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HOW TO USE THIS MONOGRAPH

This CME activity contains both audio and print components. To receive credit, the participant should listen to the CDs or tapes, review the monograph and complete the post-test and evaluation form located in the back of this monograph or on our website. This monograph contains edited comments, clinical trial schemas, graphics and references that supplement the audio program. **BreastCancerUpdate.com** includes an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**. The first CD and website also contain PowerPoint® files of the slides located at the end of the monograph.

Breast Cancer Update: A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

- 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 2 of *Breast Cancer Update* is to support these global objectives by offering the perspectives of Drs Henderson, Howell and Gralow on the integration of emerging clinical research data into the management of breast cancer.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

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

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

I Craig Henderson, MD, FACP, FRCP	Stock Shareholder: Johnson & Johnson Pharmaceuticals Honorarium: AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Novartis Pharmaceuticals, Pfizer Inc, Roche Laboratories Inc
Anthony Howell, MD, MSc, FRCP	No financial interests or affiliations to disclose
Julie R Gralow, MD	Grants/Research Support and Consultant: Amgen Inc, Aventis Pharmaceuticals Inc, Bristol-Myers Squibb Company, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals, Ortho Biotech Products LP Honorarium: Amgen Inc, AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals Inc, Bristol-Myers Squibb Company, Genentech BioOncology, GlaxoSmithKline, Novartis Pharmaceuticals, Ortho Biotech Products LP, Pfizer Inc

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
clodronate	Not FDA approved	—
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Various	Various
epirubicin hydrochloride	Ellence®	Pfizer Inc
epoetin alpha	Procrit®	Ortho Biotech Products
	Epogen®	Amgen Inc
exemestane	Aromasin®	Pfizer Inc
filgrastim	Neupogen®	Amgen Inc
fluorouracil, 5-FU	Various	Various
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
goserelin acetate	Zoladex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals Corp
paclitaxel	Taxol®	Bristol-Myers Squibb Company
pegfilgrastim	Neulasta®	Amgen Inc
risedronate	Actonel®	Procter & Gamble
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech BioOncology
zoledronic acid	Zometa®	Novartis Pharmaceuticals Corp
investigational drug	GW572016	GlaxoSmithKline

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Editor's Note

Talmudic scholar

The first time I chatted with Craig Henderson was on a chilly Boston afternoon in 1986 in a pre-Starbucks era coffee shop. Sipping espresso, I needed every available caffeine molecule to follow the man's circuitous but fascinating train of thought.

At that time Craig was the resident breast cancer maven at Dana-Farber, and he and several other semi-maverick researchers had just turned breast cancer research on its ear. A recent NIH consensus conference had just blessed tamoxifen as adjuvant therapy for postmenopausal women, mainly based on Richard Peto's spectacular presentation of the first international breast cancer meta-analysis.

I have a grainy video of Peto's talk, which could realistically be labeled as one of the major turning points of contemporary oncology research. His eyes studiously avoid the attendees as he pushes them to focus on the data contained in his slides. However, he sneaks glances at the audience hoping to see if they follow.

Craig, Mike Baum and Peto were the ringleaders of the overview movement, which held its first trialists meeting at Heathrow Airport just a few months before the consensus conference. Like most great ideas, the basis for the overview was simple: modest improvements in important outcomes in common diseases with substantial mortality have great public health significance. In order to detect modest advances, large numbers of the key events must be measured — in this case breast cancer mortality. Thus the overview was born.

The Boston "coffee talk" was the first in a series of brain-numbing conversations I have had with Craig over the years, many of which have appeared in this audio series. Editing these serpentine and usually lengthy dialogues is like deconstructing a Russian novel. Craig once told me that he likens his and other research leaders' insatiable interest in breast cancer research minutia to the zeal of Talmudic scholars inspecting each word of the ancient text looking for hidden meaning. He often cites unplanned subset analyses of trials I haven't even heard of, and in this issue he educated me on the many variations of FAC, CAF and FEC like a wine connoisseur describing vintage Bordeaux.

The great thing about these conversations is that at the center of these volcanic data eruptions are usually some very simple, highly practical patient care strategies. No one has to agree with these conclusions — and I always receive a couple of emails from oncologists whose buttons are pushed by Craig's viewpoints — but I personally find his "pearls" very enlightening.

This most recent interview includes at least two such nuggets:

1. Craig discusses a concept that is very intuitive if one reviews the entire evolution of data on adjuvant systemic therapy. When a treatment is established to produce maximum antitumor effect in women with node-positive tumors, one can assume that this therapy will also maximally reduce the rate of recurrence and death in women regardless of risk, including those with node-negative tumors. For example, if one believes, as Craig does, that dose-dense AC followed by paclitaxel chemotherapy is as effective or more effective than any other chemotherapy regimen for women with node-positive breast cancer, then it follows that this regimen will have the same relative impact on women with node-negative tumors. Thus, if Craig uses chemotherapy, he generally utilizes this treatment regardless of the risk of relapse.

2. After holding out judgment on adjuvant aromatase inhibition for the last two years, Craig has joined the rapidly growing group of research leaders and community physicians who now prefer this approach over tamoxifen for postmenopausal women. Interestingly, the ATAC trial still stands alone as the only reported randomized study of up-front treatment with an aromatase inhibitor, specifically anastrozole. However, from Craig's perspective, two other "switching" trials put the "nail in the tamoxifen coffin." In November, Goss et al reported a Canadian trial demonstrating a recurrence-free survival advantage for letrozole versus placebo in postmenopausal women completing five years of adjuvant tamoxifen. Then, in December, Boccardo et al presented an Italian study at the San Antonio Breast Cancer Symposium demonstrating an advantage to switching from tamoxifen to anastrozole after two to three years of tamoxifen compared to completing five years of tamoxifen.

These two studies seem to have affected many research leaders who previously recommended up-front tamoxifen in spite of very encouraging efficacy and tolerability data from the 47-month follow-up of the ATAC study presented more than a year ago and published last November. It will be interesting to see if the ASCO Technology Assessment group comments on the new Canadian and Italian data.

The clinical research strategy of searching for modest improvements in outcome by either meta-analysis or launching huge studies like ATAC has perhaps had an unexpected outcome on individual breast cancer patients and their physicians. Today, we can say with reasonable confidence to women with even a 10 percent risk of relapse that systemic therapy can further lower that risk by a couple percentage points.

This has created vexing decisions not commonly seen in other areas of cancer care. One can now debate the advisability of, for example, receiving adjuvant chemotherapy for a one or two percent improvement in relapse rate or whether a woman should receive anastrozole or tamoxifen for a similar marginal gain, albeit with perhaps reduced toxicity.

In that regard, we have enclosed a report from a unique "Breast Cancer Patient Perspectives" project that we implemented last year to bring patients' opinions and thoughts into our audio series and other educational efforts. This monograph includes results from anonymous keypad polling of more than 700 breast cancer survivors at three town meetings. These women were presented with common adjuvant treatment decisions, and a nationally respected faculty of breast cancer research leaders discussed their take on the risk-to-benefit ratios of a variety of interventions, including clinical trial participation.

This initiative was in no way a scientific study but rather a living demonstration of the heterogeneity of patient perspectives on situations for which multiple acceptable evidence-based treatment options exist. As our CME group moves forward, we hope that the experience gained through this project and others like it will allow us to serve as a communication conduit for the key constituents in the breast cancer crucible — "Talmudic scholars" like Craig Henderson and other research leaders, community-based clinicians and the women who struggle daily with this disease.

—Neil Love, MD

Doctors with Cancer:

Research To Practice is launching a unique continuing medical education project and we seek your assistance. Our intention is to gather information via an anonymous survey of physicians with either a personal diagnosis of cancer or an immediate relative or spouse with a cancer diagnosis. The data will identify patient and family needs to be addressed in our CME programs. The survey may be completed by phone or email and a modest honorarium is available to a limited number of participants.

To launch this project, we are seeking physicians in either of the following situations:

1. A prostate cancer diagnosis
2. A diagnosis of any cancer for which chemotherapy has been administered

For more information please go to CliniciansWithCancer.com or email me (NLove@ResearchToPractice.net).

Thank you for your assistance.

Edited comments by I Craig Henderson, MD, FACP, FRCP

Role of the aromatase inhibitors in the adjuvant setting

The aromatase inhibitors are now clearly viewed as the most effective and important adjuvant endocrine therapy. In the last three or four years, we've seen an unexpected shift from tamoxifen, the "star" for 30 years, to the aromatase inhibitors. After the presentation of the initial ATAC trial results, ASCO did not recommend the aromatase inhibitors as adjuvant therapy because there were no survival data. Interestingly, the FDA approved anastrozole as adjuvant therapy. It's also clear to me that community-based doctors are using adjuvant anastrozole to a greater extent than most academic physicians.

The dramatic results from the NCIC-CAN-MA17 trial (Figure 1.1) of letrozole after tamoxifen have thrown everyone into turmoil. The levels of significance are so great that neither physicians nor patients can ignore them. Again, we don't have survival data, and it will be difficult to evaluate survival at any point in the future. Additionally, we won't be able to replicate those results because it wouldn't be ethical to repeat that study. In fact, the NSABP trial evaluating exemestane in postmenopausal patients with receptor-positive breast cancer, which was identical in design, was closed to accrual immediately. I don't think it's possible to ignore the ATAC trial results anymore.

Disease-free survival and survival as endpoints in adjuvant trials

Disease-free survival and survival are important endpoints for patients. Patients asked to weigh these two endpoints invariably rate survival as the most important; however, when two treatments offer no difference in survival, patients face a difficult decision. I'm concerned, as are others, that neither the ATAC trial nor the MA17 trial will provide clear answers about survival.

Aromatase inhibitors following five years of adjuvant tamoxifen

It may be reasonable to offer an aromatase inhibitor to patients who completed a five-year course of adjuvant tamoxifen as long as five or 10 years previously. However, with every year that passes, the absolute risk of recurrence decreases;

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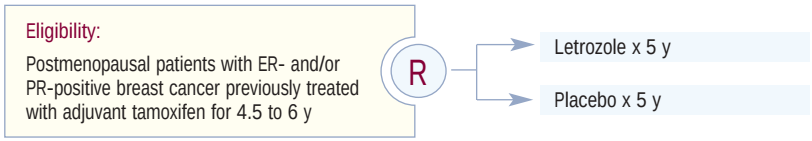
therefore, the risk-to-benefit ratio changes. Every year, the risks become more important relative to the benefit. As the risk of recurrence decreases, the toxicities of therapy become much more important.

Figure 1.1

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

Accrual: 5,187 (Closed)
Protocol IDs: CAN-NCIC-MA17, CLB-49805, E-JMA17, EORTC-10983, IBCSG-BIG97-01, JRF-Vor-Int-10, NCCTG-CAN-MA17, NCCTG-JMA.17, SWOG-CAN-MA17, SWOG-JMA17



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

	Letrozole (n=2575)	Placebo (n=2582)	*p*-value
Estimated 4-year DFS	93%	87%	$p < 0.001$
Local or metastatic recurrences or new contralateral primary	75 (2.9%)	132 (5.1%)	$p < 0.00008$

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

NCI Physicians Data Query, January 2004.

Italian Tamoxifen Arimidex® (ITA) trial: Adjuvant anastrozole following two years of adjuvant tamoxifen

In the ITA trial (Figure 1.2), patients received a total of five years of therapy — either tamoxifen alone or tamoxifen for at least two years followed by anastrozole. Results from the ITA trial confirm the data from the MA17 trial in which patients received five years of adjuvant tamoxifen and then an aromatase inhibitor. It is unknown whether 10 years of an adjuvant aromatase inhibitor alone would be more effective than five years of adjuvant tamoxifen followed by five years of an adjuvant aromatase inhibitor. Although the ITA trial was a small study, I'm willing to accept it as being fundamentally correct because the results are consistent with those from the MA17 trial. In both trials, a clear advantage was demonstrated for the crossover to an aromatase inhibitor after tamoxifen.

Figure 1.2

ITA Trial: Anastrozole (A) versus Tamoxifen (T) in Women Already Receiving Adjuvant Tamoxifen (Median Follow-Up, 24 months)[1]

Treatment	Event-free survival		Progression-free survival	
	Hazard ratio	*p*-value	Hazard ratio	*p*-value
Tamoxifen (n=225)	1.0	0.0004	1.0	0.002
Anastrozole (n=223)	0.36 (95% CI 0.21-0.63)		0.35 (95% CI 0.18-0.69)	

"Conclusion: These findings confirm the role of A in the treatment of early breast cancer. Furthermore, the findings show that switching patients on adjuvant T to treatment with adjuvant A appears to decrease their risk of relapse and death. A was found to be more effective and induce less serious adverse effects than T in women already on treatment with this antiestrogen."[2]

SOURCES: [1]Boccardo F. Presentation, San Antonio Breast Cancer Symposium, 2003.
[2]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**.

Initiating adjuvant hormonal therapy

In a postmenopausal woman for whom I am initiating adjuvant hormonal therapy, I am now more likely to start with an aromatase inhibitor. I wouldn't rule out the possibility of tamoxifen, and I would discuss both options with the patient. If the patient asks what I recommend, I say an aromatase inhibitor. This is a recent change for me; the MA17 trial was the "final nail."

Continued adjuvant therapy following five years of adjuvant anastrozole

Kent Osborne proposed the possibility of studying the use of adjuvant tamoxifen in women who have already received five years of adjuvant anastrozole. Most physicians are concerned about this strategy because there are no data to support it. Another option would be 10 years of an adjuvant aromatase inhibitor. Most physicians seem to be more comfortable with that strategy.

Switching to adjuvant anastrozole while receiving adjuvant tamoxifen

In a postmenopausal woman who has received two to three years of adjuvant tamoxifen and is doing well, I wouldn't recommend changing to adjuvant anastrozole. I would tend to have the patient finish the five years of adjuvant tamoxifen and then change to an aromatase inhibitor. If the patient felt strongly about switching or was having some symptoms on tamoxifen, I'd be very comfortable switching therapy at two or three years.

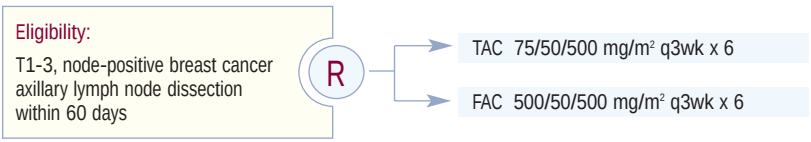
BCIRG-001: Adjuvant TAC versus FAC

The TAC data were not surprising (Figure 1.3); I expected them to become positive for survival and disease-free survival. The analysis was very clear — no question — TAC is better than FAC. Now, the question is: Is the dose-dense regimen presented by Marc Citron last year, of AC every two weeks for four cycles with growth factors, followed by dose-dense paclitaxel for four cycles, better or worse than TAC?

The trial comparing TAC to FAC utilized an intravenous FAC regimen, but we've known for a long time that the SWOG FAC regimen is probably better. SWOG FAC uses daily oral cyclophosphamide, which prolongs its administration compared to the all-intravenous regimen. As established by randomized trials, classic CMF using oral cyclophosphamide is superior to an all-intravenous CMF regimen. Therefore, it's even more plausible that classic FAC would be better than the all-intravenous FAC regimen. Although TAC is better than intravenous FAC, it cannot be concluded that TAC is better than the SWOG FAC regimen.

Figure 1.3

Adjuvant TAC versus FAC: Disease-Free Survival (DFS) and Overall Survival (OS) after a Median Follow-Up of 55 Months (n=1,491)



	Hazard ratio TAC/FAC (95% CI)	*p*-value
DFS		
Adjusted for nodal status	0.72 (0.59-0.88)	0.0010
1-3 nodes (n=923)	0.61 (0.46-0.82)	0.0009
≥4 nodes (n=568)	0.82 (0.63-1.08)	0.1629
Hormone receptor-positive	0.73 (0.57-0.94)	0.0132
Hormone receptor-negative	0.66 (0.47-0.93)	0.0163
OS		
Adjusted for nodal status	0.70 (0.53-0.91)	0.0080

CI = confidence interval

SOURCE: Martin M et al. **TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 43.**

Role of adjuvant docetaxel

Adjuvant AC followed by docetaxel is being used by many oncologists in practice, but we don't know how it compares to dose-dense AC followed by paclitaxel. Indirect evidence suggests that docetaxel is better than paclitaxel. A direct comparison between paclitaxel and docetaxel administered every three weeks in patients with metastatic breast cancer, presented at the 2003 San Antonio Breast Cancer Symposium, demonstrated a survival advantage for docetaxel (Figure 1.4).

Figure 1.4

TAX-311: A Phase III Randomized Trial Comparing Docetaxel to Paclitaxel in Patients with Metastatic Breast Cancer (n=449)

Overall response rate in the patients evaluable for response (n=388)

Docetaxel	Paclitaxel	*p*-value
37.4%	26.4%	0.02

Efficacy: Intent-to-treat analysis

	Docetaxel (n=225)	Paclitaxel (n=224)	*p*-value
Overall response rate (CR + PR)	32.0%	25.0%	0.10
Median time to progression (months)	5.7	3.6	0.0001
Median overall survival (months)	15.4	12.7	0.03

Safety analysis: Grade III/IV toxicity

	Docetaxel (n=222)	Paclitaxel (n=222)
Neutropenia	93.3%	54.5%
Asthenia	23.9%	6.8%
Infection	14.0%	5.0%
Edema	11.3%	4.5%
Stomatitis	10.4%	0.5%
Neuromotor	9.0%	4.5%
Neurosensory	8.6%	4.5%

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

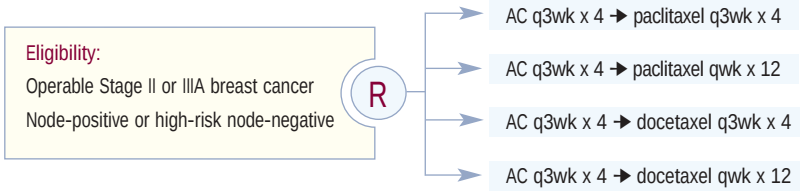
Ravdin P et al. **Phase III comparison of docetaxel and paclitaxel in patients with metastatic breast cancer.** Presented at European Cancer Conference 2003. *Eur J Cancer Suppl* 2003;1(5 Suppl):201; **Abstract 670.**

The data from the randomized Intergroup adjuvant trial will be reported in the next 18 to 24 months, and I will wait to draw a final conclusion at that time (Figure 1.5). In that trial, which is closed to accrual, patients were randomly assigned to either paclitaxel or docetaxel and to either an every three-week regimen or a weekly regimen. I believe paclitaxel may be better when administered weekly, and docetaxel may be better when administered every three weeks. It will be interesting to see how weekly paclitaxel will compare to every three-week docetaxel.

Figure 1.5

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

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



SOURCE: NCI Physician Data Query, February 2004.

Selection of adjuvant chemotherapy

The most effective regimens are perceived to be TAC and dose-dense AC followed by paclitaxel. Without a comparative trial, it's difficult to say whether one is better than the other. A direct comparison is required to obtain a clear answer. I am most likely to use dose-dense AC followed by paclitaxel, but I helped to develop that regimen and we often use what we have the most experience with (Figure 1.6).

I believe Marc Citron and Cliff Hudis were surprised that dose-dense therapy wasn't more toxic; they feel that the dose-dense regimen is less toxic than the every three-week regimen, and their data support that.

Figure 1.6

Toxicities Observed in CALGB-9741 Adjuvant Clinical Trial of Dose-Dense versus Conventionally Scheduled Chemotherapy

Toxicity	1 Sequential q3wk	2 Sequential q2wk	3 Concurrent q3wk	4 Concurrent q2wk
No. treated	488	493	501	495
No. studied for toxicity	99	96	101	101
Granulocytes <0.5/uL	24%	3%	43%	9%
Febrile neutropenia hospitalized	3%	2%	5%	2%
Red blood cell transfusion	0%	2%	3%	13%
Neurologic: Severe sensory loss or motor weakness	1.9%	1.9%	3.9%	4.5%

SOURCE: Citron MI. Presentation, San Antonio Breast Cancer Symposium, 2002.

Adjuvant chemotherapy in patients with node-negative disease

Unlike many of my colleagues, my recommendations for selection of a chemotherapy regimen in patients with node-negative disease are the same as for a patient at high risk. I believe that if you're going to use chemotherapy and expose the patient to the toxicities, you should do it right. The estimated three-year survival advantage at 10 years that physicians generally discuss with patients is based on the recent regimens. If you discuss those numbers with patients and then treat them with a less toxic regimen, like CMF or four cycles of AC, I consider that "bait and switch." Those regimens do not provide the benefit that was quoted.

Influence of estrogen-receptor status on the use of adjuvant chemotherapy

I probably use less chemotherapy in postmenopausal women than many of my colleagues, although I've recently increased my usage. I wouldn't have treated any 60-year-old women with adjuvant chemotherapy five years ago, but I've made a real change since the results from CALGB-9344 were published (Figure 1.7). The effects of chemotherapy are usually reported in all patients — those with ER-positive disease and those with ER-negative disease — but evidence suggests that chemotherapy is less effective in patients with ER-positive disease and more effective in patients with ER-negative disease.

Figure 1.7

CALGB-9344: Hazard of Recurrence According to Hormone-Receptor Status in an Unplanned Subset Analysis

	Hazard ratio (CA + paclitaxel)/CA	95% CI
Hormone receptor-positive	0.91	0.78 – 1.07
Hormone receptor-negative/unknown	0.72	0.59 – 0.86

CA = cyclophosphamide and doxorubicin; CI = confidence interval

SOURCE: 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**

I'm now convinced that the effect of chemotherapy in a 60-year-old woman with ER-negative disease is the same as in a 45-year-old premenopausal woman with ER-negative disease. I would treat that 60-year-old woman with chemotherapy, and I would give her the best chemotherapy available.

On the other hand, in an otherwise healthy 60-year-old woman with a 2.5-cm, moderately well-differentiated tumor that has 80 percent estrogen receptor staining and 40 percent progesterone receptor staining, I would very likely use adjuvant endocrine therapy alone. I would discuss and offer chemotherapy,

particularly if she had node-positive disease. If the patient asked, “What do you recommend?” I’d say, “Most of your benefit is going to come from the endocrine therapy, and you’re going to possibly obtain a little benefit from chemotherapy in the range of one-half to one-and-a-half percent. If you want to be treated, that is fine.” My approach would be different in a woman with ER-negative disease because I would give a much higher estimate of the benefit from chemotherapy.

Select publications

Publications discussed by Dr Henderson

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

Albain KS et al. **Overall survival after cyclophosphamide, Adriamycin, 5-FU, and tamoxifen (CAFT) is superior to T alone in postmenopausal, receptor(+), node(+) breast cancer: New findings from phase III Southwest Oncology Group Intergroup Trial S8814 (INT-0100).** *Proc ASCO* 2002;**Abstract 94**.

Baum M et al. **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359(9324):2131-9. **Abstract**

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**

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

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

Henderson IC et al. I**mproved 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**

Jones S et al. **Randomized trial comparing docetaxel and paclitaxel in patients with metastatic breast cancer.** *Breast Can Res Treat* 2003;82(Suppl 1):9;**Abstract 10**.

Martin M et al. **TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** *Breast Cancer Res Treat* 2003;82(Suppl 1);**Abstract 43**.

Edited comments by Anthony Howell, MD, MSc, FRCP

ATAC trial findings and hormone receptor phenotype

The analysis of recurrence according to estrogen and progesterone receptor status was the first translational research component of the ATAC trial to be reported. The data indicate patients with ER-positive and PR-negative tumors — approximately 20 percent of postmenopausal ER-positive patients with breast cancer — have a 50 percent reduction in the hazard for recurrence with anastrozole compared to tamoxifen, whereas those with ER / PR-positive tumors have about a 20 percent reduction in the hazard ratio (Figure 2.1).

We need to be cautious because these are early data and it's the first time this pattern has been reported. Biologically, it makes sense because patients with ER-positive, PR-negative disease tend to be HER2-positive in other trials with which we've been involved. Additionally, in the letrozole preoperative trial and the IMPACT neoadjuvant anastrozole trial, patients with ER-positive, HER2-positive disease responded better to aromatase inhibitors than to tamoxifen.

Figure 2.1

Results of Analysis of Time to Recurrence in the ATAC Trial According to Estrogen and Progesterone Receptor Status

Receptor status	n	Anastrozole vs tamoxifen*
ER-positive, PgR-positive	5,704	0.82 (0.65-1.03)
ER-positive, PgR-negative	1,370	0.48 (0.33-0.71)
ER-negative, PgR-positive	220	0.79 (0.40-1.5)
ER-negative, PgR-negative	699	1.04 (0.73-1.47)

*Hazard ratios less than one indicate values in favor of anastrozole

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

Dr Howell is a Professor of Medical Oncology at the University of Manchester in Manchester, England.

HER2 status and response to endocrine therapy

We haven't yet evaluated HER2 status in the ATAC trial, but in the NATO trial 30 percent of patients with ER/PR-negative disease were HER2-positive, whereas only 10 percent of those with ER/PR-positive disease were HER2-positive. We believe there's an association between HER2 and ER. Activation of growth factor receptors may turn off progesterone receptor synthesis.

The hypothesis that PR is a downstream function of ER and an indication of how ER is functioning is also reasonable. In advanced disease, patients with ER/PR-positive disease are more likely to respond to endocrine therapy than those with ER-positive, PR-negative disease.

However, these observations have all been with tamoxifen, and data first presented at the 2003 San Antonio Breast Cancer Symposium suggest the aromatase inhibitors may be more effective than tamoxifen in patients with the ER-positive, PR-negative phenotype.

This is a potentially important finding, but it appears that the aromatase inhibitors are also more effective for patients with ER/PR-positive disease.

Current limitations in measuring and defininig ER positivity

The patient subset with ER-negative, PR-positive tumors has been recognized for many years, and there are different viewpoints about this subgroup. It's a very small group of patients — only about 250 out of the 6,000 patients we looked at in the ATAC trial had that phenotype. In older trials of advanced disease, these patients responded to tamoxifen, so it's not a reason for failing to offer endocrine therapy. The estrogen receptor is almost certain to be present at very low levels, but we're not measuring it.

Assessment of ER status remains problematic. In the past, assays were standardized by biochemical methods that were widely utilized. The immunohistochemical method can be performed in any pathology laboratory, but quality control is poor in some laboratories.

The real problem with false-negative results occurs for tumors with low levels of ER — between one and 20 percent of positively staining cells — which comprises 10 percent of patients. The concern is that these patients will be labeled ER-negative and will not receive the benefit of endocrine therapy.

Another concern is that we don't know how patients with low levels of ER respond to therapy, although the IMPACT trial had a lower response rate for patients in the lowest quartile of positivity. Having said that, these patients do respond to endocrine therapy. I believe we should be administering endocrine therapy to all patients who demonstrate any ER positivity.

Many laboratories are beginning to utilize the Allred scoring system, which is good because the Baylor group has the most data on the immunohistochemical measurement of ER.

ATAC trial subprotocol analyses: Quality of life and side-effect profiles

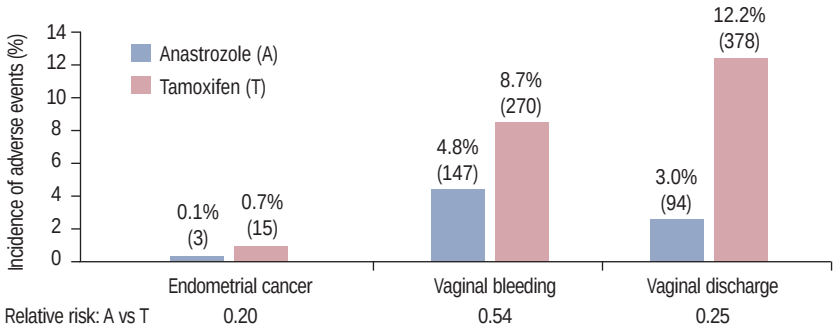
The quality-of-life subprotocol resulted in no difference between tamoxifen and anastrozole; however, anastrozole was more effective in preventing relapse.

Other important differences favoring anastrozole over tamoxifen were fewer strokes, deep vein thromboses, heart events and endometrial cancers (Figure 2.2). These extremely important advantages of anastrozole outweigh the relatively minor side effects — aching in the joints and dryness in the vagina.

The major side effect associated with anastrozole is the decrease in bone mineral density. The bone subprotocol — out to two years — shows a greater reduction in bone density with anastrozole than with tamoxifen (Figure 2.3). There's about a four percent bone loss with anastrozole and no bone loss with tamoxifen.

Figure 2.2

Incidence (%) of Endometrial Cancer, Vaginal Bleeding and Vaginal Discharge in the Updated Analysis of the ATAC Trial



SOURCE: Grana G. Poster presentation, Lynn Sage Breast Cancer Symposium, 2003.

Use of bisphosphonates with adjuvant anastrozole

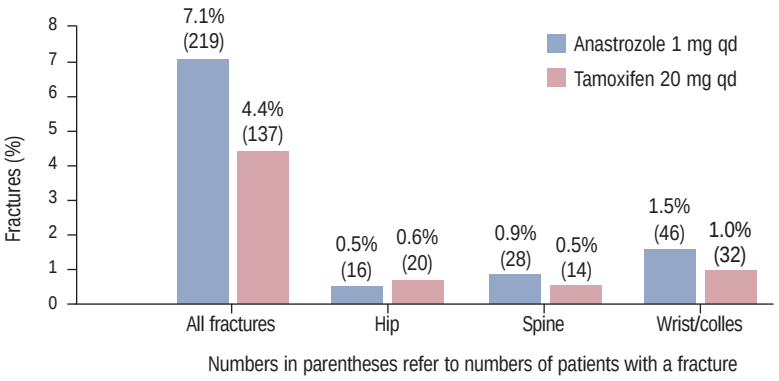
Increasingly, we're seeing patients who have ER-positive tumors and good prognoses, so we have to think of their global quality of life for the remainder of their lives. One could argue that assessing bone density in women over 60 is a public health measure, irrespective of whether they have breast cancer or not.

In a nonprotocol setting, I think we should measure bone density and prescribe bisphosphonates if necessary. The Austrian data, which are highly important, are holding up and demonstrate that bone mineral density loss associated with anastrozole can be prevented with the bisphosphonate zoledronate.

We don't really know which bisphosphonate to use, although it's likely any of the good bisphosphonates will be efficacious. The IBIS-II prevention trial comparing anastrozole to placebo has a bone subprotocol in which we will measure the baseline

Figure 2.3

Bone Fracture Adverse Events at the Updated Safety Analysis



SOURCE: Locker G. Poster presentation, Lynn Sage Breast Cancer Symposium, 2003.

bone mineral density in 900 women, with repeat assessments at one, three, five and seven years. If their bone density is normal at entry, we won't intervene. If they have osteoporosis, we'll treat them with weekly risedronate.

The patients with osteopenia are interesting because they are the ones who are likely to be tipped into osteoporosis during the five years of treatment with an aromatase inhibitor. In the United Kingdom, patients with osteopenia would be treated by their family doctors and would not receive a bisphosphonate until they developed osteoporosis. In the IBIS-II study, those patients will be randomly assigned to weekly risedronate or placebo.

ASCO Technology Assessment on the Use of Adjuvant Aromatase Inhibitors

It's interesting that relatively small improvements from chemotherapy have been accepted, whereas the ASCO Technology Assessment was equivocal with regard to the adjuvant use of anastrozole. Unlike other clinical trial results, they suddenly wanted to see a survival advantage. One could make the argument for the use of aromatase inhibitors due to the delay in relapse and the side-effect profile, particularly with regard to the endometrium and deep vein thrombosis. Anastrozole offers other advantages, and I believe that a survival advantage will become evident in time. The first analysis of survival data will likely occur in the summer of 2004.

More data are being reported on aromatase inhibitors. The MA17 trial demonstrated the value of aromatase inhibitors after five years of tamoxifen, and the Boccardo trial indicated that the switch from tamoxifen to anastrozole at two or three years from the start of treatment results in a disease-free survival advantage and nearly a survival

advantage, with a *p*-value of 0.06. Increasingly, more data are emerging to support the superiority of aromatase inhibitors over tamoxifen.

Selection of an aromatase inhibitor in the adjuvant setting

A good scientist and clinician will treat patients according to the available data. In the adjuvant setting, the ATAC data support using anastrozole up front, the Boccardo data support switching to anastrozole after two to three years of tamoxifen, and MA17 supports the use of letrozole after five years of tamoxifen.

So at this point, if you are starting adjuvant therapy, you should use anastrozole because we have data on that. If you are going to switch at two to three years, you switch to anastrozole because we have data on that. But if you're going to give treatment after five years, you use letrozole because we have data on that.

IMPACT neoadjuvant trial: Anastrozole versus tamoxifen versus the combination

The IMPACT trial can be thought of as preoperative ATAC, with treatment given for three months. Response rates were similar in all three arms — approximately 30 percent by calipers — but breast conservation rates were significantly higher with anastrozole (Figure 2.4).

In the biological study reported, anastrozole resulted in approximately a 20 percent reduction in the proliferation index Ki67 compared to either tamoxifen or the combination. These results were similar to the ATAC trial results. Additionally, the response rate was higher in patients with HER2-positive disease, which mirrors Matt Ellis' data with letrozole.

Figure 2.4

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.**

Role of fulvestrant in the sequence of hormonal therapies

In trials 20 and 21, anastrozole and fulvestrant were equivalent as second-line therapy after tamoxifen failure, but fulvestrant had a significantly longer duration of response in the North American study. In the first-line study, tamoxifen was slightly superior to fulvestrant, which was a very surprising result. In the ER/PR-positive group, fulvestrant was slightly (but not significantly) better than tamoxifen. In other words, it's a drug that is equivalent to anastrozole as second-line therapy and nearly equivalent to tamoxifen as first-line therapy.

We have to ask, "Why wasn't fulvestrant better than tamoxifen?" That's what we expected. The answer may be in the dosing of fulvestrant, because it takes about six months to achieve steady state levels.

Clinical trials (Figure 2.5) will evaluate loading-dose schedules of fulvestrant. Our modeling analyses indicate these approaches will increase the dose of the drug sooner, and then we will be able to investigate whether that is the reason fulvestrant was not better than tamoxifen in the first-line trials.

Figure 2.5

Ongoing and Future Clinical Trials of Fulvestrant

Study	Trial design	Dosing/scheduling of fulvestrant	Status (accrual)
NCCTG-N0032	Phase II trial of fulvestrant in postmenopausal women after progression on an AI ± tamoxifen	250 mg monthly	Ongoing (57/89)
SAKK	Phase II trial of fulvestrant in postmenopausal women after progression on tamoxifen and a nonsteroidal AI	250 mg monthly	Ongoing (69/93)
EFECT	Double-blind, placebo-controlled Phase III trial of fulvestrant vs exemestane in postmenopausal women after progression on a nonsteroidal AI	500 mg day 0, 250 mg days 14, 28 and then monthly	Not yet open (0/660)
SOFEA	Phase III trial of fulvestrant vs fulvestrant + anastrozole vs exemestane in postmenopausal women with ER-positive and/or PgR-positive breast cancer who progressed on anastrozole or letrozole	250 mg monthly	Planned (0/750)
SWOG-S0226	Phase III trial of anastrozole vs fulvestrant in postmenopausal women with ER-positive and/or PgR-positive advanced breast cancer	250 mg monthly	Planned (0/690)
FACT	Phase III trial of anastrozole + fulvestrant vs anastrozole in postmenopausal women with ER-positive and/or PgR-positive metastatic breast cancer or premenopausal women on goserelin	500 mg day 0, 250 mg days 14, 28 and then monthly	Planned (0/558)
ECOG-4101	Phase II trial of fulvestrant + gefitinib vs anastrozole + gefitinib in postmenopausal women with ER-positive and/or PgR-positive metastatic breast cancer	250 mg monthly	Not yet open (0/204)

AI = aromatase inhibitor

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

It remains unclear where fulvestrant should be utilized in the sequence of hormonal therapies for metastatic disease. Several new North American trials and the SOFEA trial should help to clarify its role in our armamentarium of hormonal therapies. The SOFEA trial is a three-arm comparison between exemestane, fulvestrant and fulvestrant plus anastrozole after progression on a nonsteroidal aromatase inhibitor. It's possible that by discontinuing the aromatase inhibitor, sufficient estrogen will be produced to circumvent the effects of fulvestrant. The SOFEA trial will provide an indication of whether fulvestrant is better than exemestane as second-line therapy and also whether it's necessary to suppress the levels of estrogen.

Research strategies for the chemoprevention of breast cancer

The ATAC, Boccardo ITA and MA17 trials demonstrated dramatic reductions in contralateral breast cancer in patients receiving an aromatase inhibitor compared to tamoxifen. We estimate tamoxifen provides about a 50 percent reduction in contralateral breast cancer, whereas anastrozole may result in a 70 to 80 percent reduction, so it's logical to consider using an aromatase inhibitor for prevention.

The IBIS-II trial will compare anastrozole with placebo in 6,000 women at high risk for the development of breast cancer. We did not include tamoxifen as the comparator because we were concerned about tamoxifen's side-effect profile.

Select publications

Publications discussed by Dr Howell

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

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

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

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**.

Dowsett M, 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**.

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**

Winer EP et al. **American Society of Clinical Oncology technology assessment working group update: Use of aromatase inhibitors in the adjuvant setting.** *J Clin Oncol* 2003;21(13):2597-9. **Abstract**

Edited comments by Julie R Gralow, MD

Planned SWOG trial evaluating the use of adjuvant bisphosphonates

Our Intergroup trial will compare clodronate to risedronate, a more potent oral bisphosphonate, and to zoledronate, an intravenous bisphosphonate, which would be considered our standard of care in the metastatic setting. Our primary endpoints will be prevention of bone metastases and disease-free and overall survival. Clodronate and risedronate will be administered daily for three years, and zoledronate will be given monthly for the first six months, and then on an every three-month schedule for the remaining two and a half years.

We will accrue approximately 6,000 patients and eligibility is pretty basic. We want to enroll patients who are receiving adjuvant treatment. Patients enrolled can receive any type of hormonal therapy or chemotherapy. We're also allowing co-enrollment in other clinical trials, as long as bone density isn't a major endpoint. Any patient at a low enough risk that they would not receive adjuvant systemic therapy will be excluded from the study.

There is some preclinical data suggesting the aminobisphosphonates risedronate and zoledronate may have some direct antitumor effect. My hypothesis is that these more potent agents have some slightly different mechanisms than clodronate and will be more effective. There is a reasonable chance that the bisphosphonates can impact survival and decrease bone metastases.

That being said, I'm not sure how bisphosphonates will be used, especially in patients at low risk, because I believe they will cause some toxicity. In the future, we may select a group of patients who are most likely to develop bone metastases and collect tumor blocks and serum for markers of bone turnover. One somewhat controversial hypothesis in this regard relates to the parathyroid hormone-related peptide (PTHrP) receptor. There are some measurable tumor characteristics that may predict for tumors more likely to metastasize to the bone.

We will also have a small substudy population — about 20 patients in each arm — in whom we will perform bone biopsies so we can evaluate bone quality by labeling, compression and nuclear medicine techniques. These studies should allow us to truly see what is happening to bone quality.

Dr Gralow is an Associate Professor of Medical Oncology at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle, Washington.

Rationale for evaluating bisphosphonates in the adjuvant setting

Among breast cancer patients who develop metastases, 70 to 80 percent will have bone metastases. In 40 to 50 percent it will be the first site of metastases. Before breast cancer tumor cells are evident as bone metastases, they can secrete a variety of cytokines that stimulate osteoclasts. They can also impact osteoblasts, macrophages and other cells. In stimulating the osteoclasts, the cell is encouraging bone breakdown and, in turn, the bone microenvironment — osteoclasts, osteoblasts and macrophages — will make cytokines that stimulate the breast tumor cells, so breast cancer cells and the osteoclasts have an intimate relationship and can feed each other. We know from the metastatic setting that bisphosphonates can inhibit osteoclasts and prevent or delay bone breakdown.

Prior clinical trials of adjuvant bisphosphonates

Three clinical trials evaluating adjuvant bisphosphonates have been reported from Europe (Figure 3.1). The first trial, reported by Dr Diel from Germany, selected patients who had known positive bone marrow aspirates but no other metastatic disease. Approximately 300 patients were randomly assigned to clodronate or placebo. Those receiving clodronate had reduced bone metastases and improved survival.

A study from Scandinavia demonstrated virtually the opposite findings. Three years of adjuvant clodronate resulted in a worse survival compared to placebo. That study resulted in no difference in the incidence of bone metastases.

Trevor Powles presented data from a United Kingdom-led trial with about 1,000 unselected patients receiving adjuvant therapy. That study reported a small but significant survival benefit. During the two years patients received clodronate on study, fewer bone metastases were observed. As soon as patients discontinued clodronate, the bone metastases seemed to even out in the two groups.

The data are not conclusive. We have one negative trial, and the largest trial demonstrated a small but real survival benefit. Recent letters to the editors of journals suggest that long-term, high-dose bisphosphonates may potentially cause some problems. While we need to investigate the protective effect of bisphosphonates, we also need to be certain we aren't inducing toxicity in patients.

Bisphosphonate-associated osteonecrosis

Bisphosphonates increase bone density, but they also remain in the bone for years and years. That is a potential problem because they may impair bone quality. Although bones treated with bisphosphonates may appear to be denser on a Dexascan, they may not be scaffolded and structured as well in terms of their laydown of calcium and phosphate.

Two recent letters to the editor in the *Journal of Oral Maxillofacial Surgery* and the *Journal of Clinical Oncology* document patients who had dental extractions that failed to heal. The patients developed osteonecrosis and needed to be treated with antibiotics. This may be a phenomenon peculiar to the jaw and may not have anything to do with fractures or surgery anywhere else, but we need to look at this.

Figure 3.1

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

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

SOURCES: Diel I et al. **Reduction in new metastases in breast cancer with adjuvant clodronate treatment.** *N Engl J Med* 1998;339(6):357-63. **Abstract**

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

Saarto T et al. **Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial.** *J Clin Oncol* 2001;19(1):10-7. **Abstract**

ABCSG-12: LHRH agonist with tamoxifen or anastrozole with or without zoledronate

The Austrian Breast Cancer Study Group (ABCSG) trial 12 demonstrated increased bone density from zoledronate at six months and one year among patients treated with an LHRH agonist plus tamoxifen or anastrozole. We need to follow that study because these were early data from only about 100 patients, and it's a much larger trial than that.

I'm regularly asked, "Should I automatically administer a bisphosphonate when starting an aromatase inhibitor?" I would prefer to monitor bone density. There are patients who won't need a bisphosphonate at all. In our update of the MA17 trial of letrozole versus placebo after five years of tamoxifen, we really don't have substantial numbers of fractures. Currently, there is a one percent fracture rate in the study. Most of our patients aren't going to run into big trouble quickly, so you can do a baseline Dexascan, monitor patients and institute bisphosphonates at an appropriate time based on the WHO criteria for osteoporosis and osteopenia.

Fulvestrant in combination with a dual tyrosine kinase inhibitor

We're going to perform a Phase II study combining fulvestrant with GW572016, a dual HER1 and HER2 tyrosine kinase inhibitor, in patients with metastatic disease. There were several abstracts presented in San Antonio suggesting that HER2-positive, ER-positive tumors have resistance to tamoxifen, fulvestrant and the aromatase inhibitors. Targeting HER1 — the epidermal growth factor receptor — and HER2 might allow us to overcome resistance to endocrine therapy.

Fulvestrant for metastatic breast cancer

Fulvestrant is an active agent, but I'm not sure we're utilizing the best dose. I'd be interested in whether it is feasible to utilize a loading dose or more frequent administration initially to get the levels up.

Many of my patients have received adjuvant tamoxifen, so I typically use first-line aromatase inhibitors off-study and administer fulvestrant upon progression. Subsequently, we may readminister tamoxifen, utilize progestin agents or try another aromatase inhibitor. Many of our patients with hormone receptor-positive metastatic disease can be maintained on hormonal therapies for several years before we have to treat them with chemotherapy.

SWOG trial S0221: Dose-dense versus metronomic scheduling of chemotherapy

SWOG has just opened the new Intergroup adjuvant trial S0221 (Figure 3.2). It is testing the dose-dense concept of every two-week AC and every two-week paclitaxel versus a metronomic dosing schedule. Doxorubicin is administered weekly and oral cyclophosphamide is given daily.

It's a two-by-two design, so we have two different ways of administering the anthracycline and cyclophosphamide and two different ways of administering the paclitaxel. We're comparing paclitaxel every two weeks plus growth factor support to a weekly schedule of the drug.

Data indicate that oral cyclophosphamide, in both the metastatic and adjuvant combination regimens, may be the better way of administering the agent, and that the weekly doxorubicin has more myelotoxicity and bone marrow toxicity but less cardiotoxicity and swings in fatigue. Over time, any chemotherapy adds up, but because you're giving smaller doses more frequently, there are fewer ups and downs.

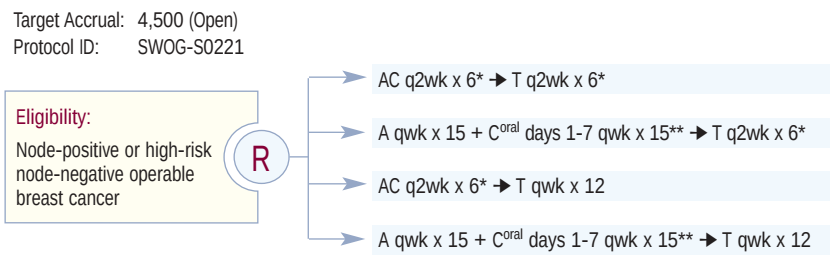
We tested this regimen in the neoadjuvant setting in SWOG-9625, led by Dr Georgiana Ellis. In that study, we just gave the anthracycline and cyclophosphamide without the taxane. The primary endpoint was pathologic complete response rate.

We only enrolled patients with T3 and T4 tumors, and approximately one-half had inflammatory breast cancer; this was a pretty high-risk group. We administered 16 weeks of therapy with this regimen and growth factor support. It was tolerable in a multi-institution setting and resulted in a pathologic complete response rate of 25 percent.

That pathologic complete response rate occurred with an anthracycline and an alkylating agent and without a taxane. Those results are comparable to the results of AC followed by docetaxel in NSABP-B-27. SWOG-9625 wasn't a randomized trial, but with such a good pathologic complete response rate, we're very interested in comparing it to what now probably is considered to be the standard of care in many places — the every two-week, dose-dense schedule.

Figure 3.2

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



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

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

SOURCE: NCI Physician Data Query, October 2003.

Nonprotocol adjuvant chemotherapy

Currently, the weight of the evidence probably supports the dose-dense AC/paclitaxel regimen. TAC may be as efficacious as the dose-dense regimen. Data from the TAC/FAC adjuvant study have been updated and demonstrate a survival benefit for replacing 5-FU with the taxane. AC in combination with docetaxel in a sequential manner is probably tolerated better and may be just as efficacious, but again, we only have surgery data from NSABP-B-27, not long-term results.

The Aberdeen trial — CVAP, and if responding to four cycles, randomized to four more cycles of CVAP versus docetaxel — was recently updated. This small, 160-patient study had significantly better pathologic complete response rates — even in responders to an anthracycline — than switching to docetaxel. It's impressive that they were able to demonstrate a statistically significant survival advantage with such small numbers.

We don't have a head-to-head comparison between docetaxel and paclitaxel in the adjuvant setting. The recent update of the TAX-311 study demonstrated that in metastatic disease, docetaxel every three weeks was superior to paclitaxel every three weeks. That's the reason we're looking at different ways of giving paclitaxel — weekly versus every two weeks with growth factors.

Adjuvant clinical trials of chemotherapy in lower-risk patients

We're participating in the Intergroup trial, CALGB-40101, led by Larry Shulman, which asks, "Is AC for six cycles better than four cycles?" This study also attempts to determine whether anthracyclines are necessary or whether they could be replaced with a taxane to avoid the cardiotoxicity. It's a four-arm study — AC for

four cycles or six cycles every two weeks, or paclitaxel administered every two weeks for four versus six cycles. After the dose-density data were presented they decreased the timing from every three weeks to every two weeks, all with growth factor support.

In our older patients, Hyman Muss is leading CALGB-49907, evaluating whether we can administer capecitabine as a single agent in the adjuvant setting. Capecitabine may not result in the hair loss associated with other regimens, and it may be less toxic. These studies in more fragile patients and patients at lower risk are asking whether we can avoid anthracycline-based regimens entirely with equivalent results and less toxicity.

CALGB trial 49907 of adjuvant chemotherapy in the elderly

CALGB-49907 randomly assigns patients to conventional chemotherapy, AC or CMF versus capecitabine. There were many discussions early on regarding the dose of capecitabine. Few physicians are starting at the FDA-approved dose of 2,500 mg / m^2 daily in two divided doses — two weeks on, one week off. Thus, the trial was started at 2,000 mg / m^2 daily in two divided doses.

We had to halt the study after two deaths occurred in the capecitabine arm. One death happened in the fifth or sixth cycle in a patient who was somewhat removed from the medical system due to family problems. She continued taking capecitabine despite GI toxicity and subsequently died. The other death was clearly a classic case of dihydropyrimidine dehydrogenase (DPD) deficiency. We struggled with that since we really don't know how to test for it in a reliable way.

We know that DPD deficiency will occasionally occur with 5-FU or a 5-FU pro-drug like capecitabine, and its estimated incidence is probably about one to two percent. However, we cannot have deaths occurring in people who may already be cured, so we put the capecitabine arm on hold while we tried to figure out how to identify those rare cases of DPD deficiency and how we could better monitor our patients.

We have recently reopened the capecitabine arm with a mandated medical visit within the first week. During this visit, blood counts are taken and if they're very low — meaning a sudden sharp fall, potentially related to DPD deficiency — then the patient will discontinue capecitabine immediately even before she has been on the drug for one week.

Efficacy of capecitabine in the metastatic setting

Currently, many of our patients receive anthracyclines and taxanes in the adjuvant setting, so an increasing number of patients will be treated with capecitabine even as first-line therapy. Most of the data we currently have is from patients who have already received anthracyclines and taxanes, and as we use capecitabine earlier we see more benefit.

Capecitabine is a potent agent. In the capecitabine / docetaxel versus single-agent docetaxel study led by Joyce O'Shaughnessy, the combination clearly proved to

be quite potent as well. We all have questions about what would have happened if the single-agent docetaxel arm was followed with capecitabine. Would there have been equivalent survival and less toxicity? My guess is that overall survival would have ultimately been the same with a higher response rate and longer time to progression with the combination.

There aren't many studies that have truly tested a combination versus the same drugs in sequence. The best and largest study was the recently published ECOG-1193 trial evaluating doxorubicin and paclitaxel sequentially with crossover at progression versus the combination. The results were exactly as would be expected. The response rate was higher for the combination, but overall survival was identical at about 20 months in all three of the arms. Notably, patients treated with the combination had more toxicity.

Now, in patients with life-threatening disease in whom I am worried that if they don't respond to the first agent I won't have time to get a second one in, I start combination therapy up front. But many of my patients with metastatic disease don't have a lot of symptoms early on, so giving them the best quality of life is also really important.

Nonprotocol management of patients with HER2-positive metastatic disease

Generally, I start patients with HER2-positive disease on a taxane and trastuzumab. If I'm really trying to capitalize on synergistic combinations, it makes sense to add a platinum agent, knowing that synergy up front has improved survival.

Being in the Northwest, I have a lot of patients who are into holistic approaches and would prefer to delay introducing chemotherapy into their systems as long as possible. Thus, I frequently offer trastuzumab monotherapy as an option.

Response rates with first-line, single-agent trastuzumab are in the 35 percent range. We know from the pivotal trial that if you administer chemotherapy with trastuzumab, you do better than if you give chemotherapy followed by trastuzumab second-line. Even though 65 percent of the patients in the chemotherapy-alone arm ultimately received trastuzumab after they progressed, a five-month survival advantage was still demonstrated. Interestingly, however, we don't know whether giving trastuzumab alone up front and then adding chemotherapy at progression changes survival at all.

I discuss the data on combination and single-agent trastuzumab and tell patients that we actually don't know if it is better to give the combination up front or if there is any harm in giving trastuzumab alone and then adding the chemotherapy at progression. Generally, in a patient with life-threatening disease, I'm going to go for the best response and will recommend giving chemotherapy with trastuzumab. But for patients who have pretty low-volume or quiescent disease and are not symptomatic, or older patients in whom cardiac problems may arise, I think trastuzumab monotherapy is a reasonable option.

Select publications

Publications discussed by Dr Gralow

Bear HD et al. T**he effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27.** *J Clin Oncol* 2003;21(22):4165-74. **Abstract**

Diel IJ et al. **Reduction in new metastases in breast cancer with adjuvant clodronate treatment.** *N Engl J Med* 1998;339(6):357-63. **Abstract**

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**.

Heys SD et al. **Neoadjuvant docetaxel in breast cancer: 3-year survival results from the Aberdeen trial.** *Clin Breast Cancer* 2002;3(Suppl 2):69-74. **Abstract**

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

Martin M et al, on behalf of the BCIRG 001 Investigators. **TAC improves disease free survival and overall survival over FAC in node positive early breast cancer patients, BCIRG 001: 55 months follow-up.** *Breast Cancer Res Treat* 2003;**Abstract 43**.

Nabholtz JM et al. **Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: Interim analysis of the BCIRG 001 study.** *Proc ASCO* 2002;**Abstract 141.**

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**

Powles T et al. **Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer.** *J Clin Oncol* 2002;20(15):3219-24. **Abstract**

Saarto T et al. **Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial.** *J Clin Oncol* 2001;19(1):10-7. **Abstract**

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

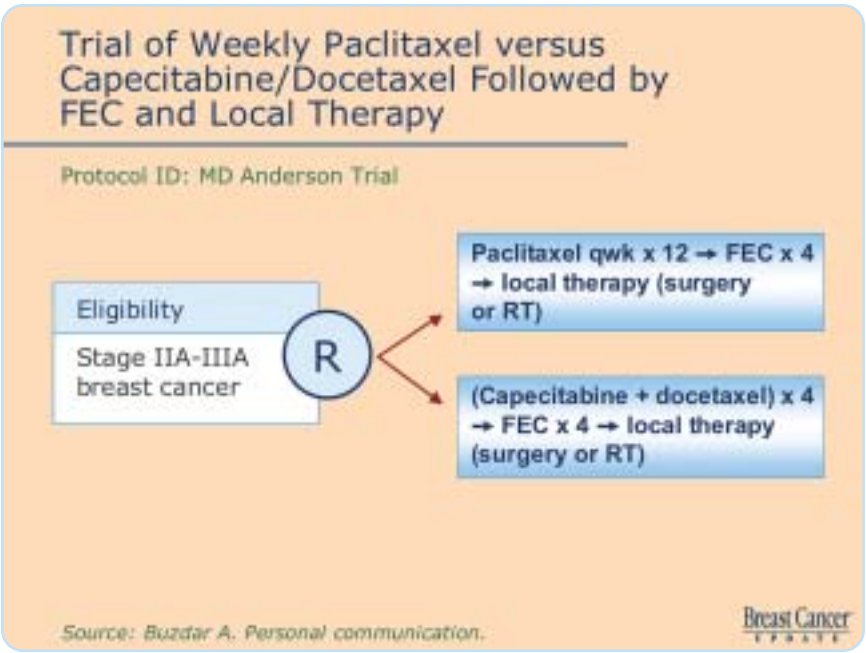
Sledge GW et al. **Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: An intergroup trial (E1193).** *J Clin Oncol* 2003;21(4):588-92. **Abstract**

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: Current Major Randomized Trials Evaluating Adjuvant Chemotherapy: Background and Design

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

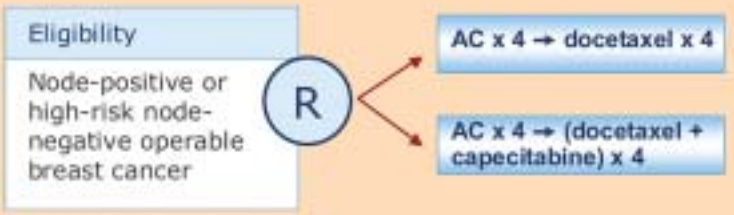
Slide 1



Slide 2

Phase III Trial Comparing AC Followed by Either Docetaxel (T) or Capecitabine Plus Docetaxel (XT)

Protocol ID: US Oncology 01-062
Accrual: 1,810



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

Source: Protocol 01-062 synopsis, June 2002.

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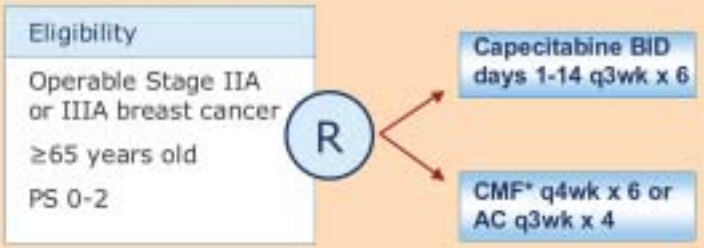
Slide 3

Phase III Study of CMF or AC versus Oral Capecitabine in Elderly Women

Protocol IDs: CALGB-49907, CAN-NCIC-CALGB-49907, ECOG CALGB-49907, SWOG-CALGB-49907, CTSU
Target Accrual: 600-1,800



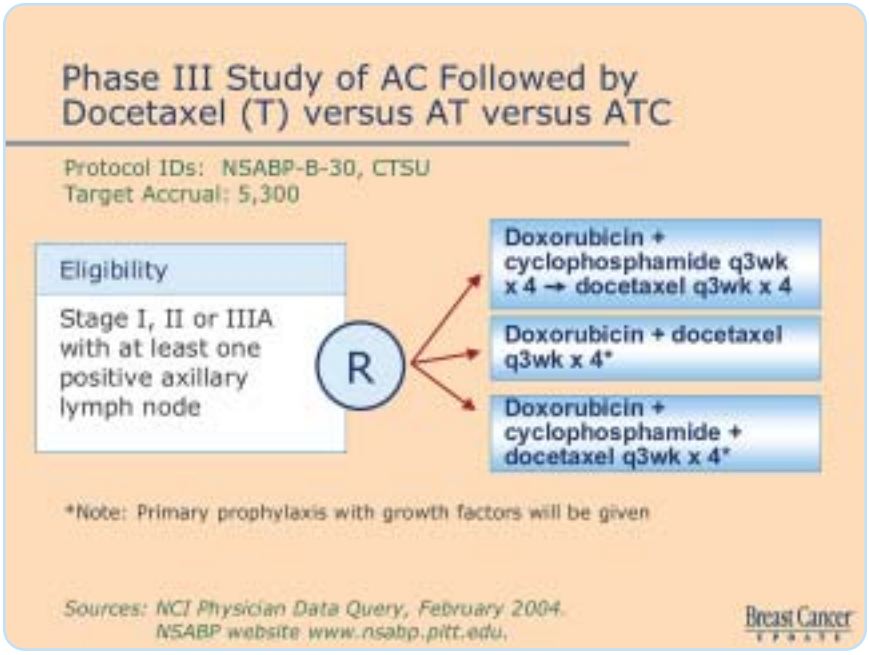
*CMF with oral cyclophosphamide

Note: Patients with insufficient LVEF must receive CMF; otherwise, choice of AC or CMF at physician discretion

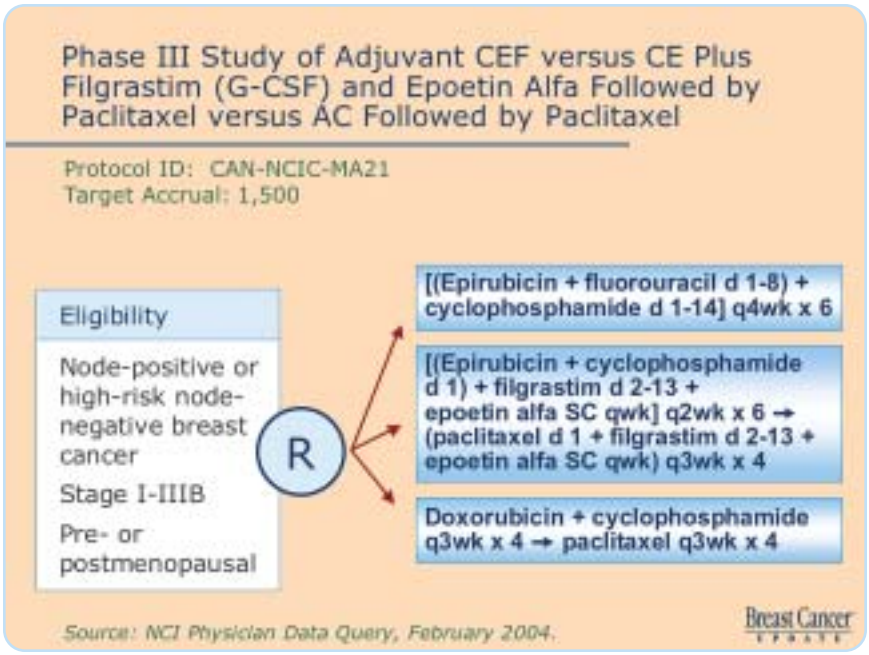
Source: NCI Physician Data Query, February 2004.

Breast Cancer Update

Slide 4



Slide 5



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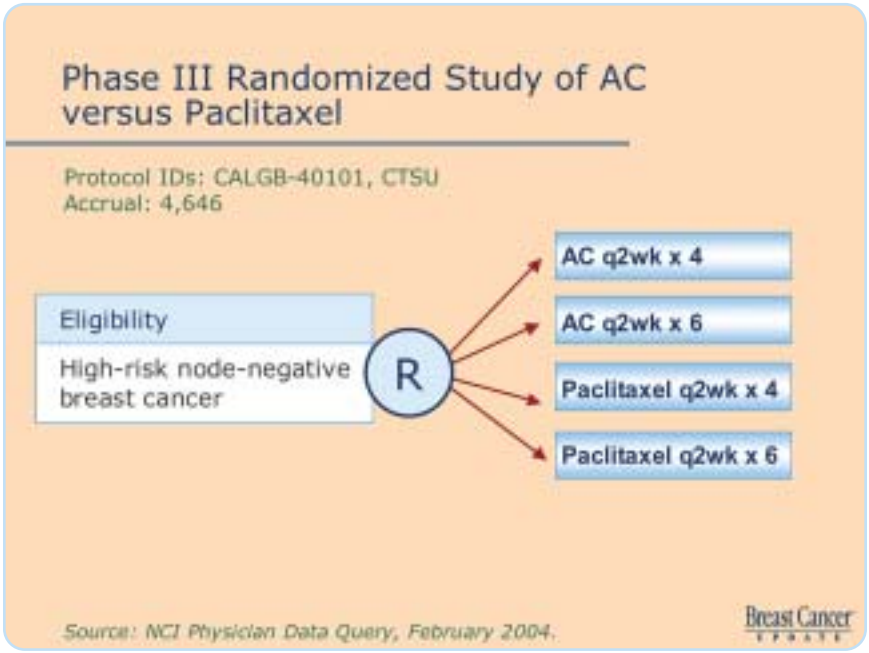

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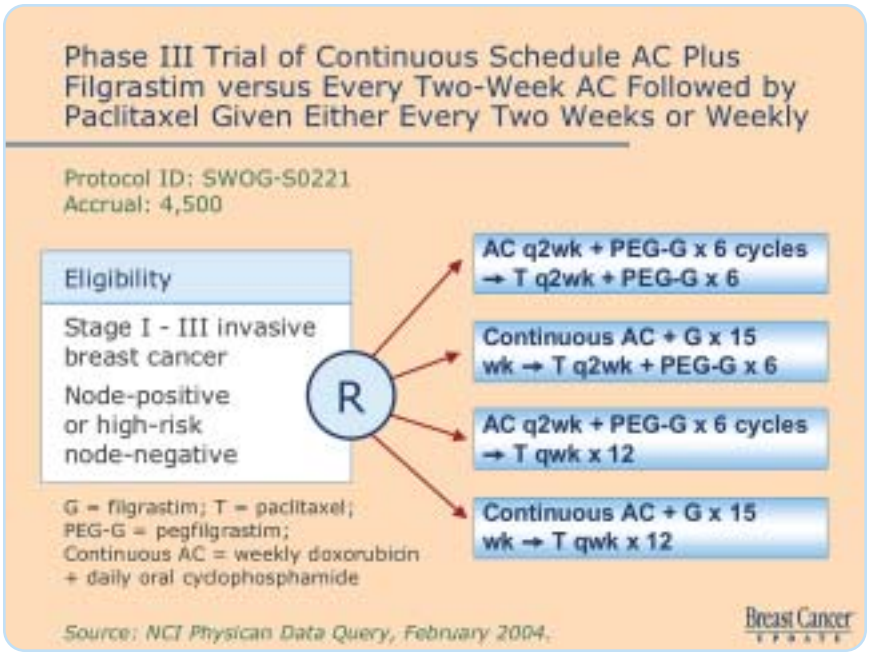
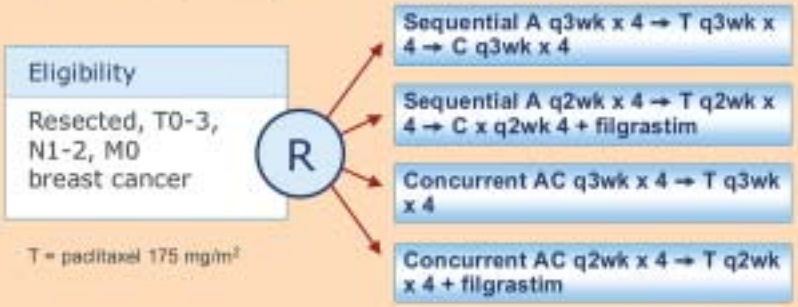


Slide 8

Phase III Study of Sequential Chemotherapy Using Doxorubicin, Paclitaxel and Cyclophosphamide or Concurrent AC Followed by Paclitaxel

Protocol IDs: CALGB-9741, ECOG-C9741, NCCTG-C9741, SWOG-C9741

Accrual: 2,005 (Closed)



T = paclitaxel 175 mg/m^2

Source: Citron ML et al. J Clin Oncol 2003;21:1431-9.

Breast Cancer Update

Slide 9

Three-Year Results of CALGB-9741

Parameters	Dose-dense scheduling	Conventional scheduling	Response rate (p-value)
Disease-free survival	85% (n=988)	81% (n=985)	RR=0.74 (p=0.010)
Overall survival	92%	90%	RR=0.69 (p=0.013)

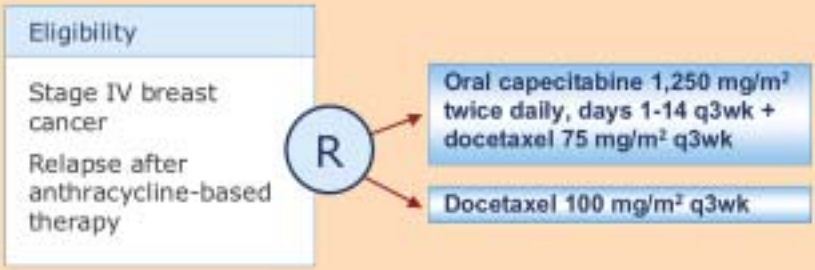
Source: Citron ML et al. J Clin Oncol 2003;21(8):1431-9.

Breast Cancer Update

Slide 10

Phase III Trial of Capecitabine/Docetaxel versus Docetaxel Monotherapy

Accrual: 511 (Closed)



Source: O'Shaughnessy J et al. J Clin Oncol 2002;20:2812-23.

Breast Cancer Update

Slide 11

Efficacy of XT versus T in Anthracycline-Pretreated Patients with Metastatic Breast Cancer

	Capecitabine/ docetaxel (XT) (n=255)	Docetaxel (n=256)	*p*-value
Time to progression	6.1 mo	4.2 mo	0.0001
Overall survival	14.5 mo	11.5 mo	0.0126
Objective response	42%	30%	0.006

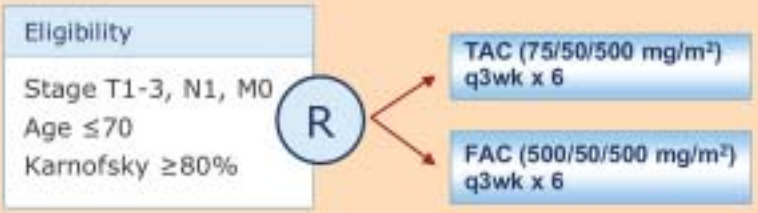
Source: O'Shaughnessy J et al. J Clin Oncol 2002;20:2812-23.

Breast Cancer Update

Slide 12

Phase III Trial Comparing Docetaxel in Combination with Doxorubicin and Cyclophosphamide (TAC) versus FAC

Protocol ID: BCIRG-001
Accrual: 1,491 (Closed)



T = docetaxel

Source: http://www.bcirg.org/Internet/Studies/BCIRG+001.htm, February 2004.

Breast Cancer Update

Slide 13

Adjuvant TAC versus FAC: Disease-Free Survival (DFS) and Overall Survival (OS) after a Median Follow-Up of 55 Months (N=1,491)

	Hazard ratio TAC/FAC (95% CI)	*p*-value
DFS		
Adjusted for nodal status	0.72 (0.59-0.88)	0.0010
1-3 nodes (n=923)	0.61 (0.46-0.82)	0.0009
≥4 nodes (n=568)	0.82 (0.63-1.08)	0.1629
Hormone receptor-positive	0.73 (0.57-0.94)	0.0132
Hormone receptor-negative	0.66 (0.47-0.93)	0.0163
OS		
Adjusted for nodal status	0.70 (0.53-0.91)	0.0080

CI = confidence interval

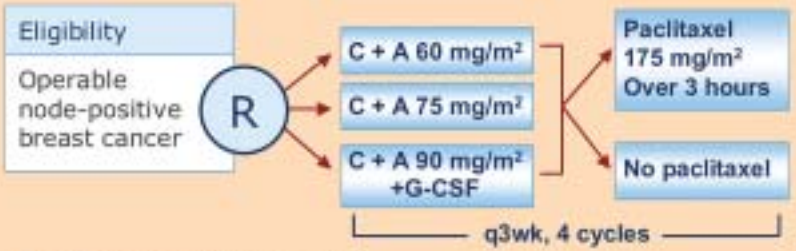
Source: Martin M et al. Breast Cancer Res Treat 2003;82(Suppl 1):Abstract 43.

Breast Cancer Update

Slide 14

Phase III Study of CA Comparing Standard- versus Intermediate- versus High-Dose Doxorubicin with versus without Subsequent Paclitaxel

Protocol IDs: CALGB-9344, ECOG-C9344, INT-0148, NCCTG-943051, SWOG-9410
Accrual: 3,121 (Closed)



C = Cyclophosphamide 600 mg/m²
A = Doxorubicin

Sources: NCI Physician Data Query, February 2004. Henderson IC et al. J Clin Oncol 2003;21:976-83.

Breast Cancer Update

Slide 15

CALGB-9344: Hazard Ratios for Recurrence and Death

Accrual: 3,104

	Hazard ratio	*p*-value
Recurrence		
Doxorubicin dose	—	0.60
60 vs 90 mg/m²	0.97	—
60 vs 75 mg/m²	0.99	—
Paclitaxel vs not	0.83	0.0023
Death		
Doxorubicin dose	—	0.31
60 vs 90 mg/m²	0.91	—
60 vs 75 mg/m²	0.96	—
Paclitaxel vs not	0.82	0.0064

Source: Henderson IC et al. J Clin Oncol 2003;21:976-83.

Breast Cancer Update

Post-test: *Breast Cancer Update*, Issue 2, 2004

Conversations with Oncology Research Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The ATAC trial demonstrated a disease-free and overall survival advantage to anastrozole compared to tamoxifen.**
   a. True
   b. False

2. **The MA17 trial randomly assigned patients who had received a five-year course of adjuvant tamoxifen to:**
   a. letrozole or placebo for five years
   b. anastrozole or placebo for five years
   c. exemestane or placebo for five years
   d. none of the above

3. **The Italian Tamoxifen Arimidex® (ITA) trial randomly assigned patients who had received at least two years of adjuvant tamoxifen to:**
   a. anastrozole or placebo
   b. anastrozole or tamoxifen
   c. letrozole or placebo
   d. letrozole or tamoxifen

4. **In the adjuvant setting, the TAC regimen has been proven superior to FAC in terms of disease-free and overall survival.**
   a. True
   b. False

5. **In CALGB-9741, the dose-dense regimen was found to be significantly more toxic than the conventionally administered regimen.**
   a. True
   b. False

6. **In the ATAC analysis of time to recurrence according to estrogen- and progesterone-receptor status, which of the following phenotypes had the greatest advantage of anastrozole over tamoxifen?**
   a. ER-positive/PR-positive
   b. ER-positive/PR-negative
   c. ER-negative/PR-positive
   d. ER-negative/PR-negative

7. **In the ATAC quality-of-life subprotocol, quality of life was superior in patients receiving tamoxifen.**
   a. True
   b. False

8. **Austrian data demonstrated bone mineral density loss associated with anastrozole can be largely prevented with zoledronate.**
   a. True
   b. False

9. **Data from the IMPACT neoadjuvant trial, comparing anastrozole, tamoxifen and the combination, show:**
   a. similar response and breast conservation rates in all three arms
   b. similar response rates in all three arms, but significantly higher breast conservation rates with anastrozole
   c. similar response rates in all three arms, but significantly higher breast conservation rates with tamoxifen

10. **Data from the North American 0021 trial, comparing fulvestrant to anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy, showed:**
    a. duration of response favored fulvestrant
    b. duration of response favored anastrozole
    c. duration of response did not differ significantly between fulvestrant and anastrozole

11. **CALGB trial 49907 of adjuvant chemotherapy in the elderly randomly assigns patients to conventional chemotherapy (AC or CMF) or single-agent capecitabine.**
    a. True
    b. False

12. **ECOG-1193 trial, evaluating doxorubicin and paclitaxel sequentially with crossover at progression versus the combination, showed:**
    a. the response rates and overall survival were identical in all three arms
    b. the response rate and overall survival were both higher for the combination
    c. the response rate was higher for the combination, but overall survival was identical in all three arms

Post-test Answer Key: 1b, 2a, 3b, 4a, 5b, 6b, 7b, 8a, 9b, 10a, 11a, 12c

Evaluation Form: *Breast Cancer Update*, Issue 2, 2004

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

Please answer the following questions by circling the appropriate rating:

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

GLOBAL LEARNING OBJECTIVES

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

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

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
I Craig Henderson, MD, FACP, FRCP	5 4 3 2 1	5 4 3 2 1
Anthony Howell, MD, MSc, FRCP	5 4 3 2 1	5 4 3 2 1
Julie R Gralow, 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 2, 2004

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___Yes ___No

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

_____

_____

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

_____

_____

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

_____

_____

Degree:

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

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