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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 on pages 42-44 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 HER2-positive breast cancer patients in your practice.
- 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 ER-positive, postmenopausal patients 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 6

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

- Utilize the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines when selecting chemotherapy, hormonal therapy and biologic therapy for patients with breast cancer.
- Consider the implications of the Phase II trial of gefitinib in women with metastatic breast cancer for the treatment of patients with metastases progressing on previous chemotherapy regimens.
- Determine which clinical trials are available to patients who are at high risk for developing breast cancer in order to counsel select patients who are interested in breast cancer chemoprevention.
- Discuss the use of sequential single-agent versus combination chemotherapy for the treatment of metastatic breast cancer.

## ACCREDITATION STATEMENT

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| | |
|---|---|
| **Monica Morrow, MD** | No financial interests or affiliations to disclose |
| **Joyce O'Shaughnessy, MD** | **Consultant:** Eli Lilly & Company, Roche Laboratories Inc, Aventis Pharmaceuticals Inc, Ortho Biotech Products LP<br>**Speakers' Bureau:** Roche Laboratories Inc, Aventis Pharmaceuticals, Eli Lilly & Company, Ortho Biotech Products LP |
| **Kathy S Albain, MD** | **Grants/Research Support/Speakers' Bureau:** AstraZeneca Pharmaceuticals LP, Aventis Pharmaceuticals Inc, Eli Lilly & Company, Bristol-Myers Squibb, Genentech Inc |
| **Robert W Carlson, MD** | **Grants/Research Support:** Eli Lilly & Company, Aventis Pharmaceuticals Inc, AstraZeneca Pharmaceuticals LP<br>**Honorarium:** AstraZeneca Pharmaceuticals LP |

### Pharmaceutical agents discussed in this program

| GENERIC | TRADE | MANUFACTURER |
|---|---|---|
| anastrozole | Arimidex® | AstraZeneca Pharmaceuticals LP |
| bevacizumab | Avastin™ | Genentech Inc |
| capecitabine | Xeloda® | Roche Laboratories Inc |
| carboplatin | Paraplatin® | Bristol-Myers Squibb Company |
| cyclophosphamide | Cytoxan® | Bristol-Myers Squibb Company |
| | Neosar® | Pfizer Inc |
| docetaxel | Taxotere® | Aventis Pharmaceuticals Inc |
| doxorubicin | Adriamycin® | Pfizer Inc |
| doxorubicin HCL liposome injection | Doxil® | Ortho Biotech Products LP |
| epirubicin hydrochloride | Ellence® | Pfizer Inc |
| estradiol | Various | Various |
| etoposide | VP-16, Vepesid® | Bristol-Myers Squibb Company |
| exemestane | Aromasin® | Pfizer Inc |
| filgrastim | Neupogen® | Amgen Inc |
| fluorouracil, 5-FU | Various | Various |
| fulvestrant | Faslodex® | AstraZeneca Pharmaceuticals LP |
| gemcitabine | Gemzar® | Eli Lilly & Company |
| gefitinib | Iressa® | AstraZeneca Pharmaceuticals LP |
| letrozole | Femara® | Novartis Pharmaceuticals Corporation |
| megestrol acetate | Megace® | Bristol-Myers Squibb Company |
| methotrexate | Various | Various |
| paclitaxel | Taxol® | Bristol-Myers Squibb Company |
| pamidronate | Zometa® | Novartis Pharmaceuticals Corporation |
| pegfilgrastim | Neulasta® | Amgen Inc |
| raloxifene hydrochloride | Evista® | Eli Lilly & Company |
| tamoxifen citrate | Nolvadex® | AstraZeneca Pharmaceuticals LP |
| trastuzumab | Herceptin® | Genentech Inc |
| vinblastine | Velban®, Velsar® | Eli Lilly & Company |
| vinorelbine | Navelbine® | GlaxoSmithKline |

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## Editor's Note

### A "functional cure" for metastatic breast cancer

In a prior issue of this audio series, Dr Kathy Miller discussed a 62-year-old woman treated in 1997 for pulmonary and hepatic metastases. After five years of treatment with chemotherapy and hormone therapy, the patient died of an unrelated stroke. During this time, she had minimal tumor-related symptoms and felt so well that she elected to have TRAM flap breast reconstruction and contralateral breast reduction for symmetry.

A prolonged clinical course with metastatic breast cancer is becoming more common, and in this issue Dr Robert Carlson presents a woman from his practice who is about four years into therapy for metastatic disease to the mediastinum. The patient was initially managed with paclitaxel, followed by anastrozole, and is currently doing very well while receiving the estrogen-receptor downregulator, fulvestrant.

These two cases are reminders of the profound complexity of metastatic breast cancer. In the last decade, many new systemic agents have become available, making treatment decisions more difficult and effective communication between oncologists and patients even more essential.

One striking contrast between these two cases is that Dr Carlson's patient — treated only a couple of years after Dr Miller's patient — was able to receive fulvestrant, a novel endocrine intervention. This agent provides another relatively nontoxic alternative for our treatment armamentarium and, combined with the introduction of the aromatase inhibitors, has led to a dramatic decrease in the use of the older and more toxic agents, such as megestrol acetate, that were an integral component of breast cancer therapy in the past.

Fulvestrant's unique mechanism of action has also taught us not to abandon new approaches to older tumor targets. In his interview, Dr Carlson voices optimism about combinations of targeted biologic interventions and endocrine agents now under active study. A previous interviewee in our series, Dr Dennis Slamon, was particularly interested in future clinical trials evaluating fulvestrant and trastuzumab.

Also in this issue, Dr Kathy Albain discusses the initial Phase II trial results with the tyrosine kinase inhibitor, gefitinib and her encouraging experience with patients experiencing relief of bone pain with this exciting new agent. It is apparent that in the next few years a number of new biologic interventions will join trastuzumab as an integral part of the breast cancer therapeutic armamentarium.

Dr Joyce O'Shaughnessy notes that perhaps the key to success for these new therapies will be the identification of molecular targets in the tumor that will aid in patient selection, in a manner similar to HER2 and trastuzumab.

Dr Monica Morrow notes that humoral factors controlling metastases are also important research considerations. She discusses an intriguing retrospective series, conducted with her surgical colleague, Dr Seema Kahn, suggesting that the removal of the primary lesion in women presenting with metastases may improve survival.

One wonders whether metastatic breast cancer will eventually mimic a chronic disease model like diabetes. Like Dr Miller's patient, these women may eventually experience minimal disease-related morbidity and live long enough to die from other causes.

A number of research leaders interviewed for this audio series have noted that the disappointment with high-dose chemotherapy in the early 1990s led researchers away from the "infectious disease eradication" breast cancer model to a chronic disease model. It also seems likely that more informative molecular analyses may identify patients with potentially indolent tumors who would better fit into that model.

Another key issue in this chronic disease approach is the availability of minimally toxic interventions, such as the endocrine treatment that both Dr Miller's and Dr Carlson's patients received. Highly targeted therapies, such as biologic modulators and endocrine interventions, may offer the opportunity for women with metastatic breast cancer to be maintained in a prolonged asymptomatic state. If survival approaches that of age-matched controls without breast cancer, a "functional" cure can be attained with minimal treatment-related morbidity.

While this clinical research goal may be less appealing than the "magic bullet" we hoped for in the past, it also may be more attainable and would confer significant benefit to our patients.

—Neil Love, MD

## Select publications

### *Long-term clinical complete remission of metastatic breast cancer*


Ciatto S, Bonardi R. **Is breast cancer ever cured? Follow-up study of 5623 breast cancer patients.** *Tumori* 1991;77(6):465-7. **Abstract**

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**

Pierga JY et al. **Response to chemotherapy is a major parameter influencing long-term survival of metastatic breast cancer patients.** *Ann Oncol* 2001;12(2):231-7. **Abstract**

Tomiak E et al. **Characterisation of complete responders to combination chemotherapy for advanced breast cancer: A retrospective EORTC Breast Group study.** *Eur J Cancer* 1996;32A(11):1876-87. **Abstract**

Yamamoto N et al. **Clinical characteristics of patients with metastatic breast cancer with complete remission following systemic treatment.** *Jpn J Clin Oncol* 1998;28(6):368-73. **Abstract**


## Monica Morrow, MD

Professor of Surgery,
Northwestern University Feinberg School of Medicine

Director, Lynn Sage Comprehensive Breast Program,
Northwestern Memorial Hospital


# Edited comments by Dr Morrow

CASE 1: 63-year-old woman with atypical hyperplasia

- Breast biopsy 12 years ago: fibrocystic changes
- Mother developed breast cancer at age 54; sister at age 58
- Gail model breast cancer risk is 15.2% at 5 years; 49.3% lifetime

Nonprotocol chemoprevention choices of 2002 Miami Breast Cancer Conference (MBCC) attendees

| | |
|---|---|
| None | 8% |
| Bilateral prophylactic mastectomy | 6% |
| Tamoxifen | 77% |
| Other chemoprevention | 6% |
| Other | 3% |

### *Dr Morrow's viewpoint*

Tamoxifen would be a good option for this woman based on her high-risk profile. Interestingly, the data we generated from our own practice clearly shows that women who are at risk on the basis of histologic lesions — atypical hyperplasia and LCIS — are far more likely to be offered and to accept tamoxifen than women with equivalent levels of risk due to other factors. Approximately 60 to 65 percent of my patients with atypia take tamoxifen. In general, only about 25 percent of women at high risk are offered tamoxifen and accept.

Genetic counseling should be considered for this patient. I would take a more detailed family history to determine how many relatives were affected and if she is of Ashkenazi descent. Her risk might be substantially higher than the Gail model suggests, and if knowing that would change the way she manages her risk, then genetic counseling would be beneficial.

Most women do not want a prophylactic mastectomy, but if a patient tells me her level of risk is unacceptable and she wants to maximally reduce her risk, then it's an option. It's important that the patient fully understands her risk, the sequelae of surgery, the possible complications and the other available options to reduce risk, such as tamoxifen or, in gene carriers, oophorectomy.

I also counsel these patients that should they develop breast cancer, the chances are 80 to 90 percent that they would be treated with a breast-conserving approach rather than mastectomy. It's difficult for me to understand why women with a breast cancer risk of less than five or ten percent would opt for such a radical approach as prophylactic mastectomy. In these women with low risk, education is particularly important because they have often been told they need this surgery because their breasts are dense and lumpy.

Studies have clearly shown that women interested in prophylactic mastectomy tend to overestimate their level of risk by approximately 10-fold, and it takes a lot of time to get past that fear. For the woman who understands that her risk is low but seems intent on prophylactic mastectomy, psychological counseling should be employed to determine what is driving that decision.

**2002 MBCC attendees' recommendations for this patient's participation in the STAR trial comparing tamoxifen to raloxifene**

| | |
|---|---|
| Strongly encourage participation | 58% |
| Provide the option of participation but not encourage very strongly | 36% |
| Discourage participation | 6% |

### *Dr Morrow's viewpoint*

The STAR trial would be an excellent option for this woman. It is designed to show whether tamoxifen or raloxifene is the better preventive agent, and it also evaluates side effects and the impact of each drug on overall health. The relatively low bioavailability of raloxifene raises concern that it may not be the ideal drug, particularly in younger, postmenopausal women. Raloxifene is currently being studied to see if it reduces the risk of coronary heart disease and, from a compliance perspective, this is important because it will probably be easier to convince women to take a drug with multiple health benefits than one that's purely a breast cancer preventive.

"The Raloxifene Use for The Heart (RUTH) trial is an international, multicenter, randomized, double blind, placebo-controlled trial designed to evaluate whether 60 mg/day of oral raloxifene compared with placebo reduces the risk of coronary events (coronary death, nonfatal myocardial infarction [MI], or hospitalized acute coronary syndromes other than MI) and risk of invasive breast cancer in postmenopausal women with documented coronary heart disease (CHD) or who are at increased risk for major coronary events."

*SOURCE:* Wenger NK. **Baseline Characteristics of Participants in the Raloxifene Use for The Heart (RUTH) Trial.** *Am J Cardiol* 2002;90:1204-10. **Abstract**

2002 MBCC attendees' recommendations for this patient's participation in the IBIS-II trial, comparing anastrozole to placebo

| | |
|---|---|
| Strongly encourage participation | 19% |
| Provide the option of participation but not encourage very strongly | 38% |
| Discourage participation | 7% |
| Discourage participation — don't like placebo arm | 36% |

### *Dr Morrow's viewpoint*

The research question about aromatase inhibitors as preventive agents is a very important one, but I am concerned that the IBIS-II trial won't give us the answer we need. We'll know if anastrozole is better than a placebo but we won't know how SERMs compare to aromatase inhibitors or which is better in terms of overall health. We will not be able to extrapolate these answers from two completely different study populations, and this will leave us with another trial to do.

I would not recommend IBIS-II to this patient with atypical hyperplasia or any woman at high risk. I don't think taking a 50 percent chance of being randomized to a placebo is a good choice. In addition, if the osteoporosis and fracture rates seen in the current aromatase inhibitor treatment trials persist, we will have another set of issues to address.

Telling women they'll just have to take another drug to protect against osteoporosis while they're taking an aromatase inhibitor to protect them against breast cancer is problematic. Aside from the highest-risk or very motivated patients, how many women are going to take multiple pills to prevent something for which they're not having any symptoms?

IBIS-II also has a randomization for women with DCIS, which compares anastrozole to tamoxifen. I agree that treating DCIS is primarily prevention — it's a lesion that carries a significantly increased risk of invasive breast cancer. We tend to think of it differently because we treat it like cancer, but the question is the same. The NSABP-B-35 trial is asking the same question, randomizing women with DCIS to anastrozole versus tamoxifen. It is a good trial, addressing an important question, and I heartily support that study.

"Anastrozole will also be tested in the upcoming NSABP Trial B-35... .Eligible subjects will be postmenopausal women with DCIS who are treated with lumpectomy and radiation therapy. They will be randomly assigned to treatment with either tamoxifen (20 mg daily) for 5 years or anastrozole (1 mg daily) for 5 years. The design and measured outcomes of the trial will be similar to those in NSABP Trial B-24: the occurrence of invasive breast cancer in either the ipsilateral or the contralateral breast, the occurrence of DCIS in the contralateral breast, and the recurrence of DCIS in the ipsilateral breast, as well as local, regional, and distant event rates."

SOURCE: Vogel VG et al. **National Surgical Adjuvant Breast and Bowel Project Update: Prevention Trials and Endocrine Therapy of Ductal Carcinoma in Situ.** *Clin Cancer Res* 2003;9:495s-501s. **Abstract**

CASE 2: 58-year-old with newly diagnosed infiltrating ductal carcinoma

- Receiving HRT for the past six years for severe vasomotor symptoms unresponsive to other interventions

MBCC attendees' recommendations regarding HRT

| | |
|---|---|
| Continue | 1% |
| Stop immediately | 72% |
| Gradually taper down and stop over several weeks | 23% |
| Gradually taper down and stop over several months | 4% |

### *Dr Morrow's viewpoint*

I think everyone agrees that patients like this should stop hormone replacement therapy. The real question is: Do they have to stop it immediately and be miserable while you're preparing them for surgery or can they taper down? I have become quite comfortable with tapering patients over a month or so.

CASE 2 (continued): Patient is treated with a lumpectomy

- Negative sentinel lymph node biopsy
- 1.2-cm infiltrating ductal carcinoma
- Strongly ER/PR-positive and HER2-positive (IHC 3+, FISH-positive)

MBCC attendees' recommendation regarding this patient's participation in the NSABP-B-32 sentinel node trial, comparing axillary dissection to no further surgery

| | |
|---|---|
| Strongly encourage participation | 33% |
| Provide the option of participation but not encourage very strongly | 39% |
| Discourage participation | 28% |

### *Dr Morrow's viewpoint*

I think the primary question asked by NSABP trial B-32, namely, whether removing negative lymph nodes improves survival, was answered by the NSABP approximately 25 years ago in B-04, so this is not my favorite trial. It's excellent for physicians learning the technique of sentinel node, but I don't believe it would benefit this patient.

"The underlying hypothesis to be tested in this trial [NSABP-B-32] states that patients who have pathologically negative SLNs will have equivalent disease-free and overall survival rates, if they are treated by sentinel node biopsy alone or sentinel node biopsy plus completion axillary dissection. A second part of this hypothesis is that the morbidity of the sentinel node biopsy alone will be significantly less than that of the sentinel node plus axillary dissection, therefore tipping the scales favoring the sentinel node biopsy procedure."

*SOURCE:* Harlow SP, Krag DN. **Sentinel lymph node—Why study it: Implications of the B-32 study.** *Sem Surg Oncol* 2001;20:224–229. **Abstract**

MBCC attendees' suggestions regarding which chemotherapy should be suggested to this patient

| | |
|---|---|
| None | 28% |
| AC x 4 | 38% |
| CMF | 11% |
| Anthracycline regimen x 6 | 6% |
| Taxane/anthracycline regimen | 9% |
| Dose-dense chemotherapy approach including ATC | 5% |
| Other | 3% |

### *Dr Morrow's viewpoint*

With a 1.2-centimeter, node-negative, estrogen receptor-positive cancer, the amount of additional benefit in terms of absolute gain from chemotherapy is very small. I would not encourage this patient to have chemotherapy for what I would estimate to be a one or two percent survival benefit. However, I think most medical oncologists in the United States would recommend chemotherapy followed by endocrine therapy in this case.

MBCC attendees' suggestions regarding which endocrine therapy should be suggested to this patient

| | |
|---|---|
| None | 1% |
| Tamoxifen | 37% |
| Anastrozole | 60% |
| Other aromatase inhibitor | 2% |

### *Dr Morrow's viewpoint*

This patient will derive the greatest benefit from endocrine therapy. For women with low-risk, ER-positive, HER2-negative breast cancers with very favorable prognosis, we still use as much tamoxifen as anastrozole. For women with HER2-positive breast cancers, as in this case, I favor an aromatase inhibitor because of the debate about whether HER2 overexpression predicts resistance to tamoxifen. The follow-up data with anastrozole from the ATAC trial are encouraging and suggest that the bone problems may be reaching a plateau.

If the patient's prognosis was less favorable, I would be more likely to treat her with an aromatase inhibitor, regardless of the tumor HER2 status. There is clearly a greater benefit from anastrozole compared to tamoxifen in the short term. In a patient whose risk of relapse is quite high, the absolute difference between these two treatments is much larger. I would favor an aromatase inhibitor in the high-risk setting, and the data we have right now in the adjuvant setting is with anastrozole.

CASE 3: 58-year-old postmenopausal patient presenting with *de novo* metastatic disease

- Presented with a 4-cm breast mass and moderate rib pain
- Breast biopsy revealed an ER/PR-positive, HER2-negative, infiltrating ductal carcinoma
- Bone scan: multiple lesions in the ribs, skull and spine with negative X-rays
- Chest X-ray and CAT scan: multiple bilateral pulmonary nodules
- Treated with pamidronate and FAC
  - After six cycles of chemotherapy, breast mass decreased to 1 cm and the pulmonary lesions also decreased in size
  - Bone pain resolved
  - Chemotherapy was stopped and the patient was switched to hormonal therapy

MBCC attendees' recommendations for management of the primary lesion

| | |
|---|---|
| No specific therapy at this time | 25% |
| Excision | 23% |
| Excision and local radiation | 24% |
| Excision and axillary dissection | 1% |
| Excision, axillary dissection and local radiation | 10% |
| Mastectomy | 6% |
| Mastectomy and axillary dissection | 5% |
| Mastectomy, axillary dissection and local radiation | 5% |
| Other | 1% |

## *Dr Morrow's viewpoint*

I have traditionally thought that in this situation we should only treat the primary tumor if it was progressing and causing local problems; however, last year my colleague, Seema Kahn, and I published a study in the Journal, *Surgery*, of over 15,000 women from the National Cancer Database of the American College of Surgeons who presented with metastatic disease. This was based on tumor registry data.

We looked at differences in survival based on surgical treatment of the primary lesion versus no surgery. We controlled for number of documented metastatic sites and visceral versus soft tissue disease, and we found a very consistent pattern wherein surgical treatment of the primary lesion was associated with improved survival. While there may be selection bias to some extent, the differences were seen in all subgroups.

This study raises some questions as we develop more effective systemic therapy and keep people alive longer. Does it make sense to reduce the tumor burden maximally, so there are fewer places the treatment has to work? We see this in renal cell carcinoma, for example, where removal of the primary tumor results in a survival advantage. I think it's an open question. However, removal of the primary lesion is a reasonable option in this patient to try to maintain local control and prevent morbidity, even if it doesn't improve survival. If the patient is clinically node-negative, I don't see that there's a lot to be gained by dissecting the axilla.

Impact of local therapy and margin status on survival in patients with metastatic disease: A review of 16,023 patients

| | 3-year survival | 5-year survival | Median survival |
|---|---|---|---|
| No surgery | 17.3% | 6.7% | 11.9 months |
| Clear margins | | | |
| Partial mastectomy | 34.7% | 16.6% | 22.9 months |
| Total mastectomy | 35.7% | 18.4% | 25.3 months |
| Involved margins | | | |
| Partial mastectomy | 26.4% | 11.3% | 17.6 months |
| Total mastectomy | 26.1% | 11.5% | 20.0 months |

*DERIVED FROM:* Khan SA et al. **Does aggressive local therapy improve survival in metastatic breast cancer?** *Surgery* 2002;132(4):620-7. Abstract

CASE 4: 37-year-old premenopausal woman presents with a 2.1-cm, ER/PR-positive, HER2-positive (IHC 3+), infiltrating ductal carcinoma

- Modified radical mastectomy with immediate implant reconstruction
- Axillary dissection demonstrates three positive nodes

MBCC attendees' recommendations regarding whether regional radiation therapy should be performed

| | |
|---|---|
| Yes | 36% |
| No | 64% |

## *Dr Morrow's viewpoint*

The risk of local relapse on the chest wall is certainly high enough to warrant radiation. There's nothing magical about three versus four positive nodes — it's a continuum. To an extent, the decision to irradiate depends on the characteristics of the metastases. Gross disease in the nodes, extranodal extension, lymphatic invasion at the primary site — features such as these would push me in the direction of radiation. Data suggest younger women have a higher risk of chest wall relapse after mastectomy, just as they have a higher risk of local failure after lumpectomy. Putting all these factors together, I would certainly discuss radiation with this patient.

MBCC attendees' recommendations regarding participation in the Intergroup trial (SWOG-S9927, RTOG-9915) comparing radiation therapy to no radiation therapy in patients with one to three positive nodes

| | |
|---|---|
| Strongly encourage participation | 35% |
| Provide the option of participation but not encourage very strongly | 48% |
| Discourage participation | 17% |

### *Dr Morrow's viewpoint*

We participate in this study and I think it's a trial that needs to be completed, but it's not accruing well. One reason may be that — in the medical oncology community — the idea that radiotherapy contributes to survival is heresy, and it's the medical oncologist who would refer these patients after their systemic therapy to radiotherapy where they would hear about the trial.

*(Editor's Note: Subsequent to this interview, RTOG-9915 was closed due to poor accrual.)*

MBCC attendees' recommendations for removing the tissue expander prior to receiving regional radiation therapy

| | |
|---|---|
| Yes | 23% |
| No | 77% |

### *Dr Morrow's viewpoint*

We would definitely not remove the expander. Our approach to reconstruction has evolved as the indications for postmastectomy radiotherapy have increased. In women who have a high likelihood of needing radiation therapy after surgery, we put in an expander to allow us to save the skin and do a small skin-sparing type of incision. These are generally patients who will also require a more prolonged course of chemotherapy and the expander gives them a breast mound. If they are satisfied with the cosmetic results afterward, they're done. If they're not satisfied, then they can undergo tram flap reconstruction.

At the completion of chemotherapy, the patient is still menstruating. MBCC attendees' recommendations regarding which endocrine therapy, if any, should be suggested

| | |
|---|---|
| None | 3% |
| Tamoxifen | 43% |
| LHRH agonist or other ovarian ablation | 12% |
| Tamoxifen plus LHRH agonist or other ovarian ablation | 24% |
| Aromatase inhibitor | 9% |
| Aromatase inhibitor plus LHRH agonist or other ovarian ablation | 9% |

### *Dr Morrow's viewpoint*

While there is no definitive evidence, there are data suggesting that ovarian suppression improves outcome in premenopausal patients with ER-positive breast cancer. Therefore, in premenopausal women with a poor prognosis, we include ovarian suppression in our treatment plan. We need clinical trials to look at the combination of ovarian suppression plus aromatase inhibitors versus ovarian suppression plus tamoxifen. That is an important comparison, and it will inform us how important the estradiol elevations are in premenopausal women receiving tamoxifen.

## The significance of micrometastatic disease in axillary nodes

The increasing use of sentinel node biopsy has raised a whole new set of questions including whether micrometastases detected by immunohistochemistry are clinically significant. This is a biologically interesting question, and I strongly agree with the College of American Pathologists' consensus statement that we do not yet understand the meaning of these micrometastases.

The retrospective studies of micrometastases have been a "mixed bag," including patients who have large areas of missed tumor in their lymph nodes and patients with small numbers of cells in subcapsular sinuses that aren't even in the node parenchyma. It's not particularly surprising that some of these studies show no survival difference, some show small survival differences, and others show very big survival differences.

This is an area where both the NSABP-B-32 sentinel node study and the American College of Surgeons Z-10 study will provide us with very important information. Until that information is available, we use immunohistochemistry only if there's diagnostic uncertainty on the basis of something seen on an H&E stain. We do not routinely perform immunohistochemical staining of sentinel lymph nodes because we don't know what to tell the patients.

## Neoadjuvant therapy

One of the more interesting observations about neoadjuvant therapy is from the recent NSABP-B-27 trial, which demonstrated that you can drive clinical and pathologic responses by adding a taxane, but the breast conservation rate is not increased. Currently, in the absence of a proven survival benefit for preoperative therapy, the only reason to give neoadjuvant therapy is to increase the rate of breast conservation.

We reserve neoadjuvant therapy for the patients who want breast conservation but have tumors that are too large to allow it. Surgery following the downsizing of such a tumor is clearly different than a primary lumpectomy. If we resect a smaller volume of the breast than was originally occupied by the tumor and there's viable tumor scattered all around the specimen, even if the margins are negative, we have to be concerned there may be tumor left in the breast and we resect again. If that's negative, then we're satisfied, but if there's viable tumor in that re-resection, then we rethink whether breast conservation is appropriate. The NSABP study showed that the local failure rate in women downstaged by chemotherapy for breast conservation was twice as high as the rate in women who originally were candidates for breast-conserving therapy.

## Underutilization of breast-conserving surgery in the United States

The NSABP-B-06 trial began when I was a surgical resident, and at that time there were violent arguments over radical versus modified radical mastectomy. We see that carryover today. There is probably no surgical operation that has

undergone as much intense scientific scrutiny as breast conservation, and yet a substantial number of women with Stage I and II breast cancer are still being treated with mastectomy in this country.

Clearly, some physicians have not gotten past the notion that mastectomy is better, and they convey that to patients. In our study of second opinions, we found that even among educated, insured women with access to the best health care, fewer than one-half of them had been advised that there are three surgical options for the treatment of breast cancer.

Still, there is clearly a population of women who prefer mastectomy, and it's difficult to know whether that's because of an unreasonable fear of local recurrence or because they want to avoid radiation.

In our experience, younger women choose breast conservation at the same rate as older women. The primary predictors for who will choose mastectomy are women who have Medicare or Medicaid and live in the South or the Midwest part of the country. Also, bad prognostic cancer features correlate with a greater likelihood of having a mastectomy, even though they have nothing to do with that choice.

## Select publications

### *Publications discussed by Dr Morrow*


Khan SA et al. **Does aggressive local therapy improve survival in metastatic breast cancer?** *Surgery* 2002;132(4):620-6;discussion 626-7. **Abstract**


### *Treatment of the primary cancer in metastatic disease*


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Osaki T et al. **Survival and prognostic factors of surgically resected T4 non-small cell lung cancer.** *Ann Thorac Surg* 2003;75(6):1745-51. **Abstract**

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## Joyce O'Shaughnessy, MD

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# Edited comments by Dr O'Shaughnessy

## Adjuvant/neoadjuvant trials incorporating capecitabine/ docetaxel (XT)

The ongoing US Oncology adjuvant clinical trial is for patients with node-positive or high-risk, node-negative breast cancer. Patients are randomized to AC x 4 cycles, followed by four cycles of docetaxel with or without capecitabine x 4 cycles. There are two other trials evaluating the XT combination: the proposed replacement study for NSABP-B-27 and the MD Anderson ongoing neoadjuvant trial in which patients are randomized to weekly paclitaxel for three months versus the XT combination with both arms followed by FEC.

### Proposed NSABP-B-27 Preoperative Chemotherapy Replacement Trial

AC q 3w ↔ docetaxel q 3w → Surgery
AC q 3w ↔ docetaxel/capecitabine q 3w → Surgery
AC q 3w ↔ docetaxel/carboplatin q 3w → Surgery
AC q 3w ↔ docetaxel/vinorelbine q 3w → Surgery

↔ In this proposed 4 x 2 factorial design, some patients will receive AC followed by docetaxel or docetaxel combination regimens; in others, the sequence of administration will be reversed.

*SOURCE:* NSABP Annual Meeting, July 2003, Orlando, Florida.

In a nonprotocol setting, my standard adjuvant approach is AC followed by docetaxel. I believe duration is important, especially for patients at high risk — patients with large tumors or positive nodes, particularly those with macrometastases in the nodes. When treating women at very high risk, I stick with the data as much as possible and use the CALGB FAC regimen at 600/60/600 mg/m$^2$ followed by docetaxel at 100 mg/m$^2$.

The data from San Antonio comparing three different dose levels of docetaxel — 100 mg/m$^2$ versus 75 mg/m$^2$ versus 60 mg/m$^2$ — resulted in response rates of

36 percent versus 23 percent versus 22 percent, respectively. That's a 50 percent improvement in response rate, which may translate into improved disease-free and overall survival. If I had breast cancer and was treated with docetaxel, I would want 100 mg/m$^2$.

### Randomized Phase III data on docetaxel dosing comparing 100 to 75 to 60 mg/m$^2$

| | 100 mg/m$^2$ (n*=139) | 75 mg/m$^2$ (n*=146) | 60 mg/m$^2$ (n*=122) |
|---|---|---|---|
| Complete response rate | 6.5% | 1.4% | 2.5% |
| Overall response rate | 36.0% | 23.3% | 22.1% |
| Median overall survival | 12.3 months | 10.3 months | 10.6 months |
| Discontinuation due to toxicity | 17% | 7% | 5% |
| Febrile neutropenia | 14% | 7% | 5% |

*n = number of evaluable patients
Conclusion: "There was a significant dose-response relationship in the range 60-100 mg/m$^2$, and RR [response rates] differed between the groups. Overall the 100 mg/m$^2$ group had the best efficacy and was associated with higher but manageable toxicity."

*SOURCE:* Mouridsen H et al. **Phase III study of docetaxel 100 versus 75 versus 60 mg/m$^2$ as second line chemotherapy in advanced breast cancer.** *Breast Cancer Res Treat* 2002:**Abstract 327.**

## Utilization of microarray profiles to predict pathologic response

In their neoadjuvant study, MD Anderson will utilize microarray technology to perform gene transcription profiling on fine needle aspirates. They will then correlate the differential gene expression with pathologic responses. Dr Pusztai has compared core biopsies to fine needle aspirations (FNAs) and found the microarrays perform equally well. If we can define a microarray signature that predicts a pathologic complete response — and apparently there's been some recent success in doing that — that would be very exciting.

### MD Anderson Neoadjuvant Trial of Weekly Paclitaxel versus Capecitabine/Docetaxel followed by FEC and Local Therapy

**Eligibility:** Stage IIA-IIIA breast cancer

ARM 1: Paclitaxel qw x 12 → FEC x 4 → local therapy (surgery or RT)
ARM 2: (Capecitabine + docetaxel) x 4 → FEC x 4 → local therapy (surgery or RT)

Note: ER/PR-positive patients will receive endocrine therapy after completion of local therapy.

*DERIVED FROM:* Livingston R. **Current and planned trials with capecitabine in adjuvant/neoadjuvant therapy of breast cancer.** *Oncology* (suppl) 2002:16(10):29-32.

We will work very closely with Dr Pusztai to repeat that trial with a different set of chemotherapy drugs which we anticipate to be FEC followed by capecitabine/docetaxel as neoadjuvant therapy. We want to see if we can

correlate the microarray profiles on the primary tumor — also collected through fine needle aspiration — to determine the sensitivity and specificity for a microarray pattern predicting whether a patient will have a pathologic complete response or not.

## Evaluating molecular markers in clinical trials of capecitabine

There are ongoing clinical trials evaluating protein and mRNA of thymidine phosphorylase (TP), dihydropyrimidine dehydrogenase ([DPD], which is the key catabolic enzyme for 5-FU), and thymidylate synthase ([TS], which is the target enzyme for 5-FU).

Preclinical and xenograph data demonstrate that the likelihood of responding to capecitabine is related to the ratio of TP to DPD. In animal models, the higher the TP level and the lower the DPD level, the more likely there will be a response to capecitabine. I think capecitabine may be one of the first chemotherapy agents we're able to select based on protein and mRNAs.

## Impact of CALGB-9741 dose-dense data on clinical practice

CALGB-9741 was a well-conducted trial, and with the hazard ratio for recurrence of 0.5 at four years, I believe the data will hold up. Dose-dense scheduling resulted in an 82 percent, four-year, disease-free survival rate.

That is exactly the same as the three-year, disease-free survival rate achieved with TAC when compared to FAC. Dose density has become an option for patients and completing therapy more quickly may be beneficial. However, there are no data to prove that a dose-dense regimen is superior to TAC or to AC followed by docetaxel.

In the adjuvant setting, if you are going to administer AC followed by paclitaxel, you should probably use the dose-dense regimen. However, we need to know whether it's true that by cycling agents every two weeks, we produce more cell kill, as the Norton-Simon hypothesis suggests.

Marjorie Green's data from MD Anderson, comparing weekly paclitaxel preoperatively to every-three-week paclitaxel — both followed by FAC — showed a doubling of the pathologic CR rate with weekly paclitaxel. Many oncologists believe that part or perhaps all of the benefit seen in CALGB-9741 could be explained by administering paclitaxel alone every two weeks, so it's not at all clear that AC should be given every two weeks.

In my practice, I have not yet incorporated dose-dense chemotherapy because I believe duration is important. I want to cure women, and I'm going to administer an agent for whatever duration I believe is necessary.

Phase III randomized trial of weekly versus every three-week neoadjuvant paclitaxel followed by FAC: Pathological complete remission rates (pCR)

| | Node-positive | | Node-negative | |
|---|---|---|---|---|
| | Weekly (n=50) | Q 3 Week (n=51) | Weekly (n=68) | Q 3 Week (n=67) |
| pCR | 14 (28%) | 7 (14%) | 20 (29%) | 9 (13%) |

*SOURCE:* Green MC et al. **Weekly (wkly) paclitaxel (P) followed by FAC as primary systemic chemotherapy (PSC) of operable breast cancer improves pathologic complete remission (pCR) rates when compared to every 3-week (Q 3 wk) P therapy (tx) followed by FAC: Final results of a prospective phase III randomized trial.** *Proc ASCO* 2002;**Abstract 135.**

## Impact of CALGB-9741 dose-dense data on clinical trial design

We would like to improve upon the CALGB-9741 data, and our clinical trial of AC followed by docetaxel versus capecitabine/docetaxel may result in the next big advance in adjuvant therapy. The US Oncology Breast Committee discussed giving docetaxel every two weeks, but there's no real rationale for doing that. It has a long half-life and capecitabine is already dose-dense because it's administered for two weeks followed by one week off. We didn't feel the need to manipulate that aspect of the clinical trial.

We considered administering AC every two weeks, but we don't have any data that it is more beneficial than an every-three-week schedule. There was a neoadjuvant trial presented in San Antonio by Euler and colleagues evaluating three cycles of epirubicin/cyclophosphamide 120 mg/m$^2$ and 600 mg/m$^2$, respectively, randomizing between administering the combination every three weeks versus every two weeks. The pathologic CR rate in the every-three-week group was 9.5 percent compared to 3.9 percent in the every-two-week group. With only 262 patients, it's not a definitive study, but it certainly doesn't suggest that giving EC every two weeks is better.

Our US Oncology Breast Committee concluded that we would watch accrual to our trial, and doctors will "vote with their feet." Currently we're accruing between 65 and 75 patients a month, and we haven't seen a big drop-off since the San Antonio meeting.

## Dose-dense scheduling of docetaxel

Approximately one-third of practitioners are using dose density in their practice. Interestingly, a question was posed at a meeting with community oncologists: "Would you use dose-dense AC followed by a taxane every two weeks?" One-third responded affirmatively. When asked: "What taxane would you use?" approximately 55 percent indicated docetaxel and 45 percent chose paclitaxel.

It is premature to use docetaxel every two weeks without more safety and efficacy data. You can administer docetaxel 100 mg/m$^2$ by itself and it's relatively safe. It's really not feasible to administer docetaxel 100 mg/m$^2$ every two weeks

following AC because there's too much skin toxicity. I don't know what you would use for dose-dense therapy in the neoadjuvant or adjuvant setting because we just don't have enough data.

## Phase III trial of nanoparticle paclitaxel versus paclitaxel

I'm closely watching the randomized Phase III trial of paclitaxel 175 mg/m$^2$ every three weeks versus ABI-007 260 mg/m$^2$ every three weeks. ABI-007, or nanopaclitaxel, is an albumin-formulated paclitaxel. It's cremophor-free, so you can raise the dose safely, and it's very well-tolerated.

In our Phase II trial of weekly ABI-007 100 mg/m$^2$, three weeks on, one week off, in taxane-refractory patients, we're seeing some very impressive responses and extremely good tolerability. If that's a positive trial, as it may well be, it will be a very important advance because you won't need steroids. In my experience, the neurotoxicity with 100 mg/m$^2$ is negligible.

**ABI-007 nanoparticle paclitaxel in taxane-refractory metastatic breast cancer: Efficacy and toxicity**

**Efficacy**

- Overall response rate (CR + PR): 18% (95% CI: 6% - 37%)
- 21% of patients have not progressed 34+ to 43+ weeks on study

**Toxicity**

| | |
|---|---|
| Neuropathy (>Grade 3) | 0% |
| Neutropenia without G-CSF (Grade 4) | 4% |
| Allergic reactions (any grade) | 0% |

*DERIVED FROM:* Presentation, JL Blum, ASCO 2003.

## CALGB trial: Adjuvant capecitabine versus CA or CMF in elderly women

We did a small, randomized Phase II trial comparing intravenous CMF and full-dose capecitabine as front-line therapy in elderly patients in the metastatic setting. The response rate with capecitabine was 30 percent compared to 16 percent with intravenous CMF.

In a randomized Phase II trial of patients pretreated with anthracycline, comparing paclitaxel 175 mg/m$^2$ every three weeks to full-dose capecitabine, 1,250 mg/m$^2$ BID, two weeks on, one week off, the response with the capecitabine was 36 percent compared to 26 percent with paclitaxel. The confidence intervals were widely overlapping, so we couldn't conclude that capecitabine is superior, but what you can say from these two studies is that it's certainly unlikely that capecitabine is worse than CMF or paclitaxel.

It's interesting how quickly capecitabine has moved to trials in the adjuvant setting. In women over age 65, 75 percent have ER/PR-positive breast cancers. I think the role of chemotherapy in that group of patients is sufficiently

unknown. For women over 70, in particular, there are so few patients in the overview analysis in that age group that I think it's very reasonable to compare capecitabine to AC or CMF. I'd be a little less comfortable with it in a younger patient population, only because the overview has clearly shown that polychemotherapy is superior to monotherapy.

## Fulvestrant in the treatment of postmenopausal ER/PR-positive metastatic disease

I've used a fair amount of fulvestrant, and it's very well-tolerated. We've had some very nice responses to fulvestrant, including one of my patients who was on the original clinical trial of fulvestrant versus anastrozole. She was on fulvestrant for three and a half years and now she's on anastrozole. The injections have not been an issue for patients, and most women are very grateful that the side-effect profile is close to nil. I think fulvestrant probably crosses the blood-brain barrier and patients do have hot flashes on it, but in general, they're quite mild.

I am a little disquieted by the fact that it can take three to five months to reach a steady state with fulvestrant. A patient with rapidly progressing disease may not benefit from fulvestrant, but fortunately most women with hormone-responsive breast cancer have relatively indolent disease. I'm very interested in the clinical trial in which they are loading fulvestrant 500 mg every two weeks for a couple of doses and then reducing it to 250 mg monthly. That makes sense to me, so I've been trying to load it a little by giving it every three weeks for several injections in an attempt to raise the levels more quickly.

## Sequencing hormonal therapies in the front-line treatment of metastatic breast cancer

When I see a postmenopausal patient who has relapsed on adjuvant tamoxifen, I tend to use an aromatase inhibitor followed by fulvestrant when the disease progresses. In the frontline metastatic trials of aromatase inhibitors versus tamoxifen, data demonstrates that regardless of whether you administer an aromatase inhibitor after tamoxifen or tamoxifen after an aromatase inhibitor, there's a 40 to 50 percent clinical benefit rate. In the second-line setting, if you administer fulvestrant after an aromatase inhibitor or an aromatase inhibitor after fulvestrant, there's approximately a 33 percent clinical benefit rate. These are all small trials and most of them are not randomized, but they show that any of these regimens can be effective and there's no mandatory sequence for these agents.

## Sequential single-agent versus combination chemotherapy for metastatic disease

George Sledge's Phase III trial of single-agent doxorubicin, paclitaxel versus the combination of doxorubicin/paclitaxel as front-line chemotherapy for metastatic breast cancer failed to show a survival benefit for the combination. It's difficult to demonstrate a survival advantage in front-line metastatic disease because,

according to the MD Anderson series, these patients live an average of four years. What you do early in their treatment may never be reflected in a survival advantage because they have many other opportunities for treatment down the line.

In chemotherapy-naïve patients with metastatic disease, I generally use capecitabine/docetaxel (XT). There's no evidence that administering an anthracycline after a taxane harms the patient in any way. I eventually use an anthracycline; I just don't feel compelled to use it up front. The decision to use single-agent taxane or single-agent capecitabine or the combination for front-line therapy depends on factors such as the patient's presentation and the extent of her disease.

As we begin later-line therapy, when patients become more symptomatic and heavily tumor-burdened, and their life expectancy is shortening, a very reasonable argument can be made for better palliation and maybe even better survival with a well-tolerated combination regimen.

## Combination chemotherapy for late-line therapy in patients with hormone refractory, HER2-negative disease

For late-line therapy in patients with hormone refractory, HER2-negative disease, I prefer a well-tolerated combination. I love the combination of capecitabine and vinorelbine. It's the nonalopecia approach to excellent palliative care, and I've used it often.

## Combination therapy with chemotherapy and antiVEGFs

In the trial comparing capecitabine with or without bevacizumab in patients with metastatic disease, the response rate was significantly improved with the combination, but the primary endpoint did not improve. It almost seemed like the VEGF antibody, bevacizumab, had an initial antiangiogenic effect that increased the response rates, which were not durable.

This suggests that perhaps, in late-line cancers, there are other proangiogenic substances that may take over. It also suggests the late-line patient population may not be the ideal place to study angiogenesis inhibitors.

The ongoing randomized study of paclitaxel with or without bevacizumab is an earlier-line trial in metastatic disease. Studies like this need to be done because we can't assume the response will be the same in early- versus late-stage disease, and we may eventually have to take it into the micrometastatic setting.

CASE 3: 58-year-old postmenopausal patient presenting with *de novo* metastatic disease

- Presented four years ago with a 4-cm breast mass and moderate rib pain
- Breast biopsy revealed an ER/PR-positive, HER2-negative, infiltrating ductal carcinoma
- Bone scan: multiple lesions in the ribs, skull and spine with negative X-rays
- Chest X-ray and CAT scan: multiple bilateral pulmonary nodules
- Treated with pamidronate and FAC
  - After six cycles of chemotherapy, breast mass decreased to 1 cm and the pulmonary lesions also decreased in size
  - Bone pain resolved
  - Chemotherapy was stopped and the patient was switched to tamoxifen

## *Dr O'Shaughnessy's viewpoint on the management of the primary lesion*

I probably would not do anything further in terms of local therapy to the breast at that point. I have a patient exactly like this in my practice. She presented with bone and lung metastases but had a locally advanced breast cancer and a mass in her other breast. When we reduced the locally advanced tumor to a manageable size, she had a salvage mastectomy because we were concerned it might cause a local control problem.

The contralateral breast still has a small nodule, which we are following closely; we will do a salvage mastectomy if it starts growing. While I think surgeons would be inclined to excise the lesion in this case, medical oncologists view it as just another indicator lesion.

Follow-up

- No local therapy was given and the patient was continued on tamoxifen for two years
  - Breast mass increased to 4 cm and pulmonary lesions increased in size
  - No change in bone scan, patient remained asymptomatic
- Treated with fulvestrant, 250 mg IM monthly
  - Breast mass and pulmonary lesions decreased in size
  - Patient tolerated therapy well
- After one year, patient progressed and was treated with anastrozole
  - There was a six-month response to anastrozole, then patient relapsed
  - Patient had severe bone pain and multiple lesions on bone scan in the ribs, skull,
  - lumbosacral spine and femur
  - Lung lesions had increased significantly in size
- Exemestane was started and radiation was delivered to the left ribs
  - One month later, the rib pain had improved but other sites of pain worsened
  - The lung lesions increased in size

MBCC attendees' recommendations for systemic treatment

| | |
|---|---|
| Endocrine therapy | 5% |
| Anthracycline | 6% |
| Taxane | 20% |
| Capecitabine | 16% |
| Vinorelbine | 1% |
| Gemcitabine | 3% |
| Capecitabine/docetaxel | 31% |
| Anthracycline/taxane | 12% |
| Other | 6% |

### *Dr O'Shaughnessy's viewpoint*

This patient could potentially be treated with a single cytotoxic agent, and I believe the best choice would be either paclitaxel, docetaxel or capecitabine. However, she's very symptomatic and better response rates are achieved with combination chemotherapy, so I would treat her with capecitabine/docetaxel. If the combination is well-tolerated, I continue administering it. If the combination becomes too toxic, I discontinue docetaxel and utilize capecitabine monotherapy.

The problem with combination therapy is you don't know whether the patient responded to the combination or one of the single agents. I've had excellent responses with this regimen, and the responses have been very durable on the continued capecitabine monotherapy. If the patient then progress on single-agent capecitabine, I usually stop the capecitabine and go to another therapy — either single-agent vinorelbine or gemcitabine/carboplatin late-line.

Combination chemotherapy has a much higher response rate than either single agent alone, but if the patient was relatively asymptomatic and had a small volume of disease, you don't really gain anything by using the combination regimen. In these patients, giving single agents sequentially is perfectly reasonable.

## Select publications

### *Publications discussed by Dr O'Shaughnessy*


Euler U et al. **Dose and time intensified epirubicin/cyclophosphamide (EC) as preoperative treatment in locally and advanced breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 154.**

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**

## *Combination versus sequential chemotherapy in the treatment of metastatic breast cancer*


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

Alba E et al. **Multicenter phase III randomized trial comparing sequential versus concomitant administration of doxorubicin (A) and docetaxel (T) as first-line treatment of metastatic breast cancer (MBC). GEICAM 9903 Study.** *Proc ASCO* 2003;**Abstract 27.**

Crown J et al. **Chemotherapy for metastatic breast cancer — report of a European expert panel.** *Lancet Oncol* 2002;3(12):719-27. **Abstract**

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

Ghosn M et al. **Vinorelbine (Navelbine) IV and capecitabine (vinocap) as front line chemotherapy in metastatic breast cancer (MBC).** *Proc ASCO* 2002;**Abstract 1978.**

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

Miles D et al. **Combination versus sequential single-agent therapy in metastatic breast cancer.** *Oncologist* 2002;7(Suppl 6):13-9. Erratum in: *Oncologist* 2003;8(1):127. **Abstract**

Nabholtz JM et al. **Combination chemotherapy for metastatic breast cancer.** *Expert Rev Anticancer Ther* 2002;2(2):169-80. **Abstract**

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

Paridaens R et al. **A randomized phase II study of alternating and sequential regimens of docetaxel and doxorubicin as first-line chemotherapy for metastatic breast cancer.** *Ann Oncol* 2003;14(3):433-40. **Abstract**

Perez EA et al. **A randomized phase II study of sequential docetaxel and doxorubicin/cyclophosphamide in patients with metastatic breast cancer.** *Ann Oncol* 2002;13(8):1225-35. **Abstract**

Rossi A et al. **Single agent vinorelbine as first-line chemotherapy in elderly patients with advanced breast cancer.** *Anticancer Res* 2003;23(2C):1657-64. **Abstract**

Seidman AD. **Monotherapy options in the management of metastatic breast cancer.** *Semin Oncol* 2003;30(2 Suppl 3):6-10. **Abstract**

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

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

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

Tripathy D. **Overview: Gemcitabine as single-agent therapy for advanced breast cancer.** *Clin Breast Cancer* 2002;3 Suppl 1:8-11. **Abstract**

Van Poznak C, Seidman AD. **Critical review of current treatment strategies for advanced hormone insensitive breast cancer.** *Cancer Invest* 2002;20 Suppl 2:1-14. **Abstract**

Zimatore M et al. **Weekly taxanes in metastatic breast cancer.** *Oncol Rep* 2002;9(5):1047-52. **Abstract**


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# Edited comments by Dr Albain

## Phase II trial of gefitinib in women with metastatic disease

Our study was an investigator-initiated, multicenter, Phase II trial in women who had received any number of prior chemotherapy regimens for metastatic disease; patients receiving first-line therapy were also eligible. Patients who received multiple regimens dominated the population, but there were a few who had no prior chemotherapy. The trial was unique in that the women had to be actively progressing on chemotherapy to qualify for the trial. They also had to have available tumor specimens for the molecular substudy.

Patients were treated with 500 mg/day of gefitinib and assessed every eight weeks. The primary endpoint of the trial was the clinical benefit rate. The design was similar to hormonal therapy trials in which complete and partial responses or stable disease for six months or more qualified as a clinical benefit.

**Open-Label, Phase II, Multicenter Trial of Gefitinib in Patients with Advanced Breast Cancer**
**Closed Protocol**

Actual Accrual: 63 patients

**Eligibility:** Patients with metastatic breast cancer

**Treatment:** Gefitinib 500 mg daily

Treatment continued until disease progression, intolerable toxicity or consensual withdrawal.

*DERIVED FROM:* Albain K et al. **Open-label, phase II, multicenter trial of ZD1839 in patients with advanced breast cancer.** *Breast Cancer Res Treat* 2002: **Abstract 20.**

### *Clinical benefit*

One patient had a partial response, and two patients had stable disease for more than six months. In addition, there were six more patients with stable disease up to six months. The median progression-free survival was 57 days, but we

had patients whose disease was free of progression for 205 or more days. In this group of women who had been actively progressing on prior therapies, the median progression-free survival was clustered at the first assessment point, but there were a number of patients who stayed on gefitinib for several months after that.

The patient whose disease had a partial response had received high-dose chemotherapy and every possible chemotherapy drug that is active in breast cancer. She was on gemcitabine for three cycles, vinorelbine for a few cycles and kept progressing through each of those. Then, her lung metastases and breast mass had a partial response to gefitinib.

The trial was not designed to assess quality of life or pain, but five out of 12 patients with bone pain had dramatic relief of their pain. It didn't matter that they had a few more liver or lung metastases; they went off of the narcotics. Although they were classified as having progressive disease, they didn't want to stop the gefitinib, because it ameliorated their pain.

I had two patients with bone pain who pleaded with me not to stop their gefitinib; they wanted to stay on it because they hadn't felt so well in months. This observation from our trial obviously needs to be followed up, but I am convinced that this is not a placebo effect. These women had undergone every conceivable therapy, and they didn't suddenly just miraculously go off all of their pain medications. Perhaps gefitinib will prove to be beneficial for patients with bone metastases.

### *Side effects*

There was no pulmonary toxicity in this trial. The acneform rash and diarrhea were very similar to that found in patients receiving gefitinib for lung cancer. The usual management for the side effects included a short drug holiday for up to 14 days, which usually helped. Four patients had a dose reduction from the 500 mg to 250 mg to ameliorate toxicity.

The rash was usually on the face or trunk, and it was typical acne. Sometimes it was pruritic or painful. Other patients had a rash that wasn't classic. The usual skin care regimes worked for the acneform rash. There was nothing unusual about the diarrhea, and we managed it with the common treatments.

## Future trials with gefitinib

Studies combining gefitinib with chemotherapy as primary neoadjuvant therapy will be conducted. Other studies will likely be performed in patients with lower-bulk disease — perhaps patients whose disease has had a complete or partial response from primary therapy. Those types of trials are worthwhile, as are those with other growth factor pathway inhibitors that will try to maximize inhibition of the cross talk among the epidermal growth factor receptor (EGFR) family. Studies combining gefitinib with antiestrogens would also be of interest.

## Intergroup trial 0100

Intergroup trial 0100 enrolled postmenopausal women with node-positive and ER-positive breast cancer. The trial stratified patients by nodal status (1-3 versus 4 or more), progesterone-receptor status (negative or positive) and time from surgery. The patients were randomized to tamoxifen alone for five years, classic CAF followed by five years of tamoxifen or CAF with concurrent tamoxifen starting on day one.

Phase III Randomized Comparison of Adjuvant Therapy with Tamoxifen versus CAF (Cyclophosphamide/Doxorubicin/5-Fluorouracil) Plus Concurrent or Delayed Tamoxifen in Postmenopausal Women with Node- and Receptor-Positive Breast Cancer **Closed Protocol**

Protocol IDs: SWOG-8814, CAN-NCIC-MA9, CLB-9194, EST-4188, INT-0100, NCCTG-883051
Actual Accrual: 1,477

**Eligibility:** Patients with Stage T1-3a, pathologic N1-2 (clinical N0-1), M0, receptor-positive breast cancer

ARM 1: Tamoxifen
ARM 2: CAF → Tamoxifen (Sequential)
ARM 3: CAFT → Tamoxifen (Concurrent)

C = cyclophosphamide, A = doxorubicin, F = 5-fluorouracil

*SOURCE:* Albain K et al. **Overall survival after cyclophosphamide, adriamycin, 5-FU, and tamoxifen (CAFT) is superior to T alone in postmenopausal, receptor(+), node (+) breast cancer: New findings from phase III Southwest Oncology Group Intergroup Trial S8814 (INT-0100).** *Proc ASCO* 2001.**Abstract 94.**

The trial enrolled 1,477 eligible patients of which 32 percent were 65 years of age and older, and 13 percent were 70 years of age and older. The first objective was to combine the two CAF arms and compare them to the tamoxifen-alone arm.

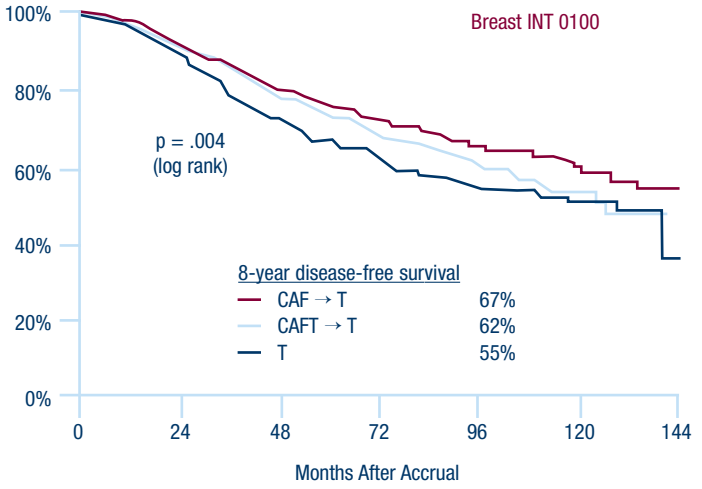
The eight-year, disease-free survival for tamoxifen alone was 55 percent and 67 percent for CAF followed by tamoxifen. That represented an absolute difference of 12 percent, which is almost unheard of in an adjuvant trial. Overall survival for tamoxifen alone and CAF followed by tamoxifen was 67 percent and 73 percent, respectively. The CAF with concurrent tamoxifen arm was in the middle.

In an updated analysis presented at ASCO 2002, we reported for the first time the breakout between the two chemotherapy arms. We still reported a major benefit for the combined chemotherapy arms compared to the tamoxifen-alone arm. That data was very mature for both disease-free survival and overall survival.

We found the eight-year, disease-free survival to be 76 percent for the CAF with sequential tamoxifen arm, 62 percent for the CAF with concurrent tamoxifen arm and 55 percent for the tamoxifen-alone arm. Although there was still a benefit for chemotherapy compared to tamoxifen alone, 50 percent of the chemotherapy benefit was lost by giving it concurrently with tamoxifen.

Frequently, I'm asked whether anastrozole would have the same effect when combined with chemotherapy, and there's just no data for that. Would shutting down estrogen production decrease the cycling of the cells, and would that matter? Or is it strictly an effect caused by tamoxifen interfering with drug uptake, and maybe anastrozole would not? I don't know the answer to those questions.

Intergroup trial 0100 comparing sequential versus concurrent CAF/tamoxifen versus tamoxifen: 8-year, disease-free survival




T=tamoxifen, C=cyclophosphamide, A=doxorubicin, F-5=fluorouracil

*SOURCE:* Presentation, KS Albain, North American Breast Intergroup Trial 0100, ASCO Virtual Meeting 2002.

Intergroup trial 0100: Relative improvement of CAF/tamoxifen to tamoxifen alone

Breast INT 0100: Relative Improvement Compared to Tamoxifen Alone*

| CAFT | DFS | S |
|---|---|---|
| Sequential | 44% | 25% |
| Concurrent | 23% | 16% |

*From hazard ratio estimates
T=tamoxifen, C=cyclophosphamide, A=doxorubicin, F-5=fluorouracil, DFS=disease-free survival, S=survival

*SOURCE:* Presentation, KS Albain, North American Breast Intergroup Trial 0100, ASCO Virtual Meeting 2002.

## Nonprotocol management of women with HER2-positive, metastatic breast cancer

In the Slamon pivotal-trial data, there was a survival benefit in a group of very poor-prognosis patients who were given a trastuzumab/chemotherapy

combination compared to a taxane or anthracycline-containing regimen alone — despite crossover to trastuzumab. Therefore, I'm a proponent of giving a taxane with trastuzumab, and now I will give a platinum agent also in hopes of optimizing survival.

There is more myelosuppression associated with trastuzumab/paclitaxel plus carboplatin than trastuzumab/paclitaxel. I've also been administering carboplatin/docetaxel with trastuzumab. With either of those regimens, I now give one dose of pegfilgrastim on day two in an effort to avoid the somewhat troublesome neutropenia.

## Pegfilgrastim in clinical practice

Since I've been using more of the platinum/taxane combinations in breast cancer, I like to prevent patients from being hospitalized due to neutropenic fever. I'll also use pegfilgrastim if I'm administering an anthracycline and docetaxel in the neoadjuvant setting or for rapid reduction in tumor burden. I've used that regimen enough to know that the patients will have a problem, therefore, I use pegfilgrastim with the first cycle.

## Future directions of breast cancer clinical research

The exciting era ahead will be to determine how to use the targeting agents and how to use a patient's own profile to determine which of these targeting agents should be prescribed. The bigger picture involves tapping into the microarray from an individual patient to select an optimal adjuvant regimen.

Another very exciting area is the upcoming analysis of our Intergroup data bank of very small tumors that were archived in the 1980s. Now, we have all of these markers that we can analyze, so we can come up with a prognostic score to determine who should receive adjuvant therapy.

There are exciting areas for survivorship and special populations research that I'm involved in through the committee I chair in SWOG — the Committee on Women and Special Populations. One such study we're about to mount is an ovarian protection study in women with ER/PR-negative disease who are ready to start adjuvant chemotherapy. They will be given a short course of an LHRH during their adjuvant therapy to put the ovaries into a rest mode until they complete their chemotherapy.

## Late cardiac effects of women randomized to CAF versus CMF

Dr Patricia Ganz reported on the late cardiac effects in women who were randomized to CAF or CMF. Five years after therapy, there was no significant difference in the incidence of ejection fractions that were below normal, but the mean ejection fraction was significantly lower for the women randomized to CAF. After another five years of follow-up, we're going to repeat the analyses.

Late cardiac effects of adjuvant CMF and CAF in women with node-negative breast cancer: Five to eight years after randomization

| | CAF (n=82) | CMF (n=75) | *p*-value |
|---|---|---|---|
| LVEF < 50% | 5% | 7% | NS |
| Mean LVEF | 61.2% | 64.9% | 0.006 |

CAF=cyclophosphamide/doxorubicin/5-fluorouracil, CMF=cyclophosphamide/methotrexate/5-fluorouracil, LVEF=left-ventricular ejection fraction

SOURCE: Ganz PA et al. **Late cardiac effects of adjuvant CMF vs CAF in women with node negative breast cancer treated on SWOG 8897: Initial results from SWOG 9342.** *Breast Cancer Res Treat* 2002;**Abstract 10.**

## Select publications

### *Publications discussed by Dr Albain*


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

Albain K et al. **Open-label, phase II, multicenter trial of ZD1839 ('Iressa') in patients with advanced breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 20.**

Albain KS et al. **Overall survival after cyclophosphamide, Adriamycin, 5-FU, and tamoxifen (CAFT) is superior to T alone in postmenopausal, receptor(+), node(+) breast cancer: New findings from Phase III Southwest Oncology Group Intergroup Trial S8814 (INT-0100).** *Proc ASCO* 2001;**Abstract 94.**

Ganz PA et al. **Late cardiac effects of adjuvant CMF vs CAF in women with node negative breast cancer treated on SWOG 8897: Initial results from SWOG 9342.** *Breast Cancer Res Treat* 2002;**Abstract 10.**

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.**

Robertson JFR et al. **A phase II study of ZD1839 ('Iressa') in tamoxifen-resistant ER-positive and endocrine-insensitive (ER-negative) breast cancer.** *Breast Cancer Res Treat* 2002;**Abstract 357.**

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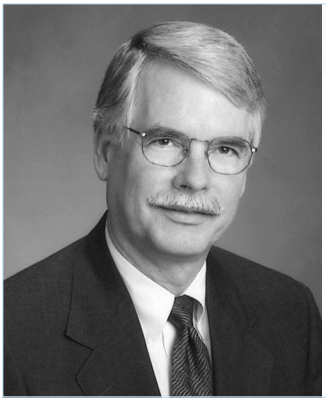

**Robert W Carlson, MD**

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# Edited comments by Dr Carlson

## Case discussion: 65-year-old woman with recurrent ER-positive, HER2-negative breast cancer

### *History*

This patient was initially diagnosed with breast cancer about a decade ago. She had ER-positive, HER2-negative, node-positive disease for which she received adjuvant CMF chemotherapy followed by tamoxifen.

Several years following the completion of tamoxifen, she experienced a biopsy-documented pulmonary recurrence. She had mediastinal lymphadenopathy with some tracheal compression evidenced by both chest X-ray and CT scan. She was active, although somewhat limited by dyspnea and cough, especially upon exertion. Her Karnofsky performance status was 70 to 80 percent. The symptoms had been evolving over several months.

Since the recurrence was quite symptomatic, she was treated initially with chemotherapy. We administered a three-hour paclitaxel infusion every three weeks, and she had a good response.

### *Follow-up*

She had symptomatic improvement quite rapidly in just four to six weeks. Ultimately, we were able to document the improvement radiographically, and we continued the taxane for about six months. She had achieved a radiographic complete response and was experiencing fatigue, alopecia and some neurotoxicity.

At that time her disease was not progressing. We discontinued the taxane and started her on anastrozole, which was maintained for a couple of years, and she continued to do well. Then she redeveloped a pulmonary recurrence that was detected radiographically. Her disease was persistently mediastinal, and she was having minimal coughing at that time.

We elected to continue hormonal therapy and switched her to fulvestrant in a single 5-mL injection. Her cough has improved, and serial chest X-rays and CT scans have documented continued improvement in her mediastinal disease. She has been on fulvestrant for almost one year.

### *Discussion*

If her disease progresses on fulvestrant and she doesn't have substantial end-organ dysfunction, I would consider another endocrine maneuver; megestrol acetate or ethinyl estradiol would be possibilities. Exemestane would also be a reasonable choice. Exemestane's toxicity profile is probably somewhat more acceptable than either megestrol acetate or ethinyl estradiol. The crossover rates of response from the nonsteroidal aromatase inhibitors to exemestane are quite modest.

When we have exhausted all hormonal therapy options, sequential single-agent vinorelbine or capecitabine would probably be my next choice for her. I would likely choose capecitabine over vinorelbine, but I think that either would be reasonable. Ultimately, she is almost certainly going to be treated with both agents.

Patients prefer the convenience of oral therapy, and the response rates for capecitabine are arguably equivalent to vinorelbine. Most patients tolerate vinorelbine, but it requires weekly administration, and a small number of women experience profound asthenia.

We do not start capecitabine at the FDA-approved dose. We typically use capecitabine at 2,000 mg/m$^2$ per day (total daily dose) divided in two doses for two weeks on and one week off. Most women tolerate that dose well for several cycles. The development of the hand-foot syndrome is a problem that ultimately may require either a dose reduction or prolongation of the one-week interval off therapy to two or sometimes even three weeks.

## Sequential single-agent versus combination chemotherapy

The available data support the use of either combination chemotherapy or sequential single agents in patients with metastatic disease. Typically, my practice is to use sequential single agents because there is generally less toxicity and, arguably, equivalent efficacy.

This is one situation in which the NCCN guidelines have changed dramatically in the last year. Previously, the guidelines called for combination chemotherapy in women with first relapse. They recommended the use of either CMF or CAF or a single-agent taxane and then, following failure, crossover to whatever had not been given.

The current NCCN guidelines acknowledge the uncertainty that combination chemotherapy is really superior. Now, we have a list of preferred single agents. We have a list of preferred combinations, and an acknowledgement that there is inadequate data to support a dogmatic statement about whether sequential

single agents or combination chemotherapy should be used. We also list a series of other active agents that could also be considered in the sequence.

### NCCN® Practice Guidelines: Preferred chemotherapy regimens for recurrent or metastatic breast cancer*

| Preferred agents | Preferred combinations | Other active agents |
|---|---|---|
| Anthracyclines | CAF/FAC | Gemcitabine |
| Taxanes | FEC | Platinoids |
| Capecitabine | AC | Oral etoposide |
| Vinorelbine | EC | Vinblastine |
| | AT | Fluorouracil CI |
| | CMF | |
| | Capecitabine/Docetaxel (XT) | |

C=cyclophosphamide, A=doxorubicin, F=fluorouracil, E=epirubicin, T=docetaxel or paclitaxel, M=methotrexate, CI=continuous infusion

*There is no compelling evidence that combination regimens are superior to sequential single agents.

*SOURCE:* National Comprehensive Cancer Network (NCCN®). **NCCN Clinical Practice Guidelines in Oncology, Breast Cancer - Version 2. 2003.**
Available at http://www.nccn.org/physician_gls/f_guidelines.html. Accessed July 9, 2003.

It's generally accepted that response rates are higher with combination chemotherapy. The duration of ultimate disease control, however, is not clearly superior for combination chemotherapy compared to sequential single agents.

The patient who is more ill when beginning therapy may be less able to tolerate aggressive combination chemotherapy; however, that's precisely the patient who needs aggressive combination chemotherapy. I think it's a situation in which clinical judgment is important, and it's crucial to involve the patient in the decision-making process.

## Chemotherapy followed by hormonal therapy

The practice of initially treating patients who have ER-positive breast cancer with chemotherapy and then switching to hormonal therapy is not addressed in the NCCN guidelines; however, it's a common strategy that makes sense.

In general, the NCCN guidelines classify women into two groups: those who should be given endocrine therapy until they sequence through all of them or develop organ impairment and those who should be given chemotherapy until they have exhausted all of the reasonable chemotherapy options.

The guidelines do, however, recommend that women who have substantial organ dysfunction — even those with hormone receptor-positive disease — be treated initially with cytotoxic chemotherapy.

## Fulvestrant in ER/PR-positive, postmenopausal patients with metastatic disease

Fulvestrant binds with the estrogen-receptor monomer in the cytoplasm and prevents the dimerization of the estrogen receptor, which is required for exertion of its maximal activity. Lack of estrogen-receptor dimerization results in accelerated degradation of the ER-fulvestrant complex. Ultimately, there is a loss of estrogen receptors within the cells.

The estrogen receptor is continually regenerated, so continued exposure to fulvestrant is required. After fulvestrant is discontinued, the estrogen receptor will, with time, reappear in cells. The fact that we see subsequent hormonal responses is convincing biological or clinical evidence that the estrogen receptors do reappear.

Injection site reactions and hot flashes are the only side effects that I've observed in patients receiving fulvestrant. There may be something about the administration technique for fulvestrant that can affect the pain that is infrequently experienced. If the injection is inadvertently given subcutaneously into fat, it's more painful than if it's given intramuscularly. It may be that many of the women who have pain with the injection are not actually receiving true intramuscular injections; this is more likely to occur in women who are obese.

## Sequencing of hormonal therapies

Women with breast cancer who fail on tamoxifen can clearly respond to fulvestrant, and the rate of response is equivalent to that seen with anastrozole. Also, in women with disease that has failed anastrozole who are then crossed over to fulvestrant, the rate of clinical benefit is substantial and in the range of about 40 percent. Patients who are crossed over from fulvestrant to aromatase inhibitors also show response rates around 40 percent.

Surprisingly, the magnitude of benefit from fulvestrant does not predict whether the cancer will respond to a subsequent hormonal maneuver. One rule of thumb in the past has been that the magnitude and duration of response to the most recent hormonal therapy predicts for the likelihood of response for subsequent hormonal therapies. A small retrospective study suggests that may not be the case with fulvestrant.

## Novel hormonal therapy combinations

There is an increasing body of preclinical evidence suggesting that breast cancers that become resistant to tamoxifen or fulvestrant have upregulation of epidermal growth factor receptor (EGFR) and HER2 expression. As those endocrine-sensitive cells become endocrine-resistant and the EGFR and HER2 upregulate, some of the sensitivity to the endocrine agents may return if those cells are exposed to EGFR inhibitors.

There are series of trials being conducted to evaluate the role of fulvestrant or other hormonal agents in combination with gefitinib. ECOG is initiating a Phase II randomized trial comparing fulvestrant/gefitinib to anastrozole/gefitinib.

**Phase II Randomized Study of Anastrozole and Gefitinib Versus Fulvestrant and Gefitinib in Postmenopausal Women with Recurrent or Metastatic Hormone Receptor-Positive Breast Cancer** **Approved protocol, not yet active**

Protocol ID: E-4101

Projected Accrual: 148 patients

Eligibility: Patients with ER/PR-positive, recurrent or metastatic breast cancer not treated with hormonal therapy for metastatic disease

ARM 1: Anastrozole + gefitinib
ARM 2: Fulvestrant + gefitinib

Courses in both arms repeat every 28 days in the absence of disease progression or unacceptable toxicity. Patients are followed every three months for two years, every six months for three years, and then annually.

Study Contact:
Eastern Cooperative Oncology Group, Robert Carlson, Chair, Tel: 650-723-7621

*SOURCE:* NCI Physician Data Query, July 2003.

Trastuzumab in combination with fulvestrant would be a very interesting study. There is evidence that HER2-overexpressing tumors are relatively more hormone-resistant. There's a lot of cross talk between those pathways, and that study would be similar to the studies looking at gefitinib plus fulvestrant. We can extend that thinking even further and look at the utilization of hormonal therapies in combination with an EGFR inhibitor and a HER2 inhibitor.

The combination of an aromatase inhibitor and fulvestrant is of some interest, but the difficulty with such a study is that fulvestrant eliminates the estrogen receptor. Theoretically, if the estrogen receptor is eliminated, then the cells shouldn't care how much estrogen is present.

## ATAC trial results

Many of us were surprised that anastrozole alone was superior to tamoxifen in the ATAC trial. The difference in contralateral breast cancers was remarkable, with a 75 percent risk reduction for anastrozole compared to what we would expect with placebo.

I'm not totally surprised that the differences were seen so soon; presumably most of the breast cancers prevented from being diagnosed in those women were pre-existing breast cancers. Relatively few women in the ATAC trial actually received cytotoxic chemotherapy, so the contralateral breast cancers should have already been present.

The ATAC trial is an important trial biologically, demonstrating that the aromatase inhibitors likely have a very important role in early breast cancer. The differences seen between tamoxifen and anastrozole, especially if they're maintained with further follow-up, are substantial and clinically significant.

## Implications of the ATAC trial on clinical practice

As a result of the ATAC trial, my practice pattern changed overnight. I am not treating all of my patients with anastrozole, but I am certainly discussing the results of the ATAC trial and the pros and cons for tamoxifen and anastrozole. I'm using shared decision-making with patients to determine which of the agents they prefer. The recent update at the San Antonio meeting in December 2002 confirmed that practice.

Generally, I recommend anastrozole; however, there are other factors to consider that would sway me one way or another. Obviously, in women with an absolute or relative contraindication to tamoxifen, it's a very easy decision. Conversely, there are patients who may have relative contraindications to anastrozole.

The major relative contraindication is severe osteoporosis. The bone mineral density loss associated with the aromatase inhibitors is a concern. Presumably, we can blunt that effect using bisphosphonates, so it is unlikely to be a major problem.

The patient's nodal status does not make a great deal of difference to me in terms of hormonal therapy recommendations. I look at the patient's HER2 status, and it does shade my thinking a bit. There is some data, although somewhat contradictory, that HER2-overexpressing tumors may be relatively resistant to tamoxifen.

Likewise, there is data suggesting that both letrozole and anastrozole maintain antitumor activity in HER2-overexpressing tumors. I think it would be reasonable to consider anastrozole, in preference to tamoxifen, for patients with tumors that have an IHC score of 2+ or 3+.

## NCCN Practice Guidelines: Adjuvant hormonal therapy

In response to the initial presentation of the ATAC results, the NCCN guidelines were modified. Tamoxifen was maintained as the recommended adjuvant therapy in the text of the guidelines. There is, however, a footnote to the guidelines stating that anastrozole should be considered as an alternative to tamoxifen. The guidelines recommend a discussion between the physician and the patient regarding tamoxifen and anastrozole as adjuvant therapy.

The guidelines state that anastrozole may, in fact, be superior to tamoxifen, but we need to recognize there is short follow-up with adjuvant anastrozole relative to very long follow-up with tamoxifen. Because of that, it's difficult to be dogmatic.

To some extent, it depends on the woman — is she someone who is an early adaptor of a new therapy, or is she someone who is more conservative in terms of adopting new technology or new therapies?

### 2003 NCCN® practice guidelines: Adjuvant hormonal therapy

- Tamoxifen 20 mg/d for 5 years
- Anastrozole 1 mg/d for 5 years

"Early evidence from a single, large, double-blind, randomized clinical trial demonstrates that anastrozole provides superior disease-free survival and a favorable toxicity profile compared to tamoxifen as adjuvant therapy for hormone receptor-positive breast cancer in women. Additional follow-up of this trial and additional experience is required before definitive conclusions can be made.

At the current time, anastrozole may be considered as an option to tamoxifen after discussion of the available data between the physician and patient. These data do not address whether women currently on tamoxifen should be changed to anastrozole. Anastrozole is not appropriate therapy for premenopausal women."

*SOURCE:* National Comprehensive Cancer Network (NCCN®). **NCCN Clinical Practice Guidelines in Oncology, Breast Cancer — Version 2. 2003.** Available at http://www.nccn.org/physician_gls/f_guidelines.html. Accessed July 9, 2003.

## ASCO Technology Assessment regarding adjuvant aromatase inhibitors

The ASCO Technology Assessment is a superb document, but it needs to be viewed for exactly what it is. A technology assessment looks at a given therapy, attempts to decide whether that therapy has utility in a given clinical situation and determines what the preponderance of data is within that clinical situation. The ASCO Technology Assessment, in both the first and second versions, states that tamoxifen remains the standard adjuvant therapy to which other therapies should be compared.

Interestingly, several members of the ASCO Technology Panel also sit on the NCCN Practice Guidelines Panel. When the NCCN Practice Guidelines Panel looked at this issue, there was no major dissension in considering anastrozole as an option. The difference between groups occurred because of the different processes.

The ASCO Technology Assessment is strictly evidence-based, and it cannot go beyond the evidence. So, there are no extrapolations beyond five years of anastrozole or the 47 months of follow-up.

In the NCCN Practice Guidelines process, we use a methodology called evidence-based consensus. We establish recommendations based on evidence, but we are also able to use expert consensus in situations where the evidence is lacking. Obviously, 10-year data with adjuvant anastrozole are lacking, but we can come up with expectations about what might happen and make recommendations that extrapolate into the unknown.

The NCCN Practice Guidelines are patient-focused, and they look at the various therapies that are available from a patient's perspective. The NCCN Guidelines Panel believes that women should consider the use of anastrozole, although we don't say it should necessarily be used in preference to tamoxifen.

## Nonprotocol use of adjuvant letrozole or exemestane

I'm not using either letrozole or exemestane in the adjuvant, nonprotocol setting, primarily because all the data we have is with anastrozole. I await, with a great deal of interest, the results of the many ongoing adjuvant trials evaluating letrozole and exemestane. Until we have that data, I think it's premature to consider they are equal or even superior to anastrozole in the adjuvant setting.

## CALGB-49907: Adjuvant chemotherapy trial in elderly women

I anticipate we will participate in Hyman Muss' trial comparing capecitabine to CA or CMF in the adjuvant setting. It's an excellent study that will compare a well-tolerated single agent to two generally well-tolerated combinations.

The difficulty with that study is two-fold. First, the magnitude of benefit from cytotoxic chemotherapy in older women is not clear, and if there are benefits, they are likely to be small. Second, it's going to be very difficult to detect differences between the combination arm and the single-agent arm if, in fact, they exist, because they are likely to be so small.

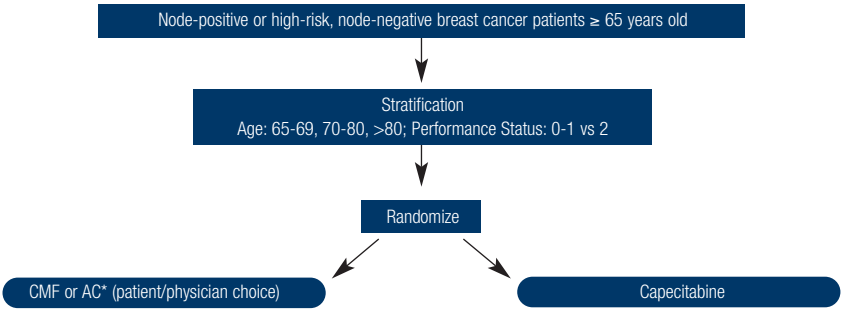
There is likely to be a significant difference in quality of life, side effects and tolerability for the three regimens. Which of those regimens — AC or CMF or single-agent capecitabine — will ultimately be better tolerated is relatively unpredictable. The hand-foot syndrome associated with capecitabine is a problem for many women, and whether they will find it more acceptable than the nausea, vomiting, alopecia, etc., associated with CMF and AC, we'll have to wait and see.

All women are concerned about alopecia as a side effect, but many women would find alopecia an acceptable side effect for the benefits associated with cytotoxic chemotherapy. However, I'm equally confident that no woman looks forward to experiencing alopecia. We underestimate how much of an issue alopecia is for women; it is very commonly the most feared side effect.

Women who have nausea and vomiting realize it's something they can experience in the privacy of their home. The same applies to myelosuppression; women may have problems with fever and neutropenia, but when they walk out of their home nobody realizes they have myelosuppression. Women who have alopecia feel very uncomfortable when they walk outside their home. Many are quite uncomfortable with their wigs and don't feel they look good. Alopecia is the toxicity women complain to me about the most.

Oral therapy is always advantageous for the compliant patient. One of the difficulties is assuring that the patients are compliant with their therapy. The oral regimens are especially beneficial in situations where accessibility to a medical oncologist is limited — in rural and underserved communities.

CALGB 49907: A randomized trial of adjuvant chemotherapy with standard regimens (CMF or AC) versus capecitabine in women 65 years and older with node-positive or high-risk, node-negative breast cancer




* Patients whose LVEF is not within lower limits of normal must receive CMF, not AC.
All ER+ or PR+ patients receive tamoxifen x 5 years.

*SOURCE:* CALGB 49907 Protocol.

## Adjuvant dose-dense chemotherapy

My expectation is that we will see dose-dense chemotherapy added to the NCCN Practice Guidelines. The real question is: How will it be weighted within the guidelines? If one looks at the duration of follow-up and magnitude of risk reduction with dose-dense chemotherapy compared to what is achieved with anastrozole, they are almost superimposable.

I have started using dose-dense therapy in selected patients. As we translate the results of dose-dense therapy into practice, one needs to be careful about who is selected for such therapies. Initially, I tend to use it more in the younger, high-risk patient. As I become more familiar with it, my indications will expand. We also need be cautious not to jump to the conclusion that dose-dense therapy will be superior when long-term data are available. I'm hopeful that it will be, I expect it to be, but we're going to have to continually look at that data.

## Select publications

### *Publications discussed by Dr Carlson*

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## *Role of gefitinib in breast cancer*

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Robertson JFR et al. **Gefitinib (ZD1839) is active in acquired tamoxifen (TAM)-resistant oestrogen receptor (ER)-positive and ER-negative breast cancer: Results from a phase II study.** *Proc ASCO* 2003;**Abstract 23.**

# Post-test: Breast Cancer Update, Issue 6, 2003

## Conversations with Oncology Leaders

*Bridging the Gap between Research and Patient Care*

QUESTIONS (PLEASE CIRCLE ANSWER):

**1. According to the NCCN Clinical Practice Guidelines, there is compelling evidence that combination chemotherapy regimens are superior to sequential single agents in the treatment of women with metastatic or recurrent breast cancer.**

a. True
b. False

**2. The NCCN Clinical Practice Guidelines list which of the following as preferred chemotherapy agents for the treatment of women with recurrent or metastatic breast cancer:**

a. Anthracyclines
b. Taxanes
c. Capecitabine
d. Vinorelbine
e. Any of the above

**3. In the Phase II trial of gefitinib in women with metastatic breast cancer, the majority of patients had disease that achieved a partial response.**

a. True
b. False

**4. In the Phase II gefitinib trial, five out of 12 patients with bone pain had dramatic relief of their pain.**

a. True
b. False

**5. Intergroup trial 0100 demonstrated that which of the following adjuvant regimens had the best eight-year, disease-free survival in postmenopausal women with node-positive, receptor-positive breast cancer?**

a. CAF
b. CAF with concurrent tamoxifen
c. CAF with sequential tamoxifen

**6. NSABP-B-35 randomizes patients with DCIS to tamoxifen or _____.**

a. Exemestane
b. Anastrozole
c. Letrozole
d. Fulvestrant

**7. Khan et al demonstrated that, compared to no surgery, resection of the primary tumor in patients presenting *de novo* with metastatic disease resulted in:**

a. Inferior overall survival
b. Equivalent overall survival
c. Improvement in overall survival

**8. The IBIS-II chemoprevention trial evaluates anastrozole versus placebo in high-risk women.**

a. True
b. False

**9. The STAR trial compares tamoxifen versus raloxifene in postmenopausal women at increased risk for breast cancer.**

a. True
b. False

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

# Evaluation Form: Breast Cancer Update, Issue 6, 2003

NL Communications Inc 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 HER2-positive breast cancer patients in your practice ..... 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 ER-positive, postmenopausal patients 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 6

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

- Utilize the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines when selecting chemotherapy, hormonal therapy and biologic therapy for patients with breast cancer ..... 5 4 3 2 1
- Consider the implications of the Phase II trial of gefitinib in women with metastatic breast cancer for the treatment of patients with metastases progressing on previous chemotherapy regimens ..... 5 4 3 2 1
- Determine which clinical trials are available to patients who are at high risk for developing breast cancer in order to counsel select patients who are interested in breast cancer chemoprevention ..... 5 4 3 2 1
- Discuss the use of sequential single-agent versus combination chemotherapy for the treatment of metastatic breast cancer ..... 5 4 3 2 1

## EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

| Faculty | Knowledge of Subject Matter | Effectiveness as an Educator |
|---|---|---|
| Monica Morrow, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Joyce O'Shaughnessy, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Kathy S Albain, MD | 5 4 3 2 1 | 5 4 3 2 1 |
| Robert W Carlson, 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 6, 2003

*Please Print Clearly*

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NL Communications Inc designates this educational activity for a maximum of 3.25 category 1 credits towards the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent on the activity. I certify my actual time spent to complete this educational activity to be ___ hour(s).

Signature: _____

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

___Yes ___No

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

_____

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

_____

_____

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

_____

_____

**Degree:**

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

To obtain a certificate of completion and receive credit for this activity, please complete the post-test, fill out the evaluation form and mail or fax both to: NL Communications Inc, 400 SE Second Avenue, Suite 401, Miami, FL 33131-2117, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.