program 01 2002

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 1, 2002 consists of discussions with three oncology leaders on a variety of issues pertinentto breast cancer. These topics include fulvestrant (an estrogen receptor downregulator), the current data on first-line hormonal therapy for metastatic breast cancer, the use and development of capecitabine (an oral fluoropyrimidine), algorithms for the assessment of HER2 status, and the current clinical applications and on-going trials of trastuzumab.

EDUCATIONAL OBJECTIVES

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

- Describe the mechanism of action and clinical trial results of fulvestrant, the estrogen receptor downregulator
- Review the current first-line data on hormonal treatment of metastatic disease
- Review the development and clinical use of the oral fluoropyrimidine, capecitabine in breast cancer treatment
- Review decision algorithms for assessment of HER2 status in breast cancer patients and identify the current clinical applications and on-going trials of trastuzumab

ACCREDITATION STATEMENT

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

DESIGNATION STATEMENT

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

FACULTY DISCLOSURE STATEMENTS

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

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HOW TO USE THIS SUPPLEMENT

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

Editor's Note

THE PROMISE OF TARGETED SYSTEMIC THERAPY

An interesting bout of community-acquired pneumonia in 1996 provided me with a very personal perspective on targeted systemic therapy. A couple of doses of Biaxin melted bilateral pulmonary infiltrates, and in 24 hours, I went from febrile immobility to a performance status of 90.

Interventions with antibiotic-like therapeutic ratios have long been sought in cancer medicine, and this issue of Breast Cancer Update provides encouraging evidence of significant progress in that direction. The three research leaders interviewed for our program were members of this year's faculty at the 19th Annual Chemotherapy Foundation meeting in New York.* Virtually all of the sessions included presentations related to targeted treatment, and the research interests of our three speakers directly connect to this theme.

Edith Perez, principal investigator of the North Central Cancer Treatment Group's Intergroup adjuvant trastuzumab trial, discusses encouraging preliminary unpublished evidence that the cardiotoxicity observed in the pivotal trials in metastatic disease has not yet been seen in the adjuvant setting — although she cautions that much longer follow-up is needed. She also reviews the challenges of quality control in both immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) determinations of HER2 status — an increasingly common topic of journal articles and meeting presentations (Figure 1).

Robert Carlson discusses several key new developments in the oldest form of targeted therapy of breast cancer — endocrine treatment. His presentation in New York on the estrogen receptor downregulator, fulvestrant, included randomized trial data providing hints that this agent — which results in the disabling and disappearance of estrogen receptors — may have greater antitumor efficacy than another recent addition to the endocrine armamentarium, the third-generation aromatase inhibitor, anastrozole.

To order the CD-ROM of this year's program from Meetings a Mail®, visit the Chemotherapy Foundation Symposium page at the Mount Sinai School of Medicine website:* ***www.mssmtv.org/tcf/*

Figure 1: Selected Trials Evaluating FISH and IHC Assay Concordance

Author	N	IHC Antibody	FISH Assay	Overall Concordance
Pauletti	856	R60	PathVysion™	66.2% *
Couturier	100	CB11	INFORM®	98.0%
Mass	529	CTA	PathVysion™	81.3%
Hoang	100	A0485	PathVysion™	90.0%
		e2-4001	PathVysion™	75.0%
Tubbs	145	A0485	PathVysion™	77.0%*
		CB11		83.4%*
Persons	100	A0485	PathVysion™	92%
Seidman	78	A0485	PathVysion™	85.9%*
		CB11	PathVysion™	89.7% *
Onody	100	A0485 & Ab3	INFORM®	90.0%*
Jacobs	90	A0485	INFORM®	91.0%
Bucher	447	A0485	PathVysion™	94.1%
Starr	65	A0485	PathVysion™	80.0%
Ridolfi	117	A0485	PathVysion™ and INFORM®	98.7% (for 0,1+, 3+) 77.8%*(for all scores)
Bloom	129	A0485-Manual	INFORM®	82.0%
		A0485-ACIS™	INFORM®	90.0%
Wang	199	A0485-Manual	PathVysion™	85.7%
		A0485-ACIS™	PathVysion™	91.0%

* = calculated, ACIS™= automated cellular imaging system, CTA = clinical trial assay (4D5 and CB11 antibodies)

The next issue of Breast Cancer Update will review new data — just presented at the San Antonio meeting — suggesting that after 15 years as the "gold standard" of adjuvant endocrine therapy, tamoxifen may soon be replaced by anastrozole (Figure 2).

Figure 2: Summary of ATAC Trial Outcomes

9,366 evaluable patients

At a median treatment duration of 2.5 years, anastrozole demonstrated superior efficacy and tolerability to tamoxifen.

Anastrozole was superior to tamoxifen in terms of disease-free survival in the overall population (HR=0.83) and in estrogen receptor-positive patients (HR=0.78).

Anastrozole was superior to tamoxifen in terms of the incidence of contralateral breast cancer in the overall population (OR=0.42).

Anastrozole was significantly better tolerated than tamoxifen with respect to:

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

Tamoxifen was better tolerated with respect to:

- Musculoskeletal disorders (arthralgias)
- Fractures

Derived from a presentation by Michael Baum, 24th Annual San Antonio Breast Cancer Symposium

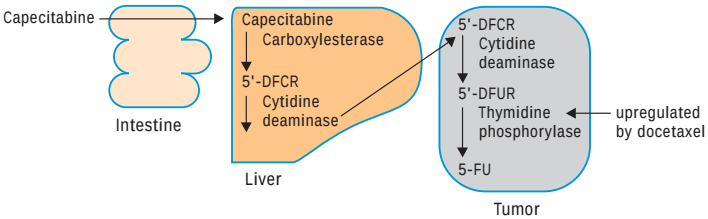
Baum M. **The ATAC (Arimidex, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal (PM) women.** *Breast Cancer Res Treat* 2001; 69(3):**Abstact 8.**

At the Chemotherapy Foundation meeting, our third speaker, Dan Budman, presented some of the most elegant translational research data currently available in oncology. Dr Budman has chaired a number of key clinical trials in the long history of research on cytotoxic regimens in the adjuvant and advanced disease setting. In our interview, he noted with displeasure the empiric basis of selecting most available combination regimens.

In contrast, the new combination of capecitabine and docetaxel goes beyond the classic rationale of combining non-crossresistant regimens with different side effect profiles. Specifically, docetaxel

upregulates thymidine phosphorylase, which in turn increases formation of 5-fluorouracil from capecitabine (Figure 3).

Figure 3: Enzymatic Conversion of Capecitabine to 5-Fluorouracil



The ultimate goal of translational research is improved clinical outcome, and Dr Budman updates the results from a randomized trial comparing docetaxel to docetaxel/capecitabine. This landmark study continues to show a significant advantage to the combination in both response rate and survival. He also presents new quality of life data further supporting the docetaxel/capecitabine combination and notes that the key determinant of performance status in the metastatic setting is tumor control.

This first 2002 issue of our series also includes a few changes that reflect our interest in targeted education. Category 1 continuing medical education credit is now being provided; the format of this audio program supplement has been modified to improve utility; and our website, **BreastCancerUpdate.com**, now includes the full transcripts of the interviews.

Every oncologist who has cared for a patient as miserable as I was with a pulmonary infection, dreams about the day that antitumor therapy will destroy tumor cells the way a few antibiotic doses quickly wiped out the organisms in my lungs. Drs Perez, Carlson and Budman provide substantial evidence that we are making significant progress towards that elusive goal.

—Neil Love, MD

Edith A Perez, MD

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Edited Comments by Dr Perez

NON–ANTHRACYCLINE REGIMENS FOR ADVANCED DISEASE

Our group has been concentrating on trials of non-anthracycline regimens for patients with advanced disease, because a majority of patients receive anthracyclines in the adjuvant setting. There are a number of agents available that appear to provide fairly similar benefits, but we do not have definite phase III studies demonstrating that one is absolutely better than another.

We started this process in 1995 with studies of paclitaxel and carboplatin as alternatives to anthracyclines, and that has evolved to a series of other trials. We're still very interested in the taxanes for the management of advanced breast cancer, and we currently have two major trials addressing this. One evaluates docetaxel in combination with carboplatin as first-line chemotherapy. It makes a lot of sense for us at the NCCTG to perform this trial, as we performed the original paclitaxel and carboplatin study in the United States. We are also conducting a first-line trial in patients with HER2-positive breast cancer evaluating two different schedules of paclitaxel and carboplatin in combination with trastuzumab, either weekly or every three weeks.

NCCTG-983252: Phase II Randomized Study of Paclitaxel, Carboplatin and Trastuzumab (Herceptin) as First-Line Chemotherapy in Women with Overexpressed HER-2, Metastatic Breast Cancer. **Protocol**

Eligibility | Women with untreated, HER2-positive (IHC 3+ or FISH-positive) metastatic breast cancer

ARM 1 | Paclitaxel IV over 3 hours followed by carboplatin IV over 30 minutes and then trastuzumab IV over 90 minutes on day 1 of week 1. Treatment repeats every 3 weeks for a maximum of 8 courses in the absence of disease progression and unacceptable toxicity. Patients also receive trastuzumab IV over 30 minutes weekly until disease progression.

ARM 2 | Paclitaxel IV over 1 hour followed by carboplatin IV over 15 minutes on day 1 of weeks 1-3. Treatment repeats every 4 weeks for up to 6 courses in the absence of disease progression and unacceptable toxicity. Patients also receive trastuzumab IV over 90 minutes immediately following carboplatin on day 1 and over 30 minutes weekly until disease progression.

Edith Perez, Chair, 904-953-7283
North Central Cancer Treatment Group

NCCTG-N9932: Phase II Study of Docetaxel and Carboplatin as First-Line Therapy in Patients with Metastatic Adenocarcinoma of the Breast. **Protocol**

Eligibility | Women with untreated metastatic breast cancer

Protocol | Docetaxel + carboplatin q 3 weeks in the absence of disease progression or unacceptable toxicity

Patients who achieve stable disease, partial response or complete response may receive 4 additional courses.

Edith Perez, Chair, 904-953-7283
North Central Cancer Treatment Group

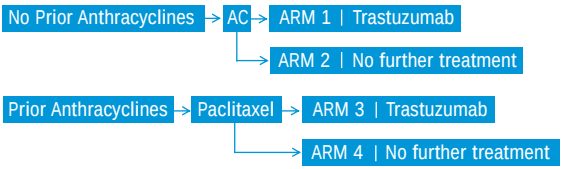
RATIONALE FOR ADJUVANT TRASTUZUMAB TRIALS

The data from NSABP B-15 have not been published in full but are contained within the background of the NSABP B-31 protocol. We see poorer outcomes in patients with node-positive, HER2-positive breast cancer, who only receive AC chemotherapy. Even patients with one to three positive nodes have only a 50-50 chance of being alive and free of disease at five to ten years. We must try to improve their survival rate, and trastuzumab is the best agent we have right now that is targeted specifically to this group of women.

Phase III Randomized Study of Chemotherapy with vs without Monoclonal Antibody HER2 in Women with Metastatic Breast Cancer Overexpressing HER2/neu and Previously Untreated with Cytotoxic Chemotherapy (Closed to accrual) **Protocol**

Protocol IDs: GENENTECH-HO648G; NCI-V95-0714

Eligibility	Patients with HER2 overexpressing tumors and without prior chemotherapy for metastatic breast cancer



Clinical benefit, duration of response and cardiotoxicity in chemotherapy versus chemotherapy plus trastuzumab regimens

	Chemo Alone (n=234)	Chemo + H (n=235)	AC Alone (n=138)	AC + H (n=143)	Paclitaxel Alone (n=96)	Paclitaxel + H (n=92)
Median time to progression (months)	4.6	7.4	6.1	7.8	3.0	6.9
Median duration of response (months)	6.1	9.1	6.7	9.1	4.5	10.5
Median survival (months)	20.3	25.1	21.4	26.8	18.4	22.1
Complete + partial response	74/234 32%	118/235 50%	58/138 42%	80/143 56%	16/96 17%	38/92 31%
Cardiac dysfunction	2%	10%	3%	16%	1%	2%

Derived from Slamon DJ et al. *NEJM* 2001;344(11):783-792. **Abstract**

ADJUVANT CLINICAL TRIALS OF TRASTUZUMAB

Intergroup trial 9831 is an adjuvant study that was activated in May 2000. We have enrolled 700 patients with node-positive, HER2-positive breast cancer. This trial will join the three other worldwide studies being conducted to help answer the question of whether trastuzumab adds benefit to chemotherapy in this group of poor-prognosis women. We are also testing the question of whether trastuzumab should be used sequentially or concurrently with chemotherapy.

NSABP B-31 has very similar eligibility criteria. The NSABP uses paclitaxel every three weeks, while we are utilizing paclitaxel weekly. Another difference between the two trials is that the NSABP starts tamoxifen — if indicated — concurrent with AC, whereas in the Intergroup trial, tamoxifen is started after the completion of the six months of chemotherapy. Additionally, we are submitting an amendment to our protocol to administer trastuzumab once every three weeks, whereas NSABP will maintain weekly trastuzumab for one year.

If someone uses adjuvant trastuzumab outside of a clinical trial setting, they're essentially shooting in the dark. We do not yet understand for how long this therapy should be given, what schedule should be used in combination with chemotherapy, and the potential risks or benefits the patients may derive from such treatment.

CARDIOTOXICITY AND TRASTUZUMAB

Both adjuvant trastuzumab trials — NCCTG N9831 and NSABP B-31 — are carefully attending to cardiac tolerability. At this time, no red flags have been raised. In our adjuvant trial, we have attempted to ameliorate the risk of cardiotoxicity by not using trastuzumab concurrently with anthracyclines and by limiting the dose of doxorubicin to 240 milligrams per meter squared. In the pivotal trastuzumab metastatic study, the increased risk of cardiotoxicity in terms of congestive heart failure was seen when the cumulative dose of doxorubicin was greater than 300 milligrams per meter squared.

We are accumulating data to help us understand what AC chemotherapy leads to in terms of ejection fractions, because this has never been investigated thoroughly. We are developing a companion cardiac tolerability study, and the NSABP will be conducting a similar study as well. We are attempting to determine whether we can find plasma factors that predict for clinical cardiotoxicity. There's a lot of cardiology

literature regarding the potential value of various factors, and we're going to look at these in a prospective fashion to see if any correlate with clinical outcome.

We are also going to look at the correlation between ejection fractions obtained by MUGA versus echocardiogram, evaluating ejection fractions before study entry, after AC, after paclitaxel, and nine and 18 months into treatment. If we see more than 5% cardiotoxicity in the investigational arms compared to the standard arm, we will stop the trial.

NCCTG-N9831: Phase III Randomized Study of Doxorubicin plus Cyclophosphamide Followed by Paclitaxel with or without Trastuzumab (Herceptin) in Patients with HER2 Overexpressing Breast Cancer **Protocol**

Eligibility | HER2-positive adenocarcinoma with ≥ 1 positive lymph node

ARM 1 | AC x 4 → T qw x 12

ARM 2 | AC x 4 → T qw x 12 → H qw x 52

ARM 3 | AC x 4 → (T + H) qw x 12 → H qw x 40

AC=doxorubicin/cyclophosphamide; T=paclitaxel; H=trastuzumab
All ER/PR-positive patients receive tamoxifen x 5 years.

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NSABP B-31: Phase III Randomized Study of Doxorubicin and Cyclophosphamide Followed by Paclitaxel with or without Trastuzumab (Herceptin) in Women with Node-positive Breast Cancer that Overexpresses HER2 **Protocol**

Eligibility | HER2-positive adenocarcinoma with ≥ 1 positive lymph node

ARM 1 | AC x 4 → T x 4

ARM 2 | AC x 4 → T x 4 + H (qw x 52 weeks)

AC=doxorubicin/cyclophosphamide; T=paclitaxel; H=trastuzumab
ER/PR-positive patients receive tamoxifen for 5 years. Patients > 50 years old or who are ER/PR-negative or indeterminable and have received prior chemopreventive tamoxifen may be treated with tamoxifen at investigator's discretion.

Edward H Romond, Chair, 859-323-8043
National Surgical Adjuvant Breast and Bowel Project

DISCORDANCE IN THE ASSESSMENT OF HER2 STATUS

There is a significant problem with HER2 testing in the community. When we designed our adjuvant study — evaluating trastuzumab in combination with chemotherapy — we included a plan for central analysis of HER2 status. Unfortunately, when we looked at the initial 119 patients, we found a high level of discordance in HER2 testing by IHC, and even by FISH, when comparing measurements in the community versus central testing.

We found discordant results in six of the nine FISH test assays. These were FISH-positive in the community, but FISH-negative in the central lab. The number of patients is very, very small to date, so we cannot conclude that FISH is a bad test to be performed in the community, but we need to look into why this discordance occurs. IHC concordance between the community and central laboratories was about 75 percent.

We've done another study of HER2 testing, based on 1,500 specimens sent to Mayo medical laboratories over a five-month period. We took 213 specimens labeled as HER2 2+ and evaluated them for protein overexpression and gene amplification, and we found that only 12 percent of the tumors scored as 2+ by the HercepTest™ actually were FISH-positive.

CONTINUATION OF TRASTUZUMAB AFTER DISEASE PROGRESSION IN THE METASTATIC SETTING

My standard practice is to use trastuzumab until progression or toxicity. Whether it should be continued after disease progression is an issue we're wrestling with on a day-to-day basis, and nobody knows the answer. We will join Dr Pusztai from MD Anderson in his trial to help us answer this question in patients who have progressed on a taxane-trastuzumab combination. The randomization will be to continue on trastuzumab and add vinorelbine or stop the trastuzumab and use vinorelbine alone. Everybody should embrace this study, because it will help us answer this very, very important question.

Randomized Study of Weekly Vinorelbine (Navelbine) plus Trastuzumab (Herceptin) for Patients with HER2-positive Breast Cancer Who Have Failed Previous Taxane/Trastuzumab Combination Therapy

Protocol ID: DM99-315

Eligibility	Women with HER2 overexpressing (IHC 3+ or FISH-positive) metastatic breast cancer who have failed paclitaxel or docetaxel concurrent with trastuzumab

ARM 1 | trastuzumab + vinorelbine

ARM 2 | vinorelbine

Lajos Pusztai, Principal Investigator, 713-792-2740
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DOCETAXEL–CAPECITABINE STUDY

In the docetaxel-capecitabine trial, concurrent use of docetaxel and capecitabine was better than single-agent docetaxel, and this surprised some people. The trial has been criticized, because not every patient who received docetaxel went on to receive second-line capecitabine. For the purist, trying to answer the question of sequential versus concurrent therapy, this trial doesn't give us the exact answer. However, it is dramatic that there was a survival advantage in this trial, and we have to take that very seriously.

AMELIORATION OF CAPECITABINE–ASSOCIATED SIDE EFFECTS WITH DOSE REDUCTION

The side effects associated with capecitabine are minimal except for hand-foot syndrome. Occasional myelosuppression or diarrhea may occur, but I have not seen those often. Using 2,000 milligrams per meter squared per day for 14 days, hand-foot syndrome usually will occur in less than 25 percent of patients. If it does occur, I adjust the schedule and the dose a bit — sometimes I drop the dose to 1,500 milligrams per meter squared per day for 14 days, and I've tried one week on and one week off. We try to find a regimen that allows the patient to have the best quality of life.

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Edited Comments by Dr Carlson

ESTROGEN RECEPTOR DOWNREGULATORS: MECHANISM OF ACTION

The new class of hormonal agents known as estrogen receptor downregulators has a fundamentally different interaction with the breast cancer cell than other hormonal agents. These agents occupy the estrogen receptor and inhibit dimerization of the receptor and both activation functions 1 and 2, causing estrogen receptor downregulation. The estrogen receptor is unable to interact with the estrogen response element in the nucleus, causing a complete failure of transcription.

CLINICAL TRIALS OF FULVESTRANT VERSUS ANASTROZOLE

The results of the European and North American trials of fulvestrant in postmenopausal women with hormone-responsive metastatic breast cancer are quite consistent and demonstrate a similar time to progression compared to anastrozole. The data suggest that fulvestrant is at least as active as anastrozole, and the North American trial suggests that it is more active.

The superiority in duration of response in the North American trial, however, was not observed in the European trial. It remains to be seen whether that is because there really is no superiority or because of methodological differences between the trials.

In the North American trial, a monthly fulvestrant placebo injection was given to anastrozole-treated women, and an anastrozole placebo was given to fulvestrant-treated women. While the women received injections every month, their period of evaluation for time to progression was every three months. In this study, the duration of response was almost twice as long with fulvestrant as with anastrozole.

In contrast, women in the European trial got their monthly fulvestrant injections in an unblinded fashion, and patients randomized to anastrozole were evaluated every three months.

We would expect to see a shorter time to progression in the fulvestrant arm, even if the two therapies were absolutely equivalent, because monthly evaluations give many more opportunities to see evidence of progressive disease. Based on the mechanism of action and pre-clinical data, I would expect fulvestrant to have superior clinical activity, but randomized trials are necessary to confirm that optimism.

Trials 20/21: Phase III Randomized Study of ICI 182780 (Faslodex) versus Anastrozole in Postmenopausal Women with Advanced Breast Cancer (Closed to accrual)

Eligibility | Postmenopausal women progressing on prior endocrine therapy

ARM 1 | Faslodex 250 mg IM + oral placebo*

ARM 2 | Arimidex 1 mg PO + sham injection*

A third arm in Trial 21, Faslodex 125 mg, was closed after planned analysis demonstrated that pre-defined efficacy criteria were not met at that dose

*Only the North American trial (21) had placebo controls.

Trials 20 and 21: Study Design Differences

	Trial 20 (European)	Trial 21 (North American)
Receptor unknown	Allowed	Not allowed
Double-blind	No	Yes
Multi-institutional	Europe, Australia, South America	North America
Multiple dose levels	No	Yes, initially
Dosing	Single injection	Divided injections
Evaluations - fulvestrant	Monthly	Every three months
Evaluations - anastrozole	Every three months	Every three months

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Trials 20 and 21: Clinical Endpoints

	Trial 20 (European)		Trial 21 (N American)	
	fulvestrant (n=222)	anastrozole (n=229)	fulvestrant (n=206)	anastrozole (n=194)
Objective Response (CR + PR)	46 (20.7%)	36 (15.7%)	36 (17.5%)	34 (15.7%)
Clinical Benefit (CR + PR + SD > 24 wks)	99 (44.6%)	103 (45.0%)	87 (42.2%)	70 (36.1%)
Duration of Response	14.3 months	14.0 months	19.3 months	10.5 months

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SEQUENCING OF FULVESTRANT

Estrogen receptor-positive cells exposed to fulvestrant actually lose estrogen receptors on immunohistochemistry — a true estrogen receptor downregulation. This has caused concern that breast cancers treated with fulvestrant may become refractory to subsequent hormonal therapies. As a result, sequencing of fulvestrant in relation to the other hormonal therapies is one of the uncertainties we have. In limited studies of patients treated with fulvestrant followed by one of the selective nonsteroidal aromatase inhibitors or megestrol

acetate, objective responses were in the range of 20 percent — about what we would expect for a third-line hormonal therapy.

In addition, in preclinical systems, recent data suggest that the estrogen receptor does reappear in the cells after fulvestrant is withdrawn. So, some of the concerns about the tumor evolving into a hormone refractory state appear to be unfounded.

Phase II Study of Fulvestrant (ICI 182780) in Women with Metastatic Breast Cancer Who Have Failed Aromatase Inhibitor Therapy **Protocol**

Protocol ID: NCCTG-N0032
Projected Accrual: 41-94 patients within 10 months

Eligibility	ER and/or PR-positive or unknown metastatic breast cancer with disease progression after prior third-generation aromatase inhibitor
Protocol	Fulvestrant q 28 days in the absence of disease progression or unacceptable toxicity

Patients are followed every 3 months for 5 years or until disease progression. After disease progression, patients are followed every 3 months for 2 years and then every 6 months for 3 years.

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North Central Cancer Treatment Group

ADVANTAGES OF FULVESTRANT

While estrogen receptor modulators stimulate the endometrium and are associated with low frequencies of endometrial carcinoma, it appears that estrogen receptor downregulators will not have that stimulatory effect. Although the monthly intramuscular injection can be viewed as a disadvantage of fulvestrant, it can also be viewed as an advantage, because you can assure compliance. In addition, fulvestrant doesn't cross the blood-brain barrier, so there is hope that there will be fewer hot flashes than with the selective estrogen receptor modulators. In the comparative trials with anastrozole, the occurrence of hot flashes was in the range of about 20 percent in both treatment groups.

FULVESTRANT IN PREMENOPAUSAL WOMEN

There is no reason to believe that fulvestrant would not be effective in premenopausal women. Although we do not yet have long-term disease-oriented clinical trials, the agent appears to have acceptable

toxicity in short-term trials in premenopausal women. I would still, however, be cautious about considering this agent in premenopausal populations outside the confines of a clinical trial.

In preclinical systems, fulvestrant has limited effects on bone density and serum lipids. The data in humans are quite early, and those questions will have to be addressed by clinical trials. Certainly, these issues are especially important if fulvestrant is moved into the adjuvant setting, as we certainly expect it to be, because women in this setting are likely to be long-term survivors in whom bone and cardiovascular events are of substantial concern.

NCCN GUIDELINES ON FIRST–LINE HORMONAL THERAPY OF METASTATIC DISEASE

The nonsteroidal aromatase inhibitors are superior to tamoxifen as first-line treatment in metastatic disease. Therefore, in the current NCCN guideline, the use of aromatase inhibitors has been moved forward to a first-line option for postmenopausal women with hormone-responsive breast cancer. Tamoxifen also remains a first-line option, because we have such a preponderance of data using tamoxifen in this setting that the panel did not want to remove it as a first-line therapy.

Only the nonsteroidal aromatase inhibitors — anastrozole and letrozole — are included in the first-line guideline. Although I have no criticism of practitioners who prefer letrozole, I tend to use anastrozole. It was the first of the selective aromatase inhibitors available, and it's one that I became very comfortable with. I personally use anastrozole almost exclusively in my practice.

The steroidal aromatase inhibitor, exemestane, is not included in the guideline as a first-line hormonal agent, because we don't have good comparative data yet available from large randomized studies.

In premenopausal women, the NCCN panel thought it was premature to consider combining an LH-RH agonist/antagonist with an aromatase inhibitor. I personally believe that this is a very important area for future research and would anticipate randomized trials of this combination. The superiority of the aromatase inhibitors in postmenopausal women does suggest that this may be a very effective strategy in premenopausal women, but at this point, the evidence is simply lacking to support that approach.

2002 NCCN PRACTICE GUIDELINES: HORMONAL THERAPY FOR METASTATIC DISEASE

Women considered to be appropriate candidates for initial hormonal therapy for treatment of recurrent or metastatic disease include those whose tumors are estrogen- and/or progesterone-positive, those with bone or soft tissue disease only or those with limited, asymptomatic visceral disease. In postmenopausal women with prior antiestrogen therapy and who are within one year of antiestrogen exposure, recent evidence supports the use of a selective, nonsteroidal aromatase inhibitor such as anastrozole or letrozole as the preferred second-line therapy (Buzdar et al, 2001; Buzdar et al, 1998). For postmenopausal women who are antiestrogen naïve or who have not been exposed to antiestrogen therapy for greater than one year, the selective, nonsteroidal aromatase inhibitors appear to have superior outcomes compared with tamoxifen, although the differences are modest (Bonneterre et al, 2000; Mouridsen et al, 2001; Nabholtz et al, 2000; Vergote et al, 2000). Therefore, either tamoxifen or an aromatase inhibitor is an appropriate option.

ASSESSING HER2 STATUS

The NCCN guidelines call for HER2 testing of all breast cancers; however, this year we were much more specific than in the past. We call for HER2 testing by IHC, and if the IHC result is 2+ by the HercepTest™, we call for FISH analysis. This is primarily because in the metastatic setting, when you're looking for benefit or lack thereof from trastuzumab, FISH-positivity is by far the best predictor of responsiveness. Women whose breast cancers are IHC 3+ by the HercepTest™ are almost all FISH-positive, while those that are IHC 0 or 1+ are almost always FISH-negative. This is based upon the study reported by Chuck Vogel, which looked at trastuzumab as a single agent and found very good rates and long duration of response in those women who were either IHC 3+ or IHC 2+ and FISH-positive.

TRASTUZUMAB WITH OR WITHOUT CHEMOTHERAPY

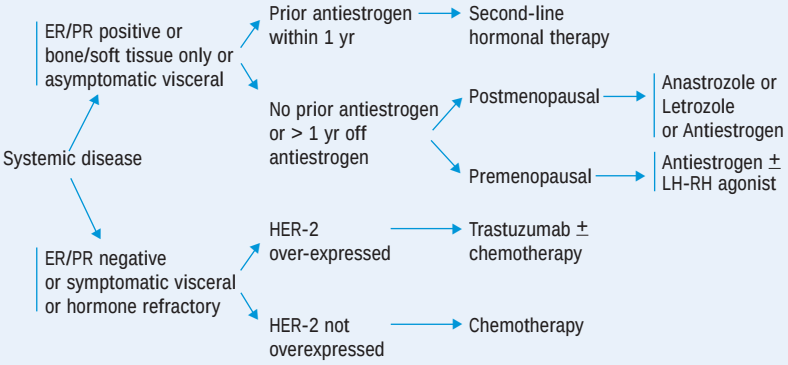
In HER2-positive patients in the metastatic setting, where hormonal therapy is not selected as initial therapy, the guideline

calls for the use of either single-agent trastuzumab or trastuzumab in combination with chemotherapy. We are fairly inclusive in terms of the selection of the chemotherapeutic agent. Although the highest level evidence available is for trastuzumab in combination with paclitaxel, the guideline acknowledges that there is nonrandomized, lower level evidence looking at trastuzumab in combination with docetaxel, vinorelbine, cisplatin and carboplatin. So, in the guideline, we do allow for the utilization of trastuzumab in combination with any of those agents.

2002 NCCN PRACTICE GUIDELINES: ALGORITHM FOR HER2 ASSESSMENT & SELECTION OF PATIENTS TO RECEIVE TRASTUZUMAB

Patients with tumors that overexpress HER2/neu may derive benefit from treatment with trastuzumab as a single agent or in combination with selected chemotherapeutic agents. The optimal method of selecting the subset of patients most likely to benefit from trastuzumab is rapidly evolving. When tested by the DAKO HercepTest, IHC staining of 2+ or 3+ appears to correlate with disease response to trastuzumab. However, benefit from trastuzumab treatment in patients with breast cancer IHC 2+ for HER2/neu appears to be limited to those tumors that are FISH-positive for HER2/neu amplification. Therefore, the panel recommends selecting patients for trastuzumab who have tumors either IHC 3+ for HER2/neu by the HercepTest or IHC 2+ for HER2/neu by the HercepTest and FISH-amplified (Field, 2001; Tubbs, 2001; Wang, 2000). Patients with tumors IHC 0 or 1+ for HER2/neu have very low rates of trastuzumab response, and therapy with trastuzumab is not warranted. In patients with metastatic or recurrent breast cancer whose tumors overexpress HER2/neu, trastuzumab as a single agent (Cobleigh, 1999; Vogel, 2001) or in combination with selected chemotherapeutics (Slamon, 2001) may be considered. A single randomized trial demonstrates benefit from adding trastuzumab to paclitaxel chemotherapy in patients with IHC 2+ or 3+ for HER2/neu. Early non-randomized data are available supporting the addition of agents such as docetaxel, vinorelbine and platinum compounds in combination with trastuzumab. The panel believes the 27% frequency of significant cardiac dysfunction in patients treated with the combination of trastuzumab and doxorubicin/ cyclophosphamide chemotherapy is too high for use of this combination outside the confines of a prospective clinical trial (Slamon, 2001).

NCCN algorithm for first-line therapy of metastatic disease



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TREATMENT OF RECURRENCE

Surgery, radiation, or regional chemotherapy (e.g., intrathecal methotrexate) indicated for localized clinical scenarios:

1. Brain metastases
2. Leptomeningeal disease
3. Choroid metastases
4. Pleural effusion
5. Pericardial effusion
6. Biliary obstruction
7. Ureteral obstruction
8. Impending pathologic fracture
9. Pathologic fracture
10. Cord compression
11. Localized painful bone or soft-tissue disease

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EVOLUTION OF THE NCCN BREAST CANCER TREATMENT GUIDELINES

The breast cancer guidelines panel has expanded from six members to 20 or more panel members. The guidelines started as quite broad and relatively simple algorithms to allow flexibility among the practitioners. Although we have maintained broad treatment options within the guidelines, we have become much more detailed and specific over the years.

I find it quite fascinating that each year new evidence forces us to really change the guideline; and the breast panel of the NCCN is the only one whose guidelines undergo annual revision. This tells us something about the quality and quantity of ongoing international research in breast cancer. It has truly been a joy getting to know and working with the other panel members, a superb group of clinicians and scientists. It's also very gratifying to see the American Cancer Society and the NCCN modify the guidelines for a lay audience. Patients come into my office with the guidelines that I have — in part — been involved in developing, to talk with me about how they should be treated. That makes my job easier.

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NCCN INSTITUTIONS

- Fred Hutchinson Cancer Research Center
- UCSF Comprehensive Cancer Center
- Huntsman Cancer Institute at the University of Utah
- Stanford University Medical Center
- City of Hope Cancer Center
- Robert H Lurie Comprehensive Cancer Center of Northwestern University
- UNMC Eppley Cancer Center at the University of Nebraska Medical Center
- St. Jude Children's Research Hospital
- University of Texas MD Anderson Cancer Center
- University of Michigan Comprehensive Cancer Center
- Arthur G James Cancer Hospital & Richard J Solove Research Institute at The Ohio State University
- University of Alabama at Birmingham Comprehensive Cancer Center
- Roswell Park Cancer Institute
- Dana-Farber Cancer Institute
- Memorial Sloan-Kettering Cancer Center
- Fox Chase Cancer Center
- Johns Hopkins Comprehensive Cancer Center
- Duke Comprehensive Cancer Center
- H Lee Moffitt Cancer Center & Research Institute at the University of South Florida

INFORMATION ABOUT THE NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

These guidelines are a work in progress that will be refined as often as new significant data becomes available.

The NCCN guidelines are a statement of consensus of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN guideline is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

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SLIDE PRESENTATIONS

Targeting the estrogen receptor for destruction: New therapeutic opportunities in the treatment of breast cancer. Richard M. Elledge, MD, Baylor College of Medicine. Presented at the Chemotherapy Foundation Symposium XVIII **Web link**

ICI 182,780 ('Faslodex'): An estrogen receptor downregulator — Targeted therapy for breast cancer. V Craig Jordan, PhD, DSc **Web link**

FIRST–LINE HORMONAL THERAPY FOR ADVANCED BREAST CANCER

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OTHER RESOURCES

National Comprehensive Cancer Network (NCCN) Website Web Link

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ADJUVANT TAXANES

In node-positive, estrogen receptor-negative patients — where CALGB 9344 still shows some benefit — we have been using four cycles of AC followed by four cycles of paclitaxel. Several members of our group have switched to six cycles of FEC, based upon the Canadian experience showing that it is better than CMF. We do not utilize taxanes in estrogen receptor-positive patients, since the trial did not show any benefit in that subset. There's no information currently available that will satisfy me that node-negative patients benefit from taxanes, and I would be very reluctant to offer it to them off protocol.

MECHANISMS OF ACTION OF TAMOXIFEN VERSUS AROMATASE INHIBITORS

There are important differences in the mechanism of action between tamoxifen and anastrozole. The aromatase inhibitors may allow you to abrogate the autocrine properties of breast cancer cells and offer another dimension of activity beyond antiestrogens. In the metastatic setting, the aromatase inhibitors are exceedingly well-tolerated, with superb, very durable responses and good quality of life. Unless the AIs cause tremendous osteoporosis, I suspect they will replace antiestrogens.

CAPECITABINE: A RATIONALLY DERIVED AGENT

Capecitabine is a very intriguing, novel, chemically synthesized drug. The basis of its synthesis actually goes back to the 1980s, when various researchers described a technique called retrometabolic engineering. Capecitabine is a pro-drug, which undergoes enzymatic activation and can concentrate fluoropyrimidines in the tumor three to tenfold, to give potentially higher efficacy and selectivity due to this very clever engineering. The objective is to keep a very high concentration of the active drug — 5-FU — in the tumor and hopefully lessen host toxicity, thus increasing the therapeutic index.

Secondly, combined with other drugs such as taxanes, which up-regulate thymidine phosphorylase — the enzymatic step to convert capecitabine into its active form — you can get curative potential. Using 5-fluorouracil under the same conditions, you do not.

AVOIDANCE OF HAND–FOOT SYNDROME THROUGH DOSE REDUCTION OF CAPECITABINE

Hand-foot syndrome is a dose-related side effect of capecitabine, perhaps in part due to the polymorphism of DPD, the enzyme that degrades 5-FU. Retrospective data from Joyce O'Shaughnessy demonstrated that two grams per meter squared per day was an acceptable dose, and I start very elderly patients out at 1,500 milligrams per meter squared per day. At these doses I've encountered very few instances of hand-foot syndrome in my practice.

It's also important to educate patients about what to expect from a drug and what to look out for. I instruct patients to discontinue capecitabine if they experience redness in their hands or feet. I also emphasize that toxicity does not mean that they are going to have a response. In fact, some patients who have had the best responses have had no symptoms at all. I had one patient who travels extensively who has been on single-agent capecitabine for six months without any toxicity whatsoever — for her, it's been a godsend.

Phase III Randomized Study of Adjuvant Chemotherapy Using Standard Cyclophosphamide/Methotrexate/Fluorouracil (CMF) or Doxorubicin/Cyclophosphamide (AC) versus Oral Capecitabine in Elderly Women with Operable Adenocarcinoma of the Breast **Protocol**

Protocol IDs: CLB-49907; CTSU
Projected Accrual: 600-1,800 patients within 2-6 years

Eligibility	Postmenopausal women > 65 years old with stage IIA/IIIA operable breast cancer

ARM 1 | AC or CMF based on LVEF and/or physician/patient choice

ARM 2 | Capecitabine q 3 weeks x 6

Beginning within 12 weeks after treatment in arm I or II, ER/PR-positive patients receive tamoxifen x 5 years.

Beginning 4-6 weeks after treatment in arm I or II, eligible patients who previously underwent breast conservation surgery undergo XRT.

Richard L Schilsky, Chair, 773-834-3914
Cancer and Leukemia Group B

Phase III Randomized Study of Bevacizumab with Capecitabine versus Capecitabine Alone in Women with Previously Treated Metastatic Breast Cancer **Protocol**

Protocol IDs: GENENTECH-AVF2119g; GUMC-00299; MSKCC-01008; UAB-0028; UAB-F001009003

Projected Accrual: Approximately 400 patients within 12 months

Eligibility:	Progressive metastatic breast cancer previously treated with 1-2 conventional chemotherapy regimens for metastatic disease or previously treated with an anthracycline and taxane or relapsed within 12 months after adjuvant anthracycline and taxane regimen

ARM 1 | [Capecitabine qd x 14 days] q 3 weeks x 35

ARM 2 | [Capecitabine qd x 14 days + bevacizumab on day 1] q 3 weeks x 35

Patients with progressive disease in arm II may continue to receive bevacizumab alone or in combination with a new chemotherapy regimen or other treatment.

Ginny Langmuir, Chair, 650-225-4985
Genentech Inc.

DOCETAXEL–CAPECITABINE STUDY: QUALITY OF LIFE

There is evolving evidence from a large randomized Phase III trial of over 500 patients that patients failing anthracycline therapy can maintain quality of life and increase disease-free and overall survival with the combination of docetaxel and capecitabine. In fact, the response and survival curves now show more benefit than they did when the data was initially presented. This is a standard of care that we have to look at carefully.

Quality of life is a critical issue in treating advanced disease. If we prolong duration of response without a reasonable quality of life, we are kidding ourselves. The docetaxel-capecitabine study was one of the few clinical trials where quality of life was a major endpoint. A rigorous quality-of-life measurement was used before and during the study, showing that patients receiving combination docetaxel-capecitabine actually had a better quality of life than patients receiving full-dose docetaxel alone. Although this may seem paradoxical, my interpretation is that if a patient has a response — and for example, her fungating tumor is gone — she can get out of bed, walk around and go to work, then obviously, there's a benefit.

LACK OF CROSSOVER IN THE DOCETAXEL–CAPECITABINE STUDY

In the docetaxel-capecitabine study, only 17 percent of patients randomized to docetaxel crossed over to capecitabine after progression. However, a crossover in this trial would have been very difficult to accomplish. These were a tough group of patients. They had failed anthracyclines either in the adjuvant setting or in the metastatic setting, and, two-thirds of them had failed it in the metastatic setting. They had all received alkylating agents. Three-quarters had already received fluoropyrimidines — so they already had failed 5-FU to a great degree.

The take-home message from the study is that if you have a higher response rate, a better quality of life, and a longer duration of survival with the combination, you probably can't do as well with a sequential regimen, because you're going to have a higher tumor burden. You're going to have more morbidity. We know that if you can reduce tumor burden, then — as a group — you usually have better performance and better quality of life. A higher response rate with longer survival is obviously an advantage.

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Pharmaceutical agents discussed in this program

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

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Breast Cancer™ update

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This program was supported by educational grants from AstraZeneca Pharmaceuticals, LP, Genentech, Inc., and Roche Laboratories, Inc.

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Post test

Breast Cancer Update, Issue 1, 2002

Conversations with Oncology Leaders

Bridging the Gap Between Research and Patient Care

Questions (please circle answer):

1. Which of the following is an estrogen receptor downregulator?

a. tamoxifen
b. anastrozole
c. fulvestrant
d. letrozole

2. True/False: Fulvestrant does not cross the blood-brain barrier; therefore, theoretically it should not cause hot flashes.

3. The NCCN guidelines recommend which of the following as first-line hormonal therapy for metastatic disease in postmenopausal women?

a. tamoxifen
b. nonsteroidal aromatase inhibitors (anastrozole or letrozole)
c. steroidal aromatase inhibitors (exemestane)
d. A and B
e. A and C

4. True/False: Capecitabine-associated hand-foot syndrome is believed to be a dose-related side effect.

5. True/False: Thymidine phosphorylase — the enzyme that converts capecitabine to 5-FU intratumorally — is upregulated by taxanes as well as other chemotherapeutic agents, possibly resulting in improved efficacy from combination chemotherapy with capecitabine.

6. In the phase III docetaxel-capecitabine study of patients with advanced breast cancer who had previously failed anthracycline therapy:

A. The docetaxel-capecitabine arm resulted in both improved disease-free and overall survival.
B. The docetaxel-capecitabine arm resulted in a slight improvement in disease-free survival only.
C. The docetaxel-capecitabine arm did not demonstrate superior efficacy, but overall quality of life was better.

7. Approximately what percentage of breast cancer patients are HER2/neu-positive by FISH?

A. less than 10%
B. 20-25%
C. 55-60%
D. Over 70%

8. True/False: Fluorescence In Situ Hybridization (FISH) measures HER2/neu gene amplification

9. True/False: Studies have demonstrated benefit to continuing trastuzumab after disease progression.

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

Evaluation Form

Breast Cancer Update, Issue 1, 2002

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Postgraduate Institute for Medicine (PIM) respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. Please note, a certificate of completion is issued only upon receipt of your completed evaluation form.

Please answer the following questions by circling the appropriate rating:

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

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

• Describe the mechanism of action and clinical trial results of fulvestrant, the estrogen receptor downregulator	5	4	3	2	1
• Review the current first-line data on hormonal treatment of metastatic disease	5	4	3	2	1
• Review the development and clinical use of the oral fluoropyrimidine — and capecitabine in breast cancer treatment	5	4	3	2	1
• Review decision algorithms for assessment of HER2 status in breast cancer patients and identify the current clinical applications and on-going trials of trastuzumab	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:

_____

_____

Degree:

❑ MD ❑ DO ❑ PharmD ❑ RN ❑ PA ❑ BS ❑ Other _____

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