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Breast Cancer™ update

Conversations with Oncology Leaders: Audio Program Supplement

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Breast Cancer Update: A CME Audio Series and Activity

STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from a plethora of ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well-informed of these advances.

To bridge the gap between research and patient care, Breast Cancer Update utilizes one-on-one discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists in the formulation of up-to-date clinical management strategies.

Issue 2, 2002 of Breast Cancer Update consists of discussions with three oncology leaders on a variety of important issues, including the preliminary results from the ATAC trial presented at the 2001 San Antonio Breast Cancer Symposium, the biology of the HER2 receptor system and the mechanism of action and use of trastuzumab, and the development of a Phase III Intergroup trial comparing continuous vs. intermittent AC chemotherapy, and single-agent docetaxel versus docetaxel in combination with capecitabine.

EDUCATIONAL OBJECTIVES

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

- Describe the preliminary results from the ATAC trial
- Review the toxicity profile of anastrozole versus tamoxifen
- Review the mechanism of action of trastuzumab
- Identify the current applications and on-going trials of trastuzumab
- Describe the rationale and design of the Phase III Intergroup trial comparing continuous versus intermittent AC chemotherapy, and single-agent docetaxel versus docetaxel in combination with capecitabine.

ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Postgraduate Institute for Medicine and NL Communications, Inc. The Postgraduate Institute for Medicine is accredited by the ACCME to provide continuing medical education for physicians and takes responsibility for the content, quality and scientific integrity of this CME activity.

DESIGNATION STATEMENT

The Postgraduate Institute for Medicine designates this educational activity for a maximum of 3 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

FACULTY DISCLOSURE STATEMENTS

Postgraduate Institute for Medicine has a conflict of interest policy that requires course faculty to disclose any real or apparent commercial financial affiliations related to the content of their presentations/materials. It is not assumed that these financial interests or affiliations will have an adverse impact on faculty presentations; they are simply noted in this supplement to fully inform participants.

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HOW TO USE THIS SUPPLEMENT

This booklet supplements the audio program and contains edited sound bites, clinical trial schemas, graphics and references. **BreastCancerUpdate.com** includes a full transcription of the audio program and an easy-to-use representation of each page of this booklet, allowing users to link immediately to relevant full-text articles, abstracts, trial information and other web resources indicated throughout this guide in **blue underlined text**. This regularly updated web site also features an extensive breast cancer bibliography, clinical trial links, a "breast cancer web tour" and an audio library with excerpts from interviews and meetings catalogued by topic.

Editor's Note

ANOTHER STEP FORWARD

Recently, I had the interesting opportunity to deliver a presentation about the history of breast cancer clinical research to an unusual audience — a gathering of prostate cancer research leaders who were struggling with the clinical applicability of emerging data on the adjuvant use of the antiandrogen, bicalutamide. The maturity of these data paralleled the adjuvant tamoxifen data that was available to medical oncologists in the early 1980's. Through my lecture, I attempted to illustrate the potential road ahead for the adjuvant therapy of prostate cancer.

One of the urologists asked why breast cancer research was so far ahead of prostate cancer in the design and implementation of phase III randomized clinical trials. Since the incidence and mortality of these two cancers are similar, it was a fair question. My initial response related to the power of breast cancer advocacy groups to promote funding for research.

Yet another, perhaps equally important factor is the leadership of numerous visionary breast cancer investigators who have continuously challenged our sometimes tenaciously-held paradigms and forced us to find objective answers to important clinical questions. Of course, Dr Bernard Fisher leads the list of breast cancer "movers and shakers". His personal saga and legacy are legendary.

There are many other important figures who have extended the breast cancer research frontier, including a provocative and controversial self-described "iconoclastic Brit" who has been a frequent guest on this series since his first interview during the 1990 NIH Consensus Conference.

Dr Michael Baum has always challenged us to examine our prejudices and preconceptions, and it was no surprise that on December 10, 2001, he presented at the San Antonio Breast Cancer Symposium perhaps the most exciting new data set in breast cancer research in more than a decade.

In the early 1990's in an English pub, Dr Baum and his colleagues first outlined the concept for the ATAC trial on the back of an envelope. This study eventually became the largest cancer treatment trial ever conducted, and one of my favorite interview questions for guests on Breast Cancer Update this past year was, "What do you think the ATAC trial will show in its first data analysis?"

In an interview during the Miami Breast Cancer Conference in March 2001, Dr Baum predicted there would be no difference in the initial analysis of the three treatment arms (anastrozole, tamoxifen, and the combination). His prediction was based on the inclusion of a substantial number (about 15%) of women with ER-negative and ER-unknown tumors. These women were likely to be the first group of early relapsers. However, part of the excitement associated with well-conducted clinical research is being presented with pleasant surprises. It would not be an exaggeration to state that many of the "standing room only" San Antonio attendees were stunned by the ATAC results.

In the enclosed audio interview and print supplement, Dr Baum reviews these historic data. As with all of our programs, the transcripts of Dr Baum's interview, relevant journal articles, and protocol web links are found at BreastCancerUpdate.com. Briefly, "the headline news" includes a significant improvement in efficacy and tolerability for anastrozole compared to both tamoxifen and the combination of tamoxifen and anastrozole. In this early analysis, perhaps the most surprising finding is 58% fewer second breast cancers in women treated with anastrozole compared to those

receiving tamoxifen. The ATAC results have generated considerable discussion about the rationale for new trials using anastrozole in high-risk women and DCIS.

Just last year, an NIH Consensus Conference advocated the use of adjuvant tamoxifen in all patients with estrogen receptor-positive cancers, regardless of age, menopausal status, or recurrence risk. During the interview, Dr Baum described with amusement a lecture he had just attended by Dr Craig Jordan (another regular Breast Cancer Update guest) who began his presentation by saying, "Tamoxifen, the gold standard of endocrine therapy... until yesterday!"

The enclosed program contains two other interviews documenting the rapid evolution of breast cancer clinical research, particularly that of targeted systemic therapy. Dr Mark Pegram takes us to the cutting edge of HER2 biology and reviews how the UCLA group — headed by Dr Dennis Slamon — is utilizing trastuzumab in clinical research and practice.

In particular, Dr Pegram enthusiastically endorses routine use of the FISH assay to determine HER2 status. He refers to a San Antonio presentation, by Dr Robert Mass, that conclusively demonstrates the superiority of the FISH assay relative to the IHC assay in identifying women likely to benefit from trastuzumab.

Finally, Dr Robert Livingston describes the design of an important new adjuvant Intergroup trial based in part upon Dr Joyce O'Shaughnessy's presentation at last year's San Antonio meeting, reporting a response rate and survival advantage for capecitabine/docetaxel compared to docetaxel alone in metastatic breast cancer. The proposed Intergroup adjuvant trial is just one of several new trials designed to evaluate the capecitabine/docetaxel combination in the adjuvant and neoadjuvant setting. The rapid incorporation of clinical trial results into the design of future studies is

another example of the flexibility and efficiency we have come to expect of the breast cancer research infrastructure.

Often an outsider's perspective enhances our appreciation for what we have obtained. As my prostate cancer colleagues gazed with envy at the progressively massive number of patients in the Early Breast Cancer Trialists' Collaborative Group, I realized that thousands of breast cancer patients and researchers have set a lofty clinical research standard for oncology and medicine. This collaboration has now resulted in a 25% reduction in breast cancer mortality in the last decade, and hopefully, new steps forward — like ATAC — will further reduce the death rate in the future.

—Neil Love, MD

SELECT ABSTRACTS

2001 SAN ANTONIO BREAST CANCER SYMPOSIUM

Baum M. **The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in post-menopausal women.** *Breast Cancer Res Treat* 2001;69(3): **Abstract 8.**

Mass R et al. **Improved survival benefit from Herceptin (trastuzumab) and chemotherapy in patients selected by fluorescence in situ hybridization.** *Breast Cancer Res Treat* 2001; **Abstract 18.**

Miles D et al. **Survival benefit with Xeloda (capecitabine)/docetaxel vs docetaxel: Analysis of post-study therapy.** *Breast Cancer Res Treat* 2001; **Abstract 442.**

Twelves C et al. **Adding Xeloda (capecitabine) to docetaxel significantly improves survival and does not compromise quality of life in patients with metastatic breast cancer.** *Breast Cancer Res Treat* 2001; **Abstract 542.**

Vukelja SJ et al. **Xeloda (capecitabine) plus docetaxel combination therapy in locally advanced/metastatic breast cancer: Latest results.** *Breast Cancer Res Treat* 2001; **Abstract 352.**

Michael Baum, ChM, FRCS

Professor Emeritus of Surgery
Visiting Professor of
Medical Humanities
University College London

Chairman,
CRC Breast Cancer Trials Group

Edited Comments by Dr Baum

SUMMARY OF ATAC RESULTS

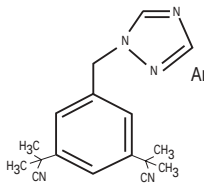
There are over 9,000 patients in this study from all over the world, with just over 3,000 patients in each arm. On average the patients were exposed to two and a half years of the treatment. There was a statistically predetermined number of events we were looking for, which triggered the first formal analysis.

The headline news is that it looks as if there is something after tamoxifen — there is a significant advantage to anastrozole compared with tamoxifen. The real surprise is that the combination of anastrozole and tamoxifen looks no different than tamoxifen alone.

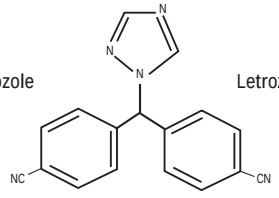
What makes these early ATAC results even more extraordinary is that about 15% of the trial population was ER-negative or ER-unknown. When you look at an analysis of the subgroup of known ER-positive patients in the study, the effect comes out even stronger. The hazard ratio for anastrozole versus tamoxifen is 0.78 — equivalent to a 22% relative reduction in risk for recurrence compared to tamoxifen.

3rd generation aromatase inhibitors

Nonsteroidal

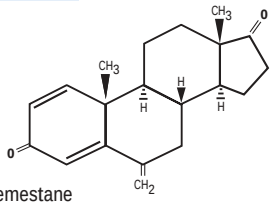


Anastrozole



Letrozole

Steroidal



Exemestane

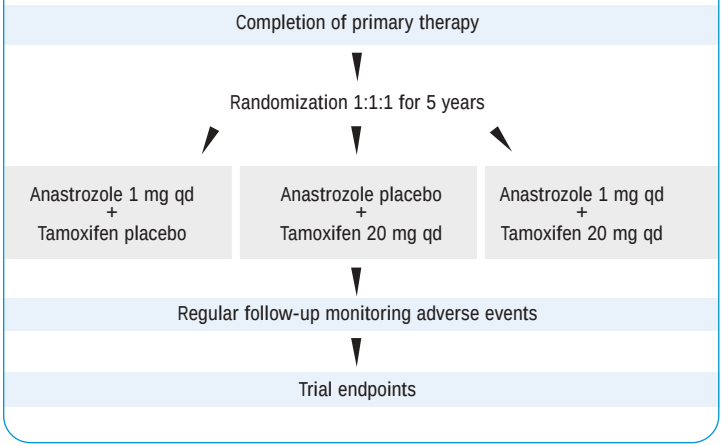
Anastrozole's Profile

- Highly selective, potent aromatase inhibitor
- Nonsteroidal
- Orally active (1 mg)
- Once-daily dosing
- Superior to tamoxifen in postmenopausal women with estrogen receptor-positive advanced breast cancer
- Survival advantage vs. megestrol acetate in metastatic disease
- Over 460,000 patient-years experience

REDUCTION IN CONTRALATERAL BREAST CANCERS

Tamoxifen produces about a 50% reduction in contralateral breast cancers, and in this trial, anastrozole produced a staggering 58% reduction over tamoxifen — and the difference emerged within one year. If these findings hold up, we can add another 60% reduction on top of the 50%, and really start translating that into effective chemoprevention of breast cancer.

ATAC Trial Design - Postmenopausal Women with Invasive Breast Cancer



Subprotocols of the ATAC Trial

- Pharmacodynamic and pharmacokinetic profiles
- Modulation of lipoprotein profiles
- Endometrial status
- Bone mineral metabolism
- Quality of life

SAFETY PROFILE OF ANASTROZOLE

One of the most exciting parts of the ATAC trial is the safety profile of anastrozole. There was a highly significant reduction in the incidence of hot flashes, vaginal discharge and vaginal bleeding. This reduction in vaginal bleeding is significant, because this will cut down the number of women referred to gynecologists to exclude endometrial cancer.

ATAC Trial - Study Endpoints

Primary Endpoints

- Disease-free survival
  - Locoregional or distant recurrence, new primary breast cancer, or death from any cause
- Safety/Tolerability

Secondary Endpoints

- Incidence of new breast (contralateral) primaries
- Time to distant recurrence
- Survival (data will be mature in ≈ 2 years)
- Hormone receptor-positive population (protocol-defined sub-group)

Perhaps even more important is the significant reduction in the anastrozole arm in life-threatening events such as strokes, cerebrovascular accidents and thromboembolic events.

In terms of side effects, about 8% of women complain about arthralgias. There is also a numerically modest (about 4%) but highly significant excess fracture rate in the anastrozole arm. Apart from bone mineral density — which I think we can handle if we anticipate it — the safety profile strongly favors anastrozole over tamoxifen.

POTENTIAL ROLE OF BISPHOSPHONATES COMBINED WITH ANASTROZOLE IN THE ADJUVANT SETTING

I'm convinced that adjuvant bisphosphonates reduce the risk of bone metastases during therapy. We need to determine if there is synergism between aromatase inhibitors and bisphosphonates. We are discussing the possibility of a second randomization within the ATAC trial to anastrozole alone versus anastrozole plus a bisphosphonate.

*ATAC Trial - Patient Characteristics**

- Mean age in the anastrozole arm was 64.1 years
- 83.7% of patients in the anastrozole arm were ER-positive
- 47.8% of patients in the anastrozole arm were treated with mastectomy
- 22.3% of patients in the anastrozole arm were treated with chemotherapy

*patients in all arms were similar

Derived from a presentation by Michael Baum, 2001 Annual San Antonio Breast Cancer Symposium

Summary of ATAC Trial Outcomes

9,366 evaluable patients

- At a median treatment duration of 2.5 years, anastrozole demonstrated superior efficacy and tolerability compared to tamoxifen
- Anastrozole was superior to tamoxifen in terms of disease-free survival in the overall population (relative reduction of 17%) and in estrogen receptor-positive patients (relative reduction of 22%)
- Anastrozole was superior to tamoxifen in terms of the incidence of contralateral breast cancer in the overall population (relative reduction of 58%)
- There were 156 patients with distant metastases in the anastrozole arm and 181 in the tamoxifen arm (not statistically different)
- There were only a total of five breast cancer deaths in the three treatment arms

Anastrozole was better tolerated than tamoxifen with respect to:

- Endometrial cancer
- Vaginal bleeding
- Vaginal discharge
- Ischaemic cerebrovascular events
- Venous thromboembolic events
- Hot flashes
- Weight gain

Tamoxifen was better tolerated than anastrozole with respect to:

- Musculoskeletal disorders (arthralgias)
- Fractures

Derived from a presentation by Michael Baum, 2001 Annual San Antonio Breast Cancer Symposium

Baum M. **The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal (PM) women.** *Breast Cancer Res Treat* 2001;69(3):**Abstract 8.**

ADJUVANT ENDOCRINE TREATMENT: IMPLICATIONS OF ATAC

In the evolution of science and medicine, there are periods of uncertainty, and we are living in such a time right now related to these ATAC findings. If the efficacy advantage for anastrozole continues to be seen, then we can start making therapeutic recommendations, but presently we have only two and one-half years of treatment data. We cannot be certain about what will happen with further therapy.

Newly diagnosed women should be informed of the ATAC data in a responsible way, and most of them will make a rational decision. Tamoxifen should continue to be considered the gold standard, at least until the trial results are updated this May at ASCO 2002. However, anastrozole is a legitimate nonprotocol adjuvant option where there are contraindications to tamoxifen. If women are already on adjuvant tamoxifen, it would be hazardous to switch them to anastrozole, since we haven't tested that therapeutic approach.

USING OTHER AROMATASE INHIBITORS IN THE ADJUVANT SETTING

I do not know if this is a class effect of aromatase inhibitors. I can only speak for anastrozole in the ATAC trial. There are subtle differences in pharmacology and pharmacokinetics between the two nonsteroidal aromatase inhibitors (anastrozole and letrozole) and even more with the steroidal aromatase inhibitor, exemestane. These differences could lead to different results. Although I suspect that they will have similar efficacy, I don't think we can assume they will have the same trade-off in adverse events.

AROMATASE INHIBITORS IN THE NEOADJUVANT SETTING

The IMPACT trial — currently being conducted at the Royal Marsden Hospital — is similar to ATAC but is in the preoperative setting. The added advantage of this type of study is the ability to take biological samples of the primary tumor in the preoperative phase to study what happens at the cellular level in the face of aromatase inhibitors.

IMPACT TRIAL: A Randomized Double Blind Trial of Preoperative Tamoxifen, Anastrozole or the Combination in Postmenopausal Breast Cancer Patients Open Protocol

Eligibility	Postmenopausal, ER/PR-positive in T2 (> 2 cm), T3, T4b N0-2, M0 breast cancer patients

ARM 1 | Tamoxifen x 3 months → Surgery

ARM 2 | Anastrozole x 3 months → Surgery

ARM 3 | Anastrozole + tamoxifen x 3 months → Surgery

Study Contact
Ian Smith, MD, Chair
Royal Marsden Hospital
London, United Kingdom

Anastrozole as Neoadjuvant Therapy in Hormone-Dependent Locally Advanced [Stage IIIA (n=29) and IIIB (n=45)] Postmenopausal Patients

	Neoadjuvant anastrozole (n=74)
Objective Response (PR + CR)	61 (83%)
Partial Response (PR)	42 (57%)
Complete Respone (CR)	19 (26%)
Pathological Complete Response	14 (23%)
Pathological Partial Response	47 (64%)
No Response	13 (18%)

Derived from Milla-Santos A et al. *Breast Cancer Res Treat* 2001; Abstract 302.

THE VALUE OF SCREENING MAMMOGRAPHY

I don't think mammographic screening has anywhere to go. Also, as systemic adjuvant treatments improve, there will be less potential impact of screening. Even in the "bad old days" before successful adjuvant therapy, screening led to a 25% reduction in mortality,

which translates into saving one in a thousand lives with ten years of screening.

In addition, you cannot compare the quality of current treatment trials (like ATAC) with the quality of the older mammographic screening trials. As a clinical trialist, if I had attempted to submit an abstract on a trial of adjuvant therapy designed like most of the screening trials, it would not have been approved. Yet we have accepted shabby clinical trials to demonstrate the benefits of mammographic screening.

SELECT PUBLICATIONS

AROMATASE INHIBITORS IN BREAST CANCER MANAGEMENT

Pharmacokinetics of anastrozole and tamoxifen alone and in combination during adjuvant endocrine therapy for early breast cancer in postmenopausal women: A sub-protocol of the "Arimidex® and Tamoxifen Alone or in Combination" (ATAC) trial. *Br J Cancer* 2001;85(3):317-324. **Abstract**

Baum M. **The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in post-menopausal women.** *Breast Cancer Res Treat* 2001;69(3):**Abstract 8.**

Dixon JM et al. **The effects of neoadjuvant anastrozole (Arimidex) on tumor volume in postmenopausal women with breast cancer: A randomized, double-blind, single-center study.** *Clin Cancer Res* 2000;6(6):2229-35. **Abstract**

Dixon JM et al. **Lessons from the use of aromatase inhibitors in the neoadjuvant setting.** *Endocrine-Related Cancer* 1999;6(2):227-230. **Full Text**

Dixon JM et al. **Letrozole as primary medical therapy for locally advanced and large operable breast cancer.** *Breast Cancer Res Treat* 2001;66:191-9. **Abstract**

Ellis MJ et al. **Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial.** *J Clin Oncol* 2001;19:3808-16. **Abstract**

Geisler J et al. **Influence of neoadjuvant anastrozole (Arimidex) on intratumoral estrogen levels and proliferation markers in patients with locally advanced breast cancer.** *Clin Cancer Res* 2001;7:1230-6. **Abstract**

Goss PE, Strasser K. **Aromatase inhibitors in the treatment and prevention of breast cancer.** *J Clin Oncol* 2001;19:881-94. **Abstract**

Hamilton A, Volm M. **Nonsteroidal and steroidal aromatase inhibitors in breast cancer.** *Oncology (Huntingt)* 2001;15:965-72;discussion 972, 977-9. **Abstract**

Ingle JN. **Aromatase inhibition and antiestrogen therapy in early breast cancer treatment and chemoprevention.** *Oncology (Huntingt)* 2001;15:28-34. **Abstract**

Milla-Santos A et al. **Anastrozole (A) as neoadjuvant (NEO) therapy for hormone-dependent locally advanced breast cancer (LABC) in postmenopausal (PM) patients (pts).** *Breast Cancer Res Treat* 2001; **Abstract 302.**

Mouridsen H et al. **Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: Results of a phase III study of the International Letrozole Breast Cancer Group.** *J Clin Oncol* 2001;19:2596-606. **Abstract**

Nabholtz JM et al. **Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Results of a North American multi-center randomized trial.** *J Clin Oncol* 2000;18(22):3758-3767. **Abstract**

SCREENING MAMMOGRAPHY

Bomalaski JJ et al. **Mammography.** *Curr Opin Obstet Gynecol* 2001;13(1):15-23. **Abstract**

Boyd NF et al. **Mammographic densities as a marker of human breast cancer risk and their use in chemoprevention.** *Curr Oncol Rep* 2001;3(4):314-21.**Abstract**

Chamot E, Perneger TV. **Misconceptions about efficacy of mammography screening: A public health dilemma.** *J Epidemiol Community Health* 2001;55(11):799-803. **Abstract**

Delorme S. **Ultrasound mammography and magnetic resonance mammography as adjunctive methods in mammography screening.** *Radiologe* 2001;41(4):371-8. **Abstract**

Dobias KS et al. **Mammography messages in popular media: implications for patient expectations and shared clinical decision-making.** *Health Expect* 2001;4(2):127-35. **Abstract**

Freer TW, Ulissey MJ. **Screening mammography with computer-aided detection: Prospective study of 12,860 patients in a community breast center.** *Radiology* 2001;220(3):781-6. **Abstract**

Gøtzsche PC, Olsen O. **Is screening for breast cancer with mammography justifiable?** *Lancet* 2000;355(9198):129-34. **Abstract**

Kerner JF et al. **Screening mammography and breast cancer treatment patterns in older women.** *Breast Cancer Res Treat* 2001;69(1):81-91. **Abstract**

Klabunde CN et al. **Quality assurance for screening mammography data collection systems in 22 countries.** *Int J Technol Assess Health Care* 2001;17(4):528-41. **Abstract**

Moss SM et al. **Routine breast screening for women aged 65-69: Results from evaluation of the demonstration sites.** *Br J Cancer* 2001;85:1289-94. **Abstract**

Olsen O, Gøtzsche PC. **Cochrane review on screening for breast cancer with mammography**. *Lancet* 2001;358(9290):1340-2. No Abstract

Olsen O, Gøtzsche PC. **Screening for breast cancer with mammography (Cochrane Review).** *Cochrane Database Syst Rev* 2001;4:CD001877. **Abstract**

Paajanen H et al. **The demands of screening mammography on surgical inpatient services of breast cancer.** *Am Surg* 2001;67(7):648-53. **Abstract**

Scheiden R et al. **Consequences of a National Mammography Screening Program on diagnostic procedures and tumor sizes in breast cancer. A retrospective study of 1540 cases diagnosed and histologically confirmed between 1995 and 1997.** *Pathol Res Pract* 2001;197(7):467-74. **Abstract**

Scinto JD et al. **Screening mammography: Is it suitably targeted to older women who are most likely to benefit?** *J Am Geriatr Soc* 2001;49(8):1101-4. **Abstract**

Smith RA et al. **American Cancer Society guidelines for the early detection of cancer.** *CA Cancer J Clin* 2002;52(1):8-22. **Full-Text**

Smith TJ et al. **American Society of Clinical Oncology 1998 update of recommended breast cancer surveillance guidelines.** *J Clin Oncol* 1999;17(3):1080-2. **Abstract**

Woolf SH. **The accuracy and effectiveness of routine population screening with mammography, prostate-specific antigen, and prenatal ultrasound: a review of published scientific evidence.** *Int J Technol Assess Health Care* 2001;17(3):275-304. **Abstract**

Mark Pegram, MD

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Director,
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Edited Comments by Dr Pegram

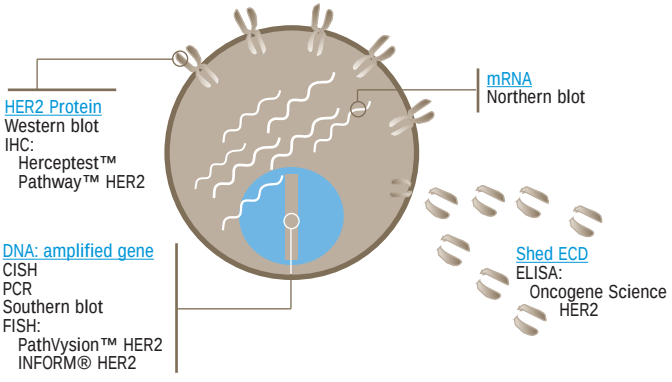
OVERVIEW OF HER2 BIOLOGY

There are four members of the human epidermal growth factor receptor (HER) family — HER1, HER2, HER3, HER4. These receptors interact with and provide signals to cells concerning their biologic behavior. Unlike HER2, the other receptors (HER1, HER3 and HER4) have ligands that bind to them directly.

The most probable explanation for HER2's lack of direct ligand binding is that HER2 is the "driver" of signaling for all members of the HER family. For example, ligands bind to HER1, but rely on HER2 to transmit and amplify their signal.

The HER family is analogous to a stereo system with a compact disk, tape and DVD player — each playing different types of media. The CDs, tapes, and DVDs are like ligands. The cell can "listen" to several types of ligands, but central to the function of the stereo system is the amplifier. HER2 is equivalent to the amplifier. When the HER2 receptor is overexpressed, the "volume" is turned all the way up on the stereo. This causes breast cancer cells to proliferate rapidly.

Molecular Targets for Determining HER2 Status and the Tests Used to Detect These Molecules.



Adapted from Schaller G et al. *Ann Oncol* 2001;12:(Suppl 1):S97-S100

mRNA = messenger RNA
ECD = extracellular domain
ELISA = enzyme-linked immunosorbent assay
IHC = immunohistochemistry
CISH = chromogenic in situ hybridization
PCR = polymerase chain reaction
FISH = fluorescence in situ hybridization

MECHANISM OF ANTITUMOR ACTION OF TRASTUZUMAB

Normal breast tissue has approximately 20,000 HER2 receptors per cell. In contrast, breast cancer cells with HER2 gene amplification have about two million receptors per cell. The high density of these receptors causes cell proliferation. This same high density of HER2, however, enhances antibody binding, making it a perfect target for trastuzumab.

Trastuzumab binds to the HER2 receptor, covering the breast cancer cell with antibodies just like antibodies cover bacteria when they fight off an infection. This antibody binding creates a potent signal for the immune system to attack the breast cancer cells. A higher density of HER2 leads to increased antibody binding to the cells and a greater immune response. Perhaps equally important, antibody binding also disrupts HER2's signaling function.

HER2 GENE AMPLIFICATION IN BREAST CANCER CELLS

Approximately 20% of women with breast cancers have HER2 gene amplification. Dr Giovanni Pauletti, together with Dr Dennis Slamon at our institution, studied a large cohort of more than 900 primary breast cancer patients from South Australia. In these tumor samples, the HER2 gene amplification rate using fluorescence in situ hybridization (FISH) was 20%. This 20% rate was also confirmed by Dr Mike Press at USC, our collaborator in the Breast Cancer International Research Group (BCIRG), in the first 600 samples collected for the BCIRG's adjuvant trastuzumab study.

EVALUATION OF HER2 ASSAYS

There is no question that FISH will replace immunohistochemistry (IHC) — sooner rather than later. FISH is clearly more accurate. Accuracy is the only acceptable way to go in medical diagnostics when dealing with patients' lives.

The inappropriate use of trastuzumab in women who will not benefit (i.e., those with false-positive IHC results) is equally as bad as denying trastuzumab to women with false-negative IHC results. One FISH assay is less expensive than one dose of trastuzumab. From an economic perspective, FISH is more cost-effective.

FISH is widely available. It may need to be sent to a reference laboratory, but almost every test that you have sent to your local hospital laboratory gets sent out. So, they'll just send the FISH slides in the same box, and you'll get the result in the mail in a day or two. It's trivial.

Not every patient who already has an IHC result must have a FISH analysis. It comes down to clinical judgment. If the clinical history fits the IHC result, then you're probably safe with an IHC assay. In a patient without a prior HER2 assay, I would perform a FISH analysis first.

Percent of Patients with HER2 Gene Amplification According to Immunohistochemistry (IHC) Score

Author	IHC Antibody	N	0	1+	2+	3+
Mass	CTA	529	4.2%	6.7%	23.9%	89.3%
Mass	CTA	451	-	-	31.0%	89.0%
Schaller	A0485	142	0	0	25.0%	100.0%
Lebeau	A0485	79	-	-	25.0%	100.0%
	CB11		-	-	81.8%	100.0%
	TAB250		-	-	66.7%	100.0%
Buehler	A0485	142	0	0	30.5%	100.0%
Tubbs	A0485	145	-	-	12.5%	75.0%
	CB11		-	-	23.5%	85.0%
Hoang	A0485	100	0	0	16.7%	88.9%
	e2-4001		1.6%		5.9%	75.0%
Ridolfi	A0485	117	1.8%		35.9%	100.0%
Seidman	A0485	78	9.1%		82.2%	
	CB11		14.3%		94.4%	
Persons	A0485	100	1.3%		68.2%	

CTA = clinical trial assay (4D5 and CB11 antibodies)

SINGLE-AGENT TRASTUZUMAB

I am impressed with Chuck Vogel's data on single-agent trastuzumab. The survival data with single-agent trastuzumab looks almost identical to that reported in the chemotherapy plus trastuzumab pivotal trial. Additionally, the patient demographics were surprisingly similar. These are not randomized trials, and I admit that I am making dangerous cross-trial comparisons. But, I am impressed that there may be a survival benefit to trastuzumab-based treatment in HER2-positive patients.

Clinical Benefit and Overall Survival in a Retrospective Evaluation of Patients Treated with First-line Trastuzumab or Trastuzumab after Progression on One or Two Chemotherapy Regimens

	Clinical Benefit* (%)	Overall Survival (months)
First-line trastuzumab		
FISH+	48%	24.5
FISH -	10%	24.4
IHC +	38%	24.4
Trastuzumab after progression		
FISH+	33%	14.2
FISH -	6%	8.8
IHC +	28%	12.8

* Clinical Benefit = CR + PR + Stable Disease > 6 months

Derived from Vogel CL et al. *Proc ASCO* 2001;Abstract 86.

MANAGEMENT OF HER2–POSITIVE PATIENTS

The management of HER2-positive, ER-negative women with metastases should take into consideration disease burden, patient age and prior therapy. If the woman has a high disease burden, a young age and a good performance status, then I would use trastuzumab in combination with chemotherapy.

In elderly women with smaller volume disease, who are not good candidates for chemotherapy, single-agent trastuzumab results in a good clinical response in about one-third of patients. Including patients with disease stabilization of six months or more, response rates are even higher. About half of the patients derive some meaningful clinical benefit from single-agent trastuzumab, without the side effects associated with chemotherapy.

Randomized Study of Standard versus Higher Dose Trastuzumab as First-line Therapy in Women with HER2-overexpressing Metastatic Breast Cancer

Eligibility | Progressive HER2-overexpressing (IHC 2+/3+) metastatic breast cancer

ARM 1 | H (4 mg/kg loading dose) → H 2 mg/kg q week

ARM 2 | H (8 mg/kg loading dose) → H 4 mg/kg q week

H = trastuzumab

Response, Clinical Benefit and Survival with First-line Trastuzumab

Subset	Objective Response	Clinical Benefit*	Median Duration of Survival
All Patients	29/111 (26%)	42/111 (38%)	24 months
ER-positive	12/52 (23%)	19/52 (36%)	–
ER-negative	16/54 (30%)	21/54 (39%)	–
IHC 3+	29/84 (35%)	40/84 (48%)	–
IHC 2+	0/27 (0%)	2/27 (7%)	–
FISH +	27/79 (34%)	38/79 (48%)	–
FISH -	2/29 (7%)	3/29 (10%)	–

*Clinical Benefit = complete, partial, or minor response or stable disease > 6 months.

Note: There was no evidence of a dose-response relationship for response, survival or adverse events.

Derived from Vogel CL et al. *J Clin Oncol* 2002;20:719-726. Abstract

TRASTUZUMAB SCHEDULING

We, like many others, have been compelled to switch to triple-dose trastuzumab administered every three weeks. When we discuss Dr Brian Leyland-Jones' results from his pharmacokinetic studies with the triple-dose, every-three-week schedule with our patients, many opt for that schedule. So far, we have not had any problems with that schedule.

At this point, however, we really do not have comparative data from large randomized trials. Many of the cooperative group studies evaluating trastuzumab are adopting the every-three-week, triple-dose schedule. In the BCIRG adjuvant trastuzumab trial, trastuzumab will be given following chemotherapy on an every-three-week schedule. Over the next couple of years, hundreds of patients will be treated with the every-three-week schedule and safety data will be collected.

From a theoretical point of view, I am not concerned about efficacy. The peak trastuzumab blood levels are actually higher on the every-three-week schedule. Since there is actually more trastuzumab on board, if anything, there could be greater efficacy. I do not believe that will necessarily be the case, but certainly there is no theoretical reason to expect a decrease in efficacy.

DURATION OF TRASTUZUMAB TREATMENT

No clinical information exists to guide the decision about continuing treatment with trastuzumab. In metastatic breast cancer patients, there comes a point where medical therapy is no longer effective. If the disease is end-stage, we certainly stop treatments. In women with a good performance status and no side effects, we continue trastuzumab. In the absence of data, we have been hesitant to discontinue it. Although trastuzumab may not prevent progression, it may slow it down. We do not have clinical answers yet.

HORMONAL THERAPY IN COMBINATION WITH TRASTUZUMAB

There is scientific rationale to combine hormonal therapy with trastuzumab. There is cross-talk between the HER family signal pathway and the estrogen receptor. The estrogen receptor is downregulated by HER2 signaling; therefore, blocking HER2 may restore hormone sensitivity through the mitigation of this estrogen receptor downregulation phenomenon.

In animal models, Dr Rich Pietras at UCLA has studied the combinations of tamoxifen and trastuzumab as well as fulvestrant

and trastuzumab. He has demonstrated striking beneficial results. There is also an ongoing study with anastrozole and trastuzumab.

In ER-positive women receiving tamoxifen or an aromatase inhibitor in combination with trastuzumab, I have observed clinical responses. Prior to the availability of trastuzumab, I did — on occasion — observe HER2-positive women respond to hormonal therapy. In the right clinical scenario, it is reasonable to consider hormonal agents in combination with trastuzumab.

In ER-positive, HER2-positive women, I usually use trastuzumab with or without hormonal therapy, and I almost always use hormonal therapy because of its low incidence of side effects. In women with ER-positive, HER2-positive disease not enrolled in a trial, it is a very logical combination that I consider early on.

It would be reasonable to give women with low-volume, ER-positive disease a trial of hormonal therapy alone. In those women without a rapid response, I would move on quickly to trastuzumab-based therapy for those who are HER2-positive.

TRASTUZUMAB IN THE ADJUVANT SETTING

This is not the standard of care; therefore, we do not use trastuzumab routinely as adjuvant therapy. We first look for a study that the patient might enter, and we are fortunate to be able to have that as our reflex, so we don't have to make the difficult decisions. There is a good chance that the trastuzumab adjuvant trials will eventually be positive. Historically, most therapies that prolong survival in metastatic breast cancer tend to have even greater benefits in the adjuvant setting.

BCIRG ADJUVANT TRASTUZUMAB STUDY

The Breast Cancer International Research Group's (BCIRG's) trastuzumab adjuvant trial 006 is evaluating conventional chemotherapy strategies — four cycles of AC followed by four cycles of docetaxel — in combination with trastuzumab. The arm we are most excited about is the docetaxel-carboplatin-trastuzumab arm.

This is a nonanthracycline combination of synergistic drugs. There is synergy between docetaxel-trastuzumab as well as carboplatin-trastuzumab. In addition, we don't have to worry as much about cardiotoxicity with that combination.

Trastuzumab Interactions with Chemotherapy Agents: Rationale for Current Clinical Trials

Cisplatin	synergism
Thiotepa	synergism
Etoposide	synergism
Doxorubicin	addition
Paclitaxel	addition
Methotrexate	addition
Vinblastine	addition
5-fluorouracil	antagonism

Derived from Pegram M et al. *Oncogene* 1999;18:2241-2251.

It is now generally accepted that identification of molecular alterations which play a role in the pathogenesis of specific human malignancies will lead to the development of targeted therapeutics which should be more effective and less toxic than currently available agents. . .

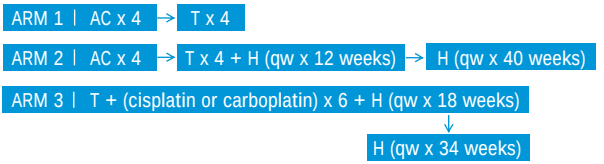
Studies leading to a greater understanding of the biological consequences of HER2/neu-directed therapies should allow the integration of this molecularly-targeted approach with currently available cancer treatments. The additive or synergistic therapeutic interaction between rhuMAb HER2 and a number of chemotherapeutic drugs suggests that such combinations could be successfully exploited in future human clinical trials.

—Pegram M et al. *Oncogene* 1999;18:2241-2251.

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

Protocol ID: BCIRG-006

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



AC=doxorubicin/cyclophosphamide, T=docetaxel
H=trastuzumab

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

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Edited Comments by Dr Livingston

OVERVIEW OF PROPOSED PHASE III ADJUVANT INTERGROUP STUDY

We are planning a Phase III, randomized, adjuvant trial in women with hormone receptor-negative, node-positive or high-risk, node-negative disease. This study should be open to accrual in about a year. The trial is designed to compare two different schedules of AC followed by either docetaxel alone or in combination with capecitabine.

Continuous — or metronomic — chemotherapy may be more effective than standard intermittent chemotherapy, because it results in a greater degree of antiangiogenic and antitumor activity. The initial randomization of this trial will be "continuous AC" versus six cycles of AC. There's a growing opinion — at least in this country — that four cycles of AC is probably an inadequate duration of treatment.

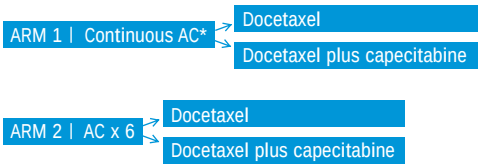
It was the opinion of the other Intergroup chairs, as well as myself, that we should give the same duration of treatment in both arms. So, the patients in the second arm will receive six cycles of AC.

The second randomization is based on the phase III randomized trial conducted by Joyce O'Shaughnessy, in which women with anthracycline-refractory stage IV disease received docetaxel or a lower dose of docetaxel plus capecitabine. The second randomization in this study will be to either docetaxel alone or docetaxel plus capecitabine.

Proposed Intergroup Trial: Phase III Study of Adjuvant Continuous versus Standard Intermittent Doxorubicin and Cyclophosphamide Followed by Capecitabine and Docetaxel versus Docetaxel Alone in Hormone Receptor-negative, Node-positive or High-risk, Node-negative Breast Cancer

Note: This trial is expected to begin accrual within the next year. Details of the trial are subject to change.

Protocol



*Continuous AC = doxorubicin q week; cyclophosphamide q day (orally)

Principal Investigator:
G Thomas Budd, MD
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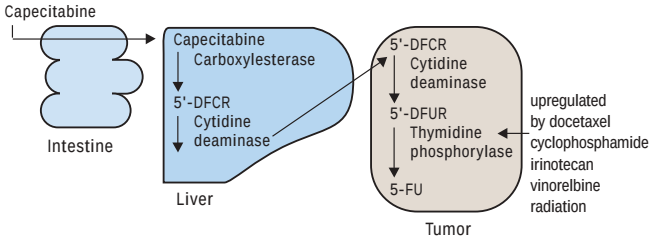
CAPECITABINE/DOCETAXEL COMBINATION IN CLINICAL PRACTICE

Outside the context of a clinical trial, we are using the combination of capecitabine and docetaxel, primarily in women who have had previous anthracycline treatment but were not exposed to either a fluorinated pyrimidine or taxane. We would start at a lower dose, because in Joyce O'Shaughnessy's phase III trial, a 25% dose reduction for both docetaxel and capecitabine was necessary in most women. They were then able to tolerate that combination at that dose for the remainder of their treatment.

Enzymatic Conversion of Capecitabine to 5-Fluorouracil



Phase III Trial of Docetaxel-Capecitabine (XT) Combination Therapy vs Docetaxel Monotherapy (T) in Metastatic Breast Cancer Closed Protocol

Eligibility	Metastatic breast cancer patients resistant to or relapsing after anthracycline-based therapy

ARM 1 | Capecitabine 2500 mg/m2 po in 2 daily divided doses + docetaxel IV 75 mg/m2 q 3 weeks

ARM 2 | Docetaxel IV 100 mg/m2 q 3 weeks

X=capecitabine, T=docetaxel

XT versus T: Baseline Characteristics

- Age (median=52-years-old), performance status, hormone-receptor status and sites of metastases were equivalent between groups
- Two-thirds of patients had ≥ 3 metastatic sites
- Prior chemotherapies: 100% had anthracyclines, 90% had alkylating agents, 75% had 5-FU and about 10% had paclitaxel
- No difference in percentage of patients being treated first-line and about two-thirds received XT or T as second- or third-line treatment

XT versus T: Dose Reductions and Quality of Life

- Dose reductions to 75% of initial dose were observed in two-thirds of patients in the XT arm for either capecitabine or docetaxel and in about one-third of docetaxel only patients
- Quality of life — assessed by EORTC QLQ-C30 global health status — showed a trend favoring XT compared to T

Derived from Vukelja S et al. *Breast Cancer Res Treat* 2001; **Abstract 352.**

Efficacy of XT vs T in Metastatic Breast Cancer

	Capecitabine/ Docetaxel	Docetaxel	Statistical Significance
Time to progression	6.1 months [5.4-6.5]	4.2 months [3.4-4.5]	log rank p=0.0001
CR + PR	42% [35.5-47.9]	30% [24.2-35.7]	p=0.006
Stable disease	38% [31.7-43.9]	44% [38.0-50.5]	
Median survival	14.5 months [12.3-16.3]	11.5 months [9.8-12.7]	log rank p=0.0126

Derived from Vukelja et al. 2001 San Antonio Breast Cancer Symposium. **Abstract 352.**

XT versus T: Post-study Treatment

Approximately two-thirds of patients received chemotherapy after XT or T.

17% of patients in the docetaxel only arm subsequently received capecitabine.

Derived from Miles et al. *Breast Cancer Res Treat* 2001; **Abstract 442**
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USE OF ADJUVANT TAXANES IN ER–POSITIVE, HER2–NEGATIVE PATIENTS

If a woman is ER-positive, HER2-negative and has fewer than four positive nodes, then I would use CMF followed by tamoxifen. I wouldn't use taxanes or doxorubicin. No trials have demonstrated that for these "garden-variety" patients, anthracycline-based therapies are any better, and neither the CALGB nor the NSABP have shown an advantage for the subsequent administration of a taxane after initial AC treatment in ER-positive women.

TREATMENT OF NODE–POSITIVE, HER2–POSITIVE PATIENTS

In women who are node-positive and HER2-positive, we routinely use anthracycline-based therapy and taxane-based consolidation,

regardless of their hormone receptor status. There is a reasonable response rate to taxanes in HER2-positive disease, and it's probably the same for HER2-negative disease that has become anthracycline-refractory. We do not have data from any completed randomized trial that speaks to the value of a taxane in ER-positive patients.

We treat women who are ER-positive and HER2-positive differently than those who are HER2-negative. We believe that HER2 overexpression confers a much greater probability of resistance, even to anthracycline-based combinations, and certainly there is a greater probability of resistance to hormonal therapies, namely tamoxifen.

TRIALS OF ANTITUBULIN COMBINATIONS

Our group has been very interested in antitubulin combinations — primarily taxanes and vincas. Since the most useful vinca for the treatment of breast cancer is vinorelbine, our trials involve that drug. In the setting of anthracycline-refractory stage IV breast cancer, we have done a series of studies using a dose-dense and dose-intense approach to the administration of vinorelbine, both alone and in combination with taxanes.

MANAGEMENT OF ER–NEGATIVE, METASTATIC BREAST CANCER

A woman with ER-negative metastatic breast cancer should be offered an anthracycline-based regimen if she has not already received it in the adjuvant setting or if she recurs over one year since receiving an adjuvant anthracycline.

We do not have irrefutable data that women with ER-negative, HER2-negative disease do better with an anthracycline-based regimen, but I would be very hesitant to give them nonanthracycline-based therapy. In a nonprotocol setting, the combination of doxorubicin and docetaxel would be reasonable, although I also use capecitabine and docetaxel.

There are some women who would be better candidates for single-agent capecitabine. One must individualize therapy based on what you see in that particular woman. For a woman in whom I was concerned about myelosuppression, or if the patient already had neurotoxicity, I would favor single-agent capecitabine.

TREATMENT ALGORITHM FOR METASTATIC BREAST CANCER

There are several algorithms for the management of a typical case of newly diagnosed metastatic breast cancer, and a well-informed, rational medical oncologist can make a good case for any of them. My approach is influenced by my interest in evaluating continuous drug exposure and combined antitubulin therapies. Empirical evidence based on phase II studies demonstrates that continuous chemotherapy with the AC regimen and combined antitubulins may be better.

One could take either of those regimens and potentially add a drug like capecitabine. Combining capecitabine with continuous AC may be problematic, but you may be able to add it to a taxane/vinorelbine regimen.

COMBINATION VERSUS SINGLE-AGENT CHEMOTHERAPY

Many young women with visceral-dominant disease, who have failed initial treatment, want an aggressive approach. If you achieve an objective response without significant toxicity in a young and relatively healthy woman, that individual's quality of life is likely to improve. However, you are more likely to achieve an objective response with combination chemotherapy. In postmenopausal women with a single site of disease, I would usually use a sequential single-agent approach.

TREATMENT OF WOMEN WHO RECEIVED PRIOR ADJUVANT ACT

In an off-study situation, we combine vinorelbine with weekly taxane administration. There is reasonably good evidence that 20 to

30% of metastatic breast cancer patients with prior exposure to every-three-week taxane treatment will achieve an objective response when subsequently given either paclitaxel or docetaxel on a weekly schedule. So, our rationale is we can give vinorelbine at almost full dose and combine it with a taxane and get both drugs in at reasonably close to full dose.

TREATMENT OF METASTATIC DISEASE IN HER2–POSITIVE WOMEN

At our institution, women with HER2-positive metastatic breast cancer receive trastuzumab plus an antitubulin combination, which does not appear to be associated with any unusual or unexpected toxicities.

In a nonprotocol setting, trastuzumab plus either vinorelbine or paclitaxel are very reasonable regimens. Only if a woman is not a candidate for chemotherapy or refuses chemotherapy, do we use single-agent trastuzumab. There is usually some rational combination to offer.

DURATION OF TRASTUZUMAB THERAPY

Trastuzumab should be continued at least until progression, and sometimes we continue it beyond that point. There is no answer about when to discontinue trastuzumab. Only a randomized trial will answer that question.

We are no longer in a situation where there is certainty that the continuation of trastuzumab is fruitless. If one believes trastuzumab is working in part through the potentiation of some other mechanism, then you must open your mind to the possibility that trastuzumab may potentiate vinorelbine after paclitaxel, for example.

I typically treat a woman with a chemotherapeutic regimen plus trastuzumab until I see a maximum response or she has serious toxicity problems. Then, I discontinue the chemotherapy and continue the trastuzumab. Since there are no randomized trials to guide us, this is an individual practice decision.

TREATMENT OF METASTATIC BREAST CANCER IN ER–POSITIVE, HER2–NEGATIVE WOMEN

In ER-positive, HER2-negative women without visceral-dominant disease, we initially treat with hormone therapy alone. If they have bone metastases, we use hormone therapy plus a bisphosphonate. In women with visceral disease, liver involvement predicts a lower likelihood or a shorter duration of response to hormone therapy. The same is not true of lung, bone, skin or chest wall involvement. If a woman with visceral disease is not a good candidate for hormone therapy alone, I use hormonal therapy plus chemotherapy, which is typically CMF.

PET SCANNING WITH LABELED ESTROGENS

David Mankoff at the University of Washington is conducting an experimental study evaluating PET scanning with labeled estrogens. The concept is very similar to the glucose PET scan. Basically, you positron label an estradiol molecule and inject it into the patient. Only those sites with the ability to selectively concentrate estradiol (i.e., those with an active estrogen receptor) take it up in sufficient quantity in order to see a hot spot in terms of PET emissions. To date, women with evidence of facilitated estrogen uptake into their tumor sites are the ones responding to hormone therapy.

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Pharmaceutical agents discussed in this program

Generic	Trade	Manufacturer
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals, LP
bicalutamide	Casodex®	AstraZeneca Pharmaceuticals, LP
capecitabine	Xeloda®	Roche Laboratories, Inc.
carboplatin	Paraplatin®	Bristol-Myers Squibb Company
cisplatin	Plantinol AQ®	Bristol-Myers Squibb Company
cyclophosphamide	Cytoxan®	Bristol-Myers Squibb Company
docetaxel	Taxotere®	Aventis Pharmaceuticals
doxorubicin hydrochloride	Adriamycin®	Pharmacia Corporation
exemestane phosphate	Aromasin®	Pharmacia Corporation
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals, LP
letrozole	Femara®	Novartis Pharmaceuticals
megestrol acetate	Megace®	Bristol-Myers Squibb Company
paclitaxel	Taxol®	Bristol-Myers Squibb Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
trastuzumab	Herceptin®	Genentech, Inc.
vinorelbine tartrate	Navelbine®	Glaxo Wellcome, Inc.

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Post-test

Breast Cancer Update, Issue 2, 2002

Conversations with Oncology Leaders

Bridging the Gap Between Research and Patient Care

Questions (please circle answer):

1. True/False: The preliminary ATAC results showed an additional 17% relative risk reduction in risk of relapse rate in the combination arm above and beyond that which can be achieved by tamoxifen or anastrozole alone.

2. Which of the following was considered a source of anastrozole toxicity in the ATAC trial?

a. Increased thrombotic events
b. Weight gain
c. Fractures
d. Hot Flashes

3. True/False: A combination of anastrozole and a bisphosphonate has been suggested as a focus for a new clinical trial.

4. In the ATAC trial, patients in the anastrozole arm compared with those in the tamoxifen arm experienced a statistically significant reduction in

a. Recurrences
b. Second breast cancers
c. Death from breast cancer
d. A and B
e. All of the above

5. Which member of the HER family lacks ligands?

a. HER1
b. HER2
c. HER3
d. HER4

6. True/False: Approximately 20% of breast cancers overexpress HER2.

7. Normal breast tissue has about how many HER2 receptors per cell?

a. 2,000
b. 20,000
c. 200,000
d. 2 million

8. True/False: Preliminary studies have demonstrated a synergistic effect between tamoxifen and trastuzumab.

10. The trial of docetaxel and capecitabine in metastatic disease demonstrated that compared with docetaxel alone, there was an improvement in

a. Response rate
b. Survival
c. A and B
d. Neither

11. The proposed dose of docetaxel in the combination arm of the Phase III is

a. 50 mg/M^2
b. 75 mg/M^2
c. 100 mg/M^2
d. None of the above

Exam Answer Key
1. False, 2. C, 3. True, 4. D, 5. B, 6. True, 7. B, 8. True, 9. B, 10. B

Evaluation Form

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Please answer the following questions by circling the appropriate rating:

5 = Outstanding
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Extent to which program activities met the identified objectives upon completion of this activity, participants should be able to:

• Describe the preliminary results from the ATAC trial	5	4	3	2	1
• Review the toxicity profile of anastrozole versus tamoxifen	5	4	3	2	1
• Review the mechanism of action of trastuzumab	5	4	3	2	1
• Identify the current applications and on-going trials of trastuzumab	5	4	3	2	1
• Describe the rationale and design of the Phase III Intergroup trial comparing continuous versus intermittent AC chemotherapy, and single-agent docetaxel versus docetaxel in combination with capecitabine.	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
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Will help me improve patient care	5	4	3	2	1
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Overall, the activity met my expectations	5	4	3	2	1
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