FROM THE PUBLISHERS OF
Breast Cancer™ UPDATE

Cancer Educators Slide Kit

Management of Patients with Estrogen Receptor-Positive Breast Cancer

Based on the Proceedings of the Inaugural Cancer Educators Working Group Meeting

FEATURING POLLING QUESTIONS AND PATIENT CASE SCENARIOS FOR THE FACILITATION OF INTERACTIVE PRESENTATIONS

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CME Certified

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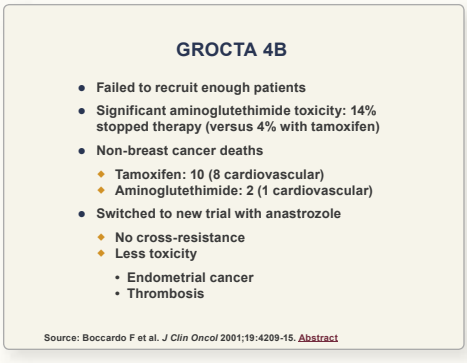
EDUCATIONAL METHOD

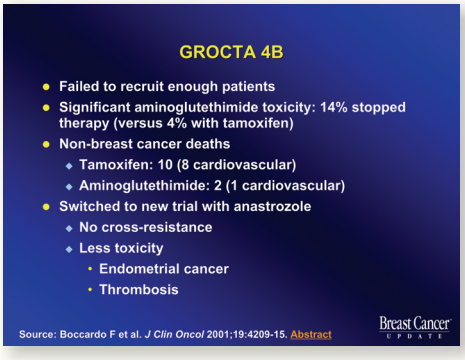
This CME activity contains a CD with PowerPoint slides and a monograph with speakers' notes. To receive credit, the participant should review the slides and speakers' notes in the monograph and complete the post-test and evaluation form located at the back of the monograph or on the BreastCancerUpdate.com/CME website.

The PowerPoint presentations used within this book are provided in two different ways: in print and on CD. The CD versions of the PowerPoint presentations were designed for optimal viewing on a large screen in a dark room. This design can be difficult to read in print, and consequently the print versions have been designed to facilitate ease of reading. See the thumbnails below.

PowerPoint in Print



PowerPoint on CD



Cancer Educators Slide Kit

STATEMENT OF NEED/TARGET AUDIENCE

Medical oncologists are often called upon to speak in educational forums to a wide range of audiences about cancer management strategies. The purpose of this CME slide kit and speakers' notes is to provide medical oncologists interested in providing breast cancer education with the tools and background necessary to facilitate interactive and effective live educational events.

The focus of these slides, specifically, is the endocrine therapy of breast cancer throughout the breast cancer continuum from the prevention of the disease to treatment in the metastatic setting, as endocrine therapy is the cornerstone of treatment for most women diagnosed with breast cancer.

This slide kit not only incorporates slides on the relevant clinical trial database of endocrine therapy, but also provides tools for improving upon the current didactic formats often employed at live education forums, such as suggested cases for discussion and sample interactive questions. These tools can be used to create a positive educational environment that fosters interactive learning.

GLOBAL LEARNING OBJECTIVES

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

- Facilitate an educational session or sessions on the endocrine therapy for breast cancer throughout the breast cancer continuum.
- Utilize suggested cases and interactive questions to stimulate discussion and interaction in a live activity on hormonal therapy for breast cancer.

ACCREDITATION STATEMENT

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

CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 4.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
aminoglutethimide	Cytadren®	Novartis Pharmaceuticals
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals LP
capecitabine	Xeloda®	Roche Laboratories Inc
celecoxib	Celebrex®	Pfizer Inc
docetaxel	Taxotere®	Aventis Pharmaceuticals Inc
exemestane	Aromasin®	Pfizer Inc
fadrozole hydrochloride	*	Novartis Pharmaceuticals
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals LP
gefitinib	Iressa®	AstraZeneca Pharmaceuticals LP
gemcitabine	Gemzar®	Eli Lilly and Company
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letrozole	Femara®	Novartis Pharmaceuticals
medroxyprogesterone acetate	Various	Various
megestrol acetate	Megace®	Bristol-Myers Squibb Company
paclitaxel	Taxol®	Bristol-Myers Squibb Company
raloxifene hydrochloride	Evista®	Eli Lilly and Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals LP
trastuzumab	Herceptin®	Genentech BioOncology
triptorelin pamoate	Trelstar™	Pfizer Inc
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*Not FDA approved

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Editor's Note

Accelerating the translation of clinical research to practice

Speed, speed, speed is the name of the game these days. Between our Palm phones, wireless email, thumb drives, instant messaging, cable modems and DSL, things are happening so fast, it almost seems like we need to schedule time just to go to the bathroom.

The pace and quality of medical education have also been significantly revved up by similar improvements in technology. Conference presentations appear on the web virtually the day after they are made, and important trial data arrives in our inboxes almost as it is released. Even within our CME group, speed and technology have changed the way we work. My audio editors now zip MPEG files to our production server, allowing me to drop these "tunes" onto my iPOD so I can work while I lounge by the pool (okay, while I'm driving my car or exercising, just like you). Our sophisticated postproduction system makes the most hesitant and stumbling speaker sound like a smooth talker.

Medical meeting presentations have also been revolutionized. Software programs like PowerPoint allow instant editing, reorganization and animation. Today many clinical research leaders are almost as adept as Pixar animators, regularly composing thoughtful and dynamic illustrated renderings. The enclosed "slide atlas" exemplifies the advantages of computerization in medical presentations and is intended to provide the necessary support for a speaker wishing to present a review of recent clinical research related to endocrine therapy for breast cancer.

In order to properly develop this comprehensive resource, some months ago we gathered 67 community-based medical oncologists and surgeons and six breast cancer clinical research leaders for a Mickey-less weekend in Orlando to debate the research issues specifically related to this slide program.

At this event, participants were provided individual laptop computers and were asked to constantly provide their perspectives using a wireless network brainstorming tool our group has pioneered. An esteemed faculty delivered presentations highlighting many important aspects of managing patients with estrogen receptor-positive tumors. These topics were discussed extensively throughout the meeting, and the dynamic discussion and input of the community faculty assisted our CME group in better understanding the types of graphics and cases that would be useful in future presentations.

The enclosed CD includes the computer files of the slides, and the instructor's manual includes a hard copy of the slides and comments regarding their use in a CME program. All of these slides can also be downloaded from our website, **www.BreastCancerUpdate.com**.

Many oncology meetings regularly use electronic handheld keypads that allow instant audience polling on multiple-choice questions. For smaller presentations, lower-tech interactive methods exist, such as asking for a "show of hands" or using multiple colored cards or lights. We strongly support the use of interactivity in any presentation and believe that audiences are more likely to learn from these potentially dynamic "talks." To that end, a number of case-based scenarios with multiple-choice questions are included in this slide kit.

When we think back to the old generation of 35-mm slide presentations, it is a testimonial to the age of electronic learning that this slide program can be distributed so quickly, inexpensively and easily. However, the most important result of this acceleration in communication is that breakthroughs in clinical research can be more rapidly and effectively integrated into everyday care for our patients.

— Neil Love, MD
NLove@ResearchToPractice.net

Presentation 1:
Adjuvant Endocrine Therapy: Postmenopausal Patients

Slide 1.1

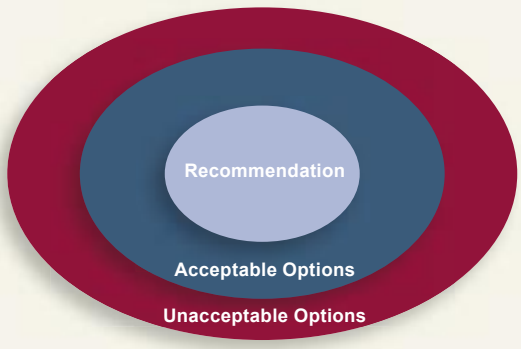
Adjuvant endocrine therapy for postmenopausal women has become one of the most rapidly expanding areas of breast cancer clinical research. The initial report from the ATAC trial in December 2001 has been followed by additional important follow-up data, and key findings have now been reported from trials sequencing aromatase inhibitors after tamoxifen.

Adjuvant Endocrine Therapy: Postmenopausal Patients

Slide 1.2

Our CME group has developed a simple model related to medical treatment decisions with multiple evidence-based therapeutic options. Options in the blue areas are supported by clinical research evidence and any of these might be considered a "standard of care." For example, both tamoxifen and anastrozole are evidence-based adjuvant endocrine therapy options in most postmenopausal cases. Within the light blue area would be the specific therapy recommended by a physician for a particular patient. Options in red denote therapies that most research leaders would not consider acceptable outside a protocol setting — for example, trastuzumab in the adjuvant setting.

Treatment Options: Translating Research Advances to Treatment Recommendations



Slide 1.3

The initial base case for discussion is an interesting scenario: a "young elderly" woman with two positive lymph nodes and an ER/PR-positive tumor. In a CME meeting format, the speaker might query the audience on how they generally manage such cases, and how their approach might change when variables in the case are altered.

Case Discussion

- A 65-year-old woman
  - S/P lumpectomy (1.2-cm, Grade 2 IDC)
  - Sentinel node-positive
  - Axillary dissection (1 other positive node)
  - ER/PR-positive (50%)

Presentation 1:
Adjuvant Endocrine Therapy: Postmenopausal Patients

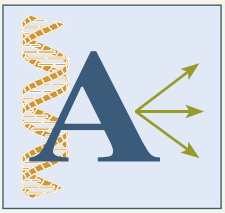
Which endocrine therapy, if any, would you most likely recommend?

- Scenario 1: Patient is HER2-positive
- Scenario 2: Patient is HER2-negative
  1. Tamoxifen
  2. Anastrozole
  3. Letrozole
  4. Exemestane
  5. Other
  6. None

Slide 1.4

This is an example of an audience poll question that might be posed to launch a discussion. The two most common answers would be tamoxifen or anastrozole. Varying the HER2 status of the case is one of many approaches likely to result in an informative discussion.

Adjuvant!: A Program to Assist in Counseling Patients about Adjuvant Therapy



- For healthcare professionals
- Estimates risk of recurrence and death in women with invasive breast cancer with and without adjuvant systemic therapy

Modified from: www.adjuvantonline.com

Slide 1.5

The breast cancer international overviews — spearheaded by Oxford's Sir Richard Peto — have sensitized physicians in the research community and community practice to the need to offer patients accurate information on prognosis and the absolute impact of various systemic therapies on risk of relapse and mortality. Consequently, a number of computerized models have been developed to assist in the counseling process. The most widely used of these is Adjuvant!, developed by medical oncologist Peter Ravdin.

Adjuvant!: Effect of Therapy on Relapse

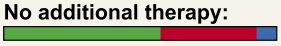
Patient Information

Age: 65
Comorbidity: Perfect health
ER Status: Positive
Tumor Grade: Grade 2
Tumor Size: 1.1-2.0 cm
Positive Nodes: 1-3
Calculate For: Relapse
10 Year Risk: 37 Prognostic

Adjuvant Therapy Effectiveness

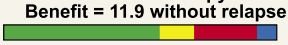
Horm: Overview 98 (Tamoxifen)
Chemo: CA × 4 + T × 4

No additional therapy:

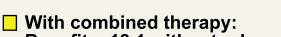


57.5 alive and without cancer in 10 years.
35.8 relapse.
6.7 die of other causes.

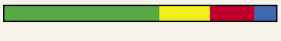
With hormonal therapy: Benefit = 11.9 without relapse



With chemotherapy: Benefit = 8.7 without relapse



With combined therapy: Benefit = 18.1 without relapse



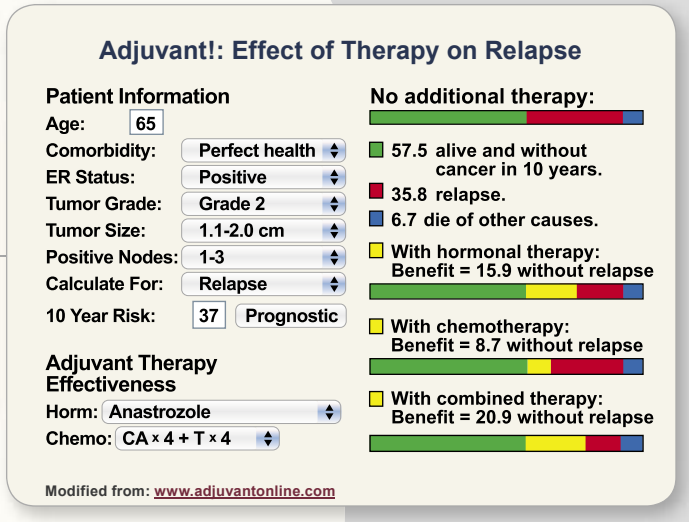
Modified from: www.adjuvantonline.com

Slide 1.6

Adjuvant! was developed for healthcare professionals and allows the user to enter tumor and patient variables to estimate relapse and mortality rates. The program is available online or can be downloaded to a PDA. Using the variables of our index case, Adjuvant! provides the risk for relapse and how this is affected by therapy with — for example — tamoxifen and chemotherapy.

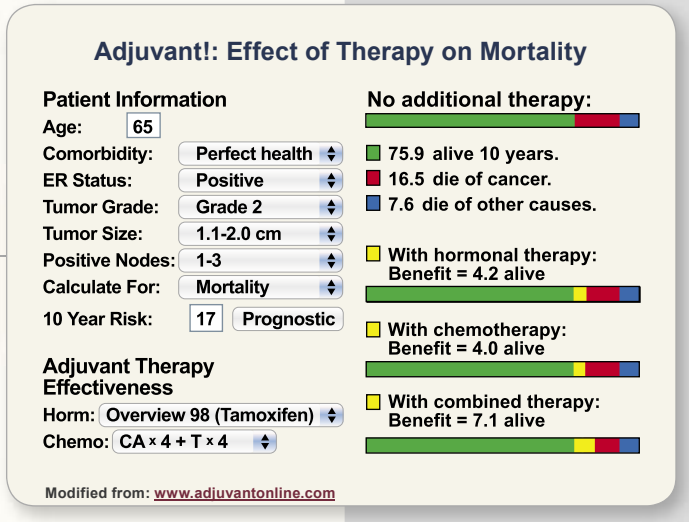
Slide 1.7

Adjuvant! also allows the user to vary the type of chemotherapy and hormonal therapy and recalculate the impact of treatment. In this case, by substituting anastrozole for tamoxifen, a lower rate of relapse is calculated.



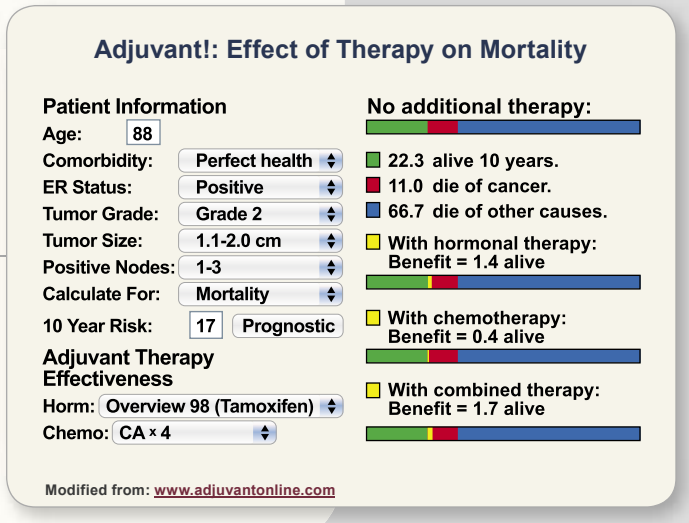
Slide 1.8

Adjuvant! also allows the user to calculate the projected impact on mortality.



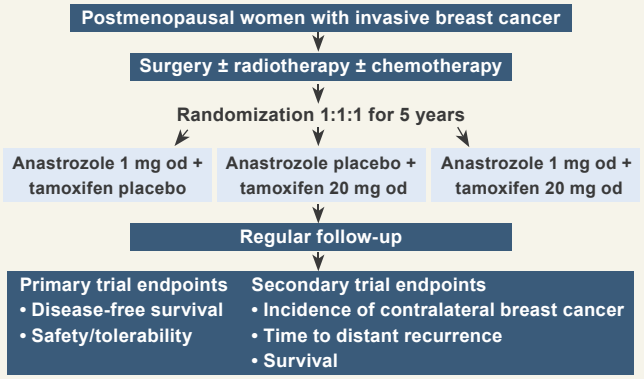
Slide 1.9

A key aspect of Adjuvant! is that noncancer causes of mortality can be factored in based on the patient's age and general health status. In this case, an 88-year-old patient with the same type of tumor would experience significantly less absolute benefit from systemic therapy because of noncancer sources of mortality.



Presentation 1:
Adjuvant Endocrine Therapy: Postmenopausal Patients

ATAC Trial Design



Source: With permission from Buzdar A. Presentation. SABCS, 2002;Abstract 13.

Slide 1.10

When one considers the research database that relates to the choice of adjuvant systemic therapy, clearly the major, new relevant data set is from the ATAC trial. The initial results of this landmark international study were reported at the San Antonio Breast Cancer Symposium in December 2001. The trial was placebo-controlled and included three randomization arms: tamoxifen, anastrozole, and the combination of tamoxifen and anastrozole.

ATAC Trial: Key Patient Characteristics

All treatment groups were well balanced

- 34% patients node-positive
- 84% patients receptor-positive
  - 8% receptor-negative
  - 8% receptor-unknown
- Mean age 64 years

Source: Buzdar A. Presentation. SABCS, 2002;Abstract 13.

Slide 1.11

Only about a third of the women enrolled in ATAC had node-positive tumors. Like many international trials of adjuvant endocrine therapy, ATAC included a small but significant fraction of women with tumors that were either ER-negative or ER-unknown. Currently, adjuvant endocrine therapy is generally not utilized in women with ER-negative tumors, and therefore key results of the ATAC trial are in women with ER-positive tumors.

ATAC Trial: Data Analysis

	Main analysis	Updated analysis
Total number of first events	1,079	1,373
Total number of first events in receptor-positive population	766	991
Median follow-up (months)	33	47

1,056 events required for statistical analysis

Source: Buzdar A. Presentation. SABCS, 2002;Abstract 13.

Slide 1.12

The initial 2001 ATAC results were updated one year later with an average follow-up of almost four years. A third analysis, which will include mortality data, is expected in late 2004.

Slide 1.13

The initial 2001 report demonstrated no advantage from the combination of tamoxifen and anastrozole and therefore the focus of subsequent data sets has been the comparison of tamoxifen and anastrozole, particularly in women with hormone receptor-positive tumors. Both local and distant recurrences were less frequent in women receiving anastrozole. This substantial reduction in contralateral breast tumors provided an impetus for clinical trials in women with DCIS and those at increased risk for the disease. Of great importance is the observation that non-breast cancer mortality was the same in both treatment groups.

ATAC Trial: First Events in Receptor-Positive Subgroup

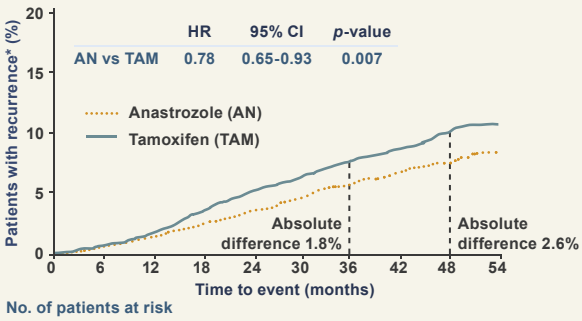
	Anastrozole n=2,617 (%)	Tamoxifen n=2,598 (%)
First event	290 (11.1)	345 (13.3)
Locoregional recurrence	49 (1.9)	62 (2.4)
Distant recurrence	133 (5.1)	158 (6.1)
Contralateral (invasive)	17 (0.6)	31 (1.2)
Contralateral (DCIS)	3 (0.1)	4 (0.2)
Death (non-breast cancer)	88 (3.4)	90 (3.5)

Source: Buzdar A. Presentation. SABCS, 2002;Abstract 13.

Slide 1.14

Plots of recurrence rates over the first four years of follow-up demonstrate that the difference between these two randomization arms is increasing with time, a finding that was also observed when tamoxifen was compared to controls in older adjuvant trials of endocrine therapy.

ATAC Trial: Probability of Recurrence in Receptor-Positive Population



No. of patients at risk

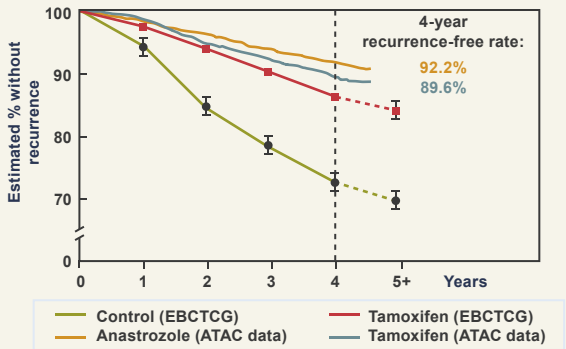
AN	2617	2533	2436	2243	1258	602
TAM	2598	2516	2386	2180	1210	574

*Censoring non-BC deaths before recurrence
Source: With permission from Buzdar A. Presentation. SABCS, 2002;Abstract 13.

Slide 1.15

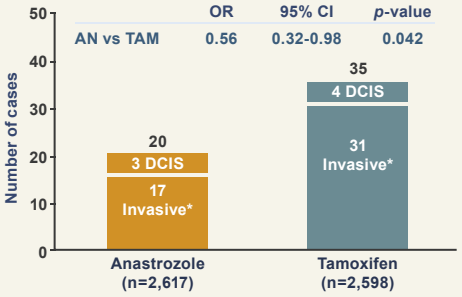
Indirect comparison of the two ATAC randomization arms to the 1995 Early Breast Cancer Trialists' Collaborative Group international meta-analysis in women over age 50 with ER-positive tumors demonstrates that the tamoxifen randomization arms are similar. This suggests a stepwise improvement in outcome with the use of anastrozole in these patients.

Comparison of ATAC Data with EBCTCG 1995 Overview[1]: Patients > 50 Years, ER-Positive



[1]*The Lancet* 1998;351:1451-67. Abstract
Source: With permission from Buzdar A. Presentation. SABCS, 2002;Abstract 13.

ATAC Trial: New (Contralateral) Breast Primaries in Receptor-Positive Subgroup



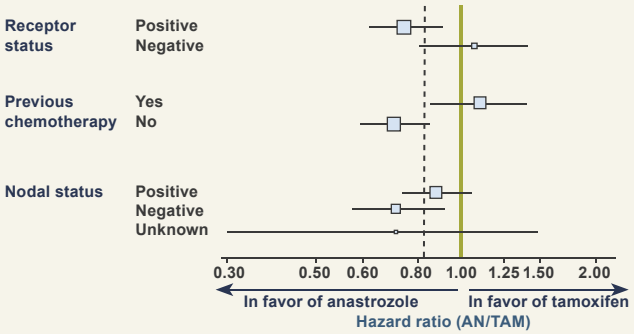
*p = 0.043 for invasive only; retrospective analysis

Source: With permission from Buzdar A. Presentation. SABCS, 2002;Abstract 13.

Slide 1.16

One of the most surprising findings in the ATAC trial was the advantage of anastrozole over tamoxifen in rate of contralateral breast tumors. Anastrozole resulted in almost a 50 percent reduction in these events compared to tamoxifen, which reduces the rate approximately 50 percent compared to no therapy.

ATAC Trial: Breast Cancer Events for Prognostic Factors

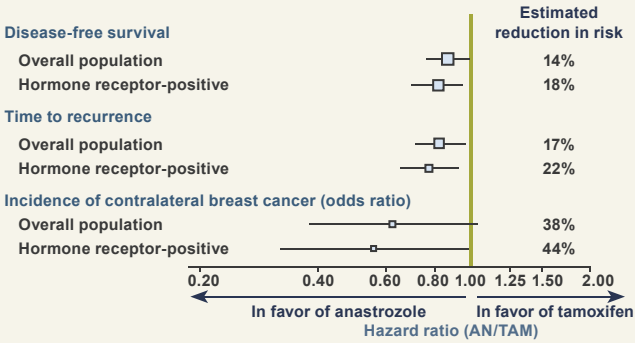


Note: Caution should be taken in interpreting subset analyses. Adapted with permission from Elsevier (*The Lancet*, 2002, 359, 2131-9). Abstract

Slide 1.17

The number of patients with receptor-negative tumors was relatively small, and in these patients, no difference was observed in the event rate. No statistically significant difference in event rates was observed for women receiving chemotherapy, although confidence levels are wide. Dr Aman Buzdar, who presented the ATAC update in 2002, has made the point that the type of chemotherapy received by patients was highly variable and a possible confounding factor in this subset analysis.

ATAC Trial: Summary (Efficacy) — Updated Analysis



Note: Caution should be taken in interpreting subset analyses.
Source: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract

Slide 1.18

The most recent analysis of the ATAC data continues to demonstrate an improvement in both the overall and receptor-positive populations for anastrozole compared to tamoxifen in disease-free survival, time to recurrence and contralateral breast tumors.

Slide 1.19

The absolute benefits of anastrozole over tamoxifen observed at four years are greater than at three years.

ATAC Trial: Absolute Benefits in Favor of Anastrozole

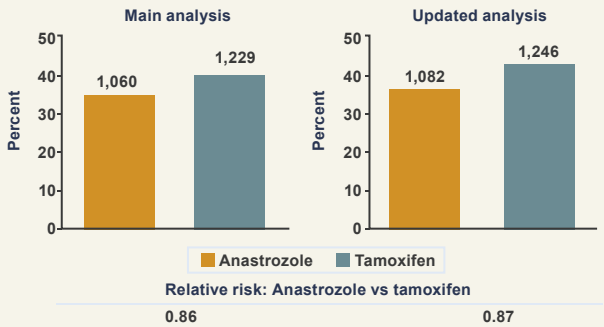
	3 years (%)	4 years (%)
Overall disease-free survival (DFS)	1.5	2.4
Overall time to recurrence (TTR)	1.7	2.3
DFS receptor-positive	1.7	2.9
TTR receptor-positive	1.8	2.6

Source: Buzdar A. Presentation. SABCS, 2002;Abstract 13.

Slide 1.20

One of the major side effects associated with tamoxifen is vasomotor symptoms, particularly in perimenopausal women. The incidence of hot flashes in ATAC was somewhat less in women receiving anastrozole compared to women receiving tamoxifen.

ATAC Trial: Hot Flashes*



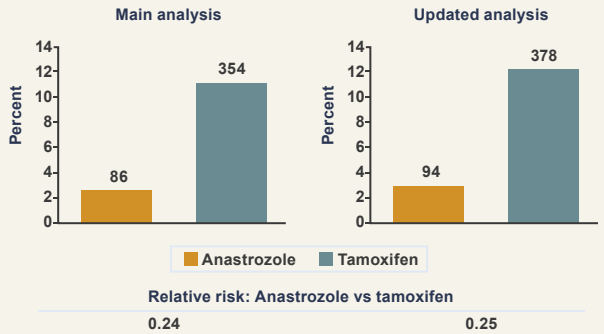
*At any time during treatment or of any severity

Sources: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract *The Lancet* 2002;359:2131-9. Abstract

Slide 1.21

The incidence of vaginal discharge in the ATAC trial was substantially reduced in women receiving anastrozole compared to women receiving tamoxifen.

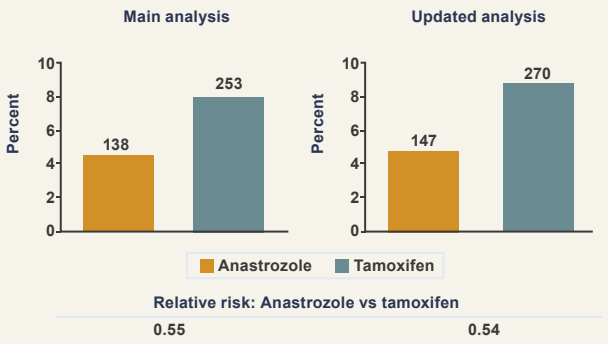
ATAC Trial: Vaginal Discharge



Sources: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract *The Lancet* 2002;359:2131-9. Abstract

Presentation 1:
Adjuvant Endocrine Therapy: Postmenopausal Patients

ATAC Trial: Vaginal Bleeding

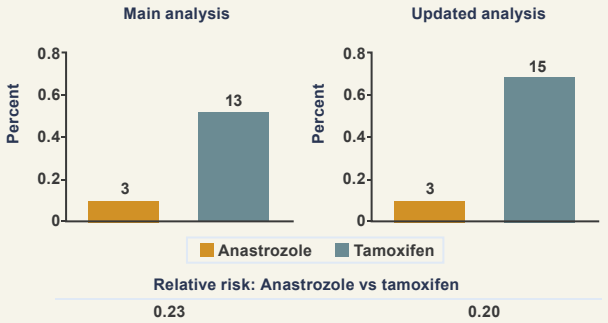


Sources: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract *The Lancet* 2002;359:2131-9. Abstract

Slide 1.22

The incidence of vaginal bleeding in the ATAC trial was also substantially reduced in women receiving anastrozole compared to women receiving tamoxifen.

ATAC Trial: Endometrial Cancer*



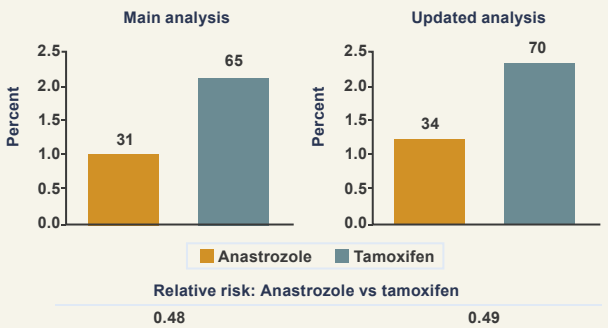
*Excluding patients with hysterectomy at baseline

Sources: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract *The Lancet* 2002;359:2131-9. Abstract

Slide 1.23

While endometrial cancer diagnosed in women receiving tamoxifen is usually curable with surgery, the increased rate of these tumors is of great concern to physicians and patients. In the ATAC trial the rate of diagnosis of these lesions was significantly lower in women receiving anastrozole compared to women receiving tamoxifen.

ATAC Trial: Ischemic Cerebrovascular Events (CVA/TIA)



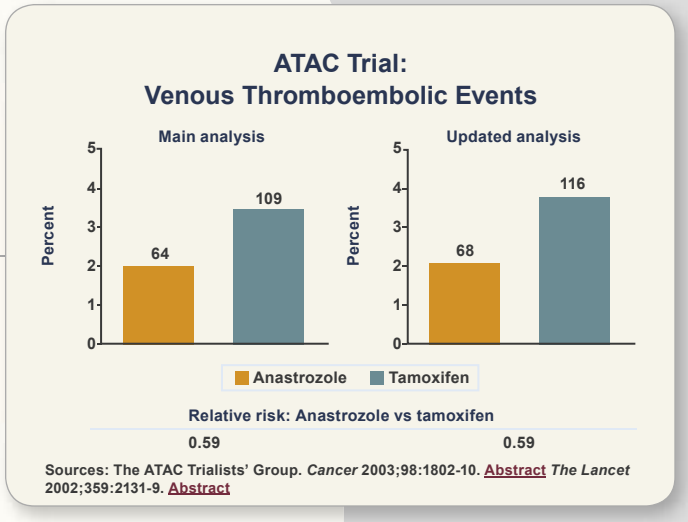
Sources: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract *The Lancet* 2002;359:2131-9. Abstract

Slide 1.24

Several randomized clinical trials have demonstrated an increased incidence of stroke in women receiving tamoxifen. The ATAC trial demonstrated significantly fewer cerebrovascular events in women receiving anastrozole compared to women receiving tamoxifen.

Slide 1.25

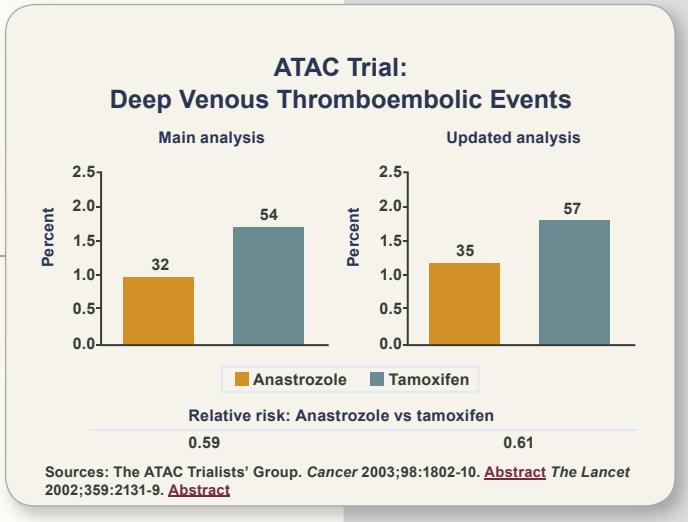
One of the most clinically important complications associated with tamoxifen therapy is an increased rate of thrombosis. The ATAC trial demonstrated significantly fewer such events in women receiving anastrozole compared to women receiving tamoxifen.



Sources: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract *The Lancet* 2002;359:2131-9. Abstract

Slide 1.26

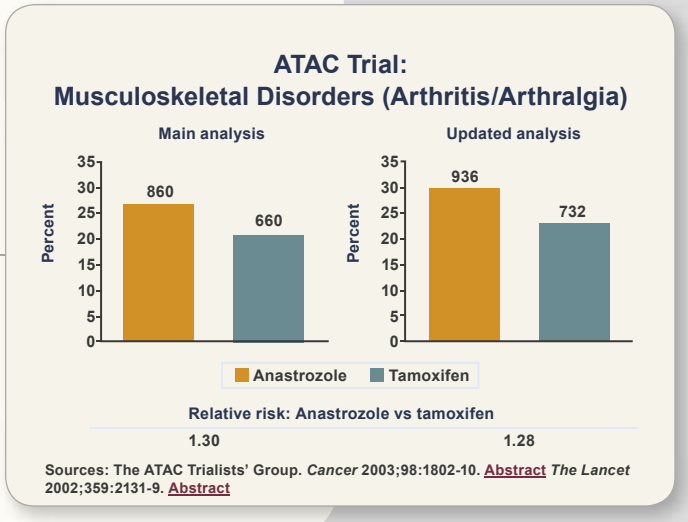
Fewer incidents of deep vein thrombosis occured in women receiving anastrozole compared to women receiving tamoxifen.



Sources: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract *The Lancet* 2002;359:2131-9. Abstract

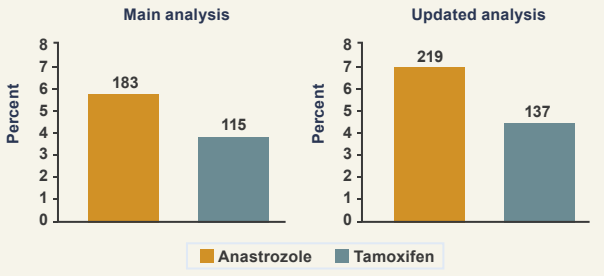
Slide 1.27

Third-generation aromatase inhibitors have been associated with musculoskeletal events. In the ATAC trial, such events were increased in women receiving anastrozole compared to women receiving tamoxifen.



Sources: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract *The Lancet* 2002;359:2131-9. Abstract

ATAC Trial: Fractures



Relative risk: Anastrozole vs tamoxifen

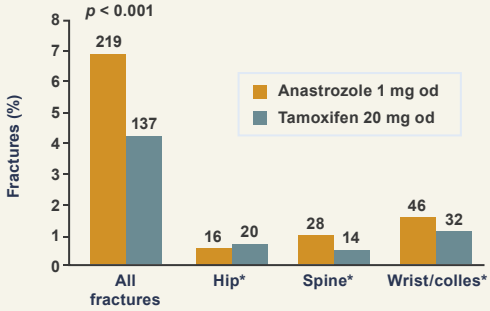
1.59	1.60

Sources: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract *The Lancet* 2002;359:2131-9. Abstract

Slide 1.28

Another complication associated with aromatase inhibitors is decreased bone mineral density. The ATAC trial demonstrated a greater incidence of bone fractures in women receiving anastrozole compared to women treated with tamoxifen.

ATAC Trial: Bone Fracture Adverse Events at the Updated Safety Analysis



*p-value not available

Source: Locker G, on behalf of the ATAC Trialists' Group. Poster. Lynn Sage Breast Cancer Symposium, 2003.

Slide 1.29

At this point, there is no difference in incidence of hip fractures, but an increased incidence of fractures of the spine and wrist was observed.

ATAC Trial: In Favor of Anastrozole

	Anastrozole (n=3,092) n	(%)	Tamoxifen (n=3,093) n	(%)
Venous thromboembolic events	68	(2.2)	116	(3.8)
Ischemic cerebrovascular events	34	(1.1)	70	(2.3)
Endometrial cancer*	3	(0.1)	15	(0.7)
Vaginal bleeding	147	(4.8)	270	(8.7)
Vaginal discharge	94	(3.0)	378	(12.2)
Hot flashes	1,082	(35.0)	1,246	(40.3)

*Excluding patients with hysterectomy at baseline

Source: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract

Slide 1.30

This slide summarizes complications seen more frequently in women randomly assigned to tamoxifen, including thrombotic and gynecologic events.

Slide 1.31

This slide summarizes complications seen more frequently in women randomly assigned to anastrozole, specifically musculoskeletal events and fractures.

ATAC Trial: In Favor of Tamoxifen

	Anastrozole (n=3,092) n	(%)	Tamoxifen (n=3,093) n	(%)
Musculoskeletal disorders	936	(30.3)	732	(23.7)
Fractures	219	(7.1)	137	(4.4)

Source: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract

Slide 1.32

This slide summarizes overall complications observed in the ATAC trial.

Summary

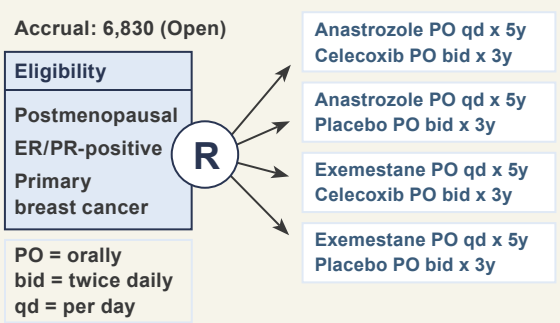
- Anastrozole significantly better tolerated with respect to:
  - Endometrial cancer
  - Vaginal bleeding
  - Vaginal discharge
  - Ischemic cerebrovascular events
  - Venous thromboembolic events
  - Hot flashes
- Tamoxifen better tolerated with respect to:
  - Musculoskeletal disorders
  - Fractures

Source: The ATAC Trialists' Group. *Cancer* 2003;98:1802-10. Abstract

Slide 1.33

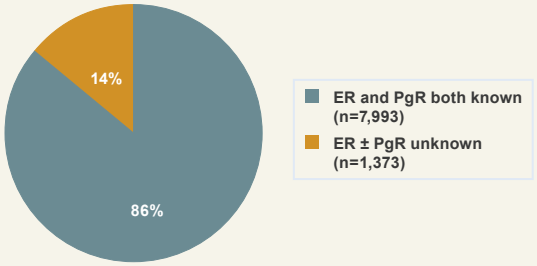
A new generation of clinical trials is addressing questions generated by the ATAC trial. One important new trial with a two-by-two factorial design compares anastrozole to the steroidal aromatase inhibitor exemestane and the use of celecoxib versus control.

NCIC and US Intergroup MA27 Trial



Source: NCI Physician Data Query, May 2004.

ATAC Trial: Numbers of ER and PgR Known

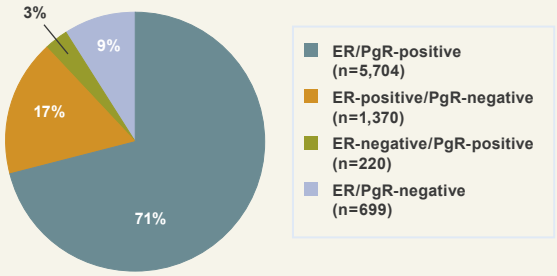


Source: Dowsett M. Presentation. SABCS, 2003;Abstract 4.

Slide 1.34

The vast majority of patients enrolled in the ATAC trial had steroid receptor analysis performed.

ATAC Trial: Percent of Patients in ER and PgR Subgroups



Source: Dowsett M. Presentation. SABCS, 2003;Abstract 4.

Slide 1.35

Most of the patients enrolled in the ATAC trial had ER/PR-positive tumors.

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

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

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

Source: Dowsett M, on behalf of the ATAC Trialists' Group. *Breast Cancer Res Treat* 2003;Abstract 4.

Slide 1.36

At the 2003 San Antonio Breast Cancer Symposium, a new data set from ATAC was presented that evaluated the impact of therapy based on PR status in women with ER-positive tumors. A relative risk reduction in recurrence rate of 18 percent for anastrozole over tamoxifen was observed in women with ER- and PR-positive tumors. A striking relative risk reduction of 52 percent was observed in women with ER-positive, PR-negative tumors. The difference in relative benefit based on PR was statistically significant in ER-positive tumors, but ER-negative subsets had too few events to determine treatment impact.

Slide 1.37

While all patients with ER-positive tumors benefited from anastrozole more than tamoxifen, after adjusting for a number of tumor-specific characteristics and prior chemotherapy, a significantly decreased relapse rate was observed in the ER-positive, PgR-negative subset of patients.

ATAC Trial: Hazard Ratios (A versus T) Adjusted for Baseline Characteristics

- Effect of PgR on risk of relapse adjusted for:
  - Nodal status (negative, 1-3, ≥4)
  - Tumor size (≤2 cm, 2-5 cm, ≥5 cm)
  - Tumor grade (well, moderate, poor)
  - Adjuvant chemotherapy (no/yes)
- Hazard ratios (A versus T) ER-positive:
  - Crude model PgR+ 0.82; PgR- 0.48
  - Adjusted model PgR+ 0.80; PgR- 0.48

Source: Dowsett M. Presentation. SABCS, 2003;Abstract 4.

Slide 1.38

Most medical oncologists are utilizing anastrozole as opposed to tamoxifen for adjuvant endocrine therapy for postmenopausal patients.

Adjuvant Endocrine Therapy Use in Postmenopausal Patients

- Which adjuvant endocrine therapy did you use in the last postmenopausal patient you evaluated with an ER-positive breast tumor who also received chemotherapy?

Therapy	Node-positive	Node-negative
Tamoxifen	42%	28%
Anastrozole	50%	60%
Other aromatase inhibitors	8%	12%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 1.39

While speculation exists about the comparability of the third-generation aromatase inhibitors, most physicians appear to be guided by large randomized clinical trial data, and the vast majority utilize anastrozole up front in the adjuvant setting.

Use of Other Aromatase Inhibitors in the Adjuvant Setting

- When you use aromatase inhibitors in the adjuvant setting, which agent do you generally use?

Anastrozole	84%
Letrozole	14%
Exemestane	2%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Impact of Age on Choice of Adjuvant Endocrine Therapy

- **Postmenopausal woman with 2.2-cm, ER-positive, HER2-negative IDC and two positive nodes: If you recommend adjuvant endocrine therapy, which agent would you select?**

Patient age	Tamoxifen	Anastrozole	Other aromatase inhibitor
55	35%	60%	5%
65	31%	63%	6%
77	31%	64%	5%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 1.40

In postmenopausal women with high-risk disease, age does not appear to have a significant influence on the choice of therapy, and nearly two thirds of oncologists utilize anastrozole regardless of patient age.

Impact of Tumor Size and Nodal Status on Choice of Adjuvant Endocrine Therapy

- **A 65-year-old woman with ER-positive, HER2-negative IDC: If you recommend adjuvant endocrine therapy, which agent would you recommend?**

Tumor characteristics	Tamoxifen	Anastrozole	Other aromatase inhibitor
2.2-cm, 10 positive nodes	34%	59%	7%
2.2-cm, negative nodes	33%	61%	6%
0.8-cm, negative nodes	43%	45%	2%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 1.41

In postmenopausal women with low-risk disease (ie, very small tumors, node-negative), physicians were equally likely to recommend tamoxifen or an aromatase inhibitor. In women with larger tumors and higher-risk disease, however, approximately two thirds of physicians recommended an aromatase inhibitor, anastrozole in particular.

Bone Density in Patients on Adjuvant Aromatase Inhibitors

- **Do you routinely evaluate bone density in your patients on adjuvant aromatase inhibitors?**

Yes	80%
No	20%

- **Do you use bisphosphonates preventively in your patients on adjuvant aromatase inhibitors?**

Yes	39%
No	61%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 1.42

Most breast cancer research leaders believe that a baseline bone mineral density evaluation is indicated when aromatase inhibitors are started as adjuvant therapy, and that bisphosphonates should not be used for prevention of bone loss in women with normal bone density. Oncologists surveyed do not uniformly follow these procedures.

Presentation 2:
Sequencing of Aromatase Inhibitors and Tamoxifen

Slide 2.1

Three important data sets have become available in the past year demonstrating a benefit from sequencing aromatase inhibitors after tamoxifen. These studies address the safety and efficacy of switching from tamoxifen to an aromatase inhibitor.

Sequencing of Aromatase Inhibitors and Tamoxifen

Slide 2.2

This case scenario presents a patient with ER-positive, high-risk disease in whom adjuvant endocrine therapy is a key part of her treatment, but who believes her weight gain is associated with tamoxifen.

Case Discussion

- A 67-year-old woman
  - S/P lumpectomy (1.2-cm, Grade 2 IDC)
  - Sentinel node-positive
  - Axillary dissection (1 other node positive)
  - ER/PR-positive (50%)
  - HER2-positive (IHC 3+)
  - Completed two years of tamoxifen
  - Has gained 12 pounds and is unhappy about it

Slide 2.3

While large-scale randomized trials have failed to demonstrate an association between tamoxifen and weight gain, it is a common perception among physicians and patients that such a relationship exists. This poll question may stimulate discussion on this topic.

When you initiate tamoxifen, what counseling do you provide about weight gain?

1. Not associated with weight gain
2. Rarely associated with weight gain
3. Sometimes associated with weight gain
4. Commonly associated with weight gain

At this point, how would you manage this patient's systemic therapy?

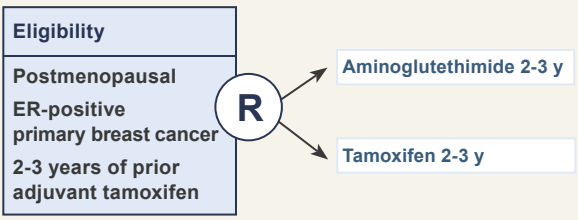
1. Stop tamoxifen
2. Continue tamoxifen
3. Stop tamoxifen, start anastrozole
4. Stop tamoxifen, start letrozole
5. Stop tamoxifen, start exemestane
6. Other

Slide 2.4

In light of the emerging data on switching from tamoxifen to an aromatase inhibitor, the heterogeneity in audience responses likely to be seen in this question can be used to stimulate an interesting discussion.

GROCTA 4B Study: Aminoglutethimide versus Tamoxifen after Adjuvant Tamoxifen

Protocol ID: GROCTA 4B
Accrual: 380 (Closed)



Source: Boccardo F et al. *J Clin Oncol* 2001;19:4209-15. Abstract

Slide 2.5

The GROCTA 4B trial — reported in 2001 — randomly assigned patients to aminoglutethimide or tamoxifen after completing two to three years of adjuvant tamoxifen.

GROCTA 4B

- Failed to recruit enough patients
- Significant aminoglutethimide toxicity: 14% stopped therapy (versus 4% with tamoxifen)
- Non-breast cancer deaths
  - Tamoxifen: 10 (8 cardiovascular)
  - Aminoglutethimide: 2 (1 cardiovascular)
- Switched to new trial with anastrozole
  - No cross-resistance
  - Less toxicity
    - Endometrial cancer
    - Thrombosis

Source: Boccardo F et al. *J Clin Oncol* 2001;19:4209-15. Abstract

Slide 2.6

GROCTA 4B failed to accrue enough patients due to the high incidence of aminoglutethimide-associated side effects. The investigational agent in the next trial by this research group was changed to anastrozole because the newer third-generation aromatase inhibitors are associated with a more favorable toxicity profile.

Slide 2.7

Despite failure to recruit the intended number of patients to GROCTA 4B, a reduction in the number of breast cancer deaths was observed in patients who were switched to amino-glutethimide compared to those who continued to receive tamoxifen. Note that the total number of metastatic events in the two groups was the same.

GROCTA 4B: Metastatic Events and Breast Cancer Deaths

Metastatic events	Total	Visceral	Bone/ST
Tamoxifen	42	16	26
Aminoglutethimide	42	6	36

ST = soft tissue

"Switching patients to aminoglutethimide led to a reduced risk of dying of breast cancer."

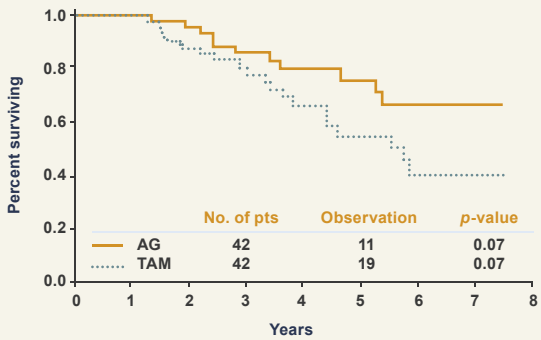
Breast cancer deaths	
Tamoxifen	19
Aminoglutethimide	10

Source: Boccardo F et al. *J Clin Oncol* 2001;19:4209-15. Abstract

Slide 2.8

The survival of patients who experienced relapse, from the time of relapse, was longer for patients who were switched to aminoglutethimide than for patients who continued to receive tamoxifen.

GROCTA 4B: Survival after Relapse



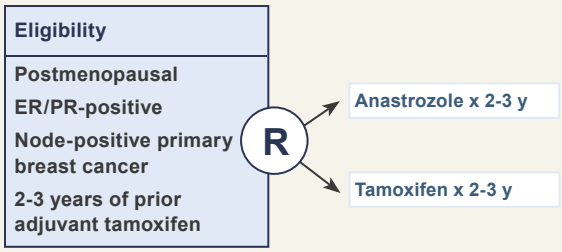
Source: With permission from Boccardo F et al. *J Clin Oncol* 2001;19:4209-15. Abstract

Slide 2.9

The Italian Tamoxifen Arimidex® (ITA) trial, presented at the 2003 San Antonio Breast Cancer Symposium, randomly assigned postmenopausal patients with ER-positive, node-positive breast cancer to anastrozole or tamoxifen after completing two to three years of adjuvant tamoxifen.

ITA Study: Anastrozole versus Tamoxifen Following Adjuvant Tamoxifen

Protocol ID: ITA (Italian Tamoxifen Arimidex®)
Accrual: 445 (Closed)



Source: Boccardo F. Presentation. SABCS, 2003;Abstract 3.

Presentation 2:
Sequencing of Aromatase Inhibitors and Tamoxifen

ITA Trial: Breast Cancer Events

Median follow-up: 24 months
Accrual: 426

Breast events	
Continue tamoxifen	26 (19 recurrences)
Switch to anastrozole	10 (8 recurrences)

Hazard rates for women switched to anastrozole

Relapse: 0.36 (0.17 - 0.75, $p = 0.006$)
Death: 0.18 (0.02 - 1.57, $p = 0.07$)

Source: Boccardo F et al. *Breast Cancer Res Treat* 2003;Abstract 3.

Slide 2.10

The ITA trial demonstrated that anastrozole significantly reduced the risk of relapse, and a trend toward improved survival was also observed, although the trend was not statistically significant.

ITA Trial: Serious Adverse Events

Median follow-up: 24 months
Accrual: 426

Serious adverse events	
Continue tamoxifen	29
Switch to anastrozole	14

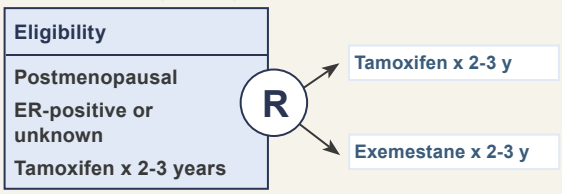
Source: Boccardo F et al. *Breast Cancer Res Treat* 2003;Abstract 3.

Slide 2.11

In the ITA trial, the third-generation aromatase inhibitor anastrozole resulted in half the number of serious adverse treatment events when compared to continuing tamoxifen.

Phase III Randomized Study of Adjuvant Exemestane versus Tamoxifen

Protocol IDs: ITA CRC-TU-TEAM, EU-20149
Accrual: 4,742 (Closed)



Source: Coombes C et al. *N Engl J Med* 2004;350(11):1081-92. Abstract

Slide 2.12

In 2004, Coombes and colleagues reported in the *New England Journal of Medicine* the results of a large, international Phase III randomized trial comparing exemestane after two to three years of adjuvant tamoxifen versus continued tamoxifen in postmenopausal patients.

Slide 2.13

After a median follow-up of 30.6 months, the unadjusted hazard ratio in the exemestane group as compared with the tamoxifen group was 0.68, which is a 32 percent reduction in risk of relapse and corresponds to an absolute benefit in terms of disease-free survival of 4.7 percent. Overall survival was not significantly different in the two groups, with 93 deaths occurring in the exemestane group and 106 in the tamoxifen group.

Hazard Ratios in the Exemestane Group as Compared with the Tamoxifen Group

Endpoint	Unadjusted hazard ratio (95% CI)	*p*-value
Disease-free survival	0.68 (0.56-0.82)	<0.001
ER-positive	0.64 (0.52-0.79)	
PR-positive	0.66 (0.51-0.87)	
PR-negative	0.58 (0.38-0.90)	
Breast cancer-free survival	0.63 (0.51-0.77)	<0.001
Time to contralateral breast cancer	0.44 (0.20-0.98)	0.04
Overall survival	0.88 (0.67-1.16)	0.37

Source: Coombes C et al. *N Engl J Med* 2004;350(11):1081-92. Abstract

Slide 2.14

Analysis of adverse events revealed significantly more visual disturbances, osteoporosis, arthralgias and diarrhea in patients treated with exemestane. Tamoxifen was associated with significantly more gynecologic symptoms, vaginal bleeding, cramps and thromboembolic events.

Significantly Different Adverse Events: Exemestane and Tamoxifen

Type of event	Exemestane group, any Grade	Tamoxifen group, any Grade	*p*-value
Visual disturbances	7.4%	5.7%	0.04
Osteoporosis	7.4%	5.7%	0.05
Gynecologic symptoms	5.8%	9.0%	<0.001
Arthralgia	5.4%	3.6%	0.01
Diarrhea	4.3%	2.3%	<0.001
Vaginal bleeding	4.0%	5.5%	0.05
Cramps	2.8%	4.4%	<0.001
Thromboembolic events	1.3%	2.4%	0.007

Source: Coombes C et al. *N Engl J Med* 2004;350(11):1081-92. Abstract

Slide 2.15

This case reflects a common clinical scenario: a postmenopausal patient with high-risk, ER-positive disease who is evaluated after completing five years of adjuvant tamoxifen.

Case Discussion

- A 70-year-old healthy woman
  - S/P lumpectomy (1.2-cm, Grade 2 IDC)
  - Sentinel node-positive
  - Axillary dissection (1 other node positive)
  - ER/PR-positive (50%)
  - HER2-positive (IHC 3+)
  - Just completed five years of tamoxifen

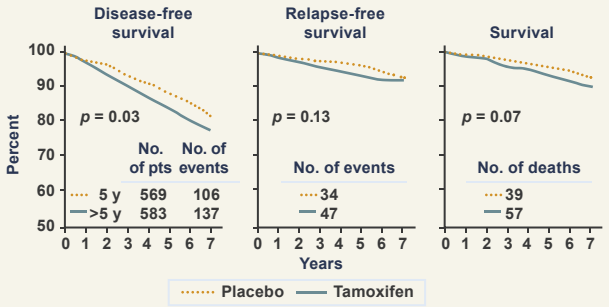
At this point, how would you manage this patient's systemic therapy?

1. Stop tamoxifen
2. Continue tamoxifen
3. Stop tamoxifen, start anastrozole
4. Stop tamoxifen, start letrozole
5. Stop tamoxifen, start exemestane
6. Stop tamoxifen, start raloxifene
7. Other

Slide 2.16

This interactive question will engender a discussion about how these new data sets are translated into clinical practice.

7 Years Follow-Up of NSABP-B-14: 5 versus > 5 Years of Adjuvant Tamoxifen: Node-Negative, ER-Positive



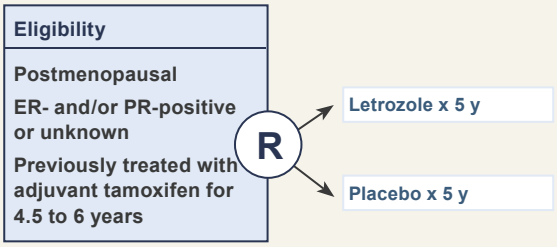
Source: Fisher B et al.Five versus more than five years of Tamoxifen… *J Natl Cancer Inst* 2001;93:684-90, by permission of Oxford University Press. Abstract

Slide 2.17

The risk of disease recurrence continues after five years of adjuvant tamoxifen, and methods to reduce this risk have been a subject of investigation. NSABP-B-14 demonstrated no advantage to continuing tamoxifen beyond five years in women with node-negative, ER-positive disease and, in fact, there was a reduced disease-free survival and a trend toward reduced overall survival in those women receiving more than five years of adjuvant tamoxifen. Research strategies have focused on other hormonal therapies with different mechanisms of action and potentially different mechanisms of resistance.

Letrozole versus Placebo in Women Completing at Least 5 Years of Adjuvant Tamoxifen

Protocol ID: CAN-NCIC-MA17
Accrual: 5,187 (Closed)



Source: Goss P et al. *N Engl J Med* 2003;349(19):1793-802. Abstract

Slide 2.18

CAN-NCIC-MA17 randomly assigned postmenopausal patients with hormone receptor-positive breast cancer who had received 4.5 to six years of adjuvant tamoxifen to letrozole or placebo for five years.

Slide 2.19

The trial included postmenopausal women with ER- and/or PR-positive primary breast cancer with no evidence of recurrence who had completed 4.5 to six years of tamoxifen.

MA17: Inclusion Criteria

- Postmenopausal women
- Histo-/cytologically confirmed breast carcinoma
- ER-positive and/or PgR-positive or both receptors unknown
- Any axillary lymph node status
- Completed approximately five years (4.5 to 6 years) of adjuvant tamoxifen
- No evidence of recurrence at time of randomization
- Performance status 0-2 (ECOG)

Source: NCI Physician Data Query, May 2004.

Slide 2.20

The MA17 trial was published in the *New England Journal of Medicine* in November 2003. Patient characteristics were virtually the same in the letrozole and placebo arms of the study.

MA17 Results: Patient Demographics

	Letrozole (n=2,575)	Placebo (n=2,582)
Median age (y)	62	62
Hormone receptor status (%)		
ER+ and/or PgR+	98	98
Both unknown	2	2
ECOG performance status (%)		
0	90.0	90.0
1	9.5	9.5
2	0.5	0.5

Source: Goss P. Presentation. SABCS, 2003;Abstract 42.

Slide 2.21

A six percent improvement in the estimated four-year disease-free survival rate associated with letrozole was statistically significant but was based on less than one percent of patients having been followed for four or more years.

MA17 Results: Disease-Free Survival and Recurrences

	Letrozole (n=2,575)	Placebo (n=2,582)	*p*-value
Estimated 4-y DFS rate*	93%	87%	<0.001
Events	75 (2.9%)	132 (5.1%)	<0.00008

Median duration of follow-up was 2.4 years.

*Based on <1% of patients having been followed for ≥4 years

Source: Goss P et al. *N Engl J Med* 2003;349(19):1793-802. Abstract

MA17 Results: Overall Survival

	Letrozole (n=2,575)	Placebo (n=2,582)	Hazard ratio (95% CI)	*p*-value
4-y OS rate	96%	94%	0.76 (0.48-1.21)	0.25
Events	31	42		

Median duration of follow-up was 2.4 years.

Source: Goss P et al. *N Engl J Med* 2003;349(19):1793-802. Abstract

Slide 2.22

While there was an advantage to letrozole in disease-free survival, the difference in overall survival was not statistically significant.

MA17 Results: Subanalysis of Nodal Status

	Risk of recurrence	Hazard ratio	*p*-value
Node-negative (n=2,581)	↓ 53%	0.47	0.005
Node-positive (n=2,370)	↓ 40%	0.60	0.003

Source: Goss P. Presentation. SABCS, 2003;Abstract 42.

Slide 2.23

Subset analysis revealed that letrozole decreased the risk of recurrence in patients with node-negative disease and in patients with node-positive disease.

MA17: Safety Profile

	Percent of patients		
	Letrozole (n=2,154)	Placebo (n=2,145)	*p*-value
Hot flashes	47	41	0.001
Arthralgia	21	17	<0.001
Myalgia	12	10	0.02
Edema	17	16	0.17
Hypercholesterolemia	12	12	0.67
Cardiovascular events	4	4	0.40
Fractures	4	3	0.24
Osteoporosis	6	5	0.07
Vaginal bleeding	4	6	0.01

The number of patients discontinuing treatment due to side effects was not significantly different in the letrozole and placebo arms (4.5% vs 3.6%, respectively; $p = 0.11$).

Source: Goss P et al. *N Engl J Med* 2003;349(19):1793-802. Abstract

Slide 2.24

Hot flashes and musculoskeletal symptoms were more common in the letrozole group than in the placebo group. Vaginal bleeding was more common in the placebo group. There was a suggestion of a higher rate of osteoporosis and fractures in the letrozole group than in the placebo group. While letrozole appears to be generally well tolerated, it is possible that the long-term adverse effects associated with letrozole therapy have been underestimated because the trial was stopped early.

Slide 2.25

This slide summarizes the key trial findings.

MA17: Summary of Efficacy Results

- MA17 met its primary endpoint, disease-free survival, at first interim analysis (based on 207 events, August 2003)
- Letrozole lowers the risk of recurrence by 43% compared to placebo ($p = 0.00008$)
- Letrozole improves the estimated four-year disease-free survival rate based on <1% of patients having been followed for ≥4 years: 93% of patients receiving letrozole; 87% of patients receiving placebo

Source: Goss P et al. *N Engl J Med* 2003;349(19):1793-802. Abstract

Slide 2.26

Since publication of the MA17 trial, a controversial question is how these data apply to patients with high-risk disease who completed five years of adjuvant tamoxifen several years earlier and are at risk of delayed relapse.

Case Discussion

- A 70-year-old healthy woman
  - S/P lumpectomy (1.2-cm, Grade 2 IDC)
  - Sentinel node-positive
  - Axillary dissection (1 other node positive)
  - ER/PR-positive (50%)
  - HER2-positive (IHC 3+)
  - Completed five years of tamoxifen three years ago

Slide 2.27

This interactive question will provoke a discussion about whether or not a cutoff exists in the time since adjuvant tamoxifen was completed. Note that the time can be varied in this question to generate discussion.

At this point, how would you manage this patient's systemic therapy?

1. Start letrozole
2. Start anastrozole
3. Start exemestane
4. No systemic therapy

Presentation 2:
Sequencing of Aromatase Inhibitors and Tamoxifen

Adjuvant Trials of Aromatase Inhibitors: Substitute or in Sequence with Tamoxifen

Slide 2.28

Worldwide, several ongoing and closed randomized clinical trials evaluate substituting or sequencing aromatase inhibitors with adjuvant tamoxifen.

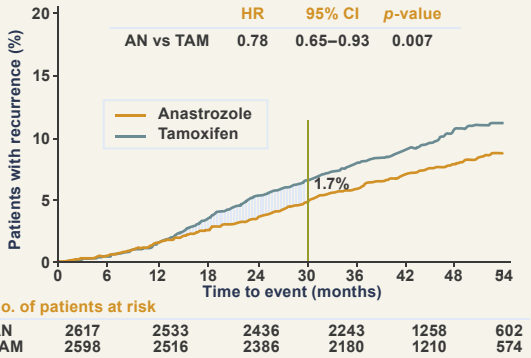
Aromatase Inhibitors: Adjuvant and Switching Trials

- Adjuvant: ATAC (advantage to anastrozole)
- Switch from tamoxifen at two to three years (advantage to aminoglutethimide, anastrozole and exemestane)
- Sequencing after five years of tamoxifen (advantage to letrozole)

Slide 2.29

The ATAC trial demonstrated a significant advantage for up-front adjuvant anastrozole. Several trials of switching to an aromatase inhibitor after two to three years of adjuvant tamoxifen also resulted in an advantage over continuing tamoxifen. The MA17 trial demonstrated benefit from continuing letrozole after five years of tamoxifen. Taken together, these data raise the question of whether the benefit seen with switching to an aromatase inhibitor simply reflects the advantage of utilizing optimal therapy (an aromatase inhibitor) rather than tamoxifen, and whether this "optimal therapy" would have been better given up front.

ATAC: Breast Cancer Events in the First 2.5 Years (ER-Positive)



*Censoring non-BC deaths before recurrence

Source: With permission from Buzdar A. Presentation. SABCS, 2002;Abstract 13.

Slide 2.30

One argument in favor of starting therapy with anastrozole as opposed to starting with tamoxifen and switching to an aromatase inhibitor is that during the first two to three years of follow-up with the ATAC trial, there was already a difference in relapse rates, so that delaying the use of anastrozole results in early relapses that might have been avoided.

Presentation 3:
Adjuvant Endocrine Therapy: Premenopausal Patients

Slide 3.1

In young patients with ER-positive disease, endocrine therapy may be as important as, or even more important than chemotherapy. Ongoing clinical trials are evaluating the strategy of ovarian suppression in combination with aromatase inhibitors. The long-term toxicity of adjuvant therapies is a particular concern when treating these young women. The implications of possible fertility impairment and premature menopause require consideration when discussing adjuvant therapy.

Adjuvant Endocrine Therapy: Premenopausal Patients

Slide 3.2

This case is an example of a young patient with high-risk disease. Note that, as in this case, many young premenopausal women continue to menstruate after chemotherapy, which has implications for the selection of adjuvant hormonal therapy.

Case Discussion

- A 33-year-old healthy woman
  - S/P lumpectomy (2.2-cm, Grade 2 IDC)
  - Sentinel node-positive
  - Axillary dissection (1 other positive node)
  - ER/PR-positive (50%)
  - HER2-positive (IHC 3+)
  - Received dose-dense AC→T (still menstruating)

Slide 3.3

Tamoxifen with or without ovarian suppression is a standard therapeutic option for premenopausal patients with primary breast cancer. Because the ATAC trial demonstrated that anastrozole was superior to tamoxifen in postmenopausal patients, several ongoing trials are evaluating ovarian suppression combined with aromatase inhibitors in premenopausal patients. Note: The use of single-agent aromatase inhibitors is contraindicated in premenopausal patients.

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

1. Tamoxifen
2. LHRH agonist
3. LHRH agonist + tamoxifen
4. LHRH agonist + anastrozole
5. LHRH agonist + another aromatase inhibitor
6. Aromatase inhibitor
7. None
8. Other

In a patient who ceases menstruation after chemotherapy, which endocrine therapy would you recommend?

1. Tamoxifen
2. LHRH agonist
3. LHRH agonist + tamoxifen
4. LHRH agonist + anastrozole
5. LHRH agonist + another aromatase inhibitor
6. Anastrozole
7. Another aromatase inhibitor
8. None
9. Other

Slide 3.4

This question is an opportunity to highlight to the audience the importance of confirmation of menopausal status in the selection of endocrine therapy, as menses may recur after brief interruption from chemotherapy in younger premenopausal women.

1995 Oxford Overview — Chemotherapy versus Tamoxifen: Premenopausal, ER-Positive

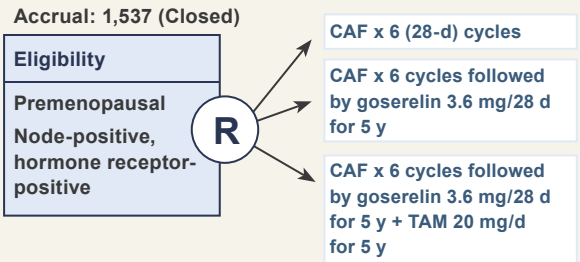
Relative risk reduction (%)	Recurrences	Deaths
Chemotherapy (n=565)	↓ 33 ± 8	↓ 20 ± 10
Tamoxifen 5 y (n=661)	↓ 45 ± 8	↓ 32 ± 10

Sources: Early Breast Cancer Trialists' Collaborative Group. *The Lancet* 1998;351(9114):1451-67. Abstract Early Breast Cancer Trialists' Collaborative Group. *The Lancet* 1998;352:932-42. Abstract

Slide 3.5

The 1995 Oxford Overview clearly demonstrated the importance of adjuvant hormonal therapy relative to chemotherapy in premenopausal patients with ER-positive disease.

Intergroup Trial 0101



Source: Davidson N. Presentation. ASCO, 2003;Abstract 15.

Slide 3.6

Intergroup trial 0101 randomly assigned premenopausal patients with node-positive, ER-positive disease to CAF chemotherapy, CAF plus goserelin, or CAF plus goserelin and tamoxifen. Unfortunately, the trial did not include a CAF plus tamoxifen-alone arm, preventing comparison with a common treatment for premenopausal patients.

Presentation 3:
Adjuvant Endocrine Therapy: Premenopausal Patients

Slide 3.7

The Austrian Breast Cancer Study Group Trial 12 randomly assigned premenopausal patients with ER-positive disease to goserelin plus anastrozole versus tamoxifen with a secondary randomization to the bisphosphonate zoledronate versus placebo.

Austrian Breast Cancer Study Group Trial 12 (ABCSG 12)

Accrual: 960 (Closed)

Eligibility

Premenopausal women with hormone-responsive breast cancer

R

- G + A + zoledronate
- G + A + control
- G + T + zoledronate
- G + T + control

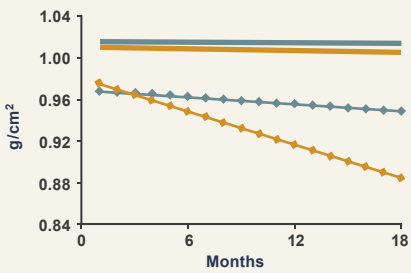
G = goserelin; A = anastrozole; T = tamoxifen

Source: Gnant M. Presentation. SABCS, 2002;Abstract 12.

Slide 3.8

While there is concern about the effects of long-term use of adjuvant aromatase inhibitors on bone, Dr Michael Gnant presented data at the 2002 San Antonio Breast Cancer Symposium demonstrating that zoledronate with anastrozole resulted in preservation of bone mineral density similar to that seen in patients receiving tamoxifen with zoledronate.

ABCSG Trial 12 BMD Regression L1-L4



Source: Adapted from Gnant M. Presentation. SABCS, 2002;Abstract 12.

Slide 3.9

The Suppression of Ovarian Function Trial (SOFT) randomly assigns premenopausal patients with ER-positive disease to tamoxifen, ovarian function suppression plus tamoxifen, or ovarian function suppression plus exemestane. Three thousand patients will be enrolled worldwide.

Suppression of Ovarian Function Trial (SOFT)

Target accrual: 3,000 (Open)

Eligibility

Premenopausal

Estradiol (E_2) in the premenopausal range either after or without chemotherapy

ER ≥ 10% and/or PgR ≥ 10%

R

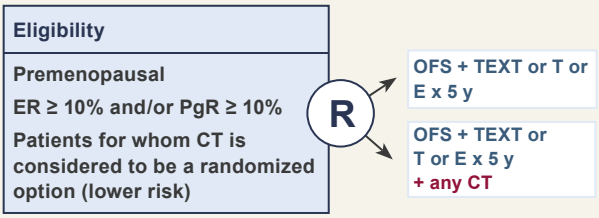
- Tamoxifen x 5 y
- OFS + tamoxifen x 5 y
- OFS + exemestane x 5 y

OFS = ovarian function suppression using triptorelin x 5 years or surgical oophorectomy or ovarian irradiation

Source: www.ibcsg.org

Premenopausal Endocrine Responsive CHEmotherapy Trial (PERCHE)

Target accrual: 1,750 (Open)



CT = chemotherapy; OFS = ovarian function suppression using triptorelin or surgical oophorectomy or radiation; TEXT = randomized trial comparing tamoxifen (T) versus exemestane (E)

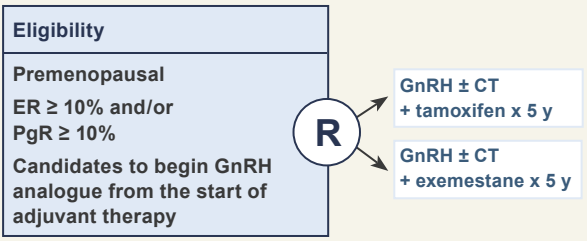
Source: www.ibcsg.org

Slide 3.10

The Premenopausal Endocrine Responsive Chemotherapy (PERCHE) trial will examine the value of adding chemotherapy to hormonal therapy in premenopausal patients with ER-positive disease. Patients are randomly assigned to endocrine therapy with or without chemotherapy. This trial will enroll 1,750 patients.

Tamoxifen and EXemestane Trial (TEXT)

Target accrual: 1,845 (Open)



CT = chemotherapy; GnRH = triptorelin x 5 years, but oophorectomy or radiation is allowed after 6 months

Source: www.ibcsg.org

Slide 3.11

The Tamoxifen and Exemestane Trial (TEXT) will enroll 1,845 premenopausal patients with ER-positive disease. Patients will be randomly assigned to a GnRH analogue and either tamoxifen or exemestane for five years with or without chemotherapy.

Aromatase Inhibitors in Premenopausal Women

- Have you prescribed aromatase inhibitors in the adjuvant setting for premenopausal women?

No	66%
Yes, alone	4%
Yes, with ovarian suppression	30%
Yes, both (alone and with ovarian ablation)	0%

- Have you prescribed aromatase inhibitors in the metastatic setting for premenopausal women?

No	49%
Yes, alone	8%
Yes, with ovarian suppression	37%
Yes, both (alone and with ovarian ablation)	6%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 3.12

Considerable controversy exists about the nonprotocol role of aromatase inhibitors in premenopausal women. While several important ongoing randomized trials are addressing this crucial question in the adjuvant setting, approximately one third of oncologists are already adapting this strategy into their practices.

Slide 4.1

In patients with hormone receptor-positive disease who wish to have breast conservation, neoadjuvant endocrine therapy has increasingly been considered a therapeutic option. Although the time to optimal tumor response may be longer than with chemotherapy, the efficacy and tolerability of hormonal therapy make it a particularly attractive option.

Neoadjuvant Endocrine Therapy

Slide 4.2

This case scenario involves an elderly patient with locally advanced high-risk disease in whom neoadjuvant therapy might be considered in view of her interest in breast conservation.

Case Discussion

- A 75-year-old healthy woman
  - Presents with a 4.4-cm breast mass
  - Biopsy reveals IDC
  - ER/PR-positive (50%)
  - HER2-positive (IHC 3+)
  - Metastatic workup is negative
  - Breast is small relative to tumor size
  - Patient wishes to have breast conservation

Slide 4.3

This interactive question will likely result in a broad range of responses. Traditionally, neoadjuvant hormonal therapy is more commonly utilized in Europe than in the United States, but it may be a more tolerable option in an elderly patient such as this woman.

What initial therapy would you most likely recommend?

1. Mastectomy
2. Neoadjuvant chemotherapy
3. Neoadjuvant aromatase inhibitor
4. Neoadjuvant tamoxifen
5. Neoadjuvant trastuzumab
6. Neoadjuvant chemotherapy plus trastuzumab
7. Neoadjuvant endocrine therapy plus trastuzumab
8. Other neoadjuvant therapy

BCS Rates: Neoadjuvant Hormone Therapy

Drug	No. of patients	No. of mastectomies pretherapy	No. of mastectomies post-therapy	Change (%)
Tamoxifen	65	41	15	63
Aromatase inhibitors	71	53	6	89

Source: Dixon M. Presentation. Cancer Educators Working Group Meeting, 2003.

Slide 4.4

At the 2003 Cancer Educators Working Group Meeting, Dr Michael Dixon reported a neoadjuvant endocrine study comparing tamoxifen and aromatase inhibitors in postmenopausal patients with ER-positive disease. Patients receiving the aromatase inhibitors had a 26 percent greater likelihood of breast preservation compared to those patients taking tamoxifen.

Russian Study of Neoadjuvant Endocrine Therapy (N=87)

	A	T	A+T	*p*-value
Overall objective response (clinical)	70%	44.4%	49%	0.048
Mammographic response	56%	36%	40%	0.058
Ultrasound response	44%	30%	32%	0.072
Breast-conserving surgery	42%	28%	30%	0.056

A = anastrozole; T = tamoxifen

Source: Semiglazov V et al. *Proc ASCO* 2003;Abstract 3538.

Slide 4.5

Semiglazov and colleagues conducted a neoadjuvant study of endocrine therapy mirroring the ATAC trial investigational arms. They demonstrated that anastrozole resulted in a significantly higher overall objective response, response by mammography and ultrasound, and rate of breast conservation than tamoxifen.

Response Rates: Neoadjuvant Anastrozole for Locally Advanced Breast Cancer

Tumor response	All patients (n=112)	HER2-negative (n=79)	HER2-positive (n=33)	Ki67 <10% (n=61)	Ki67 ≥10% (n=51)
Clinical complete response (cCR)	54.5%	60.8%	39.4%	63.9%	43.1%
Clinical partial response (cPR)	28.6%	34.2%	15.2%	32.8%	23.5%
Objective response (cCR+cPR)	83.0%	95.0%	54.5%	96.7%	66.7%
Pathological complete response	16.1%	21.5%	3.0%	23.0%	7.8%

Source: Milla-Santos A et al. *Proc ASCO* 2003;Abstract 154.

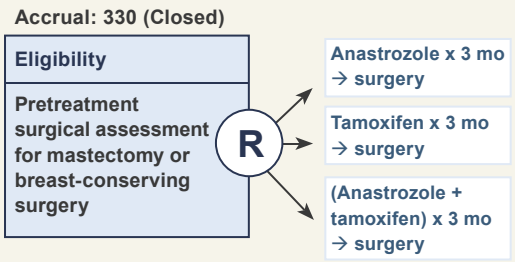
Slide 4.6

In a study by Dr Milla-Santos and colleagues, neoadjuvant anastrozole resulted in significant rates of clinical and pathologic complete response and overall objective response in patients with ER-positive disease, but response was greater in patients with HER2-negative disease than in patients with HER2-positive disease.

Slide 4.7

The IMPACT trial randomly assigned 330 patients with hormone receptor-positive disease to neoadjuvant anastrozole, tamoxifen or the combination, also mirroring the design of the adjuvant ATAC trial.

IMPACT: Study Design



Source: Smith I et al. Presentation. SABCS, 2003;Abstract 1.

Slide 4.8

Patients were postmenopausal with ER-positive, operable breast tumors greater than two centimeters. Patients eligible for breast conservation or mastectomy were included.

IMPACT Trial: Main Inclusion Criteria

- Postmenopausal
- Core biopsy invasive ER-positive breast cancer
- Operable ≥2 cm in diameter (excluding inflammatory)
- Patients eligible for breast-conserving surgery or mastectomy

Source: Smith I et al. Presentation. SABCS, 2003;Abstract 1.

Slide 4.9

The primary endpoint in the IMPACT trial was objective clinical response. Several secondary biological endpoints and conversion rates of planned mastectomy to breast-conserving surgery were evaluated.

IMPACT Main Endpoints

- Primary endpoint
  - Objective clinical response (caliper) (WHO ≥50% reduction in product of diameters)
- Secondary endpoints
  - Biological effects (reduction in Ki67)
  - Conversion rates of planned mastectomy to breast-conserving surgery
  - Clinical response in HER2-positive
  - Safety
  - Ultrasound response
  - Estradiol levels, lipids and bone markers over three months

Source: Smith I et al. Presentation. SABCS, 2003;Abstract 1.

IMPACT Trial: Patient Demographics

	Anastrozole (n=113)	Tamoxifen (n=108)	Combination (n=109)
Median age (range)	73 (52-90)	72 (50-88)	73 (52-86)
Tumor diameter by caliper by ultrasound	 4 (1-7) 3 (1-9)	 4 (2-10) 2 (1-11)	 4 (2-15) 2 (1-6)
<3cm* 3-5cm* >5cm*	20% 51% 27%	13% 60% 26%	16% 57% 25%
ER-positive	98%	99%	96%
Previous HRT	22%	26%	18%

*Tumor diameter measured in cm, median (range)

Source: Smith I et al. Presentation. SABCS, 2003;Abstract 1.

Slide 4.10

Results of the IMPACT trial were initially reported at the 2003 San Antonio Breast Cancer Symposium. Patient and tumor characteristics were well balanced across the three treatment arms. Note that a relatively high percentage of patients had tumors less than three centimeters.

IMPACT Trial: Key Findings

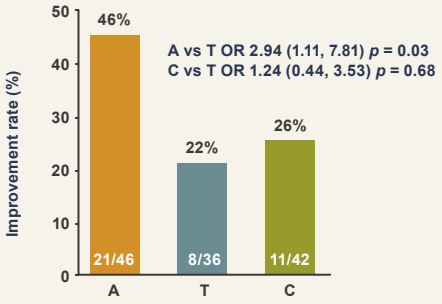
	A	T	C
Objective clinical tumor response	37.2%	36.1%	39.4%
Patients who became eligible for breast-conserving surgery after 3 months of treatment	45.7%	22.2%	26.2%
Geometric mean reductions in Ki67 after 2 weeks of treatment	76%	59%	64%

Sources: Smith I et al. *Breast Cancer Res Treat* 2003;Abstract 1. Dowsett M el al. *Breast Cancer Res Treat* 2003;Abstract 2.

Slide 4.11

Nearly one half of patients receiving preoperative anastrozole were eligible for breast-conserving surgery compared to 22 percent of patients receiving tamoxifen. A significant reduction in the tumor proliferation marker Ki67 was also observed with anastrozole. Note that no significant difference was observed in the rates of objective clinical tumor response.

IMPACT Trial: Improvement in Rates of Breast-Conserving Surgery



OR = odds ratio

Source: Smith I et al. Presentation. SABCS, 2003;Abstract 1.

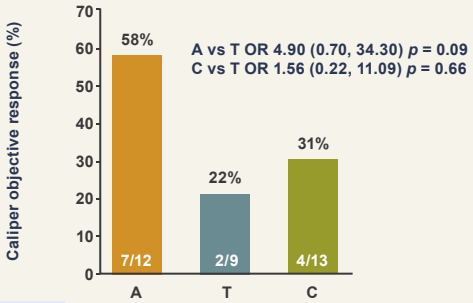
Slide 4.12

Rates of breast-conserving surgery were doubled for patients receiving anastrozole compared to those receiving tamoxifen. The combination of anastrozole plus tamoxifen was no more effective than tamoxifen alone.

Slide 4.13

Objective clinical response rate in patients with HER2-positive disease was significantly higher in patients receiving anastrozole compared to tamoxifen, with 58 and 22 percent response rates, respectively, in a modest number of patients.

IMPACT Trial: Clinical Response in HER2-Positive Tumors (34 out of 239 Patients)



OR = odds ratio

Source: Smith I et al. Presentation. SABCS, 2003;Abstract 1.

Slide 4.14

Dr Matt Ellis published the results of a Phase III trial that randomly assigned 324 patients with hormone receptor-positive disease not amenable to breast-conserving surgery to four months of preoperative letrozole or tamoxifen.

Phase III Trial of Letrozole versus Tamoxifen as Preoperative Therapy

Accrual: 324 (Closed)

Eligibility

- Postmenopausal women
- 10% ER and/or PgR staining by IHC
- Tumors not amenable to breast-conserving surgery

R → Letrozole x 4 mo → surgery

R → Tamoxifen x 4 mo → surgery

Tumor markers analyzed before and after treatment

Source: Ellis MJ et al. *J Clin Oncol* 2001;19:3808-16. Abstract

Slide 4.15

Patients with HER2-positive disease were more likely to respond to letrozole than to tamoxifen, although in a modest number of patients. Overall response rates and percent of patients undergoing breast-conserving surgery were improved in patients receiving four months of preoperative letrozole compared to patients receiving tamoxifen.

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

	Letrozole		Tamoxifen		
	Responders	%	Responders	%	*p*-value
Overall response	74/124	60	52/126	41	0.004
ErbB-1/2 positive	15/17	88	4/19	21	0.0004
ErbB-1/2 negative	55/101	54	42/100	42	0.0780
Underwent BCS*	60/124	48	45/126	36	0.036

*At baseline, all tumors were considered not amenable to breast-conserving surgery.

Source: Ellis MJ et al. *J Clin Oncol* 2001;19:3808-16. Abstract

Presentation 5:
Endocrine Therapy for DCIS and Women at High Risk for Breast Cancer

Endocrine Therapy for DCIS and Women at High Risk for Breast Cancer

Slide 5.1

The positive results of the Breast Cancer Prevention Trials NSABP-P-1 and NSABP-B-24 demonstrated benefit from tamoxifen in women at high risk and those with DCIS. These findings have stimulated interest in endocrine therapy for these women. Data from the ATAC trial have led to the development of further studies in both the chemoprevention and DCIS settings evaluating anastrozole for postmenopausal women.

Case Discussion

- A 63-year-old woman
  - 0.8-cm comedo DCIS
  - Margins clear to 1 cm
  - ER/PR-positive (50%)
  - Patient is receiving post-lumpectomy breast irradiation

Slide 5.2

This case can be used to initiate a discussion of some of the key current research issues in DCIS, such as the use of endocrine therapy and the need for radiation therapy.

Do you routinely request ER/PR assays in DCIS specimens?

- Yes
- No

Slide 5.3

While invasive cancer specimens are routinely assessed for hormone receptor status, it will be interesting to determine whether or not this is true of the audience's management of DCIS.

Slide 5.4

In this poll question, the most frequent responses will be tamoxifen or no therapy. Discussions may include the reduction in contralateral cancers associated with anastrozole in the ATAC trial, clinical trials evaluating the role of aromatase inhibitors in DCIS, such as NSABP-B-35 and IBIS-II, and nonprotocol use of these agents.

The tumor is ER- and PR-positive. What endocrine therapy, if any, would you most likely recommend?

1. Tamoxifen
2. Anastrozole
3. Letrozole
4. Exemestane
5. Other
6. None

Slide 5.5

Several key management issues in DCIS are controversial and are being investigated in ongoing clinical trials.

Key Issues in the Management of DCIS

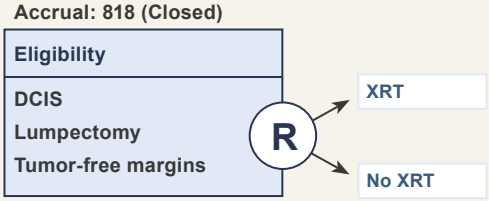
- Selection of patients for breast conservation
- Selection of patients for lumpectomy without radiation therapy
- Role of partial breast irradiation
- Role of tamoxifen and the impact of ER status
- Future endocrine therapy strategies

Slide 5.6

NSABP-B-17 established the value of radiation therapy in the treatment of DCIS.

NSABP-B-17: Radiation Therapy after Lumpectomy for DCIS

Protocol ID: NSABP-B-17
Accrual: 818 (Closed)



Stratification: Age, pathologic characteristics, detection method, axillary dissection

XRT = radiation therapy

Source: Fisher B et al. *J Clin Oncol* 1998;16(2):441-52. Abstract

NSABP-B-24: Tamoxifen versus Placebo after Lumpectomy and Irradiation for DCIS

Protocol ID: NSABP-B-24
Accrual: 1,804 (Closed)

Eligibility

DCIS including DCIS with LCIS, treated with lumpectomy

Node-negative

R

→ XRT + placebo x 5 y

→ XRT + tamoxifen x 5 y

Stratification: Age, pathologic characteristics, detection method, margin status

XRT = radiation therapy

Source: Fisher B et al. *The Lancet* 1999;353:1993-2000. Abstract

Slide 5.7

NSABP-B-24 demonstrated a stepwise improvement in local and contralateral tumor control with the use of breast radiotherapy and tamoxifen in women treated with lumpectomy.

NSABP-B-24: All Breast Cancer Events

	No. of events	Annual rate/100	Cumulative incidence (%)	RR	*p*-value
Placebo	130	2.93	13.4		
Tamoxifen	84	1.83	8.2	0.63	0.0009

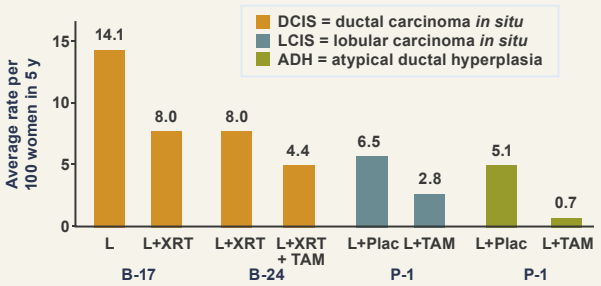
RR = rate ratio

Source: Fisher B et al. *The Lancet* 1999;353:1993-2000. Abstract

Slide 5.8

In the B-24 trial, patients treated with tamoxifen had a relative risk reduction of breast cancer events of 37 percent and an absolute improvement of 5.2 percent.

Invasive Cancer Risk Reduction in NSABP Studies of DCIS and Chemoprevention



L = lumpectomy; XRT = radiation therapy; TAM = tamoxifen; Plac = placebo

Sources: Fisher B. *Semin Oncol* 2001;28:400-18. Abstract Fisher B et al. *J Natl Cancer Inst* 1998;90(18):1361-70. Abstract

Slide 5.9

This slide demonstrates the impact of tamoxifen in reducing the risk of invasive cancer as seen in the NSABP clinical trials across the continuum of preinvasive disease, LCIS, ADH and DCIS.

Slide 5.10

An important outcome from the ATAC trial was the dramatic reduction in both noninvasive and invasive contralateral breast tumors observed in the anastrozole-treated group.

Contralateral Breast Cancers (CBC) in the ATAC Trial

	Anastrozole (n=3,125)	Tamoxifen (n=3,116)
CBC (invasive)	20	35
CBC (DCIS)	5	5

"Reductions in contralateral breast cancer rates remained in favor of anastrozole (OR = 0.62 [0.38-1.02], *p* = 0.062), with statistical significance achieved in the hormone receptor-positive sub-group (OR = 0.56 [0.32-0.98], *p* = 0.042)."

Sources: Buzdar A et al. *Breast Cancer Res Treat* 2002;Abstract 13. The ATAC Trialists' Group. *Cancer* 2003;98(9):1802-10. Abstract

Slide 5.11

At the 2002 San Antonio Breast Cancer Symposium, Craig Allred presented the analysis of more than 600 tumor blocks from NSABP-B-24 to determine the effects of tamoxifen on clinical outcomes as a function of ER status.

Retrospective Analysis of NSABP-B-24

- Baylor College of Medicine retrospectively evaluated the effects of tamoxifen on clinical outcomes as a function of ER status in NSABP-B-24.
- Analysis was based on 676 of the 1,804 patients (37% in the trial).
- Placebo (n=344), tamoxifen (n=332)

Source: Allred DC. Presentation. SABCS, 2002;Abstract 30.

Slide 5.12

In NSABP-B-24, approximately one fourth of patients were found to have ER-negative DCIS upon central laboratory review.

NSABP-B-24: Distribution of ER Status

ER status	Placebo	Tamoxifen	Overall
Negative	25%	20%	23%
Positive	75%	80%	77%

Source: Allred DC. Presentation. SABCS, 2002;Abstract 30.

Allred Score for ER Status (0-8)*

Percent staining score	Proportion of positive staining cells	Intensity score	Average intensity of positively stained cells
0	None	0	None
1	<1/100	1	Weak
2	1/100 to 1/10	2	Intermediate
3	1/10 to 1/3	3	Strong
4	1/3 to 2/3		
5	>2/3		

*Allred score = percent staining score + intensity score

Source: Harvey JM et al. *J Clin Oncol* 1999;17(5):1474-81. Abstract

Slide 5.13

This slide demonstrates Allred's scoring system to define ER positivity based on IHC. This scoring system is a combination of the proportion and intensity of the cells stained.

Distribution of ER Levels and Comparison between Central and Outside Labs

	Central assays (n=450)			Outside assays (n=226)
	Score	Cases (%)	Overall	Overall
neg	0	19.5		
	2	0.3	20% negative	30% negative
low	3	3.6		
	4	8.0		
	5	13.3		
	6	21.5	80% positive	70% positive
	7	18.7		
high	8	15.1		

Source: Allred DC. Presentation. SABCS, 2002;Abstract 30.

Slide 5.14

This slide demonstrates ER assay results in community and central reference laboratories.

Clinical Comparison of ER-Negative Results from Outside and Central Labs

Outside ER-negative results (n=64)

Events/patients (%)		Relative risk	*p*-value
Placebo	Tamoxifen	0.43 (↓57%)	0.20
10/39 (26%)	3/25 (12%)		

Central ER-negative results (n=89)

Events/patients (%)		Relative risk	*p*-value
Placebo	Tamoxifen	0.99 (↓1%)	0.98
11/48 (23%)	11/41 (27%)	no benefit	

Source: Allred DC. Presentation. SABCS, 2002;Abstract 30.

Slide 5.15

Patients identified by outside laboratories as having ER-negative disease benefit from tamoxifen, demonstrating that many of these are likely false negatives. In contrast, patients defined as having ER-negative disease by the central laboratory did not benefit from tamoxifen.

Slide 5.16

This analysis demonstrated convincingly that benefit from tamoxifen was entirely restricted to the cohort with ER-positive DCIS. This 50 to 60 percent benefit was seen in the reduction in risk of overall events and ipsilateral and contralateral recurrences.

NSABP-B-24: Recurrence Rates by ER Status and Tamoxifen Use

	ER-negative		ER-positive	
	Placebo	Tamoxifen	Placebo	Tamoxifen
Any event	26%	23%	23%	10%
Ipsilateral recurrence	18%	18%	13%	7%
Contralateral recurrence	6%	5%	8%	3%

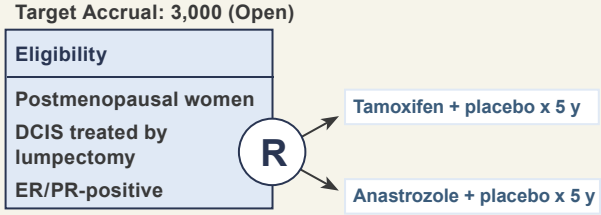
Source: Allred DC. Presentation. SABCS, 2002;Abstract 30.

Slide 5.17

NSABP-B-35 is a double-blind, placebo-controlled trial of tamoxifen versus anastrozole in postmenopausal women with ER-positive DCIS treated with lumpectomy. Note that this is the first NSABP DCIS trial requiring ER status confirmation.

NSABP-B-35: Anastrozole versus Tamoxifen in Postmenopausal Patients with DCIS

Protocol IDs: NSABP-B-35, CTSU
Target Accrual: 3,000 (Open)



Stratification: Age (<60 versus >60)

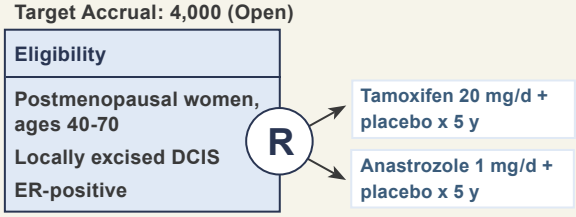
Source: NCI Physician Data Query, May 2004.

Slide 5.18

IBIS-II is being conducted in Europe with essentially the same design as the NSABP-B-35 trial for patients with DCIS.

IBIS-II: Tamoxifen versus Anastrozole in Postmenopausal Women with DCIS

Protocol IDs: CRUK-IBIS-II, EU-20226
Target Accrual: 4,000 (Open)



Source: www.ibis-trials.org/dcis

Case Discussion

- A 64-year-old woman
  - Recent breast biopsy: atypical hyperplasia
  - Mother died of breast cancer at age 56
  - Mild cerebrovascular accident two years ago

Slide 5.19

This is an example of a case of a woman at high risk for developing breast cancer with a potential contraindication to tamoxifen.

What chemoprevention strategy would you most likely recommend?

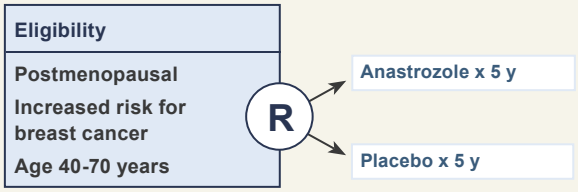
1. None
2. Tamoxifen
3. Anastrozole
4. Letrozole
5. Exemestane
6. Raloxifene

Slide 5.20

This question can be used to probe the audience for their current off-protocol management strategy for chemoprevention and for identifying patients who may not be candidates for tamoxifen.

Randomized Breast Cancer Prevention Trial of Anastrozole versus Placebo

Protocol ID: IBIS-II
Target Accrual: 6,000 (Open)



Source: IBIS-II Protocol, March 20, 2003. Cancer Research (UK) website, accessed February 2004. www.ibis-trials.org.

Slide 5.21

The IBIS-II trial not only evaluates anastrozole for the treatment of DCIS, but also examines this agent's potential in the treatment of women at high risk for developing breast cancer. The placebo control for the high-risk part of the trial highlights the international differences in interpretation of prevention strategies and overall women's health.

Slide 5.22

This question will tease out whether or not the audience is comfortable randomly assigning women at high risk of developing breast cancer to potentially receive a placebo. While some physicians are likely to be uncomfortable with this randomization because of the striking benefit seen with tamoxifen in NSABP-P-1, others regard IBIS-II as evaluating the effects of aromatase inhibitors on overall health, and, because of the incidence of serious side effects with this agent, remain unconvinced that tamoxifen provides more benefit than risk in otherwise healthy women.

If the IBIS-II trial (placebo versus anastrozole) were available to you, would you encourage participation for this patient?

- Yes
- No

Slide 5.23

In NSABP-P-1, women at high risk for developing breast cancer (Gail risk >1.66 or age ≥60) were randomly assigned to receive placebo or tamoxifen for five years. Over 13,000 women were enrolled in this landmark study.

NSABP-P-1: Placebo-Controlled Trial of Tamoxifen for Breast Cancer Prevention

Protocol IDs: NSABP-P-1, BCPT-1, NCI-P91-0022
Target Accrual: 13,388 (Closed)

Eligibility

Premenopausal women at high risk or postmenopausal women ≥60 years of age

R → **Placebo x 5 y**

R → **Tamoxifen 20 mg/d x 5 y**

Stratification: Age, Gail model risk, race, history of LCIS

Source: Fisher B et al. *J Natl Cancer Inst* 1998;90:1371-88. Abstract

Slide 5.24

The IBIS-I trial in Europe randomly assigned over 7,000 patients at high risk for developing breast cancer to receive placebo or tamoxifen.

IBIS-I: Study of Tamoxifen for Prevention of Breast Cancer in Women at High Risk

Protocol IDs: NCRI-IBIS, EU-94041, UKCCCR-IBIS
Accrual: 7,152 (Closed)

Eligibility

Pre- and postmenopausal women at high risk

Ages 35-70

R → **Placebo x 5 y**

R → **Tamoxifen 20 mg/d x 5 y**

Stratification: Study site

Source: IBIS Investigators. *The Lancet* 2002;360:817-24. Abstract

NSABP-P-1 and IBIS-I Studies: Breast Cancer Events

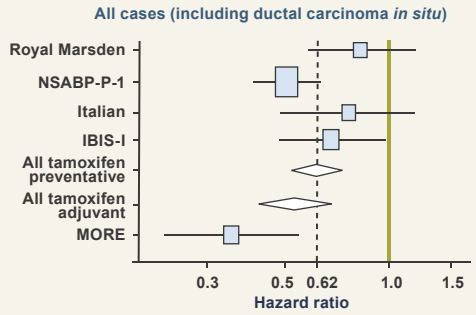
Trial	Total invasive and noninvasive cancer		
	Placebo	Tamoxifen	Odds ratio 95% CI
NSABP-P-1	244	124	0.51 0.39-0.66
IBIS-I	101	69	0.68 0.50-0.92

Sources: Chlebowski RT et al. *J Clin Oncol* 2002;20(15):3328-43. Abstract IBIS Investigators. *The Lancet* 2002;360(9336):817-24. Abstract

Slide 5.25

In the P-1 trial, a 49 percent reduction in the relative risk of developing breast cancer was associated with tamoxifen use. With less than one half of the number of breast cancer events, IBIS-I reported a 32 percent relative risk reduction. The absolute risk reduction expected in an individual woman depends on her calculated breast cancer risk, with women at higher risk having greater potential benefit.

Chemoprevention Meta-Analysis Incidence of Invasive Cancer: All Cases

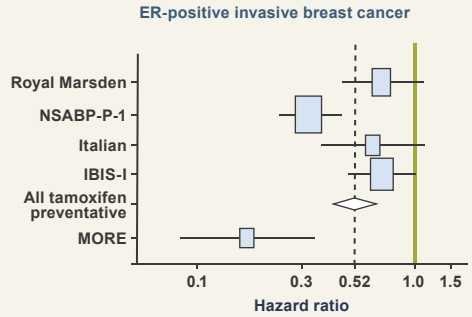


Source: With permission from Cuzick et al. *The Lancet* 2003;361:296-300. Abstract

Slide 5.26

A meta-analysis of published tamoxifen chemoprevention trials demonstrated a reduction in breast cancer incidence of 38 percent with tamoxifen.

Chemoprevention Meta-Analysis Incidence of ER-Positive Cancer



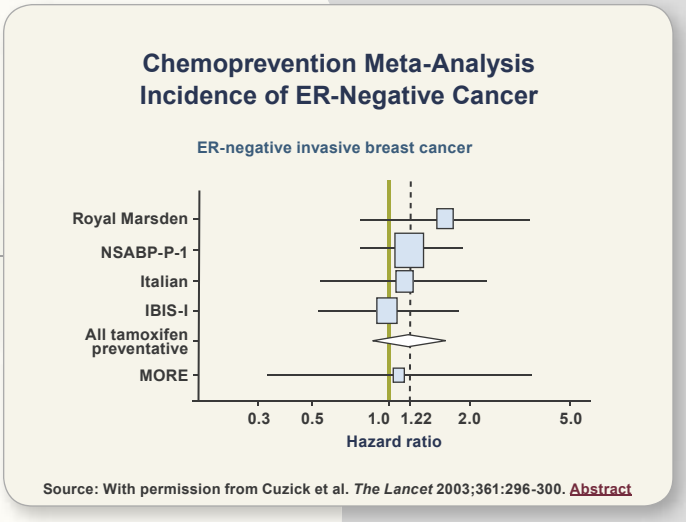
Source: With permission from Cuzick et al. *The Lancet* 2003;361:296-300. Abstract

Slide 5.27

The incidence of invasive ER-positive cancer was reduced by 48 percent in the tamoxifen prevention trials.

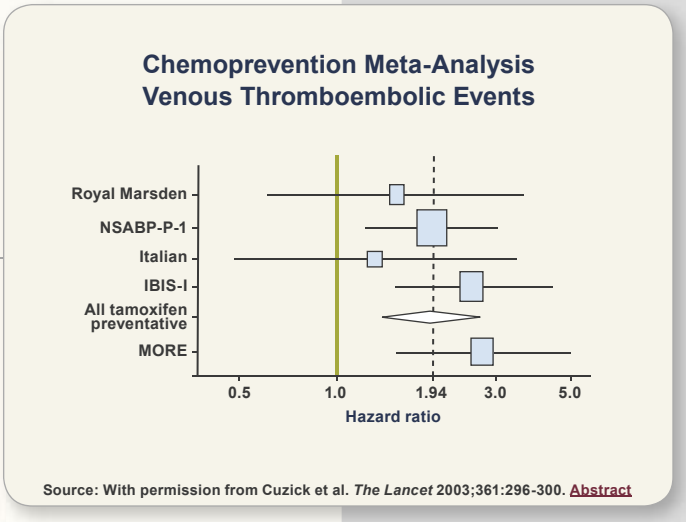
Slide 5.28

No statistically significant change in the incidence of ER-negative invasive breast cancer was observed.



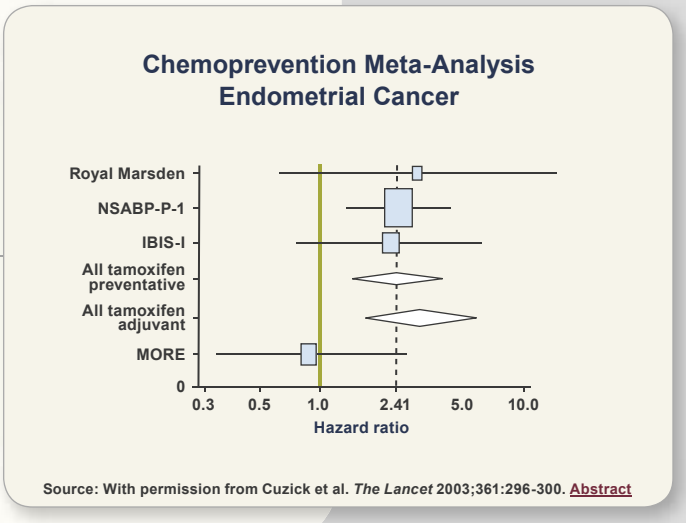
Slide 5.29

The combined data from the prevention trials indicated that the incidence of both venous thromboembolic events and strokes were significantly greater in women receiving tamoxifen. The Oxford Overview update indicated that tamoxifen-associated excess mortality related to vascular events was approximately one death attributed to pulmonary embolus per 1,000 postmenopausal women treated for five years.

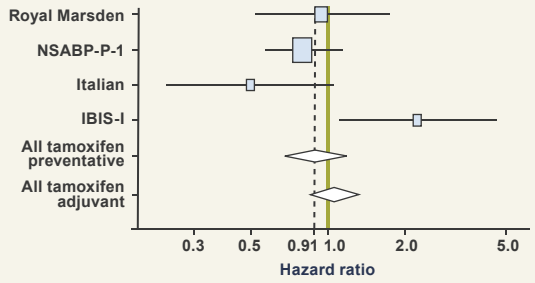


Slide 5.30

Tamoxifen increases endometrial cancer risk in postmenopausal women approximately two- to four-fold. In the Oxford Overview update, tamoxifen-associated excess mortality related to endometrial cancer was approximately one death per 1,000 postmenopausal women.



Chemoprevention Meta-Analysis Death from Any Cause



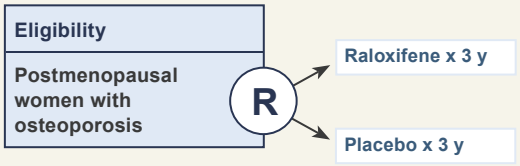
Source: With permission from Cuzick et al. *The Lancet* 2003;361:296-300. Abstract

Slide 5.31

Overall, tamoxifen had no effect on all-cause mortality in the tamoxifen prevention trials. No excess deaths resulted from endometrial or other types of cancer, or cardiac and vascular events except for pulmonary embolism.

Multiple Outcomes of Raloxifene Evaluation (MORE)

Protocol ID: MORE trial
Accrual: 7,705 (Closed)



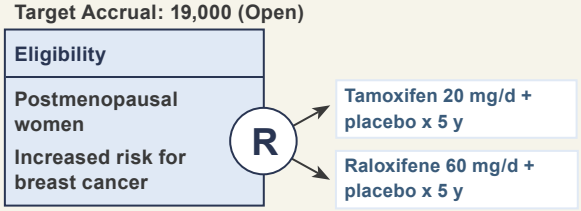
Source: Cummings SR et al. *JAMA* 1999;281:2189-97. Abstract

Slide 5.32

The MORE trial was designed to test whether three years of raloxifene reduced the risk of fractures in postmenopausal women with osteoporosis. Reduction in the risk of invasive breast cancer, a secondary endpoint, was 76 percent during treatment with raloxifene compared to placebo.

Phase III Study of Tamoxifen and Raloxifene for Breast Cancer Prevention

Protocol ID: STAR, NSABP-P-02
Target Accrual: 19,000 (Open)



Stratification: Age, Gail model risk, race, history of LCIS, hysterectomy status

Source: NSABP Protocol P-2, May 2, 2003.

Slide 5.33

The STAR trial (NSABP-P-2) is currently open for accrual, with a target of 19,000 women. This trial randomly assigns postmenopausal women at high risk for developing breast cancer to tamoxifen or raloxifene. The interest in raloxifene as a chemopreventive agent stems from observations in the MORE (Multiple Outcomes of Raloxifene) trial in which a decreased incidence of breast cancer was noted. Importantly, the MORE trial was not designed to specifically evaluate the effects of this agent on breast cancer risk, as it was performed in a group of women with osteoporosis and was designed to evaluate its effect on bone.

Slide 6.1

The number of endocrine agents available to treat women with ER-positive metastatic disease is expanding. The optimal sequencing of these agents in the metastatic setting is controversial.

Management of ER-Positive Metastatic Disease

Slide 6.2

This case scenario describes a woman with an ER-positive primary breast tumor who develops metastases while receiving adjuvant tamoxifen. Following this case is a series of similar related cases for comparison.

Case Discussion

- A 68-year-old woman
  - History of breast cancer three years ago
  - Two nodes positive
  - ER/PR-positive (50%)
  - HER2-negative
  - Received AC → T followed by tamoxifen
  - While on tamoxifen, develops bone and lung metastases (minimal rib pain)
  - Markers elevated

Slide 6.3

This case should elicit a discussion of the up-front treatment options in postmenopausal patients with ER-positive metastatic disease (ie, single-agent versus combination chemotherapy; chemo-therapy versus hormonal therapy).

What systemic therapy would you most likely recommend?

1. Hormonal therapy
2. Single-agent chemotherapy
3. Combination chemotherapy
4. Chemotherapy combined with or followed by hormonal therapy
5. None
6. Other

What endocrine therapy, if any, would you most likely recommend?

1. Anastrozole
2. Letrozole
3. Exemestane
4. Fulvestrant
5. Megestrol acetate
6. Other
7. None

Slide 6.4

This woman is typical of many patients who have been treated with adjuvant tamoxifen. Most research leaders believe that aromatase inhibitors and fulvestrant are equally effective and tolerable in this scenario. Choices in this type of situation are often determined by patient preference for the method of administration.

Case Discussion

- A 68-year-old woman
  - History of breast cancer three years ago
  - Two nodes positive
  - ER/PR-positive (50%)
  - HER2-negative
  - Received AC → T followed by anastrozole
  - While on anastrozole develops bone and lung metastases (minimal rib pain)
  - Markers elevated

Slide 6.5

This is the same case scenario, but this woman received adjuvant anastrozole rather than tamoxifen. This scenario is becoming increasingly common as the use of anastrozole in the adjuvant setting increases.

What endocrine therapy, if any, would you most likely recommend?

1. Tamoxifen
2. Fulvestrant
3. Letrozole
4. Exemestane
5. Megestrol acetate
6. Other
7. None

Slide 6.6

This question can be used to launch a discussion of the choice of endocrine therapy after failure of a nonsteroidal aromatase inhibitor.

Presentation 6:
Management of ER-Positive Metastatic Disease

Slide 6.7

This is the same case scenario, but this woman presents *de novo* with metastatic disease (ie, did not receive any adjuvant chemotherapy or endocrine therapy).

Case Discussion

- A 68-year-old woman
  - Presents with 2-cm breast tumor
  - ER/PR-positive
  - HER2-negative
  - Found to have lung and bone metastases (minimal rib pain)
  - Markers elevated

Slide 6.8

This question can be used to start a discussion about selection of systemic therapy in patients presenting *de novo* with metastatic disease.

What systemic therapy would you most likely recommend?

1. Hormonal therapy
2. Single-agent chemotherapy
3. Combination chemotherapy
4. Chemotherapy combined with or followed by hormonal therapy
5. None
6. Other

Slide 6.9

If endocrine therapy is selected for first-line treatment, this question can be used to launch a discussion about selection of therapy in a patient who is hormone therapy naïve.

What endocrine therapy, if any, would you most likely recommend?

1. Tamoxifen
2. Anastrozole
3. Letrozole
4. Exemestane
5. Fulvestrant
6. Megestrol acetate
7. Other
8. None

Advances in the Treatment of Metastatic Breast Cancer

- Hormonal therapy
  - Anastrozole, letrozole, exemestane, fulvestrant
- Chemotherapy
  - Docetaxel, paclitaxel, albumin nanoparticle paclitaxel, capecitabine, gemcitabine, vinorelbine
- Biologic agents
  - Trastuzumab
- Supportive care
  - Colony stimulating factors, bisphosphonates

Source: Ravdin M. Presentation. Cancer Educators Working Group Meeting, 2003.

Slide 6.10

This slide provides an overview of advances in the treatment of metastatic disease with hormonal therapy, chemotherapy, biologic therapy and supportive care.

Canadian Study of Metastatic Breast Cancer: Overall Survival

Cohort	N	Median	1 year	2 year	New agents
1991-1992	424	435 days	56%	34%	—
1994-1995	561	449 days	55%	33%	paclitaxel, vinorelbine
1997-1998	641	562 days	64%	44%	docetaxel, aromatase inhibitors
1999-2001	525	661 days	71%	45%	capecitabine, trastuzumab

Source: Chia SKL. ASCO, 2003;Abstract 22.

Slide 6.11

A Canadian epidemiological study of survival after diagnosis of metastatic disease demonstrates an improvement in median overall survival over the past 10 years with the addition of newer therapeutic agents. From 1991 to 2001, the median overall survival increased from 435 days to 661 days — more than a seven-month improvement.

Use of Hormonal Therapies for Metastatic Breast Cancer

	1991-1992	1994-1995	1997-1998	1999-2001
Tamoxifen	50%	46%	48%	36%
Megestrol acetate	42%	45%	30%	10%
Aminoglutethimide	18%	18%	4%	0%
Nonsteroidal AI	6%	16%	44%	48%
Steroidal AI	1%	3%	7%	9%

AI = aromatase inhibitor

Source: Chia SKL. Presentation. ASCO, 2003;Abstract 22.

Slide 6.12

Over the past decade, hormonal therapy for metastatic disease, using tamoxifen, megestrol acetate and aminoglutethimide, has declined, but utilization of third-generation aromatase inhibitors, especially nonsteroidal aromatase inhibitors, has significantly increased.

Slide 6.13

Extending the duration and quality of life remain the primary treatment goals in metastatic breast cancer. In addition, the metastatic setting is utilized as a testing ground for adjuvant treatment strategies.

What are the Goals of the Treatment of Metastatic Breast Cancer?

- Palliation
- Prevention of symptoms
- Improvement in overall survival
- Research: Testing ideas for adjuvant therapy

Source: Ravdin M. Presentation. Cancer Educators Working Group Meeting, 2003.

Slide 6.14

More options for hormonal therapy, chemotherapy, targeted biologic agents and supportive care treatments are available for patients in the metastatic setting.

What are the Tools for the Treatment of Metastatic Breast Cancer?

- Hormonal therapy
- Chemotherapy
- Targeted therapy
- Supportive care (for bone, bone marrow, pain)

Source: Ravdin M. Presentation. Cancer Educators Working Group Meeting, 2003.

Slide 6.15

One of the most important principles guiding treatment of metastatic breast cancer is palliation, reflected in TWiST. This entails utilizing treatments with a favorable therapeutic index, with reduction of tumor symptoms without adding toxicity. Countering that approach is the idea that early aggressive therapy may be toxic, but in the end, may improve survival. The most dramatic example is high-dose chemotherapy with stem-cell support. A final important principle is to use targeted therapeutic approaches whenever possible, based on ER and HER2 status.

What are the Principles Guiding the Treatment of Metastatic Breast Cancer?

- **T**ime **W**ithout **S**ymptoms or **T**oxicity (**TWiST**)
- Early treatment may be best
  - Why adjuvant therapy works
- If possible, use targeted therapy
  - By ER/PgR status, HER2 status

Source: Ravdin M. Presentation. Cancer Educators Working Group Meeting, 2003.

Special Considerations in Selecting Treatment

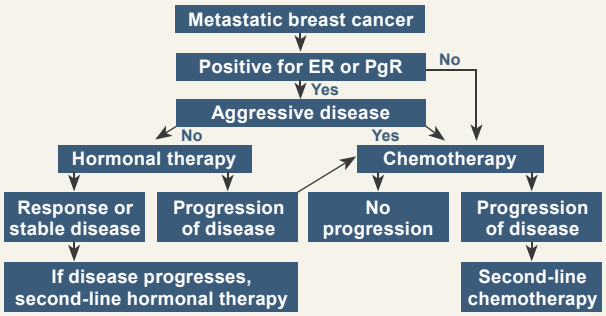
- Tumor-related symptoms, organ dysfunction
- Comorbidity, performance status
- ER/PgR and HER2 status
- Prior systemic therapy
- Patient goals and preferences

Source: Ravdin M. Presentation. Cancer Educators Working Group Meeting, 2003.

Slide 6.16

Selection of treatment is driven by the severity of the disease — whether it is life threatening or causing symptoms — and how much a rapid response is needed. It's also driven by knowledge of ER/PgR and HER2 status and by what therapy the patient has previously received. Comorbidity is also an important factor to consider. Finally, the patient's goals and preferences must be understood and discussed. Some patients may want a response at any cost, while others prefer to minimize toxicity.

Treatment of HER2-Negative Metastatic Breast Cancer



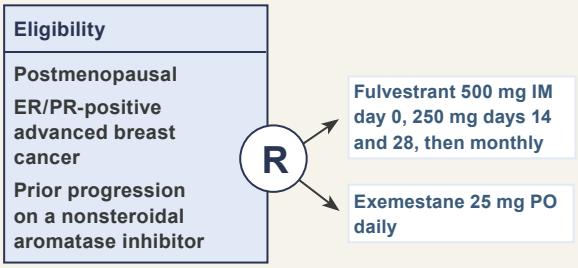
Source: Ravdin M. Presentation. Cancer Educators Working Group Meeting, 2003.

Slide 6.17

This slide provides a general schema for the treatment of HER2-negative metastatic breast cancer. Patients who have aggressive disease may receive chemotherapy, whereas those patients who have more indolent disease receive hormonal therapy. Of course, patients with ER-negative tumors will receive chemotherapy. These essentially reflect the NCCN guidelines approach.

Evaluation of Fulvestrant and Exemestane Clinical Trial (EFECT)

Protocol ID: EFECT
Target Accrual: 660 (Open)



Source: Sahmoud T. Poster. Lynn Sage Breast Cancer Symposium, 2003.

Slide 6.18

The Evaluation of Fulvestrant and Exemestane Clinical Trial (EFECT) will randomly assign 660 postmenopausal women with ER-positive advanced breast cancer who have disease progression on a nonsteroidal aromatase inhibitor to receive either fulvestrant or exemestane. In this study, patients receiving fulvestrant will be given an initial loading dose of fulvestrant, followed by standard monthly doses.

Slide 6.19

Fulvestrant is the first in a novel class of agents called selective estrogen receptor downregulators (SERDs). Its chemical structure is similar to that of estradiol with the addition of an alkylsulphinyl side chain.

Slide 6.20

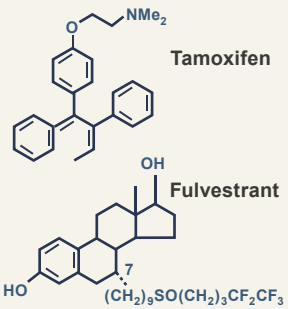
Unlike tamoxifen, which has both agonistic and antagonistic effects on the estrogen receptor, fulvestrant is a "pure" antiestrogen. This agent binds to the estrogen receptor with 100 times greater affinity than tamoxifen and results in receptor degradation. Fulvestrant is also unique in that it does not cross the blood-brain barrier. In preclinical testing it was found to be more effective than tamoxifen in xenograft models and effective in tamoxifen-resistant tumors. It is administered as a 250-mg intramuscular injection (either two 2.5-cc injections or one 5-cc injection).

Slide 6.21

This slide is a schematic of fulvestrant's mode of action. (1) Fulvestrant binds to the ER, disassociating receptor-associated proteins (RAPS). (2) Fulvestrant triggers degradation (downregulation) of ER. (3) The fulvestrant-ER complex results in reduced dimerization and nuclear localization. (4) There is reduced binding of the fulvestrant-ER complex to estrogen-sensitive genes. (5) Transcription of estrogen-sensitive genes is blocked. AF1 and AF2 are both inactive; thus, no coactivators are recruited to stimulate or inhibit the activity of RNA polymerase II (RNA POLII).

Fulvestrant Profile

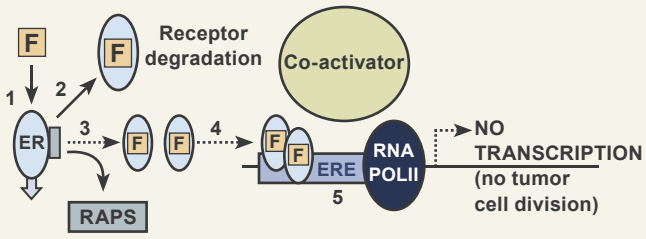
- The first in a novel drug class
- ER downregulator
- Steroidal antiestrogen
- Alkylsulphinyl side chain



Steroidal "Pure" Antiestrogen Fulvestrant

- Binds to ER resulting in receptor degradation
- Affinity for ER approximately 100 times that of tamoxifen
- Does not cross the blood-brain barrier
- More effective than tamoxifen in xenograft models and effective in tamoxifen-resistant tumors
- 250-mg monthly IM injection

Mode of Action of Fulvestrant



F = fulvestrant
RAPS = receptor associated proteins

Adapted with permission from: Wakeling AE. *Endocr Relat Cancer* 2000;7:17-28. Abstract

Trials 20 and 21: Fulvestrant versus Anastrozole

Postmenopausal women with advanced breast cancer who previously received endocrine treatment for advanced breast cancer

↓

Trial 20: International, randomized 1:1, open, parallel-group
Trial 21: North American, randomized 1:1, double-blind, double-dummy, parallel group

↓

Fulvestrant 250 mg IM once monthly	Anastrozole 1 mg daily orally
Trial 20: 1 x 5 mL (n=222)	Trial 20: (n=229)
Trial 21: 2 x 2.5 mL (n=206)	Trial 21: (n=194)

↘ ↙

Analysis after 340 events (progression or death prior to progression)

Sources: Howell A et al. *J Clin Oncol* 2002;20:3396-403. Abstract Mauriac L et al. *Eur J Cancer* 2003;39(9):1228-33. Abstract Osborne CK et al. *J Clin Oncol* 2002;20:3386-95. Abstract

Slide 6.22

Trials 20 (International) and 21 (North American) included postmenopausal women with advanced breast cancer who had previously received endocrine treatment. These trials randomly assigned patients to receive either fulvestrant or anastrozole.

Differences between North American and International Fulvestrant Trials

Blinding	North American double-blind	International open-label
Frequency of follow-up		
Fulvestrant	1 mo	1 mo
Anastrozole	1 mo	3 mo
Fulvestrant administration (intramuscular)	2 X 125 mg (2.5 mL each)	1 X 250 mg (5 mL)

Sources: Howell A et al. *J Clin Oncol* 2002;20:3396-403. Abstract Mauriac L et al. *Eur J Cancer* 2003;39(9):1228-33. Abstract Osborne CK et al. *J Clin Oncol* 2002;20:3386-95. Abstract

Slide 6.23

Although these studies were designed for combined analysis, key differences exist between the two trials. The North American trial (21) had a double-blind, double-dummy design, and patients on both arms were evaluated in monthly follow-up. In contrast, the International trial (20) was an open-label study in which patients receiving fulvestrant were evaluated monthly, whereas those receiving anastrozole were seen every three months.

Fulvestrant versus Anastrozole: Efficacy Data

	Trial 0020[1]		Trial 0021[2]		Combined analyses[3]	
	F	A	F	A	F	A
	n=222	n=229	n=206	n=194	n=428	n=423
Median time to progression	5.5 mo	5.1 mo	5.4 mo	3.4 mo	5.4 mo	4.1 mo
Clinical benefit*	44.6%	45.0%	42.2%	36.1%	43.5%	40.9%
Median duration of response	15 mo	14.5 mo	19.0 mo	10.8 mo	16.7 mo	13.6 mo

Clinical benefit (CR + PR + SD ≥ 24 weeks)

F = fulvestrant; A = anastrozole

Sources: [1]Howell A et al. *J Clin Oncol* 2002;20:3396-403. Abstract [2]Osborne CK et al. *J Clin Oncol* 2002;20:3386-95. Abstract [3]Parker LM et al. *Proc ASCO* 2002;Abstract 160.

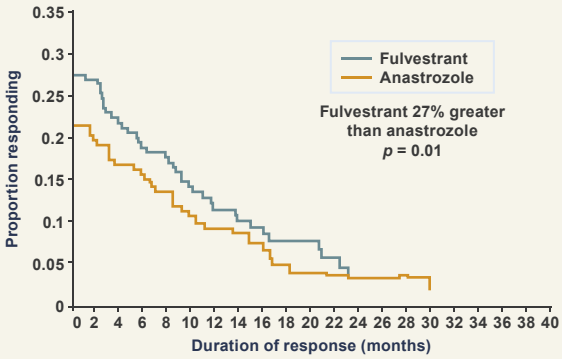
Slide 6.24

Overall, in both trials, fulvestrant and anastrozole had comparable efficacy in terms of median time to progression and clinical benefit. A duration of response advantage was observed for fulvestrant versus anastrozole (19 months vs 10.8 months) in the North American but not the International study. The discrepancy between these data sets may be related to the differences in trial design and frequency of follow-up previously mentioned. The combined analysis further evaluated the duration of response in patients responding, and again showed an advantage for fulvestrant.

Slide 6.25

When duration of response was examined from the onset of response (as opposed to from randomization), the duration of response was 27 percent greater for fulvestrant than for anastrozole in Trial 20.

Trial 20: Duration of Response from Start of Response to Progression (All Patients)

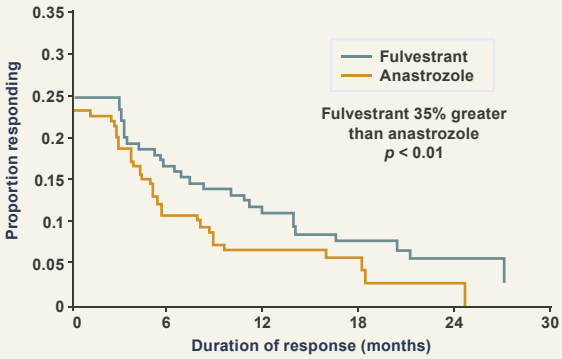


Source: With permission from Howell A et al. *J Clin Oncol* 2002;20:3396-403. Abstract

Slide 6.26

Again, defining duration of response as the time from the start of the response to disease progression, fulvestrant had a 35 percent greater duration of response than anastrozole in Trial 21.

Trial 21: Duration of Response from Start of Response to Progression (All Patients)



Source: With permission from Osborne CK et al. *J Clin Oncol* 2002;20:3386-95. Abstract

Slide 6.27

In Trials 20 and 21, patient characteristics and prior therapies were well balanced between the fulvestrant and anastrozole treatment arms.

Trials 20, 21: Patient Characteristics

	Fulvestrant (n=428)	Anastrozole (n=423)
Mean age (years)/range	63 (33-89)	63 (33-94)
Mean weight (kg)/range	70 (37-127)	70 (40-134)
Hormone receptor status (%)		
ER- and/or PR-positive	80	83
ER/PR unknown	15	12
ER- and/or PR-negative	5	5
Prior treatment (%)		
Cytotoxic chemotherapy	52	52
Endocrine therapy for advanced disease	55	53
Adjuvant endocrine therapy	57	56

Source: Robertson JFR et al. *Cancer* 2003;98(2):229-38. Abstract

Trials 20, 21: Best Objective Response

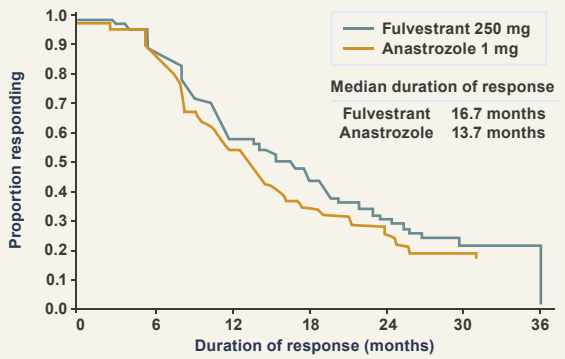
	Number of patients (%)	
	Fulvestrant (n=428)	Anastrozole (n=423)
Complete response (CR)	20 (4.7)	11 (2.6)
Partial response (PR)	62 (14.5)	59 (13.9)
Objective response (CR+PR)	82 (19.2)	70 (16.5)
Stable disease ≥ 24 weeks	104 (24.3)	103 (24.3)
Clinical benefit (CR + PR + SD ≥ 24 weeks)	186 (43.5)	173 (40.9)

Source: Mauriac L. *Eur J Can* 2003;39:1228-33. Abstract

Slide 6.28

Combined analysis of Trials 20 and 21 did not demonstrate a significant difference in objective response rates, stable disease or clinical benefit between fulvestrant and tamoxifen.

Trials 20, 21: Duration of Response from Randomization to Progression

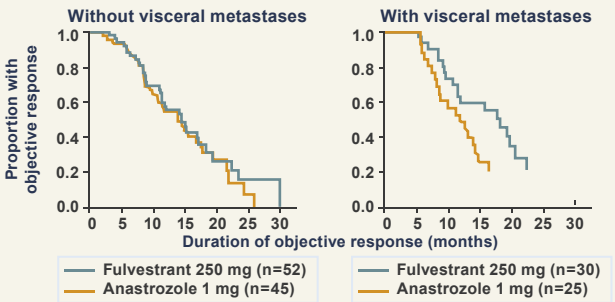


Source: With permission from Robertson J et al. *Cancer* 2003;98(2):229-38. Abstract

Slide 6.29

In the combined analysis, an extended follow-up to a median of 22.1 months was performed to further evaluate duration of response. The duration of response from randomization to progression in patients responding was significantly greater with fulvestrant than with anastrozole (16.7 months versus 13.7 months).

Trials 20, 21: Duration of Objective Response



Reprinted from *European Journal of Cancer*, Vol 39, Mauriac L, Fulvestrant (Faslodex™) Versus Anastrozole for the Second-Line Treatment of Advanced Breast Cancer in Subgroups of Postmenopausal Women with Visceral and Non-Visceral Metastases: Combined Results From two Multicentre Trials: 1228-33, 2003, with permission from Elsevier. Abstract

Slide 6.30

In a retrospective subgroup analysis of combined data from Trials 20 and 21, responses to fulvestrant versus anastrozole were evaluated in patients with and without visceral metastases. The median duration of objective response of 17.5 months with fulvestrant and 11.7 months with anastrozole in patients with visceral metastases suggest that responses to both agents are durable. Overall, this analysis demonstrated that fulvestrant is effective in patients with and without visceral metastases.

Slide 6.31

In terms of tolerability of the agents, patients receiving fulvestrant experienced significantly fewer joint disorders than those receiving anastrozole. The rate of other adverse events was similar between the two treatment groups.

Trials 20, 21: Tolerability — Predefined Adverse Events

	Number of adverse events (%)		
	Fulvestrant (n=423)	Anastrozole (n=423)	*p*-value
Hot flashes	89 (21.0)	87 (20.6)	0.91
Gastrointestinal disturbances	196 (46.3)	185 (43.7)	0.53
Weight gain	4 (0.9)	7 (1.7)	0.35
Vaginitis	11 (2.6)	8 (1.9)	0.51
Thromboembolic disease	15 (3.5)	17 (4.0)	0.68
Joint disorders	23 (5.4)	45 (10.6)	0.0036
Urinary tract infection	31 (7.3)	18 (4.3)	0.06
Withdrawn due to AE	12 (2.8)	8 (1.9)	—

Source: Robertson J et al. *Cancer* 2003;98(2):229-38. Abstract

Slide 6.32

Local injection site reactions were mostly mild to moderate, and the frequency of these events was dependent on the method and volume of injection. These reactions occurred in approximately 1.1 percent of courses in patients who received the single 5-cc injection of fulvestrant (Trial 20), 4.6 percent of courses in patients who received the two 2.5-cc fulvestrant injections (Trial 21) and 4.4 percent of courses in patients receiving the two 2.5-cc placebo injections (Trial 21). Across both studies, only two patients in the fulvestrant group withdrew as a result of an injection site reaction.

Trials 20, 21: Injection Site Adverse Events

	Fulvestrant* (n=425)	Anastrozole** (n=193)
Patients with injection site AEs	71 (16.7%)	45 (23.3%)
Patients withdrawing due to an injection site AE	2 (0.5%)	0
Treatment courses associated with an injection site event	1.1% (Trial 20) 4.6% (Trial 21)	4.4%

*Combined data, Trials 20 + 21
**Placebo injections administrated in Trial 21 only

Sources: Robertson J et al. *Cancer* 2003;98:229-38. Abstract Osborne CK et al. *J Clin Oncol* 2002; 20:3386-95. Abstract Howell A et al. *J Clin Oncol* 2002;20:3396-403. Abstract

Slide 6.33

At a median follow-up of 14.5 months, no significant difference was seen between fulvestrant and tamoxifen for the primary endpoint of time to progression. No differences were observed in women with ER-positive tumors for any of the efficacy endpoints, including objective response rate, stable disease and clinical benefit rate.

Trial 25: Fulvestrant versus Tamoxifen in Postmenopausal Patients with Advanced Breast Cancer

- Objective tumor response to treatment in patients with ER-and/or PR-positive tumors

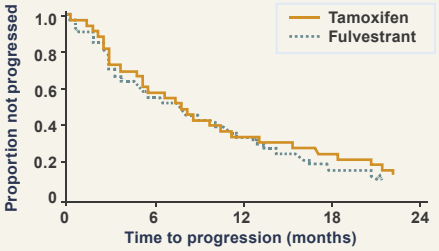
	Fulvestrant (n=247)	Tamoxifen (n=212)	*p*-value
Complete response	8.90%	5.70%	NR
Partial response	24.3%	25.5%	NR
Stable disease ≥ 24 wk	23.9%	31.6%	NR
Objective response rate	33.2%	31.1%	0.64
Clinical benefit rate*	57.1%	62.7%	0.22
Time to progression	8.2 mo	8.3 mo	0.39

NR = not reported

*Complete response + partial response + stable disease ≥ 24 weeks

Source: Howell A et al. *J Clin Oncol* 2004;22(9):1605-13. Abstract

Trial 25: Fulvestrant versus Tamoxifen in Postmenopausal Patients with Advanced Breast Cancer



Kaplan-Meier plot for time to progression (patients with estrogen receptor-positive and/or progesterone receptor-positive tumors)

Source: With permission from Howell A et al. *J Clin Oncol* 2004;22(9):1605-13. Abstract

Slide 6.34

Observe the nearly overlapping Kaplan-Meier curves for time to progression in patients with ER- and/or PR-positive tumors.

Trial 25: Fulvestrant versus Tamoxifen in Postmenopausal Patients with Advanced Breast Cancer

- Incidence of prospectively defined adverse events (all patients)

	Fulvestrant (n=310)	Tamoxifen (n=271)	*p*-value
Gastrointestinal disturbance	37.1%	43.2%	0.16
Hot flashes	17.7%	24.7%	0.05
Vaginitis	3.90%	6.30%	0.26
Thromboembolic disease	5.80%	3.30%	0.22

Source: Howell A et al. *J Clin Oncol* 2004;22(9):1605-13. Abstract

Slide 6.35

The incidence of prospectively defined adverse events was comparable, with the exception of significantly more hot flashes in patients randomly assigned to tamoxifen.

Sequence of Therapy in Postmenopausal Women with ER-Positive Tumors

	2001	2004
First-line/adjuvant	TAM	Aromatase inhibitor
Second-line	Aromatase inhibitor	TAM/fulvestrant
Third-line	Progestin	Fulvestrant/TAM
		Progestin

TAM = tamoxifen

Slide 6.36

Note the evolution of endocrine therapy sequencing since publication of the ATAC trial and introduction of fulvestrant. In 2001, tamoxifen was the standard for adjuvant endocrine therapy and the agent of choice for first-line treatment of metastases. This agent was followed by an aromatase inhibitor and progestin upon progression. Aromatase inhibitors are frequently utilized in the adjuvant and first-line settings; tamoxifen and fulvestrant are second-line options and can be utilized in succession upon disease progression. Progestins have been relegated to fourth-line therapy and beyond.

Slide 6.37

This study evaluated patients deriving clinical benefit from fulvestrant in Trials 20 and 21. Of patients achieving clinical benefit, 46 percent achieved clinical benefit from subsequent endocrine therapy.

Response to Endocrine Therapy in Patients Deriving Clinical Benefit from Fulvestrant

	Number of patients with clinical benefit			
	PR	SD ≥ 24 wk	Progression	Total
Endocrine therapy	4	21	29	54
Aromatase inhibitors	3	16	27	46
Megestrol acetate	1	5	2	8

46% with clinical benefit. Combined data from Trials 0020 and 0021.

PR = partial response
SD = stable disease

Source: Vergote I et al. *Breast Cancer Res Treat* 2003;79:207-11. Abstract

Slide 6.38

Of patients who failed to derive benefit from fulvestrant in Trials 20 and 21, 35 percent (18/51) derived benefit from subsequent endocrine therapy.

Trials 20, 21: Response to Further Endocrine Therapy in Patients Not Benefiting from Fulvestrant

	Clinical benefit	SD ≥ 24 wk	Progression	Total
Aromatase inhibtors	1	15	26	42
Megestrol acetate	0	1	5	6
Medroxyprogesterone acetate	0	1	2	3
Endocrine therapy	1	17	33	51

SD = stable disease

Source: Vergote I et al. *Breast Cancer Res Treat* 2003;79:207-11. Abstract

Slide 6.39

The SAKK study is an ongoing Phase II multicenter trial evaluating response to endocrine therapy in patients who have received an aromatase inhibitor. Patients were stratified by responsiveness versus resistance to aromatase inhibitors.

SAKK: Study Design

- An ongoing Phase II multicenter noncomparative study
- Recruitment of up to 93 patients from up to nine SAKK centers
- Two levels of stratification:
  - Stratum A — AI-responsive patients (progressed on AI treatment after initial objective response or disease stabilization >24 weeks)
  - Stratum B — AI-resistant patients (did not respond to AI treatment or showed disease stabilization <24 weeks)

AI = aromatase inhibitor

Source: Perey L et al. Poster. SABCS, 2002.

Overall Response Rate to Fulvestrant

	Clinical benefit*	Partial response	Stable disease	Disease progression
Number of patients (%)	11 (34)	2 (6)	9 (28)	21 (66)

*Partial response or stable disease ≥ 24 weeks

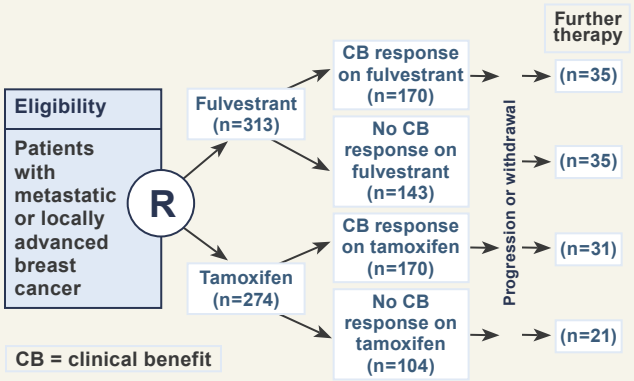
- Preliminary data available for 32 eligible patients followed for at least six months
- Four patients did not meet eligibility requirements and were excluded from analysis

Source: Perey L et al. Poster. SABCS, 2002.

Slide 6.40

In this small Phase II study, 34 percent of patients achieved clinical benefit from fulvestrant after having progressive disease on an aromatase inhibitor.

Response to Endocrine Therapies after Progression on Tamoxifen or Fulvestrant



Source: Howell A. Poster 251. SABCS, 2002.

Slide 6.41

At the 2002 San Antonio Breast Cancer Symposium, Dr Anthony Howell presented the results of a study in postmenopausal patients with advanced breast cancer who were previously treated with first-line fulvestrant or tamoxifen. Responses to subsequent endocrine therapy were compared between patients who did and did not derive clinical benefit from trial therapy.

Response to a Second Endocrine Agent after First-Line Fulvestrant or Tamoxifen

Clinical benefit (CB) with second-line agent

	No. of patients	Percent
First-line fulvestrant (n=70)		
Patients who derived CB (n=35)	20	57
Patients who did not derive CB (n=35)	15	43
First-line tamoxifen (n=52)		
Patients who derived CB (n=31)	19	61
Patients who did not derive CB (n=21)	12	57

Source: Howell A. Poster 251. SABCS, 2002.

Slide 6.42

Patients who respond to first-line fulvestrant or tamoxifen may retain sensitivity to subsequent endocrine therapy. In patients deriving clinical benefit from fulvestrant and tamoxifen, 57 percent and 61 percent, respectively, derived clinical benefit with a second-line endocrine therapy. Note the percent of patients who derived clinical benefit from second-line therapy despite a lack of benefit from first-line fulvestrant or tamoxifen.

Slide 6.43

Clinical benefit was achieved with subsequent endocrine therapy in 20 of 35 patients (57 percent) who had initially derived benefit from fulvestrant.

Response to Endocrine Therapy in Patients Deriving Clinical Benefit from Fulvestrant

	Total	CR	PR	SD	CB	Prog
Endocrine therapy	35	1	2	17	20	15
Aromatase inhibitors	22	1	1	9	11	11
Anastrozole	16	1	0	8	9	7
Letrozole	5	0	1	0	1	4
Fadrozole	1	0	0	1	1	0
Tamoxifen	10	0	1	7	8	2
Megestrol acetate	1	0	0	1	1	0
Medroxyprogesterone acetate	2	0	0	0	0	2

CR = complete response; PR = partial response; SD = stable disease; CB = clinical benefit

Source: Howell A. Poster 251. SABCS, 2002.

Slide 6.44

Clinical benefit was achieved with subsequent endocrine therapy in 19 of 31 patients (61 percent) who had initially derived benefit from tamoxifen.

Response to Endocrine Therapy in Patients Deriving Clinical Benefit from Tamoxifen

	Total	CR	PR	SD	CB	Prog
Endocrine therapy	31	2	1	16	19	12
Aromatase inhibitors	24	2	1	13	16	8
Anastrozole	15	2	0	7	9	6
Letrozole	4	0	1	3	4	0
Fadrozole	2	0	0	0	0	2
Exemestane	3	0	0	3	3	0
Megestrol acetate	5	0	0	2	2	3
Fulvestrant	1	0	0	0	0	1
Medroxyprogesterone acetate	1	0	0	1	1	0

Source: Howell A. Poster 251. SABCS, 2002.

Slide 6.45

Clinical benefit was achieved with subsequent endocrine therapy in 15 of 35 patients (43 percent) who did not benefit from fulvestrant.

Response to Endocrine Therapy in Patients Who Did Not Benefit from Fulvestrant

	Total	CR	PR	SD	CB	Prog
Endocrine therapy	35	0	3	12	15	20
Aromatase inhibitors	19	0	0	8	8	11
Anastrozole	12	0	0	7	7	5
Letrozole	3	0	0	1	1	2
Fadrozole	3	0	0	0	0	3
Exemestane	1	0	0	0	0	1
Tamoxifen	12	0	3	2	5	7
Megestrol acetate	1	0	0	1	1	0
Medroxyprogesterone acetate	3	0	0	1	1	2

Source: Howell A. Poster 251. SABCS, 2002.

Response to Endocrine Therapy in Patients Who Did Not Benefit from Tamoxifen

	Total	CR	PR	SD	CB	Prog
Endocrine therapy	21	0	4	8	12	9
Aromatase inhibitors	16	0	3	7	10	6
Anastrozole	9	0	2	5	7	2
Letrozole	6	0	1	2	3	3
Exemestane	1	0	0	0	0	1
Megestrol acetate	4	0	1	1	2	2
Medroxyprogesterone acetate	1	0	0	0	0	1

CR = complete response; PR = partial response;
SD = stable disease; CB = clinical benefit

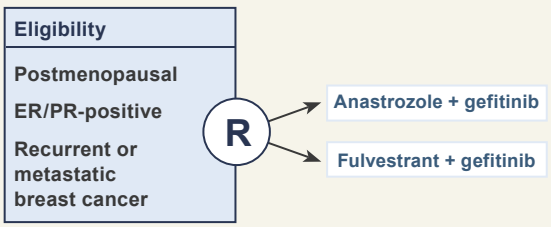
Source: Howell A. Poster 251. SABCS, 2002.

Slide 6.46

Clinical benefit was achieved with subsequent endocrine therapy in 12 of 21 patients (57 percent) who did not benefit from tamoxifen.

ECOG-4101: Phase II Randomized Study

Target Accrual: 148 patients within two years (Open)



Treatment continues in the absence of disease progression or unacceptable toxicity.

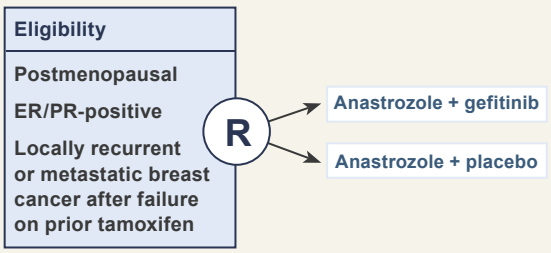
Source: NCI Physician Data Query, May 2004.

Slide 6.47

A number of small ongoing randomized trials are evaluating combinations of biologic agents with endocrine therapy. These trials explore strategies to overcome endocrine therapy resistance by taking advantage of alternative growth pathways. ECOG-4101 is a Phase II randomized trial in postmenopausal women with ER/PR-positive recurrent or metastatic breast cancer that randomly assigns women to receive either anastrozole or fulvestrant plus the EGFR inhibitor gefitinib.

EORTC-10021, IDBBC-10021: Phase II Study

Target Accrual: 108 (Open)



Treatment continues in the absence of disease progression or unacceptable toxicity.

Source: NCI Physician Data Query, May 2004.

Slide 6.48

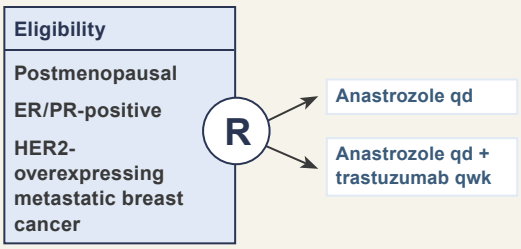
EORTC-10021 is a Phase II randomized trial in postmenopausal women with ER/PR-positive recurrent or metastatic breast cancer who have failed tamoxifen therapy. This trial randomly assigns women to receive anastrozole with or without gefitinib.

Slide 6.49

CWRU-030118 is a Phase II/III study of anastrozole with or without trastuzumab in postmenopausal women with ER/PR-positive and HER2-positive metastatic breast cancer.

CWRU-030118: Phase II/III Randomized Study of Anastrozole with or without Trastuzumab

Target Accrual: 202 (Open)



Source: NCI Physician Data Query, May 2004.

Slide 6.50

The vast majority of oncologists have utilized the selective estrogen receptor downregulator fulvestrant. Physicians utilizing fulvestrant report very few patients with difficulty tolerating the injections or experiencing significant side effects. In the two large randomized trials of fulvestrant versus anastrozole, only 0.5 percent of patients withdrew from the trial due to injection site reactions.

Use and Tolerability of Fulvestrant

- **Have you used fulvestrant?**
  Yes 98%
  No 2%
  - **What percentage of your patients receiving fulvestrant reported difficulty tolerating the injection?**
    Mean 6%
  - **What percentage of your patients receiving fulvestrant reported significant side effects?**
    Mean 3%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 6.51

The recent availability of aromatase inhibitors and the estrogen receptor downregulator fulvestrant has complicated the algorithm for management of metastatic breast cancer in postmenopausal women.

Sequencing Therapy in Endocrine-Naïve Patients with Metastatic Disease

- **How do you normally sequence endocrine therapy in postmenopausal patients with metastases and no prior endocrine therapy?**

Agent	1st-line	2nd-line	3rd-line	4th-line
Anastrozole	36%	16%	4%	2%
Tamoxifen	18%	36%	12%	12%
Letrozole	46%	4%	8%	2%
Fulvestrant	—	20%	36%	32%
Exemestane	—	22%	36%	10%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

First-Line Endocrine Therapy for ER-Positive Metastatic Disease

- What is your typical first-line hormonal therapy in postmenopausal women with ER-positive metastatic disease?

	Adjuvant endocrine therapy		
Agent	No adjuvant endocrine therapy	Completed adjuvant tamoxifen four years ago	Relapsed on anastrozole
Anastrozole	36%	44%	2%
Letrozole	46%	48%	6%
Tamoxifen	18%	8%	40%
Fulvestrant	—	—	32%
Exemestane	—	—	20%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 6.52

A key issue in sequencing of endocrine agents is previous use of adjuvant endocrine intervention. For patients who have had no prior treatment, the nonsteroidal aromatase inhibitors are clearly first-line therapy. In this situation, tamoxifen followed by fulvestrant or exemestane are the next agents utilized.

Sequencing Therapy after Tamoxifen in Patients with Metastatic Disease

- In postmenopausal women with metastases who did not receive adjuvant endocrine therapy, which agents do you generally use after first-line tamoxifen?

Agent	2nd-line	3rd-line	4th-line
Anastrozole	67%	17%	—
Letrozole	25%	17%	—
Exemestane	—	33%	42%
Fulvestrant	8%	25%	25%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 6.53

In postmenopausal patients with metastatic disease who did not receive adjuvant endocrine therapy but who received first-line tamoxifen, the nonsteroidal aromatase inhibitor anastrozole is most commonly utilized as second-line therapy. The steroidal aromatase inhibitor exemestane and the selective estrogen receptor downregulator fulvestrant are common third-line choices.

Sequencing Therapy after Anastrozole in Patients with Metastatic Disease

- In postmenopausal women with metastases who did not receive adjuvant endocrine therapy, which agents do you generally use after first-line anastrozole?

Agent	2nd-line	3rd-line	4th-line
Tamoxifen	67%	13%	7%
Fulvestrant	—	47%	27%
Exemestane	20%	33%	13%
Letrozole	13%	—	7%
Megestrol acetate	—	7%	26%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 6.54

In postmenopausal patients with metastatic disease who did not receive adjuvant endocrine therapy but who received first-line anastrozole, tamoxifen is clearly preferred by physicians for second-line therapy, with fulvestrant and exemestane most frequently sequenced as third-line therapy.

Slide 6.55

For postmenopausal women who have previously received adjuvant tamoxifen, nonsteroidal aromatase inhibitors are generally first-line therapy, followed by either fulvestrant or exemestane.

Endocrine Therapy in Patients with Tumor Recurrence after Receiving Adjuvant Tamoxifen

- How do you normally sequence endocrine therapy in postmenopausal patients with metastases who completed adjuvant tamoxifen four years previously?

Agent	1st-line	2nd-line	3rd-line	4th-line
Anastrozole	44%	10%	4%	—
Letrozole	48%	6%	2%	4%
Exemestane	—	34%	30%	6%
Fulvestrant	—	38%	36%	14%
Tamoxifen	8%	12%	10%	12%

Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 6.56

A new generation of patients is emerging who develop metastatic disease while receiving adjuvant nonsteroidal aromatase inhibitors (mainly anastrozole). For these patients, tamoxifen, exemestane and fulvestrant are often utilized at first relapse.

Endocrine Therapy in Patients with Tumor Recurrence on Adjuvant Anastrozole

- How do you normally sequence endocrine therapy in postmenopausal patients who develop metastases while receiving adjuvant anastrozole?

Agent	1st-line	2nd-line	3rd-line	4th-line
Tamoxifen	40%	20%	6%	4%
Fulvestrant	32%	36%	16%	6%
Exemestane	20%	22%	22%	4%
Letrozole	6%	6%	4%	6%
Anastrozole	2%	—	2%	—
Megestrol acetate	—	4%	12%	6%

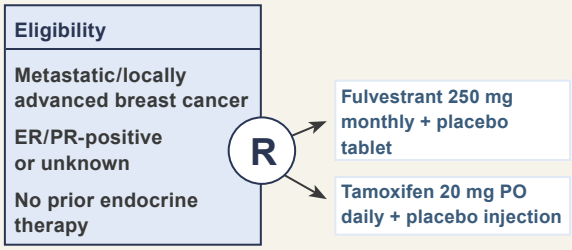
Source: 2004 Patterns of Care Study (www.BreastCancerUpdate.com/POC)

Slide 6.57

The results of a double-blind, randomized trial comparing fulvestrant and tamoxifen as first-line therapy in patients with ER-positive, locally advanced or metastatic breast cancer were published in the *Journal of Clinical Oncology* in 2004.

A Multinational, Double-Blind, Randomized Trial of Hormonal Therapy in Metastatic or Locally Advanced Breast Cancer

Protocol ID: 9238IL-0025
Target Accrual: 587 (Closed)



Source: Howell A et al. *J Clin Oncol* 2004;22(9):1605-13. Abstract

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Post-test:
Cancer Educators Slide Kit

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Adjuvant! program allows the user to enter tumor and patient variables and determine estimates of relapse and mortality rates.**
   a. True
   b. False

2. **In the NSABP-P-1 trial, tamoxifen use resulted in approximately a 50 percent relative reduction in the risk of developing breast cancer.**
   a. True
   b. False

3. **NSABP-P-2 (the STAR trial) is currently comparing _____ and _____ as chemopreventive agents in women at high risk of developing breast cancer.**
   a. Raloxifene and placebo
   b. Anastrozole and placebo
   c. Raloxifene and tamoxifen
   d. None of the above

4. **NSABP-B-17 and NSABP-B-24 in patients with DCIS demonstrated:**
   a. That failure to achieve clear surgical margins did not affect risk of recurrence.
   b. The stepwise improvement in risk of recurrence associated with radiation therapy and tamoxifen after lumpectomy.
   c. That ER status did not predict benefit from tamoxifen therapy.

5. **NSABP-B-35 evaluates the following agents for the treatment of postmenopausal patients with ER-positive DCIS:**
   a. Tamoxifen and letrozole
   b. Tamoxifen and exemestane
   c. Tamoxifen and anastrozole
   d. None of the above

6. **The ATAC adjuvant trial evaluated which of the following treatments in postmenopausal patients with ER-positive disease?**
   a. Tamoxifen
   b. Anastrozole
   c. Anastrozole plus tamoxifen
   d. All of the above

7. **In the ATAC trial, no significant disease-free survival difference was observed among the study arms.**
   a. True
   b. False

8. **Which of the following trials have reported benefit from switching from tamoxifen to an aromatase inhibitor?**
   a. ITA trial of anastrozole versus tamoxifen after two to three years of adjuvant tamoxifen
   b. CRC-TU-TEAM trial of exemestane versus tamoxifen after two to three years of adjuvant tamoxifen
   c. CAN-NCIC-MA17 trial of letrozole versus placebo after five years of adjuvant tamoxifen
   d. All of the above

9. **Which of the following ongoing adjuvant trials specifically evaluate(s) therapeutic options for premenopausal patients with ER-positive disease?**
   a. SOFT
   b. PERCHE
   c. TEXT
   d. All of the above

10. **The Intergroup adjuvant trial 0101 in premenopausal patients with ER-positive disease, which evaluated CAF chemotherapy alone or in combination with goserelin (CAFZ) or goserelin plus tamoxifen (CAFZT), demonstrated a disease-free survival advantage for:**
    a. CAFZ versus CAF
    b. CAFZT versus CAFZ
    c. Both a and b
    d. Neither a nor b

11. **The IMPACT neoadjuvant trial in postmenopausal patients with ER-positive disease compared:**
    a. Anastrozole
    b. Tamoxifen
    c. Anastrozole plus tamoxifen
    d. All of the above
    e. Both a and c

12. **A randomized neoadjuvant trial comparing letrozole and tamoxifen in postmenopausal patients with ER-positive disease reported a significantly higher response rate for letrozole in patients with HER1/2-positive disease.**
    a. True
    b. False

13. **In the combined analysis of Trials 20 and 21, which compared fulvestrant and anastrozole as second-line therapy in postmenopausal patients with metastatic breast cancer, a significantly longer duration of response was observed for:**
    a. Anastrozole
    b. Fulvestrant
    c. Neither a nor b

14. **Trial 25, a Phase III study comparing first-line fulvestrant and tamoxifen in postmenopausal patients with ER-positive metastatic disease, demonstrated an advantage to fulvestrant in:**
    a. Objective response rate
    b. Clinical benefit rate
    c. Time to progression
    d. None of the above

Post-test answer key: 1a, 2a, 3c, 4b, 5c, 6d, 7b, 8d, 9d, 10b, 11d, 12a, 13b, 14d

Evaluation Form: Cancer Educators Slide Kit

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

Please answer the following questions by circling the appropriate rating:

5 = Outstanding 4 = Good 3 = Satisfactory 2 = Fair 1 = Poor

GLOBAL LEARNING OBJECTIVES

To what extent does this *Cancer Educators Slide Kit* address the following global learning objectives?

- Facilitate an educational session or sessions on the endocrine therapy for breast cancer throughout the breast cancer continuum. 5 4 3 2 1
- Utilize suggested cases and interactive questions to stimulate discussion and interaction in a live activity on hormonal therapy for breast cancer. 5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

Objectives were related to overall purpose/goal(s) of activity. 5 4 3 2 1
Related to my practice needs 5 4 3 2 1
Will influence how I practice 5 4 3 2 1
Will help me improve patient care 5 4 3 2 1
Stimulated my intellectual curiosity 5 4 3 2 1
Overall quality of material 5 4 3 2 1
Overall, the activity met my expectations 5 4 3 2 1
Avoided commercial bias or influence 5 4 3 2 1

Will the information presented cause you to make any changes in your practice or delivery of lectures?

☐ Yes ☐ No

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

.....

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

.....

Degree:

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

FOLLOW-UP

As part of our ongoing, continuous, quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

☐ Yes, I would be willing to participate in a follow-up survey.

☐ No, I'm not willing to participate in a follow-up survey.

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

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To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Evaluation Form and mail or fax both to: Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131, FAX 305-377-9998. You may also complete the Post-test and Evaluation online at www.BreastCancerUpdate.com/CME.

Cancer Educators Slide Kit

Management of Patients with Estrogen Receptor-Positive Breast Cancer

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