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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CME Certified

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STATEMENT OF NEED/TARGET AUDIENCE

Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from 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 — clinicians must be well informed of these advances. To bridge the gap between research and patient care, the program features discussions with leading oncology investigators. By providing access to the latest research developments and expert perspectives, this CME program assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Select appropriate adjuvant therapy for patients with HER2-positive breast cancer, based on tumor characteristics and the risk-benefit profiles of the treatments.
- Evaluate the potential clinical utility of newly emerging technologies to assess ER and HER2 status of breast tumors.
- Incorporate results from the Onco*type* DX™ assay, along with other prognostic factors, into clinical decisions regarding adjuvant chemotherapy regimens for patients with node-negative and node-positive breast cancer.
- Assess the emerging data on novel chemotherapy and biologic agents, and determine if these treatments should be used for appropriate patients with metastatic breast cancer.
- Evaluate emerging breast cancer clinical trial data, and determine how the data should be applied to clinical practice.
- Counsel appropriately selected patients about the option of participating in ongoing clinical trials, based on an awareness of the latest research.

PURPOSE OF THIS ISSUE OF *BREAST CANCER UPDATE*

The purpose of this special edition of *Breast Cancer Update* is to support the learning objectives by offering the perspectives of Drs Carlson, Geyer, Gralow, Hudis, Mackey, Muss, Paik, Perez, Robert, Smith and Wolff on the integration of emerging clinical research data into the management of breast cancer.

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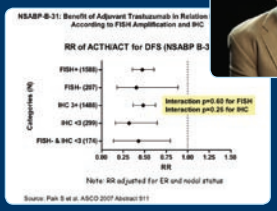

This Think Tank program includes a special multimedia enhancement of the presentation by Dr Soonmyung Paik and the debate that followed. To view, read or listen to these discussions please go to www.BreastCancerUpdate.com/Video08Paik

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Select Excerpts from the Discussion

Controversies in adjuvant hormonal therapy

Track 22

DR LOVE: Hy, how are you approaching postmenopausal patients who have received prior adjuvant tamoxifen? How long can a patient be off tamoxifen for you to be comfortable starting an aromatase inhibitor — three years, four years, even five years after tamoxifen?

DR MUSS: Five years may be pushing it, although patients have had late relapses at that point. One of the MA17 papers evaluated hazard ratios over time. In MA17, patients randomly assigned to the placebo arm had the option of receiving letrozole after the trial was unblinded.

Paul Goss has published those data, which are hard to evaluate for survival because patients weren't randomly assigned to the treatment, but they seem to show that starting letrozole even several years later may be beneficial (Goss 2008; [1.1]).

That being said, it's a proportional benefit. In an elderly person with a low-grade, node-negative tumor, I don't believe it will be especially helpful. Judy Ann Chapman showed some of the causes of death in MA17, and a majority of those patients will die of non-breast cancer causes (Chapman 2008). For a younger postmenopausal patient with node-positive disease who is in good health and has not received any other therapy for a few years, I believe it's worthy of consideration.

1.1 MA17 Trial: Outcomes for Women Initially Assigned to Placebo (Median Follow-Up = 5.3 Years)

	Adjusted hazard ratio Switch to letrozole: Continue placebo	*p*-value
Disease-free survival (DFS)	0.37 (95% CI: 0.23-0.61)	<0.0001
Distant DFS	0.39 (95% CI: 0.20-0.74)	0.004
Overall survival	0.30 (95% CI: 0.17-0.53)	<0.0001
Contralateral breast cancer	0.18 (95% CI: 0.06-0.58)	0.004

Hazard ratio < 1.0 favors switching to letrozole; CI = confidence interval

SOURCE: Goss PE et al. *J Clin Oncol* 2008;26(12);[Epub ahead of print]. **Abstract**

Track 24

DR LOVE: The recent 100-month update of the ATAC trial (1.2) showed an increased carryover benefit in years five through nine of anastrozole compared to tamoxifen for recurrence. Cliff, what's your current view of these data?

DR HUDIS: Frequently, the reason to administer adjuvant therapy or to choose one regimen over another regimen is to improve survival. However, we make many choices that do not relate to survival but rather are made for other concrete reasons, such as better quality of life associated with no recurrence or administering a less toxic drug. The progression-free survival results are still being discussed as suggestive of an overall survival advantage, although one may not exist.

DR CARLSON: I believe that progression-free survival is an important endpoint in the adjuvant setting. Most of the treatment options for a woman who has recurrent breast cancer have significant toxicities, so progression-free survival in the absence of a clear-cut survival signal is important.

1.2

ATAC Trial 100-Month Update: Outcomes for Patients with Hormone Receptor-Positive Early Breast Cancer

	Anastrozole (n = 2,618)	Tamoxifen (n = 2,598)	Absolute difference	Hazard ratio (95% CI)	*p*-value
Disease-free survival					
Nine-year	25.8%	29.9%	4.1%	0.85 (0.76-0.94)	0.003
Five-year	13.9%	16.4%	2.5%		
Recurrence rate					
Nine-year	17.0%	21.8%	4.8%	0.76 (0.67-0.87)	0.0001
Five-year	9.7%	12.5%	2.8%		
Distant recurrence rate					
Nine-year	13.2%	15.6%	2.4%	0.84 (0.72-0.97)	0.022
Five-year	7.8%	9.1%	1.3%		
Contralateral breast cancer rate					
Nine-year	2.5%	4.2%	1.7%	0.60 (0.42-0.85)	0.004
Five-year	1.0%	1.8%	0.8%		
Death after recurrence	9.4%	10.4%	1.0%	0.90 (0.75-1.07)	0.2
Death — all causes	18.0%	18.4%	0.4%	0.97 (0.86-1.11)	0.7

CI = confidence interval

"The findings of this report extend the previously reported superior efficacy of anastrozole over tamoxifen at 68 months of follow-up to 100 months. We also show a carryover benefit for recurrence in the hormone-receptor positive population, which is larger than that previously shown for tamoxifen. The difference in recurrence rates has continued to increase, and the smoothed hazard plots show clearly that lower recurrence rates are maintained with anastrozole, even after treatment has been completed."

SOURCE: Forbes JF et al. *Lancet Oncol* 2008;9(1):45-53. **Abstract**

Track 18

DR LOVE: Ian, how do you think the data from the clinical trials of fulvestrant in metastatic disease might influence the study of it in the adjuvant setting?

PROF SMITH: For patients with metastatic breast cancer who have failed a nonsteroidal aromatase inhibitor, the SoFEA trial is comparing the steroidal aromatase inhibitor exemestane to fulvestrant alone or fulvestrant with anastrozole, a nonsteroidal aromatase inhibitor (1.3).

If the SoFEA trial were positive and reported an additional gain for fulvestrant either after a nonsteroidal aromatase inhibitor or in combination with a nonsteroidal aromatase inhibitor, then that would support an adjuvant trial. My instinct is that if a benefit occurs, it probably will be with the combination. However, the comparative studies of fulvestrant versus tamoxifen (Howell 2004) or the aromatase inhibitors (Howell 2005) have demonstrated equivalency and not superiority.

DR GRALOW: SWOG-S0226, which is accruing well, is an ongoing trial in the metastatic setting of anastrozole with or without fulvestrant. Crossover from the anastrozole-alone arm to fulvestrant is strongly encouraged (1.3).

1.3

Active Phase III Trials of Fulvestrant in Combination with Aromatase Inhibitor (AI) Therapy

Study/ completion date	N	Eligibility/setting	Randomization
SWOG-S0226, CAN-NCIC-MAC7 March 2007	690	Postmenopausal, ER+ First-line mBC	Anastrozole ± fulvestrant
SoFEA Completed	750	Postmenopausal, ER+ Failure on a nonsteroidal AI	Fulvestrant ± anastrozole Exemestane
FACT June 2009	512	Postmenopausal, ER+ First-line mBC	Anastrozole ± fulvestrant LD
GEICAM/2006-10 November 2015	3,180	Postmenopausal, ER+ Adjuvant	Anastrozole x 5y ± fulvestrant x 3y

LD = 500 mg day 0 + 250 mg days 14 and 28, then 250 mg monthly thereafter

SOURCE: NCI Physician Data Query, April 2008.

Evaluating patients for treatment with adjuvant trastuzumab

Tracks 28-29

DR LOVE: Cliff, what are your thoughts on the selection of adjuvant therapy for an older woman with, for example, a 2-cm, node-negative, hormone receptor-negative, HER2-positive breast tumor?

DR HUDIS: A woman like that would have been eligible for the randomized Intergroup trastuzumab trial, and I would treat her conventionally with AC → taxane/trastuzumab, if she were interested and willing.

DR GRALOW: The studies support an anthracycline- and taxane-containing regimen that is a little more aggressive than I want to administer. However, docetaxel/carboplatin/trastuzumab (TCH) is a tough regimen. Even though you might have less cardiotoxicity, I believe that you trade it for some other toxicities.

I would try to enroll an older patient in our Phase II trial of weekly paclitaxel/trastuzumab, but I don't have data to do that off study. Off study, I would probably use AC → weekly paclitaxel with trastuzumab.

DR MACKEY: Off study, I would offer this woman TCH. I believe that the anthracyclines are a major confounding problem with the cardiotoxicity that we see with trastuzumab. I have found that TCH is reasonably well tolerated.

DR ROBERT: Like John, I was involved with BCIRG 006, and we've prescribed a fair amount of TCH. If the patients had HER2-negative disease, I would consider four cycles of docetaxel/cyclophosphamide. For patients with HER2-positive tumors at lower risk, I believe we find some comfort in using less chemotherapy. So off study I would administer TCH, but I wouldn't be wedded to six cycles.

DR LOVE: Do you use growth factors?

DR ROBERT: For an older patient, I would use growth factors because some patients become profoundly neutropenic. It is interesting, although not well known, that in the US Oncology adjuvant trial of TC versus AC, prophylactic antibiotics were used routinely (Jones 2006; [1.4]).

That is something that everyone needs to be aware of because if not, patients may run into problems. I am more comfortable using a nonanthracycline regimen, and we are conducting a trial at US Oncology evaluating docetaxel/cyclophosphamide concomitantly with trastuzumab (1.5).

DR MACKEY: We conducted a quality-of-life analysis in BCIRG 006. If anything, it favored TCH over AC → TH. The patient-reported toxicities and quality of life were superior with TCH in some components. The global

1.4

US Oncology Adjuvant Trial Comparing Four Cycles of Docetaxel and Cyclophosphamide (TC) to Four Cycles of AC in Women with Node-Negative or Node-Positive Early Breast Cancer: Seven-Year Follow-Up

Endpoint	TC (n = 506)	AC (n = 510)	*p*-value
Disease-free survival	81%	75%	0.033
Overall survival	87%	82%	0.032

SOURCE: Jones S et al. San Antonio Breast Cancer Symposium 2007;**Abstract 12**.

1.5

Phase II Trial of TC (Docetaxel/Cyclophosphamide) with Trastuzumab (H) for HER2-Positive Early Breast Cancer

Protocol IDs: US Oncology 06038, NCT00493649
Target Accrual: 260 Start Date: June 2007

Protocol treatment → **TC x 4 + H qwk x 4 → H q3wk to one year**

Eligibility

- Stage I to IIIA breast cancer
- HER2-positive (immunohistochemistry [IHC] staining of 3+ [uniform, intense membrane staining of >30 percent of invasive tumor cells] or a FISH result of 0.6 HER2 gene copies per nucleus or a FISH ratio [HER2 gene signals to chromosome 17 signals] of >2.2; patients with equivocal FISH ratio results 1.8-2.2 are also eligible if IHC is 3+)
- Adequate tumor specimen available for FISH analysis of TOPO II-A status
- Known ER and PR status

Study Contact

US Oncology
Stephen E Jones, MD, Principal Investigator

SOURCE: www.clinicaltrials.gov

1.6

BCIRG 006: Quality of Life for Patients Treated with Docetaxel/Carboplatin/Trastuzumab (TCH) versus Doxorubicin/Cyclophosphamide Followed by Docetaxel/Trastuzumab (AC → TH)

"Systemic Therapy Side Effects change scores were significantly better for TCH pts at the EOC [end of chemotherapy], and by response analysis, supporting that this regimen is better tolerated. Physical Function [PF] was slightly worse at Cycle 4 for TCH compared to pts just starting their taxane on AC-TH, but otherwise similar between arms. Fewer patients on TCH had a clinically important worsening PF by response analysis."

SOURCE: Au H-J et al. San Antonio Breast Cancer Symposium 2007;**Abstract 3064**.

quality-of-life index that was used did not show a statistically significant difference except at one time point. The trend throughout the entire trial, however, was in favor of TCH over AC → TH (Au 2007; [1.6]).

Tracks 34-38

DR LOVE: Soon, can you summarize your work on the relation of HER2 status to the benefit derived from adjuvant trastuzumab?

DR PAIK: It is expected that if HER2 is measured correctly, the assay would provide linear prediction of benefit. The bottom line is that in the adjuvant setting, there is no perfectly linear assay to demonstrate trastuzumab response, including degree of FISH amplification. If the best assay methodology fails to demonstrate linear correlation and any interaction, then we may have to look

for alternative mechanisms of action. As there is no proof either way, a validation study is needed.

DR PEREZ: My initial reaction to the data was, "It doesn't make any sense." This is a targeted drug that has revolutionized the management of breast cancer.

However, we should take seriously the data being accumulated from NSABP-B-31 (Paik 2007), NCCTG-N9831 (Reinholz 2007) and HERA (McCaskill-Stevens 2007) that show a lack of correlation between degree of HER2 gene amplification or HER2 overexpression and benefit from trastuzumab.

Also, we should consider the data from the central testing of NSABP-B-31 (1.7) and NCCTG-N9831 (1.8), by which patients with HER2-negative tumors appear to derive the same hazard ratio benefit from trastuzumab as those with HER2-positive tumors.

Those specimens were tested by several independent expert pathologists — we've gathered the same data. I believe it's worthy of study because we're still not curing everyone diagnosed with breast cancer.

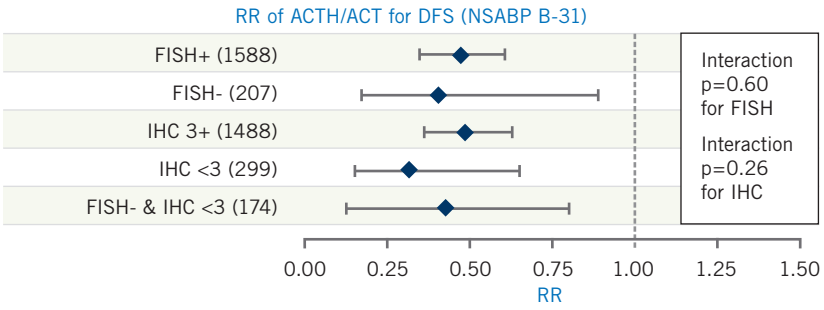
DR HUDIS: Keep in mind that all these patients with so-called HER2-negative tumors in the adjuvant trials who seemed to benefit from trastuzumab were labeled HER2-positive at some point by somebody.

In CALGB-9840, we explicitly selected patients with "HER2-normal" metastatic breast cancer and randomly assigned them to trastuzumab or not. It's a negative trial, although to be fair and supportive, a separation of the curves exists visually that may favor the use of trastuzumab (Seidman 2004).

So the question has been asked prospectively for patients with HER2-negative disease, and it's been asked for lapatinib in patients with HER2-negative

1.7

NSABP-B-31: Disease-Free Survival (DFS) Benefit Associated with Adjuvant Trastuzumab According to HER2 Test Results



Note: RR adjusted for ER and nodal status

SOURCE: With permission from Paik S et al. *Proc ASCO* 2007;**Abstract 511**.

1.8

NCCTG-N9831: Disease-Free Survival (DFS) Benefit Associated with Adjuvant Trastuzumab in Patients with Normal HER2 Test Results

AC → T	N	Events	DFS 3y	DFS 5y
IHC 0, 1, 2+	142	20	88.2	67.6
HER2 FISH ratio < 2.0	74	19	82.0	63.7
IHC 0, 1, 2+ and HER2 FISH ratio < 2.0	44	14	82.6	60.9
AC → T + H				
IHC 0, 1, 2+	191	19	89.1	82.3
HER2 FISH ratio < 2.0	82	11	91.0	80.8
IHC 0, 1, 2+ and HER2 FISH ratio < 2.0	59	9	90.2	81.2

SOURCE: Reinholz MM et al. Presentation. San Antonio Breast Cancer Symposium 2007;**Abstract 36**.

disease. A little subtlety exists here in that the patients we keep saying have HER2-negative disease in this adjuvant setting are a subset of patients who were first classified as having HER2-positive disease. I believe that's distinct from other patients with HER2-negative disease.

DR LOVE: Based on these findings, will a trial be conducted of adjuvant trastuzumab for patients with HER2-negative disease?

DR PAIK: Pending further analysis of the NSABP-B-31 central assay data, we have a concept being reviewed by CTEP that will evaluate chemotherapy with or without trastuzumab for patients with early breast cancer and low HER2 expression (IHC 1+/2+, FISH-negative).

DR GRALOW: I believe it's important to study trastuzumab in the HER2-negative population, but I'm not ready to use trastuzumab off study for a patient who clearly has HER2-negative disease.

I am starting to get calls now that the American Society for Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines have defined an equivocal range for HER results (Wolff 2007).

DR WOLFF: The ASCO/CAP guidelines use the term *equivocal* as part of an attempt to force further characterization of these specimens. If you have a specimen with a low FISH ratio that is around two, you should perform immunohistochemistry. The documents explicitly state that these patients were eligible for the adjuvant trastuzumab trials. So at this point, the guidelines do not say that these patients should not be offered trastuzumab (Wolff 2007).

Based on the data we have from the prospective studies, in which patients with a FISH ratio of two and higher or with IHC 3+ disease were eligible, I believe it is appropriate to offer trastuzumab to those patients.

DR LOVE: Should we use the entry criteria from the adjuvant trials when deciding who should receive adjuvant trastuzumab?

DR WOLFF: That is exactly what the guidelines state. The guidelines cannot be used by anybody as support to deny trastuzumab to these patients.

DR CARLSON: I believe two underlying assumptions may be incorrect, and if they are discarded, the responsiveness of this HER2-negative subset may make more sense. First, the so-called HER2-negative tumors do have HER2 present on the cell surface. These tumors are not technically HER2-negative, but rather they are HER2-low expressing or HER2-normal. So in fact, a target may still exist for trastuzumab.

The other assumption is that if high levels of HER2 are present, then there's a lot of signal transduction, and trastuzumab will interfere with that signal transduction. However, many data indicate that trastuzumab has other mechanisms of action. It may be that inhibiting signal transduction is not the biologically active mechanism in the adjuvant setting. Indeed, a fair amount of data suggests that it is immunologic.

Clinical trials incorporating adjuvant bevacizumab

Tracks 42-43

DR LOVE: Can you discuss the rationale for using docetaxel/carboplatin/trastuzumab (TCH) as the base regimen for the BETH trial evaluating bevacizumab in patients with HER2-positive tumors?

DR MACKEY: In 2006, when we presented the second analysis of the BCIRG 006 trial at the San Antonio Breast Cancer Symposium, the findings related to the critical toxicities associated with an anthracycline-containing trastuzumab regimen were a bit of a "lone cry in the woods" (Slamon 2006; [1.9]).

However, over time some interesting data have come from a number of sources suggesting that there is something to this HER2-anthracycline interaction and that the cardiotoxicity and leukemogenecity are perhaps real concerns, particularly for women who are older than 65 years of age.

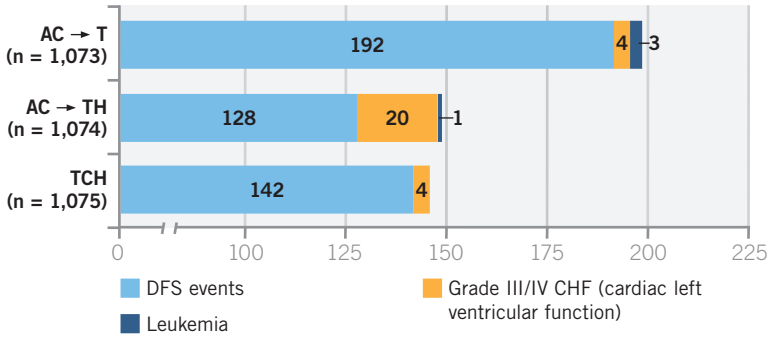
In addition, we're all hopeful that the adjuvant anti-angiogenic strategies will provide the way forward in the population with HER2-positive disease. This would require a relatively noncardiotoxic background because all the currently available agents carry some potential risk for exacerbating cardiotoxicity.

DR LOVE: Chuck, can you discuss the BETH trial?

DR GEYER: The NSABP, by participating in the BETH trial and choosing TCH as the standard arm, is answering yes to its use (1.10). In reviewing the efficacy data from BCIRG 006, it seems impossible to truly differentiate between TCH and AC → TH at this point (Slamon 2006; [1.9]).

The curve for disease-free survival is slightly higher with the anthracycline-containing regimen, but statistically the confidence intervals overlap. In addition, the nonanthracycline-containing arm yields fewer serious toxicities. So far, it clearly has less cardiotoxicity and possibly fewer cases of leukemia

1.9 BCIRG 006: Disease-Free Survival (DFS) Events and Critical Adverse Events at the Second Interim Analysis



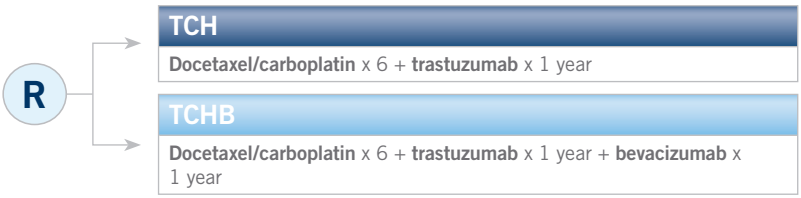
"Considering the published data just this month from the US Oncology trial that Steve Jones led that showed that docetaxel and cyclophosphamide outperforms significantly Adriamycin and cyclophosphamide for all breast cancers, and now the recent data we have from our update of BCIRG 006, that for HER2-positive malignancies, the difference in disease-free survival events and overall survival events in favor of the AC → TH are now exceeded by critical toxicities with regard to leukemias and congestive heart failure, the question becomes this: What is the role of anthracyclines in the adjuvant treatment of breast cancer?"

— Dennis J Slamon, MD, PhD
San Antonio, December 14, 2006

SOURCE: Slamon D et al. BCIRG 006 Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

1.10 BETH: Proposed NSABP/CIRG Trial of Adjuvant Monoclonal Therapy in Patients with HER2-Positive Early Breast Cancer

Target Accrual: 2,875



Eligibility

- Node-positive or high-risk, node-negative early breast cancer
- HER2-positive by central FISH testing

Stratification

- Number of positive nodes
- Hormone receptor status

SOURCE: Slamon D. The Art of Oncology Satellite Symposium at ECCO 14, Barcelona, Spain. September 26, 2007.

(Slamon 2006; [1.9]). When I talk to patients in clinical practice, I explain both regimens, and I find patients generally opt for the regimen that seems to be less cardiotoxic. Now maybe I'm biasing my presentation, but I provide them the information and the safety factor seems to be swaying my patients.

Track 10

DR LOVE: Julie, can you discuss the data presented at the 2007 San Antonio Breast Cancer Symposium on the cardiac safety of dose-dense AC followed by nanoparticle albumin-bound (*nab*) paclitaxel combined with bevacizumab?

DR GRALOW: This was an adjuvant trial with 80 patients with HER2-negative, early-stage breast cancer and normal LVEF. Patients received dose-dense AC with growth factor support followed by dose-dense *nab* paclitaxel at 260 mg/m^2 every two weeks times four with growth factor support.

Bevacizumab at 10 mg/kg was administered concurrently with the chemotherapy every other week and then switched to 15 mg/kg every three weeks to complete one year (McArthur 2007; [1.11]). Patients did not exhibit symptomatic left ventricular dysfunction. However, three out of 80 patients, or four percent, had uncontrolled hypertension. I believe that as we administer bevacizumab in the long term, we will struggle with hypertension the most as an obvious toxicity.

1.11

Safety of Adjuvant Bevacizumab with Dose-Dense AC Followed by *Nab* Paclitaxel (N = 80)

Protocol ID: MSKCC-06019
Accrual: 80

Protocol treatment

AC + bevacizumab (B) → *nab* paclitaxel + B → B
(**AC** + **bevacizumab** 10 mg/kg) q2wk x 4 → (***nab* paclitaxel** 260 mg/m^2 + **bevacizumab** 10 mg/kg) q2wk x 4 → **bevacizumab** 15 mg/kg q3wk x 12

Pegfilgrastim was administered on day 2 after chemotherapy. Radiation and endocrine therapy were administered according to standard practice.

SOURCE: McArthur HL et al. Poster. San Antonio Breast Cancer Symposium 2007;**Abstract 3065**.

Determining which patients are candidates for adjuvant chemotherapy

Tracks 46-48

DR LOVE: Julie, do you believe the Onco*type* DX™ assay can be utilized to determine whether patients with node-positive breast cancer should receive adjuvant chemotherapy?

DR GRALOW: For a select group of patients with positive nodes, I do. I have ordered it a couple of times, such as for patients with low nodal burden. I am not ready to order it for a patient with 10 positive nodes and use it to trump the other features of their disease. For a patient who I believe is highly sensitive to endocrine therapy and has a little nodal disease, I would consider it.

DR HUDIS: I recently saw a 78-year-old woman in otherwise good health with a 2-cm, ER-positive (100 percent), PR-negative (zero), HER2-normal tumor and a single positive lymph node out of 14. Her attitude was that she would accept chemotherapy if it was needed. That was one of the first times I've ordered an Onco*type* DX assay for a patient with node-positive disease.

Conversely, I believe it is risky to withhold adjuvant chemotherapy from cohorts of patients for whom it's been recommended, especially among those with node-positive disease, based on relatively small absolute numbers of events. When the patient is on the fence about receiving chemotherapy and you're having a discussion, that's a different situation.

DR MUSS: It is reasonable to use Onco*type* DX for a patient with one positive node who is on the fence about whether or not to take chemotherapy. Like Cliff, I would be nervous about using this routinely, except for an occasional patient.

Also, these studies we're discussing have notably small numbers of patients (Goldstein 2007; Albain 2007; [1.12]). We're pruning them down and ending up with 200 patients in a subset analysis. We need to be cautious. ■

1.12

Impact of Adding Chemotherapy to Tamoxifen for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer According to the Onco*type* DX Recurrence Score

	10-year disease-free survival point estimates (%, 95% CI)	
	Tamoxifen (n = 148)	CAF → tamoxifen (n = 219)
Low recurrence score (<18)	60 (40, 76)	64 (50, 75)
Intermediate recurrence score (18-30)	49 (32, 63)	63 (48, 74)
High recurrence score (≥31)	43 (28, 57)	55 (40, 67)

CI = confidence interval

SOURCE: Albain K et al. San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

SELECT PUBLICATIONS

Albain K et al. **Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal, node-positive, ER-positive breast cancer (S8814, INT0100).** San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

Au H-J et al. **BCIRG 006: Quality of life (QoL) of patients (pts) treated with docetaxel and trastuzumab-based regimens in node positive and high risk node negative HER2 positive early breast cancer.** San Antonio Breast Cancer Symposium 2007;**Abstract 3064**.

Chapman JA et al. **Competing causes of death from a randomized trial of extended adjuvant endocrine therapy for breast cancer.** *J Natl Cancer Inst* 2008;100(4):252-60. **Abstract**

Fisher ER et al. **Pathobiology of small invasive breast cancers without metastases (T1a/b, N0, M0): National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-21.** *Cancer* 2007;110(9):1929-36. **Abstract**

Forbes JF et al. **Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial.** *Lancet Oncol* 2008;9(1):45-53. **Abstract**

Goldstein LJ et al. **Prognostic utility of the 21-gene assay in hormone receptor positive operable breast cancer and 0-3 positive axillary nodes treated with adjuvant chemohormonal therapy: An analysis of Intergroup trial E2197.** ASCO 2007;**Abstract 526**.

Goss PE et al. **Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen.** *J Clin Oncol* 2008;26(12);[Epub ahead of print]. **Abstract**

Howell A et al. **Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: A prospectively planned combined survival analysis of two multicenter trials.** *Cancer* 2005;104(2):236-9. **Abstract**

Howell A et al. **Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double-blind, randomized trial.** *J Clin Oncol* 2004;22(9):1605-13. **Abstract**

Jones SE et al. **Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer.** *J Clin Oncol* 2006;24(34):5381-7. **Abstract**

McArthur HL et al. **Cardiac safety of adjuvant bevacizumab plus dose-dense doxorubicin/cyclophosphamide followed by nanoparticle albumin-bound paclitaxel in patients with early stage breast cancer.** Poster. San Antonio Breast Cancer Symposium 2007;**Abstract 3065**.

McCaskill-Stevens W et al. **Disease-free survival according to local immunohistochemistry for HER2 and central fluorescence in situ hybridization for patients treated with adjuvant chemotherapy with and without trastuzumab in the HERA (BIG 01-01) trial.** San Antonio Breast Cancer Symposium 2007;**Abstract 71**.

Paik S et al. **Benefit from adjuvant trastuzumab may not be confined to patients with IHC 3+ and/or FISH-positive tumors: Central testing results from NSABP B-31.** *Proc ASCO* 2007;**Abstract 511**.

Reinholz MM et al. **The clinical significance of polysomy 17 in the HER2+ N9831 intergroup adjuvant trastuzumab trial.** Presentation. San Antonio Breast Cancer Symposium 2007;**Abstract 36**.

Seidman AD et al. **CALGB 9840: Phase III study of weekly (W) paclitaxel (P) via 1-hour(h) infusion versus standard (S) 3h infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC.** *Proc ASCO* 2004;**Abstract 512**.

Slamon D. The Art of Oncology Satellite Symposium at ECCO 14, Barcelona, Spain. September 26, 2007.

Slamon D et al. **BCIRG 006: 2nd interim analysis 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 Her2neu positive early breast cancer patients.** Presentation. San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Wolff AC et al. **American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer.** *J Clin Oncol* 2007;25(1):118-45. **Abstract**

Select Excerpts from the Discussion

Management of patients with HER2-positive metastatic disease

Track 2

DR LOVE: Antonio, how do you make a decision in terms of which anti-HER2 therapy to administer to a patient with cancer relapse after adjuvant trastuzumab?

DR WOLFF: I'm surprised that, thus far, I haven't had any patients who have had cancer relapse after receiving adjuvant trastuzumab, and we were active participants in NCCTG-N9831. Maybe the window of relapse will be early, and it may plateau later on. Perhaps some of these patients who have not had a relapse will not have one — and that would be wonderful.

The major concern is that we have absolutely no idea of what prior trastuzumab will mean in this situation. I am not sure what these artificial boundaries of six, 12 or 24 months mean, but at some point you need to draw the line.

I believe that if someone has an immediate relapse within the first year after trastuzumab, I would be more nervous about attempting to use a trastuzumab-containing regimen and may proceed to lapatinib. But again, I believe we are making artificial decisions.

DR GRALOW: You can select one or two years. If it's a short interval since the completion of adjuvant trastuzumab, I believe lapatinib plays a role, although I might go back to trastuzumab at some later time. If it's a longer interval, our group is comfortable with trastuzumab.

Integrating bevacizumab into clinical trials and practice

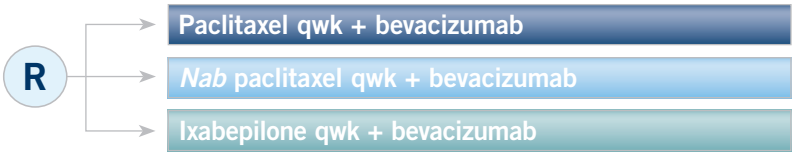
Track 13

DR LOVE: Cliff, can you discuss the planned CALGB trial evaluating first-line therapy with bevacizumab in combination with paclitaxel, *nab* paclitaxel or ixabepilone (2.1)?

DR HUDIS: Hope Rugo is a principal investigator of this prospective, randomized, Phase III trial along with Alvaro Moreno from the NCCTG. They proposed a Phase II randomized trial of ixabepilone versus paclitaxel in combination with bevacizumab. We proposed a Phase III trial of weekly

2.1

Proposed Randomized Trial of Chemotherapy/Bevacizumab as First-Line Treatment for Metastatic Breast Cancer



SOURCES: Personal communication. Clifford Hudis, MD, 2007; Interview. O'Shaughnessy J. December 2007.

paclitaxel versus *nab* paclitaxel. CTEP asked us to collaborate and join these two studies.

Weekly paclitaxel, for three weeks out of four, with bevacizumab is the control regimen. The two experimental arms administer weekly ixabepilone or weekly *nab* paclitaxel, both with bevacizumab.

Significant correlative science studies are also built into the study. The cooperative groups wrote the study with progression-free survival as an endpoint. However, FDA-related discussions are ongoing as to whether or not this study will be adequate for drug approval and, therefore, how we should move forward.

Track 19

DR LOVE: Chuck, what's your opinion about the use of overall survival as an endpoint in trials of metastatic breast cancer?

DR GEYER: It's a problem to make overall survival your ultimate bar for a disease in which we have so many therapies that have an impact on patients. They maintain their performance status, and their volume of disease is controlled by changing drugs around.

What bothers me about the ECOG-E2100 bevacizumab data is that a doubling of progression-free survival is substantial in breast cancer. We're not talking about 1.5 to three months. In breast cancer, we're talking about substantial time (Miller 2007; [2.2]).

DR LOVE: Bob, what discussions have occurred within the NCCN Breast Cancer Committee regarding the use of bevacizumab in metastatic disease?

DR CARLSON: Currently the use of bevacizumab and paclitaxel in the first-line treatment of metastatic disease is included in the NCCN guidelines as an option. The NCCN panel does not require FDA approval of an agent and a specific indication to incorporate it into the guidelines, nor does FDA approval mean that it is incorporated into the guidelines.

2.2

ECOG-E2100: A Phase III Randomized Trial of Paclitaxel with or without Bevacizumab as First-Line Therapy for Women with Locally Recurrent or Metastatic Breast Cancer

	Paclitaxel (n = 326)	Paclitaxel/bevacizumab (n = 347)
Age (mean)	55 years (27-85)	56 years (29-84)
Efficacy		
Progression-free survival	5.9 months	11.8 months
	HR = 0.60, $p < 0.001$	
Overall survival	25.2 months	26.7 months
	HR = 0.88, $p = 0.16$	
One-year survival	73.4%	81.2%
	$p < 0.01$	
Objective response rate	21.2%	36.9%
	$p < 0.001$	

HR = hazard ratio

SOURCE: Miller K et al. *N Engl J Med* 2007;357(26):2666-76. **Abstract**

DR LOVE: Within the NCCN Breast Cancer Committee, how much weight do you give to overall survival versus progression-free survival in the metastatic setting?

DR CARLSON: The panel to date doesn't focus specifically on progression-free survival, overall survival or toxicity. It's more a gestalt or a balance among the experts on the panel in terms of weighing the different advantages.

One of the issues in this discussion, though, is that none of the results from ECOG-E2100 indicate that bevacizumab does not provide a survival advantage. They show that the survival differences are not statistically significant as they were analyzed. The *p*-value was 0.16, which means there's an 84 percent chance that it is better (Miller 2007; [2.2]).

If a Wilcoxon analysis were performed on those data, it would become statistically significant. So some of this relates to your statistician and which method of analyzing the data you prefer. ■

SELECT PUBLICATIONS

Di Leo A et al. **Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: A Phase III randomized, double-blind study of 580 patients.** *Proc ASCO* 2007;**Abstract 1011**.

Gradishar WJ et al. **Randomized comparison of weekly or every-3-week (q3w) *nab*-paclitaxel compared to q3w docetaxel as first-line therapy in patients (pts) with metastatic breast cancer (MBC).** *Proc ASCO* 2007;**Abstract 1032**.

Miller K et al. **Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer.** *N Engl J Med* 2007;357(26):2666-76. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In an adjuvant trial of 80 patients with early-stage breast cancer receiving bevacizumab and dose-dense AC followed by *nab* paclitaxel, the primary study objective was to determine the _____ of this treatment regimen.**
   a. Cardiac safety
   b. Disease-free survival
   c. Overall survival

2. **For patients with metastatic breast cancer, a planned Phase III CALGB trial aims to evaluate bevacizumab in combination with _____ as first-line therapy.**
   a. Paclitaxel
   b. *Nab* paclitaxel
   c. Ixabepilone
   d. All of the above

3. **Which of the following trials evaluated the optimal duration of therapy with adjuvant tamoxifen?**
   a. ATLAS
   b. aTTom
   c. NSABP-B-14
   d. Both a and b
   e. All of the above

4. **Which of the following is NOT included in the Phase III SoFEA trial for postmenopausal women with ER-positive and/or PR-positive metastatic breast cancer that has progressed during endocrine therapy with a nonsteroidal aromatase inhibitor?**
   a. Anastrozole
   b. Docetaxel
   c. Exemestane
   d. Fulvestrant

5. **SWOG-S0226 is a Phase III randomized study of anastrozole with or without _____ as first-line therapy for postmenopausal women with metastatic breast cancer.**
   a. Bevacizumab
   b. Exemestane
   c. Fulvestrant

6. **According to the ASCO/CAP guideline recommendations for HER2 testing in breast cancer, patients are candidates for adjuvant trastuzumab if they meet the eligibility criteria for the adjuvant trastuzumab clinical trials, such as NCCTG-N9831.**
   a. True
   b. False

7. **Among the patients enrolled in MA17 who were randomly assigned to placebo after the completion of five years of adjuvant tamoxifen, a benefit appeared to starting letrozole after being on placebo for several years.**
   a. True
   b. False

8. **The 100-month analysis of the ATAC trial revealed statistically significant evidence of a larger carryover effect after five years of adjuvant treatment with anastrozole compared to tamoxifen.**
   a. True
   b. False

9. **The five-year follow-up data from CALGB-9741 reported an incidence of MDS/AML of _____.**
   a. 0.3 percent
   b. 0.7 percent
   c. 1.5 percent

10. **In BCIRG 006, the incidence of Grade III/IV congestive heart failure was _____ with TCH compared to AC → TH.**
    a. Lower
    b. Higher
    c. The same

11. **The proposed BETH trial by the CIRG and NSABP will evaluate the combination of chemotherapy/trastuzumab with _____ for women with HER2-positive early breast cancer.**
    a. Bevacizumab
    b. Cetuximab
    c. Erlotinib
    d. Lapatinib
    e. None of the above

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Think Tank Issue 1, 2008

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- **Updated data on adjuvant endocrine therapy** 4 3 2 1
- **HER2 status and response to adjuvant trastuzumab** 4 3 2 1
- **Chemotherapy options for patients with HER2-positive early breast cancer** 4 3 2 1
- **Role of the Onco*type* DX assay for node-positive breast cancer** 4 3 2 1
- **Bevacizumab/paclitaxel in the treatment of metastatic breast cancer** 4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- **Updated data on adjuvant endocrine therapy** 4 3 2 1
- **HER2 status and response to adjuvant trastuzumab** 4 3 2 1
- **Chemotherapy options for patients with HER2-positive early breast cancer** 4 3 2 1
- **Role of the Onco*type* DX assay for node-positive breast cancer** 4 3 2 1
- **Bevacizumab/paclitaxel in the treatment of metastatic breast cancer** 4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: .....

Please respond to the following LEARNER statements by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = Learning objective not met N/A = Not applicable

As a result of this activity, I will:

- Select appropriate adjuvant therapy for patients with HER2-positive breast cancer, based on tumor characteristics and the risk-benefit profiles of the treatments... 4 3 2 1 N/M N/A
- Evaluate the potential clinical utility of newly emerging technologies to assess ER and HER2 status of breast tumors.. 4 3 2 1 N/M N/A
- Incorporate results from the Onco*type* DX™ assay, along with other prognostic factors, into clinical decisions regarding adjuvant chemotherapy regimens for patients with node-negative and node-positive breast cancer.. 4 3 2 1 N/M N/A
- Assess the emerging data on novel chemotherapy and biologic agents, and determine if these treatments should be used for appropriate patients with metastatic breast cancer.. 4 3 2 1 N/M N/A
- Evaluate emerging breast cancer clinical trial data, and determine how the data should be applied to clinical practice.. 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the option of participating in ongoing clinical trials, based on an awareness of the latest research.. 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

May we include you in future assessments to evaluate the effectiveness of this activity?

☐ Yes ☐ No

PART TWO — Please tell us about the faculty for this educational activity

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

Faculty	Knowledge of subject matter	Effectiveness as an educator
Robert W Carlson, MD	4 3 2 1	4 3 2 1
Charles E Geyer Jr, MD	4 3 2 1	4 3 2 1
Julie R Gralow, MD	4 3 2 1	4 3 2 1
Clifford Hudis, MD	4 3 2 1	4 3 2 1
John Mackey, MD	4 3 2 1	4 3 2 1
Hyman B Muss, MD	4 3 2 1	4 3 2 1
Soonmyung Paik, MD	4 3 2 1	4 3 2 1
Edith A Perez, MD	4 3 2 1	4 3 2 1
Nicholas J Robert, MD	4 3 2 1	4 3 2 1
Ian E Smith, MD	4 3 2 1	4 3 2 1
Antonio C Wolff, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Degree:

☐ MD ☐ DO ☐ PharmD ☐ NP ☐ BS ☐ RN ☐ PA ☐ Other .....

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

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

To obtain a certificate of completion and receive credit for this activity, please complete the Post-test, fill out the Educational Assessment and Credit Form and fax both to (800) 447-4310, or mail both to Research To Practice, One Biscayne Tower, 2 South Biscayne Boulevard, Suite 3600, Miami, FL 33131. You may also complete the Post-test and Educational Assessment online at www.BreastCancerUpdate.com/ThinkTank/CME.

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