synergistic. As discussed previously, other investigators have noted antagonism between fluoropyrimidines and trastuzumab in cell line model systems. Therefore, we have a clinical dilemma in that the effect of the combination of trastuzumab with 5'DFUR in a model system does not give a global answer whether or not this is a useful combination. There is additional data to suggest that this combination may be of value as Fujimoto-Ouchi and coworkers have examined a xenograft model of breast cancer in which the combination of 5'DFUR and trastuzumab were at least

additive. Hence, ongoing studies of trastuzumab with capecitabine are necessary to define the role of this combination in the clinical treatment of breast cancer.

4.28

Conclusions

- Cytotoxic adjuvant therapy is appropriate in the elderly, especially if no comorbidity.
- Benefit parallels results in the younger population.
- Capecitabine may offer a quality-of-life advantage over more classical adjuvant therapy without loss of efficacy (evaluated in current adjuvant study).
- Capecitabine can be combined with many agents including the two taxanes and at least preclinically with trastuzumab (human studies ongoing).

SLIDE 4.28 In conclusion, adjuvant cytotoxic chemotherapy is appropriate in elderly patients, but one must consider comorbidities. I urge physicians to consider enrolling patients in CALGB trial 49907, in which doctors choose AC or CMF versus capecitabine. If capecitabine turns out to be equivalent, then we have a kinder, gentler way of treating patients. Capecitabine can also be combined with numerous other chemotherapy and targeted agents, and these approaches are being evaluated in adjuvant trials.

Select publications

Blum JL et al. **Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer.** *J Clin Oncol* 1999;17(2):485-93. Abstract

Crivellari D et al. **Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: The International Breast Cancer Study Group Trial VII.** *J Clin Oncol* 2000;18(7):1412-22. Abstract

Fujimoto-ouchi K et al. **Antitumor activity of combinations of anti HER2 neu antibody trastuzumab and oral fluoropyrimidines capecitabine / 5'DFurd in human breast cancer models.** *Cancer Chemother Pharmacol* 2002;211-16. Abstract

Ishitsuka H. **Capecitabine: Preclinical pharmacology studies.** *Invest New Drugs* 2000;18(4):343-54. Abstract

Miles D et al. **Survival benefit with Xeloda (capecitabine)/Taxotere (docetaxel) (XT) versus Taxotere: Analysis of post-study therapy. 2001 San Antonio Breast Cancer Symposium, Poster 442.** Abstract 287.

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

Pegram M et al. **Inhibitory effects of combinations of HER-2/neu antibody and chemotherapeutic agents used for treatment of human breast cancers.** *Oncogene* 1999;18(13):2241-51. Abstract

Schuller J et al. **Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients.** *Cancer Chemother Pharmacol* 2000;45(4):291-7. Abstract

Post-test:
Breast Cancer Update — Issue 8, 2004

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In a recent *New England Journal of Medicine* article, measurement of troponin T was demonstrated to be a very sensitive in predicting whether an anthracycline is causing myocardial damage or not.
   a. True
   b. False

2. In the MD Anderson neoadjuvant study of paclitaxel + FEC with or without trastuzumab, patients receiving trastuzumab achieved a pathologic complete response rate of about:
   a. 25 percent
   b. 35 percent
   c. 45 percent
   d. 65 percent

3. SWOG-S0221, a Phase III randomized study of adjuvant chemotherapy, evaluates four different schedules of which agents?
   a. Doxorubicin, cyclophosphamide, docetaxel
   b. Doxorubicin, cyclophosphamide, paclitaxel
   c. Epirubicin, docetaxel
   d. Epirubicin, paclitaxel

4. In an Austrian trial comparing three versus six cycles of neoadjuvant epirubicin/docetaxel plus G-CSF, which schedule proved the most efficacious:
   a. Three cycles
   b. Six cycles
   c. Neither, they were equivalent

5. In the three-year results of CALGB-9741 — the Phase III randomized study comparing dose-dense versus conventional scheduling and sequential versus combination adjuvant chemotherapy for node-positive breast cancer — dose-dense therapy had superior overall and disease-free survival rates.
   a. True
   b. False

6. The GONO-M1G1 trial, which compared six cycles of 5-FU/epirubicin/cyclophosphamide given every two weeks versus every three weeks, demonstrated a significant difference between the two schedules.
   a. True
   b. False

7. The primary objective of the CALGB-49907 randomized adjuvant trial of CMF or CA versus capecitabine in women ≥ 65 years old is:
   a. Overall survival
   b. Relapse-free survival
   c. Comorbidity and functional status
   d. a+b

8. Clinical trials have shown fulvestrant to be efficacious in postmenopausal women with advanced breast cancer who have relapsed on prior endocrine therapy.
   a. True
   b. False

9. Which of the following regimens were evaluated in the IMPACT trial?
   a. Anastrozole
   b. Tamoxifen
   c. Anastrozole plus tamoxifen
   d. All of the above
   e. Both a and b

10. In the neoadjuvant setting, both letrozole and anastrozole have resulted in an increased rate of breast conservation compared to tamoxifen.
    a. True
    b. False

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

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Breast Cancer Update — Issue 8, 2004

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment. . . . . 5 4 3 2 1 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
G Thomas Budd, MD	5 4 3 2 1	5 4 3 2 1
Aman U Buzdar, MD	5 4 3 2 1	5 4 3 2 1
Matthew J Ellis, MB, PhD, FRCP	5 4 3 2 1	5 4 3 2 1
Daniel R Budman, 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 N/A
Related to my practice needs . . . . . 5 4 3 2 1 N/A
Will influence how I practice . . . . . 5 4 3 2 1 N/A
Will help me improve patient care. . . . . 5 4 3 2 1 N/A
Stimulated my intellectual curiosity . . . . . 5 4 3 2 1 N/A
Overall quality of material . . . . . 5 4 3 2 1 N/A
Overall, the activity met my expectations. . . . . 5 4 3 2 1 N/A
Avoided commercial bias or influence . . . . . 5 4 3 2 1 N/A

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.....

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