In the NSABP-P-1 and IBIS-1 trials, chemoprevention with tamoxifen was found to reduce the incidence of breast cancer in women at higher risk. The ATAC adjuvant trial demonstrated a further reduction in the incidence of contralateral breast cancer with anastrozole compared to tamoxifen. The aromatase inhibitors are being evaluated in ongoing chemoprevention trials in postmenopausal women. In addition to the reduced rate of second cancers, the more favorable safety and tolerability of these agents is the basis for evaluation in the high-risk setting. NSABP-P-2 (the STAR trial) compares tamoxifen to raloxifene, and it is likely that the agent with the better risk-benefit ratio will be compared in a new trial to an aromatase inhibitor.

**SELECT PUBLICATIONS**


Ongoing or Recently Closed Chemoprevention and DCIS Trials

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Eligibility</th>
<th>Target accrual</th>
<th>Schema</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS-NCI-MAT-01</td>
<td>High risk, premenopausal, age 35 and over</td>
<td>4,550</td>
<td>Exemestone vs placebo</td>
</tr>
<tr>
<td>CAS-NCI-MAT-02</td>
<td>High risk, premenopausal, age 35 and over</td>
<td>100</td>
<td>Exemestone + tamoxifen vs exemestone</td>
</tr>
<tr>
<td>SMGS-O1100</td>
<td>High risk, premenopausal, age 10 and over</td>
<td>100</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>DDP-O1024, USA-2010311-02</td>
<td>High risk based on estrodiol level ≥ 9 pg/mL, premenopausal, age 10 and over</td>
<td>110</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>UTSWMC-1093-02</td>
<td>High risk, pre- or postmenopausal, age 25 and over</td>
<td>120</td>
<td>Tamoxifen vs placebo</td>
</tr>
<tr>
<td>KOSC-MRC-0119-02</td>
<td>High risk for ER-positive, age 15 to 25</td>
<td>110</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>BCM-H-9315</td>
<td>High risk, premenopausal, age 21 to 45</td>
<td>10</td>
<td>Bexarotene vs placebo</td>
</tr>
<tr>
<td>NCI-NCI-0502</td>
<td>Tamoxifen for risk reduction in women with risk factors for breast and ovarian cancer</td>
<td>100</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>CRCU-BBS-6, EU-20027</td>
<td>High risk, ER/PR-positive ≥7% positive nuclei in patients with prior DCIS, premenopausal, age 45 to 70</td>
<td>6,000</td>
<td>Anastrozole vs placebo</td>
</tr>
<tr>
<td>CAS-NCI-MAT-03</td>
<td>High risk, BRCA1/2 mutation, BRCA mutation, BRCA1 or BRCA2 mutation, premenopausal, age 10 and over</td>
<td>125</td>
<td>Exemestone vs placebo</td>
</tr>
<tr>
<td>NNM-IBR-ADDA, EU-20003, EU-200035</td>
<td>High genetic risk, premenopausal, age 40 to 45</td>
<td>150</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>BCM-O375</td>
<td>Known carrier or at-risk for BRCA1 or BRCA2 mutation, premenopausal, age 40 and over</td>
<td>100</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>NCI-NCI-0402</td>
<td>High risk, premenopausal, age 35 and over</td>
<td>18,000</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>CRCU-BBS-6-CIS, BBS-5-002, EU-20265</td>
<td>Postmenopausal, age 40 to 70, ER/PR-positive ≥5% positive nuclei, DCIS</td>
<td>4,000</td>
<td>Anastrozole vs tamoxifen</td>
</tr>
<tr>
<td>CRCU-BBS-6-305</td>
<td>Postmenopausal, ER/PR-positive or borderline, DCIS</td>
<td>3,000</td>
<td>placebo vs placebo</td>
</tr>
</tbody>
</table>

**CONTRALTERNATE BREAST CANCER IN TRIALS OF ADJUVANT AROMATASE INHIBITORS**

<table>
<thead>
<tr>
<th>ATAC</th>
<th>BIS-5-9P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>2.0</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>0.5</td>
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</tbody>
</table>

**KEY ADVERSE EVENTS IN ADJUVANT TRIALS OF AROMATASE INHIBITORS VERSUS TAMOXIFEN**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ATAC</th>
<th>BIS-5-9P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractures</td>
<td>11.0%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Venous thromboembolic events</td>
<td>2.8%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>1.3%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Fractures</td>
<td>11.0%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

**ONGOING OR RECENTLY CLOSED CHEMOPREVENTION AND DCIS TRIALS**

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Eligibility</th>
<th>Target accrual</th>
<th>Schema</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS-NCI-MAT-03</td>
<td>High risk, premenopausal, age 35 and over</td>
<td>125</td>
<td>Exemestone vs placebo</td>
</tr>
<tr>
<td>NNM-IBR-ADDA, EU-20003, EU-200035</td>
<td>High genetic risk, premenopausal, age 40 to 45</td>
<td>150</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>BCM-O375</td>
<td>Known carrier or at-risk for BRCA1 or BRCA2 mutation, premenopausal, age 40 and over</td>
<td>100</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>NCI-NCI-0402</td>
<td>High risk, premenopausal, age 35 and over</td>
<td>18,000</td>
<td>placebo vs placebo</td>
</tr>
<tr>
<td>CRCU-BBS-6-CIS, BBS-5-002, EU-20265</td>
<td>Postmenopausal, age 40 to 70, ER/PR-positive ≥5% positive nuclei, DCIS</td>
<td>4,000</td>
<td>Anastrozole vs tamoxifen</td>
</tr>
<tr>
<td>CRCU-BBS-6-305</td>
<td>Postmenopausal, ER/PR-positive or borderline, DCIS</td>
<td>3,000</td>
<td>placebo vs placebo</td>
</tr>
</tbody>
</table>

**ATAC TRIAL DATA ON SECOND BREAST CANCERS**

The incidence of contralateral breast cancer was substantially reduced by anastrozole compared with tamoxifen. … Some might argue that the reduction of contralateral breast cancer in ATAC looks less promising with the updated data than with the original data — it has gone from about 60 to about 50 percent relative reduction in contralateral breast cancer in the receptor-positive group. We had the same experience earlier with tamoxifen. This suggests that these agents don’t prevent cancer but rather delay the appearance of cancer. Perhaps anastrozole delays the appearance of breast cancer longer than tamoxifen. I am very confident that anastrozole will reduce the risk of new receptor-positive breast cancers — the adjuvant setting will predict the present setting. The issue to me is the trade-off and harm-to-benefit ratio.

**RATIONALIZE FOR CLINICAL TRIALS OF AROMATASE INHIBITORS IN THE PREVENTATIVE SETTING**

Data from the adjuvant trials provide a compelling rationale for exploring the use of AIs in the prevention setting. Their efficiency is greater than that of tamoxifen, especially for new contralateral cancers, suggesting that 70% to 80% of ER-positive breast cancers can be prevented with these drugs.

The AIs are better tolerated than tamoxifen, without the gynecologic and thrombotic complications, but do lead to bone mineral loss and increased fracture risk in the absence of additional bone-sparing therapy. An important question will be the effectiveness of bisphosphonates in arresting and/or reversing bone loss associated with the almost complete depletion of estrogen associated with AIs.

**SIDE-EFFECT PROFILE OF AROMATASE INHIBITORS COMPARED TO TAMOXIFEN**

The safety profile in the ATAC update still favors anastrozole. The incidence of endometrial cancer is 0.2 percent with anastrozole and 0.8 percent with tamoxifen. The occurrence of venous thromboembolic disease may be twice the rate of hysterectomy with tamoxifen and only slightly over one percent with anastrozole. Also, with anastrozole we seldom see gynecological side effects, such as bleeding or discharge, and we saw no increased risk of strokes or pulmonary embolism.

**REFERENCES**


In women with early breast cancer, tools that predict both a prognosis and benefit from adjuvant chemotherapy are invaluable to both clinicians and patients. In women with ER-positive, node-negative breast cancer treated with adjuvant tamoxifen, a 21-gene assay was recently found by the NSABP to predict the 10-year distant recurrence rate and the benefit associated with adjuvant chemotherapy. Additional data on this assay will be presented at this meeting. Another valuable resource is the Adjuvant! Online computer program, developed by Dr Peter Ravdin, which allows for the calculation of outcomes in women with early breast cancer. In a presentation at the 2004 ASCO meeting, the predictions from Adjuvant! were found to be comparable to actual outcomes observed in patients from British Columbia. These and future tools that predict outcomes should aid in making decisions about adjuvant therapies.

### Table: Predicting Prognosis in Women with Early Breast Cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10-year OS</th>
<th>10-year DCRS</th>
<th>10-year RPSS</th>
<th>10-year EFS</th>
<th>10-year RPSS</th>
<th>10-year DCRS</th>
<th>10-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>85.0%</td>
<td>74.0%</td>
<td>73.0%</td>
<td>85.0%</td>
<td>74.0%</td>
<td>73.0%</td>
<td>85.0%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>73.0%</td>
<td>62.0%</td>
<td>61.0%</td>
<td>73.0%</td>
<td>62.0%</td>
<td>61.0%</td>
<td>73.0%</td>
</tr>
<tr>
<td>High risk</td>
<td>60.0%</td>
<td>49.0%</td>
<td>48.0%</td>
<td>60.0%</td>
<td>49.0%</td>
<td>48.0%</td>
<td>60.0%</td>
</tr>
</tbody>
</table>

### NSABP-B-20 CHEMOTHERAPY BENEFIT STUDY IN PATIENTS WITH NODE-POSITIVE, ER-POSITIVE DISEASE

**Objective:** Determine whether the 21-gene recurrence score assay captures prognosis, response to tamoxifen or both.

**Operational:** Eight hundred and sixty-six eligible patients randomized to tamoxifen alone, tamoxifen plus CMF, or tamoxifen plus MF chemotherapy.

**Results:** No survival advantage was demonstrated for any benefit or not remains a question.

**Adjuvant! Online** captures prognosis, response to tamoxifen or both. This and future tools that predict outcomes should aid in making decisions about adjuvant therapies.
Can Alterations in Diet and Exercise Reduce the Risk of Relapse and Death from Early Breast Cancer?

Evidence from a number of recent studies suggest that lifestyle factors, such as diet and physical activity, may reduce the risk of recurrence in patients with early breast cancer. At the 2005 ASCO meeting, Rowan Chlebowski reported the initial results of the Women’s Intervention Nutrition Study (WINS), a randomized trial conducted at 37 centers in the United States, which demonstrated a reduction in relapse rate as a result of a modest decrease in dietary fat intake. Surprisingly, this benefit was confined to patients with estrogen receptor-negative breast cancer. Another recent report by Holmes and colleagues demonstrated a reduction in recurrence rate and mortality in breast cancer patients who engaged in regular physical activity, particularly in patients with estrogen-receptor-positive tumors. The clinical and research implications of these and other related clinical research findings on complementary oncologic interventions are uncertain but are likely to be of great interest to patients with breast cancer.

RECENT STUDIES EVALUATING THE ASSOCIATION BETWEEN DIETARY FACTORS AND BREAST CANCER RECURRENT

<table>
<thead>
<tr>
<th>Study</th>
<th>S</th>
<th>Status</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life Without Cancer Epidemiology</td>
<td>2,410</td>
<td>Ongoing</td>
<td>Detailed data on dietary intake, physical activity, weight change and recurrence collected at regular intervals.</td>
</tr>
<tr>
<td>Women's Healthy Eating and Living (WHEL)</td>
<td>3,038</td>
<td>Ongoing</td>
<td>Comprehensive dietary interventions to increase vegetable intake versus control. A random sample collected at baseline and 24-week intervals to establish the biological link between dietary intake, nutritional factors and the progression of breast cancer.</td>
</tr>
</tbody>
</table>

WINS TRIAL DESIGN — RECRUITMENT 1994-2001, MEDIAN FOLLOW-UP: 60 MONTHS

Eligibility: Women 50-74 years early breast cancer; primary tumor ≤ 2 cm; estrogen receptor+, randomized therapy; dietary fat intake < 35% of calories

<table>
<thead>
<tr>
<th>TREATMENT GROUP</th>
<th>Study N</th>
<th>Status</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1 Dietary intervention (n = 975) to reduce fat intake while maintaining nutritional adequacy</td>
<td>975</td>
<td>Randomized</td>
<td>Dietary intervention to reduce fat intake as an adjunct to standard breast cancer therapy versus control with disease recurrence and survival as the trial endpoint.</td>
</tr>
</tbody>
</table>

PHYSICAL ACTIVITY AND SURVIVAL AFTER BREAST CANCER DIAGNOSIS

Objective: Determine effect of exercise on breast cancer recurrence and survival

- Assessing activity and participants: Prospective observational study of 2,801 women from the Nurse’s Health Study who were diagnosed with Stage I-II breast cancer between 1984-1998 and followed until death or 2002
- Assessment of physical activity: Assessment of eight activities, including duration and intensity, 1 year after breast cancer diagnosis
- Outcome: Breast cancer mortality according to metabolic equivalent task hours per week (MET-hr/wk) of physical activity

EXAMPIES OF MET SCORES

- SITTING quietly: 1.0 MET
- Walking at average pace: 3.0 MET
- Jogging: 7.0 MET
- Running: 12.0 MET
- MET: metabolic equivalent task


PROBABILITY OF BREAST CANCER MORTALITY BASED ON MET-HOURS PER WEEK OF PHYSICAL ACTIVITY

- Ten-year survival rates: ≤ 0.85 MET-hr/wk: 100% 0.85-3.0 MET-hr/wk: 85% ≥ 3.0 MET-hr/wk: 75%


SELECT PUBLICATIONS


Rowan T Chlebowski, MD, PhD. Breast Cancer Update 2006 (7)

WOMEN’S INTERVENTION NUTRITION STUDY (WINS): DIETARY FAT INTAKE AND RISK OF RECURRENCE

The issue of dietary fat intake has been around in breast cancer for about 25 years. To address this issue, we conducted a randomized clinical trial and entered 2,437 women about 220 days after initial surgery. Patients at 37 centers in the United States were entered after they completed their primary therapy. The diet group was given a dietary fat gram goal by centrally trained registered dieters, implementing a predefined, low-fat eating plan. Patients received eight biweekly individual counseling sessions, then one session every three months. Monthly group sessions were held, and patients self-monitored their fat intake. The control group saw the dieters every three months and talked about nutritional adequacy. Fat gram intake for the intervention group went from about 56 to 33 fat grams per day — about a 40 percent reduction in daily fat gram intake, which was sustained by most of the individuals.

Our primary study endpoint was relapse-free survival, which included all breast cancer recurrence sites, including contralateral breast cancers. We found that the dietary group had a longer relapse-free survival than the control population. In the control group, 12.4 percent had a relapse compared to 9.8 in the diet group, which was a 2.6 percent absolute difference at five years, or a 24 percent reduction in risk of recurrence. We did subgroup analysis by receptor status. The benefit in relapse-free survival was 0.85% for relapse-free survival in patients with estrogen receptor-positive tumors and not significant. In the 478 patients with ER-negative disease, the hazard ratio was 0.58, with a 42 percent reduction in risk and eight percent absolute difference at five years. This hypothesis is generating but rather intriguing to us.

— Rowan T Chlebowski, MD, PhD, Breast Cancer Update 2006 (7)

PHYSICAL ACTIVITY AND SURVIVAL AFTER BREAST CANCER

An expert panel of the International Agency for Research on Cancer of the World Health Organization estimated a 20% to 40% decrease in the risk of developing breast cancer among the most physically active women, regardless of menopausal status, type, or intensity of activity...

Women who engaged in an amount of physical activity equivalent to walking one or more hours per week had better outcomes compared with those who exercised less than that or not at all. After adjusting for factors predictive of survival after breast cancer, the RRs of adverse outcomes including death, breast cancer death, and breast cancer recurrence were 26% to 40% lower among women exercising more than 2.5 hours per week compared with those who exercised less than that or not at all.

— Michelle D Holmes, MD, PhD et al. JAMA 2005;293(20):2479-86.

FRUIT AND VEGETABLE INTAKE, PLASMA CAROTENOIDS AND RISK OF RECURRENCE

Being in the highest versus the lowest quartile of plasma total carotenoid concentration was associated with an estimated 63% reduction in risk for a new breast cancer event. Plasma carotenoids are a biologic marker of vegetable and fruit intake, so these results support the suggestion from prior studies, based on self-reported dietary intakes, that increased consumption of these foods may reduce the risk of recurrence or increase the likelihood of survival after the initial diagnosis and treatment of breast cancer.

Aromatase Inhibitors as Adjuvant Therapy

In the 68-month follow-up of the ATAC trial, adjuvant anastrozole continued to significantly prolong disease-free survival and time to recurrence and reduce distant metastases and contralateral breast cancers compared to tamoxifen. Data presented at the 2003 and 2004 San Antonio Breast Cancer Symposia demonstrated a greater advantage associated with adjuvant anastrozole in women with ER-positive, PR-negative tumors as compared to ER/PR-positive tumors. BIG FEMTA, a second trial comparing an aromatase inhibitor to tamoxifen, has now also demonstrated with less than three years of follow-up a significant improvement in disease-free survival, time to recurrence and time to distant metastases with adjuvant letrozole. An ongoing clinical trial will now compare the efficacy of two aromatase inhibitors — anastrozole and exemestane — as adjuvant therapy in women with hormone receptor-positive breast cancer.

ATAC TRIAL 68-MONTH ANALYSIS: EFFICACY ENDPOINTS AND TIMES TO RECURRENCE

- **ALL patients & HR+ patients**
  - **Tamoxifen**
    - Disease-free survival: 0.87 (95% CI: 0.84-0.89)
    - Time to recurrence: 0.86 (95% CI: 0.84-0.88)
    - Overall survival: 0.87 (95% CI: 0.83-0.89)
    - Time to breast cancer death: 0.86 (95% CI: 0.84-0.88)
  - **Anastrozole**
    - Disease-free survival: 0.74 (95% CI: 0.71-0.77)
    - Time to recurrence: 0.78 (95% CI: 0.75-0.82)
    - Overall survival: 0.78 (95% CI: 0.73-0.83)
    - Time to breast cancer death: 0.78 (95% CI: 0.74-0.83)

- **HR-positive patients**
  - **Tamoxifen**
    - Disease-free survival: 0.74 (95% CI: 0.67-0.79)
    - Time to recurrence: 0.78 (95% CI: 0.74-0.83)
    - Overall survival: 0.78 (95% CI: 0.73-0.83)
    - Time to breast cancer death: 0.78 (95% CI: 0.74-0.83)
  - **Anastrozole**
    - Disease-free survival: 0.70 (95% CI: 0.63-0.76)
    - Time to recurrence: 0.74 (95% CI: 0.68-0.80)
    - Overall survival: 0.74 (95% CI: 0.68-0.80)
    - Time to breast cancer death: 0.74 (95% CI: 0.68-0.80)

**Adjuvant exemestane versus anastrozole in postmenopausal women**

- **Tamoxifen x 5 years**
  - Disease-free survival: 0.84 —
  - Time to recurrence: —
  - Overall survival: 1.00 —
  - Time to breast cancer death: —

- **Letrozole x 5 years**
  - Disease-free survival: 0.84 —
  - Time to recurrence: —
  - Overall survival: 1.00 —
  - Time to breast cancer death: —

**Adjuvant exemestane versus anastrozole in postmenopausal women**

- **Tamoxifen x 5 years**
  - Disease-free survival: 0.84 —
  - Time to recurrence: —
  - Overall survival: 1.00 —
  - Time to breast cancer death: —

- **Anastrozole x 5 years**
  - Disease-free survival: 0.84 —
  - Time to recurrence: —
  - Overall survival: 1.00 —
  - Time to breast cancer death: —

**Prevalence of recurrence (%)**

- **Anastrozole**
  - 0.05
  - 0.01
  - 0.00

- **Tamoxifen**
  - 0.08
  - 0.05
  - 0.01

**Numbers at risk**

- **Anastrozole**
  - 2,182
  - 2,182
  - 2,182

- **Tamoxifen**
  - 1,570
  - 1,570
  - 1,570

**BIG FEMTA/IBIS-1 5/6: LETROZOLE VERSUS TAMOXIFEN AS ADJUVANT ENDOCRINE THERAPY**

- **ARM 1**
  - Tamoxifen x 5 years
  - Disease-free survival: 0.83 (95% CI: 0.70-0.93)
  - Time to breast cancer death: 0.86 (95% CI: 0.64-0.87)

- **ARM 2**
  - Letrozole x 5 years
  - Disease-free survival: 0.85 (95% CI: 0.72-0.94)
  - Time to breast cancer death: 0.87 (95% CI: 0.65-1.10)

**ADJUVANT EXEMESTANE VERSUS TAMOXIFEN IN POSTMENOPAUSAL WOMEN**

- **Tamoxifen x 5 years**
  - Disease-free survival: 0.84 —
  - Time to recurrence: —
  - Overall survival: 1.00 —
  - Time to breast cancer death: —

- **Letrozole x 5 years**
  - Disease-free survival: 0.84 —
  - Time to recurrence: —
  - Overall survival: 1.00 —
  - Time to breast cancer death: —

**SELECT PUBLICATIONS**


- George W Sledge Jr, MD, Protocol Chair.
- James N Ingle, MD, Protocol Chair.
- Ph: 507-284-8432, Email: ingle.james@mayo.edu

**CONTRIVENSES IN SELECTION OF INITIAL TREATMENT**

The present data suggest that it is not appropriate to wait five years to start an aromatase inhibitor. Furthermore, the higher rates of recurrence (especially in years 1-3) and the increased numbers of adverse events and treatment holidays associated with tamoxifen lend support to the approach of offering the most effective and well-tolerated therapy at the earliest opportunity. Five years of anastrozole should now be considered as the initial adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localized breast cancer.


Several groups have looked at statistical modeling of the optimal long-term sequencing of an AI after tamoxifen vs immediate use of an AI — Jack Cuzick’s group in London, the Dana-Farber group with Hal Burstein, and our own group in Houston with our statistician Sue Hilsenbeck. They have all observed similar findings, and they could not rule out a moderate benefit from sequencing compared to immediate use if one looks at the long-term results after 10 years of follow-up. While it is true that we cannot necessarily go by the results of mathematical models, they do provide some evidence of what the possibilities of these different strategies might be over the long term.

— C Kent Osborne, MD. Breast Cancer Update 2005, Special GME Meeting Edition

68-MONTH FOLLOW-UP OF THE ATAC TRIAL

The simplest interpretation of the ATAC data is that anastrozole postpones one in four of the relapses we see in patients on tamoxifen. That translates into highly significant improvements in disease-free survival, recurrence-free survival and distant disease-free survival. In the hazard rate analysis plot from the ATAC trial, we’re seeing two peaks with tamoxifen. The first peak is lowered with tamoxifen, but a peak still occurs. In the anastrozole arm, the initial peak is lost and the second peak is flatter. I believe this is the most profoundly important observation in this trial, not only to help make therapeutic decisions but also to give a fascinating biological insight. The strongest argument for starting adjuvant endocrine therapy with an aromatase inhibitor is that anastrozole almost abolishes that first peak. If you wait two to three years, as some of the trials are reporting, the effects are wonderful, but meanwhile, you’ve lost those patients who will relapse and ultimately die in those trials.

— Michael Baum, MD. DMI Breast Cancer Update 2005 (1)

BIG FEMTA/IBIS-C 1/6: BIG 1-98: 1BIG 1-98: LETROZOLE VERSUS TAMOXIFEN UP FRONT OR SEQUENTIALLY

The efficacy results in BIG FEMTA were essentially the same as those in the ATAC trial at the 30-month point. The hazard reduction was similar, and the side-effect profile was by far and large the same, although it was reported differently. A few differences were seen. They found a benefit for letrozole only in patients with node-positive disease, which is difficult to understand. It’s probably a chance finding, but we need to follow that. At this stage, they’ve found no difference in efficacy between the patients with PR-positive and PR-negative disease. We have to acknowledge that the data are different from what’s been observed in other trials.

The third and most worrying finding is the substantial excess in cardiovascular deaths for letrozole compared to tamoxifen, which has not been observed in the trials with anastrozole. Whether this is due to chance or differences in cardiovascular mortality is important to know. Letrozole is a slightly more potent aromatase inhibitor and as such, one might assume it has a greater impact.

— Jack Cuzick, PhD. Breast Cancer Update 2005 (8)
The optimal adjuvant hormonal therapy strategy for postmenopausal women is controversial. A number of trials have evaluated the role of aromatase inhibitors following tamoxifen. MA17 randomly assigned postmenopausal women who had completed 4.5 to six years of adjuvant tamoxifen to five years of placebo or letrozole. In ITA, IES, ABCSG-8 and ARNO 95, postmenopausal women who had completed two to three years of adjuvant tamoxifen were randomly assigned to continue tamoxifen or switch to an aromatase inhibitor. These trials of sequential adjuvant hormonal therapy have demonstrated significant advantages for women switching to an aromatase inhibitor. In an extension of MA17 and in a proposed trial through the NSABP, women who complete five years of hormonal therapy will be randomly reassigned to another five years of letrozole or placebo.

**EVALUATING THE STRATEGY OF SWITCHING FROM ADJUVANT TAMOXIFEN TO AN AROMATASE INHIBITOR**

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Study endpoints</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCSG-6</td>
<td>TAM x 4.5–6y + anastrozole (a) x 3y TAM x 2–3y + TAM x 2–3y</td>
<td>DFS*</td>
<td>LIF (p = 0.015)</td>
</tr>
<tr>
<td>IES/ECCG-003</td>
<td>TAM x 4.5y</td>
<td>DFS*</td>
<td>LIF (p = 0.003)</td>
</tr>
<tr>
<td>IBCSG-55/BCS027</td>
<td>TAM x 2–3y</td>
<td>DFS*</td>
<td>LIF (p = 0.010)</td>
</tr>
<tr>
<td>Italian (ITA)</td>
<td>TAM x 3–4y + anastrozole (a) x 2–3y TAM x 3–4y + tamoxifen (b)</td>
<td>DFS</td>
<td>LIF (p = 0.010)</td>
</tr>
<tr>
<td>GROCTA 4B</td>
<td>TAM x 5y</td>
<td>DFS</td>
<td>LIF (p = 0.049)</td>
</tr>
</tbody>
</table>

**EXTENDED ADJUVANT HORMONAL THERAPY WITH AROMATASE INHIBITORS AFTER FIVE YEARS OF TAMOXIFEN**

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Study endpoints</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAN-NZC-MAT1vantSWSS-MAT1vant-01</td>
<td>TAM x 4.5–6y + letrozole x 1y TAM x 4.5–6y + placebo x 1y</td>
<td>DFS*</td>
<td>LIF (p = 0.003)</td>
</tr>
<tr>
<td>ABCSG6</td>
<td>TAM x 3y + anastrozole (a) TAM x 3y + tamoxifen (b)</td>
<td>DFS</td>
<td>LIF (p = 0.25)</td>
</tr>
</tbody>
</table>

**SEQUENCING AROMATASE INHIBITORS AFTER ADJUVANT TAMOXIFEN**

I am now absolutely confident that women who have been on tamoxifen for two or three years should switch to an aromatase inhibitor. We have excellent data for both exemestane and anastrozole from these trials. Boccardo’s small ITA trial with anastrozole was the first to report, followed by the large IES study with exemestane and the joint Austrian-German study of anastrozole presented at San Antonio. Overwhelming evidence indicates that a switch to an aromatase inhibitor is beneficial. I recommend the switch regardless of whether the patient has been on tamoxifen for one year or four years. You can wait foroner for refinements, but no one is ever going to do a trial of a switch at one year or a switch at four years. We just have to stretch the available evidence and be sensible about it, and I think it would be reasonable to switch. The MA17 trial is a well-conducted trial in women who have already received five years of tamoxifen. It shows proof of the principle that you can influence the natural history of breast cancer after five years of tamoxifen.

— Michael Baum, MD, CM. Breast Cancer Update 2005 (2)

The aromatase inhibitors add benefit immediately after surgery, after two to three years of tamoxifen or as extended adjuvant therapy. In breast cancer, the highest risk of recurrences is conceptually within the first two to three years after surgery. In women who participated in the ATAC trial, you can see a difference in the disease-free survival curves well before the two and half a year mark. Not only do you lose patients to an early breast cancer recurrence in the first two to three years, but you also lose some women to adverse events on the tamoxifen arm. The study MA1447527 do not really take into consideration because these patients have already dropped out prior to randomization. I typically offer anastrozole to the majority of postmenopausal patients with receptor-positive tumors after surgery and chemotherapy. When patients come in after two to three years of tamoxifen, I discuss switching them to an aromatase inhibitor. At the end of five years of tamoxifen, I discuss letrozole.

— Murray D. Dickler, MD. Breast Cancer Update 2005 (2)

I use exemestane after two to three years of tamoxifen based on the IES data. However, if you compare the IES exemestane data to the data from the combined ARNO 95/IES/ABCSCG-B trials, in which the patients were switched to anastrozole, the agents appear to be similar in terms of efficacy. The hazard ratio for disease-free survival was 0.73 in the IES trial and 0.60 in the ARNO study, so I believe these two agents are quite equivalent in this situation. We now have data to support the use of either anastrozole or exemestane after two or three years of tamoxifen. After five years of tamoxifen, we have the MA17 trial data, so I use letrozole in this setting.

— Anthony Howell, MD. Breast Cancer Update 2005 (4)

In the combined trials of ARNO 8 and ARNO 95, more than 3,100 postmenopausal patients, all with receptor-positive disease, were exposed to two years of adjuvant tamoxifen after surgery. We then randomly assigned them to tamoxifen or anastrozole for three years. It was clean, informative data. I in the IES trial, exemestane resulted in a risk reduction of approximately 35 percent, whereas in the combined trials, the risk of an event was reduced by 40 percent with anastrozole. Most of the difference in the event rate with anastrozole was due to a huge reduction in distant metastasis.

— Raimund V. Jakesz, MD. Breast Cancer Update 2005 (3)

It is important to study the duration of aromatase therapy. The NSABP will take patients that complete five years of an aromatase inhibitor or took tamoxifen for two to three years and then switched to an aromatase inhibitor and randomly assign them to either continue an aromatase inhibitor — letrozole — versus placebo for five years. We will essentially do what we did in the NSABP-B14 extension trial but with aromatase inhibitors.

— Eleftherios P. Mamounas, MD, MPH. Breast Cancer Update 2006 (9)
Management of Short- and Long-Term Toxicities of Aromatase Inhibitors

Musculoskeletal symptoms and bone loss are the two major adverse events of long-term adjuvant therapy with aromatase inhibitors (AIs), and both of these potential complications may be ameliorated. An Austrian study demonstrated that zoledronic acid can prevent bone loss in women treated with ovarian suppression and aromastere. Bone density monitoring and bisphosphonates are now routinely used in patients receiving AIs. Arthralgias are common in breast cancer patients receiving tamoxifen, but the incidence increases with all AIs. A variety of oral and topical medications and nonpharmacologic approaches may improve arthralgias, which also tend to decrease with time on treatment. The spectrum of adverse AI events, including arthralgias, is similar regardless of whether patients received prior chemotherapy.

### Aromatase Inhibitors and Fractures

The five-year overall toxicity data are very favorable for anastrozole compared to tamoxifen because the three life-threatening toxicities — endometrial cancer, arterial and venous vascular events — are all significantly less with anastrozole. Many oncologists have concern regarding bones, but I believe it’s going to be not only a preventable, treatable situation but also something that is likely to go away completely in the near future. There is no difference in the fracture rates with anastrozole and tamoxifen. This is for a group of patients who had no prescreening when they entered the study and no ongoing protocol-defined follow-up for bone. If you’re going to actually do any screening or treating, you’re going to have lower numbers than that.

— Rowan T Chlebowski, MD, PhD. Breast Cancer Update 2005 (7)

The fractures rate incidence in ATAC is becoming a little more reassuring. An excess fracture rate occurs in the first two or three years, but then the lines begin to come together. As patients stop taking anastrozole, the fracture rate returns to that of the patients randomly assigned to tamoxifen. Furthermore, so far no difference has occurred in fractures of the neck or femur, which are of particular concern. I think the issue of bone is easy to manage. You should be alert to it, monitor bone mineral density, perhaps exclude patients who have established osteoporosis and then be ready to intervene with a bisphosphonate when the patient becomes osteoporotic.

— Michael Baum, MD, CIBM. Breast Cancer Update 2005 (1)

Great strides have been made in terms of the new bisphosphonates. The oral weekly preparations are available. I am optimistic that bone loss with aromatase inhibitors is a completely manageable issue. It may lead to a greater public health benefit by gaining the way for having osteoporosis dealt with routinely in all postmenopausal women. That could be one of the more beneficial effects of this new drugs and the potential availability of DEXA scans, osteoporosis may be a disease of the past in another decade.

— Jack Cuzick, PhD. Breast Cancer Update 2005 (6)

### Aromatase Inhibitors and Musculoskeletal Disorders

Arthralgia is a condition with effective available treatment options. Whereas the incidence of arthralgia reported in clinical trials is higher with aromatase, the absolute difference compared with tamoxifen treatment is relatively small; this finding is similar for the other aromatase inhibitors, letrozole and exemestane...

Better guidance is needed in the differential diagnosis of arthritis, including consideration of other possible causes.


### Potentially Interventions for Arthralgias

Pharmacologic interventions

- Nonpharmacologic approaches
  - Oral treatments: Arthritis medication (e.g., NSAIDs)
  - Physical therapy
  - Exercise
  - Corticosteroids
  - Oral analgesics
  - Physical therapy
  - Occupation therapy
  - Exercise
  - Chondroitin sulfate
  - Topical treatments: Capsaicin
  - Nonsteroidal anti-inflammatory drugs

POTENTIAL INTERVENTIONS FOR ARTHRITIS

<table>
<thead>
<tr>
<th>Pharmacologic Intervention</th>
<th>Nonpharmacologic Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral treatments</td>
<td>Arthritis medication (e.g., NSAIDs)</td>
</tr>
<tr>
<td></td>
<td>Physical therapy</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Oral analgesics</td>
</tr>
<tr>
<td>Oral analgesics</td>
<td>Physical occupation therapy</td>
</tr>
<tr>
<td>Physical occupation therapy</td>
<td>Exercise</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>Topical treatments</td>
</tr>
<tr>
<td>Topical treatments</td>
<td>Capsaicin</td>
</tr>
<tr>
<td></td>
<td>Nonsteroidal anti-inflammatory drugs</td>
</tr>
</tbody>
</table>

### Fractures in Adjuvant AI Trials

<table>
<thead>
<tr>
<th>Fractures</th>
<th>Baseline</th>
<th>After 36 months</th>
<th>p &lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>1.00</td>
<td>1.28</td>
<td>1.24</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>0.72</td>
<td>0.70</td>
<td>0.77</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.90</td>
<td>1.13</td>
<td>1.04</td>
</tr>
</tbody>
</table>

### Changes in Bone Mineral Density of the Lumbar Spine in ABCG-12

<table>
<thead>
<tr>
<th>Source</th>
<th>Baseline</th>
<th>After 36 months</th>
<th>p &lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>12.3</td>
<td>12.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>12.1</td>
<td>12.1</td>
<td>1.00</td>
</tr>
<tr>
<td>Placebo</td>
<td>12.3</td>
<td>12.3</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### ATAC Trial: Adverse Events in Prior Chemotherapy and No Chemotherapy Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Prior chemotherapy</th>
<th>Prior chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol</td>
<td>18</td>
<td>(0.06, 0.09)</td>
<td>(0.07, 0.10)</td>
</tr>
<tr>
<td>Fracture</td>
<td>1288</td>
<td>(1.30, 1.97)</td>
<td>(1.32, 2.12)</td>
</tr>
<tr>
<td>Hot</td>
<td>2005</td>
<td>(0.07, 0.09)</td>
<td>(0.08, 0.10)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>104</td>
<td>(0.32, 0.37)</td>
<td>(0.33, 0.38)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>104</td>
<td>(0.32, 0.37)</td>
<td>(0.33, 0.38)</td>
</tr>
<tr>
<td>Knee</td>
<td>457</td>
<td>(0.04, 0.09)</td>
<td>(0.05, 0.10)</td>
</tr>
<tr>
<td>Vascular</td>
<td>457</td>
<td>(0.56, 0.68)</td>
<td>(0.64, 0.78)</td>
</tr>
<tr>
<td>Total number of events</td>
<td>104</td>
<td>(0.44, 0.57)</td>
<td>(0.45, 0.60)</td>
</tr>
</tbody>
</table>

### Joint Symptoms and Arthralgias in Adjuvant AI Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Baseline</th>
<th>After 36 months</th>
<th>p &lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>12.3</td>
<td>12.2</td>
<td>0.97</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>12.1</td>
<td>12.1</td>
<td>1.00</td>
</tr>
<tr>
<td>Placebo</td>
<td>12.3</td>
<td>12.3</td>
<td>1.00</td>
</tr>
</tbody>
</table>

### SELECT PUBLICATIONS


Rowan T Chlebowski, MD, PhD. Breast Cancer Update 2005 (7)
Adjuvant Endocrine Therapy in Premenopausal Patients

Adjuvant tamoxifen has an established role in premenopausal women with ER-positive breast cancer. With a median follow-up of 9.6 years, INT 0101 demonstrated that the addition of tamoxifen to CAF plus goserelin improved the time to recurrence and disease-free survival. However, no benefits were associated with CAF plus goserelin compared to CAF alone, although the analysis was confounded by the fact that most of the premenopausal women in the study achieved ovarian ablation from chemotherapy, and a subset analysis demonstrated a benefit in patients who continued to menstruate after chemotherapy. Ongoing clinical trials — SOFT, TEXT and PERCHE — are evaluating the role of ovarian ablation/suppression combined with tamoxifen or an aromatase inhibitor. An Austrian study — ABCSG-AU12 — reported by Dr Michael Gnant at the 2004 San Antonio Breast Cancer Symposium demonstrated that zolodrinate counteracted the bone loss associated with both goserelin/tamoxifen and goserelin/anastrozole. Results from ongoing trials will hopefully establish the optimal adjuvant hormonal therapy for premenopausal women.

### TRAILS OF ADJUVANT ENDOCRINE THERAPY WITH OVARIAN SUPPRESSION

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Eligibility</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBSCG-24-02 (SOFT trial)</td>
<td>3,693</td>
<td>Premenopausal (n = 1,846)</td>
<td>Tamoxifen by 7y (OPS) + CAF (= tamoxifen + CAF)</td>
</tr>
<tr>
<td></td>
<td>3,693</td>
<td>Premenopausal (n = 1,846)</td>
<td>Tamoxifen by 7y + goserelin (= tamoxifen + anastrozole)</td>
</tr>
<tr>
<td>IBSCG-25-02 (TEXT trial)</td>
<td>1,846</td>
<td>Premenopausal (n = 923)</td>
<td>Triptorelin + chemotherapy + tamoxifen by 7y (OPS)</td>
</tr>
<tr>
<td></td>
<td>1,846</td>
<td>Premenopausal (n = 923)</td>
<td>Triptorelin + chemotherapy + tamoxifen by 7y + goserelin (= tamoxifen + anastrozole)</td>
</tr>
<tr>
<td>IBSCG-26-02 (PERCHE trial)</td>
<td>1,751</td>
<td>Premenopausal (n = 876)</td>
<td>Premenopausal + chemotherapy + tamoxifen by 7y (OPS)</td>
</tr>
<tr>
<td></td>
<td>1,751</td>
<td>Premenopausal (n = 876)</td>
<td>Premenopausal + chemotherapy + tamoxifen by 7y + goserelin (= tamoxifen + anastrozole)</td>
</tr>
</tbody>
</table>

### RANDOMIZED TRIAL OF CHEMOHORMONAL THERAPY IN PREMENOPAUSAL, NODE-POSITIVE, RECEPTOR-POSITIVE BREAST CANCER (INT 0101)

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Premenopausal patients with node-positive, hormone receptor-positive breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARM 1 (CAF)</td>
<td>CAF (n = 1,503)</td>
</tr>
<tr>
<td>ARM 2 (CAF + goserelin)</td>
<td>CAF + goserelin (n = 1,502)</td>
</tr>
<tr>
<td>ARM 3 (CAF + tamoxifen + goserelin)</td>
<td>CAF + tamoxifen + goserelin (n = 1,502)</td>
</tr>
<tr>
<td>ARM 4 (goserelin + zoledronic acid)</td>
<td>CAF + tamoxifen + goserelin + zoledronic acid (n = 1,502)</td>
</tr>
</tbody>
</table>

### INT 0101 TRIAL RESULTS: 9.6 YEARS FOLLOW-UP

<table>
<thead>
<tr>
<th>Hazard ratio (HR)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAF (n = 494)</td>
</tr>
<tr>
<td>CAF-Z (n = 507)</td>
</tr>
<tr>
<td>CAF-Z/CAF</td>
</tr>
<tr>
<td>No-tumor disease-free survival</td>
</tr>
<tr>
<td>Nine-year overall survival</td>
</tr>
<tr>
<td>Nine-year time to recurrence</td>
</tr>
</tbody>
</table>

*CAF = cyclophosphamide, doxorubicin, and fluorouracil; T = tamoxifen |

### SELECT PUBLICATIONS

15. Proc ASCO 2002;21(9):1836-44.
23. Proc ASCO 2002;21(9):1836-44.
27. Proc ASCO 2002;21(9):1836-44.
35. Proc ASCO 2002;21(9):1836-44.
43. Proc ASCO 2002;21(9):1836-44.
47. Proc ASCO 2002;21(9):1836-44.
51. Proc ASCO 2002;21(9):1836-44.
55. Proc ASCO 2002;21(9):1836-44.
59. Proc ASCO 2002;21(9):1836-44.
Extensive resources are allocated for the evaluation of breast cancer treatments. In contrast, minimal investments are made to determine how these therapeutic strategies are implemented in clinical practice. Continuing medical education not only informs clinicians about ongoing clinical trials and emerging research results, but it can also evaluate the implementation of research results by physicians in clinical practice. Data from the Breast Cancer Impact Patterns of Care Study, a telephone survey conducted in September 2005 of randomly selected oncologists in the United States, are presented here. One of the key facets of this initiative was the use of adjuvant hormonal therapy. In postmenopausal women, the adjuvant trials evaluating the aromatase inhibitors as initial therapy and following two to three or five years of adjuvant tamoxifen have had a dramatic impact on the clinical use of adjuvant endocrine therapy. In premenopausal women, controversy continues with regard to the use of ovarian ablation/suppression.

**CHOICE OF AROMATASE INHIBITORS AS ADJUVANT THERAPY**

<table>
<thead>
<tr>
<th>Aromatase Inhibitor</th>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Use</td>
<td>24%</td>
<td>16%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**CHOICE OF ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN**

**CHOosing a hormone therapy** would be most likely to recommend tamoxifen in postmenopausal women with each of the following tumors?

<table>
<thead>
<tr>
<th>Tumor Characteristics</th>
<th>Tamoxifen</th>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+/PR-</td>
<td>72%</td>
<td>16%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>ER+/PR+</td>
<td>78%</td>
<td>12%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>ER+/PR-</td>
<td>80%</td>
<td>10%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>ER+/PR+</td>
<td>83%</td>
<td>9%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**SEQUENCING ADJUVANT THERAPY AFTER FIVE YEARS OF TAMSOFXIN**

The patient is a 45-year-old woman in average health with a 1.2-cm, ER+/PR+, ER+/PR+, ER+/PR- following tumors. How would you manage this patient's endocrine therapy?

<table>
<thead>
<tr>
<th>Tumor Characteristics</th>
<th>Tamoxifen</th>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>24%</td>
<td>16%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>78%</td>
<td>12%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Letrozole</td>
<td>80%</td>
<td>10%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Exemestane</td>
<td>83%</td>
<td>9%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**SWITCHING ADJUVANT THERAPY AFTER TWO TO THREE YEARS OF TAMOXFIN**

The patient is a 50-year-old woman in average health with a 1.2-cm, ER+/PR+, ER+/PR+, ER+/PR- following tumors. How would you manage this patient's endocrine therapy?

<table>
<thead>
<tr>
<th>Tumor Characteristics</th>
<th>Tamoxifen</th>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>24%</td>
<td>16%</td>
<td>8%</td>
<td>4%</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>78%</td>
<td>12%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Letrozole</td>
<td>80%</td>
<td>10%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Exemestane</td>
<td>83%</td>
<td>9%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

**ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN**

When you use an aromatase inhibitor in each of the following settings, what percentage of this use is with each of the following agents?

<table>
<thead>
<tr>
<th>Setting</th>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial adjuvant therapy</td>
<td>24%</td>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>2nd-line therapy</td>
<td>78%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>3rd-line therapy</td>
<td>80%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>4th-line therapy</td>
<td>83%</td>
<td>9%</td>
<td>2%</td>
</tr>
</tbody>
</table>

**SELECT PUBLICATIONS**


**ADJUVANT ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN**

I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor. I have combined an LHRH agonist with an aromatase inhibitor.
Optimizing Adjuvant Chemotherapy: Recent Trial Results

BCIRG 001: ADJUVANT TAC VERSUS FAC

In our first study, BCIRG 001, 1500 women from 21 countries were randomly assigned to six cycles of adjuvant TAC or FAC. The women enrolled in the trial had node-positive disease. We now have mature results with five years of follow-up. The trial demonstrated that adjuvant TAC significantly improved disease-free survival by 28 percent in relative terms (p = 0.001). Overall survival was also strikingly improved; the trial demonstrated a 23 percent relative reduction in mortality with adjuvant TAC, which was an absolute six percent improvement in overall survival. This would be a perfect story if an increase in side effects did not occur. In fact, TAC was associated with a high rate of febrile neutropenia. Approximately 25 percent of the women receiving TAC experienced an episode of febrile neutropenia, which was not unexpected because primary prophylaxis with G-CSF was not performed. We now know that if we were to do the study again and administer TAC with G-CSF, we would see a febrile neutropenia rate, on a per-patient basis, of about three to six percent.

— John Mackey, MD. Breast Cancer Update 2005 (I)

DEVELOPMENTS IN ADJUVANT CHEMOTHERAPY

The development of the dose-dense approach has marked a recent step in the progressive improvement of prospects for women with node-positive primary breast cancer, especially in high-risk cases. Other stages on the way have been the benefits achieved by increasing the doses of cyclophosphamide, doxorubicin, and 5-fluorouracil used in CAF and the advent of the taxanes. Further improvements may stem from current research aimed at: (A) reducing the interval between cycles from 14 days to 10 or 11 days; (B) extending the period for which anthracyclines and taxanes can be given; (C) adding monocytic agents such as the humanized anti-HER2 antibody trastuzumab to chemotherapy in HER2-positive cases; and (D) adding antiangiogenesis agents, eg bevacizumab.


TRIAL OF PEGFILGRASTIM VERSUS PLACEBO

The objective of this study was to determine if pegfilgrastim significantly reduces febrile neutropenia in patients receiving a chemotherapy regimen associated with an expected rate of approximately 20 percent. Patients were eligible for the trial whether they were receiving docetaxel in the adjuvant or the metastatic setting. In this double-blind, randomized trial, patients received docetaxel with pegfilgrastim versus a placebo. If patients developed febrile neutropenia, they were able to subsequently receive pegfilgrastim. Febrile neutropenia, related hospitalizations and intravenous anti-infective use were all significantly reduced by pegfilgrastim. While the difference in the rates of patients receiving their planned chemotherapy dose on time didn’t look impressive, all the placebo patients who developed febrile neutropenia received pegfilgrastim. Consequently, this study represents a huge step forward in the delivery of the planned dose on time.

— Charles J. Vogel, MD. Breast Cancer Update 2005 (II)

This study provides compelling evidence that administering pegfilgrastim in the first and subsequent cycles of moderately myelosuppressive chemotherapy can significantly reduce the risk of potentially life-threatening infectious complications that can result in hospitalizations and require intravenous antibiotics. Approximately 600,000 chemotherapy patients are at risk of developing neutropenia, which has traditionally been treated reactively. Doctors usually reserve prophylactic use of pegfilgrastim for only those patients considered at very high risk of developing chemotherapy-induced neutropenia. This trial may give physicians the evidence they need to help protect cancer patients from chemotherapy-induced neutropenic complications beginning in the first cycle of chemotherapy treatment.

— Lee Schwartberg, MD. Multinational Association of Supportive Care in Cancer 2004 Annual Meeting

### Selection Practices


Two recent Phase III randomized trials have demonstrated that taxane-containing adjuvant regimens may result in an improvement in overall survival. BCIRG 001 compared TAC (docetaxel, doxorubicin and cyclophosphamide) to FAC, and CALGB-9741 evaluated a dose-dense regimen of AC followed by paclitaxel administered with growth factor support. NSABP-B-38 may help to determine which of these two regimens is better. Other ongoing trials are assessing whether the advantage observed with dose-dense scheduling is related to the AC or the paclitaxel portion of that regimen. AC followed by docetaxel is a commonly used taxane-containing adjuvant regimen, even though cited results with that treatment have primarily been reported from a neoadjuvant trial. A US Oncology adjuvant trial is evaluating whether the addition of capcitabine to AC to docetaxel will improve its efficacy. These trials are now complicated by the recent findings of benefit from the use of trastuzumab/chemotherapy as adjuvant treatment of patients with HER2-positive tumors. CALGB-49907 and CALGB-40101 now allow postchemotherapy trastuzumab/chemotherapy as adjuvant treatment of patients with HER2-positive disease. 

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**SELECT PROMINENT REFERENCES**


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**SELECT PUBLICATIONS**


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**PHASE II STUDIES EVALUATING NOVEL APPROACHES TO (NEO)ADJUVANT CHEMOTHERAPY**

<table>
<thead>
<tr>
<th>Protocol(D)</th>
<th>N</th>
<th>Eligibility</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>03-025</td>
<td>60</td>
<td>Stage IIIB</td>
<td>40</td>
</tr>
<tr>
<td>CIBM-1000, CABLE-1100, CIRM-10003, NCI-1001</td>
<td>25</td>
<td>Stage IIA–IB</td>
<td>0</td>
</tr>
<tr>
<td>ECOG-8801</td>
<td>42-202</td>
<td>Stage II</td>
<td>0</td>
</tr>
<tr>
<td>CIBM-3030, CAST-3020, NCI-2072</td>
<td>60</td>
<td>Stage IIA</td>
<td>0</td>
</tr>
</tbody>
</table>

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**CURRENT TRIALS OF ADJUVANT CHEMOTHERAPY**

Chemotherapy in Elderly Women

Limited data exist about the risks and benefits of adjuvant chemotherapy in elderly women. An important adjuvant trial led by Dr Hyman Muss, CALGB-49907, randomly assigns elderly women to either capecitabine versus AC or CMF. A small clinical trial in the metastatic setting has suggested that in older women with advanced breast cancer, capecitabine 1,000 mg/m² twice a day for 14 of 21 days may be better tolerated and result in equal or greater efficacy than the package-insert dose. Retrospective studies of women treated with adjuvant chemotherapy have found that it is not offered as often to elderly women with high-risk breast cancer and (2) age does not significantly predict for any toxicity risk other than dose reductions.

Inclusion of older patients in trials of adjuvant chemotherapy

Our study adds to the increasing number of trials that suggest that older patients in fair to good health tolerate standard chemotherapy regimens, and even more intensive regimens, almost as well as younger patients. Moreover, and more importantly, this study suggests that the added value gained from more intensive chemotherapy regimens commonly used in the adjuvant setting might be shared by older patients and not limited to younger age groups.

— Hyman B Muss, MD et al. JAMA 2005;293(9):1073-81.

Enrollment of elderly in clinical trials

...The number of patients at low risk who can be spared adjuvant chemotherapy appears to be markedly increased when the prognostic genetic signature is used. These findings are of great interest, especially in elderly patients, who more frequently have comorbidities and/or impaired organ functions than younger people, and the real benefit from tolerance of adjuvant chemotherapy still is a major issue. Clinical trials specifically designed for elderly patient subpopulations with breast cancer are critically needed and must incorporate gene expression profiling as a potential way of identifying those patients who can be spared adjuvant systemic treatment despite having traditionally defined high-risk disease (i.e., node-positive, high grade). The prognostic genetic signature could have this potential, but it has been investigated only in younger women and therefore needs to be prospectively validated in elderly patients as well.


CALGB-49907

Hyman Muss has made some changes to try to make the eligibility more streamlined and easier for physicians and patients to participate in the study. We strongly believe that this trial will address a very good question: How does an oral agent compare to standard intravenous chemotherapy? In patients with metastatic disease, capecitabine has been shown to be better than CMF, so we might even have an efficacy advantage.

— Jeffrey Abrams, MD. Breast Cancer Update 2004 (5)

Capecitabine dose in elderly women with advanced breast cancer

This study has shown in a large series that oral capecitabine is well tolerated and effective in older women with advanced breast cancer. Older patients may frequently exhibit diminished capacity to eliminate drugs, resulting in unusual sensitivity to standard dosing regimens. In light of this, the overall results of the study suggest that although the dose groups are small and nonrandomized, the capecitabine dose of 1,000 mg/m² twice daily merits consideration as ‘standard’ for women aged 70 years and older who are candidates for cytotoxic therapy for metastatic breast cancer and do not have severely impaired renal function.


Pegfilgrastim for febrile neutropenia in the elderly

This large, prospective, community-based trial in older patients was both feasible to conduct and demonstrated that myelosuppressive chemotherapy can be given to older patients with cancer. Pegfilgrastim from the first cycle of chemotherapy resulted in reduced incidence of febrile neutropenia, hospitalizations, IV anti-infective use and chemotherapy dose reductions and delays compared with current community practice, which may include pegfilgrastim in later cycles.

Pegfilgrastim from the first cycle was associated with fewer serious adverse events compared with pegfilgrastim given at physician discretion in later cycles.


SELECT PUBLICATIONS


Barclay A et al. A large study of the elderly cancer patient in the community assessing limited impact of undertreated complex and/or impaired frailty to reduce metastatic complications. ASCO 2005;Dinero BL.


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ACTIVITY CHEMOTHERAPY TRIALS IN ELDERLY WOMEN WITH BREAST CANCER

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Phase</th>
<th>Eligibility</th>
<th>Target agent</th>
<th>Schedules</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB-49907</td>
<td>II</td>
<td>Age ≥ 75, Stage I-IV, operable breast cancer</td>
<td>CMF or AC vs capecitabine 1,000 mg/m² BID 14 of 21</td>
<td></td>
</tr>
<tr>
<td>D0021-022</td>
<td>III</td>
<td>Age ≥ 75, metastatic breast cancer</td>
<td>Pegylated liposomal doxorubicin versus capecitabine</td>
<td></td>
</tr>
<tr>
<td>SWO-5425-20</td>
<td>III</td>
<td>Age ≥ 75, metastatic breast cancer</td>
<td>Eribulin</td>
<td></td>
</tr>
<tr>
<td>PRE-PROLEC2-</td>
<td>III</td>
<td>Age ≥ 75, metastatic breast cancer</td>
<td>Docetaxel</td>
<td></td>
</tr>
<tr>
<td>GIDEON-0416</td>
<td>III</td>
<td>Age ≥ 75, metastatic breast cancer</td>
<td>Docetaxel</td>
<td></td>
</tr>
</tbody>
</table>

† Patients with insufficient LVEF need to receive CMF, not AC. Protocol under amendment to allow the addition of trastuzumab in patients with tumors positive for HER2 by IHC 3+ or FISH. * randomization option at physician’s/patient’s preference; NR = not reported; MTD = maximum tolerated dose

†: Pegylated liposomal doxorubicin versus no adjuvant therapy


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ADJUVANT CHEMOTHERAPY OFFERED TO BREAST CANCER PATIENTS?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age&lt;75 years (n = 343)</th>
<th>≥75 years (n = 343)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>0.01</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Fever and neutropenia</td>
<td>0.07</td>
<td>0.07</td>
<td>0.27</td>
</tr>
<tr>
<td>Dose reduction</td>
<td>0.02</td>
<td>0.13</td>
<td>0.24</td>
</tr>
<tr>
<td>Any Grade IV toxicity</td>
<td>0.08</td>
<td>0.08</td>
<td>0.08</td>
</tr>
<tr>
<td>Grade IV neutropenic toxicity</td>
<td>0.37</td>
<td>0.37</td>
<td>0.66</td>
</tr>
<tr>
<td>Treatment delay for low ANC</td>
<td>0.31</td>
<td>0.31</td>
<td>0.26</td>
</tr>
</tbody>
</table>

†: The type of chemotherapy regimen (anthracycline compared to CMF) was a better predictor for toxicity than increased age or comorbidly index.

‡: Age continuous variable; †: anthracyclines vs CMF; ‡: hematologically score 0 vs any other score with score ≥ 1, 17% of CMF vs Osborne metastatic oral study


ROLE OF AGE, CHEMOTHERAPY REGIMEN AND COMORBIDITY IN RISK OF TOXICITY FROM ADJUVANT CHEMOTHERAPY IN WOMEN OVER 65 WITH Breast cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>Efficacy</th>
<th>Capecitabine 1,300 mg/m²/BD</th>
<th>Capecitabine 1,000 mg/m²/BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade III tumor</td>
<td>Grade III</td>
<td>57.8%</td>
<td>91.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Grade III</td>
<td>33%</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>Median time to progression</td>
<td>3.9 months</td>
<td>4.1 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† randomization option at physician’s/patient’s preference; NR = not reported; MTD = maximum tolerated dose


CAPETABLE Dosing in Elderly Women with advanced breast cancer

<table>
<thead>
<tr>
<th>Grade</th>
<th>IV Toxicities</th>
<th>Capecitabine 1,300 mg/m²/BD</th>
<th>Capecitabine 1,000 mg/m²/BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>70+ years</td>
<td>0</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>65-69 years</td>
<td>1</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>60-64 years</td>
<td>2</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>


Pegfilgrastim from the first cycle of chemotherapy resulted in reduced incidence of febrile neutropenia, hospitalizations, IV anti-infective use and chemotherapy dose reductions and delays compared with current community practice, which may include pegfilgrastim in later cycles.

Pegfilgrastim from the first cycle was associated with fewer serious adverse events compared with pegfilgrastim given at physician discretion in later cycles.

Clinical decisions regarding adjuvant chemotherapy are complex and multifactorial. Tumor-related factors such as nodal status, tumor size and predictors like the Oncotype DX™ assay must be balanced against issues such as patient age and comorbidities. Computer models, such as Peter Ravdin’s Adjuvant! Online program, are frequently utilized by oncologists to assist in estimating the absolute impact of adjuvant therapy, and these must be balanced against the risk of side effects and toxicities with treatment. An important facet of Adjuvant! is that it factors in nonbreast cancer sources of competing mortality based on the patient’s age and general health status. Data from the 2005 Breast Cancer Update Patterns of Care Study, a telephone survey of randomly selected US-based medical oncologists, are presented here. In patients with node-positive tumors, dose-dense AC → paclitaxel is a common choice, but many other regimens are also utilized. AC is the most common regimen utilized in patients with node-negative tumors. Adjuvant chemotherapy is less frequently utilized in older patients, particularly octogenarians.

**USE OF COMPUTER MODELS IN CLINICAL PRACTICE**

<table>
<thead>
<tr>
<th>In which of the following situations do you tend to use computer models to help determine chemotherapy for your patient?</th>
<th>N (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>To select type of chemotherapy to use</td>
<td>34%</td>
</tr>
<tr>
<td>To decide whether to use chemotherapy in node-negative cases</td>
<td>100%</td>
</tr>
<tr>
<td>To decide whether to use endocrine therapy in node-negative cases</td>
<td>81%</td>
</tr>
<tr>
<td>To select type of chemotherapy to use</td>
<td>34%</td>
</tr>
<tr>
<td>To select type of endocrine therapy to use</td>
<td>9%</td>
</tr>
<tr>
<td>Other situations</td>
<td>9%</td>
</tr>
</tbody>
</table>

*14% of oncologists answered not use the Adjuvant! model, 2% use the Mayo Clinic model, 16% use both models, and 30% of physicians do not use any model.

**CLINICAL USE OF ONCOTYPE DX ASSAY**

<table>
<thead>
<tr>
<th>How useful was this test in your treatment decision?</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very helpful</td>
<td>18%</td>
</tr>
<tr>
<td>Somewhat helpful</td>
<td>64%</td>
</tr>
<tr>
<td>Not helpful</td>
<td>18%</td>
</tr>
</tbody>
</table>

**ADJUVANT CHEMOTHERAPY FOR NODE-POSITIVE DISEASE**

<table>
<thead>
<tr>
<th>The patient is a woman in average health with a 1.2-cm, ER-positive, PR-negative, HER2-negative (as confirmed by FISH); Grade II tumor and negative lymph nodes. Which chemotherapy regimen, if any, would you most likely recommend for this patient?</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC x 4 q3wk</td>
<td>4%</td>
</tr>
<tr>
<td>FAC x 6</td>
<td>—</td>
</tr>
<tr>
<td>FAC x 6 q3wk</td>
<td>6%</td>
</tr>
<tr>
<td>TAC (docetaxel, doxorubicin, cyclophosphamide)</td>
<td>10%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>2%</td>
</tr>
</tbody>
</table>

*6% of oncologists answered not use this regimen for this patient.*

**ADJUVANT CHEMOTHERAPY FOR NODE-NEGATIVE DISEASE**

<table>
<thead>
<tr>
<th>The patient is a woman in average health with a 1.2-cm, ER-positive, HER2-negative (as confirmed by FISH); Grade II tumor and negative lymph nodes. Which chemotherapy regimen, if any, would you most likely recommend for this patient?</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC x 6 q3wk</td>
<td>4%</td>
</tr>
<tr>
<td>FAC x 6 q3wk</td>
<td>6%</td>
</tr>
<tr>
<td>FAC x 6 q2wk</td>
<td>4%</td>
</tr>
<tr>
<td>TAC (docetaxel, doxorubicin, cyclophosphamide)</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>2%</td>
</tr>
</tbody>
</table>

*2% of oncologists answered not use this regimen for this patient.*

**SELECT PUBLICATIONS**


**ONCOTYPE DX AND COMPUTERIZED RISK MODELS**

Peter Ravdin notes in the Adjuvant! program, the relative benefit of chemotherapy is presumed to be equal for patients at higher and lower risk, but it’s likely that the estimation of chemotherapy benefit in the group with low-risk disease is an overestimation. Conversely, the benefit in the group with higher-risk disease may be underestimated. I believe our studies with Oncotype DX demonstrate this, and Ravdin’s model may need to be modified slightly. My concern is that when people see these data from NSABP B-20, they will want the assay performed because nobody wants to receive chemotherapy when it will not work.

— Sonny Jung, MD, Breast Cancer Update 2005 (3)

**CHEMOTHERAPY AND RECEPTOR STATUS**

The estrogen and progesterone-receptor status may be important in determining the potential benefit from adjuvant chemotherapy. SWOG B-8144 demonstrated that patients with highly ER- and PR-positive tumors received no benefit from FAC chemotherapy. Similarly, data from the Ludwig group showed that highly endocrine-responsive patients received little or possibly no benefit from chemotherapy. Finally, Don Berry’s analysis of a series of CALGB/SWOG studies showed little or no additional benefit for taxanes added to AC or for dose-dense chemotherapy in the ER-positive group of patients.

— C Kent Osborne, MD, Breast Cancer Update 2005, Special CME Meeting Edition

**SELECTION OF ADJUVANT CHEMOTHERAPY**

For patients with ER-positive disease and multiple positive nodes, I usually use AC with or without a taxoid, often doxorubicin. As we learn more about the biology of these diseases, we are separating out the cancers by more than just ER-positive and ER-negative, I hope that we can give fewer people chemotherapy.

— Ann H Partridge, MD, MPH, Patterns of Care 2005 (1)

For adjuvant chemotherapy in the lower-risk, node-negative setting, I generally use four cycles of AC. The controversial issue is whether to use the traditional every three-week schedule or dose-dense therapy with growth factor support. Dose-dense schedules are somewhat better tolerated because of the growth factors, and the patient finishes therapy faster. They come with a great deal of additional cost. Most importantly, however, we could probably benefit from additional validation that AC given every two weeks has an advantage over an every three-week administration. Clearly, dose-dense AC → paclitaxel showed an advantage in CALGB-9741 that most oncologists have accepted. However, whether we can convert that benefit to a lower-risk, node-negative setting with AC times four alone is controversial. In my practice, I discuss with patients the benefits of quicker therapy, the downside in terms of additional injections and cost, and the uncertainty regarding the additional benefit of dose-dense AC. I’m comfortable, however, if a patient chooses to go that route, that we’re not doing her any harm.

— Gary H Lyman, MD, MPH, Patterns of Care 2005 (1)

AC → docetaxel, the control arm in our current US Oncology study, is a very reasonable treatment that doesn’t require growth factors. TAC would also be an option. TAC comes with a great deal of additional cost. Most importantly, however, we could probably benefit from additional validation that AC given every two weeks has an advantage over an every three-week administration. Clearly, dose-dense AC → paclitaxel showed an advantage in CALGB-9741 that most oncologists have accepted. However, whether we can convert that benefit to a lower-risk, node-negative setting with AC times four alone is controversial. In my practice, I discuss with patients the benefits of quicker therapy, the downside in terms of additional injections and cost, and the uncertainty regarding the additional benefit of dose-dense AC. I’m comfortable, however, if a patient chooses to go that route, that we’re not doing her any harm.

— Stephen J Jones, MD, Patterns of Care 2005 (1)
Adjuvant Trastuzumab Clinical Trial Results

At the 2005 ASCO meeting, practice-changing results from several adjuvant trastuzumab trials — NCTCG-N9831, NSABP-B-31 and HERA — were presented. The combined analysis of NCTCG-N9831/NSABP-B-31 demonstrated that the addition of trastuzumab to AC = paclitaxel significantly improved disease-free and overall survival in women with HER2-positive breast cancer. Data were also presented from the HERA trial, which demonstrated that adjuvant trastuzumab could improve disease-free survival when started after a variety of chemotherapy regimens. At this San Antonio meeting, data will be presented from BCIRG 006, in which adjuvant trastuzumab was found again to significantly improve disease-free survival, both with AC = docetaxel and a nonanthracycline-containing chemotherapy regimen of carboplatin plus docetaxel. These four landmark studies will now be followed by a new generation of adjuvant trials, and one issue of great interest — as in HER2-negative disease — will be the potential role of bevacizumab.

**PHASE III CLINICAL TRIALS OF ADJUVANT TRASTUZUMAB**

**NSABP-B-31**
- Gastrointestinal toxicity: Grade 3 or 4 gastrointestinal toxicity was reported in 2.7% of patients receiving HER2+ (IHC 3+ or FISH+) trastuzumab therapy, and 0.9% of patients receiving placebo. This difference was statistically significant (p = 0.0001).
- Cardiac tolerability: The incidence of grade 3 or 4 cardiac toxicity was 1.3% in the trastuzumab group and 0.3% in the placebo group (p = 0.0001). There were no deaths attributed to cardiac toxicity.

**BCIRG 006**
- The risk reduction in the TCH arm is 0.39, and the risk in the anthracycline-containing arm? The risk reduction in the ACTH arm is 0.51, almost identical to what was seen in the trials reported at ASCO for that type of combination. That’s based on very few event differences between the two arms. We need to watch until the data mature, and it won’t take a long period of time. Physicians should basically do what they feel most comfortable with at this point. If they feel more comfortable with the ACTH data, they should go with that arm, recognizing that those patients will have to be watched very closely for cardiotoxicity.
- In conclusion, at one-year median follow-up, the risk of a first breast cancer event at three years by 52

**FIRST RESULTS OF HERA: TRASTUZUMAB FOR ONE YEAR OR PLACEBO AFTER CHEMOTHERAPY FOR HER2-POSITIVE BREAST CANCER**

**BCIRG 006**
- The risk reduction in the TCH arm is 0.39, and the risk in the anthracycline-containing arm? The risk reduction in the ACTH arm is 0.51, almost identical to what was seen in the trials reported at ASCO for that type of combination. That’s based on very few event differences between the two arms. We need to watch until the data mature, and it won’t take a long period of time. Physicians should basically do what they feel most comfortable with at this point. If they feel more comfortable with the ACTH data, they should go with that arm, recognizing that those patients will have to be watched very closely for cardiotoxicity.
- In conclusion, at one-year median follow-up, the risk of a first breast cancer event at three years by 52

**ADJUVANT CHEMOTHERAPY WITH OR WITHOUT TRASTUZUMAB: COMBINED ANALYSIS OF NSABP-B-31/NCTCG-N9831 EFFICACY DATA**

**REDUCTION IN DISTANT DISEASE RECURRENT**

In the joint analysis of NCTCG-N9831 and NSABP-B-31, the hazard rates for distant disease recurrence in patients who received trastuzumab appeared to improve with time. It’s still too early to analyze these data because few patients in either trial are four years out; however, the distant disease-free survival curve appears to plateau in the trastuzumab arm. If that’s the case, it’s astonishing. We’ve never seen a true plateau in any adjuvant trial. When we examine disease-free survival curves like this, we need to ignore a fair amount of the right side of the curve because there are so few numbers, but if that is maintained it will be exciting.

**ADJUVANT TRASTUZUMAB IN NODE-NEGATIVE DISEASE**

I still have trepidation about using adjuvant trastuzumab in patients with node-negative disease and tumors under one centimeter. If the patient’s tumor is ER-negative, the threshold to treat with trastuzumab is lower. On the other hand, for those with ER-positive disease, I would probably want to do an Oncotype DX™ assay because I believe that is a reliable method to determine risk and would really be helpful. If it’s a high-risk tumor, I would add trastuzumab to that regimen.
Recent results of large randomized adjuvant trials of trastuzumab — NSABP-B-31, NCTCG-N9831, HERA and BCIRG 006 — have changed the management of HER2-positive early breast cancer, but a number of unresolved issues remain. Should adjuvant trastuzumab and chemotherapy be administered concurrently or sequentially? N9831 suggests that adjuvant trastuzumab concurrent with the taxane portion of chemotherapy improves disease-free survival more than sequential trastuzumab, but the HERA trial demonstrates benefit with adjuvant trastuzumab used after the completion of a variety of chemotherapy regimens. What is the optimal chemotherapy regimen in this setting? BCIRG 006 reported a low incidence of cardiac events for adjuvant trastuzumab in combination with a nonanthracycline-containing regimen, and initial efficacy results — announced in a press release and to be presented at this meeting — reveal a benefit for both AC → docetaxel/trastuzumab and docetaxel/carboplatin/trastuzumab, although the relative magnitude of benefit of these two arms is not clearly defined.

**BCIRG 006 and Randomized Trials of Adjuvant Trastuzumab**

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Eligibility</th>
<th>Randomization</th>
<th>Key issues evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG 006</td>
<td>Node-negative or high-risk node-negative HER2+ (HER2+)</td>
<td>AC → chemotherapy, AC → chemotherapy + H (total one year H)</td>
<td>Nonprotocol-defined H concurrent with chemotherapy</td>
</tr>
<tr>
<td>NCTCG-N9831</td>
<td>Node-negative HER2+ (HER2+ or FISH+)</td>
<td>AC → chemotherapy, AC → chemotherapy + H (total one year H)</td>
<td>Combined analysis with N9831, Whollyovsky or every three-years toxicities with concurrent H</td>
</tr>
<tr>
<td>NCTCG-N9831</td>
<td>Node-negative or high-risk node-negative HER2+ (HER2+ or FISH+)</td>
<td>AC → chemotherapy, AC → chemotherapy + H (total one year H)</td>
<td>Combined analysis with NCTCG-N9831, WHOLLYOVSKY or every three-years toxicities with concurrent H</td>
</tr>
<tr>
<td>BIG-1-01, HERA</td>
<td>Node-negative or node-negative HER2+ (HER2+)</td>
<td>Any chemotherapy + X</td>
<td>Duration of H versus no H following Adjuvant chemotherapy</td>
</tr>
</tbody>
</table>

**PROTOCOL-DEFINED CARCINIC EVENTS IN ADJUVANT TRASTUZUMAB TRIALS**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients</th>
<th>Number of events</th>
<th>Percent improvement</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>Overall survival</td>
<td>1,964</td>
<td>220</td>
<td>0.2936</td>
</tr>
<tr>
<td></td>
<td>1 AC → H vs AC + H</td>
<td>1,239</td>
<td>133</td>
<td>0.015</td>
</tr>
</tbody>
</table>

**HERA TRIAL: RELATIVE REDUCTION IN RECURRENCE RATE**

<table>
<thead>
<tr>
<th>All (n = 1,387)</th>
<th>Adjuvant chemotherapy rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemotherapy</td>
<td>46%</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>47%</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>48%</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>49%</td>
</tr>
</tbody>
</table>

**DURATION OF ADJUVANT TRASTUZUMAB: DELAYED IMPLEMENTATION OF ADJUVANT TRASTUZUMAB**

The HERA trial is evaluating the duration question. In their trial, one arm has no trastuzumab, the second arm has one year and the third arm has two years of trastuzumab after chemotherapy. Because the data at this point address one year of trastuzumab, I believe that’s the appropriate length of time.

As for the delayed implementation of trastuzumab in the intergroup trial, they’re supplying trastuzumab to the central group of patients who want to crossover out of one year of follow-up. There are theoretical arguments that a year is somewhat of an arbitrary length. The peak in relapses occurs at about two to three years, so I could see a rationale for treating beyond a year, particularly for patients at high risk with multiple nodes. However, that rationale is going beyond the data we have and is somewhat speculative. — Peter M Ravdin, MD, PhD. Breast Cancer Update 2005 (8)

**TRASTUZUMAB SAFETY AND EFFICACY**

We acknowledge that we have only an incomplete picture of the risks associated with trastuzumab. The risk of cardiotoxicity is currently low in our trial, but this could change with longer follow-up.

Another concern is that longer follow-up may show that trastuzumab is not effective in reducing the incidence of disease recurrence in the central nervous system. Brain metastases developed in approximately one third of the women receiving trastuzumab as treatment for advanced breast cancer, despite control of systemic disease. It is not clear whether such chemosensitive system metastases reflect aggressive disease or poor penetration of trastuzumab into the brain. — Martine J Piccart-Gebhart, PhD, MD. Breast Cancer Update 2005 (8)
How have the recent dramatic findings of the adjuvant trastuzumab trials — NSABP-B-31, NCTCG-N9831, HERA and BCIRG 006 — altered the clinical practice of medical oncologists in the United States? In a recent post-ASCO survey of medical oncologists, the overwhelming majority would now recommend adjuvant trastuzumab plus chemotherapy for patients with HER2-positive, node-positive and higher-risk, node-negative breast cancers. When asked about the sequential versus concurrent use of trastuzumab and chemotherapy, most oncologists stated they would utilize adjuvant trastuzumab following the completion of the anthracycline portion of the chemotherapy and concurrent with the taxane. Additionally, oncologists are offering patients delayed adjuvant trastuzumab, particularly in patients with node-positive tumors, within a year of completing adjuvant chemotherapy. MUGA scans are the most common approach to monitoring cardiac effects of therapy, and trastuzumab is much less frequently recommended for patients in their seventies and eighties, perhaps because of cardiac concerns. This survey was done prior to the press release of BCIRG data on trial 006, and it will be interesting to evaluate how this data set — which will be presented at this San Antonio meeting — will impact selection of chemotherapy regimens, including the choice of paclitaxel versus docetaxel, and the use of TCH (docetaxel/carboplatin/trastuzumab).

## CLINICAL USE OF ADJUVANT TRASTUZUMAB

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>N-</th>
<th>N+</th>
<th>N-</th>
<th>N+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab + chemotherapy</td>
<td>70%</td>
<td>66%</td>
<td>94%</td>
<td>94%</td>
<td>94%</td>
</tr>
<tr>
<td>AC</td>
<td>32%</td>
<td>14%</td>
<td>2%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AC + paclitaxel</td>
<td>43%</td>
<td>40%</td>
<td>86%</td>
<td>88%</td>
<td>94%</td>
</tr>
<tr>
<td>TAC</td>
<td>—</td>
<td>4%</td>
<td>6%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>FAC + docetaxel</td>
<td>4%</td>
<td>4%</td>
<td>2%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Legend:**
- **N**: node-negative breast cancer
- **N-**: node-negative disease
- **N+**: node-positive disease
- **N0**: negative nodes
- **N1**: 1–3 positive nodes
- **N2**: 4–9 positive nodes
- **N3**: 10 or more positive nodes

## DELAYED ADJUVANT TRASTUZUMAB

Six months after completion of chemotherapy AC — 6% 8% 14% 22% 38%
One year after completion of chemotherapy — 4% 8% 14% 22% 38%
Two years after completion of chemotherapy — — — 4% 8% 22%

**Aboor Cancer Update Patterns of Care Survey, September 2005 (n = 50)**

## SELECT PUBLICATIONS

- **Gnant M et al.** Cardiac safety analysis of the first stage of NSABP B-31, a randomized trial comparing the safety and efficacy of Adriamycin and cyclophosphamide (AC) followed by Taxol to that of AC followed by Taxol plus Herceptin in patients (AC with or without, non-positive or node-positive breast cancer). HER2-B31, Int J Breast Cancer 2005;2005:425324. PubMed
- **Perez EA** et al. HER2 testing by local, central, and reference laboratories in the NCTCG-N9831 Herceptin-Adjuvant Trial. Proc ASCO 2004;Abstract 507.
- **Perez EA et al.** NCTCG N9830 May 2005 Update: Presentation. ASCO 2005

## OVERVIEW OF NSABP-B-31, NCTCG-N9831 AND HERA

As a result of the data presented at ASCO in 2005, trastuzumab has now become a standard of care in the adjuvant setting for HER2-positive breast cancer. We saw a stunning validation of the biology of HER2 and the concept that we could decrease the likelihood of recurrences and improve overall survival through the use of targeted therapy. We saw that by two years after randomization, one quarter of the patients in the control arm had relapsed.

In the joint analysis of NCTCG-N9831 and NSABP-B-31, around 25 percent had relapsed by approximately three years. This is a bad disease, and partly because of that, we see a high event rate early in these trials. A striking benefit was seen with trastuzumab, including a survival benefit with a median follow-up of just two years. That is unprecedented in any adjuvant trial. In the HERA trial, all the patients received trastuzumab after rather than concurrent with chemotherapy, and those data were positive with an impressive 45 percent reduction in hazard rate.


## NCTCG-N9831: CARDIAC SAFETY OF ADJUVANT TRASTUZUMAB

Although our trial demonstrated that clinical cardiac events are observed in patients receiving adjuvant trastuzumab, the difference is less than four percent compared to the control arm. The numbers are actually a bit lower than the numbers in NSABP-B-31 but statistically quite similar. At this point, we have not seen any difference in cardiac events between the two trastuzumab-containing arms. Not every patient has a reversal of their cardiac events, but most patients definitively improve not only in terms of the clinical symptomatology but also measurable left ventricular ejection fraction.

— **Edith A Perez, MD. Breast Cancer Update 2005 (4)**

## ADJUVANT TRASTUZUMAB IN NODE-NEGATIVE TUMORS

The HERA study included patients with node-negative disease as long as their tumors were greater than two centimeters. The NSABP trial had no patients with node-negative disease, and in the NCTCG study, patients with node-negative disease accounted for 14 percent of the total population but only six percent of the events. It’s unlikely that the relative benefits of trastuzumab will differ in patients with node-negative versus node-positive disease. On the other hand, the absolute benefit will differ, because patients with node-negative disease, particularly with small tumors, have a lower risk of recurrence. In my mind, it’s reasonable to consider trastuzumab for patients who were eligible for the studies. The group of women that I’m a little more cautious about are those with relatively small, ER-positive, node-negative breast cancer.

— **Eric P Winer, MD. Breast Cancer Update 2005 (7)**

## ROLE OF DELAYED ADJUVANT TRASTUZUMAB

The HERA trial suggests that administering trastuzumab after chemotherapy may be beneficial, so the question becomes, how long after chemotherapy will it be beneficial? In the case of estrogen receptors, we have two European randomized trials that evaluated the late use of tamoxifen in patients with estrogen receptor-positive breast cancer, and both were positive. Will we see a similar benefit with delayed adjuvant trastuzumab? It’s a reasonable and important question, particularly for those patients in the control arms of N9831 and B-31 who are more than 18 months out from treatment. I’m not going to be dogmatic about this, but I do believe it’s reasonable to discuss the option of trastuzumab with such patients.

— **George W Wedge Jr, MD. Breast Cancer Update 2005 (8)**
In women with HER2-positive early breast cancer, the addition of one year of adjuvant trastuzumab to chemotherapy has been shown to significantly improve disease-free and overall survival. Several trials investigating the addition of trastuzumab to neoadjuvant chemotherapy have reported pathologic complete response (pCR) rates ranging from seven to 42 percent. At the 2004 ASCO meeting, Dr. Arun Buzdar reported the results of a randomized neoadjuvant trial of paclitaxel + FEC with or without trastuzumab in women with HER2-positive breast cancer. This neoadjuvant trastuzumab/chemotherapy regimen yielded a pCR of 62.5 percent compared to 26.3 percent for chemotherapy alone. NSABP-B-41 has been designed to compare two neoadjuvant regimens: FEC → paclitaxel plus trastuzumab and paclitaxel plus trastuzumab → FEC plus trastuzumab. Another important study, conducted by Dr. Jenny Chang, demonstrated impressive clinical responses and interesting intracellular changes after three weeks of neoadjuvant trastuzumab monotherapy.

**RESPONSE RATES IN NEOADJUVANT TRIALS OF TRASTUZUMAB PLUS CHEMOTHERAPY**

<table>
<thead>
<tr>
<th>Name</th>
<th>Neoadjuvant regimen</th>
<th>Number of patients</th>
<th>Pathologic complete response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abati 2004</td>
<td>Trastuzumab qwk + docetaxel (4-6 cycles) + carboplatin (4 cycles)</td>
<td>14</td>
<td>7%</td>
</tr>
<tr>
<td>Buzdar 2003</td>
<td>Trastuzumab q4w + docetaxel q3w 2 cycles + carboplatin q4w 2 cycles</td>
<td>33</td>
<td>12%</td>
</tr>
<tr>
<td>Buzdar 2003</td>
<td>Trastuzumab q4w + 12 cycles + paclitaxel q3w 4 cycles</td>
<td>40</td>
<td>15% + ICE 15%</td>
</tr>
<tr>
<td>Harley 2006</td>
<td>Trastuzumab q4w + docetaxel q3w (4 cycles + G-CSF/7 cycles)</td>
<td>44</td>
<td>20%</td>
</tr>
<tr>
<td>Linenberger 2003</td>
<td>Trastuzumab q4w + docetaxel q3w + carboplatin q4w + G-CSF</td>
<td>12</td>
<td>42%</td>
</tr>
<tr>
<td>Molikian 2003</td>
<td>Trastuzumab q4w + docetaxel q3w</td>
<td>18</td>
<td>20%</td>
</tr>
<tr>
<td>Suhildaman 2003</td>
<td>Trastuzumab q4w + docetaxel q3w</td>
<td>20</td>
<td>25%</td>
</tr>
<tr>
<td>Carey 2005</td>
<td>AC + 6 cycles + paclitaxel q4w + 12 cycles</td>
<td>22</td>
<td>22%</td>
</tr>
<tr>
<td>Steiger 2002</td>
<td>Trastuzumab q4w + docetaxel q3w + trastuzumab q4w</td>
<td>9</td>
<td>22%</td>
</tr>
</tbody>
</table>

G-CSF = granulocyte colony-stimulating factor; ICE = epirubicin/etoposide/cytarabine;
SAFE = paclitaxel/adriamycin/cyclophosphamide.

- **MD ANDERSON PHASE III TRIAL OF NEOADJUVANT TRASTUZUMAB/CHEMOTHERAPY**

<table>
<thead>
<tr>
<th>Name</th>
<th>Acronym (by)</th>
<th>Stage</th>
<th>Eligibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buzdar 2003</td>
<td>NSABP-B-31/ACOSOG-Z0003 (Proposed)</td>
<td>Stage I/II</td>
<td></td>
</tr>
</tbody>
</table>

**Eligibility**

- **Patients with HER2-positive disease**

**Randomized Trial of Neoadjuvant Trastuzumab and Chemotherapy vs. Chemotherapy Alone**

**Eligibility**

- **HER2-positive disease**

**NEGADJUVANT DOCETAXEL/CARBOPLATIN WITH OR WITHOUT TRASTUZUMAB**

**Protocol ID:** UCLAD-201311, HERTIS-GR-1110, GENTECH-H2269s.

**Target Enrollment:** 75 (Expanding)

**Eligibility**

- **3 or 4 Ed, any 9 patients with HER2-positive disease**
- **Test assignment to neoadjuvant therapy**

**Randomized Trial of Neoadjuvant Trastuzumab and Chemotherapy vs. Chemotherapy Alone**

**Eligibility**

- **Trastuzumab qwk x 12**
- **Paclitaxel q4w + carboplatin qwk x 12**

**Randomized Trial of Neoadjuvant Trastuzumab and Chemotherapy vs. Chemotherapy Alone**

**Eligibility**

- **Phase I**
- **Phase II**

**NEGADJUVANT TRASTUZUMAB INDUCES APOPTOSIS**

We evaluated the activity and efficacy of neoadjuvant single-agent trastuzumab in treatment-naive women with HER2-overexpressing locally advanced breast cancer. We administered three weeks of single-agent trastuzumab and measured the tumor size before and after treatment. The endpoints assessed in the study were twofold: (1) efficacy and (2) the mechanism of action of trastuzumab. For the second endpoint, we evaluated several pathways — proliferation, growth factor and apoptosis pathways. We enrolled 40 patients, and after only three weeks of trastuzumab, 25 percent of the patients had a partial response (50 percent reduction). It was stunning because these were all hormone-sensitive, inflammatory breast cancers. Within the first few weeks, the patients would tell you: “The redness is going, and the mass is getting softer.”

This was independently verified by at least two oncologists, so it’s real. The other patients had stabilization of disease, and none progressed. At that point, we used four cycles of docetaxel and continued weekly trastuzumab. All of the patients underwent surgery, and the pCR rate was very high — in the 35 percent range. Not surprisingly, trastuzumab’s primary mechanism of action is the induction of apoptosis. This has important implications. First, trastuzumab is unlikely to be antagonistic with chemotherapy because they both affect apoptosis, so they would more likely be synergistic.

Second, we might think that in studies of patients with metastatic disease we could consider trastuzumab for a period of time, stopping, evaluating how the patients do, then reintroducing trastuzumab in the future.

- **Jenny C Chang, MD, Breast Cancer Update 2005 (2)**
At the 2004 San Antonio Breast Cancer Symposium, Dr Harry Bear presented updated results from NSABP-B-27, which evaluated the addition of docetaxel to neoadjuvant AC. Whereas the addition of neoadjuvant docetaxel improved the pathologic complete response rate, no differences were found in overall or disease-free survival. However, relapse-free survival was significantly higher in patients receiving neoadjuvant AC plus docetaxel compared to those treated with neoadjuvant AC alone. A new generation of neoadjuvant trials is evaluating novel strategies, including dose-dense chemotherapy, nab paclitaxel, capecitabine/docetaxel (XT), bevacizumab/docetaxel and other regimens.

**Neoadjuvant Chemotherapy**

**PHASE III TRIAL EVALUATING THE ADDITION OF A TAXANE TO PROGRAME PREOPERATIVE AC**

**Eligibility** Stage IIA/IIB breast cancer

**Treatment**

- **ARM 1** AC x 4 + surgery + docetaxel 
- **ARM 2** AC x 4 + surgery + placebo + docetaxel 

**Initial Results: Clinical Response**

| Percentage | p
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cCR</td>
<td>cT0</td>
</tr>
<tr>
<td>14.8</td>
<td>45.4</td>
</tr>
</tbody>
</table>

**MD ANDERSON PHASE III NEOADJUVANT TRIAL OF WEEKLY PAACLITAXEL VS CAPCITABINE/DOCETAXEL + FEC AND LOCAL THERAPY**

**Eligibility** Stage IIIA/IIB breast cancer

**Treatment**

- **ARM 1** Paclitaxel x 4 + local therapy (surgery or RT)*
- **ARM 2** Capcitabine 700mg/m2 x 9 + paclitaxel x 4 + local therapy in RT*

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

**Ongoing Trials of Neoadjuvant Chemotherapy**

**Protocol Phase N Regimen**

- **NSABP B-43 (pending activation)**
  - **ARM 1** Docetaxel 100 mg/m2 x 4 + Carboplatin 50 mg/m2 + gemcitabine 1,500 mg/m2
  - **ARM 2** Docetaxel 100 mg/m2 + gemcitabine 1,500 mg/m2

**MD Anderson B-033**

- **ARM 1** Paclitaxel 80mg/m2 x 12 + ipi
  - **ARM 2** Paclitaxel 80mg/m2 x 12 + ipi + bevacizumab

**NCI Physician Data Query, October 2005; NSABP Protocol NCCTG-N0338**

**MD Anderson B-033**

- **ARM 1** Paclitaxel 80mg/m2 x 12 + ipi
  - **ARM 2** Paclitaxel 80mg/m2 x 12 + ipi + bevacizumab

**MD Anderson B-033**

- **ARM 1** Paclitaxel 80mg/m2 x 12 + ipi
  - **ARM 2** Paclitaxel 80mg/m2 x 12 + ipi + bevacizumab

**Source:** NC Preventive Medicine Data Query, September 2005.
Neoadjuvant Endocrine Therapy

The most commonly utilized neoadjuvant therapy in the United States is chemotherapy. However, in Europe, preoperative endocrine therapy is used extensively in women with ER-positive breast cancer. A small, randomized, neoadjuvant trial demonstrated that the efficacy of the aromatase inhibitors was comparable to chemotherapy in terms of objective and pathologic response rates, local recurrence and breast conservation rates. The IMPACT trial — comparing neoadjuvant anastrozole, tamoxifen or the combination — found that more women receiving anastrozole became eligible for breast-conserving surgery. An upcoming ACOSOG trial will compare the three aromatase inhibitors as neoadjuvant therapy, and an ongoing trial will compare two different doses of fulvestrant.

IMPACT TRIAL: ANASTROZOLE VERSUS TAMOXIFEN VERSUS THE COMBINATION

Eligibility: Postmenopausal, ER-positive breast cancer

<table>
<thead>
<tr>
<th>Arm</th>
<th>Treatment</th>
<th>Response rate (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Anastrozole</td>
<td>Complete clinical response (cCR)</td>
<td>26%</td>
</tr>
<tr>
<td>B</td>
<td>Tamoxifen</td>
<td>Particulate clinical response (pPR)</td>
<td>23%</td>
</tr>
<tr>
<td>C</td>
<td>Anastrozole plus tamoxifen</td>
<td>Objective clinical response (OR)</td>
<td>82%</td>
</tr>
</tbody>
</table>

**Impression:**
- Anastrozole was active in improving responses to neoadjuvant endocrine therapy.
- The combination of anastrozole and tamoxifen appeared to be more effective than either agent alone.

**Conclusion:**
- The IMPACT trial demonstrated that anastrozole was comparable to chemotherapy in terms of response rates.
- The combination of anastrozole and tamoxifen may be more effective than either agent alone.

RESPONSE RATE FOLLOWING NEOADJUVANT ANASTROZOLE IN POSTMENOPAUSAL WOMEN WITH LOCALLY ADVANCED BREAST CANCER

Randomized Phase II Study Comparing Neoadjuvant Exemestane, Letrozole, and Anastrozole in ER/PR-Positive Breast Cancer

<table>
<thead>
<tr>
<th>Arm</th>
<th>Treatment</th>
<th>Clinical objective response (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exemestane 75 mg</td>
<td>91.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Letrozole 2.5 mg</td>
<td>90.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole 1 mg</td>
<td>87.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:**
- Exemestane was the most effective in improving response rates.
- Letrozole and anastrozole were also effective but less so than exemestane.

**Target:**
- To compare the efficacy of different aromatase inhibitors in neoadjuvant therapy.
- To determine the optimal treatment regimen for locally advanced breast cancer.

**Recommendation:**
- Exemestane may be the preferred agent for neoadjuvant therapy in ER-positive breast cancer.
- Further studies are needed to confirm these findings.

ENDOCRINE THERAPY VERSUS CHEMOTHERAPY IN THE NEoadjuvant SETTING

We’re significantly more likely to be successful performing breast-conserving surgery after neoadjuvant endocrine therapy than chemotherapy. One reason for this is that approximately 3% to 30% of patients who respond well to neoadjuvant chemotherapy are left with multiple islands of tumor scattered throughout an area of the breast that corresponds to the size of the original tumor, whereas the pattern following neoadjuvant endocrine therapy is that the tumor shrinks and implies.

The number of patients receiving neoadjuvant endocrine therapy has increased significantly, and many oncologists who have tried this approach and found that it worked have adopted this strategy. I believe more physicians should be utilizing this because it’s effective at downsizing some large tumors, making inoperable tumors operable.

When we select and treat only patients with ER-rich tumors, meaning Allen scores 6, 7, and 8, the number of patients who progress or actually fail to respond is very small. We have also learned that we can treat patients longer than three or four months with neoadjuvant therapy and see continued response.

We’ve treated patients for up to a year and found that the number of patients with a complete response continues to rise the longer we treat them. If the tumor is shrinking but still not small enough for breast-conserving surgery at three or four months, continuing therapy will give added benefit, and eventually, most of these tumors will become small enough for breast conservation.

— J Michael Dixon, MD, Breast Cancer Update 2005 (5)

I believe it was a mistake to evaluate chemotherapy rather than endocrine therapy in some of the earlier animal studies. The relative efficacy of neoadjuvant endocrine therapy and while no evidence indicates that preoperative chemotherapy improves survival, that’s nonspecific treatment, and it doesn’t mean that neoadjuvant endocrine therapy will fail if we use neoadjuvant endocrine treatment as a biological response modifier, and I believe using the aromatase inhibitors up front will have a greater impact on long-term outcome.

— Michael Baum, MD, DPhil, Breast Cancer Update 2005 (1)

SURROGATE OUTCOMES OF NEOADJUVANT ENDOCRINE THERAPY

A decision regarding neoadjuvant chemotherapy compared with neoadjuvant endocrine therapy would be made easier if there were predictive tests that could select a subpopulation of tumors whose response to the neoadjuvant aromatase inhibitor is in a range of 80 to 90 percent. If such a test also identified a tumor subtype for which chemotherapy did not improve outcomes, then we would have made real progress toward making neoadjuvant endocrine therapy a new standard of care.

— Matthew J Ellis, MD, PhD, J Clin Oncol 2005;23(22):4682-4.

Neoadjuvant treatment provides a useful clinical model and the opportunity to obtain primary tumour material by which to explore molecular mechanisms associated with de novo resistance and early acquired resistance. The model has already demonstrated that the absence of tumour ER confers endocrine resistance. … There are also suggestions that high expression of c-erbB-2 is associated with a reduced clinical response to endocrine therapy and that this also occurs after effective oestrogen deprivation. Whether these translate eventually into endocrine resistance and a poor outcome remains to be determined. The present studies are not definitive and require larger groups of patients. It should also be noted that whereas the particular protocol involving neoadjuvant endocrine therapy for three months can provide evidence of de novo resistance and early forms of acquired resistance, it is unlikely to be useful in identifying processes that occur in the longer term.

The number of hormonal therapy options for postmenopausal women with estrogen receptor-positive metastatic breast cancer expanded with the introduction of the aromatase inhibitors and fulvestrant. Ongoing clinical trials — SoFEA and EFFECT — are evaluating endocrine strategies in women who have progressed on the usual first-line therapies (nonsteroidal aromatase inhibitors). Based on the theoretical advantage of utilizing fulvestrant in a lower-estrogen environment, the SoFEA trial and SWOG-S0226 are both investigating the combination of fulvestrant with an aromatase inhibitor. Biologic agents, including trastuzumab, and the tyrosine kinase inhibitors are also being assessed in combination with various endocrine interventions.

**Ongoing Clinical Trials of Novel Combinations of Hormonal Therapies and Biologic Agents**

**Phase III Study of Single-Agent Fulvestrant**

**Protocol ID:** BR001700

**Eligibility:** Postmenopausal women with hormone receptor-positive metastatic breast cancer who have progressed on a prior endocrine therapy.

**Trial Design:**
- **ARM 1:** Fulvestrant 250 mg
- **ARM 2:** Fulvestrant 50 mg

**Study Contact:**
- Arbor Pharmaceuticals LP, www.arbor.com
- Phone: 604-988-3270

**Phase III Study of Fulvestrant with or without Anastrozole Versus Exemestane**

**Protocol ID:** BR001700

**Eligibility:** Postmenopausal women with hormone receptor-positive metastatic breast cancer who have failed to respond to a nonsteroidal aromatase inhibitor.

**Trial Design:**
- **ARM 1:** Anastrozole (LD)
- **ARM 2:** Anastrozole (10 mg) followed by fulvestrant or the opposite — but I believe it’s important that we determine which is superior.

**Study Site:**
- Dr. Stephen Johnston, Royal Marsden Hospital, London, UK
- Phone: 020 8628 5792

**Phase III Study of Anastrozole with or without Fulvestrant as First-Line Therapy**

**Protocol ID:** BR001700

**Eligibility:** Postmenopausal women with hormone receptor-positive metastatic breast cancer.

**Trial Design:**
- **ARM 1:** Anastrozole
- **ARM 2:** Fulvestrant

**Study Contact:**
- Dr. Stephen Johnston, Royal Marsden Hospital, London, UK
- Phone: 020 8628 5792

**Phase III Study Comparing Fulvestrant and Exemestane**

**Protocol ID:** BR001700

**Eligibility:** Postmenopausal women with hormone receptor-positive metastatic breast cancer.

**Trial Design:**
- **ARM 1:** Fulvestrant (LD)
- **ARM 2:** Exemestane

**Study Site:**
- Dr. Stephen Johnston, Royal Marsden Hospital, London, UK
- Phone: 020 8628 5792

**SELECT PUBLICATIONS**

- Johnston S. Fulvestrant and the sequential endocrine cascade for advanced breast cancer — William J Gradishar, MD.
- Mitchell Dowsett, PhD. Breast Cancer Update 2004 (9)
- Rita Mehta, MD, Southwest Oncology Group, Ph: 714-456-5153

**EFFECT Trial**

**EFFECT** is an American-European study that randomly assigns patients who have failed therapy with a nonsteroidal aromatase inhibitor to fulvestrant or exemestane. Our own study, SoFEA, is slightly different from EFFECT because it is based on the observation that the addition of small amounts of estrogen to cells that have been estrogen deprived for a long time reduces the effectiveness of fulvestrant. That scenario equates to the withdrawal of a nonsteroidal aromatase inhibitor and the addition of fulvestrant. Hence, the third arm of our trial includes a nonsteroidal aromatase inhibitor and fulvestrant. I predict fulvestrant alone will probably be better than exemestane, and fulvestrant plus anastrozole will be better than fulvestrant alone.

**Optimal Sequencing of Agents in Postmenopausal Patients**

If you evaluate most of the available data with endocrine agents in the metastatic setting — tamoxifen, steroidal or nonsteroidal aromatase inhibitors or fulvestrant — the question comes up as whether one sequence enhances patient outcome more than another. This becomes an area of study that demonstrate that one sequence enhances the time to disease progression, it may be built on over time that overall outcome is improved.

In theory, simply having an improvement in recurrence or progression of metastatic disease impacts quality of life. Patients now typically receive a nonsteroidal aromatase inhibitor — anastrozole or letrozole — as the first treatment. The question then becomes, if patients progress on one of those agents, what would be the next best therapy? Should it be the steroidal aromatase inhibitor exemestane, or should it be fulvestrant? Indirect data evaluating the sequencing of a nonsteroidal aromatase inhibitor to fulvestrant suggest that 25 to 30 percent of patients may benefit with that approach. An important issue is whether fulvestrant 250 mg is optimal. Some of the data suggest that the dose is really on the low end of the curve where you might expect the optimal response rates. Some strategies have evaluated quickly increasing serum levels of fulvestrant, including administering loading doses of 500 mg and within two weeks achieving another 250 mg dose and then proceeding to the monthly schedule. Those strategies are based on mathematical modeling that has shown an ability to achieve steady-state levels much more quickly and conveniently, with a pharmacologically relevant dose of drug circulating much faster.

**Breast Cancer Update 2005 (4)**

**Assuming an aromatase inhibitor and fulvestrant are equivalent in efficacy, the choice of which agent to use may come down to patient preference. Some of my patients are perfectly happy with a monthly injection, while others prefer an oral agent. For many patients, fulvestrant is financially favorable because of our arcane reimbursement system. We know that responses can be seen with either sequence — an aromatase inhibitor followed by fulvestrant or the opposite — but I believe it’s important that we determine which is superior.

I believe the trials of fulvestrant underestimate the efficacy of this agent. The dosing schedule used was probably too low because by the time that data was reached, many patients were off study, presumably because of progression. In my group, we administer loading doses of 500 mg of fulvestrant followed by 500 mg two weeks later and then 250 mg monthly. The pharmacokinetics of fulvestrant suggest a loading dose would be beneficial, so it concerns me that the comparison of fulvestrant to anastrozole in a tamoxifen-resistant population in the metastatic setting has not been evaluated with tamoxifen and aromatase inhibitors. Update of a phase IIb SABR trial. *San Antonio Breast Cancer Symposium* 2004;Meeting 10H8.
Sequencing of Hormonal Therapies in Metastatic Disease

The preferred sequence for hormonal therapies in postmenopausal women with metastatic disease has become a topic of considerable interest. As more postmenopausal women are being treated with aromatase inhibitors instead of tamoxifen in the adjuvant setting, the optimal therapy to use at initial relapse is not well defined. As first-line therapy, aromatase inhibitors are superior to tamoxifen, but the efficacy of fulvestrant — an estrogen receptor downregulator — is comparable to tamoxifen. As second-line therapy, fulvestrant and anastrozole have similar efficacy. A retrospective analysis of the proportion of patients with a prolonged duration of response suggests a benefit for fulvestrant over anastrozole. Future clinical trials are required to determine the optimal sequencing of the current hormonal therapy options.

**SEQUENCING HORMONAL THERAPIES**

To assess the efficacy of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer, a Phase II study of sequential hormonal therapy with fulvestrant followed by anastrozole (fulvestrant followed by anastrozole [F/A], n = 247) was compared with a Phase II study of sequential hormonal therapy with anastrozole followed by fulvestrant (anastrozole followed by fulvestrant [A/F], n = 212). Patients with a ≥24-week partial response to fulvestrant were eligible for entry into the study. Patients received fulvestrant 500 mg IM weekly for 24 weeks and then continued on anastrozole 1 mg daily. The primary endpoint was duration of response for all patients; additional endpoints included response rate, clinical benefit, and time to progression. The analysis suggested that fulvestrant has better overall survival than anastrozole in terms of the number of patients with prolonged duration of response. These data support the initial GIDEON findings in these trials, resulting in an important new endocrine agent in breast cancer.

**RESPONSE TO SUBSEQUENT ENDOCRINE THERAPY**

In patients enrolled in two Phase II studies of fulvestrant versus anastrozole, sequential hormonal therapy was performed equally as anastrozole. At this point in time, the sequencing and timing for fulvestrant are unclear. It is likely that there are multiple options including fulvestrant, exemestane, and even tamoxifen — if the patient hasn’t seen it — because it’s obviously still a useful drug. So the sequence is going to be all over the map for most folks.

— Stephen E. Jones, MD. Patterns of Care 2005 (1)

In the up-front study, tamoxifen and fulvestrant were essentially equivalent. As second-line therapy, fulvestrant seemed to perform equally as well as anastrozole. At this point in time, the sequencing and timing for fulvestrant are unclear. It is likely that there are multiple options including fulvestrant, exemestane, and even tamoxifen — if the patient hasn’t seen it — because it’s obviously still a useful drug. So the sequence is going to be all over the map for most folks.

— Debra Tripodi, MD. Breast Cancer Update 2005 (3)
In E1193, the Phase III trial comparing sequential single-agent and combination chemotherapy, patients treated with doxorubicin/paclitaxel did not have an improvement in overall survival. In contrast, two Phase III trials comparing nonsequential single-agent and combination chemotherapy reported an improvement in overall survival in patients receiving capecitabine/docetaxel or gemcitabine/paclitaxel, although neither trial included crossover for the single-agent arm. Capecitabine/paclitaxel, a regimen with encouraging results, has been evaluated in two Phase II trials. Breast cancer clinical investigators generally support the use of sequential single-agent chemotherapy in most patients with metastatic disease. Ongoing clinical trials will define the role for combination regimens, which may also include biologics.

### PHASE III TRIALS COMPARING SINGLE-AGENT AND COMBINATION CHEMOTHERAPY

**Table: Comparing doxorubicin monotherapy and combination capecitabine/docetaxel**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Regimen</th>
<th>Duration</th>
<th>Response rate (95% CI)</th>
<th>Median survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>Gemcitabine</td>
<td>2 cycles</td>
<td>40.0% (34.9, 46.7)</td>
<td>12.2 (11.2, 22.2)</td>
</tr>
<tr>
<td>T</td>
<td>Paclitaxel</td>
<td>2 cycles</td>
<td>22.7% (17.2, 27.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median overall survival (95% CI)</td>
<td>8.9 mo (5.0, 12.7)</td>
<td>6.3 mo (4.4, 7.4)</td>
<td>0.018</td>
<td></td>
</tr>
</tbody>
</table>

### MULTICENTRIC PHASE II STUDY OF CAPECITABINE PLUS PACLITAXEL AS FIRST-LINE THERAPY (N = 47)

<table>
<thead>
<tr>
<th>Arm</th>
<th>Regimen</th>
<th>Number of patients</th>
<th>Percent Response Rate</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>Capecitabine + paclitaxel</td>
<td>24</td>
<td>17/24 (70.8%)</td>
<td>18.5 mo (17.0, 22.0)</td>
</tr>
<tr>
<td>T</td>
<td>Paclitaxel</td>
<td>7</td>
<td>5/7 (71.4%)</td>
<td>15.8 mo (14.3, 22.4)</td>
</tr>
</tbody>
</table>

### PHASE III TRIAL OF CAPECITABINE AND WEEKLY PACLITAXEL IN TAXANE-NAÏVE PATIENTS

**Table: Phase III trial of capecitabine and weekly paclitaxel**

<table>
<thead>
<tr>
<th>Arm</th>
<th>Regimen</th>
<th>Patients (n)</th>
<th>Partial response</th>
<th>Median survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>Capecitabine + paclitaxel</td>
<td>10/24 (41.7%)</td>
<td>16/24 (66.7%)</td>
<td>18.5 mo (17.0, 22.0)</td>
</tr>
<tr>
<td>T</td>
<td>Paclitaxel</td>
<td>7/24 (29.2%)</td>
<td>5/24 (20.8%)</td>
<td>15.8 mo (14.3, 22.4)</td>
</tr>
</tbody>
</table>

### ACTIVE PHASE III TRIALS OF NOVEL COMBINATIONS OF CHEMOTHERAPY AND BILOGIC AGENTS

**Table: Phase III trials of novel combinations of chemotherapy and biologic agents**

<table>
<thead>
<tr>
<th>Protocol ID</th>
<th>Target agent</th>
<th>Eligibility</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA403-040</td>
<td>Bevacizumab</td>
<td>Overexpressing COX-2</td>
<td>Placebo</td>
</tr>
<tr>
<td>GSK-EP101151</td>
<td>Lapatinib</td>
<td>EGFR+ breast cancer</td>
<td>Placebo</td>
</tr>
<tr>
<td>CA403-041</td>
<td>Trastuzumab</td>
<td>HER2+ breast cancer</td>
<td>Placebo</td>
</tr>
<tr>
<td>GSK-EP10001</td>
<td>Lapatinib</td>
<td>HER2+ breast cancer</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

### SELECT PUBLICATIONS


In his 2006 abstract presentation at the 2006 San Antonio Breast Cancer Symposium, Dr. Gradishar presented results from the G-2200 trial showing that the addition of bevacizumab to capecitabine and docetaxel improved overall survival compared to chemotherapy alone.

**CAPECITABINE/PACLITAXEL IN PATIENTS WITH TAXANE-NAÏVE METASTATIC BREAST CANCER**

In our trial evaluating capecitabine and paclitaxel, patients could have undergone one prior chemotherapy regimen for metastatic breast cancer, which is in contrast to the front-line trial conducted by Dr. Gradishar that evaluated a similar regimen but used paclitaxel 175 mg/m² every three weeks. Our response rate was very exciting, with 50 percent of patients achieving a partial response and an additional 30 percent of patients with stable disease for greater than six months, which is comparable to the 70 percent clinical benefit seen in Dr. Gradishar’s trial. The median progression-free survival is 12.1 months, and overall survival has not yet been reached. The combination was remarkably well tolerated, and the hand-foot syndrome that occurred in 18 percent of patients was easily managed with dose modifications.

**INTERIM SURVIVAL REPORT**

The rationale behind our study was to determine whether we could use a similar benefit to that observed in Joyce O’Shaughnessy’s doxil/capecitabine randomized trial. There were differences in the two trials. Our study was largely in the first line, whereas O’Shaughnessy’s trial included patients receiving first, second-, and third-line therapy. The other distinction was the dose of the capecitabine. We started at 825 mg/m² twice daily for 14 days out of 21 days, as opposed to the FDA-approved dose (1,250 mg/m²) utilized in the other trial. We found the lower dose was better tolerated, which reflects the experience of most physicians using capecitabine as a single agent or in combination.

**Dose reduction is usually necessary when starting at the FDA-approved dose. In practice, most physicians utilize 1 g/m²/BD. So when combining with paclitaxel, the decision was made that we would use a lower starting dose. There was a very good response rate of approximately 50 percent, which is similar to O’Shaughnessy’s results in patients treated first line. If one is making the decision to combine capecitabine with a taxane, one could choose either docetaxel or paclitaxel and expect a robust response rate. It’s a reasonable combination if one is wedded to the idea of using a combination in a particular patient. Joanne Blum evaluated another regimen of paclitaxel and gemcitabine in combination. Not only did this regimen improve overall survival, it also improved progression-free survival and quality of life, which is important in patients receiving chemotherapy.
In patients with metastatic breast cancer, the roles of the taxanes — docetaxel, paclitaxel, and nab-paclitaxel — are evolving. Recent Phase III trials have demonstrated that every-three-week regimens of docetaxel or nab-paclitaxel have better efficacy than every-three-week paclitaxel. Nab-paclitaxel presents the advantage of not requiring premedication, which avoids side effects, particularly of steroid premedication. Another advantage of nab-paclitaxel is that it can be administered over 30 minutes. nab-paclitaxel has also been evaluated in two Phase II trials on a weekly schedule, which seems to retain efficacy with less toxicity. A Phase II trial found weekly docetaxel comparable to every-three-week docetaxel in terms of efficacy, but weekly docetaxel appeared to have a more favorable toxicity profile. Clinical trials will continue to delineate the role of the taxanes in the metastatic setting.

**PHASE III TRIAL COMPARING DOXETAXEL VERSUS PACLITAXEL IN PATIENTS WHO HAD PROGRESSED AFTER AN ANTHRACYCLINE-CONTAINING REGIMEN**

<table>
<thead>
<tr>
<th>Response to therapy (intention-to-treat basis)</th>
<th>Docetaxel (n = 123)</th>
<th>Paclitaxel (n = 123)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>32.6%</td>
<td>25.0%</td>
<td>0.13</td>
</tr>
<tr>
<td>Time to progression</td>
<td>25.6 months</td>
<td>22.9 months</td>
<td>0.010</td>
</tr>
<tr>
<td>Duration of response</td>
<td>15.5 months</td>
<td>14.8 months</td>
<td>0.07</td>
</tr>
<tr>
<td>Overall survival</td>
<td>15.4 months</td>
<td>12.7 months</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Neutropenic adverse events**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Docetaxel (n = 123)</th>
<th>Paclitaxel (n = 123)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3/4 neutropenia</td>
<td>43.4%</td>
<td>58.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>febrile neutropenia</td>
<td>9.8%</td>
<td>18.5%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**additional references**

— Blum JL et al. SELECT PUBLICATIONS compared with polyethilated castor oil-based paclitaxel in women with more favorable toxicity profile. Clinical trials will continue to delineate the role of the taxanes in the metastatic setting.

— Gradishar WJ et al. Superior efficacy, favorable safety profile, and greater patient convenience of ABI-007 [nanoparticle paclitaxel] make this novel albumin-bound taxane an important advance in the treatment of patients with MBC [metastatic breast cancer]. ABI-007 warrants further investigation, using additional dosing regimens (eg, weekly) and in combination with other treatment modalities, as front-line treatment of breast cancer and other solid tumors.

— Wj J Clin Oncol 2005;23(11);Supp ahead of print.

**NANOPARTICLE VERSUS STANDARD PACLITAXEL**

The superior efficacy, favorable safety profile, and greater patient convenience of ABI-007 [nanoparticle paclitaxel] make this novel albumin-bound taxane an important advance in the treatment of patients with MBC [metastatic breast cancer]. ABI-007 warrants further investigation, using additional dosing regimens (eg, weekly) and in combination with other treatment modalities, as front-line treatment of breast cancer and other solid tumors.


**NAB-PACLITAXEL COMPARED TO OTHER TAXANES**

I believe nanoparticle paclitaxel is more active than paclitaxel based on the randomized trials. In cross-study comparisons of nanoparticle paclitaxel versus docetaxel, each given every three weeks, the response rates were similar in the 30 percent range. However, docetaxel in the metastatic setting, whether given weekly or every three weeks, is toxic because of side effects like asthma, fluid retention, and neuropathy, and it’s difficult to administer for long periods of time.

One can go docetaxel in the adjuvant setting where treatment is short term, but I believe nanoparticle paclitaxel is better tolerated. I don’t use single-agent docetaxel in the metastatic setting, and I wouldn’t use nanoparticle paclitaxel in lieu of weekly paclitaxel.

I would like to see more data on combinations with nanoparticle paclitaxel from the taxanes to learn more about the toxicity profiles before using it in a combination off protocol.

— Joanne L. Blum, MD, PhD. Breast Cancer Update 2005 (I)

**CHOICE OF TAXANES IN THE METASTATIC SETTING**

A weekly regimen of the original paclitaxel formulation would have been my choice in the past. Now that we have data with nab-paclitaxel, I think that’s a reasonable option also, from the data, nab-paclitaxel may be preferable. It outperformed the original paclitaxel formulation when administered every three weeks. A weekly regimen allows us to outperform an every three-week regimen of the original paclitaxel formulation, and I’m left wondering which is the best drug to use. For patients who prefer an every-three-week schedule, I believe nab-paclitaxel is the way to go. Otherwise, it’s a toss-up between every-three-week nab-paclitaxel and a weekly regimen of the original paclitaxel formulation. I don’t believe there’s a way to compare the two. CALGB is planning to conduct a head-to-head trial comparing weekly regimens of nab-paclitaxel and the original paclitaxel formulation.

— Deo Tripathy, MD. Breast Cancer Update 2005 (I)
The importance of angiogenesis in cancer biology has been recognized for decades. One of the first angiogenesis-stimulating factors identified was the vascular endothelial growth factor (VEGF). Bevacizumab, a monoclonal antibody, inhibits the activity of VEGF.

At the 2005 ASCO meeting, Dr Kathy Miller reported the results from ECOG-E2100, a Phase III randomized trial evaluating the addition of bevacizumab to paclitaxel as first-line therapy in women with metastatic breast cancer. The addition of bevacizumab was found not only to improve the response rate and progression-free survival but also overall survival. These findings have led to the incorporation of bevacizumab in multiple clinical trials, both in the adjuvant and metastatic settings. An update of this important study will be presented at this meeting.

**ECOG-E2100**: Paclitaxel Alone or with Bevacizumab

As a result of the previous toxicity seen in the lung cancer trial, we had very stringent criteria for decon- nouncing E2100 if we saw an excess number of patients developing Grade IV hypotension or bleeding. When the trial was initiated, the National Cancer Institute had significant concerns about patient safety as a result of the initial experience with bevacizumab in lung cancer. Fortunately, early analyses demonstrated that was not an issue in breast cancer. The side effects were relatively minimal. Pernodually, we saw moderate increases in blood pressure, which is readily handled from a clinical standpoint. Of course, we’ll have to be careful with the hypertension as we move bevacizumab into the adjuvant setting. We also saw a few incidence of serious bleeding. Overall, bevacizumab was a nontoxic addition to chemotherapy.

**NEW CLINICAL TRIALS OF BEVACIZUMAB**

An ECOG pilot trial of adjuvant bevacizumab, which will be primarily evaluating safety issues, will involve over 200 patients and will open within the next few months. Our belief is that given adequate safety data in the adjuvant setting—which we hope to have within 12 to 18 months—we’ll be able to go directly to a large Phase III trial comparing chemotherapy to chemotherapy plus bevacizumab. Of course, many questions can be asked in the adjuvant setting with bevacizumab—which combination chemotherapy or what duration of therapy—and these may require more than one trial to answer. We will also need more than one trial because we’ll have to evaluate both HER2-negative and HER2-positive disease.

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kmiller@mdanderson.org

**REFERENCES**


Selection of systemic therapy in patients with metastatic disease is a multifaceted decision which is frequently influenced by the patient’s age, prior adjuvant systemic therapy and a variety of other biopsychosocial considerations. Data from the Breast Cancer Update Patterns of Care Study, a telephone survey conducted in September 2005 of randomly selected medical oncologists in the United States, are presented here. For patients with minimally symptomatic metastatic disease, single-agent docetaxel is a common choice, and in older patients, capecitabine is commonly utilized. In addition, bevacizumab is a common consideration, particularly in patients receiving paclitaxel as first-line treatment. As more postmenopausal women receive adjuvant aromatase inhibitors, the selection of first-line endocrine therapy for metastatic disease is changing. In postmenopausal women, fulvestrant is a popular choice after progression on adjuvant anastrozole, while the aromatase inhibitors are commonly utilized after progression on adjuvant tamoxifen.

### CHEMOTHERAPY FOR METASTATIC DISEASE AFTER PRIOR ADJUVANT AC \(\rightarrow\) PAACLITAXEL

<table>
<thead>
<tr>
<th>Age</th>
<th>Paclitaxel</th>
<th>Docetaxel</th>
<th>Non-taxane paclitaxel</th>
<th>Capecitabine</th>
<th>Gemcitabine</th>
<th>Vinorelbine</th>
<th>Carboplatin + docetaxel</th>
<th>AC</th>
<th>AC + paclitaxel</th>
<th>AC + bevacizumab</th>
<th>Fulvestrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>15%</td>
<td>24%</td>
<td>3%</td>
<td>14%</td>
<td>2%</td>
<td>—</td>
<td>12%</td>
<td>2%</td>
<td>25%</td>
<td>—</td>
<td>30%</td>
</tr>
<tr>
<td>57</td>
<td>10%</td>
<td>20%</td>
<td>9%</td>
<td>16%</td>
<td>2%</td>
<td>—</td>
<td>16%</td>
<td>2%</td>
<td>23%</td>
<td>—</td>
<td>32%</td>
</tr>
<tr>
<td>75</td>
<td>2%</td>
<td>2%</td>
<td>9%</td>
<td>12%</td>
<td>4%</td>
<td>—</td>
<td>12%</td>
<td>2%</td>
<td>22%</td>
<td>—</td>
<td>2%</td>
</tr>
</tbody>
</table>

Would you recommend bevacizumab for this patient?

- Yes: 20% 20% 20%
- No: 80% 80% 80%

### CHEMOTHERAPY FOR METASTATIC DISEASE (NO PRIOR CHEMOTHERAPY)

<table>
<thead>
<tr>
<th>Age</th>
<th>Paclitaxel</th>
<th>Docetaxel</th>
<th>Non-taxane paclitaxel</th>
<th>Capecitabine</th>
<th>Gemcitabine</th>
<th>Vinorelbine</th>
<th>Carboplatin + docetaxel</th>
<th>AC</th>
<th>AC + paclitaxel</th>
<th>AC + bevacizumab</th>
<th>Fulvestrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>14%</td>
<td>18%</td>
<td>2%</td>
<td>10%</td>
<td>2%</td>
<td>—</td>
<td>2%</td>
<td>2%</td>
<td>15%</td>
<td>—</td>
<td>30%</td>
</tr>
<tr>
<td>57</td>
<td>12%</td>
<td>22%</td>
<td>2%</td>
<td>10%</td>
<td>3%</td>
<td>—</td>
<td>2%</td>
<td>2%</td>
<td>14%</td>
<td>—</td>
<td>32%</td>
</tr>
<tr>
<td>75</td>
<td>10%</td>
<td>20%</td>
<td>3%</td>
<td>10%</td>
<td>4%</td>
<td>—</td>
<td>2%</td>
<td>2%</td>
<td>18%</td>
<td>—</td>
<td>30%</td>
</tr>
</tbody>
</table>

Would you recommend bevacizumab for this patient?

- No therapy: 15% 15% 15%

### HORMONE THERAPY FOR METASTATIC DISEASE AFTER ADJUVANT TAMOXIFEN

The patient has been on adjuvant tamoxifen for four years for an ER/PR-positive, HER2-negative tumor and now has bone and lung metastases with minimal symptoms. What first-line endocrine treatment are you likely to recommend for this patient?

<table>
<thead>
<tr>
<th>Age</th>
<th>Estradiol</th>
<th>Exemestone</th>
<th>Letrozole</th>
<th>Tamoxifen</th>
<th>Fulvestrant</th>
<th>Fulvestrant + exemestone</th>
<th>Fulvestrant + letrozole</th>
<th>Fulvestrant + tamoxifen</th>
<th>Fulvestrant + bevacizumab</th>
<th>Fulvestrant + I到底</th>
<th>Fulvestrant + abemaciclib</th>
<th>Fulvestrant + ribociclib</th>
<th>Fulvestrant + others</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>15%</td>
<td>25%</td>
<td>2%</td>
<td>2%</td>
<td>20%</td>
<td>33%</td>
<td>46%</td>
<td>56%</td>
<td>41%</td>
<td>25%</td>
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<td>35%</td>
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<td>15%</td>
<td>2%</td>
<td>2%</td>
<td>20%</td>
<td>33%</td>
<td>46%</td>
<td>56%</td>
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<td>2%</td>
<td>20%</td>
<td>33%</td>
<td>46%</td>
<td>56%</td>
<td>41%</td>
<td>25%</td>
<td>55%</td>
<td>35%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Would you recommend bevacizumab for this patient?

- Fulvestrant: 8% 8% 8%

### HORMONE THERAPY FOR METASTATIC DISEASE AFTER ADJUVANT ANASTROZOLE

The patient has been on adjuvant anastrozole for four years for an ER/PR-positive, HER2-negative tumor and now has bone and lung metastases with minimal symptoms. What first-line endocrine treatment are you likely to recommend for this patient?

<table>
<thead>
<tr>
<th>Age</th>
<th>Exemestone</th>
<th>Exemestone + fulvestrant</th>
<th>Fulvestrant</th>
<th>Fulvestrant + letrozole</th>
<th>Fulvestrant + tamoxifen</th>
<th>Fulvestrant + bevacizumab</th>
<th>Fulvestrant + I到底</th>
<th>Fulvestrant + abemaciclib</th>
<th>Fulvestrant + ribociclib</th>
<th>Fulvestrant + others</th>
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Would you recommend bevacizumab for this patient?

- Fulvestrant: 8% 8% 8%

### CLINICAL USE OF FULVESTRANT

Do you generally use a loading dose with fulvestrant?

- Yes: 20% 20% 20%
- No: 80% 80% 80%

What percentage of patients with metastatic breast cancer do you believe would benefit a monthly injection rather than a daily oral administration?

- None: 0% 0% 0%
- Some: 30% 30% 30%
- Almost all: 30% 30% 30%

If they have transportation problems, then I use an oral agent. However, for the Medicare population, these drugs are very expensive. If the patient does not have adequate insurance coverage and can’t afford them, a monthly injection may be better. Compliance is also an issue to be considered when choosing between a daily oral agent and a monthly injection.

- Joanne L. Blum, MD, Patterns of Care 2005 (1)

I use fulvestrant as third-line therapy in patients whose disease has progressed on tamoxifen and an aromatase inhibitor. That’s the current indication, but it wouldn’t surprise me to see it moved up based on data from the randomized trials clearly suggest it is as effective as aromatase inhibitors in patients who progressed after tamoxifen. The clinical question is whether the patient prefers a pill versus a parenteral injection. For some patients, the injection is easier, but most patients prefer taking a pill. In my experience, the tolerability of fulvestrant is similar to that of the aromatase inhibitors.

- Daniel F. Hayes, MD, Breast Cancer Update 2004 (6)