Adjuvant Therapy for Breast Cancer: Where We Are, Where We’re Headed

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Proceedings from a Collaborative Education Session Held in Conjunction with the 50th Anniversary of the NSABP

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OVERVIEW OF ACTIVITY
Breast cancer is one of the most rapidly evolving fields in medical oncology. Published results from ongoing and completed clinical trials lead to the continual emergence of new therapeutic strategies and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with experts’ perspectives, this CME program is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies for the care of patients with breast cancer.

LEARNING OBJECTIVES
• Compare and contrast the safety and efficacy of anthracycline- and nonanthracycline-containing adjuvant regimens when recommending chemotherapy for patients with early breast cancer.
• Recall emerging safety data from ongoing studies when screening patients for enrollment into adjuvant bevacizumab trials.
• Explain the clinical evidence and scientific rationale for ongoing trials evaluating combination biologic treatments for patients with HER2-positive early breast cancer.
• Critically assess the controversial efficacy of adjuvant trastuzumab in the setting of HER2-negative breast cancer, considering the value of central laboratory testing and subgroup analyses.
• Incorporate the use of validated biomarkers and genomic assays into the quantification of disease risk and the selection of appropriate treatment for patients with breast cancer.
• Devise an algorithm for the endocrine treatment of pre- and postmenopausal women with ER-positive early breast cancer, addressing total duration of therapy and the evolving role of bisphosphonates.
• Discriminate the incremental risk of cardiotoxicity when selecting adjuvant systemic treatment for patients with Stage I to Stage III breast cancer.
• Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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50 years of innovation and achievement

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On a recent steamy Friday summer night down the road from us at the Diplomat Hotel in Hollywood, Florida, the NSABP membership came together once again to compare notes about the group’s current and future clinical trials. However, this gathering was much more than just another meeting, as the event marked the 50th anniversary of this pioneering cooperative research group. The weekend featured a number of celebrations, including presentations by NSABP legend Dr Bernard Fisher and former NCI director Dr Vincent DeVita.

To provide additional educational perspectives, our CME group was invited to contribute to this important weekend and partnered with the NSABP to host a special CME symposium focusing on key research issues in early breast cancer and the current and future trials (Figure A) of the group addressing many of these questions.

What was perhaps most striking about the issues discussed is just how profound an effect the NSABP has had on contemporary cancer research and standards of care. Following the early leadership of Dr Fisher, Norman Wolmark, Richard Margolese, Edwin Fisher and many others, NSABP members have been the backbone of breast and colorectal cancer clinical investigation for five decades, and the scientific methods championed by the group have paved the way for similar research endeavors by other cooperative research groups and medical specialties.

I first had the good fortune to work with the NSABP in the mid-1980s as a member/trialist while on the faculty at the University of Miami and also as a neophyte educator wishing to create new and better education resources for colleagues. In 1985, Bernie and Richard were gracious enough to participate in a special educational retreat I organized to discuss the findings of a recent NIH Consensus Conference on adjuvant therapy, and a couple of years later, Bernie became the first person I interviewed for the Breast Cancer Update audio series — then just on cassette but now spun out on CD and Podcasts internationally.

Since that time, I have maintained a profound respect and admiration for the NSABP and have greatly enjoyed attending group meetings, particularly those a few years back when Bernie owned the podium, spitting fire and motivating the troops to move forward. It was an honor to be a part of this most recent NSABP gathering, and the enclosed program includes highlights from our
CME symposium, along with individual interviews with the participating faculty members and Drs Fisher and DeVita.

At the symposium, Dr Wolmark added yet another innovative protocol to the group’s list by announcing their collaboration on what is now being called the “TIC-TAC-TOE” study (Figure B) evaluating the critical question of the adjuvant use of anthracyclines and the role of bevacizumab/chemotherapy in the adjuvant setting. Of course the NSABP is well versed in the latter clinical question as their successful C-08 adjuvant study promises an answer in colon cancer very soon.

Special thanks to Norm and Chuck Geyer for working with us again to develop and execute this exciting education project, and particular thanks to Bernie for once again sitting down with us and sharing his experiences and wisdom.

— Neil Love, MD
DrNeilLove@ResearchToPractice.com
October 20, 2008

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**Figure A**

**Current NSABP Phase III Breast Cancer (BC) Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Title</th>
<th>Status</th>
<th>Cumulative accrual*</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-37</td>
<td>Adjuvant chemotherapy for resected, locoregional, relapsed BC</td>
<td>Open</td>
<td>131</td>
</tr>
<tr>
<td>B-39</td>
<td>Adjuvant whole breast irradiation vs partial breast irradiation for women with Stage 0/I/II BC</td>
<td>Open</td>
<td>3,233</td>
</tr>
<tr>
<td>B-40</td>
<td>Six different neoadjuvant chemotherapy regimens +/- neoadjuvant and adjuvant bevacizumab for patients with operable, early-stage BC</td>
<td>Open</td>
<td>424</td>
</tr>
<tr>
<td>B-41</td>
<td>Neoadjuvant AC ↔ paclitaxel + trastuzumab or lapatinib or both for patients with HER2-positive, resectable, invasive BC</td>
<td>Open</td>
<td>70</td>
</tr>
<tr>
<td>B-42</td>
<td>Letrozole for postmenopausal women with ER-positive BC who have completed five years of treatment with an AI or tamoxifen</td>
<td>Open</td>
<td>1,517</td>
</tr>
<tr>
<td>BP-59</td>
<td>Bone marrow analysis in early-stage BC</td>
<td>Open</td>
<td>331</td>
</tr>
<tr>
<td>B-34</td>
<td>Adjuvant clodronate +/- systemic chemotherapy +/- hormone therapy for women with early-stage BC</td>
<td>Closed</td>
<td>3,323</td>
</tr>
<tr>
<td>B-36</td>
<td>Adjuvant FEC x 6 vs AC x 4 for patients with node-negative BC</td>
<td>Closed</td>
<td>2,700</td>
</tr>
<tr>
<td>B-38</td>
<td>Adjuvant TAC vs dose-dense AC ↔ paclitaxel vs dose-dense AC ↔ paclitaxel + gemcitabine for women with node-positive BC</td>
<td>Closed</td>
<td>4,894</td>
</tr>
</tbody>
</table>

*Accrual as of 9/26/08
Figure B

Proposed Amendment to US Oncology 06090: A Phase III Trial of Adjuvant TC versus TAC versus TC/Bevacizumab in Patients with HER2-Negative, Early-Stage Breast Cancer

Protocol IDs: NCT00493870, US Oncology 06090, 11271
Target Accrual: 3,900
Date Activated: May 2007

Docetaxel + doxorubicin + cyclophosphamide (TAC) x 6

Docetaxel + cyclophosphamide (TC) x 6

TC x 6 + bevacizumab (proposed)

Select Eligibility Criteria

- FISH-confirmed HER2-negative breast cancer
- Operable Stage I to IIIC breast cancer
- Meets one of the following criteria:
  - T1-3N1-3M0 if ER-positive or ER-negative
  - T2-3N0M0 if ER-positive or ER-negative
  - T1N0M0 if ER-negative and PR-negative
- No prior chemotherapy within the past five years
- Normal cardiac function

Study Contact

Joanne L Blum, MD, Principal Investigator


SELECT PUBLICATIONS


Adjuvant anthracyclines for HER2-positive or HER2-negative disease

Select Excerpts from the Discussion

Track 2

DR LOVE: When you’re choosing adjuvant systemic therapy for patients off protocol, in which situations are you generally recommending anthracyclines?

DR SWAIN: Currently, I’m using anthracyclines only for patients with node-positive, HER2-negative disease. This is somewhat irrational because I believe the anthracyclines are probably not important for any patients with HER2-negative disease. So, if I believe that, I shouldn’t be using anthracyclines even for the patients with node-positive tumors. However, I can’t give them up yet with the recurrence rates being so high in that population — about 40 percent. For patients with HER2-positive disease, I prefer TCH, so I do not use an anthracycline.

DR GEYER: For patients with HER2-positive disease, I tend to use TCH also. Anthracyclines might demonstrate a slight difference. You can’t tell from the data, but it is evident that any difference is more than offset by the cardiac issue (Slamon 2006; [1.1]). When I explain to patients that these small benefits are possible but the cardiac risk is clear, they prefer to go with TCH.

For patients with HER2-negative disease, I’m swayed somewhat by the cyclophosphamide/docetaxel (TC) versus AC data (Jones 2007; [1.2]), so I tend to go with TC off protocol, particularly for patients with ER-positive, node-negative, smaller tumors and any kind of comorbidity (eg, hypertension, advanced age). However, for younger, healthier patients and those with tumors that are larger and have lower estrogen-receptor (ER) levels and higher grades, I’m still using anthracycline-containing regimens.

Track 34

DR LOVE: Can you review what we know about the relationship between the TOPO II gene and the efficacy of anthracyclines?

DR PEGRAM: The topoisomerase II (TOPO II) gene is close geographically to the HER2 gene on the long arm of chromosome 17. Consequently, when the HER2 gene is amplified — which it is in approximately 20 percent of human breast cancer cases worldwide — the TOPO II gene is coamplified 35 percent of the time. TOPO II is apparently the target for the anthracyclines.

With amplification of TOPO II and subsequent high levels of TOPO II expression and activity, cells will be uniquely sensitive to the action of the anthracyclines. A number of published series have examined the relationship between
TOPO II gene amplification and response to anthracyclines in breast cancer. The data have consistently indicated a strong relationship between those two.

**DR LOVE:** What do we know about the benefits of anthracyclines in HER2-negative breast cancer?

**DR PEGRAM:** Again, the data are almost alarmingly consistent. Whenever this question has been addressed, no additional activity of the anthracyclines has been recorded above and beyond alkylator-based or taxane-based combination chemotherapy. However, these are all retrospective subset analyses that used different probes to measure HER2.

This research question demands carefully controlled, prospective randomized trials, which is what we’re doing. US Oncology and the NSABP will join forces to conduct a prospective, large randomized trial for patients with HER2-negative disease comparing TAC to TC (Figure B, page 5). The trial has an additional arm of TC with bevacizumab, which is of no consequence with regard to the TOPO II and anthracycline question.

### 1.2

**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**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>TC (n = 506)</th>
<th>AC (n = 510)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td>81%</td>
<td>75%</td>
<td>0.033</td>
</tr>
<tr>
<td>Overall survival</td>
<td>87%</td>
<td>82%</td>
<td>0.032</td>
</tr>
</tbody>
</table>

**SOURCE:** Jones S et al. San Antonio Breast Cancer Symposium 2007; Abstract 12.
Clinical trials of adjuvant bevacizumab for HER2-negative disease

Track 30

DR LOVE: Can you discuss the NSABP collaboration with US Oncology on the TC-TAC trial?

DR SWAIN: We have been in serious discussion with US Oncology about their TC-TAC trial. NSABP will take the lead in adding onto that trial an arm called TOE. The trial will evaluate TC versus TAC versus TC and bevacizumab in women with node-positive or high-risk, node-negative disease (Figure B, page 5). I believe it’s an important trial that will include bevacizumab without an anthracycline. Only one other study will have any data on that — the BEATRICE trial, which will evaluate seven adjuvant chemotherapy regimens with or without bevacizumab in patients with triple-negative disease.

Tracks 4, 8

DR LOVE: Can you review the safety data for adjuvant bevacizumab from the NSABP-C-08 adjuvant colon cancer trial that were presented at the ASCO meeting?

DR WOLMARK: We petitioned our data monitoring committee to release the safety data because no unexpected or unanticipated toxicities were associated with bevacizumab. We’re using it with a FOLFOX regimen in colon cancer, which is a little different from breast cancer, both anatomically and regarding the regimens used. The reason we disclosed the data is that bevacizumab was remarkably well tolerated (Allegra 2008; [2.1]).

DR LOVE: It seemed that there was no increase in bowel perforations.

DR WOLMARK: We saw one less bowel perforation in the bevacizumab arm, and you can draw your own conclusions.

| NSABP-C-08: Adjuvant FOLFOX with or without Bevacizumab in Stage II/III Colon Cancer |
|---------------------------------|-----------------|-----------------|
|                                 | FOLFOX n = 1,321 | FOLFOX + bevacizumab n = 1,326 |
| Cardiac ischemia                | n = 10, 0.76%    | n = 20, 1.51%    |
| CNS ischemia                    | n = 5, 0.38%     | n = 6, 0.45%     |
| Peripheral arterial ischemia    | n = 3, 0.23%     | n = 0, 0%        |
| Gastrointestinal perforation    | n = 2, 0.15%     | n = 4, 0.3%      |
| Hemorrhage                      | n = 25, 1.9%     | n = 25, 1.9%     |

**DR LOVE:** Terry, what are your thoughts on wound healing and bevacizumab?

**DR MAMOUNAS:** That is a concern. It appears, so far, that the concern is not for wounds that already have undergone some healing by the time you start bevacizumab but for wounds that occur while bevacizumab is being administered — for example, if a patient has to have emergency or semi-elective surgery before you have enough time to stop the bevacizumab. The healing is different when a patient is receiving bevacizumab, so we have to be careful.

**Track 47**

**DR LOVE:** Kathy, can you comment on your study, ECOG-E5103 (2.2), evaluating adjuvant bevacizumab in combination with AC → paclitaxel?

**DR MILLER:** This is a large adjuvant study open to patients with node-positive or node-negative, high-risk disease. The practical element is that we allow patients and their physicians to select whether they prefer AC every two or three weeks, which will be stratified so as not to impact the results. The backbone chemotherapy is four cycles of AC → weekly paclitaxel, based on historical data from E1199, and especially E2100, suggesting potential synergy between more continuous, lower-dose taxane exposure with bevacizumab. Bevacizumab will be administered in two different durations. One group will receive it for around six months concurrently with chemotherapy, while another group will receive it for approximately one year with chemotherapy followed by an additional six months after the completion of chemotherapy, and of course the control group will not receive any bevacizumab. The duration of therapy is questionable in terms of if it will be long enough. Perhaps chronic therapy will be needed, and this will not eliminate microscopic disease but will merely keep it from growing.

### Phase III Randomized Study of Adjuvant AC → Paclitaxel (Pac) with or without Bevacizumab (Bev)

**Protocol IDs:** ECOG-E5103, NCT00433511; **Accrual:** 4,950 (Open)

**Eligibility**
- Pre- or postmenopausal
- ER and PR status known, HER2-negative
- Node-positive and high-risk, node-negative disease

**SOURCE:** NCI Physician Data Query, October 2008.
DR LOVE: Would you discuss the BETH trial?

DR SWAIN: This is a collaboration between the CIRG and NSABP examining a nonanthracycline-containing regimen combined with trastuzumab with or without bevacizumab (3.1). We feel strongly in the NSABP, as does Dr Slamon, about using nonanthracycline regimens. We chose TCH from BCIRG 006. The second interim analysis from that trial showed a significant benefit with TCH compared to AC → docetaxel (Slamon 2006; [1.1]).

This is a large international collaboration with many investigators in Europe who don’t belong to the CIRG or NSABP, and they wanted to include an anthracycline-containing regimen. So a cohort will receive docetaxel/trastuzumab → FEC with or without bevacizumab. We hope the study will accrue quickly, because many physicians don’t want to use anthracyclines anymore.

I believe the data are convincing, especially if you consider BCIRG 006 (Slamon 2006; [1.1]) and the Gennari meta-analysis showing that patients with HER2-negative disease don’t benefit from anthracyclines and those with HER2-positive disease do (Gennari 2008). If you put all this together, you either need an anthracycline or trastuzumab for a patient with a HER2-positive tumor. Of course, we have chosen trastuzumab, not the anthracycline.

### BETH: NSABP/CIRG Trial of Chemotherapy and Trastuzumab with or without Bevacizumab in Patients with HER2-Positive Early Breast Cancer

Protocol IDs: NSABP-B-44-I, CIRG (TRIO) 011, BETH, NCT00625898
Target Accrual: 3,500

**Eligibility**

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

T = docetaxel; C = carboplatin; H = trastuzumab; F = 5-FU; E = epirubicin; C' = cyclophosphamide; B = bevacizumab

*Chemotherapy used by NSABP/CIRG investigators (Cohort 1)
†Chemotherapy used by independent investigators (Cohort 2)

**SOURCE:** NCI Physician Data Query, October 2008.
New research strategies for HER2-negative disease

Track 44

**DR LOVE:** Can you discuss NSABP-B-40?

**DR GEYER:** NSABP-B-40 (4.1) is a neoadjuvant study to follow up NSABP-B-27, which added docetaxel in sequence to AC and resulted in the still intriguing and somewhat inexplicable doubling of the pCR rate but no advantage in terms of disease-free survival, recurrence-free survival, et cetera (Bear 2006). NSABP-B-40 started out as a trial to assess the addition of capecitabine or gemcitabine to docetaxel, a straightforward three-arm trial.

We decided to add a wrinkle by reversing the order and putting the taxane ahead of AC. We were close to activating NSABP-B-40 but decided that the bevacizumab data in metastatic disease were compelling (Miller 2007) and took it from a three-arm trial to a highly complicated study. It’s now a three-by-two study of neoadjuvant therapy with a secondary randomization to bevacizumab or not.
**Tracks 41-42**

**DR LOVE:** Soon Paik and the NSABP published a letter to the editor in *The New England Journal of Medicine* on HER2 status and adjuvant trastuzumab. Mark, what are your thoughts on that?

**DR PEGRAM:** It was a provocative retrospective subset analysis of NSABP-B-31 (4.2). When Soon retested the samples in his lab, he found a small fraction of the patients had tumors that were HER2-negative by IHC and nonamplified by FISH. When he analyzed the benefit of trastuzumab in these patients with ostensibly HER2-negative tumors, the hazard ratio was about the same as for those with HER2-positive breast cancer treated with trastuzumab (Paik 2008).
This suggests that trastuzumab might have some activity even in HER2-negative disease. One has to view this type of retrospective subset analysis with great caution, but Dr Paik did show results that reached statistical significance. On retrospective analysis, the NCCTG-N9831 data set had similar hazard ratios to the NSABP-B-31 hazard ratios for their subset with HER2-negative disease. However, it did not reach statistical significance (Perez 2007). Is this an artifact of retesting in the NSABP laboratory? After all, someone once called these cases HER2-positive. Or is it real, because we know all epithelial breast malignancies express some HER2? Could trastuzumab have immunologic activity that might function even in HER2-negative cases?

The first order of business is to make sure that Dr Paik’s results are not some sort of technical artifact. The NSABP has announced that they will obtain a round-robin reanalysis of those samples by three blinded pathologists. That’s the critical validation to make these results credible. If they’re real and can be validated by independent pathologists, then the next research question becomes, should we be considering HER2-targeted therapies even for patients with HER2-negative disease? I don’t know the answer, but it’s certainly provocative.

**DR WOLMARK:** Dr Paik exhaustively analyzed this using a number of methodologies — with expression and with mRNA-based assays. Consistently, those individuals with HER2-low disease on IHC or FISH had HER2-low disease in terms of expression also. He went so far as to evaluate genes that were adjacent to HER2, and if the HER2 level was low, the levels of adjacent genes were also low. We’re confident that this is not a misinterpretation of morphology, IHC or FISH analysis — this is real.

### 4.2 HER2 Status and the Efficacy of Adjuvant Trastuzumab in NSABP-B-31

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ACT</th>
<th>ACTH</th>
<th>Relative risk (95% CI)</th>
<th>p-value</th>
<th>p-value for the interaction</th>
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<tbody>
<tr>
<td>Disease progression</td>
<td></td>
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<tr>
<td>HER2-positive</td>
<td>163/875</td>
<td>85/804</td>
<td>0.47 (0.37-0.62)</td>
<td>&lt;0.001</td>
<td>0.47</td>
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<tr>
<td>HER2-negative</td>
<td>20/92</td>
<td>7/82</td>
<td>0.34 (0.14-0.80)</td>
<td>0.014</td>
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<tr>
<td>Death</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>HER2-positive</td>
<td>55/875</td>
<td>38/804</td>
<td>0.66 (0.43-0.99)</td>
<td>0.017</td>
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<tr>
<td>HER2-negative</td>
<td>10/92</td>
<td>1/82</td>
<td>0.08 (0.01-0.64)</td>
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</tbody>
</table>

DR MILLER: I had used the Oncotype DX assay for a couple of patients with node-positive disease before Kathy Albain’s presentation in December 2007 (Albain 2007; [5.1]). I don’t use it routinely for patients with node-positive disease because we have one study, which is a subset analysis, and the numbers are small. But I believe it tells us about consistent biology.

At this point, I’ve used it in special situations, such as for patients who have a higher risk from chemotherapy, patients who are opposed to chemotherapy but would consider it if I can show them substantial benefit and patients with particular social situations in which chemotherapy would be difficult and they would like to avoid it if the predicted benefit would be small or nonexistent. I’ve certainly found it helpful in some of those situations.

DR LOVE: Sandy, are there any situations in which you might want to use the Oncotype DX assay for patients with node-positive tumors?

DR SWAIN: I have done it for several patients. The only caveat is that you still have a 40 percent risk of recurrence even for the patients at low risk. It makes us nervous about not using chemotherapy, because we know the risk is so high. I’m not sure that’s a good rationale because it may be that their risk is high, but we’re not doing them any good with chemotherapy and they can develop toxicity. So I would like to see more data, and I know investigators were talking about extending the TAILORx trial to include patients with node-positive disease.

<table>
<thead>
<tr>
<th>Low-risk Recurrence Score (&lt;18)</th>
<th>N</th>
<th>10-year DFS¹</th>
<th>10-year OS²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-risk Recurrence Score (18-30)</td>
<td>46</td>
<td>49%</td>
<td>68%</td>
</tr>
<tr>
<td>High-risk Recurrence Score (≥31)</td>
<td>47</td>
<td>43%</td>
<td>51%</td>
</tr>
</tbody>
</table>

¹ Stratified log-rank \( p = 0.017 \) at 10 years; ² stratified log-rank \( p = 0.003 \) at 10 years; DFS = disease-free survival; OS = overall survival


New strategies for ER-positive disease

Track 21

DR LOVE: Peter, what are your thoughts on the duration of adjuvant endocrine therapy?
DR RAVDIN: I believe it’s reasonable to continue therapy in some situations beyond five years. We have data that the disease remaining after five years of hormonal therapy is sensitive to additional hormonal therapy from both the ATAC trial (Forbes 2008; [6.1]) and the National Cancer Institute of Canada Clinical Trials Group MA17 trial, which randomly assigned patients to placebo and letrozole after five years of tamoxifen (Goss 2008).

These patients have clearly hormonally sensitive tumors and still have a substantial risk of recurrence. The majority of the risk of recurrence and mortality for estrogen receptor-positive breast cancer does not occur within the first five years.

We were in a similar situation with tamoxifen a few years ago. We had absolutely no data until the long-term findings from the NSABP-B-14 study were reported (Fisher 2004). Up until that point, you had to have a serious discussion with the patient about the fact that we had no data on continuing endocrine therapy beyond five years. Some patients wanted to stop in that situation, and others felt that the only reason they were faring well was because of tamoxifen.

I believe many clinicians are swayed by the level of perceived patient risk. In other words, if the patient had multiple positive nodes, she had much greater enthusiasm for continuing the tamoxifen than if the patient had node-negative disease or had, for example, one to three positive nodes.

This is an ideal situation for a clinical trial assessment, because we truly don’t know.

DR LOVE: Based on what I see on Adjuvant!, it looks like in years five through 10 there is about a 20 percent risk of recurrence in node-positive disease and 10 percent in node-negative tumors. Is that in the ballpark?

DR RAVDIN: Absolutely. It’s discouraging that the recurrence rates remain high even after five years for patients with ER-positive disease. Even after 10 years, the recurrence rates are substantial.

6.1 ATAC Trial 100-Month Update — Carryover Effect: Increased Absolute Difference in Tamoxifen and Anastrozole at Five Years and Nine Years of Follow-Up

“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.”

DR LOVE: Terry, can you discuss which trials are available for patients who have completed five years of adjuvant therapy with an aromatase inhibitor, including your trial, NSABP-B-42?

DR MAMOUNAS: In NSABP-B-42 (6.2), patients with ER-positive disease who are postmenopausal and disease free after five years of an aromatase inhibitor or after five years of hormonal therapy consisting of two to three years of tamoxifen followed by two to three years of an aromatase inhibitor are randomly assigned to five years of letrozole or placebo.

The primary reason we’re doing this trial is to show whether a benefit exists and, if it does, at what cost. Issues arise with the aromatase inhibitors that we cannot ignore: decreased bone density, increased fracture rates and, potentially, cardiovascular effects. None of these data are so definitive that we can say the aromatase inhibitors have a detrimental effect, but prolonged estrogen deprivation may not be a good practice in terms of cardiovascular risk.

### 6.2
**NSABP-B-42: Adjuvant Letrozole After Completion of Five Years of Hormonal Therapy with Either an Aromatase Inhibitor or Tamoxifen Followed by an Aromatase Inhibitor**

**Eligibility**
- Postmenopausal
- No later than six months after completion of five years of hormonal therapy
- ER-positive and/or PR-positive
- Invasive breast cancer

**Primary Endpoint**
- Disease-free survival

**Secondary Endpoints**
- Survival, recurrence-free interval, distant recurrence-free interval, osteoporotic fracture rate, arterial thrombosis

**Target Accrual:** 3,840 over 5.25 years

**Current Accrual:** 1,343 (08/19/08)

**Date Activated:** August 14, 2006

**Study Contact**
National Surgical Adjuvant Breast and Bowel Project
Eleftherios P Mamounas, MD, MPH
Protocol Chair

**SOURCES:** NSABP-B-42 Protocol, October 2008; [www.nsabp.pitt.edu](http://www.nsabp.pitt.edu)

**SELECT PUBLICATIONS**
Allegra CJ et al. Initial safety report of NSABP C-08, a randomized phase III study of modified 5-fluorouracil (5-FU)/leucovorin (LCV) and oxaliplatin (OX) (mFOLFOX6) with or without bevacizumab (bev) in the adjuvant treatment of patients with stage II/III colon cancer. *Proc ASCO* 2008; Abstract 4006.


Fisher B et al. Five versus more than five years of tamoxifen for lymph node-negative breast cancer: Updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. *J Natl Cancer Inst* 2001;93(9):684-90. Abstract


Jones S et al. Extended follow-up and analysis by age of the US Oncology adjuvant trial 9735: Docetaxel/cyclophosphamide is associated with an overall survival benefit compared to doxorubicin/cyclophosphamide and is well-tolerated in women 65 or older. San Antonio Breast Cancer Symposium 2007; Abstract 12.


Pegram M et al. Phase II combined biological therapy targeting the HER2 proto-oncogene and the vascular endothelial growth factor using trastuzumab (T) and bevacizumab (B) as first line treatment of HER2-amplified breast cancer. San Antonio Breast Cancer Symposium 2006; Abstract 301.


Slamon D et al. BCIRG 006: 2nd interim analysis phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in Her2neu positive early breast cancer patients. BCIRG 006 Presentation. San Antonio Breast Cancer Symposium 2006; Abstract 52.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. The TC-TAC-TC/bevacizumab trial is a collaboration between US Oncology and the NSABP evaluating the role of adjuvant bevacizumab in combination with _______ for women with HER2-negative breast cancer.
   a. TC
   b. TAC
   c. Both a and b
   d. None of the above

2. In NSABP-C-08, which is assessing the safety and efficacy of adjuvant bevacizumab in patients with colon cancer, significantly more bowel perforations occurred in patients treated with bevacizumab and FOLFOX than in those receiving FOLFOX alone.
   a. True
   b. False

3. ECOG-E5103 is evaluating adjuvant bevacizumab with _______ in women with node-positive or high-risk, node-negative, HER2-negative disease.
   a. Paclitaxel
   b. Docetaxel
   c. AC
   d. AC → paclitaxel
   e. All of the above

4. For patients with HER2-positive early breast cancer, the BETH trial will determine the role of adjuvant bevacizumab in combination with _______.
   a. TCH
   b. Docetaxel/trastuzumab → FEC
   c. Both a and b
   d. None of the above

5. The interim analysis of a trial evaluating bevacizumab with trastuzumab as first-line therapy for HER2-positive, metastatic breast cancer reported a response rate of about _______.
   a. 75 percent
   b. 50 percent
   c. 25 percent
   d. Five percent

6. Which of the following anti-HER2 strategies is being tested with adjuvant chemotherapy in the ALTTO trial?
   a. Trastuzumab alone
   b. Lapatinib alone
   c. Lapatinib with trastuzumab
   d. Trastuzumab followed by lapatinib
   e. All of the above

7. For patients with metastatic disease that had progressed on trastuzumab, the combination of lapatinib and trastuzumab was superior to lapatinib alone.
   a. True
   b. False

8. Which biologic agent is being evaluated as neoadjuvant therapy in NSABP-B-40?
   a. Trastuzumab
   b. Lapatinib
   c. Bevacizumab
   d. All of the above

9. In a retrospective subset analysis of NSABP-B-31, patients with disease that was found to be HER2-negative upon retesting at the NSABP laboratory had a similar hazard ratio when treated with adjuvant trastuzumab to those patients with HER2-positive disease.
   a. True
   b. False

10. NSABP-B-42 is investigating an extended duration of adjuvant therapy with which aromatase inhibitor?
    a. Anastrozole
    b. Exemestane
    c. Letrozole
    d. All of the above
    e. None of the above

Post-test answer key: 1a, 2b, 3d, 4c, 5b, 6e, 7a, 8c, 9a, 10c
EDUCATIONAL ASSESSMENT AND CREDIT FORM

Adjuvant Therapy for Breast Cancer: Where We Are, Where We’re Headed
Proceedings from a Collaborative Education Session Held in Conjunction with the 50th Anniversary of the NSABP

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?

<table>
<thead>
<tr>
<th>Topic</th>
<th>4 = Very good</th>
<th>3 = Above average</th>
<th>2 = Adequate</th>
<th>1 = Suboptimal</th>
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<td>NSABP/US Oncology adjuvant TC-TAC-TC/bevacizumab study</td>
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<td>1</td>
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</tr>
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<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
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<td>3</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Clinical implications of the zoledronic acid data from ABCSG-12</td>
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</table>

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

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<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Statement</th>
<th>4 = Yes</th>
<th>3 = Will consider</th>
<th>2 = No</th>
<th>1 = Already doing</th>
<th>N/M = Learning objective not met</th>
<th>N/A = Not applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td>As a result of this activity, I will be able to:</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>N/M</td>
<td>N/A</td>
</tr>
<tr>
<td>• Compare and contrast the safety and efficacy of anthracycline- and nonanthracycline-containing adjuvant regimens when recommending chemotherapy for patients with early breast cancer.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>• Recall emerging safety data from ongoing studies when screening patients for enrollment into adjuvant bevacizumab trials.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>N/M</td>
<td>N/A</td>
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<tr>
<td>• Explain the clinical evidence and scientific rationale for ongoing trials evaluating combination biologic treatments for patients with HER2-positive early breast cancer.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>N/M</td>
<td>N/A</td>
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</tr>
<tr>
<td>• Critically assess the controversial efficacy of adjuvant trastuzumab in the setting of HER2-negative breast cancer, considering the value of central laboratory testing and subgroup analyses.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>• Incorporate the use of validated biomarkers and genomic assays into the quantification of disease risk and the selection of appropriate treatment for patients with breast cancer.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>• Devise an algorithm for the endocrine treatment of pre- and postmenopausal women with ER-positive early breast cancer, addressing total duration of therapy and the evolving role of bisphosphonates.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>• Discriminate the incremental risk of cardiotoxicity when selecting adjuvant systemic treatment for patients with Stage I to Stage III breast cancer.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>• Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>N/M</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

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:

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.

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

4 = Very good  3 = Above average  2 = Adequate  1 = Suboptimal

<table>
<thead>
<tr>
<th>Faculty</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincent T DeVita Jr, MD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Bernard Fisher, MD</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Charles E Geyer Jr, MD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Eleftherios P Mamounas, MD, MPH</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Kathy D Miller, MD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Mark D Pegram, MD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Peter M Ravdin, MD, PhD</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Sandra M Swain, MD</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Norman Wolmark, MD</td>
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<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderator</th>
<th>Knowledge of subject matter</th>
<th>Effectiveness as an educator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neil Love, MD</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Please recommend additional faculty for future activities:

Other comments about the moderator and faculty for this activity:

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:
☐ MD  ☐ DO  ☐ PharmD  ☐ NP  ☐ RN  ☐ PA  ☐ Other  .................................................

Medical License/ME Number: ................................................. Last 4 Digits of SSN (required): .................................................

Street Address: ................................................. Box/Suite: .................................................

City, State, Zip: .................................................

Telephone: ................................................. Fax: .................................................

Email: .................................................

Research To Practice designates this educational activity for a maximum of 4 **AMA PRA Category 1 Credits™**. 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: .................................................

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.ResearchToPractice.com/NSABP_2008/CME.