2005 · Vol 2 · Issue 3

Patterns of Care in Medical Oncology

Management of Breast Cancer in the Adjuvant and Metastatic Settings

Adjuvant Systemic Therapy

HER2-Positive Disease

Chemotherapy for Metastatic Disease

Endocrine Therapy for Metastatic Disease

Editor

Neil Love, MD

A Case Survey Comparing Practices of Breast Cancer Investigators and General Oncologists

CME Certified

FROM THE PUBLISHERS OF:

Breast Cancer® UPDATE | Colorectal Cancer™ UPDATE | Lung Cancer™ UPDATE | Non-Hodgkin's Lymphoma™ UPDATE | Prostate Cancer™ UPDATE

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Continuing Medical Education (CME) Information

STATEMENT OF NEED/TARGET AUDIENCE

It is important for practicing oncologists to be aware of similarities and differences between his or her practice patterns, those of others in community practice and those of breast cancer clinical research leaders. It is also important for oncologists to recognize that heterogeneity exists in the oncology community, especially in clinical situations for which there is suboptimal research evidence.

This program focuses on the self-described practice patterns of randomly selected medical oncologists on a variety of key clinical issues in cancer. Also included is research leader commentary and references addressing these issues. This CME program will provide medical oncologists with information on national cancer patterns of care to assist with the development of clinical management strategies.

GLOBAL LEARNING OBJECTIVES FOR THE *PATTERNS OF CARE* SERIES

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

- Compare and contrast management strategies of community oncologists and cancer research leaders for the treatment of cancer.
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care.
- Counsel cancer patients about multiple acceptable treatment options when they exist.

PURPOSE OF THIS ISSUE

The purpose of this issue of *Patterns of Care* is to support these objectives by comparing the perspectives of 100 randomly selected community medical oncologists interviewed in depth in August and September of 2005 with those of 45 breast cancer researchers surveyed, and to offer in-depth commentary from faculty regarding their practice patterns in the management of breast cancer.

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Editor's Note: Cool numbers

Below find some of the more interesting data points that came from this most recent Patterns of Care survey, completed in August and September 2005 by 45 breast cancer clinical investigators and 100 randomly selected US-based medical oncologists.

1. 80%

Fraction of breast cancer specialists who have ordered the Oncotype DX™ assay (Figure 6, page 10).

This percentage contrasts markedly with the fraction of community-based oncologists who have ordered this innovative assay (34%). The clinical scenario targeted in related research reported by the NSABP and Genomic Health is one of the most common in early breast cancer — a patient with an ER-positive, node-negative tumor and, more specifically, a situation in which both the patient and physician are unsure about the value of adding chemotherapy to endocrine treatment.

Our prior Patterns of Care studies have documented that this is perhaps the most common situation in which clinicians utilize online models, such as Peter Ravdin's Adjuvant!. The Onco*type* DX assay appears to provide synergistic information that can be very helpful in assisting in one of the most vexing decisions in current medical oncology.

While one might speculate that the discrepancy in the use of this assay is based on reimbursement concerns (Figure 3, page 7), which perhaps are greater in a community practice setting, it is also quite possible that researchers are more familiar with and confident in the supporting research.

It is particularly plausible that community-based clinicians may not have been exposed to the unpublished NSABP data set reported at the December 2004 San Antonio Breast Cancer Symposium (SABCS) demonstrating a very dramatic benefit from adjuvant chemotherapy in the 25% of patients with high recurrence scores and no benefit in the remaining 75% of patients with low and intermediate recurrence scores.

2. 82%

Fraction of breast cancer clinical investigators who would start a 55-year-old postmenopausal woman with an ER/PR-positive, HER2-negative, node-positive tumor on an aromatase inhibitor (AI) (Figure 7, page 11).

The optimal long-term adjuvant endocrine treatment strategy for postmenopausal women is a topic guaranteed to generate debate, and at one of our group's recent CME meetings, several nationally recognized investigators revealed that they start some women with ER/PR-positive tumors on tamoxifen.

Their rationale is that the ATAC study showed minimal difference in relapse rate between anastrozole and tamoxifen in the unplanned analysis of this ER/PR-positive subset.

Other AI trials have not reported a difference based on PR, but a very common counterargument that invariably comes up is that even if the antitumor benefits of these two therapies are equivalent, AIs show a significant toxicity advantage over tamoxifen in terms of thrombotic events and endometrial cancer.

A number of the "tamoxifen first" renegade contingency believe that many breast cancer specialists buy into their theoretical argument that even though there are more recurrences during an initial course of tamoxifen, there might be fewer recurrences in the long run.

Our survey demonstrates that very few investigators embrace this approach in their clinical practices, although when the case is switched to a woman with a node-negative tumor, more researchers (Figure 21, page 18) start with tamoxifen.

3. 5%

Fraction of investigators who would continue tamoxifen in a 65-year-old postmenopausal woman with an ER/PR-positive tumor with three positive nodes who has been on tamoxifen for two years (Figure 10, page 12).

Our previous survey, conducted earlier this year, demonstrated this same result, but at that time we noted an important gap between investigators and community docs, with 56 percent of community oncologists continuing tamoxifen. In our current survey this fraction has decreased to 24 percent.

Three randomized trials have clearly demonstrated that patients who switch to either exemestane (IES study) or anastrozole (Austrian-German and ITA studies) have about a 40 percent lower risk of relapse and experience fewer serious adverse effects than those who continue tamoxifen.

Clearly, there is a rapidly building consensus that five years of adjuvant tamoxifen is an inferior therapy for postmenopausal women compared to a treatment plan that includes or consists of an AI.

Four years after the first ATAC presentation, with a number of other AI trials also reporting advantages for AIs over tamoxifen, it is clear that an important change in practice has occurred, and the minority of oncologists who still use five years of tamoxifen in postmenopausal women should re-evaluate their positions in fairness to their patients.

If I were a postmenopausal woman with a breast cancer who relapsed after having received tamoxifen for initial upfront therapy without having had the option of switching discussed, I would be very unhappy. Yes, AIs cost more, but if an inferior therapy is being recom-

mended to save money, the patient needs to know that is happening and literally "buy in" to the plan.

4. 5%

Fraction of patients treated by community-based oncologists with AIs who have arthralgias significant enough to consider discontinuation or switching to another therapy (Figure 9, page 12).

A key issue in management of these musculoskeletal symptoms is diagnosis. A recent report from the ATAC trialists noted that about one third of patients on tamoxifen had arthralgias, and while that number is higher with a significant *p*-value for anastrozole, the ***absolute*** increase is only about 5 percent.

These data remind us that arthralgias in a patient on either tamoxifen or an AI may be caused by something other than the endocrine therapy. The ATAC trialists urge that oncologists attempt to make a precise diagnosis in this situation and carefully rule out other important causes of this nonspecific syndrome.

The trialists also urge that physicians utilize an integrated management plan (Figure 1) in an attempt to relieve musculoskeletal complaints before therapy is switched to another agent (tamoxifen) that also has the potential for side effects and toxicities and a greater risk for cancer relapse. Note that intolerable vasomotor symptoms are commonly reported with tamoxifen (25% of patients; see Figure 9, page 12).

5. 53%

Fraction of breast cancer specialists who generally utilize dose-dense AC → T in 35-year-old patients with ER-positive, node-positive tumors (Figure 23, page 19).

Our prior surveys also demonstrate that the dose-dense regimen is the one most commonly used in node-positive tumors. However, over the past year, data have begun to emerge from a variety of sources suggesting less benefit from chemotherapy in general, and perhaps dose-dense therapy in particular, in patients with ER-positive tumors. Our survey suggests that to this point, docs have not changed their practices in that regard.

One change that is emerging in the selection of chemotherapy is a switch in the Number 2 spot from AC → docetaxel to TAC. While many clinical investigators have proclaimed for several years that TAC and dose-dense AC → T are the two adjuvant regimens with the best supporting evidence bases, docs in practice were commonly using AC → docetaxel rather than TAC.

One might guess that the shift this year away from AC → docetaxel to TAC is attributable to the disappointing results with that regimen in NSABP-B-27, reported in December 2004 at San Antonio.

6. 100%

Fraction of clinical researchers who would recommend trastuzumab as adjuvant therapy in younger women with node-positive tumors (Figure 38, page 28).

Adjuvant trastuzumab has now clearly arrived on the scene. Our CME group has been following emerging clinical cancer research for more than 20 years and has never witnessed such a rapid and complete uptake of a new treatment strategy.

To put this in perspective: With other recent advances in the adjuvant setting — such as the aromatase inhibitors after the ATAC presentation in December 2001 and the first report a year later of the effects of dose-dense chemotherapy in CALGB-9741 — only about a third to a half of oncologists changed their practices in the year following the initial key reports for both of these treatment strategies, and it took about two years in total to hit a "steady state" of utilization.

The immediate acceptance and implementation of adjuvant trastuzumab reflects several factors, including the following:

1. Virtually all breast cancer researchers expected the adjuvant trastuzumab trials to show benefit.

FIGURE 1

Treatment Management Strategies for Arthralgia

Nonpharmacologic Strategies

- *Patient education*
- *Self-management programs*
- *Personalized social support through telephone*
- *Weight loss*
- *Aerobic exercise*
- *Physical/occupational therapy*
- *Heat*
- *Muscle strengthening exercises*
- *Assistive devices for ambulation*
- *Patellar taping*
- *Appropriate footwear*
- *Lateral wedged insoles*
- *Joint protection*

Pharmacologic Strategies

- *Oral treatment*
  - *Acetaminophen (not to exceed 4 g/day)*
  - *NSAID*
  - *COX-2 inhibitor*
  - *Safeguard for peptic ulcer disease*
  - *Tramadol*
  - *Opioids*
  - *Glucosamine*
  - *Chondroitin sulfate*
- *Topical treatments*
  - *Capsaicin*
  - *Methylsalicylate*

SOURCE: **P Plourde et al. Lynn Sage Breast Cancer Symposium 2005.**

FIGURE 2

Education about Adjuvant Trastuzumab

To this point, where have you heard about or obtained information about the adjuvant trastuzumab trials presented at ASCO?

Attended ASCO	36%
Attended ASCO review meeting	58%
Attended other CME program	8%
Print publications	50%
Breast Cancer Update audio series	44%
Lay press/news media	18%
Colleague	20%

2. The magnitude of benefit was impressive.

3. Extremely rapid and efficient methods of disseminating clinical research data and perspectives now exist in the medical oncologist community. (See the next cool number.)

7. 44 %

Fraction of community docs who cited the* Breast Cancer Update *audio series as a source of information about data from the adjuvant trastuzumab trials presented at ASCO on May 16, 2005 (Figure 2, above).

In August, when this Patterns of Care survey was executed, our CME group had distributed one *Breast Cancer Update* audio program discussing the adjuvant trastuzumab data presented at ASCO 2005. It is interesting to note that at the time of the survey, this piece — which included interviews with George Sledge and Edward Romond — had already been heard by almost half of the oncologists in this country, and perhaps another 20 to 30 percent are likely to hear this program and others covering trastuzumab in the next few months.

Like all contemporary physicians, medical oncologists learn about emerging clinical research findings in a variety of ways. In addition to live events such as scientific meetings like ASCO and a mélange of tumor boards, grand rounds and CME meetings, docs also keep up to date by the individual use of information delivery vehicles.

I started my medical education career as a video producer, and while this medium was fun and interesting, it requires the user to focus solely on the program, which is a problem because docs are busy as hell and have scarce time to allocate for continuing education.

Our initial attraction to audio for oncology CME in the late 1980s was based on the hypothesis that the ability to multitask (mainly drive a car or exercise) while listening would present an important advantage. Today, we know from more than a dozen external studies of our work over the last five years that about three quarters of oncologists in the United States are regular listeners to our programs and that most of this use occurs in the car.

It's both awesome and scary to think that our CME group has the opportunity to pass on critical clinical research information such as the adjuvant trastuzumab data, and we take this responsibility very seriously.

8. 98%

Fraction of clinical investigators who start adjuvant trastuzumab concurrently with the taxane portion of chemotherapy (Figure 38, page 28).

This finding has a potentially interesting international twist, and one wonders if investigators in Europe — where the HERA trial was executed — have the same practice pattern as we do in the United States.

Note that HERA demonstrated that the post-chemotherapy use of trastuzumab resulted in an impressive reduction in risk of recurrence of about 50 percent, as in the NSABP-NCCTG combined analysis of concurrent trastuzumab (with taxanes).

On the other hand, the NCCTG data presented at ASCO revealed a non-statistically significant 13 percent reduction in relapse rate following sequential therapy à la HERA, while the concurrent arm of that trial (with paclitaxel) demonstrated a statistically significant reduction in relapse rate of 36 percent.

Many oncologists in practice find these results contradictory, and a third of these docs currently favor a HERA-like strategy. The sequential approach may also lessen the risk of cardiac toxicity, but that is speculation at this point. Perhaps the clinical investigators in our survey are more uniform in their preference for concurrent therapy because they feel more confident in their own data.

9. About a third

Fraction of clinical investigators and community oncologists who would offer a year of trastuzumab to a 55-year-old woman treated two years previously for HER2-positive disease with 10 positive axillary nodes (Figure 39, page 30).

Most oncologists are considering delayed trastuzumab, probably because the clinical research groups who performed the adjuvant trastuzumab studies offered that therapy to participating patients who were randomly assigned to chemotherapy alone and were less than a year out from the completion of therapy.

I am very concerned about these "missed the window of opportunity" patients, who remind me of the tens of thousands of postmenopausal women

FIGURE 3

Reimbursement Issues in Breast Cancer

How often do you encounter situations in which you would like to use each of the following agents or assays but are unable to or restricted because of reimbursement issues?

	Bevacizumab (breast cancer only)	Trastuzumab (metastatic setting)	Trastuzumab (adjuvant setting)	Nanoparticle paclitaxel	Fulvestrant	Oncotype DX assay
Very frequently	28%	—	2%	9%	2%	17%
Frequently	10%	—	13%	7%	2%	13%
Infrequently	12%	22%	22%	25%	28%	13%
Very infrequently	8%	76%	41%	43%	66%	10%
Not applicable (have not used)	42%	2%	22%	16%	2%	47%

who relapsed or had thrombotic events while on tamoxifen in the year or two after the ATAC trial was first presented.

When patients and their loved ones face the tragedy of distant recurrence, it is important for them to believe that they did all they could to prevent it, and patients who don't at least hear about new treatment options like aromatase inhibitors and trastuzumab — initially and at delayed time points — are not receiving state-of-the-art advice.

10. 38%

Fraction of community-based oncologists who would recommend bevacizumab to a 40-year-old taxane-naïve patient as part of first-line therapy in the metastatic setting (Figure 45, page 34).

The fraction of ***clinical investigators*** who would use bevacizumab and, specifically, paclitaxel-bevacizumab is almost double this fraction. At CME meetings and other venues, many community-based oncologists have noted that they are frankly confused about what to do concerning the data presented at ASCO by Kathy Miller on ECOG-E2100, demonstrating a progression-free and overall survival benefit when bevacizumab was added to paclitaxel.

This is particularly interesting in view of the common utilization of "bev" by community-based oncologists for metastatic colon cancer. Part of the issue with breast cancer is concern about reimbursement for this non-FDA-approved, pricey therapy (Figure 3, above), but perhaps equally important is the skepticism often found in community docs when only one trial demonstrates benefit, particularly in a noncurative situation.

There also is a general belief among oncologists that so many options exist for metastatic breast cancer that the use of bev seems less compelling than, for example, in non-small cell lung cancer, where FDA approval of bev/carbo/paclitaxel is likely to be followed by a stampede of use similar to what we saw in colon cancer.

11. 53%

Fraction of investigators who recommend capecitabine as first-line therapy for metastatic disease in a 40-year-old patient who is minimally symptomatic and had received prior adjuvant therapy with an anthracycline and a taxane (Figure 47, page 36).

As in our prior surveys, capecitabine is far more commonly utilized by investigators than community docs. What is particularly interesting is that half of the researchers who would utilize capecitabine would add bevacizumab in this situation.

A study in the late-line metastatic setting of this combination — also by Kathy Miller — did not meet its primary endpoint of progression-free survival, although there was an increased response rate in patients treated with bev. Some investigators consider this a positive trial, and others do not. The capecitabine/bevacizumab regimen was well tolerated, and cited by Eric Winer in his ASCO discussion of Kathy's paper as one of several considerations for patients who are not good candidates for taxanes.

12. Greater than 90%

Fraction of oncologists who consider the short infusion time and lack of need for premedication clinically significant benefits for the use of nanoparticle paclitaxel (Figure 53, page 39).

Clinicians are clearly putting their feet in the water gingerly with this new and somewhat costly therapy, but one might expect that as reimbursement issues are resolved and additional research is generated, many more patients will be treated with this interesting agent.

Note that docs are currently split in terms of weekly versus three-weekly use of *nab* paclitaxel (Figure 52, page 39), with the weekly contingent likely

basing their preference on Phase II US Oncology data from Joanne Blum.

13. About 90%

Fraction of clinical investigators (and community docs) who believe that the efficacy of nab paclitaxel is equal to or greater than both paclitaxel and docetaxel (Figure 54, page 40).

Complementing this somewhat uniform perspective about antitumor efficacy is the perception that *nab* paclitaxel is also better tolerated than the other two available taxanes. If these oncologists are correct, it seems possible that *nab* paclitaxel will emerge over the next couple of years as perhaps the dominant taxane utilized in breast and perhaps other cancers.

14. Greater than 50%

Fraction of investigators and community docs who would use fulvestrant in a postmenopausal patient who relapses on adjuvant anastrozole (Figure 61, page 46).

This choice is interesting, particularly because there are no data comparing tamoxifen to fulvestrant in this situation, although there are data showing essentially equivalent results of these two agents in hormone-naïve patients. Other research has demonstrated at least equivalence between fulvestrant and anastrozole in patients who progress on tamoxifen.

Note also that about half of the investigators use a loading dose of fulvestrant, while this approach is much less commonly utilized in the community setting (Figure 64, page 48).

This is our fifth issue of *Patterns of Care* devoted exclusively to the management of breast cancer. With each new survey, I eagerly anticipate the opportunity to look at the data because in my mind these findings truly provide a glimpse into what clinical investigators and oncologists in practice consider state-of-the-art patient care.

I can't wait to see what cool numbers emerge in 2006.

— Neil Love, MD
NLove@ResearchToPractice.net

The data in this monograph reflect a series of telephone/fax/email surveys conducted in August/September 2005 of 100 randomly selected US-based medical oncologists who spend more than 50 percent of their time in patient care. Sample sizes of 50 are presented. In addition the survey was completed by 45 clinical investigators who spend more than 80 percent of clinical time caring for breast cancer patients. Survey results were reviewed by Clifford Hudis, MD and Debu Tripathy, MD.

SELECT PUBLICATIONS

Arpino G et al. **Estrogen receptor positive (ER+), progesterone receptor negative (PgR) breast cancer: New insights into molecular mechanisms and clinical implications.** *Breast Cancer Res Treat* 2004;**Abstract 105**.

Bajetta E et al. **Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women.** *J Clin Oncol* 2005;23(10):2155-61. **Abstract**

Baum M, Ravdin PM. **Decision-making in early breast cancer: Guidelines and decision tools.** *Eur J Cancer* 2002;38(6):745-9. **Abstract**

Berry DA et al. **Effects of improvements in chemotherapy on disease-free and overall survival of estrogen-receptor negative, node-positive breast cancer: 20-year experience of the CALGB and US Breast Intergroup.** *Breast Cancer Res Treat* 2004;**Abstract 29**.

Bertelli G et al. **Intergroup exemestane study: Results of the endometrial subprotocol.** *Breast Cancer Res Treat* 2004;**Abstract 402**.

Boccardo F et al. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole Trial.** *J Clin Oncol* 2005;23(22):5138-47. **Abstract**

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

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

Coleman RE et al. **Intergroup exemestane study: 1 year results of the bone subprotocol.** *Breast Cancer Res Treat* 2004;**Abstract 401**.

Coombes RC et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. **Abstract**

Cuzick J, Howell A. **Optimal timing of the use of an aromatase inhibitor in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer.** Presentation. ASCO 2005;**Abstract 658**.

Distler W et al. **Impact of age on the gynecologic adverse event (AE) profile of anastrozole (A) or tamoxifen (T) in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2004;**Abstract 770**.

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;83(Suppl 1):7;**Abstract 4**.

Duffy S, on behalf of the ATAC Trialist's Group. **Gynecological adverse events including hysterectomy occur less frequently with anastrozole than with tamoxifen: Data from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2005;**Abstract 723**.

Duric V et al. **Predictors of the benefits women consider necessary to make adjuvant chemotherapy (ACT) worthwhile for early breast cancer (EBC).** *Proc ASCO* 2004;**Abstract 787**.

Fallowfield LJ et al. **Intergroup exemestane study: Results of the quality of life sub-protocol.** *Breast Cancer Res Treat* 2004;**Abstract 4**.

Felson DT, Cummings SR. **Aromatase inhibitors and the syndrome of arthralgias with estrogen deprivation.** *Arthritis & Rheumatism* 2005;52(9):2594-8. **Abstract**

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

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

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-7803. **Abstract**

Henderson IC et al. **Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.** *J Clin Oncol* 2003;21(6):976-83. **Abstract**

Hortobagyi GN. **Trastuzumab in the treatment of breast cancer.** *N Engl J Med* 2005;353(16):1734-6. No abstract available

Houghton J et al. **Using anastrozole as initial adjuvant treatment prevents early recurrences and reduces adverse events: Updated data from**

the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial. *Proc ASCO* 2005;Abstract 582.

Howell A et al. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. Abstract

Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *J Clin Oncol* 2004;22(9):1605-13. Abstract

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20(16):3396-403. Abstract

Jakesz R et al. **Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a).** *Proc ASCO* 2005;Abstract 527.

Jakesz R et al. **Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial.** *Lancet* 2005;366(9484):455-62. Abstract

Jakesz R et al. **Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: Combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial.** *Breast Cancer Res Treat* 2004;Abstract 2.

Jones SE et al. **Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer.** *J Clin Oncol* 2005;23(24):5542-51. Abstract

Jones SE et al. **A retrospective analysis of the proportion of patients responding for 1, 1.5 and 2 years in two phase III studies of fulvestrant vs anastrozole.** *Breast Cancer Res Treat* 2004;Abstract 6047.

Locker GY et al. **The time course of bone fractures observed in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2003;Abstract 98.

Lonning PE et al. **Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer.** *J Clin Oncol* 2005;23(22):5126-37. Abstract

Loprinzi CL, Ravdin PM. **Decision-making for patients with resectable breast cancer: Individualized decisions for and by patients and their physicians.** *JNCCN* 2003;1(2):189-96.

Mamounas EP et al. **Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28.** *J Clin Oncol* 2005;23(16):3686-96. Abstract

Martin M et al; Breast Cancer International Research Group 001 Investigators. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13. Abstract

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. *Proc ASCO* 2005. No abstract available

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005;23(4):792-9. Abstract

Morales L et al. **Acute effects of tamoxifen and third-generation aromatase inhibitors on menopausal symptoms of breast cancer patients.** *Anticancer Drugs* 2004;15(8):753-60. Abstract

Muss HB et al. **Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer.** *JAMA* 2005(9):1073-81. Abstract

Nowak AK et al. **Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer.** *Lancet Oncol* 2004;5(6):372-80. Abstract

Olivotto IA et al. **Population-based validation of the prognostic model ADJUVANT! for early breast cancer.** *J Clin Oncol* 2005;23(12):2716-25. Abstract

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20(16):3386-95. Abstract

O'Shaughnessy JA et al. **Weekly nanoparticle albumin paclitaxel (Abraxane) results in longterm disease control in patients with taxane-refractory metastatic breast cancer.** San Antonio Breast Cancer Symposium 2004;Abstract 1070.

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

Paik S et al. **A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer.** *N Engl J Med* 2004;351(27):2817-26. Abstract

Paik S et al. **Expression of the 21 genes in the Recurrence Score assay and prediction of clinical benefit from tamoxifen in NSABP study B-14 and chemotherapy in NSABP study B-20.** *Breast Cancer Res Treat* 2004;Abstract 24.

Paik S et al. **Risk classification of breast cancer patients by the Recurrence Score assay: Comparison to guidelines based on patient age, tumor size, and tumor grade.** *Breast Cancer Res Treat* 2004;Abstract 104.

Peele PB et al. **Decreased use of adjuvant breast cancer therapy in a randomized controlled trial of a decision aid with individualized risk information.** *Med Decis Making* 2005;25(3):301-7. Abstract

Perez EA et al. **Interim cardiac safety analysis of NCCTG N9831 Intergroup adjuvant trastuzumab trial.** *Proc ASCO* 2005;Abstract 556.

Perez EA et al. **NCCTG N9831: May 2005 update.** Presentation. ASCO 2005;Abstract 556.

Perez EA. **Effect of letrozole versus placebo on bone mineral density in women completing > 5 years (yrs) of adjuvant tamoxifen: NCIC CT MA17b.** *Breast Cancer Res Treat* 2004;Abstract 404.

Piccart-Gebhart MJ. **First results of the HERA trial.** Presentation. ASCO 2005. No abstract available

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. Abstract

Plourde P et al. **Arthralgia in postmenopausal breast cancer patients on adjuvant endocrine therapy: A risk-benefit analysis.** Poster. Lynn Sage Breast Cancer Symposium 2005.

Punglia RS et al. **Optimizing adjuvant endocrine therapy in postmenopausal women with early-stage breast cancer: A decision analysis.** *J Clin Oncol* 2005;23(22):5178-87. Abstract

Ravdin PM et al. **Computer program to assist in making decisions about adjuvant therapy for women with early breast cancer.** *J Clin Oncol* 2001;19(4):980-91. Abstract

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38. Abstract

Romond EH et al. **Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 positive operable breast cancer combined analysis of NSABP-B31/NCCTG-N9831.** Presentation. *ASCO* 2005. No abstract available

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. Abstract

Tan-Chiu E et al. **Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.** *J Clin Oncol* 2005;23(31):7811-9. Abstract

Thürlimann B et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;Abstract 511.

Wasan KM et al. **The influence of letrozole on serum lipid concentrations in postmenopausal women with primary breast cancer who have completed 5 years of adjuvant tamoxifen (NCIC CTG MA.17L).** *Ann Oncol* 2005;16(5):707-15. Abstract

Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004.** *J Clin Oncol* 2005;23(3):619-29. Abstract

Adjuvant Systemic Therapy

FIGURE 4

Use of Computer Models in Clinical Practice

How often do you use computer models/programs in your practice to evaluate individual patients in the adjuvant setting?

Always	27%	40%
Sometimes	53%	47%
Rarely	18%	13%
Never	2%	—

FIGURE 5

Use of Computer Models in Clinical Practice

Which of the following models do you use to estimate your breast cancer patients' risk of relapse and/or mortality?

Peter Ravdin's Adjuvant! model	78%	44%
Charles Loprinzi's Mayo Clinic model	—	2%
Both	22%	18%
Neither	—	36%

FIGURE 6

Clinical Use of Onco*type* DX Assay

Have you ordered the Oncotype DX assay?

Yes	80%	34%
No	20%	66%
If yes, in how many patients?		
Mean	8	5
If yes, how helpful was it in your treatment decisions?		
Very helpful	26%	18%
Somewhat helpful	61%	64%
Not helpful	13%	18%

Onco*type* DX assay

Breast Cancer Update for Surgeons 2005 (1)

DR NORMAN WOLMARK: We wanted to determine whether the Onco*type* DX assay could predict the benefit of chemotherapy, so we examined the data from NSABP-B-20, which randomly assigned patients with receptor-positive, node-negative disease to tamoxifen versus tamoxifen plus CMF chemotherapy versus tamoxifen plus MF chemotherapy. We found that patients who were at high risk based on their recurrence scores derived benefit from chemotherapy, but patients at low risk, who comprised 50 percent of the cohort, did not appear to derive substantial benefit from the addition of chemotherapy to tamoxifen. The intermediate group comprised only 20 to 25 percent of the cohort, and we didn't have the power to determine if they benefit from the addition of chemotherapy.

We were surprised to find that the relative risk reduction was not uniform — different risk groups did not have the same relative risk reduction. The greatest relative risk reduction was seen in patients at highest risk.

Computerized models and the Onco*type* DX assay

Breast Cancer Update for Surgeons 2005 (3)

DR ELEFTHERIOS P MAMOUNAS: John Bryant presented data at the last St Gallen meeting evaluating the recurrence score and Adjuvant! Online, and they seem to perform independently to a certain extent. Adjuvant! Online will add to the recurrence score, and the recurrence will add to Adjuvant! Online. Peter Ravdin is working with us to modify Adjuvant! Online to introduce the recurrence score; they provide complementary information, which is important for the patient. However, Adjuvant! Online doesn't provide any prediction on benefit from therapy, whereas the recurrence score adds prognostic and predictive value.

FIGURE 7

Adjuvant Hormonal Therapy for ER/PR-Positive, Node-Positive Disease

- *Woman in average health*
- *1.2-centimeter, Grade II tumor*
- *ER/PR-positive, HER2-negative*
- *3 positive nodes*

Which endocrine therapy, if any, would you most likely recommend for this patient?

	Age 35		Age 55		Age 75		Age 85	
Anastrozole	2%	6%	78%	80%	80%	80%	81%	84%
Letrozole	—	—	4%	—	2%	—	4%	—
Tamoxifen for 5 years and no further hormonal treatment	47%	54%	—	4%	—	2%	—	4%
Tamoxifen for 2-3 years and then switch to aromatase inhibitor	—	4%	16%	8%	16%	8%	13%	8%
Tamoxifen for 5 years and then switch to aromatase inhibitor	9%	10%	2%	8%	2%	10%	2%	4%
Aromatase inhibitor + LHRH agonist or ovarian ablation	22%	6%						
Tamoxifen + LHRH agonist or ovarian ablation	20%	20%						

FIGURE 8

Use of Adjuvant Aromatase Inhibitors

Which aromatase inhibitor(s) do you use in each of the following settings?

	Initial adjuvant		After 2-3 years of adjuvant tamoxifen		After 5 years of adjuvant tamoxifen	
Anastrozole only	62%	58%	2%	20%	—	12%
Letrozole only	—	2%	2%	6%	80%	60%
Exemestane only	—	—	33%	23%	—	4%
Anastrozole, letrozole and exemestane	16%	20%	26%	23%	14%	16%
Anastrozole and letrozole only	22%	18%	—	10%	4%	6%
Anastrozole and exemestane only	—	2%	28%	16%	—	—
Exemestane and letrozole only	—	—	9%	2%	2%	2%

The role of adjuvant aromatase inhibitors in postmenopausal women

Breast Cancer Update 2005 (2)

DR I CRAIG HENDERSON: Based on data from various adjuvant endocrine therapy trials, I believe it is unreasonable to withhold aromatase inhibitors from postmenopausal women with hormone receptor-positive disease. ATAC is still the definitive adjuvant trial in terms of comparing tamoxifen to an aromatase inhibitor, and the data are very compelling. An aromatase inhibitor is now my drug of choice, and that changed in just the past few years.

As for switching patients from tamoxifen to an aromatase inhibitor, I discuss this with every postmenopausal patient on tamoxifen. We don't know

FIGURE 9

Use of Adjuvant Aromatase Inhibitors

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

	Initial adjuvant		Adjuvant after 2-3 years of tamoxifen		After 5 years of adjuvant tamoxifen	
Anastrozole	86%	86%	17%	37%	5%	19%
Letrozole	11%	11%	12%	18%	90%	73%
Exemestane	3%	3%	71%	45%	5%	8%

Tolerability of Adjuvant Endocrine Therapy

What percentage of your patients on adjuvant aromatase inhibitors have significant arthralgias? *(mean)*	28%	16%
What percentage of your patients on adjuvant aromatase inhibitors have significant arthralgias to the point that you consider discontinuation or switching agents? *(mean)*	10%	5%
What percentage of the patients you start on tamoxifen have significant vasomotor symptoms, to the point that you consider interventions such as SSRI antidepressants? *(mean)*	25%	18%

FIGURE 10

Sequencing Aromatase Inhibitors after Two Years of Tamoxifen

- *65-year-old woman in average health **on tamoxifen x 2 years**, tolerating tamoxifen as described below*
- *1.2-cm, Grade II tumor*
- *ER-positive/PR-positive, HER2-negative*
- *3 positive nodes*

How would you manage this patient's therapy?

	Without severe side effects		Complains of 20-pound weight gain		Complains of moderate hot flashes refractory to nonhormonal therapy	
Continue tamoxifen	5%	24%	2%	4%	5%	8%
Stop tamoxifen and switch to anastrozole	14%	26%	19%	40%	21%	44%
Stop tamoxifen and switch to letrozole	9%	12%	9%	14%	7%	12%
Stop tamoxifen and switch to exemestane	72%	38%	70%	40%	67%	36%
Stop tamoxifen and use no further hormonal therapy	—	—	—	2%	—	—

the optimal time to switch, and we don't know the optimal duration of various endocrine therapies. While we know that five years of tamoxifen is as good as or better than 10 years, the optimal duration of aromatase inhibitors is unknown at this time.

Breast Cancer Update 2005 (7)

DR ROWAN T CHLEBOWSKI: If you start with tamoxifen, after two and a half, three or five years, more patients will have relapsed than on an aromatase inhibitor. A substantial number of those patients will be irretrievable — they have incurable disease — and so you're banking on the fact that you'll be able to capture more patients later, but we don't have any data for that. That's just speculation.

While I believe that sequencing therapy may be better, ultimately, I still don't

FIGURE 11

Endocrine Therapy after Five Years of Tamoxifen

- *65-year-old woman in average health who has **completed 5 years of tamoxifen***
- *1.2-cm, Grade II tumor*
- *ER-positive/PR-positive, HER2-negative*
- *3 positive nodes*

How would you manage this patient's therapy at the following three time points?

	Has just completed 5 years of tamoxifen		Completed 5 years of tamoxifen 1 year ago		Completed 5 years of tamoxifen 3 years ago	
Continue tamoxifen	—	2%	—	—	—	—
Start anastrozole	2%	16%	2%	12%	—	6%
Start letrozole	98%	78%	88%	62%	20%	18%
Start exemestane	—	2%	—	2%	—	2%
Use no further hormonal therapy	—	2%	10%	24%	80%	74%

FIGURE 12

Sequencing Aromatase Inhibitors after Anastrozole

- *65-year-old woman in average health **on adjuvant anastrozole x 2 years***
- *1.2-cm, Grade II tumor*
- *ER-positive/PR-positive, HER2-negative*
- *Lymph node status as indicated below*
- ***Severe arthralgias since starting anastrozole***

How you would manage this patient's therapy?

	Negative nodes		3 positive nodes	
Continue anastrozole	—	6%	2%	6%
Stop anastrozole and use no further hormonal therapy	—	4%	—	2%
Stop anastrozole and switch to tamoxifen	31%	34%	26%	38%
Stop anastrozole and switch to letrozole	21%	30%	16%	26%
Stop anastrozole and switch to exemestane	48%	26%	56%	28%

see any reason not to start with the most effective therapy. An aromatase inhibitor followed by tamoxifen or a nonsteroidal aromatase inhibitor alone makes more sense to me. We have to wait to see the data from the BIG FEMTA trial, which includes an arm with letrozole as initial treatment followed by tamoxifen.

Breast Cancer Update 2005 (5)

DR DEBU TRIPATHY: I believe a clear, consistent story is emerging without a lot of conflicts and conundrums: Adjuvant aromatase inhibitors are better than tamoxifen. Whether the aromatase inhibitors are used at the time of initial diagnosis, after two to three years or five years of tamoxifen, there is a favorable impact on local, distant and even contralateral breast cancer recurrences.

The unresolved questions are: Should you use a little tamoxifen, maybe two years and then cross over? Should you only use an aromatase inhibitor right off the bat and maybe even think of continuing beyond five years? The trial that will provide the most information in this regard is the BIG FEMTA/BIG 1-98 trial.

Breast Cancer Update 2005 (4)

DR WILLIAM J GRADISHAR: I sit on the NCCN guidelines breast cancer

FIGURE 13

Endocrine Therapy after Five Years of Anastrozole

- *65-year-old woman in average health who has completed 5 years of adjuvant anastrozole*
- *1.2-cm, Grade II tumor*
- *ER-positive/PR-positive, HER2-negative*
- *Lymph node status as indicated below*

How would you manage this patient's therapy?

	Negative nodes		3 positive nodes	
Continue anastrozole	5%	2%	14%	6%
Stop anastrozole and use no further hormonal therapy	91%	82%	84%	80%
Stop anastrozole and switch to tamoxifen	2%	2%	2%	4%
Stop anastrozole and switch to letrozole	—	10%	—	6%
Stop anastrozole and switch to exemestane	2%	4%	—	4%

FIGURE 14

Bone Mineral Density and Adjuvant Endocrine Therapy

The patient is a 65-year-old woman whom you want to start on an aromatase inhibitor for adjuvant treatment of a 1.2-cm tumor and 1 positive node. Bone mineral density indicated below.

What would you recommend for this patient with each of the following T scores?

	T score -0.5 (within normal range)		T score -1.5 (osteopenic)		T score -2.5 (osteoporotic)	
Start aromatase inhibitor alone	90%	78%	30%	14%	—	2%
Start aromatase inhibitor and bisphosphonate	5%	18%	59%	78%	67%	58%
Start tamoxifen	5%	4%	11%	8%	9%	8%
Start tamoxifen and bisphosphonate	—	—	—	—	24%	32%

FIGURE 15

Bone Mineral Density and Adjuvant Endocrine Therapy

Same case (65-year-old woman whom you want to start on an aromatase inhibitor for adjuvant treatment of a 1.2-cm tumor and 1 positive node). However, the patient had a ***recent pulmonary embolism****.*

What would you recommend for this patient with each of the following T scores?

	T score -0.5 (within normal range)	T score -1.5 (osteopenic)	T score -2.5 (osteoporotic)
Start aromatase inhibitor alone	50%	25%	—
Start aromatase inhibitor and bisphosphonate	50%	75%	100%

BREAST CANCER SPECIALISTS GENERAL ONCOLOGISTS

FIGURE 16

Bone Mineral Density and Adjuvant Aromatase Inhibitors

The patient is a 65-year-old woman whom you want to start on an aromatase inhibitor for adjuvant treatment of a 1.2-cm tumor and 1 positive node.

Which of the following best describes your use of bone mineral density testing?		
Baseline only	—	18%
Baseline and follow-up at one point	11%	14%
Baseline and regular follow-up	85%	68%
Other	2%	—
None	2%	—

committee, and if you evaluate the next rendition of the guidelines, you'll find we have not dismissed the use of tamoxifen but rather moved the use of aromatase inhibitors up front. Within the NCCN guidelines, we're trying to select the aromatase inhibitor to be used based on the design of the study. For first-line therapy, we would use anastrozole. If a patient has been on tamoxifen for a period of time, exemestane is now a legitimate choice, and after five years of tamoxifen, letrozole is an option. We view all of these agents as active and well tolerated.

Effects of aromatase inhibitors on bone

Breast Cancer Update 2005 (7)

DR CHLEBOWSKI: The five-year toxicity data are very favorable for anastrozole compared to tamoxifen because the three life-threatening toxicities — endometrial cancer, arterial and venous vascular events — were all significantly less with anastrozole. Many oncologists have a lot of 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 hip fractures after 68 months 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, any treating, you're going to have lower numbers than that.

Breast Cancer Update 2005 (1)

DR MICHAEL BAUM: The fracture rate incidence is becoming a little more reassuring. An excess fracture rate occurs in the first two or three years, but then the lines are beginning 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. We 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 osteopenic.

Aromatase inhibitors and arthralgias

Lynn Sage Breast Cancer Symposium 2005

In the Arimidex or Tamoxifen Alone or in Combination (ATAC) trial, arthralgia was reported by 35.6% vs 29.4% of patients on anastrozole and tamoxifen, respectively, at the 68-month follow-up. While the incidence was significantly higher in the anastrozole arm ($p < 0.0001$), it is noteworthy that the incidence of arthralgia with tamoxifen was also high (29.4%), with an absolute difference of 6.2%. Most arthralgia incidences occurred early in both treatment arms (75% in the first 33 months) and were primarily mild to moderate in intensity.

— Paul Plourde et al. Poster. Lynn Sage Breast Cancer Symposium 2005.

Breast Cancer Update 2005 (4)

DR ANTHONY HOWELL: Matt Ellis' group presented an interesting abstract at San Antonio indicating that women with these joint symptoms may have lowered vitamin D levels and that giving them vitamin D improved some of the joint symptoms. The data are very early, and they are conducting more studies, but if we could solve this joint problem with vitamin D it would be extraordinary. We know from the ATAC trial that more serious adverse events are associated with tamoxifen than with anastrozole and that despite the joint symptoms, patients tend to stay on anastrozole more than they stay on tamoxifen, which is an important efficacy issue.

Adjuvant endocrine therapy in premenopausal women

Patterns of Care 2004 (2)

DR JOYCE O'SHAUGHNESSY: I have combined an LHRH agonist with an aromatase inhibitor in premenopausal women, but it's rare because for women who are at high enough risk for that therapy — multiple positive nodes or even node-positive, HER2-positive breast cancer — I generally recommend

FIGURE 17

Use of Aromatase Inhibitors in Premenopausal Women

Which of the following best describes your use of aromatase inhibitors in the following premenopausal women?

	Have not used		Have used alone		Have used with ovarian suppression/ablation		Have used both alone and with ovarian suppression/ablation	
With contraindication to tamoxifen (clotting, etc) in the adjuvant setting	16%	18%	—	12%	84%	70%	—	—
Who cannot tolerate tamoxifen due to side effects in the adjuvant setting	43%	12%	—	18%	57%	70%	—	—
With multiple positive axillary nodes	40%	18%	—	12%	60%	70%	—	—
With locally advanced disease after local therapy	37%	24%	—	6%	63%	64%	—	6%
Other	56%	94%	—	—	44%	—	—	6%

FIGURE 18

Use of Aromatase Inhibitors in Premenopausal Women

Which of the following best describes your use of aromatase inhibitors in premenopausal women in each of the following settings?

	Adjuvant		Metastatic	
Have not used	22%	66%	7%	48%
Have used alone	4%	2%	—	10%
Have used with ovarian suppression/ablation	74%	28%	91%	38%
Have used both alone and with ovarian suppression/ablation	—	4%	2%	4%

oophorectomy, and then I'm comfortable with an aromatase inhibitor.

Meet The Professors 2005 (3)

DR ROBERT W CARLSON: The data today are quite convincing that the aromatase inhibitors should play a role as adjuvant hormonal therapy for postmenopausal women with ER-positive breast cancer. Precisely how to sequence or incorporate those data into the premenopausal subset is much less clear. We do know that the aromatase inhibitors do not suppress circulating estrogen levels adequately in women with functioning ovaries, whether or not they have menstrual function. Therefore, if you're going to use an AI for a young woman, you have to be certain that she is postmenopausal, or I think she should be enrolled in one of the prospective trials evaluating the use of ovarian suppression and an AI in premenopausal women. We do know that a number of women stop having menstrual function or periods subsequent to cytotoxic chemotherapy, yet their ovaries continue to cycle. A substantial proportion of women also stop having ovarian function with cytotoxic chemotherapy, at least over the short term, but on further follow-up, their ovarian function returns.

ASCO 2004 Technology Report

Cessation of menses does not necessarily mean absence of ovarian function, as premenopausal estradiol levels may be found in women experiencing chemotherapy-related amenorrhea. There is widespread agreement that aromatase inhibitors should not be employed as monotherapy in premenopausal women. This view stems from the lack of evidence for adequate estrogen suppression and potential for stimulation of the ovaries via increased gonadotropin release.

— Eric P Winer, MD et al.
J Clin Oncol 2005;23(3):619-29.

Breast Cancer Update 2005 (4)

DR MICHAEL GNANT: We were particularly interested in younger patients because they are physiologically used to higher levels of estrogen from their functioning ovaries. We undertook ABCSG-12 to first establish the severity of that treatment-induced bone loss and, second,

FIGURE 19

Approach to Adjuvant Therapy for ER/PR-Positive, Node-Negative Disease

- *Woman in average health*
- *1.2-centimeter, Grade II tumor*
- *ER-/PR-positive, HER2-negative*
- ***Negative nodes***

Which systemic therapy, if any, would you most likely recommend for this patient?

	Age 35		Age 55		Age 75		Age 85	
Endocrine therapy alone	16%	2%	37%	24%	96%	68%	83%	86%
Endocrine therapy plus chemotherapy	84%	96%	63%	76%	2%	32%	—	14%
Chemotherapy alone	—	2%	—	—	—	—	—	—
No therapy	—	—	—	—	2%	—	17%	—

FIGURE 20

Approach to Adjuvant Chemotherapy for ER/PR-Positive, Node-Negative Disease

Which chemotherapy regimen, if any, would you most likely recommend for this patient?

	Age 35		Age 55		Age 75		Age 85	
AC x 4 q3wk	39%	44%	34%	34%	2%	10%	—	4%
AC x 4 q2wk	11%	12%	7%	10%	—	6%	—	—
FAC or FEC x 6	14%	6%	5%	6%	—	2%	—	—
AC → paclitaxel x 4 q3wk	—	4%	—	2%	—	—	—	—
AC → paclitaxel x 4 q2wk	9%	10%	5%	8%	—	2%	—	—
AC x 4 q3wk → paclitaxel x qwk 12	—	2%	—	2%	—	—	—	—
AC → docetaxel x 4 q3wk	—	—	—	2%	—	—	—	—
AC → docetaxel x 4 q2wk	—	10%	—	4%	—	2%	—	—
CMF	7%	8%	5%	8%	—	10%	—	10%
TAC x 6	2%	2%	2%	—	—	—	—	—
Other chemotherapy	2%	—	5%	—	—	—	—	—
Would not recommend chemotherapy	16%	2%	37%	24%	98%	68%	100%	86%

to see whether it can be prevented or treated. We found out that a significant loss occurs — on average close to 15 percent — in these premenopausal women treated with endocrine therapy with goserelin and with tamoxifen or anastrozole. We also discovered that it could be prevented with zoledronic acid given twice a year.

Breast Cancer Update 2005 (4)

DR HOWELL: Three important randomized trials are enrolling premenopausal women with hormone-receptive disease — SOFT, TEXT and PERCHE. The ABCSG-AU12 trial randomly assigned approximately 2,000 patients to goserelin plus tamoxifen versus goserelin plus anastrozole, with a second randomization to zoledronic acid or not. That study will tell us whether tamoxifen or an aromatase inhibitor is superior when combined with goserelin in premenopausal women. We expect that goserelin with anastrozole will be better, which is why so many patients are already being treated off protocol.

FIGURE 21

Approach to Adjuvant Endocrine Therapy for ER/PR-Positive, Node-Negative Disease

Which endocrine therapy, if any, would you most likely recommend for this patient?

	Age 35		Age 55		Age 75		Age 85	
Anastrozole	—	—	63%	72%	68%	72%	56%	72%
Exemestane	—	—	—	2%	—	—	—	—
Letrozole	—	—	5%	—	2%	—	2%	—
Tamoxifen for 5 years and no further hormonal treatment	79%	64%	5%	4%	5%	6%	9%	14%
Tamoxifen for 2-3 years and then switch to aromatase inhibitor	—	2%	25%	16%	21%	12%	16%	10%
Tamoxifen for 5 years and then switch to aromatase inhibitor	4%	16%	2%	6%	2%	10%	—	4%
Aromatase inhibitor + LHRH agonist or ovarian ablation	4%	4%						
Tamoxifen + LHRH agonist or ovarian ablation	13%	12%						
Would not recommend endocrine therapy	—	2%	—	—	2%	—	17%	—

Sequencing aromatase inhibitors after adjuvant tamoxifen

Breast Cancer Update 2005 (2)

DR BAUM: 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 three 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 in 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 forever 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.

Breast Cancer Update 2005 (2)

DR MAURA N DICKLER: 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 recurrence is typically 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 a half 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 IES study and MA17 do not really take those facts into consideration because those 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.

Breast Cancer Update 2005 (4)

DR HOWELL: 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 and ABCSG-8 trials, in which the patients were switched to anastrozole, the agents appear to be similar in terms of efficacy. The hazard ratio for relapse-free survival was 0.73 in the IES study and 0.60 in the ARNO study, so I believe these two agents are 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 only the MA17 trial data, so I use letrozole in this setting.

Breast Cancer Update 2005 (3)

DR RAIMUND V JAKESZ: In the

FIGURE 22

Approach to Adjuvant Therapy for ER/PR-Positive, Node-Positive Disease

- *Woman in average health*
- *1.2-centimeter, Grade II tumor*
- ***3 positive nodes***
- *ER/PR-positive, HER2-negative*
- *Which systemic therapy, if any, would you most likely recommend for this patient?*

	Age 35		Age 55		Age 75		Age 85	
Endocrine therapy alone	—	—	—	—	27%	14%	85%	76%
Endocrine therapy plus chemotherapy	100%	98%	100%	100%	73%	86%	13%	20%
Chemotherapy alone	—	2%	—	—	—	—	—	2%
No therapy	—	—	—	—	—	—	2%	2%

FIGURE 23

Approach to Adjuvant Chemotherapy for ER/PR-Positive, Node-Positive Disease

Which chemotherapy regimen, if any, would you most likely recommend for this patient?

	Age 35		Age 55		Age 75		Age 85	
AC x 4 q3wk	—	4%	—	4%	11%	14%	2%	—
AC x 4 q2wk	—	—	—	—	2%	2%	5%	2%
FAC or FEC x 6	—	—	—	—	2%	6%	—	2%
AC → paclitaxel x 4 q3wk	—	6%	—	6%	—	6%	—	—
AC → paclitaxel x 4 q2wk	53%	44%	55%	44%	24%	14%	2%	2%
AC x 4 q3wk → paclitaxel x qwk 12	7%	4%	7%	8%	9%	8%	2%	2%
AC → docetaxel x 4 q3wk	—	2%	—	4%	—	8%	—	—
AC → docetaxel x 4 q2wk	9%	18%	9%	18%	7%	6%	2%	2%
CMF	—	—	—	—	7%	18%	—	8%
TAC x 6	27%	22%	20%	16%	2%	2%	—	2%
Other chemotherapy	4%	—	9%	—	9%	2%	—	2%
Would not recommend chemotherapy	—	—	—	—	27%	14%	87%	78%

combined trials of ABCSG-8 and ARNO 95, more than 3,200 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. The data were clean and informative. 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 event rate with anastrozole was due to a huge reduction in distant metastases.

Breast Cancer Update 2005 (Special CME Meeting Edition)

DR C KENT OSBORNE: Several groups have looked at statistical modeling of the

FIGURE 24

Adjuvant Hormonal Therapy for ER/PR-Positive, Node-Positive Disease

Which endocrine therapy, if any, would you most likely recommend for this patient?

	Age 35		Age 55		Age 75		Age 85	
Anastrozole	2%	6%	78%	80%	80%	80%	79%	80%
Exemestane	—	—	—	—	—	—	—	—
Letrozole	—	—	4%	—	2%	—	4%	—
Tamoxifen for 5 years and no further hormonal treatment	47%	52%	—	4%	—	2%	—	4%
Tamoxifen for 2-3 years and then switch to aromatase inhibitor	—	4%	16%	8%	16%	8%	13%	8%
Tamoxifen for 5 years and then switch to aromatase inhibitor	9%	10%	2%	8%	2%	10%	2%	4%
Aromatase inhibitor + LHRH agonist or ovarian ablation	22%	6%						
Tamoxifen + LHRH agonist or ovarian ablation	20%	20%						
Would not recommmend endocrine therapy	—	2%	—	—	—	—	2%	4%

optimal long-term sequencing of an AI after tamoxifen versus 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. All of these models suggested 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 in the large subgroup of ER/PR-positive tumors. Although there is a peak in recurrence at two to three years, ultimately more patients recur after year five than in the first five years, and the sequence of tamoxifen followed by an AI could turn out to be a better strategy. While it is true that we can't 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.

Breast Cancer Update 2005 (9)

DR MAMOUNAS: It is important to study the duration of aromatase inhibitor therapy. The NSABP will take patients who 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-B-14 extension trial but with aromatase inhibitors.

68-month follow-up of the ATAC Trial

Lancet 2005

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 withdrawals 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 preferred initial adjuvant endocrine treatment for postmenopausal women with hormone receptor-positive localized breast cancer.

— ATAC Trialists' Group.
Lancet 2005;365(9453):60-2.

Breast Cancer Update 2005 (1)

DR BAUM: The ATAC trial has reached an important point in its evolution with a median follow-up of 68 months. Almost all of the patients are now off therapy, and we have one year of follow-up after the therapy was completed. I believe this is probably the most important of the three analyses, and this latest analysis allows me, as a practicing clinician, to change my mind and my practice. I now would say that anastrozole is the preferred initial treatment for postmenopausal women with hormone receptor-positive disease.

The simplest interpretation of the results is that anastrozole prevents 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

FIGURE 25

Adjuvant Chemotherapy for ER/PR-Negative, HER2-Negative Disease: Positive Lymph Nodes

- *Woman in average health*
- *1.2-centimeter, Grade II tumor*
- ***ER-negative/PR-negative, HER2-negative***
- *3 positive nodes*

Which chemotherapy regimen, if any, would you most likely recommend for this patient?

	Age 35		Age 55		Age 75		Age 85	
AC x 4 q3wk	—	6%	—	6%	7%	12%	7%	4%
AC x 4 q2wk	2%	2%	2%	4%	4%	4%	2%	4%
FAC or FEC x 6	2%	2%	2%	2%	—	4%	2%	6%
AC → paclitaxel x 4 q3wk	—	2%	—	2%	7%	14%	—	2%
AC → paclitaxel x 4 q2wk	63%	48%	65%	48%	42%	24%	9%	4%
AC x 4 q3wk → paclitaxel x qwk 12	9%	4%	9%	6%	9%	6%	2%	2%
AC → docetaxel x 4 q3wk	2%	4%	2%	6%	2%	10%	2%	2%
AC → docetaxel x 4 q2wk	2%	14%	2%	12%	4%	6%	—	2%
CMF	—	—	—	—	7%	8%	4%	26%
TAC x 6	16%	18%	11%	14%	2%	4%	—	4%
Other chemotherapy	4%	—	7%	—	16%	4%	9%	6%
Would not recommend chemotherapy	—	—	—	—	—	4%	63%	38%

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 ablates 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 first two years.

BIG FEMTA/IBCSG-1-98/BIG 1-98: Letrozole versus tamoxifen up front or sequentially

Breast Cancer Update 2005 (6)

DR JACK CUZICK: 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 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 hasn't 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 it is not clear whether that has an impact.

Breast Cancer Update 2005 (5)

J MICHAEL DIXON: The BIG 1-98 data are a short-term analysis — follow-up is only 25.8 months, whereas for the ATAC trial the follow-up is five years — and some concerns exist as to how the BIG 1-98 data are being analyzed. The trial has four arms, and patients who switched therapy after two years were included in the analysis, but only up until the time when they were switched. That's a bit unusual because one would expect some of the benefit from the first two years of tamoxifen and letrozole to continue.

BCIRG 001: Adjuvant TAC versus TAC

Breast Cancer Update 2005 (1)

DR JOHN MACKEY: In our first study, BCIRG 001, 1,500 women from 21 countries were randomly assigned to six

FIGURE 26

Clinical Use of Adjuvant Taxanes

How many times a month do you start a breast cancer patient on a taxane-containing adjuvant regimen?

Mean	6	5

FIGURE 27

Clinical Use of Adjuvant Taxanes

What percent of your patients in each of the following categories receiving adjuvant chemotherapy receive adjuvant taxanes?

Node-negative (all)	32%	28%
High-risk node-negative	70%	58%
Node-positive	92%	90%

FIGURE 28

Selection of Taxanes

What percent of your taxane use in each of the following settings is with each of the following agents?

	Adjuvant		Metastatic	
Paclitaxel	67%	58%	49%	32%
Docetaxel	33%	42%	41%	53%
Nanoparticle paclitaxel	—	—	10%	15%

FIGURE 29

Taxanes with AC in the Adjuvant Setting

Do you most often prescribe the taxane after or combined with AC when using AC and a taxane?

After AC	82%	86%
Combined with AC	9%	14%
Other	9%	—

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 30 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 allowed. 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.

NSABP trial B-38

Breast Cancer Update 2004 (3)

DR CHARLES E GEYER JR: Two key adjuvant trials have been BCIRG 001, evaluating TAC versus FAC, and the CALGB dose-dense trial 9741 of AC paclitaxel. Currently, our view is that TAC appears to be the optimal way to administer an anthracycline/docetaxel regimen, and dose-dense AC/paclitaxel is the optimal way to administer those agents.

Which is better? It's impossible to answer that question without performing a clinical trial, which is why we developed trial NSABP-B-38. It's a pragmatic design in which we regard TAC as our control arm. A clear advantage of dose-dense therapy is that it is so well tolerated, and it clearly affords the opportunity to add a fourth drug to the paclitaxel. TAC is a maximally tolerated regimen. You really can't push it much more, so we sought a candidate drug to combine with paclitaxel.

Adjuvant clinical trials incorporating capecitabine

Breast Cancer Update 2005 (3)

DR O'SHAUGHNESSY: The vinorelbine/capecitabine combination is one of numerous capecitabine combinations being evaluated in European adjuvant trials. I'm not aware of any adjuvant or neoadjuvant studies evaluating capecitabine/paclitaxel; however, a number of neoadjuvant and adjuvant trials are evaluating capecitabine/docetaxel.

Even if I had data with capecitabine/paclitaxel, I probably would not have considered evaluating that combination

FIGURE 30

Use of Nanoparticle Paclitaxel

Have you used nanoparticle paclitaxel?

Yes	73%	62%
No	27%	38%

In how many patients have you used nanoparticle paclitaxel off protocol?

Mean	4	2

FIGURE 31

Allergic Reactions to Taxanes

What percent of the breast cancer patients you have treated have experienced an allergic reaction to each of the following taxanes?

Paclitaxel	7%	9%
Docetaxel	6%	4%

FIGURE 32

Use of Steroid Premedication with Adjuvant Taxanes

How often do you use steroid premedication with each of the following taxanes?

	Paclitaxel		Docetaxel	
Always	85%	96%	84%	84%
Frequently	11%	—	14%	10%
Occasionally	2%	4%	—	4%
Never	2%	—	2%	2%

— as opposed to capecitabine/docetaxel — in our adjuvant trial. In metastatic disease, docetaxel 75 mg/m^2 in combination with capecitabine has a clear survival advantage compared to docetaxel 100 mg/m^2. Usually, we try to take that advantage in survival in metastatic disease and immediately move it into the adjuvant setting.

Inclusion of older patients in trials of adjuvant chemotherapy

JAMA 2005

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.

SELECT PUBLICATIONS

Berry DA et al. **Effects of improvements in chemotherapy on disease-free and overall survival of estrogen-receptor negative, node-positive breast cancer: 20-year experience of the CALGB and US Breast Intergroup.** *Breast Cancer Res Treat* 2004;Abstract 29.

Biganzoli L et al. **Adjuvant chemotherapy in elderly patients with breast cancer: A survey of the Breast International Group (BIG).** *Ann Oncol* 2004;15(2):207-10. Abstract

Boccardo F et al. **Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: Preliminary results of the Italian Tamoxifen Anastrozole Trial.** *J Clin Oncol* 2005;23(22):5138-47. Abstract

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

Bonadonna G et al. **Clinical relevance of different sequencing of doxorubicin and cyclophosphamide, methotrexate, and fluorouracil in operable breast cancer.** *J Clin Oncol* 2004;22(9):1614-20. Abstract

Brain EGC et al. **Phase III trial comparing doxorubicin docetaxel (AT) with doxorubicin cyclophosphamide (AC) in the adjuvant treatment of high-risk node negative (pN0) and limited node positive (pN+≤3) breast cancer (BC) patients (pts): First analysis of toxicity.** *Proc ASCO* 2004;Abstract 617.

Carlson RW et al. **Goserelin plus anastrozole for the treatment of premenopausal women with hormone receptor positive, recurrent/metastatic breast cancer.** *Breast Cancer Res Treat* 2004;Abstract 6052.

Castiglione-Gertsch M et al. **Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: A randomized trial.** *J Natl Cancer Inst* 2003;95(24):1833-46. Abstract

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

Coombes RC et al. **A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer.** *N Engl J Med* 2004;350(11):1081-92. Abstract

Cuzick J, Howell A. **Optimal timing of the use of an aromatase inhibitor in the adjuvant treatment of postmenopausal hormone receptor-positive breast cancer.** Presentation. ASCO 2005;Abstract 658.

Davidson NE et al. **Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: Results from INT 0101 (E5188).** *J Clin Oncol* 2005;23(25):5973-82. Abstract

Delozier T et al. **Reducing dose density in adjuvant chemotherapy is detrimental in early breast cancer (EBC). A review of 872 adjuvant treatments in Centre François Baclesse.** *Proc ASCO* 2004;Abstract 583.

Dowsett M, on behalf of the ATAC Trialists' Group. **Analysis of time to recurrence in the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial according to estrogen receptor and progesterone receptor status.** *Breast Cancer Res Treat* 2003;83(Suppl 1):7;**Abstract 4**.

Duffy S, on behalf of the ATAC Trialist's Group. **Gynecological adverse events including hysterectomy occur less frequently with anastrozole than with tamoxifen: Data from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2005;**Abstract 723**.

Duffy S et al. **The ATAC adjuvant breast cancer trial in postmenopausal women: Baseline endometrial subprotocol data.** *BJOG* 2003;110(12):1099-106. **Abstract**

Duric V et al. **Predictors of the benefits women consider necessary to make adjuvant chemotherapy (ACT) worthwhile for early breast cancer (EBC).** *Proc ASCO* 2004;**Abstract 787**.

Evans TR et al. **Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: An anglo-celtic cooperative oncology group study.** *J Clin Oncol* 2005;23(13):2988-95. **Abstract**

Ghani F et al. **Confirmation of C9741 intergroup results in a prospectively randomized trial comparing dose-intense chemotherapy with G-CSF support to 3-weekly chemotherapy for adjuvant therapy of nodal-positive (1-3 LN) breast cancer: Longitudinal CA 27.29 results indicate higher decay of minimal residual disease in the dose-dense arm.** *Proc ASCO* 2004;**Abstract 805**.

Giordano SH et al. **Breast cancer treatment guidelines in older women.** *J Clin Oncol* 2005;23(4):783-91. **Abstract**

Gnant M et al. **Zoledronic acid effectively counteracts cancer treatment induced bone loss (CTIBL) in premenopausal breast cancer patients receiving adjuvant endocrine treatment with goserelin plus anastrozole versus goserelin plus tamoxifen — Bone density subprotocol results of a randomized multicenter trial (ABCSG-12).** *Breast Cancer Res Treat* 2004;**Abstract 6**.

Goss PE et al. **Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: Updated findings from NCIC CTG MA17.** *J Natl Cancer Inst* 2005;97(17):1262-71. **Abstract**

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

Henderson IC et al. **Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.** *J Clin Oncol* 2003;21(6):976-83. **Abstract**

Houghton J et al. **Using anastrozole as initial adjuvant treatment prevents early recurrences and reduces adverse events: Updated data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2005;**Abstract 582**.

Howell A et al. **Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer.** *Lancet* 2005;365(9453):60-2. **Abstract**

Howell A et al. **The ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial in postmenopausal women with early breast cancer — Updated efficacy results based on a median follow-up of 5 years.** *Breast Cancer Res Treat* 2004;**Abstract 1**.

Hudis CA, Schmitz N. **Dose-dense chemotherapy in breast cancer and lymphoma.** *Semin Oncol* 2004;31(3 Suppl 8):19-26. **Abstract**

Jakesz R et al. **Extended adjuvant treatment with anastrozole: Results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a).** *Proc ASCO* 2005;**Abstract 527**.

Jakesz R et al. **Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: Combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial.** *Breast Cancer Res Treat* 2004;**Abstract 2**.

Kennecke H et al. **10 year event-free survival (EFS) in postmenopausal women with early stage breast cancer during the second five years after adjuvant tamoxifen.** *Breast Cancer Res Treat* 2004;**Abstract 1049**.

Levine MN et al; National Cancer Institute of Canada Clinical Trials Group. **Randomized trial comparing cyclophosphamide, epirubicin, and fluorouracil with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: Update of National Cancer Institute of Canada Clinical Trials Group Trial MA5.** *J Clin Oncol* 2005;23(22):5166-70. **Abstract**

Locker GY et al. **The time course of bone fractures observed in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial.** *Proc ASCO* 2003;**Abstract 98**.

Loesch D et al. **A randomized, multicenter phase III trial comparing regimens of doxorubicin + cyclophosphamide followed by paclitaxel or doxorubicin + paclitaxel followed by weekly paclitaxel as adjuvant therapy for patients with high risk breast cancer.** *Breast Cancer Res Treat* 2004;**Abstract 28**.

Loprinzi CL, Ravdin PM. **Decision-making for patients with resectable breast cancer: Individualized decisions for and by patients and their physicians.** *JNCCN* 2003;1(2):189-96.

Love RR et al. **Her-2/neu overexpression and response to oophorectomy plus tamoxifen adjuvant therapy in estrogen receptor-positive premenopausal women with operable breast cancer.** *J Clin Oncol* 2003;21(3):453-7. **Abstract**

Love RR et al. **Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnamese and Chinese women with operable breast cancer.** *J Clin Oncol* 2002;20(10):2559-66. **Abstract**

Lyman GH et al. **Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: A nationwide study of community practices.** *J Clin Oncol* 2003;21(24):4524-31. **Abstract**

Mamounas EP et al. **Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28.** *J Clin Oncol* 2005;23(16):3686-96. **Abstract**

Martin M et al; Breast Cancer International Research Group 001 Investigators. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13. **Abstract**

Martin M et al. **Prophylactic growth factor (GF) support with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) for node-negative breast cancer (BC): An interim safety analysis of the GEICAM 9805 study.** *Proc ASCO* 2004;**Abstract 620**.

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

Muss HB et al. **Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer.** *JAMA* 2005;293(9):1073-81. **Abstract**

Nowak AK et al. **Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer.** *Lancet Oncol* 2004;5(6):372-80. **Abstract**

Perez EA. **Effect of letrozole versus placebo on bone mineral density in women completing > 5 years (yrs) of adjuvant tamoxifen: NCIC CT MA.17b.** *Breast Cancer Res Treat* 2004;**Abstract 404**.

Punglia RS et al. **Optimizing adjuvant endocrine therapy in postmenopausal women with early-stage breast cancer: A decision analysis.** *J Clin Oncol* 2005;23(22):5178-87. **Abstract**

Thewes B et al. **What survival benefits do premenopausal patients with early breast cancer need to make endocrine therapy worthwhile?** *Lancet Oncol* 2005;6(8):581-8. **Abstract**

Thürlimann B. **BIG 1-98: A prospective randomized double-blind double-dummy phase III study to evaluate letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Breast* 2005;14(Suppl 1):3;S4.

Thürlimann B et al. **BIG 1-98: Randomized double-blind phase III study to evaluate letrozole (L) vs tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** *Proc ASCO* 2005;**Abstract 511**.

Vogel CL et al. **The role of growth factor support following neutropenic events in early stage breast cancer (BC) patients treated with adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC): A sub-analysis of BCIRG 001.** *Proc ASCO* 2004;**Abstract 677**.

Winer EP et al. **American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: Status report 2004.** *J Clin Oncol* 2005;23(3):619-29. **Abstract**

FIGURE 33

Clinical Use of Adjuvant Trastuzumab

Since the presentation of the data at ASCO in May, how many patients have you evaluated and considered for adjuvant trastuzumab? (mean)	18	9
Since the presentation of the data at ASCO in May, how many women have you treated with adjuvant trastuzumab? (mean)	13	6

FIGURE 34

Clinical Use of Adjuvant Trastuzumab

How have you utilized (or do you plan to utilize) trastuzumab in the adjuvant setting in patients with normal cardiac function who desire treatment?

In most or all node-positive patients	7%	22%
In most or all node-positive and high-risk node-negative patients	91%	58%
In some node-positive patients	—	4%
In some node-positive and high-risk node-negative patients	2%	16%

FIGURE 35

Approach to Adjuvant Therapy for ER-Negative, HER2-Positive Disease: Negative Nodes

- *Woman in average health*
- *1.2-centimeter, Grade II tumor*
- *ER-negative/PR-negative, HER2-positive*
- *Negative nodes*

	Age 35		Age 55		Age 75		Age 85	
Chemotherapy alone	16%	26%	20%	30%	29%	38%	4%	26%
Chemotherapy plus trastuzumab	84%	74%	80%	70%	60%	54%	9%	20%
Trastuzumab alone	—	—	—	—	—	—	11%	12%
No therapy	—	—	—	—	11%	8%	76%	42%

Combined analysis: NSABP-B-31/NCCTG-N9831

ASCO 2005

Our conclusions for high-risk HER2-positive breast cancer: Trastuzumab, when given concurrently with paclitaxel following AC chemotherapy, reduces the risk of a first breast cancer event at three years by 52 percent. This benefit should change the standard of care. The benefit was present and of similar magnitude in virtually all subsets of patients analyzed. There is not, however, statistical power to establish efficacy in the node-negative subset. The addition of trastuzumab reduced the probability of developing distant recurrence by 53 percent at three years, and the hazard of developing distant metastases appears, thus far, to decrease over time. Early results at a median follow-up of two years show a statistically significant survival advantage, with a relative risk reduction of 33

BREAST CANCER SPECIALISTS GENERAL ONCOLOGISTS

FIGURE 36

Adjuvant Therapy for ER/PR-Negative, HER2-Positive Disease: High Risk, Node-Negative

- *Woman in average health*
- ***2.4-centimeter**, Grade II tumor*
- *ER-negative/PR-negative, HER2-positive*
- ***Negative nodes***

What is your general approach to therapy?

	Age 35		Age 55		Age 75		Age 85	
Chemotherapy alone	—	12%	2%	14%	16%	30%	5%	26%
Trastuzumab only	—	—	—	—	—	—	14%	10%
Chemotherapy plus trastuzumab	100%	88%	98%	86%	84%	64%	14%	26%
AC x 4 q3wk	—	14%	2%	14%	9%	14%	5%	4%
AC x 4 q2wk	2%	—	4%	—	5%	4%	—	2%
FAC or FEC x 6	—	4%	—	4%	2%	4%	—	—
AC → paclitaxel x 4 q3wk	—	12%	—	10%	—	8%	—	—
AC → paclitaxel x 4 q2wk	29%	24%	25%	26%	14%	10%	—	2%
AC x 4 q3wk → paclitaxel qwk x 12	54%	12%	54%	12%	38%	8%	2%	2%
AC → docetaxel x 4 q3wk	9%	—	7%	—	—	—	—	—
AC → docetaxel x 4 q2wk	2%	16%	2%	16%	—	6%	—	2%
CMF	—	—	—	—	2%	6%	—	10%
TAC x 6	—	6%	—	4%	—	—	—	2%
Other chemotherapy	4%	—	4%	—	14%	4%	7%	2%
No therapy	—	—	—	—	—	6%	67%	38%
If recommending trastuzumab, which duration of trastuzumab treatment would you use?								
6 months	—	5%	—	5%	3%	6%	8%	11%
1 year	100%	90%	100%	93%	97%	94%	92%	89%
2 years	—	5%	—	2%	—	—	—	—
If recommending trastuzumab plus chemotherapy, would you most likely start the trastuzumab during or after chemotherapy?								
During	95%	59%	93%	60%	78%	50%	71%	38%
After	5%	41%	7%	40%	22%	50%	29%	62%

percent.

— Edward H Romond, MD et al. Presentation. ASCO 2005.

Breast Cancer Update 2005 (6)

DR GEORGE W SLEDGE JR: In the joint analysis of NCCTG-N9831 and NSABPB-31, the hazard rates for distant disease recurrence in patients who received trastuzumab appeared to improve with time. It's still 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

FIGURE 37

Approach to Therapy for ER/PR-Positive, HER2-Positive Disease

- *Woman in average health*
- *1.2-centimeter, Grade II tumor*
- ***ER-/PR-positive, HER2-positive***
- ***3 positive nodes***

	Age 35		Age 55		Age 75		Age 85	
Chemotherapy alone	—	—	—	—	2%	—	2%	—
Chemotherapy plus trastuzumab	4%	2%	2%	—	2%	—	—	—
Chemotherapy plus trastuzumab plus endocrine therapy	96%	88%	96%	90%	73%	64%	20%	18%
Chemotherapy plus endocrine therapy	—	10%	2%	10%	9%	22%	2%	10%
Endocrine therapy plus trastuzumab	—	—	—	—	7%	2%	9%	20%
Endocrine therapy alone	—	—	—	—	7%	12%	61%	52%
Trastuzumab alone	—	—	—	—	—	—	2%	—
No therapy	—	—	—	—	—	—	4%	—

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.

HERA: Adjuvant trastuzumab trial

ASCO 2005

In conclusion, at one-year median follow-up, trastuzumab given every three weeks for one year following adjuvant chemotherapy significantly prolongs disease-free survival and relapse-free survival and significantly reduces the risk of distant metastasis.

Trastuzumab's clinical benefits are independent of patients' baseline characteristics and of type of adjuvant chemotherapy received. Trastuzumab therapy is associated with a low incidence of severe symptomatic congestive heart failure, but, clearly, longer follow-up is needed to better quantify this risk.

All patients continue to be followed for long-term safety. Results regarding optimal trastuzumab duration, two years versus one year, should be available in 2008.

— Martine J Piccart-Gebhart, MD, PhD et al. Presentation. ASCO 2005.

Initial results of BCIRG 006

Breast Cancer Update: Special NSABP Edition 2005

DR DENNIS J SLAMON: In a three-arm trial with 300 events, we recognize that we're walking a fine line here, but still, both trastuzumab arms crossed their efficacy boundaries. The relevant question will be: How does the TCH arm, the nonanthracycline arm, look relative to the anthracycline-containing arm?

The risk reduction in the TCH arm is 0.39, and 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 wait 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.

Adjuvant trastuzumab in node-negative disease

Breast Cancer Update: Special NSABP Edition 2005

DR WOLMARK: 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 Onco*type* DX 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.

Breast Cancer Update 2005 (7)

DR ERIC P WINER: The HERA study included patients with node-negative disease as long as their tumors were greater than a centimeter. A third of the patients participating were node-

FIGURE 38

Adjuvant Therapy for ER/PR-Negative, HER2-Positive Disease: Positive Nodes

- *Woman in average health*
- *1.2-centimeter, Grade II tumor*
- ***ER-negative/PR-negative, HER2-positive***
- ***3 positive nodes***

What is your general approach to therapy?

	Age 35		Age 55		Age 75		Age 85	
Chemotherapy alone	—	6%	—	6%	7%	22%	11%	20%
Trastuzumab alone	—	—	—	—	—	—	9%	12%
Chemotherapy plus trastuzumab	100%	94%	100%	94%	91%	74%	31%	32%
AC x 4 q3wk	—	—	—	—	4%	4%	5%	—
FAC or FEC x 6	—	—	—	—	2%	2%	2%	2%
AC → paclitaxel x 4 q3wk	—	10%	—	12%	—	16%	—	2%
AC → paclitaxel x 4 q2wk	31%	36%	29%	38%	18%	14%	—	2%
AC x 4 q3wk → paclitaxel qwk x 12	51%	18%	53%	18%	45%	12%	9%	2%
AC → docetaxel x 4 q3wk	7%	6%	7%	4%	2%	4%	—	2%
AC → docetaxel x 4 q2wk	7%	12%	7%	12%	2%	6%	2%	4%
CMF	—	2%	—	—	—	6%	—	12%
TAC x 6	—	10%	—	10%	2%	4%	—	—
Other chemotherapy	4%	—	4%	—	16%	6%	13%	6%
No therapy	—	—	—	—	2%	4%	49%	36%
If recommending trastuzumab, which duration of trastuzumab treatment would you use?								
6 months	—	2%	—	2%	—	5%	6%	14%
1 year	98%	89%	100%	89%	100%	95%	94%	86%
2 years	2%	9%	—	9%	—	—	—	—
Other	—	—	—	—	—	—	—	—
If recommending trastuzumab plus chemotherapy, would you most likely start the trastuzumab during or after chemotherapy?								
During	98%	68%	98%	70%	85%	68%	73%	50%
After	2%	32%	2%	30%	15%	32%	27%	50%

negative. The NSABP trial had no patients with node-negative disease, and in the NCCTG 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 cancers.

Breast Cancer Update 2005 (6)

DR EDWARD H ROMOND: The NSABP-B-31 and NCCTG-N9831 adjuvant trastuzumab trials were initially limited to patients with node-positive disease.

However, in May 2003, the Intergroup amended their protocol to include patients with high-risk, node-negative disease, which were basically ER-negative/HER2-positive or ER-positive/HER2-positive tumors that were larger than two centimeters.

As a result, in the overall data set, approximately 100 patients in each arm had node-negative disease. The relative risk reduction in the combined data analysis of patients with node-negative disease was approximately 0.48 — the same as the entire data set.

The problem is that with 100 or fewer patients with node-negative disease in the arms of the N9831 protocol, the confidence interval goes out forever and crosses one.

That does not mean there is no biologic effect; it probably exists, but it's difficult to pin down how much benefit we gain by using trastuzumab in patients with node-negative disease. The HERA trial may be a better data set to examine the benefit of adjuvant trastuzumab in that population, because one third of those patients had node-negative disease.

Selection of chemotherapy to combine with trastuzumab

Breast Cancer Update: Special NSABP Edition 2005 (10)

DR SLAMON: In terms of nonprotocol chemotherapy-trastuzumab combinations, at this point, we try, whenever possible, to avoid anthracycline-containing regimens because of the known interaction in terms of cardiac safety of trastuzumab with anthracyclines, and we're not restricted to TCH when using a non-anthracycline regimen.

There are a number of different drugs that interact very well with trastuzumab. However, we usually do use TCH in the adjuvant setting and will continue to do so until we see that it is inferior and the safety profile doesn't make up for that inferiority.

Duration of and delayed implementation of adjuvant trastuzumab

Breast Cancer Update 2005 (8)

DR PETER M RAVDIN: 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 addresses 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 control group of patients who want to cross over out to 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 patients at high risk with multiple nodes. However, that rationale is going beyond the data we have and is somewhat speculative.

Breast Cancer Update 2005 (6)

DR SLEDGE: 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.

Clinical impact of adjuvant trastuzumab trial data

Breast Cancer Update 2005 (6)

DR SLEDGE: As a result of the data presented at ASCO in 2005, trastuzumab became 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 diminish the likelihood of recurrence and improve overall survival through the use of targeted therapy.

This validates 15 years of preclinical and clinical research, from Slamon's initial observation in the late 1980s that HER2 was a bad actor in breast cancer to the pivotal metastatic trial led by Slamon and now the adjuvant trial data.

We have consistently seen that when HER2 is overexpressed or amplified, it markedly increases a patient's risk of early relapse.

In the HERA trial, we saw that by two years after randomization, one quarter of the patients in the control arm had relapsed. In the joint analysis of NCCTG-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 survival with a median follow-up of just two years.

That is unprecedented in any adjuvant trial. It's interesting to imagine what the impact of the estrogen receptor trials would have been if we had enrolled 3,000 patients on those studies two or three decades ago. The data probably would have been similar to the adjuvant trastuzumab trial data.

The message is that if we understand biology and target it appropriately, we obtain a great result, whereas when we use relatively nonspecific therapies, we can tweak them — changing dose duration, dose density and dose intensity — and obtain slightly better results, but we'll never achieve the revolutionary results that we saw in the adjuvant

FIGURE 39

Use of Delayed Adjuvant Trastuzumab

- *55-year-old woman with normal ejection fraction who received prior adjuvant AC-paclitaxel*
- *2.4-cm, Grade II tumor*
- *ER-negative/PR-negative, HER2-positive*
- *Node status specified below*

Would you recommend adjuvant trastuzumab at each of the following time points?

	Node-negative		3 positive nodes		10 positive nodes	
6 months after completion of chemotherapy	76%	58%	96%	82%	96%	84%
1 year after completion of chemotherapy	50%	32%	70%	54%	82%	58%
2 years after completion of chemotherapy	2%	8%	14%	14%	36%	38%
4 years after completion of chemotherapy	—	4%	5%	8%	9%	22%

FIGURE 40

Impact of Cardiac Status on Use of Adjuvant Trastuzumab

- *55-year-old woman*
- *2.4-cm, Grade II tumor*
- *ER-negative/PR-negative, HER2-positive*
- *Node and cardiac status specified below*

Would you include adjuvant trastuzumab in your treatment plan for each of the following women, assuming they are asymptomatic?

	Node-negative		3 positive nodes		10 positive nodes	
Current ejection fraction = 70%	93%	72%	100%	90%	100%	94%
Current ejection fraction = 50%	73%	52%	100%	76%	100%	86%
Current ejection fraction = 40%	2%	8%	20%	28%	36%	36%
History of myocardial infarction (5 years ago) with a normal ejection fraction (60-70%)	71%	58%	93%	76%	98%	86%
History of poorly controlled hypertension	64%	54%	82%	74%	89%	84%

trastuzumab trials.

Concurrent or sequential trastuzumab administration with chemotherapy

Breast Cancer Update: Special NSABP Edition 2005 (10)

DR WOLMARK: The only test of concomitant versus sequential treatment was from N-9831, and when you look at the curves presented and the comparisons, one can't remain neutral. The concomitant arm (with paclitaxel) has a hazard rate that falls in line with what we're seeing in the other trials, whereas the sequential arm is, peer-wise, not statistically significant. It is not inappropriate for a medical oncologist to evaluate those data and be more impressed with concomitant therapy.

Breast Cancer Update 2005 (6)

DR SLEDGE: 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. On the other hand, in the Intergroup trial, it appears that concurrent therapy is superior to the sequential schedule. These are different data sets, and both trials have a short median follow-up and a relatively small number of events, so we shouldn't make too much of this yet.

Concurrent therapy after the anthracycline is probably better. I base that belief on the results of the pivotal

FIGURE 41

Impact of Cardiac Status on Use of Adjuvant Trastuzumab

- *55-year-old woman treated with adjuvant AC-T (paclitaxel) chemotherapy*
- *2.4-cm, Grade II tumor*
- *ER-negative/PR-negative, HER2-positive*
- *3 positive nodes*

Assume that she and you decide to proceed with adjuvant trastuzumab and she wants to treat the cancer "aggressively." After 3 months on adjuvant trastuzumab, her ejection fraction (EF) falls from 75% to each of the following, but she remains asymptomatic.

How would you manage this patient's therapy at the following ejection fractions?

	Current ejection fraction = 70%		Current ejection fraction = 60%		Current ejection fraction = 50%		Current ejection fraction = 40%	
Hold trastuzumab and recheck after period of time, if EF improvement, restart	—	8%	7%	20%	47%	36%	49%	34%
Hold trastuzumab and recheck after period of time, if EF improvement or stable, restart	2%	—	20%	26%	38%	36%	7%	12%
Stop trastuzumab permanently	—	2%	—	2%	4%	24%	44%	52%
Continue trastuzumab	98%	90%	73%	52%	11%	4%	—	2%

FIGURE 42

HER2 Testing and Use of Adjuvant Trastuzumab

What documentation of HER2 positivity do you/will you require to use adjuvant trastuzumab?

FISH	36%	34%
IHC 3+	—	4%
Both FISH and IHC 3+	9%	12%
Either FISH or IHC 3+	55%	50%

FIGURE 43

Cardiac Function Testing and Use of Adjuvant Trastuzumab

What form of cardiac testing do you/will you do in your patients on adjuvant trastuzumab?

MUGA	60%	60%
Echo	15%	18%
MUGA and Echo	18%	20%
MUGA or Echo	7%	2%

FIGURE 44

Use of Trastuzumab in the Metastatic Setting after Adjuvant Treatment

Assume your patient with ER-negative, HER2-positive disease received adjuvant trastuzumab and progressed. Would you generally plan to use first-line trastuzumab in the metastatic setting if she progressed at each of the following time points?

Toward the end of 1 year of adjuvant trastuzumab treatment	67%	62%
1 year after completion of adjuvant trastuzumab treatment	96%	88%
2 years after completion of adjuvant trastuzumab treatment	98%	90%

trials and on a large body of preclinical data that suggest trastuzumab is a good amplifier of chemotherapy-induced apoptosis. Also, considering how rapidly the efficacy curves separate in the joint analysis data, it almost makes one want to start trastuzumab about 10 seconds after a core biopsy is obtained.

Cardiac safety of adjuvant trastuzumab

Breast Cancer Update 2005 (4)

DR EDITH A PEREZ: 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 definitely improve not only in terms of the clinical symptomatology but also measurable left ventricular ejection fraction.

Breast Cancer Update 2005 (7)

DR WINER: The downside with receiving trastuzumab, apart from the fact that it requires a year's worth of therapy, is the cardiac toxicity, which was defined as symptomatic congestive heart failure, so we're not talking about asymptomatic drops in ejection fractions. We're talking about real problems that we hope can improve over time, but about which we have relatively limited, if any, information regarding the long-term consequences. I generally tell patients that the risk of congestive heart failure is probably in the range of two to four percent, based on what we know so far, specifically in women who receive AC followed by paclitaxel with trastuzumab.

There was some suggestion that the cardiac toxicity may be less when trastuzumab is administered sequentially, as in the NCCTG trial where paclitaxel was given and then trastuzumab followed. Maybe that relates to a longer period of time from when the anthracycline is given to the beginning of trastuzumab. There was also the suggestion of less cardiac toxicity in the HERA trial, where chemotherapy and trastuzumab were not concurrent.

In the NSABP analysis, there was the suggestion that cardiac toxicity was more of a problem in older women, specifically in women who had borderline ejection fractions at baseline versus those who had better, stronger, higher ejection fractions. All of this needs to be sorted out.

In the BCIRG trial, in the group of women who received docetaxel, carboplatin and trastuzumab, the cardiac toxicity was substantially less than in women who received the anthracycline followed by docetaxel and trastuzumab. I think all of us are very hopeful that nonanthracycline-containing regimens will be the wave of the future, but we will just have to wait for the efficacy data. We need those data from the BCIRG trial, and I'm told that we will have those some time over the next several months — certainly at San Antonio, if not before.

Continuing trastuzumab after disease progression

Breast Cancer Update 2005 (5)

DR TRIPATHY: Right now, in the absence of data, we have to use our best knowledge and extensions of the clinical and laboratory data to guide our patients. I personally believe there may be a role for continuing trastuzumab with another chemotherapeutic agent. My patients also usually feel strongly about it, and we often elect to go that route. I don't use this approach with all of my patients, and I certainly explain to them that we don't know the answer.

In this situation, trastuzumab appears to be safe. The rate of cardiotoxicity on the extension trial was very low in the patients who were already on trastuzumab and hadn't developed cardiac problems. I generally continue trastuzumab, but not indefinitely. Once a patient goes through two or three combinations, I think it's probably prudent to stop trastuzumab and try either single-agent or combination chemotherapy.

SELECT PUBLICATIONS

Adams GP, Weiner LM. **Monoclonal antibody therapy of cancer.** *Nat Biotechnol* 2005;23(9):1147-57. Abstract

Altundag K et al. **Adjuvant trastuzumab use in high-risk breast cancer patients may prevent development of contralateral estrogen receptor-negative breast tumors.** *Med Hypotheses* 2005;[Epub ahead of print]. No abstract available

Altundag K et al. **Monoclonal antibody-based targeted therapy in breast cancer.** *Curr Med Chem Anti-Canc Agents* 2005;5(2):99-106. Abstract

Ariga R et al. **Correlation of her-2/neu gene amplification with other prognostic and predic-**

tive factors in female breast carcinoma. *Breast J* 2005;11(4):278-80. Abstract

Bartlett JM. **Pharmacodiagnostic testing in breast cancer: Focus on HER2 and trastuzumab therapy.** *Am J Pharmacogenomics* 2005;5(5):303-15. Abstract

Baselga J et al. **Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule.** *J Clin Oncol* 2005;23(10):2162-71. Abstract

Benohr P et al. **Her-2/neu expression in breast cancer — A comparison of different diagnostic methods.** *Anticancer Res* 2005;25(3B):1895-900. Abstract

Buzdar AU et al. **Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer.** *J Clin Oncol* 2005;23(16):3676-85. Abstract

De Laurentiis M et al. **Targeting HER2 as a therapeutic strategy for breast cancer: A paradigmatic shift of drug development in oncology.** *Ann Oncol* 2005;16(Suppl 4):iv7-iv13. Abstract

Del Mastro L et al. **HER2 expression and efficacy of dose-dense anthracycline-containing adjuvant chemotherapy in breast cancer patients.** *Br J Cancer* 2005;93(1):7-14. Abstract

DiGiovanna MP et al. **Relationship of epidermal growth factor receptor expression to ErbB-2 signaling activity and prognosis in breast cancer patients.** *J Clin Oncol* 2005;23(6):1152-60. Abstract

Dobson R. **Trastuzumab halves risk of recurrence of breast cancer in some women.** *BMJ* 2005;331(7523):986. No abstract available

Dressler LG et al. **Comparison of HER2 status by fluorescence in situ hybridization and immunohistochemistry to predict benefit from dose escalation of adjuvant doxorubicin-based therapy in node-positive breast cancer patients.** *J Clin Oncol* 2005;23(19):4287-97. Abstract

Dybdal N et al. **Determination of HER2 gene amplification by fluorescence in situ hybridization and concordance with the clinical trials immunohistochemical assay in women with metastatic breast cancer evaluated for treatment with trastuzumab.** *Breast Cancer Res Treat* 2005;93(1):3-11. Abstract

Ellis CM et al. **HER2 amplification status in breast cancer: A comparison between immunohistochemical staining and fluorescence in situ hybridisation using manual and automated quantitative image analysis scoring techniques.** *J Clin Pathol* 2005;58(7):710-4. Abstract

Ewer MS et al. **Reversibility of trastuzumab-related cardiotoxicity: New insights based on clinical course and response to medical treatment.** *J Clin Oncol* 2005;23(31):7820-6. Abstract

Gasparini G et al. **Therapy of breast cancer with molecular targeting agents.** *Ann Oncol* 2005;16 Suppl 4:iv28-iv36. Abstract

Gong Y et al. **Reliability of chromogenic in situ hybridization for detecting HER-2 gene status in breast cancer: Comparison with fluorescence in situ hybridization and assessment of interobserver reproducibility.** *Mod Pathol* 2005;18(8):1015-21. Abstract

Hampton T. **Monoclonal antibody therapies shine in breast cancer clinical trials.** *JAMA* 2005;293(24):2985-9. No abstract available

Hicks DG, Tubbs RR. **Assessment of the HER2 status in breast cancer by fluorescence in situ hybridization: A technical review with interpretive guidelines.** *Hum Pathol* 2005;36(3):250-61. Abstract

Hobday TJ, Perez EA. **Molecularly targeted therapies for breast cancer.** *Cancer Control* 2005;12(2):73-81. Abstract

Hortobagyi GN. **Trastuzumab in the treatment of breast cancer.** *N Engl J Med* 2005;353(16):1734-6. No abstract available

Kounelis S et al. **Evaluation of HER2 gene status in breast cancer by chromogenic in situ hybridization: Comparison with immunohistochemistry.** *Anticancer Res* 2005;25(2A):939-46. Abstract

Lan C et al. **erb-b2 amplification by fluorescence in situ hybridization in breast cancer specimens read as 2+ in immunohistochemical analysis.** *Am J Clin Pathol* 2005;124(1):97-102. Abstract

Leyland-Jones B et al. **Pharmacokinetics, safety, and efficacy of trastuzumab administered every three weeks in combination with paclitaxel.** *J Clin Oncol* 2003;21(21):3965-71. Abstract

Lottner C et al. **Simultaneous detection of HER2/neu gene amplification and protein overexpression in paraffin-embedded breast cancer.** *J Pathol* 2005;205(5):577-84. Abstract

Ma Y et al. **Polysomy 17 in HER-2/neu status elaboration in breast cancer: Effect on daily practice.** *Clin Cancer Res* 2005;11(12):4393-9. Abstract

Mass RD et al. **Evaluation of clinical outcomes according to HER2 detection by fluorescence in situ hybridization in women with metastatic breast cancer treated with trastuzumab.** *Clin Breast Cancer* 2005;6(3):240-6. Abstract

Nabholtz JM, Gligorov J. **Docetaxel/trastuzumab combination therapy for the treatment of breast cancer**. *Expert Opin Pharmacother* 2005;6(9):1555-64. Abstract

Pegram MD et al. **Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer.** *J Natl Cancer Inst* 2004;96(10):739-49. Abstract

Peoples GE et al. **Clinical trial results of a HER2/neu (E75) vaccine to prevent recurrence in high-risk breast cancer patients.** *J Clin Oncol* 2005;23(30):7536-45. Abstract

Perez EA et al. **Interim cardiac safety analysis of NCCTG N9831 Intergroup adjuvant trastuzumab trial.** *Proc ASCO* 2005;Abstract 556.

Perez EA et al. **NCCTG N9831: May 2005 update.** Presentation. ASCO 2005;Abstract 556.

Perez EA et al. **HER2 testing by local, central, and reference laboratories in the NCCTG N9831 Intergroup Adjuvant Trial.** *Proc ASCO* 2004;Abstract 567.

Perez EA, Rodeheffer R. **Clinical cardiac tolerability of trastuzumab.** *J Clin Oncol* 2004;22(2):322-9. Abstract

Piccart-Gebhart MJ. **First results of the HERA trial.** Presentation. ASCO 2005. No abstract available

Piccart-Gebhart MJ et al. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. Abstract

Press MF et al. **Diagnostic evaluation of HER-2 as a molecular target: An assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials.** *Clin Cancer Res* 2005;11(18):6598-607. Abstract

Romond EH et al. **Doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab as adjuvant therapy for patients with HER-2 positive operable breast cancer combined analysis of NSABP-B31/ NCCTG-N9831.** Presentation. ASCO 2005. No abstract available

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84. Abstract

Rueckert S et al. **A monoclonal antibody as an effective therapeutic agent in breast cancer: Trastuzumab.** *Expert Opin Biol Ther* 2005;5(6):853-66. Abstract

Schmidt M et al. **Long-term prognostic significance of HER-2/neu in untreated node-negative breast cancer depends on the method of testing.** *Breast Cancer Res* 2005;7(2):R256-66. Abstract

Seidman A et al. **Cardiac dysfunction in the trastuzumab clinical trials experience.** *J Clin Oncol* 2002;20(5):1215-21. Abstract

Spector N et al. **The ErbB2 pathway in breast cancer: Best approaches for maximum efficacy.** *Breast Cancer Res Treat* 2004;Abstract MS3-4.

Spicer J et al. **Adjuvant trastuzumab for HER2-positive breast cancer.** *Lancet* 2005;366(9486):634. No abstract available

Tan-Chiu E et al. **Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.** *J Clin Oncol* 2005;23(31):7811-9. Abstract

Tripathy D. **Targeted therapies in breast cancer.** *Breast J* 2005;11(Suppl 1):30-5. Abstract

Wakeling AE. **Inhibitors of growth factor signalling.** *Endocr Relat Cancer* 2005;12(Suppl 1):183-7. Abstract

Willems A et al. **Antibody therapy for breast cancer.** *Anticancer Res* 2005;25(3A):1483-9. Abstract

Yamaguchi Y et al. **HER2-specific cytotoxic activity of lymphokine-activated killer cells in the presence of trastuzumab.** *Anticancer Res* 2005;25(2A):827-32. Abstract

FIGURE 45

Chemotherapy for Metastatic Disease: Prior Adjuvant AC

- *ER-negative/PR-negative, HER2-negative*
- ***Adjuvant AC 2 years ago***
- *Bone and lung mets, minimal symptoms*

What would your first-line treatment for this patient be?

	Age 40 (premenopausal)		Age 57		Age 75	
Paclitaxel once a week	45% (39%)*	14% (10%)	43% (34%)	16% (10%)	40% (25%)	16% (6%)
Docetaxel once a week	7% (7%)	18% (10%)	9% (7%)	22% (12%)	2% (2%)	28% (4%)
Docetaxel q3wk	16% (9%)	20% (6%)	16% (9%)	18% (6%)	—	8% (2%)
Nanoparticle paclitaxel	—	2% (2%)	—	2% (2%)	2%	4%
Capecitabine	16% (4%)	8% (2%)	18% (4%)	10% (4%)	48% (7%)	24% (10%)
Gemcitabine	—	—	—	2% (2%)	—	4% (2%)
Vinorelbine	—	—	—	—	2% (2%)	4%
XT [capecitabine + docetaxel]	4% (4%)	10%	2% (2%)	8%	2%	—
GT [gemcitabine + docetaxel]	4% (4%)	8% (2%)	4% (4%)	4%	—	2%
Carboplatin + docetaxel	2%	4% (2%)	2%	8% (2%)	2%	2%
Carboplatin + paclitaxel	4%	2% (2%)	4%	2% (2%)	—	2%
AC	—	8% (2%)	—	6%	—	—
Other chemotherapy	2% (2%)	6%	2% (2%)	2%	2% (2%)	2%
No chemotherapy	—	—	—	—	—	4%
Would you recommend bevacizumab for this patient?						
Yes	69%	38%	62%	40%	38%	24%

* ***Note:*** Numbers in parentheses are percentage of physicians who use this chemotherapy combined with bevacizumab.

Chemotherapy for metastatic disease

Breast Cancer Update 2005 (1)

DR JOANNE L BLUM: I decide whether a patient should receive combination chemotherapy or sequential single agents based on the burden and pace of the disease. For example, women with quite a bit of visceral involvement — particularly liver involvement — may need combination therapy. For the patient with much more indolent disease, particularly the patient with a long disease-free interval who may have had sequential hormonal therapy and is now hormone therapy refractory, I use sequential single agents.

Many of my patients receive capecitabine as the first chemotherapy in this situation because it's orally administered, does not cause alopecia and is extremely well tolerated. It is similar to taking a hormone pill.

Breast Cancer Update 2005 (5)

DR NANCY E DAVIDSON: Many times in metastatic disease, we use all of the available therapies, so what we're really deciding on is the order — what to start with. Many patients make that decision based on their personal values.

I find many of my older patients are attracted to capecitabine because it is an oral agent. Some of my younger patients think of intravenous therapy as more aggressive, and they prefer that strategy. However, this perception is based on gut reaction rather than reality. I am a big fan of capecitabine. Maybe it comes from being a "hormonal therapy person" who prefers pills to begin with because I

FIGURE 46

Chemotherapy for Metastatic Disease: No Prior Therapy

- *ER-negative/PR-negative, HER2-negative*
- ***No prior systemic therapy***
- *Bone and lung mets, minimal symptoms*

What would your first-line treatment for this patient be?

	Age 40 (premenopausal)		Age 57		Age 75	
Paclitaxel once a week	42% (34%)*	14% (12%)	40% (34%)	14% (12%)	41% (22%)	12% (4%)
Docetaxel once a week	2% (2%)	12% (8%)	5% (2%)	12% (6%)	—	16% (2%)
Docetaxel q3wk	7% (5%)	10% (4%)	7% (5%)	12% (6%)	2% (2%)	8% (4%)
Nanoparticle paclitaxel	—	—	—	—	2%	10%
Capecitabine	14% (5%)	12% (2%)	16% (5%)	14% (4%)	38% (6%)	26% (6%)
Gemcitabine	—	—	—	2% (2%)	—	4% (2%)
Vinorelbine	—	—	—	—	2% (2%)	4%
XT [capecitabine + docetaxel]	5% (5%)	6%	2% (2%)	4% (2%)	—	2%
GT [gemcitabine + docetaxel]	2% (2%)	4%	2% (2%)	4%	—	—
Carboplatin + docetaxel	2%	2%	2%	2%	2%	2%
Carboplatin + paclitaxel	5% (2%)	—	5% (2%)	—	—	—
AC	7% (2%)	22% (4%)	9%	18%	2%	8%
AC + docetaxel	7% (5%)	8%	5% (2%)	12%	—	—
AC + paclitaxel	—	8% (2%)	—	6% (2%)	2% (2%)	2% (2%)
Doxorubicin (Doxil)	2% (2%)	—	2% (2%)	—	5% (2%)	2%
Other chemotherapy	5%	2%	5%	—	4%	2%
No chemotherapy	—	—	—	—	—	2%
Would you recommend bevacizumab for this patient in your first-line treatment?						
Yes	64%	32%	56%	34%	36%	20%

* ***Note:*** Numbers in parentheses are percentage of physicians who use this chemotherapy combined with bevacizumab.

use capecitabine a lot for salvage chemotherapy in women who've already had an anthracycline and a taxane for metastatic disease.

In oncology, we tend to remember our successes, but I have seen several impressive responses with capecitabine in dire circumstances. I have had women on capecitabine for a considerable period of time with relatively good quality of life.

Breast Cancer Update 2005 (2)

DR DICKLER: Positive data exist for several combinations, including capecitabine/docetaxel and paclitaxel/gemcitabine. The doxorubicin/docetaxel combination improved response rate but didn't improve overall survival, and George Sledge demonstrated that sequential therapy was as good as combination treatment in terms of overall survival, so I tend to use sequential single agents for the vast majority of my patients.

In a patient who is chemotherapy naïve and needs a rapid response, I would consider an anthracycline-based combination regimen. It would probably be doxorubicin/docetaxel, but it could also be doxorubicin/paclitaxel. If a patient had dose-dense AC/paclitaxel in the adjuvant setting, I'd be very interested in incorporating a gemcit-

FIGURE 47

Chemotherapy after Adjuvant AC-Paclitaxel: One Year Prior

- *ER-negative/PR-negative, HER2-negative*
- ***Adjuvant AC-paclitaxel 1 year ago***
- *Bone and lung mets, minimal symptoms*

What would your first-line treatment for this patient be?

	Age 40 (premenopausal)		Age 57		Age 75	
Paclitaxel once a week	11% (11%)*	8% (8%)	12% (11%)	8% (8%)	17% (8%)	2% (2%)
Docetaxel once a week	—	16% (12%)	2% (2%)	16% (12%)	2% (2%)	16% (4%)
Docetaxel q3wk	7% (2%)	14% (6%)	7% (2%)	14% (6%)	2%	8% (4%)
Nanoparticle paclitaxel	7% (2%)	6% (2%)	4% (2%)	6% (2%)	—	6% (2%)
Capecitabine	53% (23%)	18% (4%)	55% (23%)	18% (4%)	67% (17%)	42% (6%)
Gemcitabine	—	6%	—	6%	—	6% (2%)
Vinorelbine	2% (2%)	—	2% (2%)	—	2% (2%)	6%
XT [capecitabine + docetaxel]	2% (2%)	10% (2%)	—	10% (2%)	2%	2%
GT [gemcitabine + paclitaxel]	—	6% (4%)	—	4% (2%)	—	2%
GT [gemcitabine + docetaxel]	7% (7%)	4%	7% (7%)	6% (2%)	—	2%
Carboplatin + docetaxel	2%	6%	2%	6%	2%	6%
Carboplatin + paclitaxel	5%	2%	5%	2%	—	—
AC + docetaxel	2% (2%)	—	2% (2%)	—	2%	—
Other chemotherapy	2% (2%)	4% (2%)	2% (2%)	4% (2%)	2% (2%)	—
No chemotherapy	—	—	—	—	2%	2%
Would you recommend bevacizumab for this patient in your first-line treatment?						
Yes	53%	40%	53%	40%	31%	20%

** **Note:** Numbers in parentheses are percentage of physicians who use this chemotherapy combined with bevacizumab.*

abine-based combination or a capecitabine-based combination.

I use a lot of capecitabine. I believe it's a great drug and is generally well tolerated when given at nonpackage-insert doses. For the patient who's had adjuvant AC → T, I frequently use capecitabine or vinorelbine as first-line therapy. For someone who's chemotherapy-naïve, my first choice would probably be weekly paclitaxel followed by either vinorelbine or capecitabine. I don't use early-line doxorubicin up front very often in my asymptomatic patients, because I think it causes a lot of fatigue and alopecia. Weekly paclitaxel also results in alopecia, but I prefer to use weekly paclitaxel more than doxorubicin in the metastatic setting.

Breast Cancer Update 2005 (5)

DR TRIPATHY: When we have many chemotherapy drugs that, as single agents, provide response rates that overlap with each other, it shouldn't be looked at as a conundrum but rather as an opportunity to individualize therapy based on the side-effect profiles. I'm starting to use drugs with less toxicity first, because we generally see the longest duration of response with the drug we use first. We might as well have that long period of time be the one with the least toxicity. Utilizing an agent that does not result in hair loss should be considered, if that's important to the patient. Or, in the patient with pre-existing neuropathy from diabetes or prior chemotherapy, avoidance of an agent with neurotoxicity is important.

For me, the single most important factor is what treatment the patient

FIGURE 48

Chemotherapy after Adjuvant AC-Paclitaxel: Five Years Prior

- *ER-negative/PR-negative, HER2-negative*
- *Adjuvant AC-paclitaxel **5 years ago***
- *Bone and lung mets, minimal symptoms*

What would your first-line treatment for this patient be?

	Age 40 (premenopausal)		Age 57		Age 75	
Paclitaxel once a week	28% (24%)*	14% (12%)	28% (24%)	14% (12%)	28% (16%)	12% (2%)
Docetaxel once a week	—	14% (8%)	—	16% (8%)	—	20% (4%)
Docetaxel q3wk	5% (2%)	12% (4%)	5%	12% (4%)	—	4% (4%)
Nanoparticle paclitaxel	7% (2%)	6%	4% (2%)	6%	5% (2%)	6%
Capecitabine	28% (14%)	14% (4%)	30% (14%)	14% (4%)	52% (9%)	34% (8%)
Gemcitabine	—	2%	—	2%	—	4% (2%)
Vinorelbine	5% (4%)	2%	5% (4%)	2%	5% (5%)	8%
XT [capecitabine + docetaxel]	5% (4%)	8% (2%)	5% (4%)	6% (2%)	2%	2%
GT [gemcitabine + paclitaxel]	—	6% (2%)	—	6%	—	—
GT [gemcitabine + docetaxel]	5% (4%)	4%	5% (4%)	4%	—	2%
Carboplatin + docetaxel	4%	8%	5%	8% (2%)	2%	4%
Carboplatin + paclitaxel	7% (2%)	—	7% (2%)	—	2% (2%)	—
AC	2%	4%	2%	4%	—	—
AC + docetaxel	—	4% (2%)	—	4% (2%)	—	—
AC + paclitaxel	—	2%	—	2%	—	2%
Other chemotherapy	2% (2%)	—	2% (2%)	—	2% (2%)	—
No chemotherapy	2%	—	2%	—	2%	2%
Would you recommend bevacizumab for this patient in your first-line treatment?						
Yes	58%	34%	56%	34%	36%	20%

* ***Note:*** Numbers in parentheses are percentage of physicians who use this chemotherapy combined with bevacizumab.

has previously received. If a patient has progressed on an adjuvant taxane, I'm more likely to use a nontaxane drug. Although, granted, you can see responses to docetaxel and nanoparticle albumin-bound (*nab*) paclitaxel upon progression with the original paclitaxel formulation.

I usually consider patients progressing after AC and a taxane as being anthracycline and taxane refractory, but if a long period has passed (ie, two or more years) since the adjuvant therapy, one could certainly retry a taxane. Nanoparticle paclitaxel or a weekly regimen of the original paclitaxel formulation would be attractive choices. However, I'm generally treating these patients as anthracycline and taxane refractory, and I'm using capecitabine. Not only is capecitabine FDA approved for that indication, it seems to have among the higher response rates in the anthracycline- and taxane-refractory group of patients. Alternatives to capecitabine would include vinorelbine and gemcitabine. I believe combinations of these drugs are also something to consider.

We're so geared toward thinking of single agents, but combinations do have a role, particularly for more symptomatic patients. It's hard to know which combination wins out. Data

FIGURE 49

Use of Taxanes after Adjuvant AC

In general, in the nonprotocol setting for a patient who receives adjuvant AC, who has disease recurrence and in whom you want to utilize a single agent taxane, which of the following best describes which agent and schedule you would most likely use?

Paclitaxel qwk	54%	26%
Paclitaxel q3wk	2%	4%
Docetaxel qwk	16%	44%
Docetaxel q3wk	20%	20%
Nanoparticle paclitaxel qwk	4%	—
Nanoparticle paclitaxel q3wk	4%	6%

FIGURE 50

Clinical Use of Nanoparticle Paclitaxel

In what situations, if any, would you consider using nanoparticle paclitaxel in the metastatic setting?

Brittle diabetic or other person you want to avoid use of steroids	78%	64%
Previous hypersensitivity to paclitaxel/docetaxel	78%	66%
None	11%	6%

exist on combinations of vinorelbine/capecitabine, gemcitabine/vinorelbine and gemcitabine/capecitabine.

Clinical use of bevacizumab: Implications of the results from E2100

Breast Cancer Update 2005 (6)

DR SLEDGE: Bevacizumab ought to be considered for use along with taxane-based therapy as front-line therapy for patients with metastatic breast cancer. I certainly would not argue with those who suggest we need safety data for bevacizumab in combination with docetaxel or *nab* paclitaxel. However, much of our preclinical testing was with docetaxel, and I would expect docetaxel to work well with bevacizumab.

I would not be surprised if nanoparticle taxane therapy would also work well. In fact, the nanoparticle taxanes have — as a possible mechanism of action — an effect on endothelial cells. We might see some synergistic activity there also. I'm not aware of any safety data for *nab* paclitaxel in combination with bevacizumab, but I suspect it would be safe. I would not have a problem with someone using the combination, and I would not expect any unusual toxicity.

Breast Cancer Update 2005 (7)

DR WINER: I believe the results of ECOG-E2100 are impressive enough that, in the absence of a contraindication to bevacizumab, I would use it in a first-line setting, optimally in combination with paclitaxel as administered in the study. I doubt that the interaction is specific between paclitaxel and bevacizumab, although I'm well aware that when given with capecitabine in more advanced disease, bevacizumab seemed to be less active. However, I believe that's probably related to the setting rather than the drug.

Nanoparticle paclitaxel compared to other taxanes

J Clin Oncol 2005

The superior efficacy, favorable safety profile, and greater patient convenience of ABI-007 [nanoparticle paclitaxel] make this novel albumin-bound paclitaxel 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.

— *William J Gradishar, MD et al.* J Clin Oncol *2005;23(31);7794-803.*

Breast Cancer Update 2005 (1)

DR BLUM: 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 asthenia, fluid retention and neutropenia, and it's difficult to administer for long periods of time.

One can give 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 would use nanoparticle paclitaxel in lieu of weekly paclitaxel. I would like to see more data on combinations with nanoparticle paclitaxel to learn more about the toxicity profiles before using it in a combination off protocol.

Breast Cancer Update 2005 (5)

DR TRIPATHY: A weekly regimen of the original paclitaxel formulation would have been my choice in the past. Now that we have data with *nab* paclitaxel,

FIGURE 51

Reasons for Not Using Nanoparticle Paclitaxel

If you have not used nanoparticle paclitaxel in breast cancer, which of the following reasons apply?

Lack of familiarity	4%	19%
Lack of clinical data	—	13%
Don't believe clinical advantage vs paclitaxel/docetaxel	11%	19%
No appropriate patients	11%	44%
Reimbursement issues	9%	25%
I intend to use but have not used to date	13%	31%
Other	4%	6%

FIGURE 52

Schedule of Nanoparticle Paclitaxel

Which of the following schedules would you generally use for nanoparticle paclitaxel?

Weekly	42%	44%
Every 3 weeks	40%	62%

FIGURE 53

Potential Advantages to Nanoparticle Paclitaxel

Relative to docetaxel and paclitaxel, how much of a benefit is each of the following properties of nanoparticle paclitaxel?

	Reduction of infusion time required		Avoidance of steroid premedication	
Significant benefit	37%	32%	55%	36%
Somewhat of a benefit	56%	52%	43%	56%
No benefit	7%	16%	2%	8%

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 also seems 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.

Phase III trial of docetaxel versus paclitaxel

J Clin Oncol 2005

This is the first clinical trial to compare directly the taxanes docetaxel and paclitaxel as monotherapy for patients with advanced breast cancer. Using US Food and Drug Administration-approved doses and schedules for each agent, this Phase III study has demonstrated that docetaxel is superior to paclitaxel in TTP (5.7 vs 3.6 months; p <.0001), response duration (7.5 vs 4.6 months; p = .01), and OS (15.4 vs 12.7 months; p = .03). The overall response rate was also greater with docetaxel (32% vs 25%; p = .10). The survival advantage for docetaxel was observed despite the increased incidence of toxicities leading to dose reductions and treatment withdrawal, and the slightly greater use of salvage treatment in patients randomly assigned to paclitaxel. The results of this study are consistent with those reported for previous Phase III studies of single-agent docetaxel and paclitaxel...

— Stephen E Jones, MD et al. J Clin Oncol *2005;23(24):5542-51.*

Dosing of bevacizumab

Breast Cancer Update 2005 (6)

DR SLEDGE: The dose we choose is based on our Phase I/II dosing in patients with breast cancer. Colon and lung cancer had different paths based on randomized Phase II trials conducted in those diseases. I don't know what represents the right dose of bevacizumab.

We know 20 mg/kg is too much because of the dose-limiting toxicity of migraines. In the Phase I trials, once we got past approximately one mg/kg, all circulating, free VEGF was bound. So somewhere in between one and 20 mg/kg is the right dose. We used 10 mg/kg in E2100. In the Phase I/II breast cancer trial, we looked at doses of three mg/kg, 10 mg/kg and 20 mg/kg. Even though the numbers were small, we had a sense that when we went from three to 10 mg/kg, the responses were more brisk, and we saw relatively more patient benefit.

FIGURE 54

Impressions of Nanoparticle Paclitaxel

What is your clinical impression (or your impression based on information you have heard or read) of the side effects and tolerability of nanoparticle paclitaxel compared to paclitaxel?

Nanoparticle paclitaxel significantly better than paclitaxel	9%	29%
Somewhat better than paclitaxel	69%	62%
Equal to paclitaxel	20%	9%
Somewhat worse than paclitaxel	2%	—
Significantly worse than paclitaxel	—	—

What is your clinical impression (or your impression based on information you have heard or read) of the efficacy (antitumor effect) of nanoparticle paclitaxel compared to paclitaxel?

Nanoparticle paclitaxel significantly better than paclitaxel	11%	12%
Somewhat better than paclitaxel	48%	41%
Equal to paclitaxel	39%	47%
Somewhat worse than paclitaxel	2%	—
Significantly worse than paclitaxel	—	—

What is your clinical impression (or your impression based on information you have heard or read) of the side effects and tolerability of nanoparticle paclitaxel compared to docetaxel?

Nanoparticle paclitaxel significantly better than docetaxel	23%	12%
Somewhat better than docetaxel	61%	67%
Equal to docetaxel	14%	21%
Somewhat worse than docetaxel	2%	—
Significantly worse than docetaxel	—	—

What is your clinical impression (or your impression based on information you have heard or read) of the efficacy (antitumor effect) of nanoparticle paclitaxel compared to docetaxel?

Nanoparticle paclitaxel significantly better than docetaxel	—	—
Somewhat better than docetaxel	22%	24%
Equal to docetaxel	67%	73%
Somewhat worse than docetaxel	11%	3%
Significantly worse than docetaxel	—	—

FIGURE 55

Clinical Use of Bevacizumab

Have you used bevacizumab for breast cancer?

Yes	73%	4%
No, but intend to use in near future	18%	64%
No, and have no immediate intention to use	9%	32%

FIGURE 56

Reasons for Not Using Bevacizumab

If you have not yet used bevacizumab, why?

Lack of familiarity	—	8%
Lack of clinical data	13%	19%
Not FDA approved	18%	56%
No appropriate patients	NA	21%
Reimbursement issues	27%	48%
I intend to use but have not used to date	13%	13%

FIGURE 57

Dosing, Scheduling and Duration of Bevacizumab

If you have used this agent, which dosage schedules do you generally use?

5 mg/kg q2wk	5%	—
5 mg/kg q3wk	5%	—
7.5 mg/kg q3wk	8%	—
10 mg/kg q2wk	55%	100%
10 mg/kg q3wk	8%	—
15 mg/kg q2wk	5%	—
15 mg/kg q3wk	11%	—
Other	3%	—

If you have used this agent, how long do you generally use it?

Until disease progression	81%	77%
Beyond disease progression	14%	21%
Other	5%	2%

SELECT PUBLICATIONS

Ahn J et al. **Phase II study of gemcitabine and capecitabine in patients with metastatic breast cancer pretreated with anthracyclines and taxanes.** *Proc ASCO* 2005;Abstract 895.

Alba E et al; Spanish Breast Cancer Research Group. **Multicenter randomized trial comparing sequential with concomitant administration of doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: A Spanish Breast Cancer Research Group (GEICAM-9903) phase III study.** *J Clin Oncol* 2004;22(13):2587-93. Abstract

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

Andres R et al. **Gemcitabine/capecitabine in patients with metastatic breast cancer pretreated with anthracyclines and taxanes.** *Clin Breast Cancer* 2005;6(2):158-62. Abstract

Bajetta E et al. **Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women.** *J Clin Oncol* 2005;23(10):2155-61. Abstract

Baweja M et al. **Phase II trial of oral vinorelbine for treatment of metastatic breast cancer in women 65 years and older: N003A.** *Proc ASCO* 2005;Abstract 740.

Bayo J et al. **Docetaxel followed by capecitabine as first-line chemotherapy in metastatic breast cancer patients: Preliminary results.** *Proc ASCO* 2005;Abstract 854.

Berruti A et al. **Paclitaxel, vinorelbine and 5-fluorouracil in breast cancer patients pretreated with adjuvant anthracyclines.** *Br J Cancer* 2005;92(4):634-8. Abstract

Biganzoli L et al. **Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial.** *J Clin Oncol* 2002;20(14):3114-21. Abstract

Blum JL et al. **A Phase II trial of combination therapy with capecitabine (C) and weekly paclitaxel (P) for metastatic breast cancer (MBC): Preliminary results in taxane-naive patients.** Poster presentation. San Antonio Breast Cancer Symposium 2004;Abstract 5053.

Blum JL et al. **ABI-007 nanoparticle paclitaxel: Demonstration of anti-tumor activity in taxane-refractory metastatic breast cancer.** *Proc ASCO* 2003;Abstract 64.

Bontenbal M et al. **Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: Results of a Dutch Community Setting Trial for the Clinical Trial Group of the Comprehensive Cancer Centre.** *J Clin Oncol* 2005;23(28):7081-8. Abstract

Bria E et al. **Impact of taxanes in association with anthracyclines in 1st line chemotherapy for**

metastatic breast cancer (MBC): Comprehensive review of 2805 patients in 7 phase III trials. *Proc ASCO* 2004;Abstract 659.

Chan S et al. **Gemcitabine plus docetaxel (GD) versus capecitabine plus docetaxel (CD) for anthracycline-pretreated metastatic breast cancer (MBC) patients (pts): Results of a European phase III study.** *Proc ASCO* 2005;Abstract 581.

Chun JH et al. **Frontline docetaxel (T)/capecitabine (X) combination therapy in patients (pts) with metastatic breast cancer (MBC): A phase II study.** *Proc ASCO* 2004;Abstract 778.

Clemons MJ et al. **Palliative chemotherapy with vinorelbine or capecitabine in women with anthracycline and taxane refractory metastatic breast cancer.** *Proc ASCO* 2004;Abstract 773.

Estevez LG et al. **Phase II study with the combination of capecitabine (C) and vinorelbine (V) in metastatic breast cancer (MBC) previously treated with anthracyclines and taxanes.** *Proc ASCO* 2004;Abstract 748.

Evans TR et al. **Phase III randomized trial of doxorubicin and docetaxel versus doxorubicin and cyclophosphamide as primary medical therapy in women with breast cancer: An anglo-celtic cooperative oncology group study.** *J Clin Oncol* 2005;23(13):2988-95. Abstract

Feher O et al. **First-line gemcitabine versus epirubicin in postmenopausal women aged 60 or older with metastatic breast cancer: A multicenter, randomized, phase III study.** *Ann Oncol* 2005;16(6):899-908. Abstract

Ghosn M et al. **Vinorelbine (N)-capecitabine (C) combination in advanced breast cancer (ABC): Long-term results of two multicentric phase II trials.** *Proc ASCO* 2005;Abstract 673.

Gradishar WJ et al. **Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer.** *J Clin Oncol* 2005;23(31):7794-7803. Abstract

Gradishar WJ et al. **Capecitabine plus paclitaxel as front-line combination therapy for metastatic breast cancer: A multicenter phase II study.** *J Clin Oncol* 2004;22(12):2321-7. Abstract

Gralow J et al. **SWOG S0102: A phase II study of docetaxel (DOC) and vinorelbine (VNR) + filgrastim for HER-2 negative, stage IV breast cancer.** *Proc ASCO* 2005;Abstract 567.

Grecea D et al. **A phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer.** *Proc ASCO* 2005;Abstract 736.

Ibrahim NK et al. **Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer.** *J Clin Oncol* 2005;23(25):6019-26. Abstract

Jones SE et al. **Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer.** *J Clin Oncol* 2005;23(24):5542-51. Abstract

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

Katsumata N et al. **Phase III trial of doxorubicin (A)/cyclophosphamide (C) (AC), docetaxel (D), and alternating AC and D (AC-D) as front-line chemotherapy for metastatic breast cancer (MBC): Japan Clinical Oncology Group trial (JCOG9802).** *Proc ASCO* 2005;Abstract 521.

Lim H et al. **A phase II study of docetaxel (T) and capecitabine (X) combination chemotherapy as first-line chemotherapy for patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2005;Abstract 889.

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. *Proc ASCO* 2005. No abstract available

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005;23(4):792-9. Abstract

Minea LN et al. **Capecitabine monotherapy for elderly patients with metastatic breast cancer.** *Proc ASCO* 2004;Abstract 797.

Moinpour C et al. **Gemcitabine plus paclitaxel (GT) versus paclitaxel (T) as first-line treatment for anthracycline pre-treated metastatic breast cancer (MBC): Quality of life (QoL) and pain palliation results from the global phase III study.** *Proc ASCO* 2004;Abstract 621.

Moulder SL et al. **Results of a planned efficacy and safety analysis for a National Comprehensive Cancer Network sponsored phase II study of gemcitabine and irinotecan (GI) in metastatic breast cancer (MBC).** *Proc ASCO* 2005;Abstract 679.

Nabholtz JM et al; TAX 306 Study Group. **Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: Results of a randomized, multicenter, phase III trial.** *J Clin Oncol* 2003;21(6):968-75. Abstract

Nole F et al. **Dose finding and pharmacokinetic study of an all-oral combination regimen of oral vinorelbine and capecitabine in metastatic breast cancer (MBC) patients: Final results.** *Proc ASCO* 2005;Abstract 666.

O'Shaughnessy JA et al. **Weekly nanoparticle albumin paclitaxel (Abraxane) results in longterm disease control in patients with taxane-refractory metastatic breast cancer.** San Antonio Breast Cancer Symposium 2004;Abstract 1070.

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

Paley M et al. **Preferences for oral and parenteral antitumor therapy: A survey of 260 patients with metastatic breast cancer.** *Proc ASCO* 2005;Abstract 619.

Palmeri S et al. **Weekly docetaxel and gemcitabine as first-line treatment for metastatic breast cancer: Results of a multicenter phase II study.** *Oncology* 2005;68(4-6):438-45. Abstract

Perez EA et al. **A phase II trial of docetaxel and carboplatin as first-line chemotherapy for metastatic breast cancer: NCCTG study N9932.** *Oncology* 2005;69(2):117-21. Abstract

Pierga JY et al; Cooperative Group of the French capecitabine compassionate use program. **Efficacy and safety of single agent capecitabine in pretreated metastatic breast cancer patients from the French compassionate use program.** *Breast Cancer Res Treat* 2004;88(2):117-29. Abstract

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

Segalla JGM et al. **Effect of capecitabine (X) on quality of life (QoL) in patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2004;Abstract 8130.

Seidman AD et al. **CALGB 9840: Phase III study of weekly (W) paclitaxel (P) via 1-hour(h) infusion versus standard (S) 3h infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC.** *Proc ASCO* 2004;Abstract 512.

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

Sikov WM et al. **Gemcitabine and capecitabine in metastatic breast cancer (MBC): A Brown University Oncology Group (BrUOG) phase II study.** *Proc ASCO* 2005;Abstract 785.

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

Stemmler J et al. **High efficacy and low toxicity of weekly docetaxel given as first-line treatment for metastatic breast cancer.** *Oncology* 2005;68(1):71-8. Abstract

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

Tong DK et al. **Phase II study of an 'all-oral' regimen of capecitabine, idarubicin and cyclophosphamide for metastatic breast cancer — Safety, efficacy and quality of life.** *Oncology* 2005;68(4-6):520-5. Abstract

Vukelja S et al. **Activity of oral irinotecan (IRI) in metastatic breast cancer (MBC) patients after prior anthracycline, taxane and capecitabine: Phase 2 study results.** *Proc ASCO* 2005;Abstract 562.

Winer EP et al. **Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: Cancer and leukemia group B trial 9342.** *J Clin Oncol* 2004;22(11):2061-8. Abstract

Zamora P et al. **Capecitabine (X) as single agent in elderly patients (p) with metastatic breast cancer (MBC).** *Proc ASCO* 2005;Abstract 843.

Zielinski C et al. **Gemcitabine, epirubicin, and paclitaxel versus fluorouracil, epirubicin, and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: A Central European Cooperative Oncology Group International, multicenter, prospective, randomized phase III trial.** *J Clin Oncol* 2005;23(7):1401-8. Abstract

FIGURE 58

Hormone Therapy after Progression on Adjuvant Tamoxifen

- *ER-positive/PR-positive, HER2-negative*
- ***On adjuvant tamoxifen for 4 years***
- *Bone and lung mets, minimal symptoms*

What would your first-line treatment for this patient be?

	Age 40 (premenopausal)		Age 57		Age 75	
Chemotherapy alone	4%	16%	2%	4%	—	2%
Chemotherapy plus endocrine therapy	7%	28%	2%	26%	—	16%
Endocrine therapy alone	89%	56%	94%	70%	100%	80%
No therapy	—	—	2%	—	—	2%
If any endocrine therapy used, which agent?						
Anastrozole	—	19%	22%	65%	25%	63%
Exemestane	—	2%	7%	2%	9%	6%
Letrozole	3%	7%	69%	31%	66%	31%
Tamoxifen	—	5%	—	—	—	—
Fulvestrant	—	10%	2%	2%	—	—
Aromatase inhibitor + LHRH agonist or ovarian ablation	69%	31%				
Tamoxifen + LHRH agonist or ovarian ablation	3%	2%				
LHRH agonist or ovarian ablation	25%	22%				
Other endocrine therapy	—	2%	—	—	—	—
Would you recommend bevacizumab for this patient in your first-line treatment?						
Yes	11%	16%	2%	14%	—	8%
If any chemotherapy were used, would you use this chemotherapy until progression, through a specific number of cycles or only until symptom improvement and then hormones?						
Until progression	60%	50%	100%	40%	—	44%
Specific number of cycles	40%	32%	—	40%	—	44%
Only until symptom and/or objective improvement	—	18%	—	20%	—	12%

Optimal sequencing of agents in postmenopausal patients

Breast Cancer Update 2005 (4)

DR GRADISHAR: 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 that comes up is whether one sequence enhances patient outcome more than another. This becomes important

■ BREAST CANCER SPECIALISTS ☐ GENERAL ONCOLOGISTS

FIGURE 59

Hormone Therapy after Adjuvant Tamoxifen: One Year Prior

- *ER-positive/PR-positive, HER2-negative*
- ***Completed 5 years of adjuvant tamoxifen 1 year ago***
- *Bone and lung mets, minimal symptoms*

What would your first-line treatment for this patient be?

	Age 40 (premenopausal)		Age 57		Age 75	
Chemotherapy alone	7%	20%	2%	6%	—	2%
Chemotherapy plus endocrine therapy	5%	26%	2%	22%	—	16%
Endocrine therapy alone	88%	54%	94%	72%	98%	82%
No therapy	—	—	2%	—	2%	—
If any endocrine therapy used, which agent?						
Anastrozole	—	17%	24%	60%	26%	57%
Exemestane	—	—	7%	—	9%	2%
Letrozole	3%	10%	69%	34%	65%	37%
Tamoxifen	—	—	—	2%	—	4%
Fulvestrant	—	7%	—	4%	—	—
Aromatase inhibitor + LHRH agonist or ovarian ablation	69%	35%				
Tamoxifen + LHRH agonist or ovarian ablation	8%	—				
LHRH agonist or ovarian ablation	20%	25%				
Other endocrine therapy	—	6%	—	—	—	—
Would you recommend bevacizumab for this patient in your first-line treatment?						
Yes	4%	14%	2%	8%	—	6%
If any chemotherapy used, would you use this chemotherapy until progression, through a specific number of cycles or only until symptom improvement and then hormones?						
Until progression	75%	48%	100%	36%	—	33%
Specific number of cycles	25%	30%	—	36%	—	45%
Only until symptom and/or objective improvement	—	22%	—	28%	—	22%

because if you can demonstrate that one sequence enhances the time to disease progression, it may be built on over time so 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 sequence 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

FIGURE 60

Hormone Therapy after Adjuvant Tamoxifen: Five Years Prior

- *ER-positive/PR-positive, HER2-negative*
- *Completed 5 years of adjuvant tamoxifen **5 years ago***
- *Bone and lung mets, minimal symptoms*

What would your first-line treatment for this patient be?

	Age 40 (premenopausal)		Age 57		Age 75	
Chemotherapy alone	5%	10%	—	2%	—	2%
Chemotherapy plus endocrine therapy	5%	24%	2%	24%	—	18%
Endocrine therapy alone	90%	66%	96%	74%	98%	80%
No therapy	—	—	2%	—	2%	—
If any endocrine therapy used, which agent?						
Anastrozole	—	9%	23%	55%	25%	57%
Exemestane	—	—	7%	—	9%	2%
Letrozole	3%	9%	66%	39%	62%	39%
Tamoxifen	3%	16%	2%	4%	2%	2%
Fulvestrant	—	4%	—	2%	—	—
Aromatase inhibitor + LHRH agonist or ovarian ablation	62%	31%				
Tamoxifen + LHRH agonist or ovarian ablation	5%	11%				
LHRH agonist or ovarian ablation	27%	20%				
Other endocrine therapy	—	—	2%	—	2%	—
Would you recommend bevacizumab for this patient in your first-line treatment?						
Yes	4%	12%	2%	10%	—	6%
If any chemotherapy used, would you use this chemotherapy until progression, through a specific number of cycles or only until symptom improvement and then hormones?						
Until progression	100%	42%	100%	38%	—	50%
Specific number of cycles	—	29%	—	38%	—	30%
Only until symptom and/or objective improvement	—	29%	—	24%	—	20%

expect the optimal response rate. Some strategies have evaluated quickly increasing serum levels of fulvestrant, including administering loading doses of 500 mg and within two weeks administering another 250 mg 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 consequently achieve a biologically relevant dose of drug circulating much faster.

Breast Cancer Update 2005 (9)

DR GABRIEL N HORTOBAGYI: 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

FIGURE 61

Hormone Therapy after Progression on Adjuvant Anastrozole

- *ER-positive/PR-positive, HER2-negative*
- ***On adjuvant anastrozole for 4 years***
- *Bone and lung mets, minimal symptoms*

What would your first-line treatment for this patient be?

	Age 57	Age 75
Chemotherapy alone	8%	8%
Chemotherapy plus endocrine therapy	24%	14%
Endocrine therapy alone	64%	76%
No therapy	4%	2%
If any endocrine therapy used, which agent?		
Exemestane	11%	13%
Letrozole	2%	9%
Tamoxifen	30%	27%
Fulvestrant	57%	51%
Would you recommend bevacizumab for this patient in your first-line treatment?		
Yes	10%	8%
If any chemotherapy used, would you use this chemotherapy until progression, through a specific number of cycles or only until symptom improvement and then hormones?		
Until progression	50%	55%
Specific number of cycles	37%	27%
Only until symptom and/or objective improvement	13%	18%

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 steady state 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 might not have revealed the true efficacy of fulvestrant. It showed fulvestrant to be at least as effective as anastrozole, but I expected it to be superior. We may need to repeat some of these studies with a more appropriate dosing schedule.

Breast Cancer Update 2004 (7)

DR ADAM M BRUFSKY: Most clinicians consider fulvestrant a third-line therapy for patients who have failed tamoxifen and an aromatase inhibitor; however, clinical trials have shown that fulvestrant is equivalent to anastrozole after tamoxifen failure and, in a recently published European study comparing front-line fulvestrant to tamoxifen, I did not view fulvestrant as inferior to tamoxifen.

I use third-line fulvestrant, but I also use it first line, particularly in women who can't afford an aromatase inhibitor. In addition, I would estimate that approximately 40 percent of my patients prefer a monthly injection to taking a pill every day.

Meet The Professors 2004 (2)

DR GERSHON LOCKER: The overall results of Trials 20 and 21 showed no significant difference between anastrozole and fulvestrant, but differences occurred in subset analyses.

The duration of response seemed to

FIGURE 62

Sequencing of Endocrine Therapy after Adjuvant Tamoxifen

*How do you normally sequence endocrine therapy in postmenopausal patients with metastases who completed **adjuvant tamoxifen one year previously?***

	1st-line	2nd-line	3rd-line	4th-line
Tamoxifen	4%	4%	10%	12%
Anastrozole	54%	8%	2%	—
Letrozole	38%	14%	—	—
Exemestane	4%	18%	34%	6%
Fulvestrant	—	54%	26%	10%
Megestrol acetate	—	—	12%	28%
High-dose estrogen	—	—	4%	—
Other	—	—	—	6%
No endocrine therapy	—	2%	12%	38%

FIGURE 63

Sequencing of Endocrine Therapy after Adjuvant Anastrozole

*How do you normally sequence endocrine therapy in postmenopausal patients with metastases who completed **adjuvant anastrozole one year previously?***

	1st-line	2nd-line	3rd-line	4th-line
Tamoxifen	38%	6%	14%	6%
Anastrozole	2%	—	—	2%
Letrozole	12%	12%	6%	4%
Exemestane	10%	22%	22%	6%
Fulvestrant	36%	36%	18%	2%
Megestrol acetate	2%	12%	12%	24%
High-dose estrogen	—	4%	—	2%
Other	—	—	2%	6%
No endocrine therapy	—	8%	26%	48%

be longer in patients who responded to fulvestrant, and patients who had visceral disease seemed to respond better than those who did not.

I think the takeaway message is that they're equally efficacious; however, there may be subsets of patients in whom you might prefer to use fulvestrant, particularly those for whom compliance may be an issue or those with visceral disease.

The other important point is that anecdotal studies argue that you can use one and switch to the other. Third-line aromatase inhibitors are efficacious after fulvestrant and vice versa.

Patterns of Care 2005 (1)

DR STEPHEN E JONES: Generally, patients are either going to relapse on tamoxifen or after adjuvant tamoxifen. In that setting as well as in the fulvestrant versus anastrozole clinical trials, evidence exists that a proportion of women have a longer response to fulvestrant than to anastrozole when given right after tamoxifen.

I've had patients with long responses to fulvestrant. I prefer fulvestrant to an aromatase inhibitor after tamoxifen because approximately 20 percent of

FIGURE 64

Use of a Loading Dose with Fulvestrant

When utilizing fulvestrant in the metastatic setting, do you generally use a loading dose?

Yes	53%	16%
No	47%	84%

FIGURE 65

Use of a Loading Dose with Fulvestrant

If you do not use a loading dose of fulvestrant, is reimbursement part of the reason?

No	79%	71%
Yes, it is part of the reason	13%	10%
Yes, it is the main reason	8%	19%

FIGURE 66

Use of Fulvestrant in Premenopausal Women

Which of the following best describes your utilization of fulvestrant in premenopausal patients with ER-positive metastatic disease in a non-protocol setting?

No, have not used	52%	74%
Yes, alone	16%	20%
Yes, but only with ovarian suppression/ablation	32%	6%

In how many women?

Mean	3	5

FIGURE 67

Patient Preferences for Method of Hormone Therapy Administration

What percentage of your patients with metastatic breast cancer would prefer to receive a monthly injection of fulvestrant rather than a daily oral endocrine agent like an aromatase inhibitor or tamoxifen?

Mean	22%	31%

patients have long responses with it in this setting. However, 99 percent of oncologists will choose an aromatase inhibitor after tamoxifen. Fulvestrant is generally being used as third line. Despite Trials 20 and 21, most physicians start with anastrozole rather than fulvestrant because of the way the data have been presented.

We are just beginning to see patients who have been treated with two or three years of adjuvant anastrozole and then relapsed. Currently, there is little data on treatment options in this setting. It's somewhat of a "dealer's choice" because there are no hard-and-fast rules. 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.

Breast Cancer Update 2005 (5)

DR TRIPATHY: 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. I think it's reasonable to use the drug — maybe not up front, but as second- or third-line therapy.

This is when you might consider the patient's preferences in terms of an intramuscular or an oral drug. A recent study of 261 women with metastatic breast cancer demonstrated that about one third preferred a monthly intramuscular injection. I've always assumed that oral drugs were preferable, if they were equally effective. Therefore, I was surprised to see that many patients preferred an intramuscular injection. I need to query my patients more when I start evaluating these options.

Patterns of Care 2005 (1)

DR HAROLD J BURSTEIN: Previously, patients received tamoxifen in the adjuvant setting, so we would use an aromatase inhibitor front line in the metastatic setting. Fulvestrant was used second line, or we could use megestrol acetate, but for many women fulvestrant has a more convenient side-effect profile. Now that more women receive aromatase inhibitors in the adjuvant setting, we're using tamoxifen or fulvestrant as first-line treatment in the metastatic setting.

Patterns of Care 2005 (1)

DR BLUM: In my experience, patients

tolerate the fulvestrant injections just fine. We have randomized data comparing fulvestrant versus anastrozole in patients who have already received tamoxifen, but the optimal sequence for using fulvestrant is still undetermined. In choosing between an aromatase inhibitor and fulvestrant, I ask my patients whether they prefer an injection or a pill. 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.

Breast Cancer Update 2004 (6)

DR DANIEL F HAYES: 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 because 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 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.

EFECT trial

Breast Cancer Update 2004 (6)

DR MITCHELL DOWSETT: EFECT is an American and 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 EFECT 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.

SELECT PUBLICATIONS

Abrial C et al. **Aromatase inhibitors and metastatic breast cancer survival.** *Proc ASCO* 2005;Abstract 767.

Bundred N. **Preclinical and clinical experience with fulvestrant (Faslodex) in postmenopausal women with hormone receptor-positive advanced breast cancer.** *Cancer Invest* 2005;23(2):173-81. Abstract

Buzdar AU. **Hormonal therapy in early and advanced breast cancer.** *Breast J* 2004;10(Suppl 1):19-21. Abstract

Buzdar AU et al. **The impact of hormone receptor status on the clinical efficacy of the new-generation aromatase inhibitors: A review of data from first-line metastatic disease trials in postmenopausal women.** *Breast J* 2004;10(3):211-7. Abstract

Cameron DA et al. **A comparative study of exemestane versus anastrozole in postmenopausal breast cancer subjects with visceral disease.** *Proc ASCO* 2004;Abstract 628.

Cardoso AA et al. **Fulvestrant after aromatase inhibitor failure: Results from the expanded access program in Rio de Janeiro, Brazil.** *Breast Cancer Res Treat* 2004;Abstract 6050.

Carlini P et al. **New aromatase inhibitors (AIs) as first-line endocrine therapy (ET) in metastatic breast cancer (MBC): A pooled analysis of 3238 women from 8 phase III trials.** *Proc ASCO* 2005;Abstract 602.

Carlson RW et al. **Goserelin plus anastrozole for the treatment of premenopausal women with hormone receptor positive, recurrent/metastatic breast cancer.** *Breast Cancer Res Treat* 2004;Abstract 6052.

Cheung K et al. **Goserelin plus anastrozole as first-line endocrine therapy for premenopausal women with oestrogen receptor (ER) positive advanced breast cancer (ABC).** *Proc ASCO* 2005;Abstract 731.

Come SE, Borges VF. **Role of fulvestrant in sequential hormonal therapy for advanced, hormone receptor-positive breast cancer in postmenopausal women.** *Clin Breast Cancer* 2005;6(Suppl 1):15-22. Abstract

Dixon JM. **Exemestane and aromatase inhibitors in the management of advanced breast cancer.** *Expert Opin Pharmacother* 2004;5(2):307-16. Abstract

Dodwell D, Vergote I. **A comparison of fulvestrant and the third-generation aromatase inhibitors in the second-line treatment of postmenopausal women with advanced breast cancer.** *Cancer Treat Rev* 2005;31(4):274-82. Abstract

Dodwell D, Vergote I. **Fulvestrant: A new, effective and well-tolerated second-line treatment option for postmenopausal women with advanced breast cancer.** *Breast Cancer Res Treat* 2004;Abstract 6051.

Dowsett M et al. **Biological characteristics of the pure antiestrogen fulvestrant: Overcoming endocrine resistance.** *Breast Cancer Res Treat* 2005;93(Suppl 4):11-8. Abstract

Ferrari L et al. **Could exemestane affect insulin-like growth factors, interleukin 6 and bone metabolism in postmenopausal advanced breast cancer patients after failure on aminoglutethimide, anastrozole or letrozole?** *Int J Oncol* 2003;22(5):1081-9. Abstract

Forward DP et al. **Clinical and endocrine data for goserelin plus anastrozole as second-line endocrine therapy for premenopausal advanced breast cancer.** *Br J Cancer* 2004;90(3):590-4. Abstract

Franco S et al. **Response to fulvestrant in heavily pretreated postmenopausal women: A single-center experience.** *Breast Cancer Res Treat* 2004;88(2):103-8. Abstract

Gradishar W. **Fulvestrant in the treatment of postmenopausal women with advanced breast cancer.** *Expert Rev Anticancer Ther* 2005;5(3):445-53. Abstract

Gralow JR. **Optimizing the treatment of metastatic breast cancer.** *Breast Cancer Res Treat* 2005;89(Suppl 1):9-15. Abstract

Gutteridge E et al. **Effects of fulvestrant on estrogen receptor levels during long-term treatment of patients with advanced breast cancer — Final results.** *Breast Cancer Res Treat* 2004;Abstract 4086.

Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *J Clin Oncol* 2004;22(9):1605-13. Abstract

Howell A et al. **A review of the efficacy of anastrozole in postmenopausal women with advanced breast cancer with visceral metastases.** *Breast Cancer Res Treat* 2003;82(3):215-22. Abstract

Howell A et al. **Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.** *J Clin Oncol* 2002;20(16):3396-403. Abstract

Iaffaioli RV et al. **Phase II study of sequential hormonal therapy with anastrozole/exemestane in advanced and metastatic breast cancer.** *Br J Cancer* 2005;92(9):1621-5. Abstract

Iaffaioli RV et al. **Preliminary data of GOIM 2107 study: Multicenter phase II study of sequential hormonotherapy with anastrozole/exemestane in metastatic breast disease.** *Proc ASCO* 2004;Abstract 820.

Ingle JN et al. **Evaluation of fulvestrant in women with advanced breast cancer and progression on prior aromatase inhibitor therapy: A phase II trial of the North Central Cancer Treatment Group.** *Breast Cancer Res Treat* 2004;Abstract 409.

Ingle JN. **Sequencing of endocrine therapy in postmenopausal women with advanced breast cancer.** *Clin Cancer Res* 2004;10(1 Pt 2):362-7. Abstract

Ingle JN, Suman VJ. **Aromatase inhibitors for therapy of advanced breast cancer.** *J Steroid Biochem Mol Biol* 2005;95(1-5):113-9. Abstract

Irish W et al. **Quality-adjusted survival in a crossover trial of letrozole versus tamoxifen in postmenopausal women with advanced breast cancer.** *Ann Oncol* 2005;16(9):1458-62. Abstract

Johnston S. **Fulvestrant and the sequential endocrine cascade for advanced breast cancer.** *Br J Cancer* 2004;90(Suppl 1):15-8. Abstract

Johnston SR et al. **Life following aromatase inhibitors - where now for endocrine sequencing?** *Breast Cancer Res Treat* 2005;93(Suppl 4):19-25. Abstract

Jones SE, Pippen J. **Effectiveness and tolerability of fulvestrant in postmenopausal women with hormone receptor-positive breast cancer.** *Clin Breast Cancer* 2005;6(Suppl)1:9-14.

Jones SE et al. **A retrospective analysis of the proportion of patients responding for > 1 year in two phase III studies of fulvestrant vs anastrozole.** *Proc ASCO* 2004;Abstract 737.

Jones SE et al. **A retrospective analysis of the proportion of patients responding for ≥ 1, 1.5 and 2 years in two phase III studies of fulvestrant vs anastrozole.** *Breast Cancer Res Treat* 2004;Abstract 6047.

Kaufmann M et al. **Exemestane improves survival in metastatic breast cancer: Results of a phase III randomized study.** *Clin Breast Cancer* 2000;(1 Suppl 1):15-8. Abstract

Marcom PK et al. **A phase II trial of letrozole and trastuzumab for ER and/or PgR and HER2 positive metastatic breast cancer: Final results.** *Proc ASCO* 2005;Abstract 596.

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

McKeage K et al. **Fulvestrant: A review of its use in hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.** *Drugs* 2004;64(6):633-48. Abstract

Milla-Santos A et al. **Anastrozole versus tamoxifen as first-line therapy in postmenopausal patients with hormone-dependent advanced breast cancer: A prospective, randomized, phase III study.** *Am J Clin Oncol* 2003;26(3):317-22. Abstract

Mouridsen H, Chaudri-Ross HA. **Efficacy of first-line letrozole versus tamoxifen as a function of age in postmenopausal women with advanced breast cancer.** *Oncologist* 2004;9(5):497-506. Abstract

Mouridsen H et al. **Superiority of letrozole to tamoxifen in the first-line treatment of advanced breast cancer: Evidence from metastatic subgroups and a test of functional ability.** *Oncologist* 2004;9(5):489-96. Abstract

Mouridsen H et al. **Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group.** *J Clin Oncol* 2003;21(11):2101-9. Abstract

Nabholtz JM et al. **Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Survival analysis and updated safety results.** *Eur J Cancer* 2003;39(12):1684-9. Abstract

Osborne CK et al. **Fulvestrant: An oestrogen receptor antagonist with a novel mechanism of action.** *Br J Cancer* 2004;90(Suppl 1):2-6. Abstract

Osborne CK et al. **Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial.** *J Clin Oncol* 2002;20(16):3386-95. Abstract

Paridaens R et al. **First line hormonal treatment (HT) for metastatic breast cancer (MBC) with exemestane (E) or tamoxifen (T) in postmenopausal patients (pts) — A randomized phase III trial of the EORTC Breast Group.** *Proc ASCO* 2004;Abstract 515.

Perey L et al. **Fulvestrant (Faslodex) as hormonal treatment in postmenopausal patients with advanced breast cancer (ABC) progressing after treatment with tamoxifen and aromatase inhibitors: Update of a phase II SAKK trial.** *Breast Cancer Res Treat* 2004;Abstract 6048.

Petruzelka L et al. **Fulvestrant in postmenopausal women with metastatic breast cancer progressing on prior endocrine therapy — Results from a compassionate use program.** *Proc ASCO* 2004;Abstract 730.

Possinger K. **Fulvestrant — A new treatment for postmenopausal women with hormone-sensitive advanced breast cancer.** *Expert Opin Pharmacother* 2004;5(12):2549-58. Abstract

Pritchard KI. **Endocrine therapy of advanced disease: Analysis and implications of the existing data.** *Clin Cancer Res* 2003;9(1 Pt 2):460-7. Abstract

Prowell TM, Davidson NE. **What is the role of ovarian ablation in the management of primary and metastatic breast cancer today?** *Oncologist* 2004;9(5):507-17. Abstract

Rivera E et al. **Pilot study evaluating the pharmacokinetics, pharmacodynamics, and safety of the combination of exemestane and tamoxifen.** *Clin Cancer Res* 2004;10(6):1943-8. Abstract

Robertson JF et al. **Endocrine treatment options for advanced breast cancer — The role of fulvestrant.** *Eur J Cancer* 2005;41(3):346-56. Abstract

Robertson JF et al. **Sensitivity to further endocrine therapy is retained following progression on first-line fulvestrant.** *Breast Cancer Res Treat* 2005;92(2):169-74. Abstract

Robertson JFR et al. **Clinical efficacy of fulvestrant and effects on estrogen receptor levels during first-line endocrine treatment of patients with advanced breast cancer.** *Breast Cancer Res Treat* 2004;Abstract 6049.

Robertson JF et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials.** *Cancer* 2003;98(2):229-38. Abstract

Sokolowicz LE, Gradishar WJ. **Implications of first-line adjuvant treatment with aromatase inhibitors in recurrent metastatic breast cancer.** *Clin Breast Cancer* 2004(5 Suppl 1):24-30. Abstract

Steger G et al. **Fulvestrant (FUL) and goserelin (GOS) in premenopausal women with advanced, hormone-sensitive breast cancer — A pilot study.** *Proc ASCO* 2005;Abstract 708.

Steger GG et al. **Fulvestrant ('Faslodex'): Clinical experience from the Compassionate Use Programme.** *Cancer Treat Rev* 2005;31(Suppl 2): S10-6. Abstract

Thürlimann B et al. **Anastrozole ('Arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: Results of the double-blind crossover SAKK trial 21/95 — A sub-study of the TARGET (Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability) trial.** *Breast Cancer Res Treat* 2004;85(3):247-54. Abstract

Thürlimann B et al; Arimidex Study Group. **Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first-line treatment for advanced breast cancer in postmenopausal women.** *Eur J Cancer* 2003;39(16):2310-7. Abstract

Traina TA et al. **A feasibility study of an aromatase inhibitor (AI), letrozole (L) and the antibody to vascular endothelial growth factor (VEGF), bevacizumab (B), in patients (pts) with hormone receptor-positive metastatic breast cancer (MBC).** *Proc ASCO* 2005;Abstract 796.

Vergote I, Robertson JF. **Fulvestrant is an effective and well-tolerated endocrine therapy for postmenopausal women with advanced breast cancer: Results from clinical trials.** *Br J Cancer* 2004;90(Suppl 1):11-4. Abstract

Vergote I et al; Trial 0020 Investigators. **Postmenopausal women who progress on fulvestrant ('Faslodex') remain sensitive to further endocrine therapy.** *Breast Cancer Res Treat* 2003;79(2):207-11. Abstract

Vogel CL. **Update on the current use of hormonals as therapy in advanced breast cancer.** *Anticancer Drugs* 2003;14(4):265-73. Abstract

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- Compare and contrast management strategies of community oncologists and cancer research leaders for the treatment of cancer. 5 4 3 2 1
- Discuss cancer management issues for which relative agreement and heterogeneity exist in patterns of care. 5 4 3 2 1
- Counsel cancer patients about multiple acceptable treatment options when they exist. 5 4 3 2 1

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Objectives were related to overall purpose/goal(s) of activity. 5 4 3 2 1

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This program is supported by education grants from Abraxis Oncology, AstraZeneca Pharmaceuticals LP and Genentech BioOncology.

This program is supported by education grants from
Abraxis Oncology, AstraZeneca Pharmaceuticals LP
and Genentech BioOncology.

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Last review date: December 2005
Release date: December 2005
Expiration date: December 2006
Estimated time to complete: 2.25 hours