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Breast Cancer™ UPDATE

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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2 audio tapes

2 audio CDs

Monograph

CME Certified

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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 **red underlined text**. This regularly updated web site also features an extensive breast cancer bibliography, clinical trial links, a "breast cancer web tour" and excerpts from interviews and meetings catalogued by topic.

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 6, 2002 of Breast Cancer Update consists of discussions with four oncology research leaders on a variety of important issues, including the use of the capecitabine/docetaxel combination, the role of trastuzumab in treating HER2-positive metastatic disease, the reliability of current HER2 assays, the biology of the estrogen receptor, the preliminary results from the ATAC trial, the role of aromatase inhibitors in the adjuvant setting and the mechanism of action for and the clinical outcomes with fulvestrant.

Educational Objectives

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

- Distinguish patients with metastatic disease for whom single-agent capecitabine or docetaxel versus the combination would be appropriate
- Compare the different mechanisms of resistance to individual hormonal therapies to develop a rationale for sequencing hormonal therapies in metastatic disease
- Utilize most current clinical data to appropriately select HER2-positive patients with metastatic disease for treatment with trastuzumab
- Recognize the value of the FISH assay for determining HER2 status to optimize selection of therapy
- Comprehend the implications of the ATAC trial for the selection of adjuvant hormonal therapy for postmenopausal patients

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.

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. ***Faculty disclosure information can be found on page 33.***

Editor's Note

A novel targeted therapy for breast cancer becomes available

"There is so much excitement about Gleevec® being the first rationally designed, targeted drug in oncology. That's baloney! In 1896, George Beatson first performed an oophorectomy and removed a growth factor, estrogen, from its receptor. This hormonal manipulation led to responses in two out of three women with locally advanced disease. In my opinion, that was the beginning of true designer drug molecular medicine. We have known about target-directed therapy for 100 years!

"We now have several options for endocrine therapy. The issues are how, when and in what order we should use these agents. As these agents make it to the clinic, I receive phone calls from my colleagues asking, 'What order do I use these in?' I do not think we know the answer. The challenge for the cooperative groups and pharmaceutical companies is to conduct trials evaluating sequential and combination endocrine therapies.

"I believe we will find that different subgroups of patients will respond differently to individual endocrine therapies. Just as we use ER status to decide who will receive endocrine therapy, in the future we may use the progesterone receptor, HER1, 2, 3 and 4 receptor or some of the coactivators and corepressors. These markers may indicate which patients should receive tamoxifen, an aromatase inhibitor or fulvestrant."

— Daniel Hayes, MD

Dr Hayes' reflection on the rapid pace of research surrounding endocrine interventions brings to mind my first introduction to the "brave new world" of targeted therapy in breast cancer, which occurred in a presentation in San Diego on the last afternoon of the 1992 ASCO meeting. Sitting in the back of an almost empty meeting room somewhat dazed from several days of information overload, I was jolted to attention by Dr Tony Howell's early laboratory data on a fascinating new compound that seemed to have a unique effect on the estrogen receptor system. The substance was then called ICI 182,780, or as Tony referred to it, "182." At that time, it was widely considered the first "pure antiestrogen."

Dr Howell's slide of the estrogen receptor cascade was far more complex than any I had previously seen. It brought back memories of earlier simplified endocrine schemas with "Pac Man-like" estrogen molecules diffusing into the cytoplasm, complexing with the estrogen receptor and then mysteriously triggering DNA replication in the nucleus. In the ten years since Dr Howell's presentation, quantum leaps have been made in understanding both the estrogen receptor cascade and the effects of "182," which is now available as the intramuscular injection, fulvestrant or Faslodex®.

As described by Dr John Robertson in the enclosed program, fulvestrant is the first and, at this point, only "estrogen receptor downregulator." Unlike the SERMS, which compete for estrogen receptor binding, and the LHRH agonists and aromatase inhibitors, which dramatically lower estrogenic ligands, fulvestrant results in the disappearance of the target receptor. This appears to be a phenotypic alteration that occurs only during therapy, and patients whose tumors progress while on fulvestrant will respond to other endocrine manipulations.

Not only does fulvestrant have a unique mechanism of action, but also the clinical risk-to-benefit ratio is very promising. In a randomized trial in postmenopausal women, fulvestrant demonstrated an equivalent response rate and a superior duration of response compared to anastrozole — a finding that was predicted by laboratory scientists, including Dr Kent Osborne.

Fulvestrant's side-effect profile also seems very favorable and similar to that of the aromatase inhibitors. Individual patients will view the monthly intramuscular injections as either a positive or negative attribute. Notwithstanding, we now have a new and very promising addition to the armamentarium of target-directed breast cancer therapies.

Dr Hayes and Dr Robertson also note that while clinical research has yet to demonstrate an advantage for combining endocrine interventions — citing the disappointing results of the tamoxifen/anastrozole arm in the ATAC trial as an example — they believe that combining fulvestrant with other biologic or endocrine agents may be more beneficial. Dr Robertson has performed extensive neoadjuvant trials looking at the effects of fulvestrant and other endocrine agents *in vivo*, and it seems likely that over the next few years we will dramatically increase our understanding about how these therapies can be utilized optimally.

— Neil Love, MD

Select publications

Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial. *Lancet* 2002;359;2131-39. **Abstract**

Jones S. **Fulvestrant ('Faslodex®') versus anastrozole ('Arimidex®') for the treatment of advanced breast cancer in postmenopausal women – safety update on the combined analysis of two multicenter trials.** *Breast Cancer Res Treat* 2001;**Abstract 455**.

Parker LM et al. **Greater duration of response in patients receiving fulvestrant ('Faslodex') compared with those receiving anastrozole ('Arimidex').** *Proc ASCO* 2002;**Abstract 160.**

Robertson JF. **Estrogen receptor downregulators: New antihormonal therapy for advanced breast cancer.** *Clin Ther* 2002;24 Suppl A:A17-30. **Abstract**

Joyce O'Shaughnessy, MD

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Edited comments by Dr O'Shaughnessy

Capecitabine/docetaxel (XT) versus docetaxel alone in metastatic disease

Follow-up of survival data

The trial comparing capecitabine/docetaxel to docetaxel alone is mature now, and the combination is definitely superior in terms of overall survival. Median survival for capecitabine/docetaxel is 14.5 months compared to 11.5 months for docetaxel. At the 12-month mark, 57% of the patients receiving the combination were alive compared to 47% of those randomized to docetaxel alone. There were few treatment-related deaths in both arms, and the rates of hospitalization and serious adverse events were similar between the two regimens.

Benefit of combination therapy in patients with significant tumor burden

"The early separation of the survival curves suggests that the combination therapy prevented early deaths in a subset of patients, the majority of whom had heavily pretreated disease and significant tumor burden in this trial. . . ."

". . .In addition, it should be taken into account that after failure of study chemotherapy in the current trial, only 60% to 70% of patients received further cytotoxic therapy. Therefore, 30% to 40% of patients did not have the opportunity to benefit from subsequent chemotherapy administered sequentially."

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

Analysis of post-study therapy

Currently, there is a question about whether to use sequential single agents or the capecitabine/docetaxel combination. David Miles from the UK did an analysis of post-trial therapy. Approximately two-thirds of the patients in both arms received chemotherapy after disease progression, and 27% of the patients who received chemotherapy after progressing on docetaxel received capecitabine.

The hazard ratio for mortality in the patients who received capecitabine after docetaxel compared to any other chemotherapy agent was 0.5 — a 50% reduction in the risk of dying. In the group who received vinorelbine after docetaxel, the hazard ratio for mortality compared to any other chemotherapy excluding capecitabine was 1.0. This data gives some credence to the folks who have been saying that it is okay to give single-agent docetaxel followed by capecitabine. The way I interpret the data from a conservative standpoint is in patients with relatively asymptomatic indolent disease, it is very reasonable to give docetaxel and capecitabine sequentially.

Conversely, given the early separation of the survival curves and the early death rate with docetaxel alone, there is a subgroup of patients with more aggressive, symptomatic disease who will not have the opportunity to receive sequential therapy. For these patients, the capecitabine/docetaxel combination may be preferred.

There is also a hypothesis, which cannot be addressed by these data, that a trial comparing capecitabine/docetaxel to docetaxel followed by capecitabine would still result in a survival advantage for the combination. The combination has a very clear biochemical and preclinical synergy, which is quite different from most other doublets. Docetaxel upregulates thymidine phosphorylase, which leads to the enhanced conversion of the capecitabine prodrug to 5-FU at the tumor site.

Quality of life

From an acute toxicity standpoint, the capecitabine/docetaxel combination has more toxicity than docetaxel alone. Docetaxel results in more febrile neutropenia, because it is more myelosuppressive. But, the capecitabine/docetaxel regimen results in more diarrhea and hand-foot syndrome.

A careful quality-of-life analysis was done in this large phase III trial. For the first four to five months of the study, the curves overlap. Afterwards they separate with capecitabine/docetaxel being superior to docetaxel alone, clearly as a result of better tumor control with the combination. The deterioration in the docetaxel arm is undoubtedly due to tumor progression. These patients were heavily tumor-burdened and intensively pretreated. Two-thirds of them received the study therapy as second- or third-line therapy, so these patients were fairly ill.

Incidence of serious adverse events: Combination versus docetaxel

"There was a higher incidence of gastrointestinal side effects and hand-foot syndrome in patients receiving combination therapy than in those receiving single-agent docetaxel; myalgia, arthralgia, and neutropenic fever were more common with single-agent docetaxel. The incidence of grade 4 adverse events was higher in the single-agent docetaxel arm, primarily because of neutropenic fever, which reflects the higher incidence of grade 4 neutropenia. The aggregate incidence of grade 3 adverse events was higher in the combination arm, predominantly because of grade 3 hand-foot syndrome, which peaked in cycle 2 (13% of patients at risk)."

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

Oral versus intravenous chemotherapy for metastatic disease

Patients who relapse after adjuvant therapy are scared to death, and most of them are still in the "fight mode" at that point. If a patient wants the most effective therapy, I will recommend combination chemotherapy. However, many older women with very indolent disease who have undergone treatment for a long time consider their quality of life to be very important. For these patients, being treated with a very effective pill is attractive.

Phase II trials comparing capecitabine to paclitaxel or CMF in patients with metastatic disease

Capecitabine versus paclitaxel

Capecitabine is quite an active compound. A small randomized phase II trial in anthracycline-pretreated patients comparing capecitabine to paclitaxel 175 mg/m^2 every three weeks was stopped prematurely, because it was difficult to randomize patients to either a pill or an intravenous treatment. The response rate with capecitabine was 36% compared to 26% with paclitaxel with widely overlapping confidence intervals — they were basically equivalent.

Capecitabine versus CMF

We conducted a larger study comparing capecitabine to CMF in elderly patients as front-line therapy. The response rate to capecitabine was 30% compared to 16% for CMF. Approximately one-half of those patients received prior adjuvant therapy, so they were not all anthracycline-pretreated. Docetaxel has a solid 30% response rate in anthracycline-pretreated patients, so it is possible that capecitabine is close to equivalent to docetaxel.

Phase II study results of capecitabine compared to standard chemotherapy in patients with metastatic breast cancer

	O'Shaughnessy et al (n=95)		Talbot et al (n=44)	
Median age	**69 years old**		**52 years old**	
Treatment setting	**first-line**		**anthracycline-pretreated**	
Regimen	capecitabine 2510 mg/m²/day for 2 wks	CMF q 3 wks	capecitabine 2510 mg/m²/day for 2 wks	paclitaxel 175 mg/m² q3 wks
Overall response (95% CI) # complete responses	30% (19-43%) 3 CR	16% (5-33%) 0 CR	36% (17-59%) 3 CR	26% (9-51%) 0 CR
Median time to progression	4.1 months	3.0 months	3.0 months	3.1 months
Median survival	19.6 months	17.2 months	7.6 months	9.4 months

O'Shaughnessy JA et al. *Ann Oncol* 2001;12:1247-54. **Abstract**
Talbot DC et al. *Br J Cancer* 2002;86:1367-72. **Abstract**

Proposed NSABP neoadjuvant capecitabine/docetaxel trial

NSABP B-27 was a three-arm neoadjuvant trial for operable breast cancer — either clinically node-negative or node-positive — which randomized patients to preoperative AC followed by surgery, preoperative AC followed by preoperative docetaxel and then surgery or preoperative AC followed by surgery and then postoperative docetaxel.

The study demonstrated a doubling of the pathologic complete response rate with preoperative AC followed by preoperative docetaxel compared to preoperative AC alone. Disease-free or overall survival data is not yet available, but the doubling of pathologic complete response rate in both ER/PR-negative and ER/PR-positive patients is impressive and a key point for clinicians.

The NSABP will make that the standard arm of their next clinical trial — preoperative AC for four cycles followed by preoperative docetaxel for four cycles — and the investigational arm will be preoperative AC x 4 followed by docetaxel/capecitabine for four cycles.

US Oncology adjuvant capecitabine/docetaxel trial

US Oncology will conduct a clinical trial in node-positive or high-risk node-negative, ER/PR-negative or ER/PR-positive patients comparing adjuvant AC followed by capecitabine/docetaxel or docetaxel alone. The doses in the combination arm will be capecitabine 950 mg/m² (B.I.D. for two weeks, then one week off), which is 1,900 mg/m²/day and docetaxel 75 mg/m². This represents a 25% dose reduction for capecitabine — down from the standard

dose of 2,500 mg/m^2/day. This is appropriate, because there have been extensive analyses of the effectiveness of capecitabine dose reductions.

In our phase III metastatic trial, the median delivered dose intensity of capecitabine in the combination arm was 75% of the intended dose, and most patients were dose-reduced by the second cycle of therapy. That dose was maintained for the rest of the study, and a survival advantage still occurred in the capecitabine/docetaxel arm.

Adjuvant taxanes in ER/PR-positive patients

In both the NSABP B-28 and the CALGB 9344 trials of adjuvant AC followed by paclitaxel, subset analyses demonstrated a very interesting and clinically significant trend toward an improved hazard ratio for mortality in ER/PR-negative patients but not in ER/PR-positive patients. I have been somewhat puzzled by those findings.

The NSABP recently reported the results of their preoperative study. In NSABP B-27, the pathologic complete response rate doubled in ER/PR-negative patients from 13% with AC compared to 25% with AC followed by docetaxel. In patients with ER/PR-positive tumors there was also a definite benefit, with complete pathologic response rates improving from 5-6% to 13-14% with the addition of the taxane to AC preoperatively. There is not yet disease-free and overall survival data, so we have to be cautious, but I view this as a rationale to use preoperative AC followed by docetaxel in higher-risk patients, even if they are ER/PR-positive.

Potential synergy of trastuzumab/gemcitabine

In 1999, we initiated a phase II trial of gemcitabine/trastuzumab in women with HER2 overexpressing (IHC 2+ or 3+) metastatic breast cancer. The patients had a median of three prior chemotherapy regimens, and almost all had received anthracyclines and taxanes. The study regimen consisted of gemcitabine 1,200 mg/m^2 on day one and day eight in a 21-day cycle and standard weekly trastuzumab. The overall response rate was 37%. Two-thirds of the patients scored 3+ on IHC for HER2 overexpression, and in that subset the response rate was 45%.

Interestingly, in Melody Cobleigh's phase II trial, patients received single-agent trastuzumab as second- or third-line therapy, and there was a 15% response rate. Single-agent gemcitabine after anthracyclines and taxanes has demonstrated response rates ranging from about 12% to 20%. So, in our study of a very heavily pretreated group of patients, the 45% response rate with the combination of gemcitabine and trastuzumab suggests that there may be synergy or at least additivity between these agents.

Kevin Fox at the Fox-Chase Cancer Center is conducting a study with gemcitabine and trastuzumab as first-line treatment for metastatic breast

cancer to see if the combination will produce the 70% to 80% response rates observed with vinorelbine, docetaxel and weekly paclitaxel. It was very well tolerated, no unexpected cardiac effects and no unexpected toxicities.

Duration of trastuzumab therapy

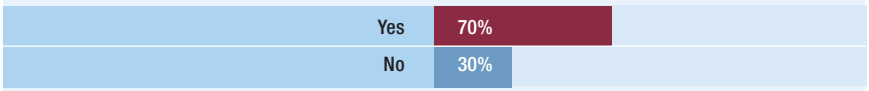
I was really impressed with the original trastuzumab pivotal trial. Some patients had stable remissions on paclitaxel and trastuzumab that lasted for years. If my patients are doing well on trastuzumab plus any chemotherapy, I do not stop therapy until progression.

However, on a daily basis, we are presented with patients with metastatic disease who have progressed on trastuzumab. There are no data to guide us in managing these patients. I will usually continue trastuzumab and add another chemotherapy agent. Trastuzumab is very well tolerated, and you are not really causing harm to the patient by continuing it. Several agents have shown remarkable activity in combination with trastuzumab. We are consistently seeing very high antitumor activity with paclitaxel, docetaxel, vinorelbine and possibly gemcitabine. We are trying to milk all the activity we can get out of these agents.

Currently, I am caring for a woman who was treated with docetaxel, vinorelbine and trastuzumab in a phase II clinical trial. She had a fantastic, long-term durable response for lung metastases. Subsequently, she developed slow, progressive disease. I treated her with capecitabine, to which she responded. After progression, she went on to receive an investigational antifolate agent, pemetrexed, but she did not respond. She never had paclitaxel, so I treated her with weekly paclitaxel and trastuzumab. She has been in remission for two and a half years, even though she had already received trastuzumab. Perhaps she would have responded to paclitaxel alone, but my instinct is that the combination is an effective regimen for her. In the absence of definitive data, we use our clinical intuition in these situations.

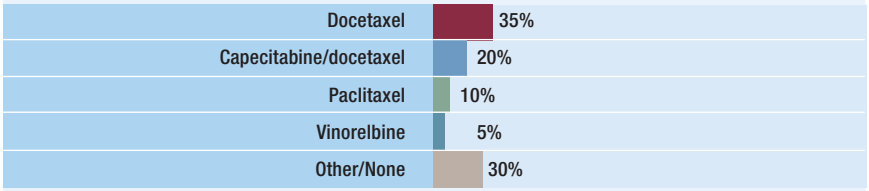
Dr O'Shaughnessy comments on Miami Patterns of Care survey results

Would you use trastuzumab in a 43-year-old patient with ER/PR-negative, HER2-positive, asymptomatic bone metastases who received prior ACT?



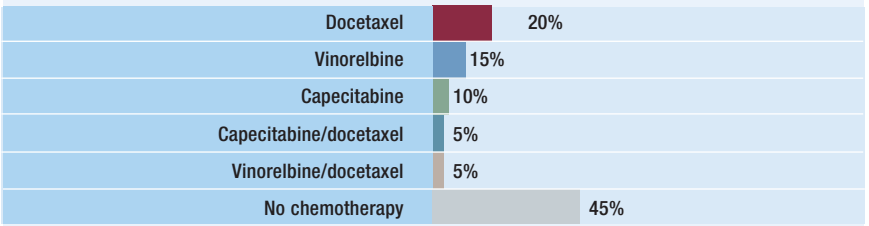
"It is not surprising that only 70% of oncologists would use first-line trastuzumab for a patient with metastatic disease. It is not widely appreciated, but if you read Slamon's paper closely, the maximal survival advantage from trastuzumab is from using it up front. The study was actually a crossover study in which two-thirds of patients eventually received trastuzumab."

Choice of therapy for a 43-year-old woman, ER/PR-negative, HER2-negative with asymptomatic bone metastases who received prior AC?



"The choice of therapy for such a patient would depend, in part, upon her disease-free interval. If she relapsed quickly with a lot of bony disease — even if she was asymptomatic — I would recommend capecitabine/docetaxel. Conversely, if her disease was minimal, then I would consider capecitabine alone or either weekly paclitaxel or docetaxel."

Choice of therapy for a 78-year-old woman, ER/PR-negative, HER2-negative with asymptomatic bone metastases with no prior adjuvant chemotherapy?



"There are a wide variety of single agents — with similar efficacy — from which to choose. Quality of life is an important consideration, and I would use either low dose capecitabine or vinorelbine. In this setting, we look for efficacy and quality of life — issues such as avoiding hair loss are important. Docetaxel is the only single-agent therapy that has a survival advantage in anthracycline pretreated patients; however, this woman is not anthracycline pretreated."

Select publications

Capecitabine: Recent publications

Ahn Sr, JH et al. **Phase II study of a combination chemotherapy of capecitabine and vinorelbine in metastatic breast cancer with previous exposure to anthracycline and taxane: Preliminary results.** *Proc ASCO* 2002;**Abstract 2030**.

Blum JL. **The role of capecitabine, an oral, enzymatically activated fluoropyrimidine, in the treatment of metastatic breast cancer.** *Oncologist* 2001;6(1):56-64. **Abstract**

Cassata A et al. **Capecitabine: Indications and future perspectives in the treatment of metastatic colorectal and breast cancer.** *Tumori* 2001;87(6):364-71. **Abstract**

Chan SC et al. **A phase II study on an all-oral regimen of capecitabine (Xeloda™) (X), idarubicin (I) and cyclophosphamide (C) (XIC) for metastatic breast cancer - safety, efficacy and quality of life.** *Proc ASCO* 2002;**Abstract 2023**.

Cunningham D, Coleman R. **New options for outpatient chemotherapy — the role of oral fluoropyrimidines.** *Cancer Treat Rev* 2001;27(4):211-20. **Abstract**

Donaldson LA et al. **A phase I/II study of carboplatin, vinorelbine and capecitabine in patients with metastatic breast cancer.** *Proc ASCO* 2002;**Abstract 1960**.

Fujimoto-Ouchi K et al. **Antitumor activity of combinations of anti-HER-2 antibody trastuzumab and oral fluoropyrimidines capecitabine/5'-dFUrd in human breast cancer models.** *Cancer Chemother Pharmacol* 2002;49(3):211-6. **Abstract**

Fujimoto-Ouchi K et al. **Schedule dependency of antitumor activity in combination therapy with capecitabine/5'-deoxy-5-fluorouridine and docetaxel in breast cancer models.** *Clin Cancer Res* 2001;7(4):1079-86. **Abstract**

Fumoleau P et al. **Capecitabine (Xeloda) in patients with advanced breast cancer (ABC), previously treated with anthracyclines and taxanes: Results of a large phase II study.** *Proc ASCO* 2002;**Abstract 247**.

Ghosn M et al. **Vinorelbine (Navelbine) IV and capecitabine (vinocap) as front line chemotherapy in metastatic breast cancer (MBC).** *Proc ASCO* 2002;**Abstract 1978**.

Gradishar WJ. **Clinical status of capecitabine in the treatment of breast cancer.** *Oncology (Huntingt)* 2001;15(1 Suppl 2):69-71;discussion 72. **Abstract**

Hess DD et al. **Phase I - II trial of capecitabine and vinorelbine in elderly patients (pts: > 65 y) with metastatic breast cancer (MBC): SAKK 25 / 99 for the Swiss Group of Clinical Cancer Research, Berne, Switzerland.** *Proc ASCO* 2002;**Abstract 2915**.

Hori T et al. **A randomized study comparing oral and standard regimens for metastatic breast cancer.** *Oncol Rep* 2001;8(5):1067-71. **Abstract**

Hwang JJ, Marshall JL. **Capecitabine: Fulfilling the promise of oral chemotherapy.** *Expert Opin Pharmacother* 2002;3(6):733-43. **Abstract**

Maher JF, Villalona-Calero MA. **Taxanes and capecitabine in combination: Rationale and clinical results.** *Clin Breast Cancer* 2002;2(4):287-93. **Abstract**

O'Shaughnessy J. **Clinical experience of capecitabine in metastatic breast cancer.** *Eur J Cancer* 2002;38 Suppl 2:10-4. **Abstract**

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

O'Shaughnessy JA et al. **Randomized, open-label, phase II trial of oral capecitabine (Xeloda®) vs a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer.** *Ann Oncol* 2001;12:1247-54. **Abstract**

Semiglazov TY et al. **Oral capecitabine (Xeloda) in the treatment of anthracycline-refractory, anthracycline and docetaxel-refractory metastatic breast cancer (MBC).** *Proc ASCO* 2002;**Abstract 2061**.

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

Twelves C. **Vision of the future: Capecitabine.** *Oncologist* 2001;6 Suppl 4:35-9. **Abstract**

Daniel F Hayes, MD

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Clinical Director, Breast Oncology Program
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Edited comments by Dr Hayes

Understanding the complexities of the estrogen receptor

What we have learned about the biology of the estrogen receptor in the last five years is mind-boggling — how it works and interacts with the other growth factor pathways, like EGFR and HER2, and how those interactions manifest clinically as well as their complexity. Every time I think I understand this system, results from another clinical trial tell me, "Nope, that's not the answer. It's completely different." The staggering complexity of this disease makes it so hard to treat.

We have learned so much in terms of endocrine therapy. We now know about the complexity of estrogen receptor ligands (i.e., estrogen, tamoxifen, raloxifene), which change the conformation of the receptor so that it is prone to phosphorylation. This phosphorylation, which occurs through the peptide growth factor signaling pathway, dimerizes estrogen receptors that then bind to the promoter of estrogen-sensitive genes and signal for coactivators and corepressors.

We have always known about estrogen receptor alpha, and now we have identified estrogen receptor beta. We recognize that the estrogen receptor actually can bind to a different part of the DNA that does not have an estrogen response element, called AP-1. We are beginning to understand why tamoxifen has this interesting duality — antiestrogenic in some cells and estrogenic in others. Understanding the biology of the estrogen receptor may help to explain why five years of tamoxifen might be optimal, why serial hormone therapies work and why hormone withdrawal elicits a response.

Mechanism of action of the SERMs

Like estrogen, all of the SERMs (tamoxifen, toremifene, raloxifene, droloxifene,

idoxifene) bind to the estrogen receptor. They all induce phosphorylation, dimerization and binding to the estrogen response element (ERE) in the promoter of the specific genes. However, they then signal for different coactivators and corepressors in the cell.

The response of a specific cell to a specific ligand depends on a number of things, such as the amount of estrogen receptor alpha and beta and the types of coactivators and corepressors present. The response may be even related to the genes that are "turned on" in one cell compared to another. The cells are primed to see these ligands as either estrogens or antiestrogens. Therefore, even though the ligands fundamentally do the same things — induce phosphorylation, dimerization, binding to ERE — they can have very different effects.

Can we design new SERMs that are antiestrogens in one place and estrogens in another? I personally do not believe so, because this is just too complex to fully understand. Then again, 15 years ago I said that I would not spend any more time on endocrine therapy, because I could not believe you could squeeze any more effect out of the estrogen receptor. I thought we had gotten all we could with tamoxifen — I was absolutely wrong. So, I am willing to have smart people like Craig Jordan prove me wrong about the SERMs.

Mechanism of action for fulvestrant

Another endocrine therapy is fulvestrant. Unlike the SERMs, which induce some biological response, fulvestrant binds to the estrogen receptor and completely shuts the system down. It prevents estrogen receptor phosphorylation, dimerization and binding to the ERE. Fulvestrant, a rationally designed drug, is truly an antiestrogen. It looks like it will be a step forward. Fulvestrant may be as active as the aromatase inhibitors, another class of rationally designed drugs.

Sequencing of endocrine therapy

We now have several options for endocrine therapy. The issues are how, when and in what order we should use these agents. As they are making it to the clinic, I get phone calls from my colleagues asking, "What order do I use these in?" I do not think we know the answer. The challenge for the cooperative groups and pharmaceutical companies is to conduct trials evaluating sequential and combination endocrine therapies.

I believe we will find that different subgroups of patients will respond differently to individual endocrine therapies. Just as we use ER status to decide who will receive endocrine therapy, in the future we may use the progesterone receptor, HER1, 2, 3 and 4, or some of the coactivators and corepressors. These markers may indicate which patients should receive tamoxifen, an aromatase inhibitor or fulvestrant. We are a long way away, but I think we will see it happen.

Hormone dependence versus hormone sensitivity

Why multiple endocrine therapies work sequentially is one of the conundrums of hormonal therapy in breast cancer. In the last five years, the concept of hormone dependence, rather than hormone sensitivity, has jelled in my mind. A cancer may start out as either hormone-dependent or hormone-independent. The cancer may remain hormone-dependent for many years, but become resistant to specific endocrine therapies that have different mechanisms of action.

For example, a patient's hormone-dependent cancer may initially be sensitive to tamoxifen. The cancer may later become resistant to tamoxifen, but may respond to another endocrine therapy like an aromatase inhibitor. So, the tamoxifen-resistant cancer is still hormone-dependent, and the next endocrine therapy will work. When hormone-dependent cancers become resistant, they are resistant to specific drugs.

Mechanisms of resistance to the SERMs

When a hormone-dependent cancer becomes resistant to a SERM, we are not sure of the exact resistance mechanism. One possibility is that cells begin to upregulate HER2, an epidermal growth factor receptor, resulting in constitutive phosphorylation, dimerization and activation of the estrogen receptor. Then, the ligand has no effect, because the estrogen receptor is already activated.

Another resistance mechanism might be the mutation of the estrogen receptor so it becomes hypersensitive to individual ligands. If that is the case, ligand-based therapy (i.e., the SERMs) might suddenly start acting like estrogen; whereas, ligand-annihilating or ligand-depleting therapy (i.e., oophorectomy, LHRH agonists and the aromatase inhibitors) might still be effective. Even with the upregulated HER2 hypothesis, it is possible that phosphorylation makes the receptor hypersensitive to the ligand. In that case again, ligand depletion might be ideal.

Fulvestrant, on the other hand, is a ligand that binds to the estrogen receptor and prevents downstream signaling. There is a constant turnover in the estrogen receptor, but the receptor is completely inactivated by fulvestrant because it cannot dimerize.

Mechanisms of resistance to the aromatase inhibitors

Since the aromatase inhibitors block the peripheral conversion of DHEA and testosterone to estradiol, then, in theory, resistance should not develop because they are somatic enzymes in the fat that are not prone to the genetic instability of cancer cells. But, we know that resistance does develop.

One possible explanation is that the cancer cells themselves mutate and produce an abnormal aromatase that converts DHEA and testosterone into estradiol. This is still speculative.

Another potential mechanism of resistance is that the cells ultimately become hormone-independent. This is analogous to a car that runs on gasoline and is retrofit with a solar panel. If the estrogen receptor is the gasoline tank and estrogen is the gasoline, the car can still run without gasoline (estrogen) through solar power. Likewise, another factor may drive the cancer cells that then become hormone-independent.

A third possible explanation is that the still hormone-dependent cells become hypersensitive to small amounts of estrogen. If this were the case, fulvestrant might work when the cells became resistant to the aromatase inhibitors. Although not yet published, Kent Osborne has been discussing the results from the trials comparing fulvestrant to anastrozole.

In the US trial, the duration of response was longer with fulvestrant than anastrozole. His explanation for this difference in the duration of response is that anastrozole may reduce estrogen levels by 99%, and the estrogen receptors then become hypersensitive to that one percent of estrogen. Fulvestrant simply does not let the estrogen get to the estrogen receptor.

There are a variety of possible mechanisms for the resistance to the aromatase inhibitors, and there may be others that we are not aware of yet. It is important to understand these mechanisms, because they may dictate how we use these drugs in the next five years.

Evolution of estrogen independence in breast cancer

Are all breast cancers initially estrogen receptor-positive with estrogen receptor-negative cancers evolving from those? Or, are there fundamentally two kinds of breast cancers — estrogen-dependent and estrogen-independent?

I believe there are fundamentally two types of cells that become malignant. Studies, by Craig Allred and others, tell us that not every epithelial cell in the normal breast is hormone-dependent. We do not know which stem cell is responsible for the development of any epithelial cancer or breast cancer, but another area of active research is trying to identify the epithelial stem cell that becomes cancer.

We will probably find that even before we identify a cancer, there are cells dedicated to becoming cancer that are either estrogen-independent or -dependent. Ultimately, those patients with estrogen-dependent cancer, whom we do not cure, develop estrogen-independent cancer. But that is probably a late event.

The estrogen receptor as an oncogene

Clearly, breast cancer is related to estrogen and the female endocrine system, but we do not understand it entirely. People have called the estrogen receptor an oncogene. Are there fundamental defects in the estrogen receptor that lead to the oncogenic process? In contrast to HER2, we have not found the classic oncogenic steps such as amplifications or activating mutations. To my knowledge, you

cannot transfect normal cells with multiple copies of estrogen receptor and make them cancerous.

It is probably a secondary phenomenon with other things in the cell producing genomic instability. In the right milieu, changes in the expression of coactivators result from some upstream change. Those, then, result in downstream effects that, in and of themselves, are not oncogenic, but set the cell up to be more responsive to external stimuli, like estrogen.

Mechanism of action for high-dose estrogen

We are beginning to understand the mechanism of action for high-dose estrogen. It has always been counterintuitive that the treatment of choice for breast cancer, prior to tamoxifen and chemotherapy, was pharmacologic doses of estrogenic-like therapies, such as DES.

Rob Nicholson's data demonstrate a biphasic response to pharmacologic doses of estrogen in MCF-7 cells. Without estrogen, these cells do not grow because they are hormone-dependent. With modest doses of estrogen, they grow quite nicely. At high doses of estrogen, they quit growing again. This is consistent with the clinical observation.

If those cells are preconditioned with different concentrations of estrogen, there is a similar biphasic response that is shifted to the right or left in regards to the estrogen concentration. The cell may have different coactivators and corepressors under one estrogenic condition. When the hormonal milieu is changed, the cells reset their coactivators.

In terms of clinical practice, we may learn that patients on hormone replacement therapy might have a different hormonal milieu when they are diagnosed with breast cancer. We might want to treat those patients differently. This concept is not ready for prime time in 2002, but it may be in 2010. In the meantime, we are beginning to understand the molecular basis of hormone dependence, treatment and resistance.

Adjuvant aromatase inhibitors

All of us are very enthusiastic about the potential for the aromatase inhibitors. However, I think we need to be very cautious about overinterpreting the ATAC trial data and implementing the aromatase inhibitors in the adjuvant setting.

Why be enthusiastic? Because of preclinical data and data in the metastatic setting, we believe the aromatase inhibitors are at least as effective and probably more effective than tamoxifen. The ATAC trial data fit our bias.

Why be cautious? The downside, I think, are the potential complications associated with these drugs. The obvious one is osteoporosis.

The ATAC trial is not the only study comparing an aromatase inhibitor to tamoxifen. There are at least two other trials that are similar in design. There are

also two other trials in which women receiving five years of tamoxifen are then randomized to an aromatase inhibitor or placebo. Before we routinely offer all postmenopausal patients an adjuvant aromatase inhibitor, we need to see those data as well as more mature ATAC trial data. On the other hand, I am already using adjuvant aromatase inhibitors for the occasional patient with a contraindication to tamoxifen — a history of deep venous thrombosis, stroke/TIA or a tamoxifen allergy.

Select publications

Estrogen receptor biology and mechanisms for the development of resistance to endocrine therapy

Atanaskova N et al. **MAP kinase/estrogen receptor cross-talk enhances estrogen-mediated signaling and tumor growth but does not confer tamoxifen resistance.** *Oncogene* 2002;21:4000-8. **Abstract**

Berry DA et al. **HER-2/neu and p53 expression versus tamoxifen resistance in estrogen receptor-positive, node-positive breast cancer.** *J Clin Oncol* 2000;18:3471-9. **Abstract**

Bieche I et al. **ERBB2 status and benefit from adjuvant tamoxifen in ERalpha-positive postmenopausal breast carcinoma.** *Cancer Lett* 2001;174:173-8. **Abstract**

Brinkman A et al. **BCAR1, a human homologue of the adapter protein p130Cas, and antiestrogen resistance in breast cancer cells.** *J Natl Cancer Inst* 2000;92:112-20. **Abstract**

Brockdorff BL et al. **Increased expression of cytochrome p450 1A1 and 1B1 genes in anti-estrogen-resistant human breast cancer cell lines.** *Int J Cancer* 2000;88:902-6. **Abstract**

Campbell RA et al. **Phosphatidylinositol 3-kinase/AKT-mediated activation of estrogen receptor alpha: A new model for anti-estrogen resistance.** *J Biol Chem* 2001;276:9817-24. **Abstract**

Cheung KL et al. **Selection of primary breast cancer patients for adjuvant endocrine therapy--is oestrogen receptor alone adequate?** *Breast Cancer Res Treat* 2001;65(2):155-62. **Abstract**

Chung YL et al. **Resistance to tamoxifen-induced apoptosis is associated with direct interaction between Her2/neu and cell membrane estrogen receptor in breast cancer.** *Int J Cancer* 2002;97:306-12. **Abstract**

Clarke R et al. **Molecular and pharmacological aspects of antiestrogen resistance.** *J Steroid Biochem Mol Biol* 2001;76:71-84. **Abstract**

Donovan JC et al. **Constitutive MEK/MAPK activation leads to p27(Kip1) deregulation and antiestrogen resistance in human breast cancer cells.** *J Biol Chem* 2001;276:40888-95. **Abstract**

Dorssers LC et al. **Tamoxifen resistance in breast cancer: Elucidating mechanisms.** *Drugs* 2001;61:1721-33. **Abstract**

Dowsett M et al. **HER-2 amplification impedes the antiproliferative effects of hormone therapy in estrogen receptor-positive primary breast cancer.** *Cancer Res* 2001;61:8452-8. **Abstract**

Geisler J, Lonning PE. **Resistance to endocrine therapy of breast cancer: Recent advances and tomorrow's challenges.** *Clin Breast Cancer* 2001;1:297-308; discussion 309. **Abstract**

Goss PE, Strasser K. **Tamoxifen resistant and refractory breast cancer: The value of aromatase inhibitors.** *Drugs* 2002;62:957-66. **Abstract**

Graham JD et al. **Nuclear receptor conformation, coregulators, and tamoxifen-resistant breast cancer.** *Steroids* 2000;65:579-84. **Abstract**

Graham JD et al. **Thoughts on tamoxifen resistant breast cancer. Are coregulators the answer or just a red herring?** *J Steroid Biochem Mol Biol* 2000;74:255-9. **Abstract**

Gu Z et al. **Association of interferon regulatory factor-1, nucleophosmin, nuclear factor-kappaB, and cyclic AMP response element binding with acquired resistance to Faslodex (ICI 182,780).** *Cancer Res* 2002;62:3428-37. **Abstract**

Hori M et al. **Overexpression of mitogen-activated protein kinase superfamily proteins unrelated to Ras and AF-1 of estrogen receptor alpha mutation in advanced stage human breast cancer.** *Pathol Res Pract* 2000;196:817-26. **Abstract**

Kato S. **Estrogen receptor-mediated cross-talk with growth factor signaling pathways.** *Breast Cancer* 2001;8:3-9. **Abstract**

Kenny FS et al. **Change in expression of ER, bcl-2 and MIB1 on primary tamoxifen and relation to response in ER positive breast cancer.** *Breast Cancer Res Treat* 2001;65(2):135-44. **Abstract**

Knoop AS et al. **Value of epidermal growth factor receptor, HER2, p53, and steroid receptors in predicting the efficacy of tamoxifen in high-risk postmenopausal breast cancer patients.** *J Clin Oncol* 2001;19:3376-84. **Abstract**

Kunisue H et al. **Anti-HER2 antibody enhances the growth inhibitory effect of anti-oestrogen on breast cancer cells expressing both oestrogen receptors and HER2.** *Br J Cancer* 2000;82:46-51. **Abstract**

Kurokawa H, Arteaga CL. **Inhibition of erbB receptor (HER) tyrosine kinases as a strategy to abrogate antiestrogen resistance in human breast cancer.** *Clin Cancer Res* 2001;7:4436s-4442s; discussion 4411s-4412s. **Abstract**

Kurokawa H et al. **Inhibition of HER2/neu (erbB-2) and mitogen-activated protein kinases enhances tamoxifen action against HER2-overexpressing, tamoxifen-resistant breast cancer cells.** *Cancer Res* 2000;60:5887-94. **Abstract**

Lee AV et al. **Cross-talk among estrogen receptor, epidermal growth factor, and insulin-like growth factor signaling in breast cancer.** *Clin Cancer Res* 2001;7:4429s-4435s; discussion 4411s-4412s. **Abstract**

Lee ES et al. **Cross-resistance of triphenylethylene-type antiestrogens but not ICI 182,780 in tamoxifen-stimulated breast tumors grown in athymic mice.** *Clin Cancer Res* 2000;6:4893-9. **Abstract**

Levenson AS et al. **Control of the estrogen-like actions of the tamoxifen-estrogen receptor complex by the surface amino acid at position 351.** *J Steroid Biochem Mol Biol* 2001;76:61-70. **Abstract**

Leveque J et al. **Benefits of complete polyamine deprivation in hormone responsive and hormone resistant MCF-7 human breast adenocarcinoma in vivo.** *Anticancer Res* 2000;20:97-101. **Abstract**

McClelland RA et al. **Enhanced epidermal growth factor receptor signaling in MCF7 breast cancer cells after long-term culture in the presence of the pure antiestrogen ICI 182,780 (Faslodex).** *Endocrinology* 2001;142:2776-88. **Abstract**

Nichols M, McCarty KS Jr. **Functional mutations of estrogen receptor protein: Assay for detection.** *Breast Cancer Res Treat* 2002;72:61-8. **Abstract**

Nicholson RI et al. **Modulation of epidermal growth factor receptor in endocrine-resistant, oestrogen receptor-positive breast cancer.** *Endocr Relat Cancer* 2001;8:175-82. **Abstract**

Osborne CK et al. **Estrogen receptor: Current understanding of its activation and modulation.** *Clin Cancer Res* 2001;7:4338s-4342s; discussion 4411s-4412s. **Abstract**

Santen R et al. **Adaptive hypersensitivity to estradiol: Potential mechanism for secondary hormonal responses in breast cancer patients.** *J Steroid Biochem Mol Biol* 2001;79(1-5):115-25. **Abstract**

Speirs V, Kerin MJ. **Prognostic significance of oestrogen receptor beta in breast cancer.** *Br J Surg* 2000;87:405-9. **Abstract**

Wakeling AE et al. **Prospects for combining hormonal and nonhormonal growth factor inhibition.** *Clin Cancer Res* 2001;7:4350s-4355s; discussion 4411s-4412s. **Abstract**

Yoshida T et al. **Distinct mechanisms of loss of estrogen receptor alpha gene expression in human breast cancer: Methylation of the gene and alteration of transacting factors.** *Carcinogenesis* 2000;21:2193-201. **Abstract**

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Edited comments by Dr Cobleigh

HER2 assessment

Every patient with metastatic breast cancer in my practice has her tumor evaluated for HER2 gene amplification by FISH. Patients with an IHC score of 3+ for HER2 overexpression should be evaluated by FISH, because they may not have gene amplification. In those with an IHC score of 0 or 1+ for HER2 expression, 3% and 7%, respectively, will have HER2 gene amplification by FISH. We need to determine HER2 status accurately, because it is a matter of life and death.

Determination of HER2 status is also important for the selection of adjuvant chemotherapy, because patients who have the HER2 alteration are more likely to benefit from the anthracyclines. These patients should not be denied anthracyclines if they have a healthy heart.

Importance of accurate HER2 assessment

"Accurate measurement of HER2 in individual patients means smaller sample size for clinical trials, fewer inconclusive or erroneous clinical trial results, and avoidance of costs associated with administering therapies to patients unlikely to benefit. The avoidance of costs on a human level is even harder to measure, but includes a lower risk of side effects in individuals receiving therapy from which they are not likely to benefit, less confusion on the part of our patients who need to know if a particular therapy is of potential benefit when making personal health-care decisions, and avoiding the loss of public trust that can occur with the dissemination of conflicting medical information."

EXCERPT FROM: Zujewski JA. **"Build quality in"--HER2 testing in the real world.** *J Natl Cancer Inst* 2002;94:788. **Abstract**

Management of patients with HER2-positive metastatic breast cancer

In patients with rapidly progressing, life-threatening, HER2-positive, ER-negative metastatic breast cancer, I use trastuzumab in combination with either paclitaxel or vinorelbine in women who have not previously received a taxane. Otherwise, I use trastuzumab monotherapy.

The disease characteristics of the patients in Chuck Vogel's front-line trastuzumab trial are very similar to those in the pivotal trial of trastuzumab with or without chemotherapy. Both of those trials demonstrated similar time to tumor progression, etcetera. That is not a direct comparison, but the model that we have always used in breast cancer is that we cannot cure metastatic disease. So, we use the treatment that will be most likely to put the patient in remission with the fewest side effects. Clearly, single-agent trastuzumab is a more benign treatment than trastuzumab plus chemotherapy.

We do not yet have prospective, randomized trial data that demonstrate a survival advantage for single-agent trastuzumab. However, if a patient responds to trastuzumab, it will be evident very quickly, often within a couple of weeks. If she progresses, you can always add chemotherapy.

For patients with HER2-positive, ER-positive metastatic breast cancer, I use tamoxifen in premenopausal women or an aromatase inhibitor in postmenopausal women. If the patient progresses, then I would add trastuzumab and continue hormonal therapy.

Duration of trastuzumab therapy

There are no data to guide us in what to do after a patient progresses while receiving trastuzumab and chemotherapy. The trastuzumab story has consistently shown that the laboratory models predict what happens in the clinic. The laboratory models demonstrate that trastuzumab when combined with most chemotherapeutic agents is more effective than when a chemotherapeutic agent is used alone. Until I see a trial that shows this is not true, I will continue trastuzumab indefinitely along with the chemotherapy.

Nonprotocol use of adjuvant trastuzumab

I have not used adjuvant trastuzumab in a nonprotocol setting. Our experience with bone marrow transplant taught us that we could not always trust our preconceived notions about what would work. We need to answer the questions regarding adjuvant trastuzumab quickly, so I have only been entering patients — even those with high-risk, 10 or more positive nodes or inflammatory disease — on clinical trials.

Investigating relationships between HER2 and other signaling pathways

There appears to be a relationship between the HER2 and both the HER1 and angiogenesis pathways. ECOG has initiated a study combining Iressa® and

trastuzumab. Another trial being launched will investigate trastuzumab in combination with an anti-VEGF. Both of these trials will address very important questions about HER2 overexpressing breast cancer. However, today few HER2-positive patients are trastuzumab naïve, so completing these trials will be difficult unless physicians enter their patients on these studies.

Molecular Assessment of Sensitivity to Herceptin (MASH) unit

A problem with the earlier trastuzumab trials was that the tissue blocks were not examined. Now, we are in a difficult situation. The mechanisms of resistance to trastuzumab cannot be investigated if the tumor was exposed to trastuzumab and chemotherapy, because you cannot determine which agent caused the molecular alterations.

Many people are using trastuzumab with chemotherapy, since that is the way it is FDA-approved for front-line therapy. So, we are collaborating with the original trastuzumab investigators to retrieve the tissue blocks from patients who were treated with single-agent trastuzumab. We are also accruing new patients who are receiving trastuzumab monotherapy to this archive.

We formed the Molecular Assessment of Sensitivity to Herceptin (MASH) unit to create tissue arrays from these tumor specimens so that investigators who wish to study novel ideas about the sensitivity and resistance to trastuzumab will have the necessary material. There is more known about the pathway now, and a rational approach would be to look at downstream elements in the pathway to determine if they are modified, so that doing something upstream would not make any sense.

Clinical implications of the ATAC trial results

The ATAC trial results are provocative, and I will be delighted to see more long-term data, particularly with regard to toxicity. I do not intend to switch patients who are receiving tamoxifen to anastrozole. I would consider using anastrozole *de novo*, in the higher-risk, node-positive patients, but I am not yet certain whether I would use anastrozole in node-negative patients.

There is no adjuvant data for the other aromatase inhibitors. Right now I would only consider anastrozole, because that is the drug that has been proven.

Neoadjuvant endocrine therapy

Data from trials of neoadjuvant endocrine therapy presented this year are impressive and will have important implications for clinical practice. I was impressed by Ellis' study of preoperative letrozole, but a study using anastrozole convinced me to begin utilizing neoadjuvant endocrine therapy. Anastrozole produced the same pathologic complete response rate as AC followed by docetaxel in the NSABP B-27 trial. Previously, when I encountered

patients with stage IIIA/B breast cancer, my immediate reaction was to consider which chemotherapeutic regimen to use. Neoadjuvant endocrine therapy appears to be just as effective as chemotherapy, and it is much more benign.

Pathologic complete response (pCR) rates for neoadjuvant chemotherapy regimens and single-agent anastrozole

Study	Stage	# Evaluable Patients	Neoadjuvant Therapy	pCR
NSABP B-27*	T1-3, N0-1	718 1,492	AC x 4 ➜ T x 4 AC x 4	26% 14%
Aberdeen Trial**	T2>4 cm, T3, T4, TxN2	50 47	CVAP x 4 responders randomized ➜ CVAP x 4 ➜ T x 4	 15% 31% 23%
Milla-Santos et al***	IIIA/B	74	Anastrozole qd x 4 months	23%

Abbreviations: AC=doxorubicin/cyclophosphamide; T=docetaxel; CVAP=cyclophosphamide/vincristine/doxorubicin/prednisolone

*NSABP. *Breast Cancer Res Treat* 2001;**Abstract 5**.
Smith IC et al. *J Clin Oncol* 2002;20:1456-66. **Abstract
***Milla-Santos A et al. *Breast Cancer Res Treat* 2001;**Abstract 302**.

Management of patients with HER2-negative, ER-negative metastatic breast cancer

The most depressing patient to meet is the woman with HER2-negative, ER-negative metastatic breast cancer, where the only therapeutic option is chemotherapy. The choice of agents depends upon what she received previously. For patients who have not had prior chemotherapy, I often use the old-fashion regimen, M➜F, as described by the NSABP. It does not cause alopecia, premature menopause, nausea and vomiting or neutropenic fever. It is given day one and day eight every four weeks, and the patient can take it indefinitely since it is not associated with cumulative neurotoxicity. It is also inexpensive, so M➜F would likely be my choice.

For patients who had prior AC recently and relapsed, I would use M➜F or weekly paclitaxel. It is very easily tolerated, except for the frequent visits. For patients who had ACT, there are a number of options, but one of the easier ones for the patient is capecitabine. It is an oral agent and only requires a visit to the doctor once every three weeks. I am extremely impressed by the activity of capecitabine. I have used it a lot since I am participating in the trial comparing capecitabine with or without anti-VEGF.

Capecitabine dose reduction

I start capecitabine at a dose of 2,500 mg/m^2/day, and many patients tolerate that dose very well. However, patient education is critical. I instruct patients to call me if they experience any changes in their hands or feet or if they develop diarrhea. At the first sign of toxicity, I reduce the dose by 25%. Hand-foot syndrome is only problematic when patients do not heed warnings to call at the first signs of symptoms. Some patients have the idea, "If I hit this really hard, I'll be cured." That is really a bad strategy.

Single-agent versus combination chemotherapy for metastatic disease

Unfortunately, patients with metastatic breast cancer are routinely getting combination chemotherapy, when sequential single-agent treatment is just as effective in terms of survival. ECOG 1193 compared doxorubicin (A) to paclitaxel (T) — with a crossover at progression — to the combination (AT). There was no difference in survival, and patients treated with AT have a worse quality of life than those treated with sequential single-agent therapy.

I do not use combination chemotherapy in the metastatic setting, except in patients with life-threatening disease. If the patient has not had an anthracycline or taxane recently, I would probably use AT. Capecitabine/docetaxel is another option for patients who have recently progressed on an anthracycline.

Select publications

Trastuzumab for the treatment of metastatic breast cancer

Baselga J. **Phase I and II clinical trials of trastuzumab.** *Ann Oncol* 2001;12 Suppl 1:S49-55. **Abstract**

Bell R. **Duration of therapy in metastatic breast cancer: Management using trastuzumab.** *Anticancer Drugs* 2001;12:561-8. **Abstract**

Bell R. **Ongoing trials with trastuzumab in metastatic breast cancer.** *Ann Oncol* 2001;12 Suppl 1:S69-73. **Abstract**

Burstein HJ et al. **Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2001;19:2722-30. **Abstract**

Castellon XC et al. **Efficacy and safety of 3-weekly trastuzumab (H) monotherapy in women with HER2-positive metastatic breast cancer (MBC): Preliminary data from a phase II study.** *Proc ASCO* 2002;**Abstract 73**.

Cobleigh MA et al. **Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease.** *J Clin Oncol* 1999;17(9):2639-48. **Abstract**

Dieras V et al. **Interaction between trastuzumab and taxanes.** *Oncology* 2001;61 Suppl 2:43-9. **Abstract**

Esteva FJ et al. **Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20:1800-8. **Abstract**

Gelmon K et al. **Pharmacokinetics (PK) and safety of trastuzumab (Herceptin®) when administered**

every three weeks to women with metastatic breast cancer. *Proc ASCO* 2001;**Abstract 271**.

Harris KA et al. **A population pharmacokinetic (PK) model for trastuzumab and implications for clinical dosing.** *Proc ASCO* 2002;**Abstract 488**.

Hortobagyi GN. **Overview of treatment results with trastuzumab (Herceptin) in metastatic breast cancer.** *Semin Oncol* 2001;28:43-7. **Abstract**

Leyland-Jones B et al. **Serum HER2 levels (shed extracellular domain) in women with HER2 positive metastatic breast cancer (MBC) treated with trastuzumab in combination with paclitaxel, both given every 3 weeks: Preliminary results of a phase II trial.** *Proc ASCO* 2002;**Abstract 1835**.

Leyland-Jones B. **Dose scheduling--Trastuzumab.** *Oncology* 2001;61 Suppl 2:31-6. **Abstract**

Leyland-Jones B et al. **Pharmacologic insights into the future of trastuzumab.** *Ann Oncol* 2001;12 Suppl 1:S43-7. **Abstract**

Mackey J et al. **Continued use of trastuzumab after disease progression in women with HER2-positive (HER2+) metastatic breast cancer (MBC): Results from a retrospective analysis of 105 cases.** *Proc ASCO* 2002;**Abstract 207**.

Miller KD et al. **Gemcitabine, paclitaxel, and trastuzumab in metastatic breast cancer.** *Oncology (Huntingt)* 2001;15:38-40. **Abstract**

Osoba D, Burchmore M. **Health-related quality of life in women with metastatic breast cancer treated with trastuzumab (Herceptin).** *Semin Oncol* 1999;26:84-8. **Abstract**

Pegram MD. **Docetaxel and Trastuzumab: Foundation for future strategies.** *Oncologist* 2001;6 Suppl 3:22-5. **Abstract**

Pegram MD, Slamon DJ. **Combination therapy with trastuzumab (Herceptin) and cisplatin for chemoresistant metastatic breast cancer: Evidence for receptor-enhanced chemosensitivity.** *Semin Oncol* 1999;26:89-95. **Abstract**

Piccart MJ. **Proposed treatment guidelines for HER2-positive metastatic breast cancer in Europe.** *Ann Oncol* 2001;12 Suppl 1:S89-94. **Abstract**

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

Seidman AD et al. **Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification.** *J Clin Oncol* 2001;19:2587-95. **Abstract**

Slamon DJ et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344:783-92. **Abstract**

Smith IE. **Efficacy and safety of trastuzumab in women with metastatic breast cancer: Results from pivotal clinical studies.** *Anticancer Drugs* 2001;12 Suppl 4:S3-10. **Abstract**

Thomssen C. **Trials of new combinations of trastuzumab in metastatic breast cancer.** *Anticancer Drugs* 2001;12 Suppl 4:S19-25. **Abstract**

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20:719-26. **Abstract**

Winer EP, Burstein HJ. **New combinations with trastuzumab in metastatic breast cancer.** *Oncology* 2001;61 Suppl 2:50-7. **Abstract**

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Combined data from the trials of fulvestrant versus anastrozole

Duration of response is one of the key issues in treating metastatic disease. In the North American trial comparing fulvestrant to anastrozole, fulvestrant had a longer duration of response than anastrozole. This was not seen in the European trial. However, determining the duration of response is problematic in any study, because you are sorting a population of patients who responded to therapy and were not identified prerandomization.

A statistical method has been proposed for this type of analysis, whereby nonresponders are said to have a response duration of zero. This method looks at all of the patients in one arm compared to another, rather than a subpopulation of responders.

Using this type of analysis on the combined data from the two trials, fulvestrant has a longer duration of response than anastrozole in responding patients. This is a new finding.

I would not say categorically that fulvestrant was better than anastrozole, because this is a retrospective analysis, and we must be statistically rigorous in interpretation. But, it does emphasize the equivalence of these drugs in the second-line setting and gives us more confidence to use fulvestrant. I hope that people embrace fulvestrant, because it is a good drug with a very good side-effect profile.

Dr Joyce O'Shaughnessy comments on the duration of response advantage for fulvestrant compared to anastrozole

"In terms of duration of response in the North American trial, there was an advantage with fulvestrant over anastrozole (~19 months vs 10 months). Fulvestrant was also well tolerated. The data on duration of response from this double-blind study are rather compelling and favor fulvestrant over anastrozole."

"Because fulvestrant is not cross-resistant with tamoxifen, it is ideal as first-line treatment of metastatic breast cancer in patients who received adjuvant tamoxifen. Data will soon become available with regards to the effectiveness of fulvestrant following an aromatase inhibitor. That is, what is the efficacy of fulvestrant as third-line therapy? For now, we definitely want to use this drug in patients who have stopped taking tamoxifen in order to achieve a prolonged duration of response."

EXCERPT FROM: Torosian M et al. **Fulvestrant: Clinical application of an estrogen receptor downregulator.** *Clinical Therapeutics* 2002;24:A34. Abstract

Fulvestrant: Mechanism of action and questions for the future

Essentially, fulvestrant prevents dimerization and increases degradation of the estrogen receptor, which reduces the protein's half-life. Fulvestrant binds to the estrogen response element of the genes and "switches off" both activation functions, AF-1 and AF-2, which prevents translation.

Interesting questions for the future include: What would happen with an even more potent concentration of fulvestrant or a new antiestrogen? Is fulvestrant the best antiestrogen that we have or is there something in development, which may completely downregulate that receptor, so that there is no expression once you are on the drug?

Hot flashes with fulvestrant

Because fulvestrant does not cross the blood-brain barrier, I do not think this drug causes hot flashes. It is difficult to confirm this, however, because many women continue to get hot flashes for years after entering the menopause. While some studies measure hot flashes, they do not assess baseline hot flashes.

It would be important to know how many women develop new symptoms or an increase in the severity of the symptoms. In the first-line study, we may see some hot flashes in the fulvestrant-treated group; however, it is possible that these symptoms were present before treatment began.

Response to endocrine therapy after treatment with fulvestrant

Sequencing of fulvestrant is a key issue to be addressed. We have data that you can see responses to aromatase inhibitors after fulvestrant and vice versa. Fulvestrant resistance is not hormone insensitivity.

We have seen responses to endocrine therapy after treatment with fulvestrant in our own center. We had a patient who was on the first phase II fulvestrant study. She received fulvestrant for six years and then had a partial response to an aromatase inhibitor. At the time she became resistant to fulvestrant, her tumor still expressed some estrogen receptor.

We do not yet know the mechanism by which cancer becomes resistant to fulvestrant. We do not believe it is an agonistic property. As in this case, we can see ER expression in patients on fulvestrant — even at the time of resistance. We are studying mechanisms of resistance with sequential biopsies to examine the specimens both when the patients are responding and resistant.

Fulvestrant in premenopausal women

Fulvestrant's affinity for the estrogen receptor is roughly equivalent to that of estradiol. Because premenopausal women have such high levels of estradiol, we do not know if the degree of estrogen receptor downregulation will be equivalent to that in the postmenopausal woman.

There is one study in premenopausal women comparing preoperative fulvestrant to placebo. The participants underwent biopsies for diagnosis and were then given 250 mg of fulvestrant or placebo, two to three weeks before surgery. Another specimen was removed at the time of surgery to assess the presence of ER and PGR as well as the degree of downregulation.

My guess is that we will see the same or slightly less downregulation in premenopausal women compared to postmenopausal patients. Hopefully, we will have the answer by the end of the year.

Interpreting the ATAC trial results

I predicted that at this early analysis the ATAC trial would show no difference between the treatments. But in fact, the trial does show a statistically significant improvement in disease-free survival with anastrozole compared to tamoxifen alone or the combination of anastrozole plus tamoxifen. Anastrozole was also better tolerated in terms of hot flashes, cerebrovascular accidents, DVTs, vaginal dryness, vaginal discharge and endometrial cancer. Tamoxifen was better tolerated with regard to musculoskeletal symptoms (i.e., joint pain) and bone fractures.

There are several reasons to think these results are true. This is the largest adjuvant endocrine study ever conducted, with 9,366 patients. When the ATAC

trial started, the largest trials to that point were the CRC study and the NSABP B-14 tamoxifen study, which had less than 3,000 patients each. Given the size of the ATAC trial, it is unlikely that the results are a chance event.

The consistency of the data internally and the data from the metastatic setting also gives us confidence. In the ATAC trial, there were fewer local and distant recurrences and contralateral breast cancers in the patients treated with anastrozole compared to those treated with tamoxifen. As first-line therapy for metastatic disease, anastrozole has a time to progression benefit in hormone receptor-positive patients compared to tamoxifen (ten versus six months). The Spanish Milla-Santos study with anastrozole and studies with other aromatase inhibitors in the metastatic setting similarly found an advantage over tamoxifen. Now we are seeing this additional benefit in the adjuvant setting.

Potential mechanisms of resistance to hormonal therapy

"In the presence of postmenopausal oestrogen concentrations, tamoxifen saturates the oestrogen receptors and acts predominantly as an antagonist of oestrogen. But since tamoxifen is a partial agonist, it exerts some oestrogen-like signalling through the oestrogen receptor, which limits the degree of antagonism. By contrast, the profound oestrogen deprivation achieved by anastrozole alone might lead to near complete obliteration of oestrogen signalling and, therefore, greater efficacy than tamoxifen. Oestrogen-receptor binding of tamoxifen and its resultant minor oestrogenic signalling is likely to be unaffected by the withdrawal of oestradiol by anastrozole in the combination. Therefore the efficacy of tamoxifen and the combination would be equal. Other potential mechanistic explanations include the possible acquisition of different molecular resistance mechanisms for tamoxifen and anastrozole."

EXCERPT FROM: **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359:2131-39. Abstract

Clinical management in light of the ATAC trial results

Should we put our postmenopausal patients on adjuvant anastrozole now? The efficacy data is pretty secure, and the curves are diverging. With tamoxifen, we see carryover effects even after the drug is stopped. I suspect the curves will continue to diverge with anastrozole as well and that the efficacy advantage will eventually transfer into a survival benefit.

There is a spectrum of responses to this data. Very cautious clinicians opt to use tamoxifen until we have long-term data. The ATAC trial results do, however, reassure these individuals that patients who are not good candidates for tamoxifen (i.e., history of thromboembolic disease or cerebrovascular accidents) can be given anastrozole. Many physicians already do this off-label, but the data

gives us more confidence to possibly lower the threshold to use anastrozole.

Other physicians believe that the efficacy data from the ATAC trial is sufficient to use adjuvant anastrozole at the present time. By the time patients have been on anastrozole for one to five years, we will have far more data to make decisions. These physicians will embrace the efficacy data and accept the possibility of the unknown long-term effects on bone mineral density, or they will treat patients prospectively with a bisphosphonate.

Overall impact of ATAC data on practice

"Evidence from this first analysis of the ATAC trial is encouraging, and these results could be as significant to breast cancer treatment as the results first seen with tamoxifen nearly 20 years ago. An important consideration at this time is how to treat newly diagnosed patients. An overall assessment of the benefits versus harm, based on current data, supports the use of anastrozole for the adjuvant treatment of early breast cancer in postmenopausal women, meaning that there is now a choice of adjuvant endocrine therapy for postmenopausal women with hormone-responsive tumours."

EXCERPT FROM: **Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: First results of the ATAC randomised trial.** *Lancet* 2002;359:2131-39. Abstract

Side-effect profile of anastrozole compared to tamoxifen

In many cases, anastrozole has a better side-effect profile than tamoxifen. Although there were more fractures in the patients on anastrozole, there were less thromboembolic events, hot flashes and endometrial cancers. In addition, while some of tamoxifen's side effects are manageable, they are usually not preventable.

In contrast, anastrozole's main side effect — bone fractures — can potentially be prevented with bisphosphonates, calcium supplements or exercise. Some clinicians would rather take the risk to gain better efficacy, and they may elect to start patients on a bisphosphonate to hopefully prevent bone mineral density loss. The large number of patients in the ATAC trial gives us confidence that there are not any serious but uncommon side effects associated with anastrozole.

Discussing anastrozole with patients

I believe the ATAC trial data should be discussed with any postmenopausal woman starting tamoxifen. If the issues are explained clearly, most women are able to understand and voice their opinion on these matters. This is one of the largest adjuvant studies ever done, and ignoring the data is a disservice to women.

The ATAC trial, however, does not answer all the questions. It simply tells us that anastrozole appears to be more active than tamoxifen. There are unknowns in terms of the effects on bone mineral density, sequencing, duration and interactions with chemotherapy. Patients should receive all of the information and make decisions based on these unknowns.

Substituting other aromatase inhibitors for anastrozole

I do not think we should use the other aromatase inhibitors — letrozole and exemestane — as adjuvant therapy. We have to wait for the adjuvant studies with these agents. We cannot extrapolate that drugs with similar efficacy in advanced disease will be exactly the same in the adjuvant setting, either in terms of efficacy or side-effect profile.

The degree of aromatase inhibition is slightly different between the agents. There have been claims that letrozole reduces estrogen levels fractionally more than the other aromatase inhibitors. While this difference may or may not translate into an efficacy benefit, there are two sides to every sword — it also may translate into a worse side-effect profile. For example, the little bit of estrogen remaining in a woman's body with anastrozole may provide some protection in terms of bone mineral density loss and bone fractures. My personal view is that the differences we will see between the aromatase inhibitors in the adjuvant setting will most likely be in terms of their side-effect profiles rather than efficacy.

Select publications

Fulvestrant (ICI 182,780; Faslodex®)

Bundred N et al. **ICI 182,780 (Faslodex) an estrogen receptor downregulator, reduces cell turnover index more effectively than tamoxifen.** *Proc ASCO* 2001;**Abstract 1660**.

Bundred N, Howell A. **Fulvestrant (Faslodex): Current status in the therapy of breast cancer.** *Expert Rev Anticancer Ther* 2002;2(2):151-60. **Abstract**

Cheung KL, Robertson JF. **Fulvestrant.** *Expert Opin Investig Drugs* 2002;11:303-308. **Abstract**

Curran M, Wiseman L. **Fulvestrant.** *Drugs* 2001;61:807-13; discussion 814. **Abstract**

Elkak AE, Mokbel K. **Pure antiestrogens and breast cancer.** *Curr Med Res Opin* 2001;17:282-9. **Abstract**

Erikstein B et al. **ICI 182,780 ('Faslodex') 250 mg monthly intramuscular (IM) injection shows consistent PK profile when given as either 1 x 5ml or 2 x 2.5 ml injections in postmenopausal women with advanced breast cancer (ABC).** *Proc ASCO* 2001;**Abstract 2025**.

Gu Z et al. **Association of interferon regulatory factor-1, nucleophosmin, nuclear factor-kappaB, and cyclic AMP response element binding with acquired resistance to Faslodex (ICI 182,780).** *Cancer Res* 2002;62(12):3428-37. **Abstract**

Howell A. **Faslodex (ICI 182780). An oestrogen receptor downregulator.** *Eur J Cancer* 2000;36 Suppl 4:S87-8. **Abstract**

Howell A. **Preliminary experience with pure antiestrogens.** *Clin Cancer Res* 2001;7:4369s-4375s;discussion 4411s-4412s. **Abstract**

Howell A et al. **Comparison of efficacy and tolerability of fulvestrant (Faslodex) with anastrozole (Arimidex) in post-menopausal women with advanced breast cancer.** *Breast Cancer Res Treat* 2000;64(1):**Abstract 6**.

Johnston SR. **Fulvestrant (AstraZeneca).** *Curr Opin Investig Drugs* 2002;3(2):305-12. **Abstract**

Jones S. **Fulvestrant ('Faslodex®') versus anastrozole ('Arimidex®') for the treatment of advanced breast cancer in postmenopausal women – safety update on the combined analysis of two multicenter trials.** *Breast Cancer Res Treat* 2001;**Abstract 455**.

Long BJ et al. **The effect of second-line antiestrogen therapy on breast tumor growth after first-line treatment with the aromatase inhibitor letrozole: Long-term studies using the intratumoral aromatase postmenopausal breast cancer model.** *Clin Cancer Res* 2002;8(7):2378-88. **Abstract**

Mauriac L. **Fulvestrant ('Faslodex®') is effective in advanced breast cancer in postmenopausal patients with visceral metastases: Comparison with anastrazole.** *Breast Cancer Res Treat* 2001;**Abstract 452**.

O'Regan RM et al. **Effects of the antiestrogens tamoxifen, toremifene, and ICI 182,780 on endometrial cancer growth.** *J Natl Cancer Inst* 1998;90:1552-8. **Abstract**

Osborne CK. **A double-blind randomized trial comparing the efficacy and tolerability of Faslodex™ (fulvestrant) with Arimidex™ (anastrozole) in post-menopausal (PM) women with advanced breast cancer (ABC).** *Breast Cancer Res Treat* 2000;64(1):**Abstract 7**.

Osborne CK et al. **Selective estrogen receptor modulators: Structure, function and clinical use.** *J Clin Oncol* 2000;18(17):3172-3186. **Abstract**

Parker LM et al. **Greater duration of response in patients receiving fulvestrant ('Faslodex') compared with those receiving anastrozole ('Arimidex').** *Proc ASCO* 2002;**Abstract 160**.

Robertson JF. **Estrogen receptor downregulators: New antihormonal therapy for advanced breast cancer.** *Clin Ther* 2002;24 Suppl A:A17-30. **Abstract**

Robertson JFR. **A comparison of the single-dose pharmacokinetics (PK) of 'Faslodex' (fulvestrant) 250 mg when given as either a one x 5-ml intramuscular (IM) injection or two x 2.5-ml injections in postmenopausal (PM) women with advanced breast cancer (ABC).** *Breast Cancer Res Treat* 2000;**Abstract 172**.

Rosenberg Z and RS et al. **Is ICI 182,780 an antiprogestin in addition to being an antiestrogen?** *Breast Cancer Res Treat* 2000;60:1-8. **Abstract**

Vergote I. **Evidence of continued sensitivity to endocrine agents in postmenopausal women with advanced breast cancer progressing on fulvestrant ('Faslodex®') treatment.** *Breast Cancer Res Treat* 2001;**Abstract 446**.

Wardley AM. **Fulvestrant: A review of its development, pre-clinical and clinical data.** *Int J Clin Pract* 2002;56(4):305-9. **Abstract**

Pharmaceutical agents discussed in this program

GENERIC	TRADE	MANUFACTURER
anastrozole	Arimidex®	AstraZeneca Pharmaceuticals, LP
capecitabine	Xeloda®	Roche Laboratories, Inc.
cyclophosphamide	Cytoxan®, Neosar®	Bristol-Myers Squibb Company, Pharmacia Corporation
docetaxel	Taxotere®	Aventis Pharmaceuticals
fulvestrant	Faslodex®	AstraZeneca Pharmaceuticals, LP
gemcitabine	Gemzar®	Eli Lilly and Co.
imatib mesylate	Gleevec®	Novartis Pharmaceuticals
letrozole	Femara®	Novartis Pharmaceuticals
paclitaxel	Taxol®	Bristol-Myers Squibb Company
raloxifene	Evista®	Eli Lilly and Co.
tamoxifen citrate	Nolvadex®	AstraZeneca Pharmaceuticals, LP
toremifene	Fareston®	Orion Pharmaceuticals
trastuzumab	Herceptin®	Genentech, Inc.
vinorelbine tartrate	Navelbine®	Glaxo Wellcome, Inc.

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Post-test

Questions *(please circle answer)*:

1. True/False: IHC is generally regarded as more accurate than FISH in terms of measuring HER2 status.

2. The future US Oncology adjuvant trial will randomize node-positive or high-risk node-negative patients to AC followed by docetaxel or AC followed by…

a. Vinorelbine/capecitabine
b. Gemcitabine/docetaxel
c. Capecitabine/docetaxel
d. Capecitabine/paclitaxel

3. Higher doses of fulvestrant have not been tested because of…

a. Definitive increases in toxicity
b. Concerns about the acceptability of the injections
c. Lack of efficacy
d. None of the above

4. True/False: Letrozole, exemestane and anastrozole have never been compared head-to-head in a large, randomized adjuvant trial.

5. The FDA-approved dose for capecitabine (2 weeks on, 1 week off) is…

a. 600 BID
b. 750 BID
c. 1,000 BID
d. 1,250 BID

6. True/False: Hormonal therapies given after treatment with fulvestrant have consistently proven to be ineffective.

7. Which of the following hormonal agents is not a SERM?

a. Toremifene
b. Raloxifene
c. Exemestane
d. Droloxifene

8. True/False: In the combined analysis of the American and European trials comparing fulvestrant and anastrozole, fulvestrant had a longer duration of response than anastrozole.

9. According to the World Health Organization menopause is defined as…

a. Six months since a woman's last period
b. One year since a woman's last period
c. One and a half years since a woman's last period
d. Two years since a woman's last period

Post-test Answer Key
1. False, 2. c, 3. b, 4. True, 5. d, 6. False, 7. c, 8. True, 9. b

Evaluation Form

02-1066-ES-12 BCUG | 2002

Conversations with Oncology Leaders

Bridging the Gap between Research and Patient Care

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Extent to which program activities met the identified objectives
Upon completion of this activity, participants should be able to:

- Distinguish patients with metastatic disease for whom single-agent capecitabine or docetaxel versus the combination would be appropriate 5 4 3 2 1
- Compare the different mechanisms of resistance to individual hormonal therapies to develop a rationale for sequencing hormonal therapies in metastatic disease 5 4 3 2 1
- Utilize most current clinical data to appropriately select HER2-positive patients with metastatic disease for treatment with trastuzumab 5 4 3 2 1
- Recognize the value of the FISH assay for determining HER2 status to optimize selection of therapy 5 4 3 2 1
- Comprehend the implications of the ATAC trial for the selection of adjuvant hormonal therapy for postmenopausal patients 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.

_____

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