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HOW TO USE THIS MONOGRAPH

This is a CME activity that 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 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 and the website, **BreastCancerUpdate.com**, where you will find an easy-to-use interactive version of this monograph with links to relevant full-text articles, abstracts, trial information and other web resources indicated here in **red underlined text**.

Breast Cancer Update: A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

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

GLOBAL LEARNING OBJECTIVES

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

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment.
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer.
- Develop and explain a management strategy for treatment of ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Develop and explain a management strategy for treatment of 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 aromatase inhibitors in the adjuvant setting.
- Evaluate the emerging data on dose-dense chemotherapy and explain its relevance to patients.

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 7

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

- Discuss the efficacy and tolerability of the trastuzumab/taxane/carboplatin combination, and the ongoing related trials to assist in the management of select patients with HER2-positive disease in the metastatic setting.
- Describe the efficacy and tolerability of fulvestrant in order to counsel patients with ER-positive metastatic disease about therapy options.
- Evaluate the Women's Health Initiative trial results to counsel women regarding the beneficial and detrimental effects associated with menopausal hormone therapy.
- Evaluate novel data regarding dose-dense scheduling of chemotherapy and the use of taxanes in the adjuvant setting.
- Describe a management strategy for the use of chemotherapy and endocrine therapy in women with metastatic disease.

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Howard A Burris III, MD	**Grants/Research Support:** Bristol-Myers Squibb Company, Aventis Pharmaceuticals, GlaxoSmithKline, Genentech Inc, Eli Lilly & Company, Roche Laboratories Inc **Consultant:** Bristol-Myers Squibb Company, Aventis Pharmaceuticals, Genentech Inc **Honorarium:** Bristol-Myers Squibb Company, Aventis Pharmaceuticals, Genentech Inc, GlaxoSmithKline, Eli Lilly & Company
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Vicente Valero, MD	No financial interests or affiliations to disclose

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Platinol®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
	Neosar®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
doxorubicin	Adriamycin®	Pfizer Inc
estradiol	Various	Various
etoposide, VP-16	Vepesid®	Bristol-Myers Squibb Company
exemestane	Aromasin®	Pfizer Inc
filgrastim	Neupogen®	Amgen Inc
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
goserelin	Zoladex®	AstraZeneca Pharmaceuticals LP
letrozole	Femara®	Novartis Pharmaceuticals Corporation
conjugated estrogen/ medroxyprogesterone acetate	Prempro™	Wyeth Pharmaceuticals Inc
paclitaxel	Taxol®	Bristol-Myers Squibb Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
triptorelin	Various	Various
trastuzumab	Herceptin®	Genentech Inc
zoledronic acid/zoledronate	Zometa®	Novartis Pharmaceuticals Corporation

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Editor's Note

Data-driven

In 1998, my education world instantly expanded at a press conference where Dr Bernard Fisher and his NSABP colleagues announced the findings of the P-1 prevention trial. Prior to that moment, our group's CME activities focused almost exclusively on oncologists, surgeons and oncology nurses. However the P-1 trial data, demonstrating a reduction in breast cancer incidence in women receiving tamoxifen, created an immediate cancer education vacuum for primary care clinicians, particularly gynecologists.

Recognizing the importance of the tamoxifen prevention data, but not entirely familiar with the primary care audience, our team ventured into these new teaching waters with uncertainty. We knew that breast cancer screening was an integral facet of primary health care for women, but we had no idea how these clinicians and their patients would react to the concept of reducing breast cancer risk with an antiestrogen.

To learn more, we conducted a series of working group meetings with gynecology research leaders and community-based doctors. We learned that pharmacological disease prevention was already deeply ingrained in the medical culture of these professionals, who had readily endorsed the widespread use of menopausal hormone therapy to reduce the risk of cardiovascular disease and osteoporosis. Among gynecologic research leaders, there was general agreement that the possible trade-off for what was perceived to be a marginally increased risk of breast cancer was very reasonable until more definitive data became available.

Lurking in the background was the massive Women's Health Initiative (WHI), a randomized, double-blind, placebo-controlled trial that was attempting to define the true risk-to-benefit ratio of "HRT," which at that time was being prescribed to about six million women in the United States.

As our group held breast cancer chemoprevention CME programs for primary care physicians, we interfaced with a number of oncologists who crossed the border into preventive oncology, including Dr Victor Vogel from the NSABP and Dr Rowan Chlebowski, who was interviewed for this program.

Having lived through the era of high-dose chemotherapy with stem cell support, these investigators were familiar with the dangers of "jumping the gun" and endorsing a treatment before randomized trial data became available. These oncologists voiced concerns about the common perception that the WHI was a "done deal" and the results were predictable.

The discussion in the first five minutes of Dr Chlebowski's interview on the audio portion of this program crushes most of those long-held beliefs. Combined estrogen and progestin therapy was found to significantly increase the risk of cardiovascular disease, breast cancer and abnormal mammograms.

In contrast to findings from a number of retrospective series, the breast cancers diagnosed in women on menopausal hormone therapy in the WHI trial were more advanced and had worse prognoses than those diagnosed in women in the placebo group.

Clinical practice changed almost overnight when these and other disturbing WHI trial data were publicized in the media. About half of women on menopausal replacement discontinued potentially harmful treatment that they and their physicians at one point believed to be beneficial. This reiterated the hard-learned lesson that retrospective studies are unreliable and that the randomized trial is the sole "gold standard" for evidence-based patient care.

With this research perspective in mind, it is interesting to consider some of the clinical questions about metastatic disease that arise in the enclosed program.

1. *What is the optimal first-line therapy for women with HER2-positive metastases?*

   Dr Howard Burris reviews what we do and do not know about this key question. The classic randomized trial by Slamon et al demonstrates that chemotherapy without trastuzumab results in inferior survival compared to chemotherapy plus trastuzumab, even though most of the women treated initially with chemotherapy in the study were crossed over to trastuzumab.

   However, no randomized data exist on many other important questions in HER2-positive tumors, including the role of trastuzumab alone as initial therapy or whether this agent should be continued after disease progression.

2. *What is the optimal hormonal therapy in postmenopausal women progressing on adjuvant tamoxifen?*

   Dr Richard Elledge notes that randomized trial data indicate that the estrogen receptor downregulator, fulvestrant, is at least as effective as the other common choice of an aromatase inhibitor, in this case, anastrozole. While many women with ER-positive metastatic disease are diagnosed during their five years on adjuvant tamoxifen, a new generation of patients is likely to relapse on adjuvant anastrozole. Dr Elledge notes the paucity of clinical research data on optimal endocrine therapy at that point.

3. *Can women with previously untreated metastatic disease be rendered disease-free (cured) with systemic therapy?*

   Dr Vicente Valero describes the classic series of such patients treated at his institution (MD Anderson) in which a small fraction of women remained disease-free for 10 or more years. He notes the lack of data for combination hormone therapy and chemotherapy in that situation. In the case discussed

in our program, Dr Valero also addresses the role of surgical excision or ablation of liver metastases. The rarity of this clinical situation means that we are unlikely to ever obtain a definitive evidence-based answer to these questions.

We live in an oncologic world where opposing forces are at work. The clinical trial is one of our most important tools to advance medical care, but the need to conserve research resources means that many important clinical questions will not be addressed in a randomized fashion. Studies that tackle critical public health issues, such as the WHI, are a vivid reminder of how such trials can significantly alter daily clinical practice.

—Neil Love, MD

Women's Health Initiative (WHI) trial

Chlebowski RT et al; WHI Investigators. **Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial.** *JAMA* 2003;289(24):3243-53. **Abstract**

Hays J et al; Women's Health Initiative Investigators. **Effects of estrogen plus progestin on health-related quality of life.** *N Engl J Med* 2003;348(19):1839-54. **Abstract**

Manson JE et al; Women's Health Initiative Investigators. **Estrogen plus progestin and the risk of coronary heart disease.** *N Engl J Med* 2003;349(6):523-34. **Abstract**

Rapp SR et al; WHIMS Investigators. **Effect of estrogen plus progestin on global cognitive function in postmenopausal women: The Women's Health Initiative Memory Study: a randomized controlled trial.** *JAMA* 2003;289(20):2663-72. **Abstract**

Rossouw JE et al; Writing Group for the Women's Health Initiative Investigators. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial.** *JAMA* 2002;288(3):321-33. **Abstract**

Shumaker SA et al; WHIMS Investigators. **Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial.** *JAMA* 2003;289(20):2651-62. **Abstract**

Wassertheil-Smoller S et al; WHI Investigators. **Effect of estrogen plus progestin on stroke in postmenopausal women: The Women's Health Initiative: A randomized trial.** *JAMA* 2003;289(20):2673-84. **Abstract**

Howard A Burris III, MD

Director of Drug Development,
The Sarah Cannon Cancer Center

Edited comments by Dr Burris

Phase II trial of weekly paclitaxel/carboplatin/trastuzumab

Trial design

Patients received double doses of induction trastuzumab for eight weeks and were then assessed by CAT scan. Those who progressed were taken off trastuzumab and started on paclitaxel/carboplatin. Those who responded to the induction trastuzumab continued on trastuzumab for an additional eight weeks before starting paclitaxel/carboplatin.

The idea was to give approximately six cycles of the three-drug combination. As the trial evolved, physicians began to continue maintenance trastuzumab at the completion of chemotherapy. There were patients who maintained responses on trastuzumab alone for more than a year.

Dr Nick Robert's trial of every-three-week administration of paclitaxel/carboplatin with weekly trastuzumab, and Dr Edith Perez's trial of weekly paclitaxel/carboplatin/trastuzumab — three weeks on, one week off — both had schedules similar to our trial. While our trial was weekly like the Perez study, the schedule was six weeks on, two weeks off, and patients did not receive trastuzumab during the break.

While we were initially criticized for that omission of trastuzumab for two weeks, we now know that it is probably not significant because of the long half-life of trastuzumab. In addition, in our trial, patients going to maintenance trastuzumab were allowed to receive it once every three weeks as that data emerged. We have learned that three weeks on, one week off, is a more convenient break pattern than the schedule used in our study, and all of our Phase II trials now follow that schedule.

Efficacy

While we saw some responses with trastuzumab alone, when we put the three drugs together, the increase in response rate was impressive. Sixty-two patients

enrolled in this trial, and 45 of the 62 received the three-drug combination. The response rate to induction trastuzumab was 15 percent, and it jumped to 70 percent when we added paclitaxel and carboplatin. The complete-response rate approached 20 percent, and a number of responding patients remained on therapy for quite some time.

The patients whose disease was resistant to trastuzumab and progressed did well with the paclitaxel/carboplatin combination. Because of the long half-life of trastuzumab, these patients probably still received some three-drug effect.

The response rate for this group was 60 percent — very similar to what has been reported. The progression-free survival was approximately 17 months, and the median overall survival was approximately 30 months. Patients with IHC 3+ and FISH-positive tumors received the most benefit from the combination, and their overall survival was approximately three years.

Ninety percent of patients on this trial benefited by attaining stable disease or better, and 70 percent experienced tumor shrinkage or better. With these high response rates, and as we've seen from Dr Robert's and Dr Perez's work, this three-drug regimen is probably as good as we first noted.

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

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

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

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

Toxicity

We wanted a nontoxic regimen and we certainly achieved that. There was no Grade 3/4 hemetologic toxicity, alopecia or mucositis.

Phase II data comparing weekly versus every-three-week administration of paclitaxel/carboplatin/trastuzumab suggests better tolerability with the weekly regimen. There isn't any response or survival data available yet, but I suspect that weekly administration will be at least as efficacious as every three weeks.

When discussing this with patients, I generally recommend the weekly regimen unless they have a long distance to travel or some other unique circumstance that makes that difficult. The weekly regimen has a very mild toxicity profile.

It surprises people that adding both paclitaxel and carboplatin to trastuzumab rather than adding one or the other doesn't seem to adversely affect the toxicity profile. People often say, "Surely there's more toxicity with a triplet than single-

agent trastuzumab," but that doesn't seem to be the case with the weekly therapies. This is one reason we chose to err on the side of being a little more aggressive.

Future investigation of the taxane/carboplatin/trastuzumab combination

We've been surprised how quickly the taxane/platinum/trastuzumab combination has moved into the adjuvant setting. The adjuvant BCIRG trial utilizing this combination is accruing over 100 patients a month. Accrual will probably be completed by early next year, and we'll see how this triplet fares in the adjuvant setting.

Phase III Randomized Study of Adjuvant Doxorubicin, Cyclophosphamide and Docetaxel with or without Trastuzumab (Herceptin®) versus Trastuzumab, Docetaxel and either Carboplatin or Cisplatin in Women with HER2-neu-Expressing Node-Positive or High-Risk Node-Negative Operable Breast Cancer **Open Protocol**

Protocol ID: BCIRG-006
Actual Accrual: 3,150 patients

Eligibility: Node-positive or high-risk node-negative, HER2-overexpressing (FISH-positive) breast cancer

ARM 1: AC x 4 → docetaxel x 4
ARM 2: AC x 4 → docetaxel x 4 + H (qw x 12 weeks) → H (qw x 40 weeks)
ARM 3: (Docetaxel + C) x 6 + H (qw x 18 weeks) → H (qw x 34 weeks)

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

Study Contact:
Linnea Chap, Chair, Tel: 310-206-6144
Jonsson Comprehensive Cancer Center, UCLA

SOURCE: NCI Physician Data Query, September 2003.

In addition, everyone wants to know how the carboplatin/trastuzumab combination would have fared in metastatic disease, so we're going to do a pilot study in which patients receive carboplatin/trastuzumab for at least two cycles, and a taxane will be added in the nonresponders. Dr Mark Pegram published the first cisplatin/trastuzumab trial in 1998, which had a 24 percent response rate for second- and third-line therapy in metastatic breast cancer. I suspect our trial will show that the benefit of adding a taxane will offset any additional toxicity.

Duration of maintenance trastuzumab

I have a patient who received a three-drug combination including trastuzumab in 1998, just after it was approved. She took a break from therapy while she traveled, and the only therapy she received after the break was trastuzumab. It has been five years now, and while she probably doesn't need the trastuzumab, I can't convince her to stop it.

In our trial, we had two complete responders who took trastuzumab for a year and then stopped because they were tired of coming in for office visits. One took no additional therapy and the other was ER-positive and went on tamoxifen. Both patients relapsed four to six months later.

These are small numbers to use in deciding whether to continue trastuzumab indefinitely, but it is enough so that I don't feel bad keeping this one patient on therapy. When patients like this relapse, it's often difficult to achieve another response, so I favor continuing therapy.

Trastuzumab alone or in combination with chemotherapy in HER2-positive metastatic disease

When I see patients with newly relapsed metastatic disease, I use a score sheet to evaluate ER status, HER2 status, time to relapse, sites of disease and symptomatology. At the bottom of the score sheet, but not to be forgotten, are the patient's comorbid conditions. While we've had some good luck with single-agent trastuzumab in a few patients, I generally give trastuzumab with chemotherapy unless I'm sufficiently concerned about a patient's underlying condition such that I am fearful of giving them chemotherapy.

In patients in whom I gave single-agent trastuzumab, trying to spare them chemotherapy, the responses lacked durability. I've had more success using chemotherapy with trastuzumab, and then stopping the chemotherapy after four to six months. Generally, if a patient relapses with visceral disease, I give three to six months of a three-drug regimen, like paclitaxel/carboplatin/trastuzumab, and the odds of a profound response are pretty high. I then use maintenance trastuzumab.

Impact of ER status on treatment of HER2-positive and HER2-negative metastatic disease

In our study we looked at the data to determine whether a tumor's ER status influenced the benefit derived. While the numbers in this trial are small, when we compare this data to data from other breast cancer trials, it is clear that many patients with ER-positive disease respond just as well to the trastuzumab as those with ER-negative disease, but it would be nice to know if it is worthwhile to add a hormone.

In patients with HER2-negative, ER-positive disease, I usually try to use as much hormonal therapy as possible before going to chemotherapy, unless they are rapidly progressing. However in patients with HER2-positive, ER-positive disease, I tend to give them hormonal therapy after they complete chemotherapy.

Paclitaxel/carboplatin/doxorubicin in the treatment of metastatic breast cancer

In HER2-negative patients, we've tried the combination of paclitaxel/carboplatin/doxorubicin, replacing cyclophosphamide with carboplatin to take advantage of carboplatin's toxicity profile. With that combination, our response rate was

approximately 55 percent, but there was a lot of toxicity. We compared our data with what Dr David Loesch reported for paclitaxel/carboplatin weekly and Dr Perez's data for paclitaxel/carboplatin given every three weeks, and we learned that doxorubicin just added toxicity.

Non-Anthracycline-Containing Regimen for Metastatic Disease

Therapy for first-line advanced and metastatic breast cancer is entering a new era with the use of combination regimens, including paclitaxel plus carboplatin. The 62 percent overall response rate obtained in this community-based, multicenter study introducing a new regimen of weekly paclitaxel and carboplatin is among the highest rates obtained in trials conducted in similar settings with current regimens for the treatment of advanced breast cancer. The toxicity profile of the combined paclitaxel and carboplatin regimen demonstrates that the schedule used in this study is less myelosuppressive than an every-three-weeks schedule and lacks the cardiotoxicity of doxorubicin regimens commonly used today.

EXCERPT FROM: Loesch D et al. **Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer.** *J Clin Oncol* 2002;20:3857-64. **Abstract**

Trastuzumab in first-line treatment of HER2-positive metastatic breast cancer

Some physicians do not include trastuzumab in first-line therapy for HER2-positive metastatic disease. I consistently hear colleagues talk about "saving" a drug or regimen. That may have been a reasonable strategy 10 or 15 years ago, but with the emergence of multiple taxanes, vincas and the topoisomerase inhibitors, I don't see a reason to save anything. It makes more sense to obtain your best response and then give the patient a break.

I tend to give at least two trastuzumab-containing regimens before bailing out. Just as in endocrine therapy, we assume that if the patient responded to one therapy, she is likely to respond to another. We know that the oncogene present in HER2-positive patients doesn't go away from primary disease to metastases, so it's more likely that they're acquiring resistance to the chemotherapy than to the trastuzumab. If the patient does progress on the second trastuzumab combination, sometimes I'll have the pathology checked, but often I'll move on to a different regimen and possibly even consider reintroducing an anthracycline.

HER2 assessment: Correlation between FISH and IHC results

Clearly, IHC is not perfect. I look at this very clinically. If the IHC result is zero, I don't worry about it, and if it is 3+, I treat it as positive because I know there is a 90 percent concordance with FISH-positivity. It's the IHC 1+ and 2+ cases that I look at carefully.

I'm very quick to order a FISH test on an IHC 1+ or 2+ tumor that I'm unsure about. The concordance rates with FISH are approximately 40 percent for IHC 2+ tumors, and 10 or 15 percent for IHC 1+ tumors. I have had several patients

whose tumor was 1+ by IHC and FISH-positive. Twenty percent of women with HER2-overexpressing breast cancer fall into the IHC 0 or 1+ category. FISH may cost $200, but if it were my wife or sister, I'd certainly tell her to have the FISH test done.

Capecitabine in patients with HER2-positive tumors and brain metastases

The brain is a common site for metastases. A European abstract presented at ASCO reported how well patients with brain metastasis did overall and encouraged physicians to be aggressive in this group of patients. We need to look at agents that cross the blood-brain barrier for those patients, such as capecitabine.

One of my partners switched a patient from docetaxel with trastuzumab to capecitabine, because she developed a brain metastasis, and she had a great response. As patients live longer, we're going to see more metastases to the brain, and we need to learn more about treating those patients.

Sequential versus combination chemotherapy in the treatment of metastatic cancer

The question of whether sequential or combination therapy is superior in metastatic cancer is still unanswered. Many interpreted ECOG-1193 as being negative for the combination approach, but I don't totally agree. The combination was superior in response rates and time to progression, and it's difficult to show a survival advantage in a crossover trial. Community oncologists want a dramatic response for their patients.

We find when we put out a single-agent Phase II trial in our network, accrual occurs slowly, but if we design a trial with an exciting combination, accrual moves quickly. You can argue about survival curves, but they're all going to meet someday, and the quality of life is important. That's what I always tell my patients, but every patient we see in the clinic is different.

Fulvestrant in the treatment of metastatic breast cancer

We've used fulvestrant in the metastatic setting for a number of different scenarios, including patients who have progressed on aromatase inhibitors, those who request it for economic reasons, and in patients who don't like dealing with pills — they come in once a month for their bisphosphonate and their fulvestrant injection.

We have observed and heard from others that sometimes the best response with this agent is two or three months down the road. We have not had any problems with side effects or toxicities with fulvestrant. Pain at the injection site is perhaps the only issue, and I believe it is because we have an older population of women who may not have the body habitus to receive the injection without difficulty.

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

	XT Trial: Comparing docetaxel monotherapy and combination capecitabine/docetaxel		Intergroup Trial E1193: Comparing doxorubicin, paclitaxel and combination doxorubicin/paclitaxel		
Treatment	Docetaxel	Capecitabine/ docetaxel	Doxorubicin	Paclitaxel	Doxorubicin/ paclitaxel
Objective response	30%	42%	36% (20% response to crossover)	34% (22% response to crossover)	47%
Median survival	11.5 months	14.5 months	19.1 months	22.5 months	22.4 months

DERIVED FROM: O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23. **Abstract**

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

Progress in the treatment of breast cancer

I'm encouraged by the progress we are making in breast cancer. I can remember when the trastuzumab pivotal trials were under way, and the endpoint was time to progression because we didn't expect to see a survival advantage. But, lo and behold, we observed a survival difference. Then we looked for a time to progression endpoint for capecitabine/docetaxel, because there was no way we could show a survival difference. And, sure enough, this combination demonstrated a survival difference.

While we get a little confused about combination versus sequential therapy and how aggressive to be in the adjuvant setting, the bottom line is that things are really going very well. We have many patients living a long time with metastatic disease, and it's encouraging that it is taking a while to see the relapses in some of these adjuvant trials. We want to see the data, but, on the other hand, it's nice that three, four or five years later we still don't have enough events to make a call.

Clinical use of adjuvant taxanes

A commonly asked question is: Should every patient receive a taxane in the adjuvant setting? First we need to decide who should still receive CMF. Most of us don't administer CMF as Bonadonna and the Italians did; we give a watered-down version.

Many oncologists have switched to utilizing AC and now they are looking at incorporating a taxane — TAC, AC followed by T or the dose-dense approach. I believe that the vast majority of patients whom you want to treat aggressively should receive a taxane. In my patients at low risk, I still use AC, but in my patients at either moderate or high risk, I use a taxane combination.

ATAC: 47-month update and the impact on clinical practice

When the ATAC data were first reported and the ASCO committee issued their Technology Assessment recommendation that we stay with tamoxifen, there was a great deal of backlash from physicians who felt like they didn't want ASCO telling them what to do with that particular issue and that every patient was an individual.

I personally have fallen on the side of looking for an excuse to give an aromatase inhibitor in those patients. I've seen my own numbers go up from when I was probably using 90 percent tamoxifen, to gradually work down to where I'm probably giving one in three tamoxifen and two out of three anastrozole. I was also impressed with the data on bisphosphonates to prevent bone loss. I am quick to use a bisphosphonate or consult an endocrinologist.

Select publications

Publications discussed by Dr Burris

Chlebowski RT et al. **American Society of Clinical Oncology technology assessment of pharmacologic interventions for breast cancer risk reduction including tamoxifen, raloxifene, and aromatase inhibition.** *J Clin Oncol* 2002;20(15):3328-43. **Abstract**

Loesch D et al. **Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer.** *J Clin Oncol* 2002;20(18):3857-64. **Abstract**

Pegram MD et al. **Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment.** *J Clin Oncol* 1998;16(8):2659-71. **Abstract**

Perez EA et al. **A phase II study of paclitaxel plus carboplatin as first-line chemotherapy for women with metastatic breast carcinoma.** *Cancer* 2001;88(1):124-31. **Abstract**

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

Rowland KM et al. **NCCTG 98-32-52: Randomized phase II trial of weekly versus every 3-week administration of paclitaxel, carboplatin and trastuzumab in women with HER2 positive metastatic breast cancer (MBC).** *Proc ASCO* 2003:**Abstract 31.**

Siena S et al. **Multicenter phase II study of temozolomide therapy for brain metastasis in patients with malignant melanoma, breast cancer, and non-small cell lung cancer.** *Proc ASCO* 2003:**Abstract 407.**

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**

Theodoulou M et al. [427] **Cardiac safety and efficacy of TLC D99 (D, Myocet™) and Herceptin (H) in advanced breast cancer (ABC).** *Breast Cancer Res Treat* 2002:**Abstract 427.**

Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for women with hormone receptor-positive breast cancer: Status report 2002.** *J Clin Oncol* 2002;20(15):3317-27. **Abstract**

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

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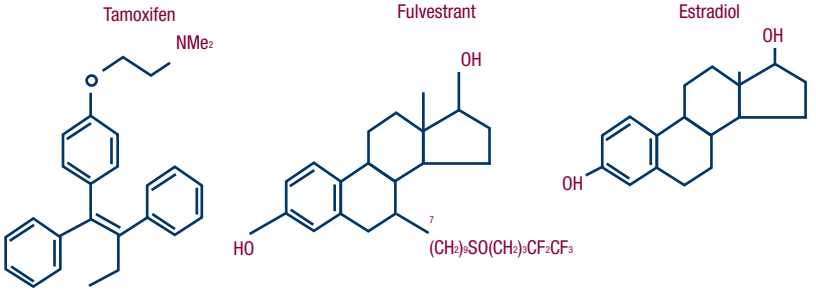
Effects of fulvestrant on estrogen receptor biology

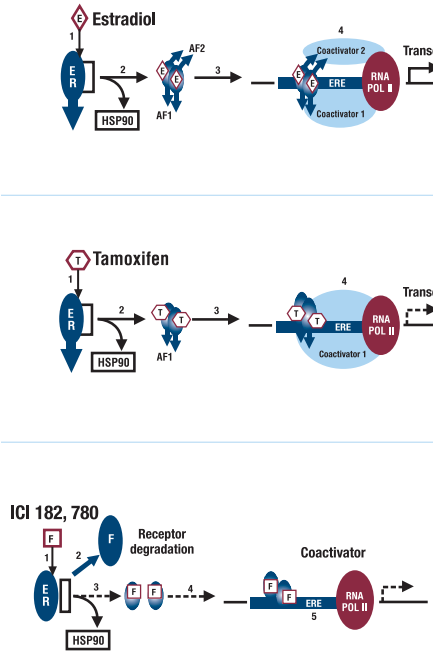
The estrogen receptor (ER) is a transcription factor that turns on and off certain genes important for regulating tumor cell growth and survival. Tamoxifen acts by binding this ER, resulting in partial stimulation and partial blockade of the receptor, depending on the context. This partial agonist/antagonist effect causes some of the side effects of tamoxifen, such as endometrial growth, and may also limit the full therapeutic application of interacting with the receptor.

Fulvestrant is in a different class of molecules than tamoxifen. While tamoxifen is a nonsteroidal molecule, fulvestrant is a steroidal molecule and an analogue of estradiol. This agent does not appear to have any stimulatory effect — it completely inhibits ER action.



In human breast cancer cells in the laboratory, fulvestrant decreases the level of ER inside the tumor cell by 80 percent to 90 percent — and many times below the level of detectability. Unlike tamoxifen, in laboratory models, fulvestrant shows no uterine stimulatory effect, which gives us promise that we won't have the endometrial cancer problem. In addition, it inhibits the growth of human

breast cancer in animal models more completely than tamoxifen or estrogen withdrawal, which is equivalent to ovarian ablation. Fulvestrant maximally shuts down a known growth stimulatory pathway in human breast cancer, compared to tamoxifen, which only shuts it down partially.



Mode of action of estradiol (E)

1. E binds with high affinity to estrogen receptor (ER) and dissociates heat shock protein 90 (HSP90).
2. E-ER complex homodimerizes and localizes preferentially in the cell nucleus.
3. E-ER homodimer binds DNA sequence at palindromic estrogen response element (ERE) in the promotor region of estrogen-sensitive genes.
4. Activation of transcription by ER involves interaction of the two transcription activation functions or ER, AF1 and AF2, with transcriptional coactivators to stimulate the activity of RNA polymerase II (RNA POL II).

Mode of action of tamoxifen (T)

1. T binds to ER with low affinity compared with E and dissociates HSP90.
2. T-ER complex homodimerizes and translocates to the cell nucleus, and AF1 (but not AF2) is active.
3. T-ER dimer binds DNA to sequence at palindromic ERE in the promotor region of estrogen-sensitive genes.
4. Transcription of E-responsive gene(s) is attenuated because AF2 is inactive, and coactivator binding is attenuated by the T-ER complex; partial agonist activity results from AF1, which remains active in the T-ER complex.

Mode of action of ICI 182,780 (F)

1. F binds to ER with affinity similar to that of E and dissociates HSP90.
2. Rapid degradation is triggered by F.
3. Reduced rate of dimerization and nuclear localization of F-ER complex.
4. Reduced binding of F-ER to ERE.

REPRODUCED WITH PERMISSION: Howell et al. **ICI 182,780 (Faslodex™) Development of a novel, "pure" antiestrogen.** *Cancer* 2000;89:817-25.

Tolerability data on fulvestrant

In the Phase II trial of fulvestrant and in the trial of women with uterine fibroids, we didn't see any stimulatory effects on the uterus as we see with tamoxifen. In fact, when given simultaneously with tamoxifen or estrogen, fulvestrant blocks the uterine stimulation caused by these agents. Fulvestrant also doesn't appear to cross the blood-brain barrier as tamoxifen does.

Randomized trials of fulvestrant versus anastrozole

The trials of fulvestrant versus anastrozole in patients progressing on tamoxifen were large, well-executed studies — in contrast to other hormone therapy trials done as recently as five years ago. The fulvestrant versus anastrozole trials

demonstrated that fulvestrant is a very safe cancer therapeutic agent. There were virtually no toxicities outside of background noise.

In terms of efficacy, these trials demonstrate that fulvestrant is at least equivalent to a third-generation aromatase inhibitor, currently our best endocrine agents for postmenopausal patients. There were some hints that fulvestrant might be a little bit better than anastrozole in terms of an increased duration of response, but, overall, I believe they're equal.

In the European trial, the time to treatment failure in the two arms was close to identical. In the American trial, the overall objective response and clinical benefit rates were slightly higher for fulvestrant, though not statistically significant.

The main difference between fulvestrant and anastrozole in the American trial was the increased duration of response in the fulvestrant arm. Not only was there a statistically significant improvement from 10 months to 19 months, but this time difference is clinically and humanly worthwhile in the metastatic setting. It tells us that this agent might give us a bit of a boost in the adjuvant setting.

Efficacy of Fulvestrant Compared to Anastrozole in Postmenopausal Women with Advanced Breast Cancer Progressing on Prior Endocrine Therapy

	North American Trial (0021)			European Trial (0020)		
	Fulvestrant (n=206)	Anastrozole (n=194)		Fulvestrant (n=222)	Anastrozole (n=229)	
Disease progression	83.5%	86.1%	HR=0.92; 95.14% CI=0.74 to 1.14; *P*=0.43	82.4%	83.4%	HR=0.98; 95.14% CI=0.80 to 1.21; *P*=0.8
Median time to progression	5.4 months	3.4 months		5.5 months	5.1 months	
Treatment failures	79.6%	84%	HR=0.96; 95% CI=0.77 to 1.19; *P*=0.69	84.7%	85.6%	HR=0.97; 95% CI= 0.80 to 1.19; *P*=0.81
Objective response	17.5%	17.5%	*P*=NS	20.7%	15.7%	*P*=NS
Median duration of response	19.0 months	10.8 months		15.0 months	14.5 months	
Deaths	35.4%	33.5%		36.9%	36.2%	

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

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20:3396-403. **Abstract**

Trials 20 and 21: Study Design Differences

	Trial 20 (European)	Trial 21 (North America)
Receptor unknown	Allowed	Not allowed
Double-blind	No	Yes
Multi-institutional	Europe, Australia, South America	North America
Multiple dose levels	No	Yes, initially
Dosing	Single injection	Divided injections
Evaluations - fulvestrant	Monthly	Every three months
Evaluations - anastrozole	Every three months	Every three months

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Side effects of fulvestrant versus anastrozole

One of the adverse events evaluated in these trials was thromboembolic events. From our experience with the aromatase inhibitors, we would not expect to see an increase in thromboembolic events with anastrozole, and in both trials of anastrozole versus fulvestrant, the number of thromboembolic events in the two arms was virtually identical. We did not see evidence in these trials that fulvestrant causes more thrombosis. Because this agent is a steroid molecule with many similarities to estrogen, this was somewhat of a concern, but I was glad to see no evidence that it is thrombogenic.

Trial of fulvestrant versus tamoxifen as first-line therapy

Much to our surprise, this trial did not demonstrate that fulvestrant was superior to tamoxifen in the first-line setting. Extrapolating what we know from previous trials of fulvestrant versus anastrozole, and of anastrozole versus tamoxifen, we predicted that fulvestrant would be better than tamoxifen. However, in the study we just didn't see it.

Some have suggested that the dose of fulvestrant was inadequate. While I believe this should be explored, I'm not entirely convinced it is the reason. Another possibility relates to the fact that most patients in the second-line study had been treated with tamoxifen or were coming straight off of tamoxifen. This may have somehow altered the phenotype, perhaps causing fulvestrant to work better in the second-line trial, as opposed to treatment-naïve tumors or those that have not been exposed to tamoxifen recently. After reviewing the data, the reason the first-line trial didn't demonstrate fulvestrant to be superior to tamoxifen is still not clear.

Clinical experience with fulvestrant

In my clinical experience, fulvestrant is very easy to administer and extremely well-tolerated. My patients have not had any problems with the intramuscular injection. One might assume that a pill is more convenient therapy for a patient

than an injection, but that is not necessarily so. Convenience is an individual choice. Some patients would rather receive a shot once a month than take a pill every day.

Not only has fulvestrant been exceptionally well-tolerated, I've seen responses in heavily pretreated patients. Fulvestrant also works after multiple endocrine failures, including on tamoxifen and the aromatase inhibitors, even in a third- or fourth-line setting. We now have a very well-tolerated endocrine agent to add to our armamentarium in the metastatic setting.

Interactions between growth factor pathways and the estrogen receptor

Possible interaction between polypeptide growth factor pathways and the estrogen receptor might present opportunities for therapy. Estrogen receptor biology has evolved over the last several years in terms of interaction between the estrogen receptor and coactivators and corepressors. These interactions may determine the final output of the estrogen receptor.

In addition, the estrogen receptor may be important in other ways beyond the classical binding to DNA and turning on estrogen-responsive genes through estrogen response elements. Estrogen receptor also binds to other types of transcription factors and helps regulate genes. There's also a growing awareness that estrogen receptor exists in the cell membrane and may be able to activate other growth factor pathways directly by interacting with the receptor via intermediate signaling molecules.

If we can block some of this activation — either the estrogen receptor activating other growth factor pathways or growth factor pathways activating the estrogen receptor — the clinical implication is that combined therapies may be better than monotherapy.

The therapies optimal for combination are those that block tyrosine kinase activity, such as gefitinib and trastuzumab. A fairly striking delay in tumor growth has been seen when gefitinib has been combined with tamoxifen or estrogen withdrawal in HER2-nonoverexpressing tumors. It would be interesting to see combination trials with the aromatase inhibitors and with fulvestrant.

Proposed NSABP trial of fulvestrant, anastrozole and gefitinib

I proposed a trial to the NSABP that would look at a combination of three agents — fulvestrant, anastrozole and gefitinib. The trial will utilize fulvestrant to downregulate the estrogen receptor. Anastrozole will then downregulate the ligand in the system, and gefitinib will decrease any crosstalk that may activate the estrogen receptor through other pathways.

The proposed NSABP trial will be a one-armed, Phase II study in 60 patients. The patients will be postmenopausal women with hormone-responsive tumors greater than three centimeters in size. The three drugs will be given in combination in a neoadjuvant fashion for four months. The therapeutic endpoint

will be tumor regression and pathologic findings at surgery.

We will also evaluate molecular endpoints. We plan to do core needle biopsies before the patient goes on study and again at two weeks, and we will obtain tissue at the time of surgery. We will study molecular changes within the tissue, specifically ER levels, AKT and MAP kinase levels and phosphorylation status.

Side effects and toxicity shouldn't be a problem. The only problem I can foresee is a possible skin rash from gefitinib, but we reduced the dose to the 250-mg level. Significant skin rash was reported in the breast cancer trial presented last year in San Antonio, but the dose used in that study was 500 milligrams.

There may be some skepticism about combining hormonal therapy after the disappointing results from the combination arm of the ATAC trial. However, the meta-analysis of three randomized studies evaluating tamoxifen plus an LHRH agonist versus an LHRH agonist alone in premenopausal patients shows not only an advantage in response rate and time-to-treatment failure, but also a survival advantage for combination hormonal therapies.

Hormone sensitivity of HER2-positive, ER-positive tumors

A good deal of laboratory evidence shows that HER2-positive, ER-positive tumors are less responsive to tamoxifen than HER2-negative, ER-positive tumors. This issue becomes less clear in the clinic. When both the ER assay and the HER2 assay are done correctly, I believe the proportion of patients with HER2-positive, ER-positive tumors is actually quite low — in the range of five percent to 10 percent of all patients. With such a small subset, it is difficult to perform adequately powered studies to provide a clear answer regarding hormone sensitivity.

Another confounding element is that the ER content in HER2-positive, ER-positive tumors, is about one-half to one-third of the ER content in the HER2-negative tumors. Some of this "resistance" may therefore be a function of lower or absent ER. Clinically it is not clear to me whether HER2 overexpression causes tamoxifen resistance. The balance of emerging data does point to a possible modest resistance.

ErbB Status and Response to Neoadjuvant Endocrine Therapy in ER-Positive Tumors

Marker status	Letrozole		Tamoxifen		*P* value
	No. of responders/total	%	No. of responders/total	%	
ErbB-1/2 positive	15/17	88	4/19	21	0.0004
ErbB-1/2 negative	55/101	54	42/100	42	0.0780

DERIVED FROM: 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**

Defining ER-positivity

European studies have shown that approximately 20 percent of ER assays are false negatives when compared to a reference lab. Estrogen receptor testing is not standardized in the United States or Europe, and this leads to a great deal of suboptimal treatment and misunderstanding of breast cancer biology. For years, we thought that some ER-negative patients responded to hormonal therapy; however, I believe this was merely a result of poor assay methodology.

Part of the problem with these assays is technical, and part is in the interpretation. On the technical side, pathologists are just not used to performing immunohistochemistry. The technique is not standardized. Many pathologists come up with their own methods and only do a few cases a week. This lack of standardization and experience causes technical issues and false-negative results. Interpretation of assay results is a problem in terms of both staining and cutoff values. Many laboratories have established a cutoff that is too high and have labeled tumors with ER as being ER-negative.

We have shown in multiple studies in the advanced-disease setting, the adjuvant setting and the DCIS setting that tumors with more than one percent of cells staining positive are hormone responsive, while tumors with less than one percent of cells staining don't appear to benefit from endocrine therapy.

I believe that medical oncologists often just assume the pathologist is correct. When we started closely reviewing results in our tumor board, it was obvious that there were big problems. Clinicians can insist on having tumors processed in a central laboratory that has a high volume that uses a clinically validated methodology.

Sequencing chemotherapy in the metastatic setting

In terms of sequencing chemotherapy in the metastatic setting, I generally start with an anthracycline in patients who did not receive them in the adjuvant setting. Otherwise, I usually begin with a taxane. Capecitabine is my next chemotherapy choice after anthracyclines and taxanes.

Especially in elderly or frail patients, I always bring capecitabine into the equation. Not only is it oral, but it is also associated with a good quality of life if the dose is somewhat attenuated and we monitor for hand-foot syndrome.

I usually start capecitabine as a single agent at 2,000 mg/m^2 for three to five cycles and then a rest. I do not routinely use it with docetaxel, though I recognize that a number of people do, and that there are some good reasons to do so in certain conditions.

Select publications

Publications discussed by Dr Elledge

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Mauriac L et al. **Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: Combined results from two multicentre trials.** *Eur J Cancer* 2003;39(9):1228-33. **Abstract**

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Sommer A et al. **Studies on the development of resistance to the pure antiestrogen Faslodex in three human breast cancer cell lines.** *J Steroid Biochem Mol Biol* 2003;85(1):33-47. **Abstract**

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Vergote I et al. **Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy.** *Breast Cancer Res Treat* 2003;79(2):207-11. **Abstract**

Wardley AM. **Fulvestrant: A review of its development, pre-clinical and clinical data.** *Int J Clin Pract* 2002;56(4):305-9. **Abstract**

Watanabe T et al. **Fulvestrant provides clinical benefit to postmenopausal women with metastatic breast cancer who have relapsed on prior antiestrogen therapy: A Japanese study.** *Proc ASCO* 2003;**Abstract 274.**

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Terminology: Hormone replacement therapy versus menopausal hormone therapy

The FDA and the NIH have removed hormone replacement therapy from their lexicon. The preferred term is menopausal hormone therapy or hormone therapy. Menopausal hormone therapy is probably more descriptive, because hormone therapy could include oral contraceptives.

Women's Health Initiative (WHI) trial

The Women's Health Initiative trial randomized 16,608 healthy postmenopausal women to conjugated equine estrogens plus medroxyprogesterone acetate (Prempro™) or placebo.

The Women's Health Initiative (WHI) Randomized Controlled Trial: Risks and Benefits of Estrogen plus Progestin in Healthy Postmenopausal Women **Closed Protocol**

Protocol ID: WHI
Actual Accrual: 16,608

Eligibility: Postmenopausal women 50 to 79 years of age with an intact uterus

ARM 1: Conjugated equine estrogens + medroxyprogesterone acetate
ARM 2: Placebo

SOURCE: Rossouw JE et al; Writing Group for the Women's Health Initiative Investigators. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial.** *JAMA* 2002;288(3):321-33.

Overall results

The estrogen/progestin part of the WHI trial was prematurely stopped after 5.2 years of follow-up because the global index, which involved life-threatening conditions, suggested that there was risk associated with estrogen plus

progestin. The adverse effects included a 29 percent increase in coronary heart disease and a 26 percent increase in breast cancer. The incidence of stroke and pulmonary embolus was also substantially increased. On the favorable side, colorectal cancer and hip fractures were significantly decreased by menopausal hormone therapy. However overall, there were still 19 more adverse events per 10,000 women per year of use of estrogen/progestin therapy.

The Women's Health Initiative (WHI) Trial Results: Number of Patients with Clinical Outcomes by Randomization Arm

Outcomes	Estrogen + Progestin (n=8,506)	Placebo (n=8,102)	Hazard Ratio
Coronary heart disease	164	122	1.29
Stroke	127	85	1.41
Deep vein thrombosis	115	52	2.07
Pulmonary embolism	70	31	2.13
Invasive breast cancer	166	124	1.26
Colorectal cancer	45	67	0.63
Hip fractures	44	62	0.66

SOURCE: Rossouw JE et al; Writing Group for the Women's Health Initiative Investigators. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial.** *JAMA* 2002;288(3):321-33. **Abstract**

Influence of menopausal hormone therapy on breast cancer risk

After a mean follow-up of 5.6 years, 349 cases of invasive breast cancer were detected — 150 in the placebo group and 199 in the estrogen plus progestin group.

In contrast to observational studies suggesting that the tumors in the estrogen plus progestin group would be low grade and easy to treat, we found these tumors to have identical histology and grade, but a more advanced stage. The tumors in the estrogen plus progestin group were larger (mean size of 1.7 versus 1.5 cm, $P = 0.04$) and more likely to have positive nodes (26 percent versus 16 percent, $P = 0.03$), which were statistically significant findings.

The cancers that developed in the estrogen plus progestin group included ER-positive and ER-negative cancers. The number of ER-positive and ER-negative cancers increased by the same amount with hormone therapy use. This indicates that estrogen plus progestin can stimulate breast cancer growth.

Influence of menopausal hormone therapy on mammograms

The mammogram results were probably the most surprising finding. After one year of estrogen and progestin use, there was a four percent absolute increase in the frequency of abnormal mammograms. A woman would have a 1-in-25 chance of having an otherwise avoidable abnormal mammogram by taking estrogen and progestin for just one year.

The Women's Health Initiative (WHI) Trial: Influence of Estrogen plus Progestin on Breast Cancer

	Estrogen + Progestin (n=8,506)	Placebo (n=8,102)	*P* value
Number of invasive breast cancer cases*	199	150	—
Mean tumor size (cm)	1.7	1.5	0.04
Positive lymph nodes	26%	16%	0.03
Regional/metastatic disease	25%	16%	0.04

*Hazard ratio=1.24

SOURCE: Chlebowski RT et al; WHI Investigators. **Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial.** *JAMA* 2003;289(24):3243-53. **Abstract**

The difference persisted throughout the study, and at the end, the women in the estrogen plus progestin group had a 30 percent chance of having an abnormal mammogram compared to about a 20 percent chance for the women in the placebo group. Previously, it was believed that there were no consequences from one or two years of estrogen plus progestin use. Now, women must consider the 1-in-25 or 1-in-10 chance of having an abnormal mammogram.

The women in the estrogen plus progestin group had more advanced-stage cancers diagnosed, even though they were the same grade, because the abnormal mammograms hindered the diagnosis. For the first three years there were fewer cancers diagnosed in the estrogen plus progestin group than the placebo group, and it looked like the breast cancer incidence decreased. In actuality, it was just harder to find the cancers.

The Women's Health Initiative (WHI) Trial: Percent of Women with Abnormal Mammograms

	Estrogen + Progestin	Placebo	*P* Value
Year 1	9.4%	5.4%	<0.001
Cumulative	31.5%	21.2%	<0.001

SOURCE: Chlebowski RT et al; WHI Investigators. **Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial.** *JAMA* 2003;289(24):3243-53. **Abstract**

Applicability of results to younger women

Over 5,000 women in the WHI trial were between the ages of 50 and 59, and about 2,000 had moderate to severe vasomotor symptoms. In the group of women 50 to 59 years of age, the increase in mammogram abnormalities was the same as for the overall group. The WHI trial raises questions about the short-term use of menopausal hormone therapy, because it identifies an important side effect.

If a woman has moderate to mild estrogen-deficiency symptoms, she must now decide whether 80-90 percent suppression of those symptoms for a year or two is worth a 1-in-25 or 1-in-10 chance of having an abnormal mammogram. This is a new thought process for women considering menopausal hormone therapy.

For the woman with severe disabling symptoms, the chance of having an abnormal mammogram, which doesn't necessarily mean she's going to have breast cancer, is probably going to be a small consideration.

The actual chronic-disease risk associated with one, two or three years of therapy for a woman 49 or 50 years of age is going to be a very small number. The breast cancer risk for the overall population involved eight additional breast cancers per year for every 10,000 women receiving menopausal hormone therapy.

There were 19 avoidable life-threatening conditions (including coronary heart disease and stroke) per 10,000 women per year of estrogen plus progestin use. For women meeting the study criteria, one in a hundred would have an otherwise avoidable life-threatening event after five years of estrogen plus progestin use. The absolute risk would be lower for 50-year-old women, but that is a statement about the population, not the individual patient.

Influence of menopausal hormone therapy on dementia

There was a 180-degree turnaround associated with the ancillary study results on dementia (see below). The prestudy assumption was that we would see a substantial reduction in dementia. In actuality, the subset of women 65 years of age and older had over a doubling of dementia cases — from 21 to 40 cases — after five years of therapy.

We speculate that the arteriovascular effects, such as subclinical stroke, may have raised the threshold so that the natural course of dementia was evident sooner. The implication for women with breast cancer is that other agents that cause arteriovascular events, like chemotherapy or tamoxifen, may be associated with the same increase in dementia. This phenomenon has not been carefully studied with these other agents in the kind of detailed analysis that was done in the WHI trial.

The Women's Health Initiative (WHI) Trial: Influence of Estrogen plus Progestin on the Development of Probable Dementia

	Estrogen + Progestin (n=2,229)	Placebo (n=2,303)	Hazard Ratio
Number of probable dementia cases	40	21	—
Rate per 10,000 person-years	45	22	2.05

SOURCE: Shumaker SA et al; WHIMS Investigators. **Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial.** *JAMA* 2003;289(20):2651-62. **Abstract**

Selection of the estrogen and progestin

The WHI trial evaluated the estrogen and progestin type, dose and schedule used by 85 percent of postmenopausal women with a uterus until two years ago. They weren't natural estrogens and progestins, even though there are some natural estrogens in conjugated equine estrogens.

The Europeans use more estradiol and micronized progestin or natural progestin. Whether those are going to be safer, we don't know. The FDA made all combined estrogen and progestin products include the same black-box warning that it required for conjugated equine estrogens and medroxyprogesterone acetate.

Estrogen-alone arm in women with a prior hysterectomy

A separate WHI trial in just over 10,000 women with a prior hysterectomy is evaluating an estrogen-alone arm. The data safety monitoring board looks at that data twice a year. There is a little over six years of follow-up, and by design, the trial results will be reported at 8.5 years or in about two years. As of May 30, 2002, there was no excess in breast cancer risk.

For several reasons, we can't be sure that it's just the progestin causing the difference. First, women who have had a hysterectomy are substantially different from women who have a uterus, in terms of their medical history characteristics. Second, this trial is smaller, and it may take longer to generate an equivalent number of events. There are also biologic reasons to believe that we might see something different in terms of breast cancer.

Dr Norman Boyd in Toronto has shown that breast density — especially inherited breast density — is associated with an increased risk of breast cancer. However, we don't know whether a short-term change in breast density is associated with breast cancer risk.

It's intriguing that estrogen plus progestin substantially increases breast density, whereas estrogen alone increases it much less. That suggests there may be a difference. Based on the more recent epidemiological data, one would think there would be less breast cancer risk associated with estrogen alone, but we don't know.

Indications for menopausal hormone therapy

Menopausal hormone therapy is almost exclusively indicated for the amelioration of hot flashes and vaginal symptoms. The FDA recommends the use of the lowest possible dose and duration, although we don't have information about the safety of those lower-dose schedules.

The FDA will hold hearings on the osteoporosis indication for estrogen plus progestin combinations, which certainly are effective in reducing the risk of hip fractures. However, since there are alternatives available to reduce the risk of hip fractures, I'm not sure an estrogen plus progestin combination is safe enough for this indication.

Trends in menopausal hormone therapy use

The use of menopausal hormone therapy was increasing and then leveled off after the Heart and Estrogen/Progestin Replacement Study (HERS) reported no coronary heart disease benefits in women with existing heart disease. At that time, there were about six million women in the United States on an estrogen plus progestin combination.

After the WHI report, the use of menopausal hormone therapy went down significantly. Less than three million women are currently using some kind of combined estrogen plus progestin therapy. Most of the three million women who stopped taking an estrogen plus progestin combination did so because they decided to stop, rather than because their gynecologist told them to stop.

Over 80 percent of estrogen plus progestin use is short term in perimenopausal women. A number of women, maybe one-fifth, are still taking it for long-term chronic use. We'll see how those numbers change after this most recent WHI trial report.

A decision-making approach to menopausal hormone therapy

This situation appears analogous to the situation we commonly face in a woman with an ER-negative tumor measuring less than one centimeter, who is deciding whether to take chemotherapy for a very small absolute benefit. I routinely try to project five years into the future.

Will it be intolerable if she doesn't take the chemotherapy and the tumor recurs? If she couldn't tolerate that and would say, "I missed my chance," then she should take the chemotherapy. Alternatively, if she projects herself five years from now and says, "I took the chemotherapy and the tumor didn't recur — that was a bad decision," then maybe she shouldn't take the chemotherapy. So, I give patients those two future scenarios.

In a woman with mild or moderate menopausal symptoms, I would say, "You may reduce the symptoms by 80 percent to 90 percent with hormones, but you will have to deal with a 1-in-25 or 1-in-10 chance of an abnormal mammogram. If you don't want to deal with an abnormal mammogram, then don't start menopausal hormone therapy and see what happens after a few months of just watching." If the patient says, "I can deal with an abnormal mammogram," which almost certainly is not going to be related to breast cancer, she should consider taking the menopausal hormone therapy for a year or two.

Managing menopausal symptoms in patients with breast cancer

I question some of the treatments we are using in breast cancer patients with menopausal symptoms. For example, low-dose progestins are effective in reducing symptoms. Medroxyprogesterone acetate, interestingly, was found to be effective in women with resected breast cancer; however, this is the same agent used in the WHI trial. I would be very concerned about using progestins, especially since many are pointing a finger at the progestin in this estrogen and progestin mix.

The estradiol vaginal ring (Estring®) is a locally released product that treats vaginal symptoms and atrophy. A study in the *Journal of Clinical Endocrinology and Metabolism* demonstrated that the estradiol vaginal ring use for one year increased HDL cholesterol and decreased LDL cholesterol, the same as full-dose estrogen and progestins.

If there is adequate absorption to change the lipid profile, it's difficult to be completely sanguine about breast safety. In terms of how to treat the patient with breast cancer and with menopausal symptoms, we've identified a problem that will require more attention.

Select publications

Publications discussed by Dr Chlebowski

Bertelli G et al. **Intramuscular depot medroxyprogesterone versus oral megestrol for the control of postmenopausal hot flashes in breast cancer patients: A randomized study.** *Ann Oncol* 2002;13(6):883-8. **Abstract**

Beral V; Million Women Study Collaborators. **Breast cancer and hormone-replacement therapy in the Million Women Study.** *Lancet* 2003; 362:419-27. **Abstract**.

Boyd NF et al. **Heritability of mammographic density, a risk factor for breast cancer.** *N Engl J Med* 2002;347(12):886-94. **Abstract**

Chlebowski RT et al; WHI Investigators. **Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: The Women's Health Initiative Randomized Trial.** *JAMA* 2003;289(24):3243-53. **Abstract**

Lagro-Janssen T et al. **Breast cancer and hormone-replacement therapy: Up to general practice to pick up the pieces.** *Lancet* 2003; 362: 419-27.

Manson JE et al; Women's Health Initiative Investigators. **Estrogen plus progestin and the risk of coronary heart disease.** *N Engl J Med* 2003;349(6):523-34. **Abstract**

Naessen T et al. **Serum lipid profile improved by ultra-low doses of 17 beta-estradiol in elderly women.** *J Clin Endocrinol Metab* 2001;86(6):2757-62. **Abstract**

Rossouw JE et al; Writing Group for the Women's Health Initiative Investigators. **Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial.** *JAMA* 2002;288(3):321-33. **Abstract**

Shumaker SA et al; WHIMS Investigators. **Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's Health Initiative Memory Study: A randomized controlled trial.** *JAMA* 2003;289(20):2651-62. **Abstract**

Vicente Valero, MD

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Edited comments by Dr Valero

Case Discussion: "Meet the Professors" 2003 Miami Breast Cancer Conference
A 45-year-old premenopausal woman with a 2-cm, ER-positive, HER2-negative breast cancer and two positive nodes underwent a segmental mastectomy and axillary dissection.

- Patient was asymptomatic but requested additional workup
- CT scan revealed two hepatic lesions suggestive of metastases (5 cm and 9 mm)
- Liver biopsy was scheduled
- Patient desired an aggressive therapeutic approach

Managing patients presenting with *de novo* metastatic disease

This woman represents the minority — about five percent — of breast cancer patients treated in the United States. Our traditional approach is somewhat different in patients who develop metastatic breast cancer after adjuvant therapy than in those who are chemotherapy-naïve. We studied more than 1,800 chemotherapy-naïve patients whose metastatic disease was treated with an anthracycline/cyclophosphamide-containing regimen, and we published the results in a study in the *Journal of Clinical Oncology*. Approximately 20 percent of these patients achieved a complete remission, and about four percent were free of disease 10 years later. The question is: Can we cure a few patients with *de novo* metastatic breast cancer? I believe it's possible, and although the likelihood is very small, it has been confirmed by a French study.

In a premenopausal patient with minimal disease and two metastatic liver lesions who wants to be treated aggressively, I would offer systemic chemotherapy followed by hormonal therapy. There are absolutely no randomized studies to confirm that administering chemotherapy for six or eight cycles, or until maximum response, followed by hormonal therapy is better than hormonal therapy alone, but that is my current approach with such patients. In a situation in which potential cure, rather than palliation, is the desired outcome, I would introduce a taxane-containing regimen, such as TAC. It would also be

reasonable to use a sequential approach with FAC or AC followed by four cycles of docetaxel or paclitaxel.

Systemic treatment of isolated liver metastases after adjuvant therapy

If this patient had previously received adjuvant anthracycline therapy, I'd treat her with hormonal therapy. Patients with hormone-sensitive tumors — even those with visceral metastases — are appropriate candidates for hormonal therapy. This patient has one large metastasis, but she doesn't have diffuse infiltration of the liver. She's asymptomatic with normal liver enzymes and her disease is not bulky. In this scenario, hormonal therapy is an appropriate option.

Choice of hormonal therapy in patients remaining premenopausal after chemotherapy

This woman has a greater-than-50-percent chance of becoming postmenopausal after chemotherapy. She'll receive either four cycles of AC, which will be 2,400 mg of cyclophosphamide, or, at MD Anderson, she'd receive 2,000 mg because we use FAC 50.

If she's still premenopausal after receiving chemotherapy and we decide to use every tool available to give her a maximal chance of cure, data support the use of an LHRH agonist plus tamoxifen rather than an LHRH agonist alone.

A meta-analysis published in the *Journal of Clinical Oncology* demonstrated a survival advantage for the combination. There has been a great deal of controversy about the meta-analysis, because they didn't examine tamoxifen alone or sequential therapy with an LHRH agonist followed by tamoxifen. In Europe, an LHRH agonist and tamoxifen would be the standard of care. In the United States, it's more controversial.

There are limited data for the role of LHRH agonists with aromatase inhibitors in premenopausal women. I participate in a multicenter trial studying the combination of anastrozole and goserelin in premenopausal patients with hormone-sensitive tumors. The Spanish investigations are conducting a randomized study in the metastatic setting. While the preliminary data looks promising, I would utilize goserelin and tamoxifen or tamoxifen alone.

Choice of hormonal therapy in patients with chemotherapy-induced menopause

If this patient ceased menstruating and had a postmenopausal profile, I would consider using an aromatase inhibitor, based on the randomized studies documenting superior efficacy of the aromatase inhibitors compared to tamoxifen in the metastatic setting. In the only randomized study comparing anastrozole to letrozole in patients with metastatic disease, both agents were similar and both are acceptable options. Exemestane has been evaluated in patients with metastatic disease, but I'm not using it for first-line therapy.

Ongoing Trials of Adjuvant Endocrine Therapy in Premenopausal Patients

Study	Entry Criteria	Intervention	Target Accrual
ABCSG-AU12	Stage I, II	Tamoxifen + goserelin ± zoledronate Anastrozole + goserelin ± zoledronate	1,250
IBCSG-24-02	T1-T3, pN0-N2	Tamoxifen Ovarian suppression + tamoxifen Ovarian suppression + exemestane	3,000
IBCSG-25-02	T1-T3, pN0-N2	Triptorelin + tamoxifen Triptorelin + exemestane	1,845
IBCSG-26-02	T1-T3, pN0-N2	Ovarian suppression + tamoxifen or exemestane Ovarian suppression + chemotherapy + tamoxifen or exemestane after chemotherapy	1,750

DERIVED FROM: NCI Physician Data Query and ASCO Technology Assessment, September 2003: **Aromatase inhibitors as adjuvant therapy for women with hormone receptor positive breast cancer.**

The meta-analysis, combining the results of four randomized, comparative trials, included more than 500 patients with 355 deaths at the time of analysis. The maturity of three of the four trials (overall death rate, 70%) means that the conclusions of this meta-analysis are unlikely to alter with time. It represents the largest randomized cohort of premenopausal breast cancer patients treated with pharmacologic endocrine therapies for advanced disease. Using combined endocrine treatment to produce maximal estrogen blockade resulted in both a clinically relevant and statistically significant reduction in the risk of dying or progression/death (a 22% lower risk of dying and a 30% lower risk of progression/death) compared with the LHRH agonist-alone group.

EXCERPT FROM: Klijn JG et al. **Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: A meta-analysis of four randomized trials.** *J Clin Oncol* 2001;19:343-53. **Abstract**

Adjuvant study of LHRH agonist plus tamoxifen or anastrozole plus or minus zoledronic acid

At San Antonio, Dr Gnant's presentation of the Austrian study data — comparing an LHRH agonist with either tamoxifen or anastrozole with or without zoledronic acid — was very important in demonstrating that a bisphosphonate could ameliorate the decrease in bone density associated with hormonal therapy. Parenthetically, chemotherapy results in a sharp decline in the production of estrogen, also resulting in bone loss.

Clearly, we have to support our patients during treatment, just as we do with growth factors for neutropenic-related events or antiemetics for nausea. This is a very important issue for women with breast cancer. The issue is: How do we incorporate the data into clinical practice?

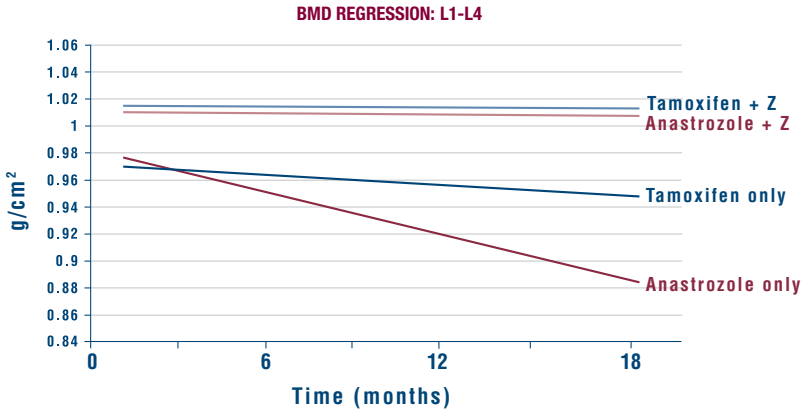
I assess bone density in postmenopausal patients receiving adjuvant anastrozole. These women are already in menopause, so we know the extent of their bone loss. The reduction in bone density from a chronic therapy, such as adjuvant anastrozole, is different than the acute bone loss from chemotherapy.

In a 60-year-old patient who has been in menopause for 10 years without significant bone loss, I'm not convinced anastrozole will produce a substantial decrease in bone density. On the other hand, in a patient who already has osteopenia or osteoporosis, anastrozole will likely exacerbate that.

You have to look at these patient populations differently. I assess bone density and, if it is normal, I repeat it one year later to determine whether or not to introduce a bisphosphonate; prophylactic zoledronic acid may not be necessary.

Positive findings have been published in the *New England Journal of Medicine* using intermittent zoledronic acid in patients with osteoporosis. The next step is to compare this approach to the conventional use of oral bisphosphonates in that setting. There are studies done in conjunction with the ATAC trial that will give us information about bone loss in patients on anastrozole versus tamoxifen.

Changes in bone mineral density caused by anastrozole or tamoxifen in combination with goserelin (± zoledronic acid) as adjuvant treatment for hormone receptor-positive, premenopausal breast cancer: Results of a randomized multicenter trial (ABCSG-12).



Z = zoledronic acid

SOURCE: Michael Gnant, Presentation 2002 San Antonio Breast Cancer Symposium

Bisphosphonates for the prevention of metastatic disease

The limited data from trials of oral bisphosphonates are controversial. Unfortunately, we don't have information using the more potent, intravenous bisphosphonates. Randomized studies with zoledronic acid are being initiated, but it will be a substantial period of time before we have data.

Zoledronic acid infusions given at intervals of up to one year produce effects on bone turnover and bone density as great as those achieved with daily oral dosing with bisphosphonates with proven efficacy against fractures, suggesting that an annual infusion of zoledronic acid might be an effective treatment for postmenopausal osteoporosis.

EXCERPT FROM: Reid IR et al. **Intravenous zoledronic acid in postmenopausal women with low bone mineral density.** *N Engl J Med* 2002;346:653-61. **Abstract**

Preclinical data support the use of bisphosphonates for the prevention of bone loss and bone metastases. Additionally, the landmark German study by Diel and colleagues suggests that bisphosphonates may also improve survival.

Increasingly, bisphosphonates are being utilized in women with early breast cancer because we're using aromatase inhibitors in that setting. How much secondary benefit these agents will provide for prevention of bone metastases will be of significant interest to physicians, and the best way to answer the question is with a large, prospective, randomized study.

The primary obstacle is that we aren't able to select which patients will have bone-only relapse. If we administer bisphosphonates to everybody without targeting the patients likely to benefit, it will be difficult to demonstrate a benefit. The absolute benefits we have seen through the years are small.

Similarly, the benefit seen with taxanes ranges from an absolute difference of one percent to eight percent. This means that the minority of our patients are benefiting from the therapy. Ideally, you'd like to look for this small percent of patients who benefit. We are trying to study this at MD Anderson, using gene profiling to try to prospectively confirm a specific gene profile to help decide which patients should and should not receive a specific therapy. This would allow us to spare toxicity and make therapies more effective by improving the tools to select patients for treatment. This is the direction the field is going, and it's very exciting.

Clinical advances with adjuvant taxanes

Several clinical trials have addressed the benefit of taxanes in the adjuvant setting. The results from CALGB trial 9344 have recently been published and demonstrate an improvement in disease-free and overall survival with the addition of paclitaxel to AC chemotherapy. BCIRG-001 — comparing TAC to FAC — also resulted in an improvement in disease-free survival. Most recently, CALGB-9741 documented an improvement in disease-free and overall survival with dose-dense AC and paclitaxel every two weeks with growth factor support.

Some physicians dismiss the findings from CALGB-9741, believing that there is minimal clinical application of the results. I disagree. Increasing the frequency of administration of AC and paclitaxel from every three weeks to every two weeks, with filgrastim support, clearly resulted in a substantial improvement in disease-free survival.

Interpretation of the results are controversial because CALGB-9741 was designed before the administration of weekly taxanes. Today studies such as the Intergroup study ECOG-N9831 — for patients with node-positive, HER2-positive disease — use weekly paclitaxel. So, there has been a shift in the administration schedule of paclitaxel, and some physicians question whether the improvement in disease-free survival was due to increasing the density of paclitaxel, of AC or of both. That issue remains unresolved, but a dose-dense approach is an acceptable option for women with node-positive early breast cancer.

Three-year Results of CALGB-9741, a Phase III Randomized Study Comparing Dose-Dense versus Conventional Scheduling and Sequential versus Combination Adjuvant Chemotherapy for Node-Positive Breast Cancer

Parameters	Dose-dense scheduling	Conventional scheduling	*P*-value
Disease-free survival	85%	81%	RR = 0.74 ($p = 0.010$
Overall survival	92%	90%	RR = 0.69 ($p = 0.013$)

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

Our results indicate interesting directions for further research. For example, sequential dose-dense, single-agent therapy could permit the rapid integration of new drugs into therapeutic regimens, including biologic agents. Shorter intertreatment intervals (i.e., beginning re-treatment as soon as the granulocyte count reaches 1,000/mL, rather than at a fixed time interval) might be investigated. Quality of life for patients receiving such treatments might also be beneficially explored. Furthermore, research into the biologic etiology of gompertzian growth and the molecular mechanisms of its perturbation could be used to hypothesize new, empirically verifiable dose-schedule manipulations.

EXCERPT FROM: 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**

Capecitabine/docetaxel (XT) in the treatment of breast cancer

Dr O'Shaughnessy's study of women with metastatic breast cancer demonstrated that the combination of capecitabine/docetaxel — compared to docetaxel alone — resulted in improved response rate, time to progression and survival.

The dosing and scheduling of the combination are controversial and remain to be defined. In the XT trial, the drugs were given simultaneously on day one. It's possible that upregulating TP with a taxane should be done before introducing capecitabine, and perhaps lower doses will result in the same benefit. If you want to utilize aggressive therapy, the combination in the XT trial was superior, and the quality of life wasn't impaired compared to the sequential approach.

We're evaluating capecitabine/docetaxel as neoadjuvant and adjuvant therapy. We're conducting a randomized study of weekly paclitaxel for 12 cycles followed by FAC for four versus docetaxel/capecitabine for four followed by FAC for four. If a patient with Stage II breast cancer (or greater) has an intact tumor, she will receive primary chemotherapy. If she has undergone locoregional therapy, she'll be randomized for adjuvant therapy.

The addition of capecitabine to docetaxel resulted in a 23 percent reduction in risk of death compared with docetaxel alone, with an increase in median survival of three months. The survival benefit with capecitabine/docetaxel combination therapy was seen early in the course of treatment and persisted throughout the study. The survival difference can clearly be attributed to the addition of capecitabine, because patients in the combination arm received a lower dose of docetaxel, and there was no excess death rate due to administration of full-dose docetaxel. A high proportion of patients in both treatment groups received poststudy chemotherapy, and the incidence of poststudy chemotherapy administration was balanced between the two treatment groups (70 percent versus 63 percent with combination therapy and single-agent docetaxel, respectively).

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

Select publications

Publications discussed by Dr Valero

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

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

Greenberg PA et al. **Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer.** *J Clin Oncol* 1996;14(8):2197-205. **Abstract**

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**

Klijn JG et al. **Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: A meta-analysis of four randomized trials.** *J Clin Oncol* 2001;19(2):343-53. **Abstract**

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**

Reid IR et al. **Intravenous zoledronic acid in postmenopausal women with low bone mineral density.** *N Engl J Med* 2002;346(9):653-61. **Abstract**

Post-test: Breast Cancer Update, Issue 7, 2003

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the Phase II, first-line trial of weekly paclitaxel/carboplatin/trastuzumab in metastatic breast cancer, what group of patients received the most benefit from the combination therapy?**
   a. IHC 3+ and FISH-positive patients
   b. IHC 1+ and 2+ patients
   c. HER2-negative patients

2. **In the Intergroup trial E-1193, comparing sequential versus combination therapy, combination therapy proved superior in:**
   a. Overall response rates
   b. Survival
   c. a and b

3. **Fulvestrant is a steroidal molecule and an analogue of estradiol.**
   a. True
   b. False

4. **Which of the following is a recognized side effect of fulvestrant?**
   a. Uterine stimulation
   b. Thromboembolic events
   c. Neutropenia
   d. None of the above

5. **In the North American trial comparing fulvestrant to anastrozole in patients with metastatic disease previously treated with tamoxifen, fulvestrant had a statistically significant improvement in duration of response compared to anastrozole.**
   a. True
   b. False

6. **Tumors with only one or two percent of cells staining positive for ER are hormone insensitive, and should be classified as ER-negative.**
   a. True
   b. False

7. **The Women's Health Initiative trial demonstrated that menopausal hormone therapy:**
   a. Increased the risk of breast cancer
   b. Increased the risk of coronary heart disease
   c. Increased the risk of having an abnormal mammogram
   d. All of the above
   e. None of the above

8. **A study published in the *Journal of Clinical Oncology* documented that approximately four percent of patients with metastatic disease and no previous chemotherapy are free of disease 10 years after treatment with an anthracycline- and cyclophosphamide-containing regimen.**
   a. True
   b. False

9. **The capecitabine/docetaxel combination is currently being evaluated in clinical trials in both the adjuvant and neoadjuvant settings.**
   a. True
   b. False

10. **CALGB-9741 demonstrated that increasing the frequency of administration of AC and paclitaxel from every three weeks to every two weeks, with filgrastim support, results in an improvement in disease-free and overall survival.**
    a. True
    b. False

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

Evaluation Form: Breast Cancer Update, Issue 7, 2003

NL Communications 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*

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 5 4 3 2 1
- Describe and implement an algorithm for HER2 testing and treatment of patients with HER2-positive breast cancer 5 4 3 2 1
- Develop and explain a management strategy for treatment of ER-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings 5 4 3 2 1
- Develop and explain a management strategy for treatment of ER-negative breast cancer in the adjuvant, neoadjuvant and metastatic settings 5 4 3 2 1
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of aromatase inhibitors in the adjuvant setting 5 4 3 2 1
- Evaluate the emerging data on dose-dense chemotherapy and explain its relevance to patients 5 4 3 2 1

SPECIFIC LEARNING OBJECTIVES FOR ISSUE 7

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

- Discuss the efficacy and tolerability of the trastuzumab/taxane/carboplatin combination, and the ongoing related trials to assist in the management of select patients with HER2-positive disease in the metastatic setting 5 4 3 2 1
- Describe the efficacy and tolerability of fulvestrant in order to counsel patients with ER-positive metastatic disease about therapy options 5 4 3 2 1
- Evaluate the Women's Health Initiative trial results to counsel women regarding the beneficial and detrimental effects associated with menopausal hormone therapy 5 4 3 2 1
- Evaluate novel data regarding dose-dense scheduling of chemotherapy and the use of taxanes in the adjuvant setting 5 4 3 2 1
- Describe a management strategy for the use of chemotherapy and endocrine therapy in women with metastatic disease 5 4 3 2 1

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty	Knowledge of Subject Matter	Effectiveness as an Educator
Howard A Burris III, MD	5 4 3 2 1	5 4 3 2 1
Richard M Elledge, MD	5 4 3 2 1	5 4 3 2 1
Rowan T Chlebowski, MD, PhD	5 4 3 2 1	5 4 3 2 1
Vicente Valero, 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 7, 2003

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_____

_____

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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