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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 3, 2002, of Breast Cancer Update consists of discussions with four oncology research leaders on a variety of important issues. The topics include the use of neoadjuvant trastuzumab in combination with paclitaxel, patients' rights to study results following clinical trial participation, ATAC trial results, anastrozole's toxicity profile, the biologic rationale for combining capecitabine with a taxane, and results of the capecitabine/docetaxel trial in metastatic breast cancer.

EDUCATIONAL OBJECTIVES

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

- Review the preliminary ATAC trial results.
- Discuss patients' rights to study results following clinical trial participation.
- Describe the current phase II trial evaluating neoadjuvant trastuzumab/paclitaxel.
- Compare the risks and benefits associated with adjuvant anastrozole and tamoxifen.
- Explain the biologic rationale for combining capecitabine with a taxane.
- Review the side effects associated with the capecitabine/docetaxel combination.

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

The 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.

HOW TO USE THIS SUPPLEMENT

This booklet supplements the audio program and contains edited comments, 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.

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Editor's Note

VOYAGES OF DISCOVERY

"This is what the Venetians sensed when Marco Polo came back from China — there was this whole cartload of exotic fruits and spices and different cloths and funny animals that no one had ever seen before, and books in different languages. As we look at the biologic agents coming along, novel hormone-based therapies, and new opportunities for chemotherapy, there is a tremendous sense of the horizons expanding. Everybody in 'Venice' is running around enthralled by all the different new choices, and they are now sending out their own 'voyages of discovery' to see what comes back. This is a taste of what people have been talking about for decades in terms of targeted therapies, and we are entering a golden age for clinical research."

— Harold Burstein, MD, PhD

Harold Burstein's enthusiasm for discussing the future of targeted systemic therapy is matched by his reluctance to detail current standards of care. Like most clinical researchers immersed in randomized trials that require a flip of the coin to determine treatment, Harold is tough to pin down about his favored interventions in specific practice situations.

However, during our recent interview on the enclosed audio program, we stumbled upon a simple way to separate clinical decisions, using the example of the management of the patient with HER2-positive breast cancer.

Interventions that are standard:

For women with HER2-positive metastatic breast cancer not being considered for endocrine therapy, Dr Burstein — like most breast cancer investigators — considers trastuzumab as a baseline for therapy, with the major question being whether chemotherapy should also be administered.

Interventions that should not be utilized outside of a clinical trial setting:

Citing the widespread accessibility to adjuvant randomized trials, Dr Burstein believes that trastuzumab should not be used in a nonprotocol setting as adjuvant therapy.

Everything else:

Oncologists are constantly challenged to choose between similar treatment options, and their decisions are often based on indirect trial comparisons and clinical experience. Again citing a common HER2 situation, Dr Burstein refers to the encouraging phase II trial data reported by his group at Dana Farber on the combination of trastuzumab and vinorelbine.

While the documented survival advantage of the trastuzumab and paclitaxel combination often leads clinicians to use this regimen as first-line therapy, Dr Burstein believes that either vinorelbine or paclitaxel is a reasonable choice to add to trastuzumab outside of a protocol setting and notes that a current randomized trial will address this key question.

In addition to Dr Burstein's comments on decisions about trastuzumab, the enclosed audio program presents the prespectives of several other research leaders on other key clinical decisions in the "everything else" category including:

The current role of anastrozole as adjuvant therapy:

Dr Jack Cuzick — independent statistician for the ATAC trial — reviews the dilemma facing clinicians with the early, but very promising results, that suggest an advantage for anastrozole compared to tamoxifen.

Combination versus sequential chemotherapy for metastatic disease:

Dr William Gradishar reviews the results from a phase II study evaluating capecitabine combined with paclitaxel. Unlike the randomized phase III trial with capecitabine/docetaxel, this new study was designed without a mechanism to document survival advantage. However, Dr Gradishar argues that both combinations are rational clinical choices, particularly in women with life-threatening metastases.

The optimal sequencing of single-agent chemotherapy for metastatic disease:

Dr David Miles reviews provocative follow-up results from the capecitabine/docetaxel trial suggesting that single-agent capecitabine has significant activity when administered after progression on docetaxel. Dr Miles believes that reversing the sequence of these agents may be a reasonable option in clinical practice.

Several months ago, the Breast Cancer Update team conducted a random national telephone survey of 200 oncologists and surgeons to increase our understanding of practice patterns in the community. Presenting scores of controversial clinical scenarios, we obtained a plethora of data, and the initial results were presented in March 2002 at the Miami Breast Cancer Conference.

A full report is currently being compiled and will be included as a special supplement to the next issue of Breast Cancer Update, and a few examples are included in this booklet. The diversity in treatment patterns is very striking and demonstrates the challenge of the "everything else" decisions.

Many other breast cancer research leaders share Dr Burstein's vision of a new era of targeted and more effective therapy, but at the moment, oncologists and patients must make daily, difficult decisions on imperfect interventions with conflicting supporting data.

The Miami Breast Cancer Conference Patterns of Care Survey suggests that there is a spectrum of clinical practice in oncology that narrows considerably whenever new randomized trial results become available. As more "voyages of discovery" lead to clinical research results, we will continue to query investigators about what this means to the patient seeking care.

— Neil Love, MD

Harold J Burstein, MD, PhD

Assistant Professor of Medicine
Dana Farber Cancer Institute
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Edited comments by Dr Burstein

NEOADJUVANT TRASTUZUMAB/PACLITAXEL TRIAL

Given that the patient population had large HER2-positive tumors, which have historically been more refractory to therapy — I'm very encouraged. This study is novel for several reasons. It is the first trial evaluating neoadjuvant trastuzumab, and there is a lot of interest in defining the response rate. Also, we performed cardiac analyses during the trastuzumab/paclitaxel therapy and again during the postsurgical adjuvant AC chemotherapy. Our results are very similar to George Sledge's — a significant number of women had a 10-20% decline in their ejection fraction. Fortunately, none of the patients developed any symptoms of congestive heart failure, and the changes in ejection fraction appear to reverse with time.

The decline in ejection fraction occurred either during or at the end of adjuvant AC in three of the four women, and did not change much during the trastuzumab/paclitaxel therapy. Most of us believe these kinds of changes in ejection fraction are consistent with what occurs with AC alone, but since this is not a randomized trial, we do not know if the addition of trastuzumab influences the ejection fraction.

PHASE II STUDY OF PREOPERATIVE TRASTUZUMAB (H) AND PACLITAXEL (T) FOR HER2 OVEREXPRESSING (HER2+) STAGE II/III BREAST CANCER

H (4 mg/kg x1 → 2 mg/kg x 11) + **T** (175 mg/m² q3w x 4) → Surgery → **AC** q3w x 4

↑		↑	↑	↑
C		C	C	C
SERA		SERA		SERA

C = Cardiac function assessment

SERA = Assessment of HER2 extracellular domain (ECD)

H= trastuzumab; T=paclitaxel; AC=doxorubicin/cyclophosphamide

PATIENT CHARACTERISTICS n=40

Age (median)	49	HER2 IHC	
Clinical stage		2+	20%
II	55%	3+	80%
III	43%	ER +	65%

SUMMARY OF RESULTS

- Neoadjuvant H+T:
  - overall clinical response rate: 73%
  - HER2 IHC 3+ clinical response rate: 84%
  - pathological complete response rate: 18%
- HER2 expression persists in some patients after trastuzumab-based therapy, even in patients with clinical response
- Sequential neoadjuvant H+T followed by surgery and adjuvant AC:
  - grade 2 cardiac toxicity: 13%
- HER2 ECD in women with HER2-positive stage II/III breast cancer:
  - ECD elevated in 24% of cases, particularly among HER2 3+patients
  - may predict clinical response to trastuzumab-based therapy

Derived from Burstein HJ et al. *2001 San Antonio Breast Cancer Symposium*;Poster 507.

INFLUENCE OF TRASTUZUMAB ON HER2 EXPRESSION

Our study is the first to evaluate tumor samples before and after trastuzumab therapy. We are in the process of analyzing these results. It will be very interesting to determine the influence of trastuzumab exposure on a tumor's HER2 status. There are confounding factors, however, because some women had no residual tumor to test after trastuzumab therapy. Of course, those are the women in whom one would be most curious as to what was going on.

As a first-order analysis, it appears to be technically feasible to test for HER2 status after exposure to trastuzumab. Grossly, the tumors appear as if there is some treatment effect. They do not look particularly different from tumors treated with chemotherapy alone. Beyond that, we're still evaluating the data.

Another component of the study is tracking the serologic response to neoadjuvant trastuzumab by measuring the circulating extracellular domain (ECD) of the HER2 protein. In women who are responding, the serum HER2 ECD is a good tumor marker, and women who respond tend to have a decline in their serum HER2 ECD.

TIMING OF TRASTUZUMAB: IMPLICATIONS FOR NEOADJUVANT AND ADJUVANT THERAPY

A larger randomized trial evaluating neoadjuvant trastuzumab-based therapy would be very interesting. For chemotherapy, we have very convincingly shown that the sequence of treatment does not matter. There are several studies demonstrating that neoadjuvant chemotherapy is equivalent to adjuvant chemotherapy.

However in the metastatic setting, earlier trastuzumab exposure may be better than later trastuzumab exposure. This is based on the fact that two-thirds of the women in the trial by Slamon and colleagues, who received chemotherapy alone, subsequently received trastuzumab. Despite that crossover, there was still a survival advantage for those receiving chemotherapy plus trastuzumab initially compared to those receiving chemotherapy alone.

Most of the ongoing adjuvant trials with trastuzumab involve sequential chemotherapy first followed by chemotherapy plus trastuzumab as the control arm. But, I wonder if earlier exposure to trastuzumab might be clinically valuable.

ADJUVANT TRASTUZUMAB

We must be cautious when introducing therapies into the adjuvant setting. I do not use adjuvant trastuzumab outside of a clinical trial. In this situation, treatment as part of a clinical trial is better than treatment outside of a clinical trial, and there are adjuvant trials available at most large cancer centers.

Trastuzumab is a very promising drug, which has generated tremendous enthusiasm, but there are concerns about long-term side effects. While all of us hope to bring the answers to our patients as soon as possible, we have tried very hard to limit the use of adjuvant trastuzumab to patients on a study.

Current Neoadjuvant Trials of Trastuzumab

TRIAL	SCHEMA
NSABP B-31 National Surgical Adjuvant Breast and Bowel Project	AC x 4 → paclitaxel x 4 AC x 4 → paclitaxel x 4 + H qw x 1 year
CALGB-49808 Cancer and Leukemia Group B	AC +/- dexrazoxane → paclitaxel qw x 12 +/- H → Surgery/radiation → +/- H qw x 40
NCCTG-N9831 North Central Cancer Treatment Group	AC x 4 → paclitaxel qw x 12 AC x 4 → paclitaxel qw x 12 → H qw x 52 AC x 4 → (paclitaxel qw + H qw) x 12 → H qw x 40
BCIRG-006 Breast Cancer International Research Group	AC x 4 → docetaxel x 4 AC x 4 → docetaxel x 4 + H qw x 52 (Docetaxel + carboplatin or cisplatin) x 6 + H qw x 52
HERA Herceptin Adjuvant Trial	Any chemo or XRT → Observation Any chemo or XRT → H q3w x 12 months Any chemo or XRT → H q3w x 24 months

TRASTUZUMAB IN COMBINATION WITH CHEMOTHERAPY FOR METASTATIC DISEASE

For a woman with HER2-positive, ER-negative breast cancer who has received prior AC and recently relapsed, trastuzumab in

combination with chemotherapy is the standard. A variety of chemotherapeutic regimens have been evaluated in combination with trastuzumab — weekly paclitaxel, vinorelbine, docetaxel and docetaxel plus the platinums. These are all very effective regimens and very reasonable choices. We choose between these active regimens based upon their side-effect profiles and personal preferences. Very little data suggest that one regimen is superior to another. In women with neuropathies, one should be cautious about using drugs that cause neuropathy, and some women may not be willing to lose their hair, so you might choose regimens that are less likely to cause alopecia.

Our group has led the development of a randomized study, which we call the TRAVIOTA trial — trastuzumab and vinorelbine or a taxane. Women are randomized to either the trastuzumab/vinorelbine combination or to a trastuzumab/taxane combination. Physicians will be allowed to choose between weekly paclitaxel or weekly docetaxel. This is a 50-institution trial with an accrual goal of 250 patients. We want to objectively characterize the response rates and toxicity profiles for these regimens. I think we will find out that these are all very reasonable regimens and will have good news for patients in that there will be several options from which to choose.

TRAVIOTA: TRASTUZUMAB (HERCEPTIN®) AND EITHER VINORELBINE (NAVELBINE®) OR TAXANE-BASED CHEMOTHERAPY IN PATIENTS WITH HER2 OVEREXPRESSING METASTATIC BREAST CANCER: A RANDOMIZED PHASE III STUDY

OBJECTIVE:	The primary endpoint is comparison of the overall response rate (complete and partial response) for patients receiving trastuzumab in combination with either vinorelbine or taxane-based chemotherapy.
ELIGIBILITY:	Stage IV, HER2-positive (IHC 3+) breast cancer. More than six weeks since prior chemotherapy or hormonal therapy and more than 12 months since adjuvant trastuzumab

ARM 1	Trastuzumab + vinorelbine
ARM 2	Trastuzumab + docetaxel or paclitaxel*

*Choice of taxane is at the physician's discretion

DURATION OF TRASTUZUMAB THERAPY

The duration of trastuzumab therapy is probably the most important question confronting us in the treatment of HER2-positive metastatic disease. We really do not have adequate data. The value of maintenance trastuzumab therapy is a huge question. In clinical practice, we often roll patients over from one trastuzumab-based chemotherapy regimen to another.

Initially, we treat women with trastuzumab plus chemotherapy. If they are fortunate to have a good response, we often stop the chemotherapy after 4-6 months and continue maintenance single-agent trastuzumab.

At the time of progression, there are a number of options. Most physicians would probably re-institute chemotherapy plus trastuzumab at that point. MD Anderson is conducting a randomized trial to assess the role of ongoing trastuzumab in such a setting. They are enrolling women who have progressed after receiving paclitaxel or docetaxel plus trastuzumab. These women are then randomized to either vinorelbine alone or vinorelbine plus trastuzumab.

Patterns of Care: Metastatic Breast Cancer

A 57-year-old woman with HER2-positive breast cancer relapses and is treated with paclitaxel and trastuzumab. After four months, she has had a good response and is doing well. Generally, how long do you continue therapy?

PACLITAXEL		
	Continue until progression	65%
	Stop before progression	35%
TRASTUZUMAB		
	Continue after progression and add another chemotherapy agent	65%
	Continue until progression, then stop	25%
	Stop before progression	10%

Source: 2002 Miami Breast Cancer Conference Patterns of Care Study

TREATING WOMEN WITH HER2–POSITIVE, ER–POSITIVE DISEASE

Some data suggest that women with HER2-positive, ER-positive disease may derive less benefit from hormone-based therapy than women with HER2-negative, ER-positive disease, but this does not mean they do not benefit.

Our clinical practice has been to use hormonal therapy as long as appropriate. When the woman needs chemotherapy, we introduce chemotherapy plus trastuzumab. Two sets of data support this practice. The pivotal trial with trastuzumab plus chemotherapy assessed the response rate as a function of ER status. Trastuzumab plus chemotherapy was equally effective in women with ER-positive and ER-negative disease. In women with ER-positive disease, the pivotal trial also evaluated the response rate as a function of prior hormonal therapy, which did not influence the response to trastuzumab plus chemotherapy.

Certainly, trastuzumab is active as a single agent, and women who do not want chemotherapy and are not candidates for further hormonal therapy could potentially start on single-agent trastuzumab — this is a reasonable option.

We are conducting a phase II trial evaluating an aromatase inhibitor in combination with trastuzumab. Without a randomized trial, we do not have data that this is superior. Of course, this commits the woman to a weekly treatment, and the beauty of hormonal therapy, aside from its effectiveness, is its convenience.

PHASE II/III RANDOMIZED STUDY OF ANASTROZOLE WITH OR WITHOUT TRASTUZUMAB (HERCEPTIN) IN POSTMENOPAUSAL WOMEN WITH HORMONE-RECEPTOR POSITIVE HER2-OVEREXPRESSING METASTATIC BREAST CANCER **Open Protocol**

Protocol IDs: ROCH-BO16216, GENENTECH-H2223g

Eligibility	ER-positive, HER2-positive (IHC 3+ or FISH-positive) metastatic breast cancer

ARM 1 | Anastrozole 1 mg qd + trastuzumab qw

ARM 2 | Anastrozole 1 mg qd

Treatment continues in both arms for at least two years in the absence of disease progression or unacceptable toxicity

STUDY CONTACT
Bernd Langer, Chair, Ph: 41-61-68-80638
Roche Global Development-Palo Alto

PRELIMINARY RESULTS OF THE ATAC TRIAL

The ATAC trial is the largest single randomized trial — with more than 9,000 women — conducted in breast cancer research. There are, however, several caveats. First, there was no survival difference, since there were very few deaths related to breast cancer. Second, there is a limited follow-up of only 2.5 years.

However, I think the time for the introduction of aromatase inhibitors in early-stage disease is rapidly arising. Compelling studies in metastatic disease and the neoadjuvant setting demonstrate that aromatase inhibitors are at least as good as tamoxifen. And now, we have this large adjuvant trial showing that anastrozole may be better than tamoxifen.

In the preliminary data from the ATAC trial, patients on anastrozole had fewer menopausal symptoms and a reduced rate of endometrial cancer and thromboembolic events. There were somewhat greater osteoporotic events in the anastrozole arm. It's not clear if this is a detrimental effect associated with the aromatase inhibitors or if it just represents the background level of osteoporotic fractures, with tamoxifen increasing the bone mineral density a little bit. This is an issue that we want some long-term data on.

For women already receiving tamoxifen, I would leave them on tamoxifen. It is a very safe and effective drug with decades of proven experience. For women finishing their course of tamoxifen, it would be interesting to study the effects of sequencing treatments such as tamoxifen followed by an aromatase inhibitor. I encourage physicians to think about enrolling women on those trials, which are ongoing at multiple sites.

Newly diagnosed women may wish to be very familiar with the ATAC results, and it is likely that we will see aromatase inhibitors used in the adjuvant setting very soon. We have already been using adjuvant aromatase inhibitors in women with a family history of uterine cancer or a personal history of uterine cancer or blood clots.

ADJUVANT TRIALS OF BREAST CANCER PATIENTS WITH CHEMOTHERAPY–INDUCED MENOPAUSE

Women who become menopausal as a result of chemotherapy tend to do better in the long term. The NIH consensus conference in November 2000 identified the role of ovarian ablation in premenopausal women as an important question in breast cancer research. The ATAC data forces a re-analysis of this issue, because the question of whether you should suppress the ovaries and then add an aromatase inhibitor is now crucial.

The Intergroup, in collaboration with the Europeans, is planning a large randomized trial for premenopausal women to evaluate ovarian ablation in women who continue menstruating after chemotherapy. The trial will compare tamoxifen alone versus ovarian ablation plus tamoxifen versus ovarian ablation plus an aromatase inhibitor.

EVALUATION OF INNOVATIVE, NONTOXIC AGENTS: PPAR GAMMA AGONISTS

At Dana-Farber, we were interested in the paroxisome proliferator activated receptors gamma — PPAR gamma — an interesting intracellular signaling family. Data indicate that stimulating the PPAR gamma chain can cause tumor cell differentiation in a variety of tumor cell lines, including breast cancer. If breast cancer cell lines are exposed to PPAR gamma agonists, the cells slow their rate of growth. There are commercially available drugs with this PPAR gamma agonist activity that are used to treat diabetes, so there is tremendous safety experience with these agents.

We conducted a small phase II study in very heavily pretreated women with metastatic breast cancer. Unfortunately, it did not make a significant clinical impact on the course of their disease. Nonetheless, it was impressive that within 7-8 months we were able to enroll 22 women to this trial. There is a wellspring of good faith among our patients. If we have innovative ideas to evaluate non-toxic treatments, patients are willing to explore them with you.

CONCURRENT PACLITAXEL AND RADIATION THERAPY

We have been interested in the concurrent use of chemotherapy and radiation therapy. There has been interest in adding a taxane to AC chemotherapy in the adjuvant setting, but that practice prolongs the length of therapy by an additional three months and typically places radiation therapy at the end. Our group was interested in determining if radiation therapy could be given at the same time as paclitaxel. We designed a phase I trial with patients receiving AC followed by paclitaxel with concurrent radiation, with paclitaxel administered either weekly or every three weeks.

Weekly paclitaxel with concurrent radiation was too toxic. Since paclitaxel is probably a radiosensitizer, weekly administration meant an unacceptably high risk of pulmonary complications, such as radiation-related pneumonitis. It did appear feasible to administer every-three-week paclitaxel with concurrent radiation therapy, but we need more data on this.

PROSPECTIVE PHASE I EVALUATION OF CONCURRENT PACLITAXEL AND BREAST RADIATION THERAPY FOLLOWING ADJUVANT DOXORUBICIN/CYCLOPHOSPHAMIDE (AC) CHEMOTHERAPY FOR STAGE II/III BREAST CANCER

Dose-limiting toxicity — pneumonitis — occurred in 2 of 7 patients receiving weekly paclitaxel concurrent with radiation therapy.

No dose-limiting toxicity was observed for patients receiving paclitaxel every three weeks plus concurrent radiotherapy.

Winer EP et al. *Proc ASCO* 2001;Abstract 152.

PATIENT PREFERENCES FOR LEARNING ABOUT THE RESULTS OF CLINICAL TRIALS

Ann Partridge at Dana-Farber conducted a study to evaluate patient preferences for learning about the results of clinical trials in which they participated. We do not usually share the clinical trial results with the participants in a systematic fashion, and no one has analyzed whether or not patients would like to learn this information.

The survey asked patients participating in a specific phase II clinical trial whether or not they would like to learn the results of the study. Of the patients responding to this survey, 96% indicated they were very interested in knowing the results. This particular phase II trial was not randomized, and patients' opinions may differ for a randomized study.

It is a fascinating and very provocative study that really challenges the clinical research community to think about ways of communicating with patients what has been learned in clinical trials. Sharing that information in a respectful and appropriate manner is something that will be challenging.

PREFERENCES AND ATTITUDES OF PATIENTS WITH METASTATIC BREAST CANCER REGARDING RECEIVING RESULTS FOLLOWING PARTICIPATION IN A CLINICAL TRIAL

	n = 25
Want to be informed when results available	96%
Believe they have a "right" to be informed	96%
Believe their desire to be informed might be influenced by response to treatment	56%
Want family/significant other to be informed if they are unable to be informed	84%
Would allow study results to be provided to their physician	84%
Would allow study results to be provided to their nurse	76%
Would allow study results to be provided to the research team	48%
Willing to be informed by mail	76%

Derived from Partridge AH et al. *Breast Cancer Res Treat* 2001;Abstract 543.

SELECT PUBLICATIONS

NEOADJUVANT/ADJUVANT TRASTUZUMAB

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Leyland-Jones B, Smith I. **Role of Herceptin in primary breast cancer: Views from North America and Europe.** *Oncology* 2001;61 Suppl 2:83-91. **Abstract**

Nabholtz JM, Slamon D. **New adjuvant strategies for breast cancer: Meeting the challenge of integrating chemotherapy and trastuzumab (Herceptin).** *Semin Oncol* 2001;28:1-12. **Abstract**

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Paik S, Park C. **HER-2 and choice of adjuvant chemotherapy in breast cancer.** *Semin Oncol* 2001;28:332-5. **Abstract**

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Sparano JA. **Cardiac toxicity of trastuzumab (Herceptin): Implications for the design of adjuvant trials.** *Semin Oncol* 2001;28:20-7. **Abstract**

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Formenti SC et al. **Concurrent paclitaxel and radiation therapy for breast cancer.** *Semin Radiat Oncol* 1999;9:34-42. **Abstract**

Hsieh CI et al. **Adjuvant sequential chemotherapy with doxorubicin plus cyclophosphamide, methotrexate, and fluorouracil (ACMF) with concurrent radiotherapy in resectable advanced breast cancer.** *Am J Clin Oncol* 2000;23:122-7. **Abstract**

Leonard CE et al. **Does administration of chemotherapy before radiotherapy in breast cancer patients treated with conservative surgery negatively impact local control?** *J Clin Oncol* 1995;13:2906-15. **Abstract**

Markiewicz DA et al. **Concurrent chemotherapy and radiation for breast conservation treatment of early-stage breast cancer.** *Cancer J Sci Am* 1998;4:185-93. **Abstract**

Markiewicz DA et al. **The effects of sequence and type of chemotherapy and radiation therapy on cosmesis and complications after breast conservation therapy.** *Int J Radiat Oncol Biol Phys* 1996;35:661-8. **Abstract**

Meek AG et al. **Concurrent radiochemotherapy in advanced breast cancer.** *Cancer* 1983;51:1001-6. **Abstract**

Recht A et al. **Integration of conservative surgery, radiotherapy, and chemotherapy for the treatment of early-stage, node-positive breast cancer: Sequencing, timing, and outcome.** *J Clin Oncol* 1991;9:1662-7. **Abstract**

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Edited comments by Dr Cuzick

UNBLINDING THE ATAC TRIAL DATA

As the independent statistician, I was the only person able to link the data from the trial with the treatment code and to provide the coded results to the data monitoring committee. As a result, I was the only person who saw the unblinded data as it evolved, and it was very, very exciting. As the results began to appear six months ago, it has been very difficult to keep quiet. Tamoxifen has been the standard endocrine treatment for breast cancer for 30 or 40 years. Now a new treatment looks better, not only in terms of efficacy but also safety. Of course, this is still early data — with two and one-half years of follow-up — but we are seeing a striking improvement in recurrence rates and a reduction in contralateral breast cancer with anastrozole.

ATAC RESULTS — EFFICACY

The most striking finding is that the combination of anastrozole and tamoxifen is no better than tamoxifen alone. Evidence in advanced disease indicates that aromatase inhibitors are more effective than tamoxifen, so although it is really gratifying to see the same results in the adjuvant setting, it is not unexpected. No one had a clear

idea of what would happen in the combination arm. Apparently, once the estrogen receptors are saturated with tamoxifen — as occurs in postmenopausal women — reducing estrogen levels with an aromatase inhibitor has no effect on the disease.

In estrogen receptor-positive women, there was almost a 25% reduction in recurrence rates in the anastrozole arm compared to tamoxifen arm. Tamoxifen produces a 40% reduction in recurrence rates compared to controls, and to obtain an additional 25% reduction beyond tamoxifen with an agent that has a more favorable side-effect profile is an enormous step forward.

Anastrozole demonstrated almost a 60% reduction in contralateral breast cancer rates over tamoxifen. Tamoxifen itself provides a 50% reduction compared to no treatment. Therefore, we are talking about a potential 80% reduction in new breast cancers. If this were the case in the prevention setting, it would be fantastic.

WHICH ADJUVANT ENDOCRINE THERAPY WOULD YOU RECOMMEND FOR THE FOLLOWING PATIENTS WITH ER-POSITIVE, HER2-NEGATIVE BREAST CANCER?

	Tamoxifen	Anastrozole	Letrozole	None/Other
65-year-old woman, 2.2 cm tumor, 10+ nodes	60%	30%	5%	5%
65-year-old woman, 2.2 cm tumor, 2+ nodes	50%	40%	5%	5%
65-year-old woman, 2.2 cm tumor, node-negative	55%	35%	5%	5%
65-year-old woman, 0.8 cm tumor, node-negative	35%	35%	10%	20%
77-year-old woman, 2.2 cm tumor, 10+ nodes	50%	40%	10%	0%

Source: 2002 Miami Breast Cancer Conference Patterns of Care Study

ATAC RESULTS — RISKS

BONE MINERAL DENSITY

The fracture rate was increased from roughly five percent in the tamoxifen arm to seven percent in the anastrozole arm. Of course, tamoxifen has a beneficial effect on bones. Probably about half of the difference in fractures may be attributable to the reduction in fracture rates associated with tamoxifen. The other half of the difference in fractures may be related to anastrozole's negative effect on bone. In a few months, there will be more data available from the bone subprotocol.

I think the effects on bone will be reversible, but if we will be giving aromatase inhibitors for a long time in the adjuvant setting, this will emerge as one of the key issues. The ATAC trial will go on for five years, but there is discussion about re-randomizing at five years to go on for ten years. The issue of how to manage bone loss is going to become paramount.

In the forthcoming IBIS II prevention trial — comparing anastrozole to tamoxifen and placebo — a subgroup of women will be randomized to receive vitamin D and calcium supplements or placebo. If vitamin D and calcium fail, then we will need to look at the bisphosphonates.

ARTHRALGIAS

There was a six percent increase in arthralgias associated with anastrozole. The arthralgias did not have a significant impact on the dropout rate from the trial. We need to look more carefully at the severity and the duration of the arthralgias.

WEIGHT GAIN

All of the evidence that is reliable indicates that there is no weight gain associated with tamoxifen, but in ATAC there was less weight gain with anastrozole. I think it is too early to look at that data — we have just touched the surface of really exploring a lot of these somewhat surprising new side effects.

GYNECOLOGIC

The endometrial cancer data are very striking — there were 11 cases in the tamoxifen arm compared to three in anastrozole arm. There was no evidence of endometrial cancer being a problem with anastrozole. There was a large difference in vaginal bleeding. Vaginal bleeding increased with tamoxifen, whereas anastrozole demonstrated an 80% reduction. Although not evident in the metastatic trials, most clinicians believe that anastrozole produces fewer vasomotor symptoms than tamoxifen. The ATAC trial demonstrated that anastrozole was associated with fewer hot flashes than tamoxifen.

STROKE/THROMBOEMBOLIC EVENTS

The stroke rate was reduced by more than 50% with anastrozole. This was highly significant and potentially very important. We saw an increase in stroke from tamoxifen in the P-1 trial, and people were still a little skeptical as to whether that was real or not. This is indirect confirmation that it is higher in the tamoxifen arm than it is in the anastrozole arm. This may be a side effect of tamoxifen.

CONTINUATION OF THE ATAC TRIAL

Most of the women enrolled on the ATAC trial are in their third or fourth year of treatment. Clearly, the women in the study will be informed of these results, and they will be asked to consent to continue in the trial. Women who want to find out which drug they are receiving will be informed and dropped from the trial. It is believed that the combination arm will be discontinued. It is likely that the women on the combination arm will be able to choose between tamoxifen and anastrozole. It is also possible that they may be randomized between the two treatments.

I hope this trial will have a re-randomization to look at duration of therapy — five versus ten years of anastrozole. I think the duration of therapy will emerge as a key issue. Probably longer is going to be better than shorter. Five years may just be the beginning — ten years may be best. Key issues will be the bone problems and

possibly cognition.

DIFFERENTIATION BETWEEN THE AROMATASE INHIBITORS

There will be much discussion as to whether these results are applicable to the other aromatase inhibitors — letrozole and exemestane, but there may be subtle differences in their side-effect and phamacokinetic profiles.

DO YOU BELIEVE THAT OTHER AROMATASE INHIBITORS (LETROZOLE, EXEMESTANE) CAN BE USED INTERCHANGEABLY WITH ANASTROZOLE AS ADJUVANT THERAPY?

45%	No - I would use anastrozole because the adjuvant safety and efficacy of the others is unproven
28%	No - I would use anastrozole because the adjuvant efficacy of others is unproven
7%	No - I would use anastrozole because the adjuvant safety of others is unproven
20%	Yes - I would use exemestane or letrozole interchangeably with anastrozole as adjuvant therapy

Source: Interactive polling, 2002 Miami Breast Cancer Conference

ADJUVANT TRIALS ON THE HORIZON

There are a number of interesting options for new adjuvant trials. One that is particularly attractive is the use of the pure antiestrogens — drugs like fulvestrant. An interesting question is whether fulvestrant has something to offer in combination with an aromatase inhibitor.

Another area where there is a need for trials is in premenopausal women. The aromatase inhibitors are better than tamoxifen in postmenopausal women, but one-third of the breast cancer cases occur in premenopausal women. In premenopausal women, the LHRH agonists are an option in those with ER-positive disease — they are as effective as chemotherapy. LHRH agonists render a woman postmenopausal, and at that stage, the addition of an aromatase inhibitor could be considered. That is an interesting question. Should we be using LHRH agonists plus an aromatase inhibitor as a more complete method to deprive tumors of estrogen? Is an LHRH agonist plus an aromatase inhibitor more effective than chemotherapy?

WHICH OF THE FOLLOWING BEST DESCRIBES YOUR INTENDED USE IN THE NEAR FUTURE OF AN AROMATASE INHIBITOR AS ADJUVANT THERAPY?

Anastrozole or letrozole interchangeably	30%
Generally anastrozole, occasionally letrozole	30%
Anastrozole	25%
Letrozole	5%
Generally letrozole, occasionally anastrozole	5%
None	5%

Source: 2002 Miami Breast Cancer Conference Patterns of Care Study

PREVENTION TRIALS IN PREMENOPAUSAL WOMEN

In order to understand how lifestyle modifications can impact on breast cancer risk, we are conducting small trials in premenopausal women. Increasing epidemiological evidence suggests that exercise has a beneficial effect on cancer. Possibly, the dietary intake of soy products may have an effect on breast cancer. The other lifestyle factor is alcohol intake. Studies demonstrate that women who consume two drinks per day increase their breast cancer risk by about 30%. It is difficult to know whether this is a causal effect.

There is interest in looking at the LHRH agonists with some sort of add-back. We are conducting pilot trials evaluating an LHRH agonist plus raloxifene to protect the bone. We need to find an add-back to control symptoms. There are lots of exciting possibilities — an LHRH agonist in combination with anastrozole plus some sort of bisphosphonate.

PILOT RANDOMIZED STUDY OF RALOXIFENE AND GOSERELIN VERSUS NO MEDICAL INTERVENTION IN WOMEN AT HIGH GENETIC RISK FOR DEVELOPING BREAST CANCER

Open Protocol

Protocol IDs: EU-20053, UKCCCR-IBIS-RAZOR

Eligibility	30-45-year-old, premenopausal women with a high genetic risk of developing breast cancer
ARM 1	(Goserelin q month + raloxifene qd) x 6-12 months
ARM 2	Screening for breast cancer every 6 months

In both arms, patients undergo annual mammograms.
Patients are followed for five years.

Study Contact
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CAPECITABINE/DOCETAXEL (XT) TRIAL

Relatively few trials have demonstrated a survival benefit in women with metastatic breast cancer. The combination of capecitabine and docetaxel improved response rates and survival compared to single-agent docetaxel. Although there was a survival advantage, there was also somewhat greater toxicity in the combination arm than the single-agent arm. As a result, many of the women in the trial required dose reductions.

As a result of the capecitabine/docetaxel trial, this combination is now being evaluated as adjuvant therapy in a number of large international trials. The pharmacologic basis for this combination involves the fact that the enzyme responsible for activating

capecitabine in tumor cells is up-regulated by the taxanes — specifically docetaxel.

LACK OF CROSSOVER IN THE XT TRIAL

One concern about the capecitabine/docetaxel trial was whether or not it was a fair assessment of the efficacy of single-agent docetaxel. Would the same results have been observed if patients received sequential docetaxel followed by capecitabine? In fact, a significant fraction of patients in the docetaxel arm received capecitabine at the time of disease progression. If one could eliminate that subset of patients, I believe that single-agent docetaxel would probably have done even worse, in terms of survival, compared to the combination.

PHASE II CAPECITABINE/PACLITAXEL TRIAL

The next natural question following the XT trial is, "Would similar results be achieved with a combination of capecitabine/paclitaxel?" We addressed this in a small phase II trial that demonstrated a 50% overall response rate and a 12% complete response rate for capecitabine/paclitaxel. Interestingly, the tolerability was somewhat better than that observed with capecitabine/docetaxel.

The regimen was well-tolerated — probably as a result of dose reductions. About 10-12% of the women experienced hand-foot syndrome. Although it is not fair to compare the results from a small phase II trial with those from a larger randomized trial, it might be worth further evaluating the capecitabine/paclitaxel combination in women with metastatic breast cancer.

PHASE II STUDY OF PACLITAXEL AND CAPECITABINE IN PATIENTS WITH METASTATIC BREAST CANCER **Closed Protocol**

Protocol IDs: ROCHE-M66104C

Eligibility	Metastatic breast cancer with at least 12 months since prior fluoropyrimidine or taxane and only one prior chemotherapy regimen in the metastatic setting
Protocol	Paclitaxel (175 mg/m^2) q 3 weeks + capecitabine (825 mg/m^2 bid) qd x 14 days. Treatment repeats every 21 days in the absence of disease progression or unacceptable toxicity.

PATIENT CHARACTERISTICS (n=47)	
Median age	52 (35-76)
ER+	23 (49%)
Prior adjuvant/neoadjuvant regimen	36 (77%)
anthracycline-containing regimen	32 (68%)
5-FU containing regimen	24 (51%)
taxane-containing regimen	4 (9%)
Chemo-naïve	11 (23%)

SUMMARY OF EFFICACY	
CR + PR	24 (51%)
Stable disease	17 (36%)

- Median time to progression was 10.5 months
- Median survival time has not yet been reached after 22 months

Derived from Meza L et al. 2001 San Antonio Breast Cancer Symposium;Poster 358.

COMBINATION VERSUS SEQUENTIAL THERAPY IN METASTATIC BREAST CANCER

In women with metastatic breast cancer not enrolled on a protocol, we generally try to optimize single agents in a sequential manner. In those with rapidly progressing visceral disease — where a quick response is important — combination chemotherapy may be a reasonable alternative. Although response rates may increase with combination chemotherapy, almost inevitably there will also be more toxicity.

The capecitabine/docetaxel combination demonstrated a superior survival outcome, but few, if any, other combinations have ever

shown a survival advantage. For the select patient with a good performance status, the combination of capecitabine/docetaxel or capecitabine/paclitaxel is perfectly reasonable. An alternative approach would be to use optimal single agents sequentially until disease progression.

There is a philosophical difference on how to approach women with metastatic disease. The real question is, "Are the side effects worth achieving a somewhat higher response rate?" Not to minimize the survival advantage — it is real — but there is a cost. However, if you know how to dose adjust, you can manage the patient's side effects.

Approximately what fraction of your patients with metastatic breast cancer receive combination chemotherapy at some point in their treatment of metastatic disease?	76%

Source: 2002 Miami Breast Cancer Conference Patterns of Care Study

CAPECITABINE AS FIRST-LINE THERAPY

Philosophically, sequential therapy involves the use of agents with the least toxicity and reasonable tumor control. An interesting question with sequential therapy would be, "Why not use capecitabine as first-line therapy followed by a taxane?" Even though capecitabine was approved as salvage therapy, this may be a reasonable approach. Since capecitabine demonstrated activity in women with refractory disease, there is no reason to believe it would not be effective as initial therapy. In select patients, those who will be compliant with an oral pill and do not want intravenous chemotherapy or those who progressed after adjuvant anthracycline-taxane therapy, capecitabine may be a reasonable choice.

Many patients will require dose adjustments when given the FDA-approved dose of capecitabine. At a reduced dose, patients may tolerate capecitabine, and the outcome may be similar to that with a taxane. The issue in first-line therapy is, "Can you make it equally effective with fewer side effects than the other alternatives

available?" If capecitabine demonstrates efficacy, there would be a big advantage for many patients to an oral agent.

Case Study in Metastatic Breast Cancer

A 55-year-old woman with asymptomatic lung metastases has been started on capecitabine, 2000 mg/m^2 in two divided doses (Two weeks on, then one week off). After three cycles, she has had no change in the lesions and no side effects. What would you generally do?

Continue therapy	35%
Increase dose to 2500 mg/m^2	25%
Stop capecitabine/change therapy	20%
Continue capecitabine/add other agent	20%

Source: 2002 Miami Breast Cancer Conference Patterns of Care Study

AROMATASE INHIBITORS: IMPLICATIONS OF THE ATAC TRIAL

Although the ATAC trial results are extremely interesting, it is still early in follow-up. The study evaluated only postmenopausal women, most of whom did not receive chemotherapy. As a result of the ATAC trial, women around the country are asking their doctors what they should be doing today. Numerous different scenarios can be envisioned. Women who have been on tamoxifen for six months, two years, three years, etc. are now asking their physicians if they should switch. The ATAC trial results do not address these situations.

The ATAC trial results are more relevant and germane to newly diagnosed postmenopausal women who are destined to receive adjuvant hormonal therapy. It would be fair and honest to discuss the ATAC results with caveats. It would be a consideration to put such a woman on an aromatase inhibitor. Using evidence-based medicine, I would likely prescribe the drug evaluated in the ATAC trial, anastrozole.

Even before the ATAC trial results were available, it was rational to use aromatase inhibitors as adjuvant therapy in women intolerant of tamoxifen. Based upon data from the metastatic disease trials, it was clear that aromatase inhibitors were very effective, as good if not superior to tamoxifen, as first-line therapy. Since we now have a 9,000-patient trial showing early on there is a clear advantage for anastrozole, there's even more of a basis.

WOMEN ABOUT TO START ADJUVANT HORMONAL THERAPY

In postmenopausal women with ER-positive breast cancer, anastrozole may be a consideration. The caveat being that we have thousands and thousands of patient years' experience with decades of follow-up for tamoxifen, whereas the ATAC trial has only about two and one-half years of follow-up.

Another issue not yet answered by the ATAC trial is the long-term effect of anastrozole on the bone. If a young woman is rendered postmenopausal by chemotherapy, her long-term outcome may be 30-40 years in the future.

What would be the consequence of depleting calcium from her bones at a much earlier age compared to a woman who is 70? We need more data about bone fractures from the ATAC trial to understand exactly what we're doing.

Trevor Powles' clodronate data raise the possibility of the addition of a bisphosphonate to an aromatase inhibitor. Perhaps, an aromatase inhibitor plus a bisphosphonate will not only provide benefit in terms of cancer risk reduction but also in terms of maintaining overall quality of health. Bisphosphonates may potentially reduce disease progression or recurrence and also maintain bone density.

A RANDOMIZED PLACEBO CONTROLLED TRIAL OF CLODRONATE ON THE INCIDENCE OF METASTASES AND MORTALITY IN PATIENTS WITH PRIMARY OPERABLE BREAST CANCER

1,069 women with breast cancer received oral clodronate 1600 mg/day or placebo x 2 years

	Clodronate	Placebo	HR	p
Bone metastases	12	28	0.44	0.016
Mortality	98	129	-	0.047

Derived from Powles TJ et al. *Breast Cancer Res Treat* 2001;Abstract 1.

ENDOCRINE TREATMENT STRATEGIES FOR PREMENOPAUSAL WOMEN

In premenopausal women still menstruating after chemotherapy, we discuss the option of ovarian ablation based upon the results from Intergroup trial 0101, but it is not the standard of care. However, in a young woman with a high risk of recurrence, it is worth discussing the potential of ovarian ablation. In women with low-risk, node-negative disease, chemotherapy alone may be adequate to reduce their risk. The benefits of additional maneuvers beyond chemotherapy may be outweighed by the long-term side effects.

AROMATASE INHIBITORS PLUS OVARIAN ABLATION IN PREMENOPAUSAL WOMEN

In a young woman with ER-positive, node-positive breast cancer, who does not become amenorrheic after chemotherapy, an LHRH agonist or ovarian ablation followed by tamoxifen may be considered. In that setting, theoretically it makes sense to consider an aromatase inhibitor. I have used an LHRH agonist plus an aromatase inhibitor in the metastatic setting, which is a very reasonable regimen in light of its tolerability.

DIFFERENTIATION BETWEEN THE AROMATASE INHIBITORS

I use all three aromatase inhibitors — anastrozole, letrozole and exemestane. As first-line therapy for metastatic breast cancer, the data are strongest for anastrozole and letrozole. Since the classes are not completely cross-resistant, a patient progressing after a

non-steroidal agent — anastrozole or letrozole — could be considered for exemestane.

If you are driven by data, then anastrozole is clearly supported as the aromatase inhibitor of choice in the adjuvant setting. Letrozole may turn out to be similar to anastrozole, but the data are not yet available.

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CAPECITABINE ALONE OR IN COMBINATION WITH TAXANES

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Edited comments by Dr Miles

POTENTIAL UNDERESTIMATION OF CAPECITABINE/DOCETAXEL SURVIVAL ADVANTAGE

In a phase III trial by Nabholtz, docetaxel was compared to mitomycin-C plus vinblastine — our standard regimen for anthracycline failures at that time. Then we participated in the capecitabine/docetaxel trial, which clearly demonstrated a survival advantage. In advanced disease, we generally discuss the palliative benefits of chemotherapy, but over the last few years, the median survival for metastatic breast cancer has gone from 9 to 11.5 months up to 14.5 months with capecitabine/docetaxel. Since 27% of the women failing single-agent docetaxel received capecitabine, the survival benefit for the combination may have been underestimated.

XT VERSUS T TRIAL: TREATMENT AFTER PROGRESSION ON SINGLE-AGENT DOCETAXEL

Increasingly, in clinical trials it is difficult to mandate therapy beyond crossover, which makes it difficult to interpret the attributable benefit of treatment up front. We looked at the

poststudy chemotherapy administered to women progressing on single-agent docetaxel. About 28% of the women failing docetaxel received capecitabine. Interestingly, those women treated with capecitabine actually did better than those treated with other chemotherapeutic agents. The hazard ratio of dying was about half for those women receiving capecitabine compared to those receiving other chemotherapeutic agents. Also, 75% of the women had previously received 5-FU, yet there was still a great response rate for docetaxel/capecitabine compared to docetaxel alone.

Many would use vinorelbine after docetaxel failure, but the with that strategy is that both agents are spindle poisons. There are a few phase II studies of vinorelbine following taxane failure, with inconsistent results. When we compared vinorelbine to other chemotherapies following failure of docetaxel, vinorelbine was not associated with any difference in the hazard ratio of death, whereas there was a significant difference with capecitabine.

POSTSTUDY CHEMOTHERAPY AFTER PROGRESSION ON TO XT OR T

	XT	T
% receiving postrandomization chemotherapy	72%	65%
# lines of chemotherapy		
1	60%	54%
2-3	34%	42%
> 4	6%	4%
Agent received**		
capecitabine	2%	28%
5-FU	11%	36%
vinorelbine	46%	28%
anthracyclines	16%	17%
taxanes	45%	25%

** Reflects combination and single-agent chemotherapy regimens, thus percentage > 100

Derived from Miles D et al. 2001 San Antonio Breast Cancer Symposium;Poster 442.

OUTCOMES OF POSTSTUDY CHEMOTHERAPY AFTER PROGRESSION ON TO SINGLE-AGENT DOCETAXEL

- Capecitabine versus all other chemotherapies resulted in a 50% decreased risk of dying (HR=0.5, p<0.005)
- Vinorelbine-containing chemotherapy versus all other chemotherapy agents did not provide benefit (HR=1.0, p=0.94)
- Median survival is 21.0 months for single-agent capecitabine versus 13.5 months for vinorelbine versus 12.5 months for patients receiving any other chemotherapy regimen

Derived from Miles D et al. 2001 San Antonio Breast Cancer Symposium;Poster 442.

CAPECITABINE/DOCETAXEL: SEQUENTIAL VERSUS COMBINATION THERAPY

The crucial question is whether combination therapy is better than sequential therapy. Since the progression-free and overall survival curves separated very early in the original phase III trial by Joyce O'Shaughnessy, many are hesitant not to use the combination of capecitabine and docetaxel in women with a good performance status. You potentially risk losing the advantage of the combination if these agents are not used together. In women who may not tolerate the combination because of toxicity, it may be reasonable to use sequential rather than combination therapy.

Until we have a trial comparing sequential to combination therapy, we will not know the degree of benefit derived from combination therapy. Without the studies, we also will not know which drug should come first. Capecitabine is a very active drug in terms of raw response rates, although it may not be quite as effective as docetaxel. However, there is a group of women in whom you may want to consider capecitabine as a single agent. Until we obtain data on sequential therapy, we have results demonstrating that the capecitabine/docetaxel combination is better than single-agent docetaxel.

CAPECITABINE/DOCETAXEL IN METASTATIC BREAST CANCER

In young, fit women with visceral disease for whom survival is a serious issue, the capecitabine/docetaxel combination should be considered as a nonprotocol regimen. For women who are less

healthy and perhaps older, some may not consider the combination as attractive. In the phase III trial, almost two-thirds of the women had dose reductions. The 75 mg/m^2 of docetaxel and 1,250 mg/m^2 of capecitabine (B.I.D. for two weeks, then one week off) may be a difficult regimen for some women, and it may need to be dose-reduced or one might consider a single agent. It's a choice that you and a woman must make together.

CAPECITABINE/DOCETAXEL TOXICITIES

With capecitabine and docetaxel, there are nonoverlapping toxicities. Myelosuppression with capecitabine is negligible, but there is GI toxicity and the hand-foot syndrome. Capecitabine's clearance is dependent on renal function. In women over 60 years of age, it is necessary to start at 1,000 mg/m^2 b.i.d.— two weeks followed by one week off. This may also be the case for younger patients receiving concomitant docetaxel. The maximum tolerated dose for docetaxel is different around the world. As evidenced by the number of women in the phase III trial with dose reductions, docetaxel 75 mg/m^2 in combination with capecitabine was difficult to administer, but the toxicity for this combination was manageable. Despite the dose reductions, there was still a survival benefit. People are anxious about the combination because of the toxicity element. But if you are interested in increasing survival in this group, I think capecitabine/docetaxel has to be considered the standard of care.

MECHANISM OF ACTION OF CAPECITABINE

Capecitabine's mechanism of action probably goes beyond that of 5-FU. Thymidine phosphorylase (TP) concentrations are higher in tumor cells than normal tissue. Additionally, drugs such as docetaxel and paclitaxel probably induce TP. Recent studies looking at the scheduling of capecitabine/docetaxel in animal models have been reported. A Japanese group looked at different schedules of the two drugs. In fact, giving capecitabine on days 1-14 and docetaxel on day eight instead of day one seemed better. Since docetaxel was used later and theoretically TP was not upregulated until later, TP may not be the whole story — there may be something else going on. There is certainly some added value for capecitabine compared to 5-FU.

TP UPREGULATION

Interestingly, the taxane-mediated upregulation of TP in preclinical studies is time dependent, with elevation of TP expression first observed at day 4 after treatment, peaking from days 6-8, and persisting for up to 10 days. This information coupled with the more favorable toxicity profile of the weekly taxane schedule would make the case for the use of weekly taxanes in combination with capecitabine.

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ROLE OF SINGLE-AGENT CAPECITABINE

Single-agent capecitabine may be considered before a taxane — perhaps in older women, or those with a poor performance status or non-life-threatening disease. In a woman who is symptomatic or whose liver function is impaired, the goal is to maximize the response rate. So, combination therapy may be considered. An interesting trial would be the comparison of capecitabine/docetaxel to docetaxel alone or capecitabine alone. More toxic treatment is not necessarily better.

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Pharmaceutical agents discussed in this program

Generic	Trade	Manufacturer
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals, LP
capecitabine	Xeloda®	Roche Laboratories, Inc.
clodronate	Not available in the USA	
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
goserelin	Zoladex®	AstraZeneca Pharmaceuticals, LP
letrozole	Femara®	Novartis Pharmaceuticals
mitomycin-c	Mutamycin®	Bristol-Myers Squibb Company
paclitaxel	Taxol®	Bristol-Myers Squibb Company
raloxifene	Evista®	Eli Lilly and Company
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
trastuzumab	Herceptin®	Genentech, Inc.
vinblastine	Velban®	Eli Lilly and Company
vinorelbine tartrate	Navelbine®	Glaxo Wellcome, Inc.

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Breast Cancer™ update

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Post-test

Breast Cancer Update, Issue 3, 2002

Conversations with Oncology Leaders

Bridging the Gap Between Research and Patient Care

Questions (please circle answer):

1. Taxanes are known to _____ the enzyme responsible for converting capecitabine into 5-FU within the tumor cell.

a. Downregulate
b. Upregulate
c. Metabolize
d. Degrade

2. True/False: In a study conducted at Dana-Farber, the majority of patients surveyed were interested in learning the results of the trial in which they were participating.

3. In advanced breast cancer, the median survival associated with the capecitabine/docetaxel combination is:

a. 4 months
b. 9 months
c. 11 months
d. 14.5 months

4. True/False: There is adequate clinical data suggesting that trastuzumab should be discontinued immediately at the time of progression.

5. In the ATAC trial, patients in the tamoxifen arm experienced a statistically significant reduction in _____ compared to those in the anastrozole arm.

A. Recurrences
B. Second breast cancers
C. Death from breast cancer
D. A and B
E. None of the above

6. In the ATAC trial, which of the following toxicities were not related to tamoxifen?

a. Thromboembolic events
b. Vaginal bleeding
c. Fractures and bone loss
d. Weight gain

7. According to the ATAC trial results, which of the following best describes anastrozole's effect on the incidence of contralateral breast cancer?

A. The same as tamoxifen
B. An additional 60% reduction over the reduction associated with tamoxifen
C. A 50% increase relative to the reduction associated with tamoxifen
D. Complete elimination of all contralateral breast cancers

8. True/False: HER2 overexpression contraindicates the use of endocrine therapy in ER-positive patients.

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

Evaluation Form

Breast Cancer Update, Issue 3, 2002

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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 current phase II trial evaluating neoadjuvant trastuzumab/paclitaxel	5	4	3	2	1
• Discuss patients' rights to study results following clinical trial participation	5	4	3	2	1
• Review the preliminary ATAC trial results	5	4	3	2	1
• Compare the risks and benefits associated with adjuvant anastrozole and tamoxifen	5	4	3	2	1
• Review the side effects associated with the capecitabine/docetaxel combination	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?

___Yes ___No

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

_____

_____

_____

_____

How committed are you to making these changes?

5 (Very committed) 4 3 2 1 (Not at all committed)

Additional comments about this activity?

_____

_____

_____

Do you feel future activities on this subject matter are necessary and/or important to your practice?

___Yes ___No

Please list any other topics or speakers that would be of interest to you for future educational activities:

_____

_____

_____

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Breast Cancer Update, Issue 3, 2002

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