# Breast Cancer® UPDATE

## Conversations with Oncology Investigators

### Bridging the Gap between Research and Patient Care

**SPECIAL ISSUE**
**Proceedings from a Clinical Investigator "Think Tank"**

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# *Breast Cancer Update*
## A Continuing Medical Education Audio Series

### 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 uses 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.

### GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions.
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings.
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients.
- Counsel appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations.
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions.

### PURPOSE OF THIS ISSUE OF BREAST CANCER UPDATE

The purpose of this special edition of Breast Cancer Update is to support these global objectives by offering the perspectives of Drs Budd, Chlebowski, Geyer, Gradishar, Henderson, Hudis, O'Shaughnessy, Ravdin, Rugo, Tripathy and Wolff on the integration of emerging clinical research data into the management of breast cancer.

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## CONTENT VALIDATION AND DISCLOSURES

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EDITOR'S NOTE

## All-Star Journal Club

The enclosed audio program contains the edited proceedings from our most recent breast cancer Think Tank and represents a new direction in our continuing quest to develop education platforms that meet the needs of medical oncologists in practice. Specifically, we asked each one of the 11 research leaders who participated in this event to prepare a journal club–like review of two or three recent abstracts and papers, many of which were presented at the 2006 ASCO meeting. Following these short discussions, the panel debated the implications of this information and its relevance to patient care. The end result was a highly informative and entertaining day of repartee that yielded the many fascinating perspectives, opinions and commentaries found on this program. ■

**— Neil Love, MD**
**NLove@ResearchToPractice.net**
**November 3, 2006**

## Papers and presentations discussed by clinical investigator panelists

### Debu Tripathy, MD

Wedam SB et al. **Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer.** *JCO* 2006;24(5):769-77. **Abstract**

Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial coordinated by the Eastern Cooperative Oncology Group (E2100).** SABCS 2005;**Abstract 3**.

### Hope S Rugo, MD

Traina TA et al. **Letrozole with bevacizumab is feasible in patients with hormone receptor-positive metastatic breast cancer.** ASCO 2006;**Abstract 3050**.

Rugo HS. **Change in circulating endothelial cells predicts progression free survival in patients with hormone receptor positive metastatic breast cancer receiving letrozole and bevacizumab.** ASCO 2006;**Abstract 3039**.

Burstein HJ et al. **Metronomic chemotherapy with and without bevacizumab for advanced breast cancer: A randomized phase II study.** SABCS 2005;**Abstract 4**.

### Peter M Ravdin, MD, PhD

Swain SM. **A step in the right direction.** *JCO* 2006;24(23):3717-8. No abstract available

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *JCO* 2006;24(23):3726-34. **Abstract**

### William J Gradishar, MD

Habel LA et al. **A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients.** *Breast Cancer Res* 2006;8(3):R25. **Abstract**

### Clifford Hudis, MD

Berry DA et al. **Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer.** *JAMA* 2006;295(14):1658-67. **Abstract**

Muss H et al. **Toxicity of older and younger patients treated with intensive adjuvant chemotherapy for node-positive breast cancer: The CALGB experience.** ASCO 2006;**Abstract 559**.

Smith I. **Trastuzumab following adjuvant chemotherapy in HER2-positive early breast cancer: Disease-free and overall survival after 2 year median follow-up.** ASCO 2006;[Special session]. **Abstract**

## I Craig Henderson, MD

Hayes DF et al. **HER2 predicts benefit from adjuvant paclitaxel after AC in node-positive breast cancer: CALGB 9344.** ASCO 2006;**Abstract 510**.

## Antonio C Wolff, MD

Lyman GH. **Guidelines of the National Comprehensive Cancer Network on the use of myeloid growth factors with cancer chemotherapy: A review of the evidence.** *J Natl Compr Canc Netw* 2005;3(4):557-71. **Abstract**

Vogel CL et al. **First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study.** *JCO* 2005;23(6):1178-84. **Abstract**

Smith TJ et al. **2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline.** *JCO* 2006;24(19):3187-205. **Abstract**

Giordano SH et al. **Congestive heart failure in older women treated with anthracycline chemotherapy.** ASCO 2006;**Abstract 521**.

Shepherd LE et al. **Left ventricular function following adjuvant chemotherapy for breast cancer: The NCIC CTG MA5 experience.** ASCO 2006;**Abstract 522**.

Sparano JA et al. **Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199.** SABCS 2005;**Abstract 48**.

## Thomas G Budd, MD

Bianco AR. **Sequential epirubicin-docetaxel-CMF as adjuvant therapy of early breast cancer: Results of the Taxit216 multicenter phase III trial.** ASCO 2006;**Abstract LBA520**.

Crown J. **Docetaxel (T) given either concurrently or sequentially to anthracycline-based (A) adjuvant therapy (adjRx) for patients (pts) with node-positive (N+) breast cancer (BrCa). Comparison with non-taxane combination chemotherapy. First results of the BIG 2-98 trial at 5 years median follow-up.** ASCO 2006;**Abstract LBA519**.

## Joyce O'Shaughnessy, MD

Jones SE et al. **Final analysis: TC has a superior disease-free survival compared to standard AC in 1016 women with early stage breast cancer.** SABCS 2005;**Abstract 40**.

Hayes DF. **HER2 predicts benefit from adjuvant paclitaxel after AC in node-positive breast cancer: CALGB 9344.** ASCO 2006;**Abstract 510**.

## Charles E Geyer Jr, MD

Geyer CE Jr et al. **A Phase III randomized, open-label international study comparing lapatinib and capecitabine vs capecitabine in women with refractory advanced or metastatic breast cancer.** ASCO 2006;[Special session]. **Abstract**

Slamon D et al. **Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study.** ASCO 2006;**Abstract 1**.

Knoop A. **TOP2A aberrations as predictive and prognostic marker in high-risk breast cancer patients. A randomized DBCG Trial (DBCG89D).** ASCO 2006;**Abstract 532**.

O'Mally FP. **Prognostic and predictive value of topoisomerase II alpha in a randomized trial comparing CMF to CEF in premenopausal women with node positive breast cancer (NCIC CTG MA.5).** ASCO 2006;**Abstract 533**.

## Rowan T Chlebowski, MD, PhD

Ingle J. **NCIC CTG MA.17: Intent to treat analysis (ITT) of randomized patients after a median follow-up of 54 months.** ASCO 2006;**Abstract 549**.

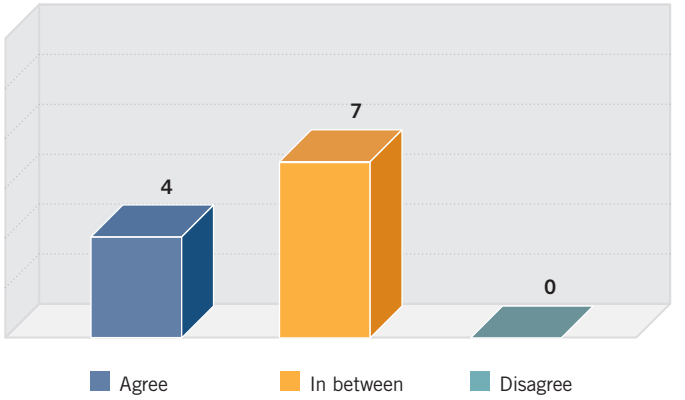
Robert NJ. **Updated analysis of NCIC CTG MA.17 (letrozole vs placebo to letrozole vs placebo) post unblinding.** ASCO 2006;**Abstract 550**.

Coombes RC. **First mature survival analysis of the Intergroup Exemestane Study: A randomised trial in disease-free, postmenopausal patients with early breast cancer randomized to continue tamoxifen or switch to exemestane following an initial 2-3 years of adjuvant tamoxifen.** ASCO 2006;**Abstract LBA527**.

## Bevacizumab Plus Chemotherapy as First-Line Therapy of Metastatic Breast Cancer

**FACULTY POLL QUESTION 1**

**A significant component of the antitumor effect of bevacizumab in breast cancer is improved delivery of cytotoxics to tumor cells.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

### Select Excerpts from the Discussion

### CD 1, Track 2

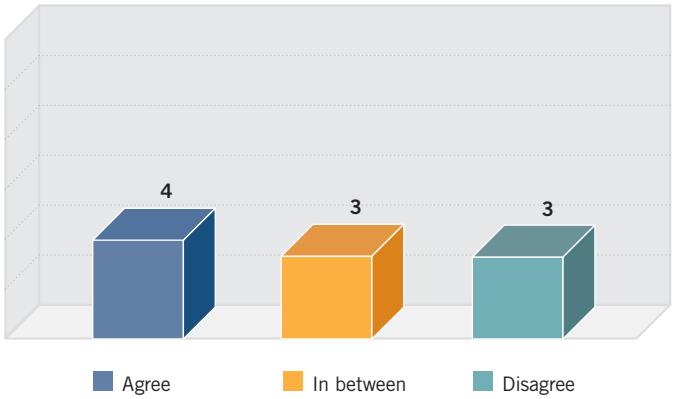
**DR TRIPATHY:** Angiogenesis is an important target in cancer. It's driven by interactions between several receptors — including the VEGF receptor, the one we are most familiar with, as well as an elaboration of proteases. So interrupting this pathway is quite a task.

An interesting correlative science study published recently by Sandy Swain's group at the NCI examined a variety of imaging and tissue indices for patients with locally advanced and, primarily, inflammatory breast cancer (Wedam 2006).

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was performed at multiple time points — after the first cycle with bevacizumab alone and following chemotherapy with bevacizumab. The imaging indices demonstrated a drop in numerous DCE-MRI-based analyses, such as the efflux of contrast, but indicated no difference between the patients who were responders and those who were nonresponders (Wedam 2006).

**FACULTY POLL QUESTION 2**

**Cost and reimbursement issues aside, bevacizumab should generally be utilized in a clinical setting when first-line chemotherapy is being initiated.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

What was interesting was that VEGFR2 (vascular endothelial growth factor receptor 2) levels decreased, especially the phosphorylated or activated version, and the localization of the receptors moved from the membrane to the cytoplasm (Wedam 2006).

## CD 1, Tracks 3, 5

**DR LOVE:** Putting cost and reimbursement issues aside, do we have the data right now to justify using bevacizumab as first-line therapy for metastatic disease, and how much of an advance was ECOG-E2100 (Miller 2005a, 2005b)?

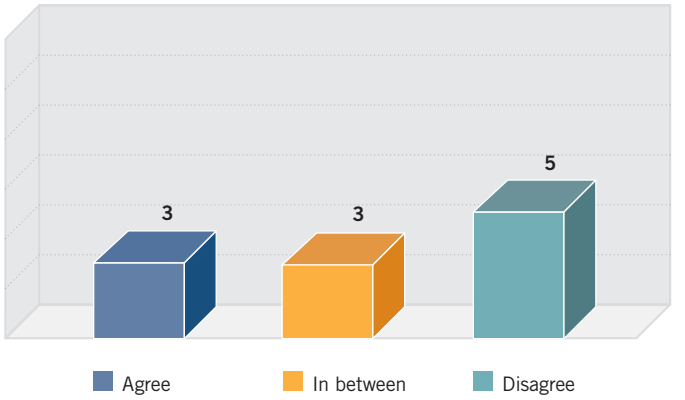
**DR RUGO:** It's a significant advance. Having participated in the initial capecitabine/bevacizumab trial (Miller 2005c) and also having used bevacizumab in a variety of clinical research settings, we've been convinced for a long time that it has clinical benefit.

ECOG-E2100 produced two important implications (Miller 2005a, 2005b). One is that we can, potentially, help patients in the metastatic setting with first-line therapy in combination with a taxane.

The second is that it allowed us to move bevacizumab into trials in the early adjuvant setting, as well as into the neoadjuvant setting, which potentially allows

**FACULTY POLL QUESTION 3**

**Cost and reimbursement issues aside, bevacizumab should generally be utilized in a clinical setting only when initiating first-line paclitaxel.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

us to identify the patient population most likely to benefit from bevacizumab.

**DR LOVE:** Bill, what are your thoughts about using bevacizumab in a clinical setting?

**DR GRADISHAR:** I believe clinicians will ultimately base their decisions on what the data show. Right now, we have positive data from ECOG-E2100 (Miller 2005a, 2005b). By that, I'm emphasizing the fact that it's used in the first-line setting.

I have no reason to believe bevacizumab in conjunction with other agents, as first-line therapy, wouldn't have a similar benefit. I don't believe we will see people restricting themselves to the use of bevacizumab with paclitaxel alone, but we don't have a lot of Phase II data for combining bevacizumab with a variety of different agents.

That said, the experience with trastuzumab is similar — we had preclinical models that guided us and then the Phase II trials followed. They all were consistent in that they demonstrated an incremental improvement when you combined the given agent with trastuzumab. I believe that when bevacizumab is combined with other chemotherapy agents, we will see the same improvement in outcome that we've seen in ECOG-E2100.

## CD 1, Track 7

**DR LOVE:** Cliff, are you using capecitabine/bevacizumab off protocol?

**DR HUDIS:** I believe any patient with Stage IV breast cancer who is healthy enough to receive bevacizumab deserves a shot at the drug. I don't buy the argument that it only works in the first-line setting and that it only works with paclitaxel.

The reasons I say that are, first, the drug has been extensively used with a variety of other chemotherapy agents. I don't have to see safety data for a drug specifically in patients with breast cancer to call it safe. We have a lot of safety data for the 5-FU/bevacizumab combination.

Second, I thought the capecitabine/bevacizumab trial by Dr Miller was a positive signal. It showed a doubling of the response rate, but it did not achieve its primary endpoint of progression-free survival (Miller 2005c).

The third reason is that you can see two patients in a clinic who are both ready to receive first-line therapy but have extraordinarily different prior chemotherapy experiences and exposure. For all these reasons, I offer bevacizumab, essentially, to all eligible patients with a line of therapy at some point in time.

**DR RUGO:** We need the data from the ongoing RIBBON-1 and RIBBON-2 trials. The trials randomly assign patients either in the first- or second-line setting to receive chemotherapy with placebo or bevacizumab, and then they allow a crossover. The potential exists to obtain a lot of information. We have a menu of chemotherapy agents to choose from in those settings. ■

### SELECT PUBLICATIONS


Hudis CA. **Clinical implications of antiangiogenic therapies.** *Oncology (Williston Park)* 2005;19(4 Suppl 3):26-31. **Abstract**

Miller KD et al. **E2100: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer.** Presentation. ASCO 2005a. No abstract available

Miller KD et al. **A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: A trial coordinated by the Eastern Cooperative Oncology Group (E2100).** Presentation. San Antonio Breast Cancer Symposium 2005b;**Abstract 3**.

Miller KD et al. **Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer.** *J Clin Oncol* 2005c;23(4):792-9. **Abstract**

Schneider BP, Miller KD. **Angiogenesis of breast cancer.** *J Clin Oncol* 2005;23(8):1782-90. No abstract available

Sledge GW Jr. **VEGF-targeting therapy for breast cancer.** *J Mammary Gland Biol Neoplasia* 2005;10(4):319-23. **Abstract**

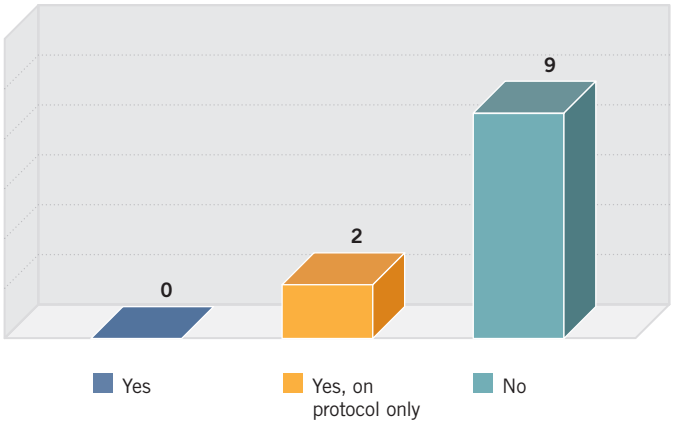
Wedam SB et al. **Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer.** *J Clin Oncol* 2006;24(5):769-77. **Abstract**

SECTION 2

## Rationale for Combining Bevacizumab and Hormone Therapy

**FACULTY POLL QUESTION 4**

**Have you utilized endocrine therapy in combination with bevacizumab?**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

### Select Excerpts from the Discussion

### CD 1, Track 8

**DR RUGO:** In addition to evaluating the combination of capecitabine/bevacizumab, another research strategy is to combine endocrine therapy with bevacizumab. Some interesting data indicate that estrogen may directly modulate angiogenesis through effects on endothelial cells in both physiologic and pathologic conditions. We also have data indicating that antiestrogen therapy blocks VEGF expression and estrogen-induced angiogenesis may be blocked by antiestrogen therapy.

Rakesh Jain's group in Boston has observed an androgen-dependent tumor model and shown that castration, interestingly, leads to initial vascular regression, and then a second wave of angiogenesis occurs with vascular regrowth in this murine tumor model.

So a hypothesis was generated that anti-VEGF therapy may overcome this resistance of the second wave of angiogenesis seen with endocrine therapy in animal models and could improve the efficacy of standard hormone therapy in hormone receptor-positive metastatic breast cancer.

### Normalization of Tumor Vasculature: An Emerging Concept in Anti-angiogenic Therapy

"Solid tumors require blood vessels for growth, and many new cancer therapies are directed against the tumor vasculature. The widely held view is that these antiangiogenic therapies should destroy the tumor vasculature, thereby depriving the tumor of oxygen and nutrients...

Emerging evidence support[s] an alternative hypothesis — that certain antiangiogenic agents can also transiently "normalize" the abnormal structure and function of tumor vasculature to make it more efficient for oxygen and drug delivery. Drugs that induce vascular normalization can alleviate hypoxia and increase the efficacy of conventional therapies if both are carefully scheduled."

SOURCE: Jain RK. *Science* 2005;307(5706):58–62. **Abstract**

In the study presented by Dr Traina at ASCO this year, 43 patients received bevacizumab at 15 mg/kg every three weeks and letrozole at 2.5 mg per day. The combination appeared to be well tolerated. The drug-related toxicities were expected and only seen in a small number of patients. The efficacy analysis, which wasn't the primary goal, was confounded by the long duration of prestudy aromatase inhibitor therapy in most patients, although it did appear that a number might have benefited from the therapy.

### Rationale for Combining Bevacizumab with Endocrine Therapy

"Both estrogens and progestins induce VEGF in breast cancer cells through their respective receptors and via characterized hormone response elements. Anti-estrogens and anti-progestins cause some hormone-dependent tumors to regress; however, some tumor cells invariably become resistant to anti-hormones and continue to grow. In certain cases, anti-hormones can even stimulate tumor growth.

Our recent data indicate that exposure of breast cancer cells to VEGF can override the effects of anti-hormone therapy, suggesting that a treatment regimen of both anti-hormonal and anti-angiogenic agents may be better for tumor suppression than a single regimen alone."

SOURCE: Hyder SM. *Endocr Relat Cancer* 2006;13(3):667-87. **Abstract**

We have planned a Phase III study within CALGB and the Intergroup in patients with hormone receptor-positive disease. The patients will be randomly assigned to endocrine therapy with placebo or bevacizumab (administered every three weeks) as first-line therapy. ■

## SELECT PUBLICATIONS


Hyder SM. **Sex-steroid regulation of vascular endothelial growth factor in breast cancer.** *Endocr Relat Cancer* 2006;13(3):667-87. **Abstract**

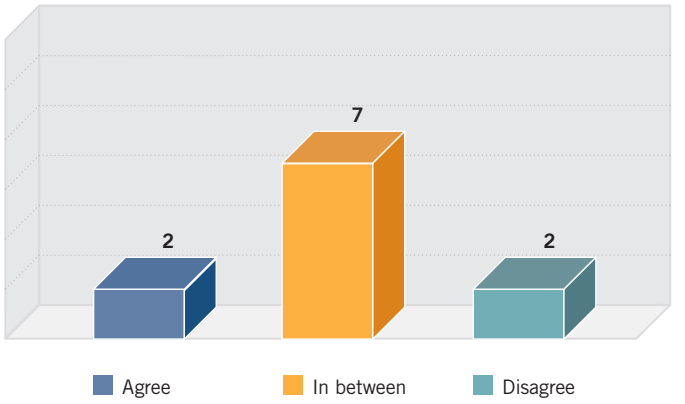
Traina TA et al. **Letrozole (L) with bevacizumab (B) is feasible in patients (pts) with hormone receptor-positive metastatic breast cancer (MBC).** *Proc ASCO* 2006;**Abstract 3050**.

SECTION 3

## Utility of the Oncotype DX™ Assay in Predicting Benefit of Adjuvant Chemotherapy

**FACULTY POLL QUESTION 5**

**Patients with ER-positive, HER2-negative, node-negative tumors should generally be offered the Oncotype DX assay.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

### Select Excerpts from the Discussion

### CD 1, Tracks 13-14

**DR RAVDIN:** Sandy Swain wrote an editorial following publication of the results from the Oncotype DX assay with the NSABP-B-20 data set entitled "A Step in the Right Direction" (Swain 2006).

She estimates that this assay could potentially spare 50,000 women per year treatment with chemotherapy on the basis of prognosis alone (Swain 2006). I would agree with her, but we also have ways of doing this on the basis of tumor size and grade.

She also commented that estrogen receptor measurements by IHC are not quantitated. So even if you wanted to use some of these other methods, they might not be as reliable as the Oncotype DX test. Some patients with high ER also have a high recurrence score. So if you simply used high ER as a correlate for chemotherapy responsiveness or, in this case, resistance, you would be fooled sometimes.

Dr Swain's conclusion was that the recurrence score appears to be beneficial

in predicting which patients will benefit and which will not (Swain 2006). However, the recurrence score is only the beginning. I believe we'd all agree that this is a very useful test, but I hope it is something that will be refined.

If you agree with Sandy Swain's editorial, you might conclude that all patients with node-negative, ER-positive disease should be tested with the Onco*type* DX assay. The major caveat is that NSABP-B-20 did not use modern regimens that we utilize in the clinic today. The chemotherapy in that trial was M → F or CMF, and it was always used in combination with tamoxifen (Paik 2006), so tamoxifen might have had confounding effects on the results.

### Utility of the Onco*type* DX Assay in Predicting Benefit of Adjuvant Chemotherapy

"We know that adjuvant therapy benefits patients. The problem is, which patients? Are we willing to forgo treatments that could potentially benefit a particular patient?

The article published by Paik et al in this issue of the *Journal of Clinical Oncology* is one of the first to attempt to answer these questions.

Patients with a high (Onco*type* DX) recurrence score (RS) have the highest distant recurrence rate. This current analysis expands on the previously published data and finds that patients with high-RS tumors who are treated with chemotherapy have a lower recurrence rate compared with those not treated with chemotherapy. Conversely, patients with a low RS do not benefit from chemotherapy."

**SOURCE:** Swain SM. *J Clin Oncol* 2006;24(23):3717-8. No abstract available

How much benefit was seen from the chemotherapy in this trial? If you look at the 10-year results, you see effectively no benefit in the low-risk group. The high-risk group showed a dramatic benefit — about a two thirds reduction in the risk of the development of metastatic disease (Paik 2006).

**DR GEYER:** I believe the recurrence score helps in counseling a woman about the importance of chemotherapy for her situation. If she has a high recurrence score, chemotherapy is the dominant part of her therapy. If she has an intermediate recurrence score, I believe the main part is the hormonal therapy, but that's not to say chemotherapy isn't helpful.

We need to develop an understanding of the importance of the various components. The Onco*type* DX results provide counseling information about the risk-to-benefit ratio that is relevent when women run into toxicities, for example — how far should they persevere through toxicities. ■

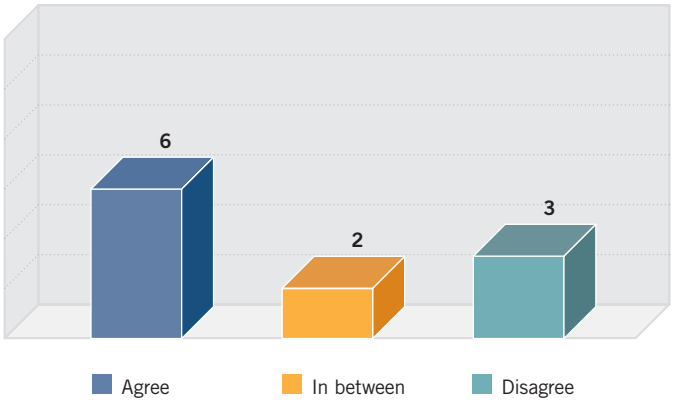
## SELECT PUBLICATIONS


Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006;24(23):3726-34. **Abstract**

Swain SM. **A step in the right direction.** *J Clin Oncol* 2006;24(23):3717-8. No abstract available

**FACULTY POLL QUESTION 6**

## Assays like Onco*type* DX will eventually replace IHC to evaluate HER2 and ER.




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

### Select Excerpts from the Discussion

### CD 1, Tracks 15-16

**DR LOVE:** Cliff, where do you see the Onco*type* DX assay being most useful, clinically?

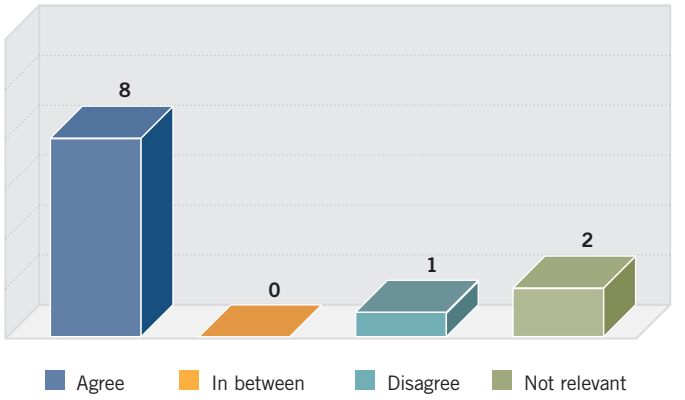
**DR HUDIS:** I see the test as particularly relevant for a patient who's on the fence about chemotherapy. For the borderline case, in which we're not sure and we have a high recurrence score, I believe it provides a valuable service. I have a little more reservation at the moment about using the test to withhold chemotherapy. A low recurrence score does not, with those confidence intervals, exclude the possibility of benefit.

I believe we're left, right now, still discussing the values the patient brings to the table. Some patients are uninterested in chemotherapy and no recurrence score will convince them. Conversely, a fair number of patients — at least in our practice — if we don't offer them chemotherapy, are going across the street for it. A low recurrence score is of no particular value to them.

**DR WOLFF:** To me the key issue with the Onco*type* DX assay, as with any

**FACULTY POLL QUESTION 7**

**The way I integrate Onco*type* DX into my practice is cost-effective to the healthcare system.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

other test, is that you should order it if you're going to do something with that specific information. At my institution, we have requested that the medical oncologists only order the Onco*type* DX assay if it's going to help make a decision with the patient. If the patient says, "I want chemotherapy regardless," or, "There's no way you're going to use chemotherapy," I don't need the Onco*type* DX assay to add information.

**DR HENDERSON:** We all think we're good at estimating risk. I believe we may not be entirely correct because we tend to weigh one bad factor out of multiple good factors disproportionately. It's too bad we have not yet conducted a study in which we test our ability prospectively to calculate risk. If we found that we weren't so good and that the Onco*type* DX assay resulted in a better distribution of the appropriate therapies for patients, the cost of the test might be more than outweighed by the appropriate use of therapies.

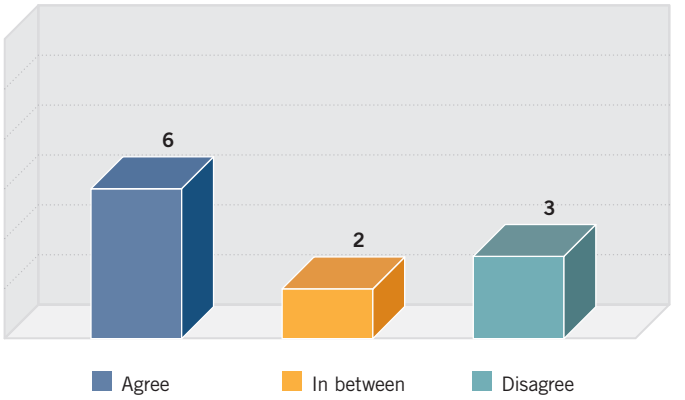
## CD 1, Track 19

**DR LOVE:** Cliff, does the Onco*type* DX assay have a role for patients with HER2-positive tumors?

**DR HUDIS:** Certainly some cases with HER2-positive tumors have a low recurrence score. If you weren't considering the use of trastuzumab in the

**FACULTY POLL QUESTION 8**

**There is essentially no role for the Onco*type* DX assay in patients with HER2-positive tumors.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

context of how it has been tested, it might matter. However, since trastuzumab is almost exclusively going to be used with chemotherapy, I don't see a role for the Onco*type* DX assay in those patients.

**DR WOLFF:** In clinical practice, I don't use the Onco*type* DX assay for patients with tumors that are smaller than one centimeter or those that are HER2-positive.

In the NSABP validation studies, only about 16 percent of 650 patients had tumors that were smaller than one centimeter. So you're talking about roughly 100 patients with tumors smaller than one centimeter (Paik 2004). A split exists across all three groups.

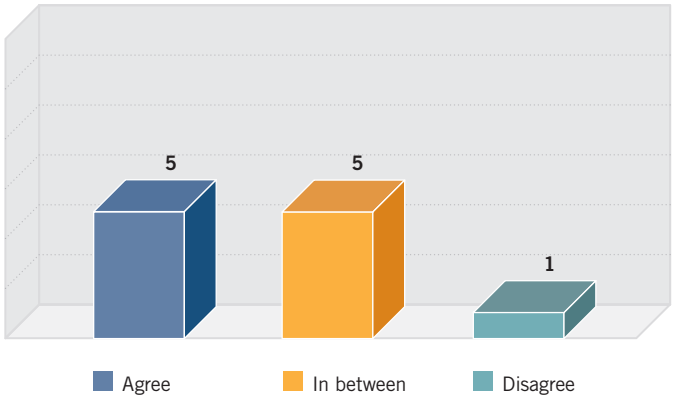
Therefore, I have no idea whether the assay results apply to smaller tumors. You have to be very careful, if you order a test, about whether your patient's case applies to the patient group.

**DR GEYER:** I would disagree with the notion that we wouldn't use the Onco*type* DX assay for patients with smaller tumors. We know that some of those smaller tumors do recur.

If you were struggling with a decision about whether to use chemotherapy, even for a small tumor, the high recurrence score would add credence, because it would suggest a benefit. The patient is going to have a substantial relative-risk reduction.

**FACULTY POLL QUESTION 9**

**Patients with smaller, ER-positive, node-negative tumors who receive chemotherapy generally do not understand the marginal benefits of chemotherapy in this situation, and if they did, many would refuse chemotherapy.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

It's hard to imagine that, biologically, the relative risk reduction for a patient with a high recurrence score is going to be different in a smaller tumor. With a 75 percent relative reduction, the absolute benefit — even with smaller tumors — could be substantial (Paik 2006c). ■

## SELECT PUBLICATIONS


Mauriac L et al. **When will more useful predictive factors be ready for use?** *Breast* 2005;14(6):617-23. **Abstract**

Mina L et al. **Predicting response to primary chemotherapy: Gene expression profiling of paraffin-embedded core biopsy tissue.** *Breast Cancer Res Treat* 2006;[Epub ahead of print]. **Abstract**

**NSABP study confirms oncotype DX predicts chemotherapy benefit in breast cancer patients.** *Oncology (Williston Park)* 2006;20(7):789-90. No abstract available

Paik S. **Methods for gene expression profiling in clinical trials of adjuvant breast cancer therapy.** *Clin Cancer Res* 2006a;12(3 Pt 2):1019-23. **Abstract**

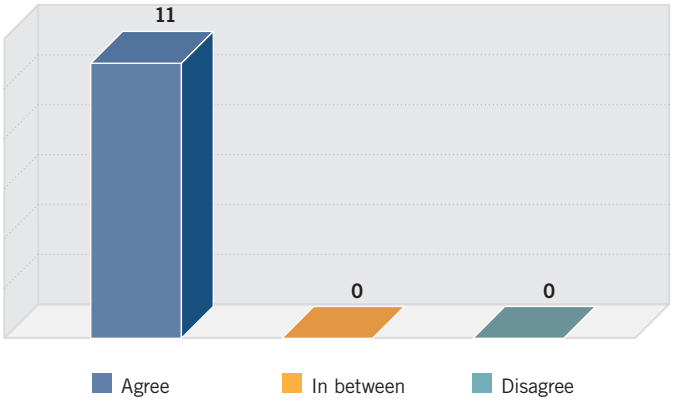
Paik S. **Molecular profiling of breast cancer.** *Curr Opin Obstet Gynecol* 2006b;18(1):59-63. **Abstract**

Paik S et al. **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol* 2006c;24(23):3726-34. **Abstract**

Williams C et al. **Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.** *Health Technol Assess* 2006;10(34):1-222. **Abstract**

**FACULTY POLL QUESTION 10**

**All other factors being the same, I am less likely to utilize adjuvant chemotherapy in women with ER-positive tumors than ER-negative tumors.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

## Select Excerpts from the Discussion

### CD 1, Track 21

**DR HUDIS:** Everybody wants to enter into a debate about TAC and dose-dense therapy. The first issue is that both of the regimens are clearly more active than what they were compared against (Hudis 2005; Martin 2005).

A practical study evaluating this issue is NSABP-B-38, which Sandy Swain is chairing. Patients are randomly assigned to TAC, dose-dense AC → paclitaxel or a third arm incorporating gemcitabine with dose-dense therapy. It's comparing six versus four cycles, every two-week versus every three-week schedules and different taxanes and different anthracycline doses.

### CD 1, Track 25

**DR LOVE:** Chuck, in NSABP-B-38, you're seeing patients who receive TAC, dose-dense AC → paclitaxel and the experimental regimen. What are your observations about quality of life, fatigue, et cetera in different arms?

**DR GEYER:** In terms of toxicity, the regimens aren't segregating to the degree that we thought we might see. We're not going to pick up differences in Grade I/II fatigue with what we're doing. Those things, certainly, you can see in the clinic. However, with the major toxicities that are monitored on the trial, we're not seeing any apparent differences with the cytokine support that everybody receives.

### Optimizing Chemotherapy for Patients with Node-Positive Disease

"On the basis of the available data, one can consider TAC to be a standard of care, as is the dose-dense regimen of doxorubicin and cyclophosphamide followed by paclitaxel, for patients with resected node-positive breast cancer. However, the exclusion of patients older than 70 years and the toxic effects associated with TAC in the BCIRG trial cannot be minimized.

With this regimen, prophylactic growth-factor support is necessary to ameliorate myelosuppression and febrile neutropenia. A recommendation for the selection of one regimen over the other must await completion of the prospective National Surgical Adjuvant Breast and Bowel Project trial B-38, for which the accrual of data is expected to be complete in the next few years."

SOURCE: Perez EA. *N Engl J Med* 2005;352(22):2346-8. No abstract available

## CD 1, Tracks 22-23

**DR LOVE:** Cliff, can you review the article about the benefits of adjuvant chemotherapy based on ER status that was published by Berry in *JAMA*?

**DR HUDIS:** Don Berry retrospectively went through three trials (CALGB-8541, CALGB-9344 and CALGB-9741). Then across those studies, he generated hypotheses about the value of treatment (Berry 2006).

I differ with the coauthors on the issue of ER testing. I'm not confident that our testing is of high enough quality to draw conclusions. Also, we did not apply standard and consistent hormone therapy for these patients. You must recognize that when trying to interpret and put this into practice.

Among the patients with ER-negative disease, a significant benefit was observed for high-dose versus low-dose CAF (CALGB-8541), paclitaxel versus no paclitaxel (CALGB-9344) and every two-week versus every three-week therapy (CALGB-9741). For the patients with ER-positive disease, the results were quite different. No discernible advantage was observed for high-dose CAF, although the low-dose CAF still appears to be inferior (Berry 2006).

Two take-home points have emerged. The first is that adjuvant chemotherapy for patients with ER-negative breast cancer, both in terms of recurrence rate and death, is a profoundly effective treatment that shouldn't be scoffed at. In terms of an indirect comparison, it is probably in the same ballpark as

hormone therapy for patients with ER-positive disease and trastuzumab for patients with HER2-positive disease.

For patients with ER-positive disease, the estimate of benefit at five years remains favorable and above the threshold most patients would consider worthwhile. An important caveat is that these data do not address whether chemotherapy works in patients with ER-positive disease. It addresses the differences between chemotherapy regimens in patients with ER-positive disease. You would need a chemotherapy-untreated control arm for the basis of comparison.

**DR LOVE:** Debu, how do you factor in ER status when selecting adjuvant chemotherapy for patients with node-positive disease?

**DR TRIPATHY:** It's clear that ER status is important. We've known this for a long time, initially in the metastatic setting and then with the Oxford overview (EBCTCG 2005), although it was never definitive because only a small percentage of those patients had ER and PR testing. It's not surprising that we're now finding that these patients derive a smaller benefit. They still benefit, however, so that has to be factored in.

Some will argue that the low-dose version of CAF in 8541 was "no-dose" chemotherapy, but that's not technically true, and that's one of the places where, again, the data let us down. They don't address that basic question: Does chemotherapy work in this subset?

The explanation that Don put forth is that it's about the hazard. This is more important than just a little parlor game, because this speaks to the biology of breast cancer. ER-negative disease has a more rapid proliferation early on, and you see a high spike in recurrence risk, which is driven down by chemotherapy.

You don't see that in patients with ER-positive disease because they don't have the early high risk. In fact, over 20 years, their risk is fairly consistent. This is the sobering news about ER-positive disease. Even though you get through the first five years doesn't mean that you're really "out of the woods." It is quite the opposite.

Should we change the numbers we currently use for the risk reduction associated with chemotherapy and assign a different number to those patients with ER-positive versus ER-negative disease? I believe we should, and incorporate them into the model.

With regard to dose-dense therapy in combination with trastuzumab, I'm still using the every three-week regimen used in the Intergroup and NSABP studies (Romond 2005). Certainly, as more safety data come in and we have more follow-up from the Memorial Sloan-Kettering study, I'm going to incorporate that — just like many other changes in my practice — slowly.

It's interesting that the cardiotoxicity may be a little bit lower, although statistically we can't confirm that. I always projected that we might see slightly

more cardiotoxicity when we used a dose-dense anthracycline, but that simply has not been seen. The trend is in the other direction (Hudis 2005).

### CD 1, Track 26

**DR HENDERSON:** CALGB-9344 was designed initially to evaluate three different doses of doxorubicin, and paclitaxel was an add-on. This created a confounded study in many ways. The paclitaxel issue, however, became the positive and the more provocative one (Henderson 2003).

**Estrogen Receptor Status and Outcomes of Modern Chemotherapy among Patients with Node-Positive Breast Cancer**

"Our study has … substantive clinical implications. First, although patients with ER-positive breast tumors may reasonably opt for chemotherapy, they should recognize that the benefits are not great as compared with those for patients with ER-negative disease.

The benefits of intensive and extensive chemotherapy for unselected patients who have ER-positive disease treated with tamoxifen are modest at best. Whether such patients should opt for chemotherapy will depend on their attitudes toward the associated negative sequelae."

SOURCE: Berry DA et al. *JAMA* 2006;295(14):1658-67. **Abstract**

We did an unplanned subset analysis evaluating the effects of adding paclitaxel for all patients. A highly significant reduction was observed in the hazard ratio in favor of the taxane group. In the subset of patients who had ER-positive disease, it was not significant. Among the patients with ER-negative disease, the hazard reduction was highly significant and larger than in the overall group (Henderson 2003).

Among the patients with HER2-negative disease, we found little evidence of benefit from paclitaxel compared to the patients with HER2-positive disease, for whom the benefit was much more robust.

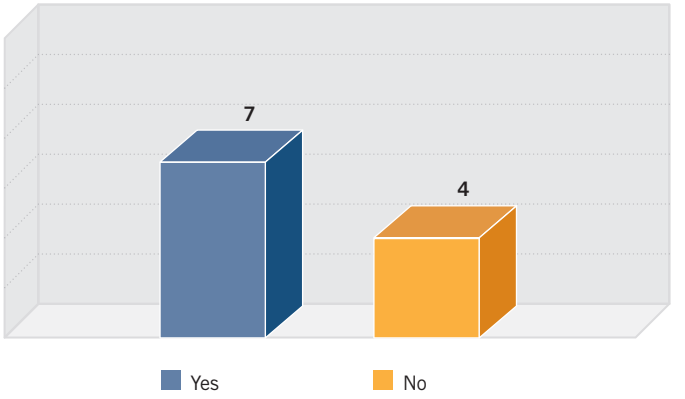
We defined four subsets by HER2 and ER status. In the group with ER-negative and HER2-negative disease, paclitaxel was advantageous. The patients with ER-negative and HER2-positive disease showed a slightly greater benefit (Hayes 2006).

For patients with ER-positive disease, as a whole, paclitaxel did not seem to confer much of an advantage. In the small group of patients with ER-positive and HER2-positive disease, a large advantage was associated with the addition of paclitaxel. Finally, in the patients with ER-positive and HER2-negative disease, no advantage appeared to be associated with the addition of paclitaxel (Hayes 2006).

Patients with ER-positive and HER2-negative tumors who were treated with tamoxifen derived little or no benefit from the addition of paclitaxel. Is HER2 only predictive for paclitaxel or is this applicable to all cytotoxic therapies? My bias — but, of course, we don't have such data — is that this is not a paclitaxel phenomenon but rather a chemotherapy phenomenon.

**FACULTY POLL QUESTION 11**

**Have you utilized dose-dense AC → paclitaxel/trastuzumab in a nonprotocol setting?**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

## CD 2, Track 1

**DR LOVE:** Hope, would you consider adjuvant chemotherapy for an otherwise healthy woman in her eighties with triple-negative disease?

**DR RUGO:** Absolutely, but even more so for the patient with an ER-negative, PR-negative and HER2-positive tumor, for whom we know that recurrence is heavily weighted in the first two or three years. As the survival of our population increases, these 81- and 82-year-old women who don't have major medical problems are reasonable candidates for limited approaches to chemotherapy.

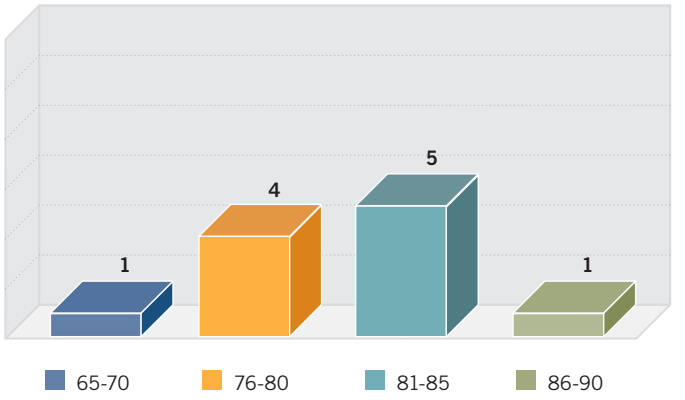
This must be within the limits that we all know to be important, such as understanding morbidities. That's one of the reasons Adjuvant! Online can be very useful in directing physicians who are treating older patients. First, in this older population, the patients with hormone receptor-negative disease are the ones for whom we are going to be thinking about chemotherapy.

Then, in regard to morbidity, if a patient has a major morbidity, such as heart failure, and is not going to be alive in three years, that is not the patient we should be treating with chemotherapy.

**DR HENDERSON:** We often make the assumption that dose-dense therapy

**FACULTY POLL QUESTION 12**

**What is the age of the oldest breast cancer patient in whom you have utilized adjuvant chemotherapy?**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

is more toxic. If anything, it's less toxic. Also, you shorten the duration of chemotherapy, and for patients, this is not a minor issue. The older the patient, the bigger the issue.

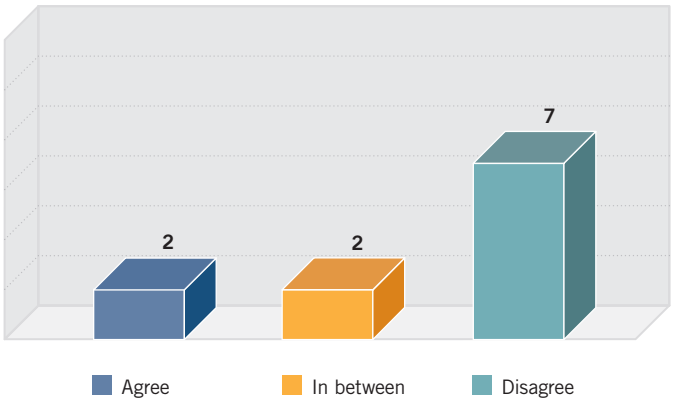
They don't have as long a life expectancy, and they're making a mental trade-off: "How much time am I going to have with a poor quality of life for a benefit?" That's the way they should be looking at it. So duration becomes important. Every time we use a more intensive regimen, we assume it's going to be more toxic. That's one of the surprising results of CALGB-9741. No matter what we compare, it's not necessarily more toxic and may be less so (Citron 2003; Hudis 2005).

**DR HUDIS:** In the quantifiable, objective ways in which we assess toxicity, you cannot support the argument that dose-dense therapy is more toxic. In CALGB-9741, it appears to be equivalent or perhaps less toxic in many ways. The one toxicity that stood out in the original Citron paper was the high rate of packed red blood cell transfusions (Citron 2003), which appears to be abrogated with the use of erythropoietin or darbepoetin as prophylaxis.

It's my subjective opinion that patients stay on schedule more easily when they receive every two-week therapy with growth factor support than when they are treated with an every three-week schedule. When patients can't plan their therapy, it is an annoyance, and it can reduce quality of life.

**FACULTY POLL QUESTION 13**

**Adjuvant taxanes should generally not be utilized in patients with ER-positive, HER2-negative, node-negative tumors.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

Also, completing therapy faster is always worthwhile. We've taken the position that unless we have a compelling reason not to administer a growth factor, we use every two-week therapy for everybody who receives AC and a taxane.

## CD 2, Tracks 4-6

**DR LOVE:** Antonio, can you discuss the study by Chuck Vogel evaluating the use of pegfilgrastim for women with breast cancer?

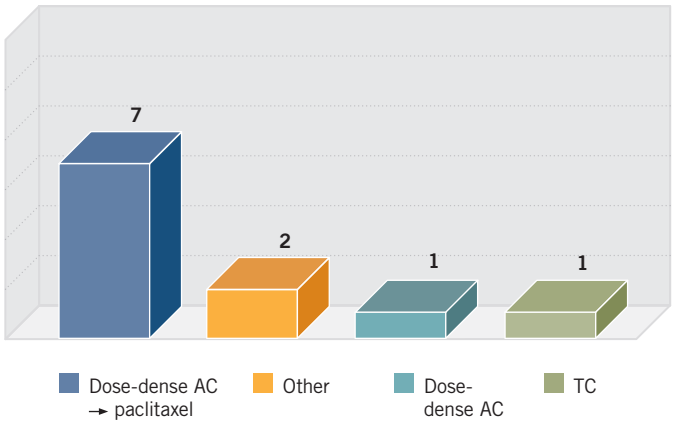
**DR WOLFF:** The study results were published last year in the *JCO*. Patients received docetaxel at 100 mg/m$^2$ every 21 days with pegfilgrastim or placebo. The data demonstrated that pegfilgrastim, compared to placebo, resulted in a significant reduction in the risk of developing febrile neutropenia (17 versus one percent), hospitalization (14 versus one percent) and intravenous anti-infective use (10 versus two percent; [Vogel 2005]).

**DR LOVE:** Can you review the current guidelines for the use of growth factor support?

**DR WOLFF:** Among the commonly used regimens in North America, those with less than a 10 percent risk of febrile neutropenia include AC, CMF and AC followed by paclitaxel every 21 days. The regimens with an intermediate risk (10 to 20 percent) of febrile neutropenia include CEF and the FEC

**FACULTY POLL QUESTION 14**

**A 77-year-old woman in good health presents with an ER-negative, PR-negative, HER2-negative tumor and three positive nodes. She wishes to receive chemotherapy. What would you likely recommend?**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

120. Those with a greater than 20 percent risk of febrile neutropenia include doxorubicin/docetaxel (AT) and TAC (Aapro 2006).

Three clinical practice guidelines have been released in the last year: NCCN (NCCN 2006), ASCO (Smith 2006) and EORTC (Aapro 2006). None of these included a cost analysis because these are very difficult to do. The recommendations are pretty uniform across the three practice guidelines when it comes to the high-risk group — recommending the use of primary prophylaxis with CSFs — and for the low-risk group (less than 10 percent risk of febrile neutropenia) — not recommending the use of primary prophylaxis with CSFs.

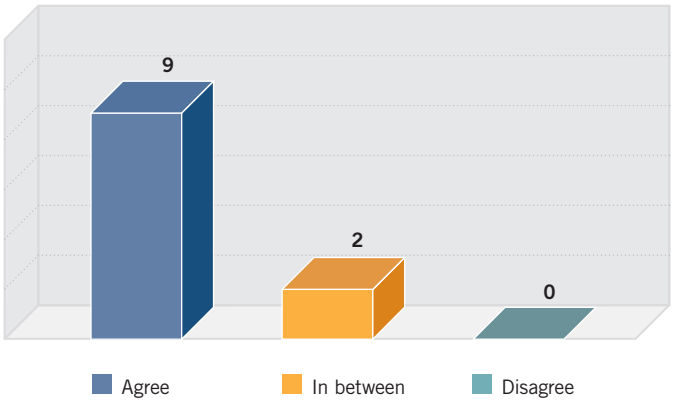
For the intermediate group, the recommendations are nuanced. The NCCN would consider the use of prophylactic CSFs, and the ASCO guidelines would not recommend them but would take into account special circumstances. The EORTC would use individual risk factors.

**DR LOVE:** Where did the threshold of 20 percent come from?

**DR WOLFF:** For the ASCO committee, we had clear evidence from the Vogel study that you were able to reduce the risk from approximately 20 percent (Vogel 2005). I can quote what we wrote in the *JCO* article: "The 2005 Update Committee agreed unanimously that reduction in febrile neutropenia was an important clinical outcome that justified the use of CSFs, regard-

**FACULTY POLL QUESTION 15**

**If an oncologist wishes to use AC → docetaxel as adjuvant therapy, the dose of docetaxel in a patient who can tolerate it should be 100 mg/m² with myeloid growth factor support.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

less of impact on other factors — even economic factors — when the risk of febrile neutropenia is approximately 20 percent and no other equally effective regimen that does not require CSFs is available" (Smith 2006).

The Vogel study included patients with metastatic and early-stage disease. About two thirds of the patients had metastatic disease, and they might have been more sensitive to the risk of neutropenia because of prior exposure to chemotherapy (Vogel 2005). If a study had shown a reduction in the incidence of febrile neutropenia from 10 percent to one percent, it is possible that the threshold might have been listed at 10 percent. ■

### First and Subsequent Cycle Use of Pegfilgrastim

"Patients receiving pegfilgrastim, compared with patients receiving placebo, had a lower incidence of febrile neutropenia (1% v 17%, respectively; $P < .001$), febrile neutropenia–related hospitalization (1% v 14%, respectively; $P < .001$) and use of IV anti-infectives (2% v 10%, respectively; $P < .001$)... .

Early intervention with pegfilgrastim prevents febrile neutropenia by 94% and further prevents hospitalizations and use of IV anti-infectives by 80%. The use of pegfilgrastim with chemotherapy regimens with a moderate rate of febrile neutropenia, such as standard-dose docetaxel and combination docetaxel, doxorubicin, and cyclophosphamide chemotherapy, is warranted."

SOURCE: Vogel CL et al. *J Clin Oncol* 2005;23(6):1178–84. **Abstract**

## SELECT PUBLICATIONS


Aapro MS et al; European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party. **EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours.** *Eur J Cancer* 2006;42(15):2433-53. **Abstract**

Berry DA et al. **Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer.** *JAMA* 2006;295(14):1658-67. **Abstract**

Carlson RW et al. **NCCN Task Force Report: Adjuvant Therapy for Breast Cancer.** *J Natl Compr Canc Netw* 2006;4(Suppl 1):1-26. **Abstract**

Citron ML et al. **Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741.** *J Clin Oncol* 2003;21(8):1431-9. **Abstract**

Crown JP et al. **Docetaxel (T) given concurrently with or sequentially to anthracycline-based (A) adjuvant therapy (adjRx) for patients (pts) with node-positive (N+) breast cancer (BrCa), in comparison with non-T adjRx: First results of the BIG 2-98 Trial at 5 years median follow-up (MFU).** *Proc ASCO* 2006;**Abstract LBA519**.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005;365(9472):1687-717. **Abstract**

Hayes DF et al. **HER2 predicts benefit from adjuvant paclitaxel after AC in node-positive breast cancer: CALGB 9344.** Presentation. *Proc ASCO* 2006;**Abstract 510**.

Henderson IC et al. **Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer.** *J Clin Oncol* 2003;21(6):976-83. **Abstract**

Hudis C et al. **Five year follow-up of INT C9741: Dose-dense (DD) chemotherapy (CRx) is safe and effective.** San Antonio Breast Cancer Symposium 2005;**Abstract 41**.

Jones SE et al. **Final analysis: TC (docetaxel/cyclophosphamide, 4 cycles) has a superior disease-free survival compared to standard AC (doxorubicin/cyclophosphamide) in 1016 women with early stage breast cancer.** San Antonio Breast Cancer Symposium 2005;**Abstract 40**.

Mamounas EP et al. **Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: Results from NSABP B-28.** *J Clin Oncol* 2005;23(16):3686-96. **Abstract**

Martin M et al; Breast Cancer International Research Group 001 Investigators. **Adjuvant docetaxel for node-positive breast cancer.** *N Engl J Med* 2005;352(22):2302-13. **Abstract**

National Comprehensive Cancer Network (NCCN®). **NCCN clinical practice guidelines in oncology, myeloid growth factors — Version 1.** 2006. Available at: **nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf**.

Perez EA. **TAC — A new standard in adjuvant therapy for breast cancer?** *N Engl J Med* 2005;352(22):2346-8. No abstract available

Smith TJ et al. **2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline.** *J Clin Oncol* 2006;24(19):3187-205. **Abstract**

Sparano JA et al. **Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: Results of North American Breast Cancer Intergroup Trial E1199.** San Antonio Breast Cancer Symposium 2005;**Abstract 48**.

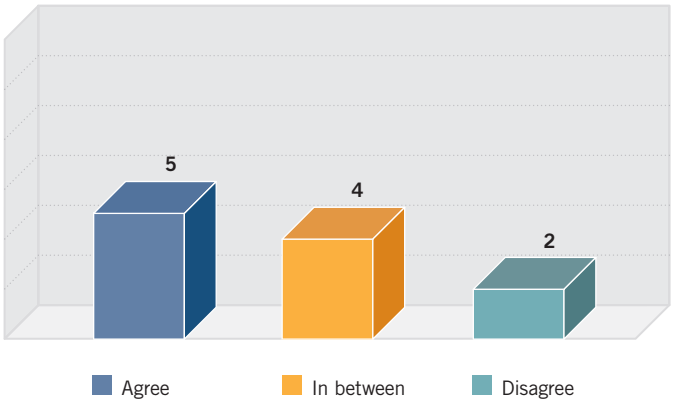
Vogel CL et al. **First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study.** *J Clin Oncol* 2005;23(6):1178-84. **Abstract**

SECTION 6

## Cardiac Toxicity Associated with Anthracycline-Based Chemotherapy (Nonanthracycline Alternatives)

**FACULTY POLL QUESTION 16**

**Docetaxel/cyclophosphamide (TC) is generally a preferable regimen to AC.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

### Select Excerpts from the Discussion

**CD 2, Tracks 8-10**

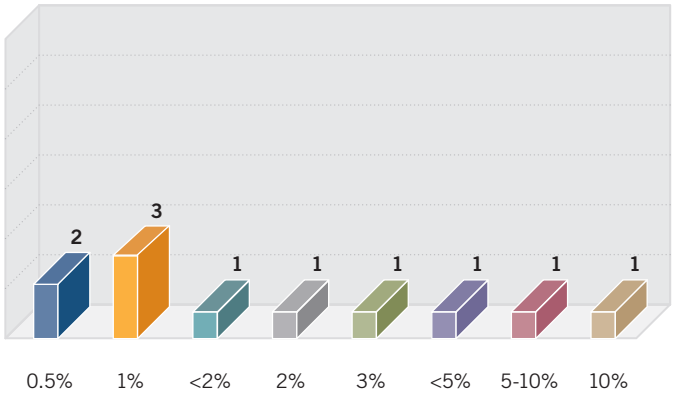
**DR LOVE:** Antonio, can you comment on the two presentations made at ASCO 2006 evaluating the cardiac toxicity associated with anthracyclines?

**DR WOLFF:** Sharon Giordano and her colleagues at MD Anderson conducted a population-based observation study using the SEER-Medicare database. The study included women 66 to 90 years of age who were diagnosed with breast cancer from 1992 to 1999 and who had no other tumors or history of congestive heart failure (CHF; [Giordano 2006]).

They ultimately identified about 31,000 women and separated them into three groups: about 27,000 who received no adjuvant chemotherapy, about 2,300 who received nonanthracycline adjuvant chemotherapy and about 1,600 who received anthracycline-based adjuvant chemotherapy. The mean age of these women was 75 years, and the mean follow-up was 68 months. The patients who received an anthracycline had higher-risk tumors (Giordano 2006).

**FACULTY POLL QUESTION 17**

**A 60-year-old woman has well-controlled hypertension. What would you tell her the risk of heart failure is for four courses of AC (240 mg/m²)?**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

They separated the patients into two specific age groups — 66 to 70 years and 71 to 90 years — and evaluated the 10-year outcomes in terms of the diagnosis of CHF using ICD9 codes.

They observed that women aged 66 to 70 years who did not receive adjuvant chemotherapy had a 73 percent chance of being free of CHF, whereas those who received chemotherapy without an anthracycline had a 74 percent chance (Giordano 2006).

On the other hand, those who received an anthracycline had a 61 percent chance of being free of CHF, which is a 13 percent absolute difference at 10 years (Giordano 2006). Factors such as hypertension, diabetes mellitus, coronary artery disease and peripheral vascular disease were significant in identifying patients at risk.

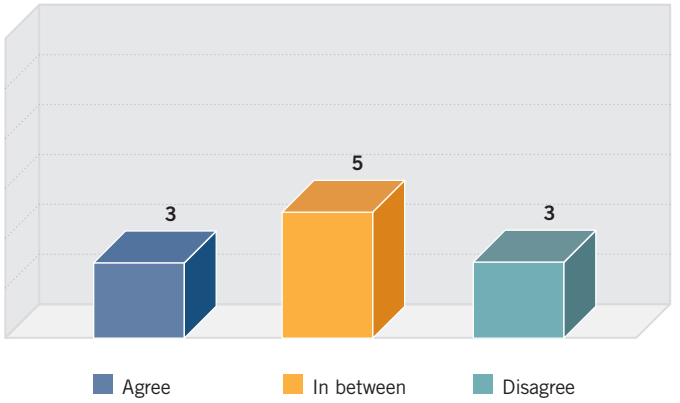
Among the women aged 71 to 90 years, no difference was seen in the incidence of CHF. The question was whether there was a selection bias or whether those patients receiving an anthracycline had lower doses of chemotherapy. However, individual records for those patients were not available.

The Shepherd study was an analysis of the MA5 trial, which included 710 pre- or perimenopausal women with node-positive breast cancer who received CEF with a cumulative epirubicin dose of 720 mg/m² or CMF.

These women received strict follow-up in terms of LVEF, which was measured at baseline, six, 12, 36 and 60 months (Shepherd 2006).

**FACULTY POLL QUESTION 18**

**The risk of cardiac failure should be discussed with all patients being considered for adjuvant chemotherapy, and most patients with node-negative tumors should be offered nonanthracycline regimens as one option.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

At the end of 60 months, 25 percent of the women treated with CEF had at least a 10 percent absolute decrease in ejection fraction, whereas approximately nine percent of the women treated with CMF had at least a 10 percent decrease.

When they assessed the women with a greater than 20 percent decrease in LVEF, the incidence was five percent in the CEF group and less than one percent in the CMF group (Shepherd 2006).

In terms of the number of women with an LVEF that went below 50 percent, the decrease was 17 percent for the CEF group and two percent for the CMF group.

Among the women who had a greater than 20 percent reduction in LVEF, only four cases of Grade III/IV CHF in the CEF group and no cases in the CMF group were observed (Shepherd 2006). Hence, what exactly is the long-term significance of these reductions in ejection fraction if most of them are asymptomatic?

**DR HENDERSON:** We have to be very careful with these data. The presentation from Shepherd is compelling and would be the basis of my recommendations. Ideally, these numbers should be risk adjusted, but I don't believe they were. The Giordano study, however, is misleading.

**DR LOVE:** What would you estimate the risk of heart failure to be for a 60-

year-old woman with well-controlled hypertension who receives four courses of AC?

**DR HENDERSON:** I would use about two percent as my estimate. I don't know what to say about the decrease in LVEF. You need to explain that to the patient, and you need to discuss both of those numbers. Obviously, CHF is the important one, but with the high frequency of LVEF decline, the story isn't over yet. You have to assume that if you follow these patients another 10 years, the one percent is going to become two or three percent.

**DR RUGO:** Based on the epirubicin data (Shepherd 2006), I'm still unclear about whether we would tell somebody who's receiving four cycles of AC that they have a greater than one percent risk of cardiac damage. I don't believe we know how to judge the cardiac-damage risk for patients with well-controlled, mild hypertension.

Again, we're not sure that hypertension, as a preexisting condition, increases the long-term risk of CHF from an anthracycline. We don't know that from the Medicare database yet. It seems to me that one percent is a reasonable number.

**DR GEYER:** I had answered 0.5 percent based on the NSABP toxicity tables and assuming you meant Grade III/IV heart failure. That's key to answering that question. Grade III/IV toxicity is consistently around 0.5 percent for four courses of AC. I have been telling patients, since watching the NSABP-B-31 cardiac data for AC → paclitaxel, that their chance of having a decline in their ejection fraction is around five or six percent.

This is why I like that we're backing off using chemotherapy for our patients with node-negative disease. I've been worrying about the use of anthracyclines for patients with ER-positive disease. I was the last person to stop using CMF in the United States because of my concern about anthracycline cardiotoxicity.

## CD 2, Track 12

**DR LOVE:** Joyce, in terms of nonanthracycline options, can you discuss the US Oncology trial Steve Jones reported comparing docetaxel/cyclophosphamide (TC) to AC in the adjuvant setting?

**DR O'SHAUGHNESSY:** It was a randomized trial comparing four cycles of either AC or TC with docetaxel at 75 mg/m$^2$. The bottom line at five years for disease-free survival, the primary endpoint, was 86 percent with TC and 80 percent with AC for a hazard ratio of 0.67 and a *p*-value of 0.015.

For overall survival, a three percent absolute improvement at five years in favor of the TC was observed. The hazard ratio was 0.76, which was trending toward significance but not statistical significance (Jones 2005).

Steve's concluding slide stated that TC should now be considered a standard

nonanthracycline adjuvant regimen for patients with operable breast cancer (Jones 2005). I agree. In my practice, I don't use AC anymore as a four-cycle regimen. I've switched over to TC. When I'm going to use four cycles for patients with lower-risk, ER-positive, node-negative disease, I use TC.

## CD 2, Track 13

**DR LOVE:** Debu, what are your thoughts about nonanthracycline regimens?

**DR TRIPATHY:** Cardiac issues are clearly important, and we underestimate this risk. After decades of attention to heart disease in this country, it's no surprise that patients are concerned. So we need regimens that are less cardiotoxic.

We don't know the long-term history for cardiac toxicity because we've never measured it systematically and it's a hard thing to measure. When you consider population-based studies, you may overestimate it because a lot of people are probably misclassified. When you consider clinical trials, you may underestimate it because of selection bias of the patients enrolled.

The TC regimen is a reasonable nonanthracycline regimen. It was a smaller study, so our level of confidence is lower, but at least everything pointed in the right direction. Despite the limitations of being a small study, being spread out over a large period of time and having broad eligibility criteria, it did show that TC is as good or probably even better than AC (Jones 2005). For patients with cardiac risk factors, it's a reasonable regimen to use.

**DR LOVE:** For patients who don't have cardiac risk factors, do you think TC should be brought up as an option?

**DR TRIPATHY:** I believe it can be. When I look at the overall toxicity profile, it's hard for me to figure out which was better tolerated because the spectrum of toxicities was different. The TC regimen had more hematologic toxicities and edema, whereas the AC regimen had more GI and cardiac toxicities.

**DR O'SHAUGHNESSY:** We observed one case of CHF in the AC arm and zero in the TC arm. We didn't do a lot of monitoring.

**DR LOVE:** Peter, what are your thoughts about TC?

**DR RAVDIN:** If we had started with TC, we wouldn't be going across to AC based on the results of this trial. The US Oncology trial is of modest size, and it shows a statistically significant disease-free survival and the same size overall survival. It's simply underpowered to make statistical significance (Jones 2005).

I would anticipate that, over the next couple of years, people who want to use a short 12-week regimen will be using TC much more frequently than a year ago.

With regard to the cardiac toxicity, I agree that the SEER analysis with

Medicare records wasn't absolutely convincing. Among other things, the numbers seemed high. I would like to know what those numbers are in a general population, but we have a major problem with the ascertainment of late toxicity in clinical trials. ■

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Bast A et al. **Protectors against doxorubicin-induced cardiotoxicity: Flavonoids.** *Cell Biol Toxicol* 2006;[Epub ahead of print]. **Abstract**

Dang C et al. **Preliminary cardiac safety results of dose-dense (DD) doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) with trastuzumab (H) in HER2/neu overexpressed/amplified breast cancer (BCA).** Poster. San Antonio Breast Cancer Symposium 2005;**Abstract 2041**.

Elkin EB et al. **Adjuvant chemotherapy and survival in older women with hormone receptor-negative breast cancer: Assessing outcome in a population-based, observational cohort.** *J Clin Oncol* 2006;24(18):2757-64. **Abstract**

Giordano SH et al. **Congestive heart failure (CHF) in older women treated with anthracycline (A) chemotherapy (C).** Presentation. *Proc ASCO* 2006a;**Abstract 521**.

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Muss HB et al; Cancer and Leukemia Group B. **Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer.** *JAMA* 2005;293(9):1073-81. **Abstract**

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Seidman AD. **Systemic treatment of breast cancer. Two decades of progress.** *Oncology (Williston Park)* 2006;20(9):983-90. **Abstract**

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Silliman RA, Ganz PA. **Adjuvant chemotherapy use and outcomes in older women with breast cancer: What have we learned?** *J Clin Oncol* 2006;24(18):2697-9. No abstract available

Villani F et al. **Non-invasive monitoring of cardiac hemodynamic parameters in doxorubicin-treated patients: Comparison with echocardiography.** *Anticancer Res* 2006;26(1B):797-801. **Abstract**

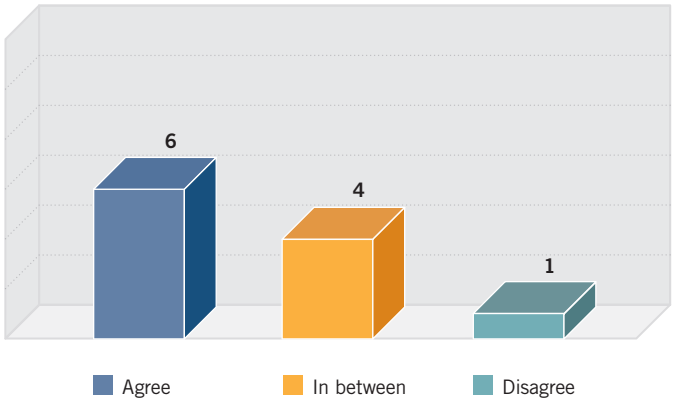
Youssef G, Links M. **The prevention and management of cardiovascular complications of chemotherapy in patients with cancer.** *Am J Cardiovasc Drugs* 2005;5(4):233-43. **Abstract**

SECTION 7

## Trastuzumab as Adjuvant Therapy for HER2-Positive Breast Cancer

**FACULTY POLL QUESTION 19**

**Trastuzumab monotherapy is a reasonable clinical option for patients who are unfit to receive chemotherapy.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

### Select Excerpts from the Discussion

**CD 2, Track 14**

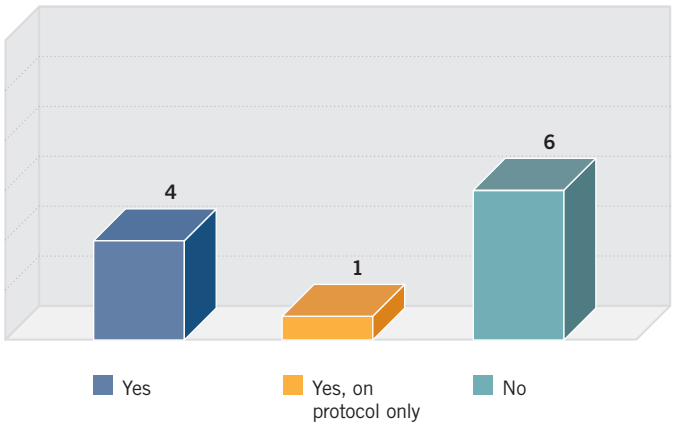
**DR LOVE:** Cliff, can you comment on the updated results from the HERA trial that were presented at ASCO 2006 by Ian Smith?

**DR HUDIS:** I was struck that the hazard for recurrence actually "blipped" upward after the year of trastuzumab ended (Smith 2006). I believe that leaves the door wide open that prolonged treatment may be better than stopping after one year.

Many were excited because of the FinHer data, which demonstrated that nine weeks of trastuzumab significantly lowered the risk of recurrence or death (Joensuu 2006). I'm not disputing that result. However, we don't have the data for two years versus one year of trastuzumab, and the hazard for recurrence went up at the end of the first year when trastuzumab was stopped. It may not turn out to be anything, but I thought it was provocative. That was the most interesting slide Ian Smith showed.

**FACULTY POLL QUESTION 20**

**Have you used TCH as adjuvant therapy in a patient with a HER2-positive tumor?**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

## CD 2, Track 17

**DR LOVE:** Craig, do you think trastuzumab without chemotherapy has a role for the older, frail patient?

**DR HENDERSON:** I would be willing to consider it, but I certainly wouldn't give it much credence. I believe the data on the synergy of trastuzumab and chemotherapy, both preclinical and clinical, are too compelling to spend much time on that for the vast majority of patients.

**DR LOVE:** Chuck, for an 82-year-old patient with an ER-negative, PR-negative, HER2-positive tumor, would you present the option of trastuzumab monotherapy?

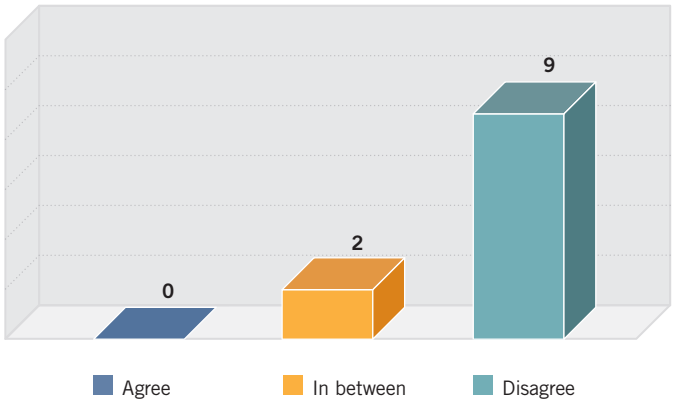
**DR GEYER:** I don't believe that's unreasonable. Again, I would have to be convinced that chemotherapy was not indicated for that patient.

**DR WOLFF:** One way to avoid this problem for an elderly person, for whom you're concerned about the potential for cardiac toxicity, might be to use a nonanthracycline regimen. You could use TCH, for which we have data (Slamon 2005).

Or, if you're concerned about the toxicity associated with the higher doses of docetaxel, you may create a regimen. One I can think of is weekly paclitaxel

**FACULTY POLL QUESTION 21**

**Breast cancers that are HER2-positive should be subjected to assays of TOPO II, which should be used to select chemotherapy regimens to combine with trastuzumab, specifically whether to include an anthracycline.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

for 12 weeks with trastuzumab, which is highly tolerable in most patients. You may be obtaining synergism from the chemotherapy/trastuzumab combination and avoiding the anthracycline cardiotoxicity, although we have no data for that.

**DR CHLEBOWSKI:** We tried to use TCH for an 83-year-old woman who had a 7-cm fungating lesion with palpable lymphadenopathy. She didn't tolerate the chemotherapy, and we stopped it. Her tumor was shrinking, so we continued with three more cycles of trastuzumab.

At surgery, she showed a pathological complete response in the breast and lymph nodes. That's the first time I've ever seen a patient with a fungating lesion have a pathological complete response.

**DR LOVE:** Joyce, have you used adjuvant trastuzumab as monotherapy?

**DR O'SHAUGHNESSY:** I usually try to sneak in a little low-dose weekly paclitaxel for patients with comorbidities. I saw a patient recently who was extremely elderly, and I was considering an aromatase inhibitor and trastuzumab alone for her.

## CD 2, Track 18

**DR GEYER:** I must bring up Soon Paik's data with cMYC, because the data are remarkable. The patients with coamplified tumors who receive chemo-

therapy alone do very poorly, whereas we're still waiting for a recurrence after two years with the addition of trastuzumab. The separation of those curves and their plateaus suggest that something important is going on. Among the patients without cMYC amplification, we're seeing the curves separate, but they look like typical chemotherapy curves in that we're continuing to see recurrences even with trastuzumab (Kim 2005).

## CD 2, Track 19

**DR LOVE:** Debu, is the TOPO II assay something that could be considered in clinical decision-making at this point?

**DR TRIPATHY:** We've known for years that TOPO II overexpression confers sensitivity to anthracyclines. This has been shown in cell-line models dating back 10 to 15 years. Now we see that TOPO II amplification seems to predict a better response to anthracyclines, and the lack of TOPO II amplification might mean that anthracyclines are not as important (Slamon 2005; Press 2005).

TOPO II is carrying more weight now. I would like to see the results from BCIRG 006 replicated in data sets from HERA and the NSABP and Intergroup studies. That should be imminently doable, and from what I understand, plans are underway.

My guess is that TOPO II amplification will end up being significant. I don't believe it's the only factor, but I do believe that it will enter into clinical utility.

I expect cases will arise in which we want to withhold an anthracycline and maybe use a taxane and trastuzumab. It's not ready for prime time use, but it should be soon. ■

### SELECT PUBLICATIONS


Joensuu H et al; FinHer Study Investigators. **Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer.** *N Engl J Med* 2006;354(8):809-20. **Abstract**

Kim C et al. **Trastuzumab sensitivity of breast cancer with co-amplification of HER2 and cMYC suggests pro-apoptotic function of dysregulated cMYC in vivo.** Presentation. San Antonio Breast Cancer Symposium 2005;**Abstract 46**.

Press MF et al. **Topoisomerase II-alpha gene amplification as a predictor of responsiveness to anthracycline-containing chemotherapy in the Cancer International Research Group 006 clinical trial of trastuzumab (Herceptin) in the adjuvant setting.** San Antonio Breast Cancer Symposium 2005;**Abstract 1045**.

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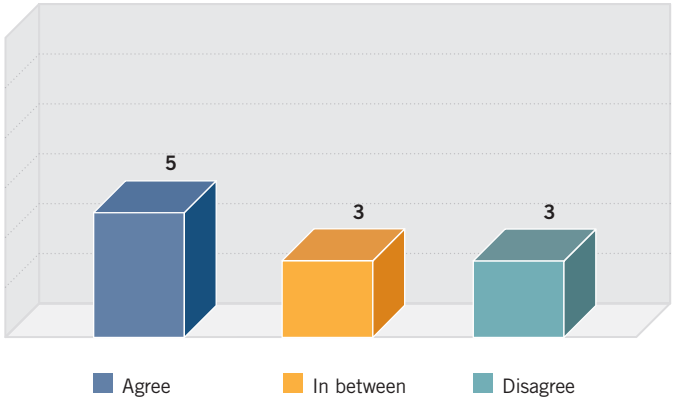
Smith IE. **Trastuzumab following adjuvant chemotherapy in HER2-positive early breast cancer (HERA trial): Disease-free and overall survival after 2 year median follow-up.** Presentation. *Proc ASCO* 2006. Late-breaking scientific session. **Abstract**

FACULTY POLL QUESTION 22

**Docetaxel/trastuzumab is a preferable treatment compared to docetaxel/carboplatin/trastuzumab for metastatic HER2-positive disease.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

## Select Excerpts from the Discussion

### CD 2, Tracks 20-25

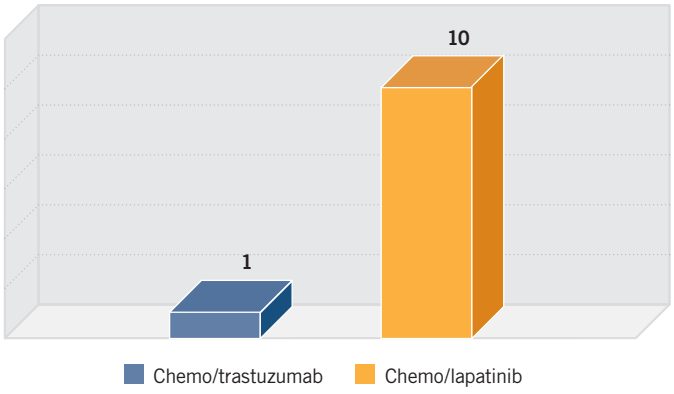
**DR LOVE:** Chuck, can you review the results from the lapatinib trial you presented at ASCO 2006?

**DR GEYER:** This was a Phase III trial comparing the approved dose of capecitabine as the control arm to the Phase I combination dose of 2,000 mg/m$^2$ of capecitabine per day on days one to 14 of 21 days with 1,250 mg of lapatinib per day continuously. The patient population included women with breast cancer who had received prior anthracycline, taxane and trastuzumab therapy. They were not allowed, however, to have received prior capecitabine (Geyer 2006).

When the Independent Data Monitoring Committee (IDMC) reviewed the data, they recommended early closure of the trial because the boundary had been crossed for superiority. The median time to progression was improved from about 4.5 to 8.5 months. The response rate was also increased from 14 to

**FACULTY POLL QUESTION 23**

**Cost and reimbursement issues aside, and assuming lapatinib were available for clinical use, how would you generally manage a patient who developed metastatic disease nine months after completing adjuvant therapy with AC → paclitaxel/trastuzumab (one year)?**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

22 percent, but it did not meet statistical significance (Geyer 2006).

An interest with lapatinib is the potential impact it might have in reducing CNS events, and this was tracked. Numerically fewer — four versus 11 — CNS relapses were recorded in the lapatinib arm. But too few total events occurred to make any definitive statement (Geyer 2006).

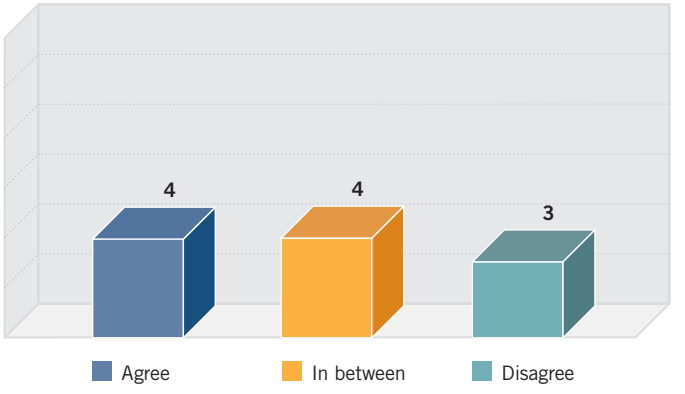
Toxicity was a concern because we saw overlapping toxicity. With the combination, we saw overall increases in diarrhea, hand-foot syndrome and skin rashes but virtually no Grade IV toxicities. The Grade III toxicities weren't appreciably different. So the concern about additive toxicity with lapatinib and capecitabine wasn't borne out (Geyer 2006).

Because of the cardiotoxicity issue with HER2 blockade, careful cardiac monitoring was provided. Patients underwent scans every six weeks for the first six months and then every 12 weeks. Conservative criteria were used to define a cardiac event (Geyer 2006).

Patients who had symptomatic heart failure, obviously, would have been considered as having an event. Also patients who had asymptomatic declines with a relative decrease of more than 20 percent from baseline to below normal were considered to have had an event. On the study, four cardiac events occurred with lapatinib/capecitabine and one with capecitabine alone, and all were asymptomatic (Geyer 2006).

**FACULTY POLL QUESTION 24**

**(Your prediction...) Clinical trials will eventually demonstrate that for patients progressing with metastatic disease on a chemo/trastuzumab regimen, another chemotherapy combined with trastuzumab/lapatinib will prove more efficacious than another chemotherapy combined with either trastuzumab or lapatinib.**




SOURCE: Survey of Think Tank Participants, June 21, 2006, Miami, Florida.

**DR LOVE:** Debu, what is your opinion of lapatinib and where it's heading?

**DR TRIPATHY:** It was interesting that this study showed almost a doubling of time to disease progression without a concomitant increase in response rate that was significantly different (Geyer 2006). I believe this is going to be a very important drug in this population of patients.

One can extend this even further and ask whether it will delay time to disease progression in patients with HER2-positive disease as up-front or adjuvant therapy.

**DR WOLFF:** One question posed after the presentation was whether this study could indirectly be addressing a question we have been unable to answer: Is the continuation of anti-HER2 therapy truly important for the patient whose disease is progressing on first-line anti-HER2 therapy?

The study that could never be done was for patients who were receiving paclitaxel and trastuzumab, and at progression they were randomly assigned to vinorelbine with trastuzumab or vinorelbine alone.

This study essentially asks, for the patient whose disease is progressing on trastuzumab, is switching to another chemotherapy drug but continuing an anti-HER2 therapy — in this case, lapatinib — better than not continuing the targeted therapy?

The answer in this case is yes. How much of this is an effect of lapatinib itself, as a drug that is active in patients whose disease has progressed on trastuzumab, and how much of it is simply a continuation of anti-HER2 therapy?

**DR LOVE:** Joyce, for a patient who experiences progression after receiving adjuvant trastuzumab, would you reinstitute trastuzumab? How would you factor in lapatinib if it were available?

**DR O'SHAUGHNESSY:** I haven't had to cross that bridge yet, but I believe it would depend on the disease-free interval. If it was very brief, I'd be inclined to use lapatinib, but it's important to find out whether we need trastuzumab to maximize the effectiveness of lapatinib.

If patients have had a decent disease-free interval, they obviously are somewhat resistant to trastuzumab but they still may retain some sensitivity. I believe the randomized trial being conducted of lapatinib alone versus lapatinib with trastuzumab is very important.

**DR RUGO:** That trial that Dr Geyer presented is interesting because it requires that patients receive two prior chemotherapy regimens and trastuzumab for metastatic disease. It's not testing what to do if a patient has relapsed within a year of adjuvant therapy.

Another trial is testing the combination of trastuzumab and lapatinib with paclitaxel, but the patients are not allowed to have relapsed on adjuvant trastuzumab. They have to be off it. They are randomly assigned to paclitaxel/trastuzumab with or without lapatinib as first-line therapy.

All these trials are going on now, and we're not going to have results for a while. Right now we have to finalize the neoadjuvant and adjuvant trial designs, which are incredibly controversial. Opinions vary tremendously.

**DR LOVE:** Cliff, can you comment on some of the options that are being discussed for the next generation of adjuvant trials for patients with HER2-positive disease?

**DR HUDIS:** The Aphrodite trial is currently written as one year of trastuzumab, one year of lapatinib, one year of trastuzumab with lapatinib or a sequence of trastuzumab for six months followed by lapatinib for six months. The neo-Aphrodite trial tries to investigate the biology by administering trastuzumab or lapatinib alone or the combination before surgery, following with the remainder of a year of treatment.

In the cooperative groups, the North Central proposal that is currently being worked on is built on the same themes of single-agent lapatinib versus single-agent trastuzumab versus the combination. We have a preoperative proposal matching that, which uses preoperative trastuzumab, lapatinib or the combination along with weekly paclitaxel for a fixed period of time. It provides a chance to observe the pathway markers and markers of resistance.

The big controversy is whether people are brave enough, as those planning

the Aphrodite trial appear to be, to commit to a year of lapatinib without any trastuzumab for a patient with HER2-positive, early-stage disease. That's either brilliant or a leap of faith.

**DR GEYER:** The NSABP and the CIRG have agreed to work together on our B-31 replacement and their BCIRG 006 replacement study, with the idea of testing chemotherapy/trastuzumab with or without bevacizumab as the question. We are waiting for more information from the pilot data to reach consensus on some of the chemotherapy backbone issues, and we hope to have the study out by the end of the year. ■

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Burris HA 3rd. **Dual kinase inhibition in the treatment of breast cancer: Initial experience with the EGFR/ErbB-2 inhibitor lapatinib.** *Oncologist* 2004;9(Suppl 3):10-5. **Abstract**

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Carlson RW et al; NCCN HER2 Testing in Breast Cancer Task Force. **HER2 testing in breast cancer: NCCN Task Force report and recommendations.** *J Natl Compr Canc Netw* 2006;4(Suppl 3):1-22. **Abstract**

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Hortobagyi GN. **Trastuzumab in the treatment of breast cancer.** *N Engl J Med* 2005;353(16):1734-6. No abstract available

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Piccart-Gebhart MJ et al; Herceptin Adjuvant (HERA) Trial Study Team. **Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1659-72. **Abstract**

Pietras RJ et al. **Remission of human breast cancer xenografts on therapy with humanized monoclonal antibody to HER-2 receptor and DNA-reactive drugs.** *Oncogene* 1998;17(17):2235-49. **Abstract**

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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(3):719-26. **Abstract**

**QUESTIONS (PLEASE CIRCLE ANSWER):**

1. **ECOG-E2100 evaluated a combination of bevacizumab with _____ as first-line therapy for women with metastatic breast cancer.**
   a. Capecitabine
   b. Paclitaxel
   c. Docetaxel
   d. Gemcitabine
   e. None of the above

2. **In a Phase III randomized trial reported by Dr Miller, capecitabine/bevacizumab demonstrated a significant improvement in _____ compared to capecitabine alone.**
   a. Overall survival
   b. Progression-free survival
   c. Response rate
   d. All of the above
   e. None of the above

3. **Among patients receiving docetaxel at 100 mg/m$^2$ every 21 days, the use of pegfilgrastim results in a significant reduction in _____.**
   a. Febrile neutropenia
   b. Hospitalizations related to febrile neutropenia
   c. Use of intravenous anti-infectives
   d. All of the above
   e. None of the above

4. **NSABP-B-38 will help determine whether dose-dense AC → paclitaxel is superior to which of the following regimens in the adjuvant setting?**
   a. Docetaxel/capecitabine
   b. TAC
   c. Dose-dense AC → TG
   d. Both b and c
   e. None of the above

5. **In a retrospective analysis of three CALGB adjuvant trials conducted by Don Berry, patients with _____ breast cancer were found to derive the most benefit from the investigational adjuvant chemotherapy regimens.**
   a. ER-positive
   b. ER-negative
   c. HER2-positive
   d. HER2-negative

6. **An unplanned subset analysis of CALGB-9344 indicated that patients with HER2-positive disease derived a benefit from the addition of paclitaxel irrespective of the patient's ER status.**
   a. True
   b. False

7. **In a retrospective analysis of the SEER-Medicare database, women (66 to 70 years of age) who received an adjuvant anthracycline demonstrated a greater risk of developing CHF compared to those who received a nonanthracycline-containing adjuvant regimen.**
   a. True
   b. False

8. **What was the duration of therapy with adjuvant trastuzumab in the FinHer trial?**
   a. Two years
   b. One year
   c. Six months
   d. Nine weeks

9. **The updated HERA trial results definitively determined that two years of adjuvant trastuzumab is significantly superior to one year of adjuvant trastuzumab.**
   a. True
   b. False

10. **In a group of women with previously treated, HER2-positive metastatic breast cancer, the addition of lapatinib to _____ _____ nearly doubled the median time to progression.**
    a. Doxorubicin
    b. Paclitaxel
    c. Docetaxel
    d. Capecitabine
    e. Gemcitabine

11. **Among patients with node-negative, ER-positive breast cancer and a high Onco*type* DX recurrence score, chemotherapy was shown to reduce the risk of metastatic disease by _____.**
    a. One third
    b. Two thirds
    c. One half

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

## EVALUATION FORM

## *Breast Cancer Update* — Think Tank Issue 2, 2006

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

**Please answer the following questions by circling the appropriate rating:**

| 5 = Outstanding | 4 = Good | 3 = Satisfactory | 2 = Fair | 1 = Poor | N/A = Not applicable to this issue of *BCU* |
|---|---|---|---|---|---|

### GLOBAL LEARNING OBJECTIVES

**To what extent does this issue of *BCU* address the following global learning objectives?**

- Critically evaluate the clinical implications of emerging clinical trial data in breast cancer treatment and incorporate these data into management strategies in the adjuvant, neoadjuvant, metastatic and preventive settings. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Counsel postmenopausal patients with ER-positive breast cancer about the risks and benefits of adjuvant aromatase inhibitors and of switching to or sequencing aromatase inhibitors after tamoxifen, and counsel premenopausal women about the risks and benefits of adjuvant ovarian suppression alone or with other endocrine interventions. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for HER2 testing and treatment of HER2-positive breast cancer in the adjuvant, neoadjuvant and metastatic settings. . . . . 5 4 3 2 1 N/A
- Evaluate the emerging data on various adjuvant chemotherapy approaches, including dose-dense treatment and the use of taxanes, and explain the absolute risks and benefits of adjuvant chemotherapy regimens to patients. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients with metastatic disease about selection and sequencing of endocrine therapy and chemotherapies and about the risks and benefits of chemotherapeutic agents and combinations . . . . . 5 4 3 2 1 N/A
- Describe the computerized risk models and genetic markers to determine prognostic information on the quantitative risk of breast cancer relapse, and when applicable, utilize these to guide therapy decisions. . . . . 5 4 3 2 1 N/A

### OVERALL EFFECTIVENESS OF THE FACULTY MEMBERS

To what extent do you feel the faculty members' comments were helpful or not helpful?

. . . . . .

. . . . . .

. . . . . .

### OVERALL EFFECTIVENESS OF THE ACTIVITY

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

### EFFECTIVENESS OF THE SPECIFIC SEGMENTS OF THIS PROGRAM

Which of the modules did you find particularly relevant to your practice? Please elaborate on what about the topics and comments was helpful to you.

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## EVALUATION FORM

### *Breast Cancer Update* — Think Tank Issue 2, 2006

**REQUEST FOR CREDIT — please print clearly**

Name: ..... Specialty: .....

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**Research To Practice designates this educational activity for a maximum of 3.25 *AMA PRA Category 1 Credit(s)™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.**

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

Signature: ..... Date: .....

**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:**

.....

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

.....

**What other faculty would you like to hear interviewed in future educational programs?**

.....

**Additional comments about this activity:**

.....

**FOLLOW-UP**

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

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

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

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

BCUTT06

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