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Breast Cancer® UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

EDITOR

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INTERVIEWS

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TUMOR PANEL CASE DISCUSSION

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Breast Cancer Update
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OVERVIEW OF ACTIVITY

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 — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with expert 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.

LEARNING OBJECTIVES

- Integrate validated genomic assays into the clinical management of hormone receptor-positive, node-negative and node-positive early breast cancer.
- Explain the clinical unmet need that underpins ongoing research evaluating therapeutic options for patients with residual disease after neoadjuvant chemotherapy.
- Communicate the benefits and risks of extended adjuvant endocrine therapy for premenopausal and postmenopausal women with ER/PR-positive early breast cancer.
- Appraise the adjunctive role of bisphosphonates in the management of ER-positive and/or PR-positive early breast cancer, and identify patients who may benefit from this course of therapy.
- Demonstrate knowledge of existing treatment strategies and ongoing investigational approaches to the management of triple-negative breast cancer.
- Compare and contrast the efficacy, safety and current clinical utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens, considering HER2 and nodal status of the primary tumor.
- Implement a therapeutic algorithm for the sequential use of combination and/or single-agent chemotherapy that allows multiple lines of treatment for patients with metastatic breast cancer.
- Distinguish those patients with advanced breast cancer who may be eligible for first-line treatment with bevacizumab, and recognize the rationale for ongoing investigation of this agent in the adjuvant setting.
- Develop a strategy for the front-line and subsequent management of HER2-positive metastatic breast cancer, including patients with known CNS involvement.
- Counsel appropriately selected patients with breast cancer about the availability of ongoing clinical trial participation.

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INTERVIEW

Paul E Goss, MD, PhD

Dr Goss is Professor of Medicine at Harvard Medical School, Director of Breast Cancer Research at MGH Cancer Center, Co-director of the Breast Cancer Disease Program at DF/HCC and Avon Foundation Senior Scholar in Boston, Massachusetts.

Tracks 1-16

Select Excerpts from the Interview

Track 1

DR LOVE: Do you have a theoretical explanation for the antitumor activity observed with zoledronic acid in the ABCSG-12 trial presented at the plenary session of ASCO?

DR GOSS: One theory is that bone metabolism — the formation and resorption of bone — engenders packages of nutrients, from which cancer cells in the bone may benefit. Moreover, cancer cells located in metastases elsewhere

may either receive the circulating nutrients or pass through the bone and derive benefit from those nutritional growth factors. By slowing down bone metabolism, the amount of nutrients available is decreased.

A parallel data set to the Austrian study presented by Allan Lipton at the 2007 San Antonio meeting precisely supported this theory (Lipton 2007, 2008; [1.1]). He evaluated breast cancer recurrence based on bone mineral density and demonstrated that patients who were the most osteoporotic or osteopenic had the highest risk of recurrence. Their data suggested that accelerated bone metabolism might engender the growth of micrometastatic cancer.

If that turns out to be true, it will be an interesting and important observation that ushers in the idea that the more quiescent bone is in the presence of cancer, the better patient outcomes will be. That is a broad, sweeping statement and may not be true for all types of breast cancer.

1.1

Mortality Among Breast Cancer Patients with Bone Metastases and Reductions in Markers of Bone Resorption (NTX) during Zoledronic Acid (ZA) Treatment

	Status of NTX after three months of ZA	
Endpoint	E-E* (n = 36)	E-N† (n = 160)
Deaths	13.9%	6.9%
Median time to death	446 days	790 days

* E-E = persistently elevated NTX from baseline to after three months of zoledronic acid
† E-N = NTX normalized from baseline to after three months of zoledronic acid

"Most breast cancer patients with bone metastases receive bisphosphonates, which can lower their levels of biochemical markers of bone metabolism. Patients with bone metastases and high levels of N-telopeptide of type I collagen (NTX) are likely to experience skeletal-related events (SREs) and reduced survival. The purpose of this study was to assess whether zoledronic acid mediated reductions in NTX levels correlate with long-term benefits. This post hoc analysis investigated whether early (3-month) suppression of NTX levels during zoledronic acid therapy correlates with prolonged survival and a reduced risk of SREs in patients with breast cancer...

Baseline NTX was elevated in 196 (60%) patients. Of these patients, 149 (76%) normalized NTX (E-N) after 3 months of zoledronic acid, and 31 (16%) patients still had elevated NTX (E-E) at 3 months. Median survival was approximately 50% longer and the risk of SREs approximately 50% lower for patients whose NTX normalized compared with patients whose NTX remained elevated (P = .0004 and P = .0034, respectively). In all patients, the percentage reduction in NTX level versus baseline corresponded with continuous decreases in the risk of SREs, death, and bone lesion progression."

SOURCE: Lipton A et al. San Antonio Breast Cancer Symposium 2007;**Poster 508**.

Track 4

DR LOVE: Based on the ABCSG data (1.2), do you believe that zoledronic acid should be presented to patients as an option right now?

DR GOSS: Yes and no. We need to take some pause regarding the efficacy of zoledronic acid in terms of the disease-free survival benefit because it was a single, small trial. Fortunately, it can change practice in terms of bone preservation. I don't believe anyone will dispute that a premenopausal patient, regardless of her ER status, who will have her ovarian functioning suppressed ought to be treated preventively with bisphosphonate therapy because she will otherwise lose an unacceptable amount of bone during the initial years of therapy.

Is zoledronic acid the best bisphosphonate? Mechanistically, it is the most powerful, but do we need it to be that powerful? It may be important for premenopausal patients but not for postmenopausal patients. A Southwest Oncology Group trial (SWOG-S0307) is evaluating zoledronic acid versus ibandronate versus clodronate to determine which agent is the most effective.

1.2

ABCSG-12: Zoledronic Acid (ZDA) Added to Adjuvant Endocrine Therapy Prolongs Disease-Free Survival (DFS) for Premenopausal Patients with Hormone Receptor-Positive Early Breast Cancer

	First DFS event per patient, n	
	ZDA (n = 899)	No ZDA (n = 904)
Locoregional recurrence	10	20
Distant recurrence	29	41
Contralateral breast cancer	6	16
Secondary cancer	9	10
Death without prior recurrence	0	2

Hazard ratio (95% CI) for DFS, versus no ZDA = 0.643 (0.48-0.91), $p = 0.011$

SOURCE: Gnant M et al. *Proc ASCO* 2008;**Abstract LBA4**.

Track 5

DR LOVE: Would you discuss the long-term natural history of breast cancer and the rationale for extended adjuvant endocrine therapy?

DR GOSS: The MA17 trial we conducted, extending adjuvant endocrine therapy from five to 10 years with letrozole after tamoxifen, reflects the chronicity of solid tumor malignancies in some patients and the opportunity to interrupt the risk of late recurrences (Goss 2003).

MA17 intrigued me because it was placebo controlled and provided an opportunity to study the natural event rate of breast cancer after five years of tamoxifen. Another important aspect of the study, recently published in the *Journal of Clinical Oncology*, was the observation that even if patients received a placebo for a while — one to seven years — after completion of five years of tamoxifen and then received delayed, extended letrozole, they still derived a profound proportional reduction in the risk of recurrence and death (Goss 2008a; [1.3]).

A simple message from this study is that a driver on cancer cells puts the patient at risk for recurrence and that driver may be present all the time, as reflected by an elevated annual hazard of recurrence that continues monotonously over time (1.4). We should attempt to interrupt that process if the risk is reasonably high and it is safe to do so.

1.3

NCIC-CTG MA17: Late Extended Adjuvant Treatment with Letrozole (LET) — Outcomes for Women Assigned Placebo (PLAC) at the Initial Random Assignment After Unblinding

Efficacy outcomes for women who chose LET (PLAC-LET group) versus those who did not (PLAC-PLAC group)

Multivariate analysis

Outcome	Adjusted HR*	95% CI	*p*-value
Disease-free survival	0.37	0.23-0.61	<0.0001
Distant disease-free survival	0.38	0.20-0.73	0.004
Overall survival	0.30	0.17-0.53	<0.0001
Contralateral breast cancer	0.18	0.06-0.58	0.004

Calculations were from the time of original random assignment and excluded patients who died or experienced relapse prior to unblinding.
HR = hazard ratio (PLAC-LET to PLAC-PLAC); CI = confidence interval
* Adjusted for ethnicity, age, performance status, time from initial diagnosis to random assignment, pathologic N stage, hormone receptor status, prior chemotherapy and axillary node dissection status

SOURCE: Goss PE et al. *J Clin Oncol* 2008a;26(12):1948-55. **Abstract**

1.4

Optimizing the Duration of Adjuvant Endocrine Therapy

"Patients with estrogen receptor (ER)–positive tumors are at continued risk of relapse for many years after initial breast cancer diagnosis. Among women treated with tamoxifen for 5 years, more than half of all recurrences occur between 6 to 15 years after diagnosis. Although tamoxifen (and probably the aromatase inhibitors [AIs]) lower the risk of recurrence for several years after they are stopped, late recurrences and deaths remain a major clinical challenge. If we want to reduce morbidity and mortality from ER-positive breast cancer, we must focus on strategies to confront this challenge...

The results of MA.17 and NSABP B-33, taken in context with the other adjuvant endocrine trials reported in the last 5 to 7 years, strongly argue for a paradigm shift in the clinical research focus and management of patients with ER-positive breast cancer. We do not have the luxury of only focusing on treatments and outcomes during the first 5 years after diagnosis. We need to identify predictors of late recurrence and treatment approaches that will change the low, but unrelenting, risk of recurrence seen in patients with ER-positive breast cancer."

SOURCE: Lin NU, Winer EP. *J Clin Oncol* 2008;26(12):1919-21. No abstract available

Tracks 6-7

DR LOVE: Can you discuss the TEACH trial, which is evaluating delayed adjuvant treatment with lapatinib?

DR GOSS: TEACH is a pragmatic clinical trial in which patients could be randomly assigned to lapatinib or placebo for one year in a double-blinded manner if they had not or could not receive adjuvant trastuzumab at diagnosis for HER2-positive early breast cancer (1.5).

The phrase "had not or could not" includes the rare patient in the United States with the up-front diagnosis of HER2-positive breast cancer who lives too far away to receive intravenous therapy or objects to the side effects of trastuzumab or for whatever reason will not be treated with adjuvant trastuzumab. In other countries, patients are unable to access trastuzumab for HER2-positive breast cancer.

We wanted at least 50 percent of the patients to be within four years of diagnosis, and we recently completed enrollment of about 3,200 patients. Approximately 80 percent of the patients are within four years of diagnosis — 20 percent are within one year, 60 percent are between one and four years — and another 20 percent were diagnosed four or more years ago.

In TEACH we have a marvelous opportunity to observe the natural history and the event rate across all subsets, including premenopausal and postmenopausal patients with ER-positive versus ER-negative and node-negative versus node-positive disease.

1.5

TEACH: A Phase III Study of Adjuvant Lapatinib in Women with HER2-Positive Early Breast Cancer Who Did Not Receive Up-Front Trastuzumab

Protocol IDs: EGF105485, NCT00374322
Target Accrual: 3,000 (Active, not recruiting)

Eligibility

- HER2-positive (IHC 3+ or FISH amplified) confirmed by central laboratory
- Stage I to IIIC, node-negative or node-positive
- Completed (neo)adjuvant chemotherapy
- Received no adjuvant trastuzumab

Study Start Date: April 2006

Estimated Study Completion Date: August 2009

SOURCE: www.clinicaltrials.gov. Accessed October 15, 2008.

Track 10

DR LOVE: What are your thoughts about the treatment of metastatic breast cancer that progresses on chemotherapy and trastuzumab?

DR GOSS: When patients with metastatic breast cancer experience disease progression on chemotherapy and trastuzumab and could receive lapatinib/capecitabine, physicians struggle with whether to simply continue trastuzumab and switch the chemotherapy.

In the original registration trial that led to the approval of lapatinib/capecitabine (Geyer 2006), a third investigational arm was glaringly absent, which was to continue the trastuzumab and administer capecitabine. Another idea is that perhaps a second anti-HER2 therapy could be added to trastuzumab (O'Shaughnessy 2008).

In another study with patients whose metastatic breast cancer was progressing on trastuzumab, trastuzumab was evaluated with the addition of capecitabine versus capecitabine alone (Von Minckwitz 2008; [1.6]). The superior strategy was to continue the trastuzumab. That study supported what doctors have been thinking but have been challenged on so strongly: "HER2 positivity is like fuel injection. You can change the chemotherapy but you must keep the cap on the fuel injection. Just because the cancer is progressing does not mean that the need to block the HER2 pathway diminishes."

These data play against switching to lapatinib/capecitabine and may argue for switching chemotherapy but continuing trastuzumab and, eventually, possibly switching the anti-HER2 therapy.

1.6

Phase III Study of Capecitabine (X) versus Capecitabine/Trastuzumab (XH) for Patients with HER2-Positive Metastatic Breast Cancer Progressing during Trastuzumab Therapy

Endpoint	X (n = 78)	XH (n = 78)	*p*-value
Time to progression	5.6mo	8.2mo	0.03
Overall survival	20.4mo	25.5mo	Nonsignificant trend
Response rate	27%	48%	0.01
Clinical benefit rate	54.0%	75.3%	0.007

SOURCE: Von Minckwitz G et al. *Proc ASCO* 2008;**Abstract 1025**.

Tracks 15-16

DR LOVE: What are your thoughts about current trials evaluating bevacizumab in the adjuvant setting?

DR GOSS: I strongly believe that the angiogenesis inhibitors will be important in the adjuvant setting in a way that we haven't observed in the metastatic

setting. I recently published a paper with Ann Chambers from the University of Western Ontario in Canada reviewing experimental approaches for studying tumor dormancy and whether it offers a therapeutic target (Goss 2008b; [1.7]).

To be simplistic, you can create a two-by-two dormancy table with quiescent or proliferative on one axis and prevascularized or vascularized on the other axis. Clinically, we potentially have four types of dormancy. You may have quiescent, prevascularized dormancy, which means no microvasculature and cells are not dividing, which is highly refractory to currently understood anticancer therapy. Patients with such tumors will not benefit from the concomitant administration of angiogenesis inhibitors or any type of antiproliferative therapy.

For the prevascularized, proliferative and the vascularized, proliferative types of dormancy, I believe that Judah Folkman's pioneering concepts will turn out to be correct. Anti-angiogenic therapy will block recurrences of solid tumor malignancy profoundly because it will prevent that critical vascularization required for tumor growth. Dr Folkman postulated what many people have shown — the tumor can rest for a long time before it is capable of crossing a "magical" threshold to vascularization.

DR LOVE: What about the other belief, that anti-angiogenic agents normalize the tumor vasculature and allow better delivery of oxygen or chemotherapy?

DR GOSS: That is an apparent contradiction, but I believe both theories are correct. Is it prevention of vascularization that will inhibit tumor growth, or is it the normalization of tumor vasculature that will allow therapy to be more effectively delivered?

In a vascularized tumor, anti-angiogenic therapy may improve blood flow and enhance radiation therapy and the delivery of chemotherapy, or you can

1.7 **Lessons Learned from Experimental Models of Tumor Dormancy**

"Many mechanisms for tumor dormancy have been proposed. Experimental studies designed to clarify tumor dormancy have described two classes of metastatic dormancy: dormant, solitary tumor cells which are quiescent, undergoing neither cell division nor apoptosis, and 'dormant', pre-angiogenic micrometastases, in which proliferation is balanced by apoptosis, resulting in no increase in size...

There is clinical evidence for both these classes of dormant metastases. Importantly, tumor cells in these two states of dormancy are expected to be differentially responsive to therapy. Cells in actively dividing but pre-angiogenic micrometastases should be responsive to cytotoxic and endocrine therapies that target dividing cancer cells, and their conversion to vascularized metastases should be prevented by anti-angiogenic strategies. In contrast, dormant, quiescent cells have been shown, at least in one experimental model, to be unaffected by therapy that targets actively dividing cells, and cytotoxic therapy did not prevent the outgrowth of late-developing metastases."

SOURCE: Goss P et al. *APMIS* 2008b;116(7-8):552-68. **Abstract**

catch the micrometastases at that critical juncture when they're beginning to develop microvasculature and stop that from happening at all. I believe we are seeing two different concepts of how the same therapy works.

One addresses established cancer, with a rich but dysfunctional blood supply that impedes delivery of therapy, versus absolutely discouraging the development of both normal and abnormal vasculature, which is necessary to encourage tumor growth. ■

SELECT PUBLICATIONS

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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**

Forbes JF et al. **ATAC: 100 month median follow-up (FU) shows continued superior efficacy and no excess fracture risk for anastrozole (A) compared with tamoxifen (T) after treatment completion.** San Antonio Breast Cancer Symposium 2007;**Abstract 41**.

Geyer CE et al. **Lapatinib plus capecitabine for HER2-positive advanced breast cancer.** *N Engl J Med* 2006;355(26):2733-43. **Abstract**

Gnant M et al. **Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12.** *Proc ASCO* 2008;**Abstract LBA4**.

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* 2008a;26(12):1948-55. **Abstract**

Goss P et al. **New clinical and experimental approaches for studying tumor dormancy: Does tumor dormancy offer a therapeutic target?** *APMIS* 2008b;116(7-8):552-68. **Abstract**

Goss PE et al. **A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer.** *N Engl J Med* 2003;349(19):1793-802. **Abstract**

Lin NU, Winer EP. **Optimizing endocrine therapy for estrogen receptor-positive breast cancer: Treating the right patients for the right length of time.** *J Clin Oncol* 2008;26(12):1919-21. **Abstract**

Lipton A et al. **Normalization of bone markers is associated with improved survival in patients with bone metastases from solid tumors and elevated bone resorption receiving zoledronic acid.** *Cancer* 2008;113(1):193-201. **Abstract**

Lipton A et al. **Survival in breast cancer patients with bone metastases and reductions in markers of bone resorption during zoledronic acid treatment.** San Antonio Breast Cancer Symposium 2007;**Poster 508**.

O'Shaughnessy J et al. **A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy.** *Proc ASCO* 2008;**Abstract 1015**.

Von Minckwitz G et al. **Capecitabine vs capecitabine + trastuzumab in patients with HER2-positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05).** *Proc ASCO* 2008;**Abstract 1025**.

INTERVIEW

Martine J Piccart-Gebhart, MD, PhD

Dr Piccart-Gebhart is Chair of the Breast International Group and Head of the Medicine Department at the Jules Bordet Institute in Brussels, Belgium.

Tracks 1-17

Select Excerpts from the Interview

Tracks 2-3

DR LOVE: How do you treat patients with smaller, node-negative, HER2-positive tumors?

DR PICCART-GEBHART: This is a real problem in daily clinical practice. Given that these patients were not allowed to enter the adjuvant trials, we have no data. I interviewed my colleagues and discovered that many do what I do, although it's based strictly on intuition. I am offering trastuzumab to women who have tumors between five millimeters and one centimeter. For tumors smaller than five millimeters, I am less comfortable with such a recommendation.

So, although tumor size has clear prognostic significance, I still believe the biology is bad. You could argue that these women should only receive an anthracycline-based chemotherapy regimen. However, trastuzumab is such an elegant therapy.

DR LOVE: Would you consider trastuzumab alone, without chemotherapy, for those patients?

DR PICCART-GEBHART: No, I would not do that presently because no data exist for that approach either. You would be doing two things that are not at all evidence based. For these women, I prefer the treatments that have been tested.

DR LOVE: Does ER status affect your decision with the smaller tumor?

DR PICCART-GEBHART: Not really. In the HERA trial, we saw a different pattern of relapse in women who had ER-positive versus ER-negative tumors (Untch 2008; [2.1]). The cancer in women with ER-negative disease tends to recur early when they don't receive trastuzumab. We observed this in the control arm of the trial. For women with ER-positive disease who were not receiving trastuzumab, we do not see an early peak of relapse. The relapse rate also appears to be lower, although it could simply be a time effect. I don't believe we can make any treatment decision based on this observation. It could be that the patients with ER-positive disease also relapse at a high rate, but it happens a little later.

Track 4

DR LOVE: Can you discuss the issue of anthracycline- versus nonanthracycline-containing chemotherapy for node-positive, HER2-positive disease?

DR PICCART-GEBHART: That's a hot topic. In Europe, we are selecting the type of chemotherapy based on risk factors for cardiotoxicity, including age, obesity, poorly controlled hypertension and a left ventricular ejection fraction that is on the low end of the normal range prior to initiating therapy. For patients who are at a higher risk for cardiotoxicity, it is reasonable to choose a nonanthracycline-based chemotherapy.

I stick to TCH, the regimen that has been piloted in the BCIRG 006 study (Slamon 2006). It is important to be able to clearly explain to patients the side effects they can expect with this regimen.

DR LOVE: How would you treat a 38-year-old woman who has five positive nodes and is otherwise perfectly healthy?

DR PICCART-GEBHART: We have two options. The five positive nodes are worrisome and indicate a higher risk for an early relapse. You do not want to administer a six-month chemotherapy regimen and then start trastuzumab. It makes sense for such a woman to receive TCH or utilize our European approach, which is three cycles of FEC — this is anthracycline based but only three cycles — and then move on to a taxane, which can be docetaxel or paclitaxel, administered concomitantly with trastuzumab.

2.1

HERA: Absolute and Relative Treatment Effects on Disease-Free Survival (DFS) Comparing One-Year Trastuzumab to Observation According to Hormone Receptor (HR) Status

Population/treatment	No. of patients	No. (%) of DFS events	Three-year DFS %	Difference in three-year DFS	Hazard ratio
Overall study population					
One-year trastuzumab	1,703	218 (12.8%)	80.6%	6.3%	0.64
Observation	1,698	321 (18.9%)	74.3%		
HR-negative					
One-year trastuzumab	843	131 (15.5%)	76.4%	6.1%	0.62
Observation	843	198 (23.5%)	70.3%		
HR-positive					
One-year trastuzumab	860	87 (10.1%)	84.6%	6.6%	0.68
Observation	855	123 (14.4%)	78.0%		

"The observation group among the hormone receptor-negative cohort (both ER and PgR reported as negative) experienced a very high risk of early recurrence, which was reduced for the trastuzumab group. Among patients with negative hormone receptors, the risk of relapse declined substantially during the second and third years of follow-up for the observation group and during the third year of follow-up for the trastuzumab group. By contrast, for the hormone receptor-positive cohort, the risk of relapse for both treatment and observation groups was relatively consistent over time, with the trastuzumab treatment effect apparent both early and later during follow-up."

SOURCE: Untch M et al. *Ann Oncol* 2008;19(6):1090-6. **Abstract**

Tracks 5-6

DR LOVE: Can you discuss the ALTTO adjuvant trial?

DR PICCART-GEBHART: When we design these trials, we have a responsibility to ask interesting questions. With the ALTTO study, we felt that it was important to compare the relative merits of two anti-HER2 treatments (2.2).

The single-agent lapatinib arm has not made everyone comfortable, but we believe that the lapatinib data in metastatic breast cancer are encouraging. It is important to examine what a small molecule administered orally can do, as opposed to an antibody that must be administered in a hospital setting. In some countries in the world, it might be a problem to go to the hospital every three weeks for a full year.

The other arms are exciting. One of them is exploring the sequence of the two drugs — three months of trastuzumab, a short washout period and then lapatinib to complete a year of treatment. The third arm, which could be the winner, is the combination of the two agents.

Chemotherapy can be introduced in two ways. One is to administer the chemotherapy first, and you have a lot of flexibility in the choice of chemotherapy regimen. The second option is the concurrent administration of the biologics with paclitaxel. Paclitaxel was chosen because the only safety data available at this time are with paclitaxel. We will probably introduce an option for docetaxel in the near future because we are beginning to see data there.

2.2

Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) Trial: Proposed Design

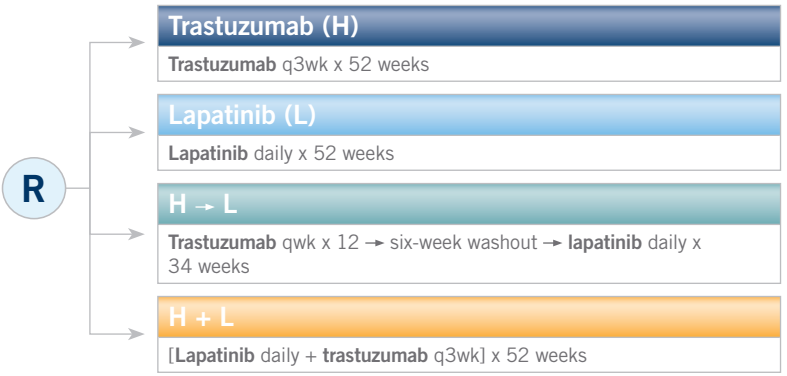
Protocol IDs: BIG 2-06, NCCTG-N063D
Target Accrual: 8,000

Eligibility

- HER2-positive breast cancer

In STRATUM 1, patients will receive weekly paclitaxel together with the anti-HER2 targeted therapy after anthracycline-based (neo)adjuvant chemotherapy

STRATUM 2 will comprise patients who complete all (neo)adjuvant chemotherapy prior to administration of targeted therapy*



* STRATUM 2: Trastuzumab qwk for first 12 weeks, then q3wk if continued

Study Contacts

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SOURCE: *Breast International Group Newsletter* Spring 2007;9(1).
Available at: **www.breastinternationalgroup.org**.

Currently, the ALTTO trial is requiring patients to receive anthracyclines, but this may also change. We don't want to be in a situation when the trial is finished in which people tell us anthracyclines are no longer needed. We are hoping to be able to allow regimens such as TCH to be used in the trial.

DR LOVE: What do we know about the safety of the paclitaxel/lapatinib combination and the combination of paclitaxel with lapatinib/trastuzumab?

DR PICCART-GEBHART: Initially we chose the doses on limited data, which now have been expanded. It has become apparent that some women experience severe diarrhea with the doses we initially selected. Although it is possible to manage this type of toxicity in sophisticated cancer centers, this trial should mean something to practices all around the world.

We made the decision to reduce the dose of lapatinib to 750 milligrams instead of the 1,000-mg dose, but we did not touch the dose of paclitaxel. We know from experiences in two cancer centers, Memorial Sloan-Kettering (Dang 2008) and the Mayo Clinic in Florida, that when you reduce the dose of lapatinib, you can continue with the treatment. We assume that if we start with this lower dose, the toxicity will be acceptable. We will monitor patients extremely closely in the adjuvant study. We hope that this is not going to compromise efficacy, but we could not run the risk of toxic deaths in a study such as the ALTTO trial.

Tracks 11-12

DR LOVE: Can you discuss the main findings of the ABCSG-12 study?

DR PICCART-GEBHART: This is a fascinating trial. If the results can be duplicated in a second study, I believe we will be entering a new era in the fight against the disease. The focus will shift away from the tumor toward the importance of the host.

We have to remember that ABCSG-12 was highly selective with its entry criteria (Gnant 2008). It was a trial for premenopausal women with endocrine-responsive breast cancer whose physicians were comfortable not administering chemotherapy. The first randomization was between two endocrine treatment strategies. The second randomization was to zoledronic acid every six months or placebo.

DR LOVE: A fair number of patients with node-positive disease were enrolled on this study, yet the five-year relapse rate was approximately six percent, which is striking.

DR PICCART-GEBHART: That's not so surprising to Europeans because we have been defending endocrine therapy for a long time. For women who do not have massive nodal involvement and whose tumor is highly endocrine responsive, we are convinced that the benefit of chemotherapy is small or nonexistent.

We have to remember that this was not a broad population but a highly selected population. Therefore, we have to wait for confirmation from one of

the other trials that has examined a larger population. When I evaluated all the preclinical work during the past 10 years that exists on bisphosphonates, particularly zoledronic acid, I began to believe that these drugs might have potential beyond ER-positive breast cancer.

I am optimistic. I believe the AZURE trial will confirm these data. AZURE is a trial for patients with node-positive disease that can be ER-positive or ER-negative. It includes younger and older women, so it will be more representative of the breast cancer population. The bisphosphonate is also administered in a more intensive fashion. If this trial is positive, I believe this agent will become a standard treatment.

DR LOVE: ABCSG-12 reported a striking 35 percent decrease in relapse rate (Gnant 2008). What was interesting was that it wasn't only in bone. It was in contralateral primary tumors and metastatic disease. Can you talk about the seed and soil hypothesis that you presented in your ASCO discussion of this paper?

DR PICCART-GEBHART: This requires that we speculate about breast cancer progression models. The seed and soil hypothesis is that breast cancer cells leave the breast much earlier than we think, find a niche in bone and from there metastasize to other organs and even go back to the initial site where they came from in the breast.

We think this occurs only in a certain type of patient. It is similar to what Larry Norton has been showing recently (Norton 2006), even before knowing about the results of the Austrian trial.

The ABCSG-12 trial is challenging our belief about this stepwise progression model, in which the cancer cell is first in the breast and then travels to the nodes and elsewhere. Maybe that's not at all what is happening in the real world.

Track 13

DR LOVE: In your ASCO discussion, you cautioned people about translating these data into practice. Right now, do you discuss this with your patients as a possibility?

DR PICCART-GEBHART: I am talking to my patients who are in exactly the scenario of the Austrian study — for example, patients whom I am treating with goserelin and tamoxifen. I've been telling my patients that I am waiting for the presentation of a second study, I hope by the end of this year.

So I've scheduled appointments for these patients for the beginning of 2009, and I've asked them to go to a dentist beforehand for a baseline evaluation because of the small risk of osteonecrosis of the jaw (ONJ). Although ONJ was not observed in the Austrian study, we know that it is a potential complication of bisphosphonate therapy.

Again, I don't know what will happen at the beginning of 2009, but if the second study is positive, then it's an easy decision. We will start administering

this agent to patients. If AZURE is not reported at San Antonio, then women have to make a decision for themselves after the full explanation of potential benefits and risks.

Track 16

DR LOVE: What are your thoughts about continuation of hormonal therapy for postmenopausal patients who have received five years of an aromatase inhibitor?

DR PICCART-GEBHART: I belong to the group of people who view hormone receptor-positive breast cancer as a disease that might be difficult to cure and might require lifelong treatment. If we are able to conduct good translational research in some of the big endocrine therapy trials, and if we are able to complete pharmacogenetic studies, we might be able to identify those patients who are at risk for long-term relapses.

Perhaps not all women with hormone receptor-positive breast cancer are at risk for long-term relapses, but right now, we don't have a way to identify who is at risk and who is not. In our practice, we observe women who have these relapses occurring nine, 12, 15 years after initial therapy.

If you believe in the long-term risk, then stopping an aromatase inhibitor after five years doesn't make a lot of sense. I am trying to continue treatment for up to seven, eight, sometimes 10 years. I recognize that we have few data, but it's a question of philosophy and how you view this disease. Unfortunately, this is a disease that probably has to be viewed as a chronic one, requiring continuous endocrine manipulation. ■

SELECT PUBLICATIONS

Dang CT et al. **Preliminary safety results of dose-dense (dd) doxorubicin and cyclophosphamide (AC) followed by weekly paclitaxel (P) with trastuzumab (T) and lapatinib (L) in HER2 overexpressed/amplified breast cancer (BCA).** *Proc ASCO* 2008;**Abstract 518**.

Gnant M et al. **Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12.** *Proc ASCO* 2008;**Abstract LBA4**.

Norton L, Massagué J. **Is cancer a disease of self-seeding?** *Nat Med* 2006;12(8):875-8. No abstract available

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

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.** San Antonio Breast Cancer Symposium 2006;**Abstract 52**.

Smith I et al; HERA study team. **2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: A randomised controlled trial.** *Lancet* 2007;369(9555):29-36. **Abstract**

Untch M et al; HERA Study Team. **Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial.** *Ann Oncol* 2008;19(6):1090-6. **Abstract**

Julie R Gralow, MD, John Mackey, MD and Hope S Rugo, MD

Tracks 1-23

Select Excerpts from the Discussion

Tracks 1, 4-5

Case 1 from the practice of John Mackey, MD

A premenopausal woman with a 5-mm, intermediate-grade, ER-positive, HER2-positive, node-negative invasive ductal carcinoma who received tamoxifen alone as adjuvant therapy

DR LOVE: How do you generally approach the care of patients with subcentimeter, node-negative, HER2-positive tumors?

DR MACKEY: For patients with these small tumors, we do not have proof of benefit from adjuvant trastuzumab. The adjuvant trastuzumab trials didn't include patients with tumors this small. At the end of the day, we have no randomized trial evidence suggesting this would be of benefit. And, unfortunately, with an effective drug such as trastuzumab, it has to be combined with chemotherapy in the adjuvant setting — at least that's where we have the evidence.

DR GRALOW: This is a tough situation because I believe trastuzumab has potential to add benefit. I don't know how much this benefit is dependent upon the synergy with chemotherapy. Within the Southwest Oncology Group, we've been talking about aromatase inhibitors with a HER2-targeted agent, at least in an ER-positive, HER2-positive setting.

We will be participating in a trial evaluating paclitaxel with trastuzumab in a group of patients with node-negative disease who have otherwise good risk features. We'll knock out the anthracycline, and weekly paclitaxel is less toxic than docetaxel/carboplatin. We struggle, however, with the thought that if we're not using chemotherapy, are we providing as much benefit from trastuzumab? If you send out for the Onco*type* DX 21-gene Recurrence Score, these patients always fall in the high-risk category.

DR LOVE: Hope, what would you expect from hormonal therapy for a patient with ER-positive, HER2-positive disease?

DR RUGO: We don't have a whole lot of data. In the trial that randomly assigned patients with ER-positive, HER2-positive, hormone therapy-naïve metastatic disease to anastrozole with or without trastuzumab, the response rate for anastrozole was not particularly high and the duration of response was particularly short at only 2.4 months. Even when trastuzumab was added, the results weren't fabulous, although they were better than with anastrozole alone (Mackey 2006; [3.1]).

I believe, however, that the adjuvant setting is different. For patients with low-risk disease, hormonal therapy may be important. We don't have data

3.1

TAnDEM: A Randomized Trial Evaluating Anastrozole with or without Trastuzumab for Patients with HER2-Positive, Hormone Receptor-Positive Metastatic Breast Cancer (N = 208)

Parameter	Anastrozole	Anastrozole + trastuzumab	*p*-value
Median progression-free survival	2.4 months	4.8 months	0.0016
Partial response rate	6.8%	20.3%	0.018
Clinical benefit rate	27.9%	42.7%	0.026
Overall survival	23.9 months	28.5 months	0.325
Overall survival for patients without liver metastasis*	32.1 months	41.9 months	0.0399

* Unplanned subgroup analysis

SOURCE: Mackey JR et al. San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

indicating that tamoxifen is not effective for that population. It simply isn't as effective as it is for patients with HER2-normal disease. I would treat a patient with HER2-positive disease as I would treat a patient with HER2-negative disease and use hormonal therapy. The bigger question is, do you add chemotherapy with or without trastuzumab?

DR LOVE: Julie, what about your trial for this patient, SWOG-S0307?

DR GRALOW: SWOG-S0307 is comparing three different bisphosphonates. We're using clodronate as our standard arm. The comparators are three years of oral ibandronate versus three years of a dose-intensive zoledronic acid regimen that is administered monthly for six months and then on an every three-month schedule.

This patient would be a candidate for SWOG-S0307. The patients have to be receiving some form of systemic treatment, either hormonal therapy or chemotherapy. Trastuzumab alone wouldn't be sufficient for enrollment in this study. If, for whatever reason, she weren't eligible or declined participation in the trial, the question would be whether she would fit the criteria for the less intensive every six-month zoledronic acid regimen used in ABCSG-12 (Gnant 2008).

ABCSG-12 enrolled a population of premenopausal women who received endocrine therapy but not chemotherapy (Gnant 2008). This patient fits these criteria, although that group also received ovarian suppression. Something about ovarian suppression and shutting off estrogen and more rapid bone loss may be occurring in that study. I believe, however, she's one of the small percentage of patients with breast cancer who meet the criteria for that study. It would be reasonable to talk with her about the results from ABCSG-12.

DR LOVE: Hope, would you offer zoledronic acid to this patient?

DR RUGO: I believe the data from the ABCSG-12 trial were impressive, and the toxicity was modest (Gnant 2008; [3.2]). They had few events in either

arm, however, so it's a little early for me. We don't have a labeled indication for zoledronic acid every six months, and we haven't used it off study. However, I have encouraged patients to enroll on SWOG-S0307. I'm fascinated with the fact that patients are hesitant because of this huge flurry in the lay press about ONJ.

DR GRALOW: In SWOG-S0307, we have one documented case of ONJ in the 500 patients enrolled on the zoledronic acid arm. In the AZURE trial, approximately 1,500 patients have received zoledronic acid, and we've seen seven cases of ONJ. I would say that ONJ is a real entity. In the AZURE trial, they weren't proactive about oral/dental screening. We are not excluding anybody based on their oral health, but we are mandating a baseline dental exam so that we can monitor risk factors.

3.2

ABCSG-12: Select and Serious Adverse Events

	TAM (n = 435)	TAM + ZDA (n = 434)	ANA (n = 436)	ANA + ZDA (n = 439)
Serious adverse event				
Arthralgia	0.0%	0.2%	0.0%	0.2%
Bone pain	0.0%	0.0%	0.0%	0.2%
Fever	0.2%	0.2%	0.2%	0.4%
Fracture	1.3%	0.9%	0.9%	1.6%
Thrombosis	0.7%	1.1%	0.0%	0.0%
Uterine polyp	8.9%	11.4%	1.6%	1.1%
Periodontal disease	0.0%	0.2%	0.0%	0.2%

SOURCE: Gnant M et al. *Proc ASCO* 2008;**Abstract LBA4**.

Tracks 7-11

Case 2 from the practice of Julie R Gralow, MD

A 55-year-old woman diagnosed with bone and liver metastases two and a half years after completing adjuvant dose-dense AC followed by weekly paclitaxel for a triple-negative, node-positive tumor

DR LOVE: Hope, which treatment options would you have considered for this patient?

DR RUGO: I believe you need to balance whether to treat this patient with a taxane/bevacizumab-type approach or something else that might not produce hair loss, for which I believe most of us would choose a capecitabine-type approach. I don't combine capecitabine with bevacizumab because I don't believe we have sufficient data with that treatment approach yet.

I would offer her, if she had significant liver metastases, a paclitaxel/bevacizumab-type approach first. If she said, "The most important thing to me is to keep my hair intact," then I'd start with capecitabine.

DR LOVE: If you were going to use paclitaxel, would you use *nab* paclitaxel?

DR RUGO: For a patient who received paclitaxel two and a half years ago, we generally use paclitaxel. If the patient experienced toxicity with the weekly steroids, then I would make the case to use *nab* paclitaxel as a first-line approach. In fact, I believe most of us prefer using *nab* paclitaxel if we can. For a patient who's received prior paclitaxel, I'm comfortable using *nab* paclitaxel and avoiding the steroids, which I think markedly improves the tolerance to therapy.

In the next few months, we will begin a first-line Phase III randomized trial, a collaboration between CALGB and NCCTG, that randomly assigns women with chemotherapy-naïve metastatic disease to paclitaxel, *nab* paclitaxel or ixabepilone, and all patients receive bevacizumab as well. Patients will receive weekly therapy three out of every four weeks (3.3).

DR LOVE: How did this patient fare with the premedication with steroids in the adjuvant setting?

DR GRALOW: She didn't have any major problem with the steroids. I would prefer *nab* paclitaxel because you don't need steroids and antihistamines. I can probably use the drug at a somewhat higher dose, with at least randomized Phase II data suggesting more efficacy. Also, it's a shorter infusion time generally. So, if I can obtain insurance approval, certainly in the metastatic setting, it would be my preference.

3.3

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

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

Tracks 16-19

Case 3 from the practice of Hope S Rugo, MD

A 65-year-old woman who underwent a lumpectomy for a 1.8-cm, intermediate-grade, low ER- and PR-positive, HER2-negative breast cancer. She had lymphovascular invasion on pathologic exam and a micrometastasis (0.1 centimeters) on sentinel lymph node biopsy. Her Onco*type* DX Recurrence Score was 42

DR LOVE: John, what would you recommend for systemic therapy for this patient?

DR MACKEY: Technically, she has node-positive, HER2-negative disease and is in good health at age 65. In this case, we'd be offering chemotherapy as an option and hormonal therapy as a component of treatment. The chemotherapy we'd discuss for women with fewer than three positive nodes would be docetaxel/cyclophosphamide (TC). So we'd recommend four cycles of TC and discuss an aromatase inhibitor.

DR GRALOW: I agree that chemotherapy should be recommended in this case. In the TAILORx trial, she would clearly fall in the range where chemotherapy would be used. Considering the high Recurrence Score, I would probably favor an anthracycline/taxane-containing regimen as long as she had good cardiac function.

Off study, I like dose-dense AC → paclitaxel. I would talk with her about clinical trials, though. I believe it would be reasonable to offer her participation in the ongoing trial of AC versus paclitaxel (CALGB-40101). I believe that patients with high Recurrence Scores have chemotherapy-responsive disease, and the manipulations we make to obtain a higher response benefit these patients the most.

We use a lot of chemotherapy in patients who don't derive a lot of benefit from it, and the difference between CMF and dose-dense AC is not as great for those patients. She has a high Recurrence Score, however, suggesting a lot of potential benefit from chemotherapy.

DR RUGO: For true node-positive disease, we tend to use dose-dense AC → T or suggest a clinical trial. I've found patients to be fairly responsive to participating in ECOG-E5103, the bevacizumab trial, and less so to the AC versus paclitaxel trial (CALGB-40101).

In a 65-year-old patient with ER/PR-positive disease who has minimal disease in the nodes, I feel comfortable offering TC. She has a high Recurrence Score, which is a bit unusual. We went back and rechecked her HER2 status, and I called Genomic Health to find out if her HER2 status fell into the positive range, but it didn't.

In this particular situation, I would discuss both regimens with the patient and get a sense from the patient about how aggressive she wanted to be. I feel comfortable using TC as a regimen. Based on Hy Muss's presentation on elderly patients, evaluating capecitabine versus the physician's choice of AC or CMF (Muss 2008; [3.4]), I believe CMF is a reasonable option.

I would also encourage this patient to take an aromatase inhibitor. However, we have to keep in mind that this patient would also benefit from tamoxifen. Some patients tolerate tamoxifen better over time. So I believe either the switching approach or an aromatase inhibitor up front would be reasonable. We tend to use the aromatase inhibitor up front. She's also a candidate for SWOG-S0307, the bisphosphonate trial.

3.4

CALGB-49907: Efficacy of Standard Chemotherapy (CMF or AC) versus Capecitabine for Patients 65 Years Old or Older with Early Breast Cancer

Endpoint	Events	Hazard ratio (HR)	95% CI for HR	*p*-value
Relapse-free survival*		2.09	1.4-3.2	0.0006
CMF/AC (n = 326)	35 (11%)			
Capecitabine (n = 307)	60 (20%)			
	Deaths			
Overall survival*		1.85	1.1-3.1	0.019
CMF/AC (n = 326)	24 (7%)			
Capecitabine (n = 307)	38 (12%)			

HR > 1.0 favors standard chemotherapy
CI = confidence interval

* Multivariate analysis controlling for tumor size, number of positive lymph nodes and hormone receptor status

SOURCE: Muss HB et al. *Proc ASCO* 2008;**Abstract 507**.

DR LOVE: John, what are your thoughts about using the Onco*type* DX assay for node-positive disease?

DR MACKEY: We don't use the Onco*type* DX assay for patients with node-positive disease. The data presented by Kathy Albain are interesting and encouraging, but if you view the relapse rate for the women who received tamoxifen alone, even if they had a low Recurrence Score, a substantial number of recurrences still occurred (Albain 2007; [3.5]). So I don't believe that the omission of chemotherapy for patients with node-positive disease is fully established, based on any molecular marker.

DR GRALOW: I feel most comfortable using the Onco*type* DX assay in patients with only a little disease in the nodes, although I'm not sure that's where we'll end up. We are able to identify a group of patients with relatively chemotherapy-resistant disease. I agree entirely that one of the most important aspects of the study is that the group with positive nodes and low Recurrence Scores don't fare well and we need to do better.

We're struggling with the successor to that analysis. We've tried to add patients with node-positive disease to the ongoing TAILORx trial, but it was rejected outright by CTEP. We're considering a trial in which we will add biologic agents or use manipulations of the endocrine therapy for this group.

If this is the group with disease that is sensitive to endocrine therapy, maybe we should be asking additional endocrine questions, such as whether to add fulvestrant to an aromatase inhibitor. I feel comfortable omitting chemotherapy for a patient like this if her Recurrence Score is low because chemotherapy won't add benefit. I don't, however, feel comfortable telling her that she will have a terrific survival rate. ■

3.5

Prognosis for Postmenopausal Women with ER-Positive, Node-Positive Breast Cancer Treated with Tamoxifen Alone According to the Onco*type* DX Recurrence Score

	N	10-year DFS[1]	10-year OS[2]
Low-risk Recurrence Score (<18)	55	60%	77%
Intermediate-risk Recurrence Score (18-30)	46	49%	68%
High-risk Recurrence Score (≥31)	47	43%	51%

[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

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**.

Dickler MN et al. **Adjuvant (adj) bevacizumab (B) plus dose-dense (dd) doxorubicin/cyclophosphamide (AC) followed by nanoparticle albumin-bound paclitaxel (*nab*-p) in early stage breast cancer (BC) patients (pts): Cardiac safety.** *Proc ASCO* 2007;**Abstract 567**.

Gnant M et al. **Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with hormone-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12.** *Proc ASCO* 2008;**Abstract LBA4**.

Mackey JR et al. **Trastuzumab prolongs progression-free survival in hormone-dependent and HER2-positive metastatic breast cancer.** San Antonio Breast Cancer Symposium 2006;**Abstract 3**.

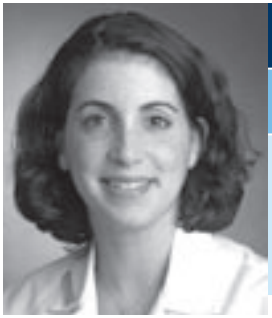
Miles D et al. **Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO.** *Proc ASCO* 2008;**Abstract LBA1011**.

Miller KD et al. **Phase II feasibility trial incorporating bevacizumab into dose dense doxorubicin and cyclophosphamide followed by paclitaxel in patients with lymph node positive breast cancer: A trial of the Eastern Cooperative Oncology Group (E2104).** San Antonio Breast Cancer Symposium 2007a;**Abstract 3063**.

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

Muss HB et al. **Standard chemotherapy (CMF or AC) versus capecitabine in early-stage breast cancer (BC) patients aged 65 and older: Results of CALGB/CTSU 49907.** *Proc ASCO* 2008;**Abstract 507**.

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**.



INTERVIEW

Erica L Mayer, MD, MPH

Dr Mayer is Instructor in Medicine at Harvard Medical School and Medical Oncologist at the Breast Oncology Center at Dana-Farber Cancer Institute and Brigham and Women's Hospital in Boston, Massachusetts.

Tracks 1-16

Select Excerpts from the Interview

Track 1

DR LOVE: Based on a recent Patterns of Care study we conducted, oncologists and investigators find the issue of significant residual tumor at the time of surgery after neoadjuvant chemotherapy very problematic. What are your thoughts on this issue?

DR MAYER: Within this population of women, it has been observed that approximately 20 percent achieve a pathologic complete response by the time

of surgery after neoadjuvant therapy. Over time this group fares well, as was evidenced in NSABP-B-18 and NSABP-B-27 (Rastogi 2008).

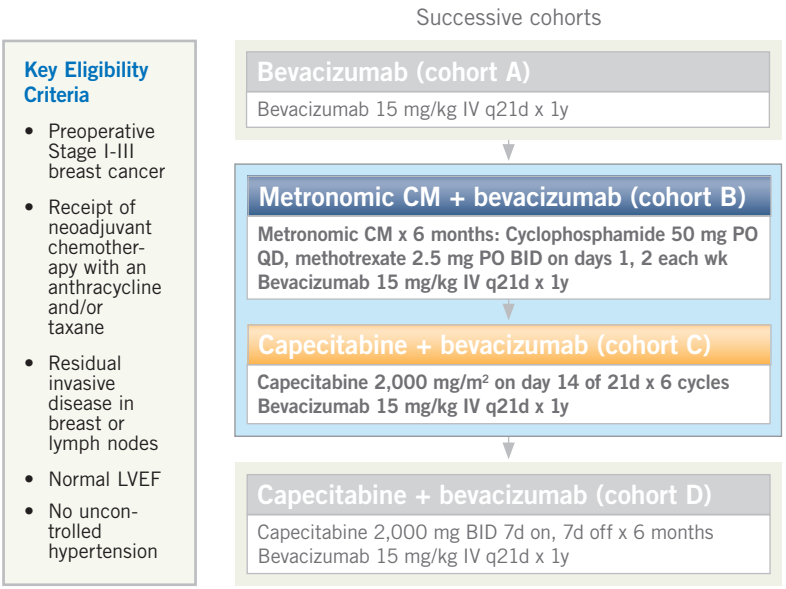
However, the women who achieve a lesser response have a worse prognosis and experience a higher rate of disease recurrence, possibly as a result of chemotherapy resistance, especially if a viable tumor is present after a neoadjuvant chemotherapy regimen is administered involving taxanes and anthracyclines.

With this scenario in mind, Hal Burstein and I developed a postoperative trial to study women who are considered to be at high risk and who may benefit from an alternative approach. Eventually, this study evolved into a multicenter collaboration and consists of four sequential cohorts (4.1).

The first consisted of one year of adjuvant bevacizumab, the second involved the use of bevacizumab in addition to metronomic chemotherapy (continuous low-dose oral chemotherapy with daily cyclophosphamide and weekly methotrexate) and the last two cohorts were capecitabine based: bevacizumab with a standard capecitabine dose and the Memorial Sloan-Kettering capecitabine schedule of seven days on, seven days off (Mayer 2008).

Safety data for cohorts B and C were presented at the 2008 ASCO meeting, with interesting toxicity differences (Mayer 2008). Patients on the metronomic

4.1 **A Multi-Institutional Pilot Study of Adjuvant Bevacizumab and Chemotherapy After Neoadjuvant Chemotherapy for High-Risk Breast Cancer: Cohorts B and C**



SOURCE: Mayer EL et al. *Proc ASCO* 2008;**Abstract 519**.

chemotherapy/bevacizumab arm experienced a higher incidence of hypertension, proteinuria and headache, whereas patients enrolled on the capecitabine-containing arm experienced more hand-foot syndrome, rash and diarrhea. Considering these results, I am curious about the underlying biologic mechanisms of each of these regimens.

Another observation we noted is the high incidence of recurrence. The three-year disease-free survival rate was approximately 60 to 70 percent for the entire group. If you evaluate the subgroups, the three-year disease-free survival rate was 50 percent for patients with triple-negative disease compared to 80 percent for patients with ER-positive disease.

Track 3

DR LOVE: What do we know about the activity of sunitinib in breast cancer, and what do you think about the NSABP postoperative study with sunitinib monotherapy?

DR MAYER: Sunitinib is the most developed of the tyrosine kinase inhibitors against VEGF, but it also demonstrates activity against other receptors, including PDGFR and C-KIT, giving it the reputation of a "dirty" receptor tyrosine kinase inhibitor. Recently, Hal Burstein and Kathy Miller published Phase II data on sunitinib monotherapy in breast cancer, demonstrating a low response rate within a refractory population (Burstein 2008; [4.2]).

Subsequently, other studies have evaluated sunitinib in breast cancer. Luca Gianni presented a small Phase I study on sunitinib with docetaxel (Mariani 2008), and Mark Kozloff presented data on sunitinib with paclitaxel (Kozloff 2007). Both data sets demonstrated relatively high response rates and are moving into further-phase studies.

Studies in the first-line refractory metastatic setting include large ongoing Phase III studies, with one comparing paclitaxel and sunitinib to the standard

4.2

Phase II Study of Sunitinib in Patients with Metastatic Breast Cancer (MBC) Previously Treated with an Anthracycline and a Taxane

"This study evaluated sunitinib activity and safety in patients with MBC. The clinical benefit rate with sunitinib treatment was 16%, with 11% of patients (n = 7) achieving a PR. Of note, clinical activity was seen irrespective of HER2 and ER status. Response rates of 15% in cases of triple-negative tumors, and 25% in trastuzumab-treated, HER2-positive tumors constitute provocative findings, given the limited treatment options available for such patients.

The safety profile of sunitinib in this study was similar to that of other single-agent sunitinib studies in patients with advanced cancer. The most frequently reported AEs were fatigue, nausea, diarrhea, mucosal inflammation, and anorexia. Most AEs were mild to moderate (grades 1 to 2) in severity."

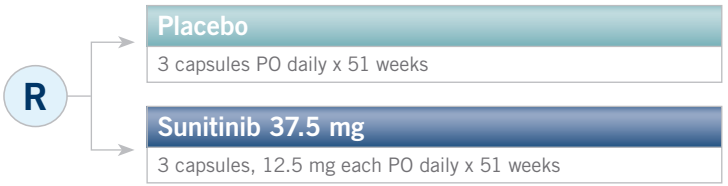
SOURCE: Burstein HJ et al. *J Clin Oncol* 2008;26(11):1810-6. **Abstract**

ECOG-E2100 paclitaxel/bevacizumab regimen. Although we have not seen a complete blockbuster data set yet, a robust program exists to develop sunitinib in breast cancer, and we are all awaiting the NSABP-B-45 study of adjuvant sunitinib monotherapy in women with residual disease after neoadjuvant chemotherapy (4.3).

4.3

NSABP-B-45: A Phase III Clinical Trial Comparing Adjuvant Sunitinib Malate to Placebo After Neoadjuvant Chemotherapy*

Target Accrual: 2,000 (Pending activation)



* Minimum of four cycles that included at least two of the following: an anthracycline, a taxane and cyclophosphamide

Select Eligibility Criteria

- Stage II, IIIA or IIIB (except T4d) invasive carcinoma before neoadjuvant therapy
- Residual invasive breast cancer after neoadjuvant therapy removed at surgery
- Neoadjuvant therapy with at least two of the following: an anthracycline, a taxane and cyclophosphamide
- HER2-negative disease

Primary Endpoint

- Invasive disease-DCIS-free survival improvement

Secondary Endpoints

- Survival, breast cancer-free interval, cardiac function, thyroid function, quality of life, validation of residual risk determination methods, exploration of potential biomarkers of response

SOURCES: NSABP Protocol Summaries, June 2008; www.nsabp.pitt.edu.

Track 4

DR LOVE: A lot of controversy has arisen with regard to the mechanism(s) of action of bevacizumab and whether it will work well in the adjuvant, postadjuvant or postneoadjuvant setting. What is your take on this controversy?

DR MAYER: The simplistic view of anti-angiogenics, cutting off the blood supply and starving the tumor, is the description I use with my patients. However, the actual mechanism is more sophisticated. Dr Rakesh Jain has proposed mechanisms of disordered tumoral blood flow coupled with increased permeability of fluids across blood barriers, making it difficult for chemotherapy to penetrate the tumor.

His theory suggests that with the addition of bevacizumab, blood flow to the tumor is normalized and the penetration of chemotherapy inside the tumor improves, decreasing the intratumoral hypertension (Jain 2008).

Although Jain's is a respected theory, another theory depicts VEGF receptors present on both the tumor and endothelial cells resulting in dual VEGF expression with the possibility of direct antitumor activity from both the tumor and the endothelial cells.

Another proposed theory suggests that endothelial cell precursors, derived from bone marrow, appear to leave the marrow in response to endothelial cell toxicity.

With the addition of chemotherapy, the combination could be highly irritating to vasculature, thus stimulating a release of endothelial precursors. When an anti-angiogenic agent is combined with chemotherapy, the agent works to "mop up" these precursors, helping to repair the vasculature.

Tracks 5-6

DR LOVE: Would you continue bevacizumab beyond disease progression if a patient who received chemotherapy and bevacizumab followed by maintenance bevacizumab responded well but then experienced slow disease progression?

DR MAYER: The RIBBON studies — RIBBON 1, RIBBON 2 and a proposal for RIBBON 3, which would specifically evaluate the idea of continuing bevacizumab — are currently addressing this question.

At present, we have no data sets to guide this decision. However, on occasion I have prescribed a continuation of bevacizumab in clinical practice.

If a patient responded well to chemotherapy with bevacizumab but had to discontinue the chemotherapy because of neuropathy, the patient could still benefit from bevacizumab. In general, however, I avoid bevacizumab in the second- and third-line settings because Phase III data indicate a lack of benefit.

DR LOVE: Recently, data have emerged suggesting that side effects such as hypertension can serve as predictors of response to bevacizumab. Do you believe a correlation exists?

DR MAYER: I am glad you asked because I have been following this story with interest. Drs George Sledge and Bryan Schneider recently reported data demonstrating a subset of individuals from the ECOG-E2100 trial who developed Grade III or greater hypertension and who seemed to have improved outcomes and improved overall survival (Schneider 2008; [4.4]).

Similar observations have been made in other tumor types. Perhaps hypertension represents a sort of pharmacodynamic marker that could be used in identifying individuals with sensitivity to angiogenesis inhibitor therapy. ■

4.4 Association of VEGF and VEGFR-2 Genetic Polymorphisms, Hypertension and Outcome with Bevacizumab in ECOG-E2100

"Recently, E2100 demonstrated an improvement in RR and PFS with the addition of bevacizumab to paclitaxel in the first-line metastatic setting of breast cancer. Although these drugs were largely touted as targeted therapy, we have had a difficult time identifying which patients will benefit most from them.

These agents all demonstrate clear therapeutic heterogeneity in that they are active in some patients but inactive and toxic in others. A biomarker to predict which patients might experience the most activity and least toxicity would be of clinical and scientific value. To our knowledge, these are the first data to describe biomarkers that seem to be associated with efficacy and toxicity for bevacizumab in cancer...

These data suggest that patients who had the VEGF-2578 AA genotype and the VEGF-1154 AA genotype had a superior median OS compared with patients with alternative genotypes...

The discovery of an association between those who experienced significant hypertension and an improved OS is also biologically provocative."

SOURCE: Schneider BP et al. *J Clin Oncol* 2008;26(28):4672-8. **Abstract**

SELECT PUBLICATIONS

Burstein HJ et al. **Phase II study of sunitinib malate, an oral multitargeted tyrosine kinase inhibitor, in patients with metastatic breast cancer previously treated with an anthracycline and a taxane.** *J Clin Oncol* 2008;26(11):1810-6. **Abstract**

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

Dang C et al. **The safety of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab in HER-2/neu overexpressed/amplified breast cancer.** *J Clin Oncol* 2008;26(8):1216-22. **Abstract**

Jain RK. **Lessons from multidisciplinary translational trials on anti-angiogenic therapy of cancer.** *Nat Rev Cancer* 2008;8(4):309-16. **Abstract**

Kerbel R. **Angiogenesis: What is the target?** Presentation. Breast Cancer Symposium 2008. No abstract available

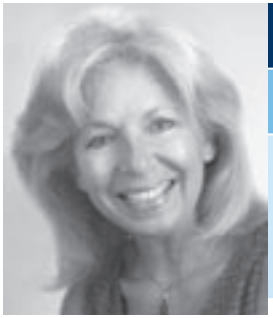
Kozloff M et al. **Preliminary results of a phase I study of sunitinib plus paclitaxel for first-line treatment of advanced breast cancer.** Breast Cancer Symposium 2007;**Abstract 163**.

Mariani G et al. **Sequential administration of sunitinib (SU) and docetaxel (D) in women with advanced breast cancer (ABC): An exploratory evaluation.** *Proc ASCO* 2008;**Abstract 14534**.

Mayer EL et al. **A pilot study of adjuvant bevacizumab and chemotherapy after neoadjuvant chemotherapy for high-risk breast cancer.** *Proc ASCO* 2008;**Abstract 519**.

Rastogi P et al. **Preoperative chemotherapy: Updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27.** *J Clin Oncol* 2008;26(5):778-85. **Abstract**

Schneider BP et al. **Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100.** *J Clin Oncol* 2008;26(28):4672-8. **Abstract**



INTERVIEW

Maria Theodoulou, MD

Dr Theodoulou is Associate Attending Physician of Breast Cancer Medicine Service in the Department of Medicine at Memorial Sloan-Kettering Cancer Center in New York, New York.

Tracks 1-8

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the issue of capecitabine dose and schedule?

DR THEODOULOU: It's interesting because, although capecitabine is a popular drug, a large dropout rate exists among patients attempting to adhere to the standard 2,500 mg/m^2 divided in two doses, 14 days on and seven days off. If we can evaluate an efficacious way of administering capecitabine in which we wouldn't compromise its ability to kill cells yet minimize toxicity, then I suspect patients could be treated for a much longer period.

It has been my practice not to rule out a regimen if patients do not tolerate it well but to make regimen adjustments instead with the goal of trying to home in on maintaining a clinical benefit while also minimizing toxicity. For some patients, I've been able to achieve a 10-day-on, seven-day-off treatment regimen, whereas for others I dose reduce. I've had about two dozen patients at any one time taking capecitabine, and they were all on different regimens with different tolerability.

Our group at Memorial has been fairly successful in evaluating capecitabine dose and schedule. We've recently published some Phase I results in the *Journal of Clinical Oncology* clearly demonstrating feasibility with the capecitabine schedule of one week on followed by one week off (Traina 2008; [5.1]). Capecitabine is now being combined with bevacizumab in non-HER2 overexpressing breast cell lines in a study that's about two thirds of the way toward completing accrual, and we're moving forward with opening a protocol evaluating capecitabine biweekly with lapatinib.

5.1

Phase I Study of a Novel Capecitabine Schedule Based on the Norton-Simon Mathematical Model in Patients with Metastatic Breast Cancer

"Experience has confirmed that mathematical modeling based on growth curve analysis can predict improved chemotherapy schedules. In animal models, this conceptual approach has determined that the 7/7 schedule of capecitabine preserves efficacy and reduces toxicity sufficiently to allow for significant dose escalation. Longer than 7 days of daily administration subjects the tumor-bearing host to greater toxicity and diminishing efficacy. That is, in preclinical models, capecitabine 7/7 provides the greatest acceptable dose-intensity and dose-density. We sought to determine the tolerability of this schedule in patients with advanced breast cancer.

The novel capecitabine schedule investigated in this population seems to be well tolerated, achieving an MTD of 2,000 mg bid when administered for 7 consecutive days followed by a 7-day rest. Patients were accrued to dose cohorts in a consecutive, nonrandomized fashion...

The most common capecitabine-related, grade 3 toxicities were HFS (17%) and diarrhea (6%). There were no grade 4/5 adverse events with this schedule."

SOURCE: Traina TA et al. *J Clin Oncol* 2008;26(11):1797-802. **Abstract**

Track 3

DR LOVE: What's your current algorithm for chemotherapy usage off study in the metastatic setting for a patient with ER-positive/HER2-negative disease who is not responding to hormonal therapy?

DR THEODOULOU: For those patients I prefer to use a bevacizumab-related regimen as early as possible, either trying to capture them first line, as in the studies reported recently by Kathy Miller and David Miles (Miller 2007; Miles 2008), or if they have been treated with other chemotherapy agents, trying to capture them as early on as possible. We don't have positive survival data currently with bevacizumab, but the response rates and the time to progression have been impressive.

DR LOVE: Are you using bevacizumab with capecitabine off study?

DR THEODOULOU: We're evaluating bevacizumab with biweekly capecitabine in our clinical trial. But if I have a choice off study currently, I administer bevacizumab with a taxane first. For a patient with indolent, minimal-

burden disease, I often use capecitabine as a single agent after anthracycline/taxane failures in the non-HER2 setting. If a patient's disease progresses on capecitabine, then I'll consider bevacizumab with a taxane.

I'm a big believer in quality of life and gentle treatment. "Innocent-bystander" organ toxicity is an important issue. Most of these patients become like family because they've been around so long, thankfully, and we are treating them for a long time. We evaluate their goals together for treatment, what their wants are and what they're willing to sustain with regard to frequency of office visits and potential side effects.

Track 4

DR LOVE: How do you approach the issue of HER2-positive metastatic disease, particularly in light of the fact that now some patients have received adjuvant trastuzumab?

DR THEODOULOU: For a patient who is trastuzumab naïve, I will administer trastuzumab. The chemotherapy regimen I use is dependent on prior therapy and how recently it was administered. Most commonly I administer a weekly taxane or vinorelbine. The choices, again, are based on the patient's lifestyle, goals of treatment, prior therapies and comorbidities.

If the patient experiences disease progression, then I springboard over to lapatinib with capecitabine. For a patient whose disease has recurred within six months of receiving trastuzumab, I administer lapatinib first. Once we reach one year, then I'm willing to consider another trastuzumab regimen.

We have many clinical trials, as most tertiary institutions do today, evaluating all sorts of HER inhibitors, whether it's HER1, HER2 or intracellular inhibition versus transjunctional membrane inhibition. The trials are exploding.

The presentation by Joyce O'Shaughnessy at ASCO this year was interesting. The study evaluated a combination of biologic agents — trastuzumab and lapatinib — in patients who were heavily pretreated, some with up to six prior regimens before entering the study. Patients were randomly assigned to lapatinib alone or in combination with trastuzumab. They reported significant clinical benefit with the combination and approximately a 12 percent benefit with lapatinib alone (O'Shaughnessy 2008; [5.2]). It appears that in the combination, lapatinib potentiated the trastuzumab benefit.

DR LOVE: What are the situations, if any, in which you might use the trastuzumab/lapatinib combination off study right now?

DR THEODOULOU: I would consider it for a patient with excellent cardiac function for whom a trastuzumab-based regimen had already failed and for whom lapatinib with capecitabine had already failed and if she were not a candidate for a clinical trial.

It is encouraging to know that a combination arm that we will be using in the adjuvant setting in the ALTTO trial is safe and feasible.

5.2

Lapatinib (L) with or without Trastuzumab (T) for Heavily Pretreated Patients with Metastatic Breast Cancer Experiencing Disease Progression on Trastuzumab Therapy

Parameter	L (n = 145)	L + T (n = 146)	Odds ratio	*p*-value
Response rate[1] (95% CI)	6.9% (3.4, 12.3)	10.3% (5.9, 16.4)	1.5 (0.6, 3.9)	0.46
Clinical benefit rate[2] (95% CI)	12.4% (7.5, 18.9)	24.7% (17.9, 32.5)	2.2 (1.2, 4.5)	0.01

Parameter	L (n = 145)	L + T (n = 146)	Hazard ratio	*p*-value
Median progression-free survival (95% CI)	8.1 weeks NR	12.0 weeks NR	0.73 (0.57, 0.93)	0.008
Median overall survival[3] (95% CI)	39.0 weeks NR	51.6 weeks NR	0.75 (0.53, 1.07)	0.106

[1] Confirmed complete responses (CR) + partial responses (PR)
[2] CR + PR + stable disease ≥ 6 months
[3] Intent-to-treat population
CI = confidence interval; NR = not reported
Odds ratio > 1, hazard ratio < 1 favors L + T

SOURCE: O'Shaughnessy J et al. *Proc ASCO* 2008;**Abstract 1015**.

Track 5

DR LOVE: Could you discuss the presentation at ASCO 2008 that reported preliminary safety results from your institution of dose-dense AC followed by weekly paclitaxel with trastuzumab and lapatinib?

DR THEODOULOU: Chau Dang's presentation at ASCO 2008 reported results of a 100-patient feasibility study of what is to be one of the four arms of the ALTTO study. On this feasibility study, patients were randomly assigned to paclitaxel weekly for 12 weeks in combination with lapatinib and trastuzumab from day one of the paclitaxel after their anthracycline-based treatment (Dang 2008a).

The primary endpoint of the trial was cardiac safety — defined as discontinuation of trastuzumab in combination with lapatinib resulting from cardiac death or congestive heart failure. If less than 20 percent of the patients were not able to complete, or if the cardiac toxicity was not any greater than what had been reported in adjuvant trastuzumab trials to date, that would be okay. But our trial was not okay. Patients couldn't tolerate the regimen. One third of these patients had extensive gastrointestinal side effects with diarrhea. Of the patients, 27 percent had to be pulled off the study, so the study was stopped at 95 patients, and the message of the study was, "This cannot be done" in the doses that were being administered for lapatinib with paclitaxel and trastuzumab.

Patients who then went on to continue paclitaxel with trastuzumab fared well, as did patients who continued lapatinib and trastuzumab. But it was that triplet that got patients into trouble. Obviously that fourth arm will change in the ALTTO trial by way of the dosing of lapatinib.

Track 6

DR LOVE: What do you think about the current data in terms of the use of lapatinib in a patient with brain metastases?

DR THEODOULOU: The initial trial by Geyer made everybody "sit up straight in their seats" when he reported 11 brain relapses in the capecitabine-alone arm and only four in the capecitabine with lapatinib arm (Geyer 2006; Cameron 2008).

A study at Dana-Farber also evaluated lapatinib in patients with brain metastases. They reported what we'd consider a minor tumor volume reduction — less than 25 percent of the volume that was initially presented as a reduction, with a lot of stable disease (Lin 2008; [5.3]). But a minor response is huge in patients with brain metastases.

5.3

Activity of Lapatinib in Patients with HER2-Positive Breast Cancer and Brain Metastases

Overall CNS activity	No. of patients (n = 39)	Percent
Overall response	1	2.6%
Complete response	0	0%
Partial response	1	2.6%
Overall non-CNS activity*	**No. of patients (n = 16)**	**Percent**
Overall response	4	25%
Complete response	0	0%
Partial response	4	25%
Stable disease ≥ 16 weeks (in both CNS and non-CNS sites)	6	15.4%

* Patients with measurable non-CNS disease

SOURCE: Lin NU et al. *J Clin Oncol* 2008;26(12):1993-9. **Abstract**

Track 7

DR LOVE: What schedule do you use when administering lapatinib/capecitabine off study?

DR THEODOULOU: I'm using our one-week-on, one-week-off capecitabine schedule. I haven't used the 14-day-on and the seven-day-off schedule for years.

DR LOVE: What are you seeing in terms of side effects and toxicity with that combination?

DR THEODOULOU: The mucositis and the diarrhea seen in the past have been attenuated markedly by using the biweekly capecitabine regimen. Lapatinib is interesting because patients do report diarrhea and acneiform rash with it, but it's tolerated pretty well. In these cases, I may choose to dose attenuate, but I am careful not to stop the regimen or dose attenuate both drugs. I'll play with the capecitabine dose more than anything else, but it's clear if a patient reports diarrhea that it's usually from the lapatinib.

With regard to the rash, not every patient will develop a rash, but those who do hate it. It's usually on the face and upper torso in the chest area. Often, it can be treated effectively with topical antibiotics. If not, I reduce the lapatinib by 250 milligrams. ■

SELECT PUBLICATIONS

Cameron D et al. **A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: Updated efficacy and biomarker analyses.** *Breast Cancer Res Treat* 2008;[Epub ahead of print]. **Abstract**

Dang CT et al. **Preliminary safety results of dose-dense (dd) doxorubicin and cyclophosphamide (AC) followed by weekly paclitaxel (P) with trastuzumab (T) and lapatinib (L) in HER2 overexpressed/amplified breast cancer (BCA).** *Proc ASCO* 2008a;**Abstract 518**.

Dang C et al. **The safety of dose-dense doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab in HER-2/neu overexpressed/amplified breast cancer.** *J Clin Oncol* 2008b;26(8):1216-22. **Abstract**

Geyer CE et al. **Lapatinib plus capecitabine for HER2-positive advanced breast cancer.** *N Engl J Med* 2006;355(26):2733-43. **Abstract**

Hayes DF et al. **Angiogenesis as targeted breast cancer therapy.** *Breast* 2007;16(Suppl 2):17-9. **Abstract**

Lin NU et al. **Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer.** *J Clin Oncol* 2008;26(12):1993-9. **Abstract**

Miles D. **Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO.** *Proc ASCO* 2008;**Abstract LBA1011**.

Miles D. **Bevacizumab in first-line treatment of metastatic breast cancer.** *Drugs* 2007;67(12):1800-1. **Abstract**

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

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* 2005;23(4):792-9. **Abstract**

O'Shaughnessy J et al. **A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy.** *Proc ASCO* 2008;**Abstract 1015**.

Traina TA et al. **Phase I study of a novel capecitabine schedule based on the Norton-Simon mathematical model in patients with metastatic breast cancer.** *J Clin Oncol* 2008;26(11):1797-802. **Abstract**

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **A study presented at the 2007 San Antonio meeting by Lipton and colleagues revealed that patients who had persistently elevated markers of bone metabolism (NTX) after three months of zoledronic acid experienced an increased likelihood of _____ compared to those with normalized NTX.**
   a. Death
   b. Skeletal-related events
   c. Both a and b
   d. None of the above

2. **According to findings from ABCSG-12, bisphosphonate therapy appears to provide which of the following benefits for premenopausal patients?**
   a. Reduction in contralateral breast cancer
   b. Reduction in locoregional recurrence
   c. Reduction in distant nonbone metastases
   d. All of the above

3. **In a recently published report from NCIC-CTG MA17 in the *Journal of Clinical Oncology*, Goss and colleagues demonstrated that patients who received delayed, extended adjuvant therapy with letrozole after five years of tamoxifen experienced significant improvements in _____ compared to patients who received placebo.**
   a. Disease-free survival
   b. Distant disease-free survival
   c. Overall survival
   d. Contralateral breast cancer events
   e. All of the above

4. **Chemotherapy is administered in the ALTTO trial as _____.**
   a. (Neo)adjuvant chemotherapy prior to targeted therapy
   b. Weekly paclitaxel together with anti-HER2 targeted therapy after anthracycline-based (neo)adjuvant chemotherapy
   c. Either a or b
   d. None of the above

5. **The BETH adjuvant trial is evaluating chemotherapy and trastuzumab in combination with which other biologic agent?**
   a. Lapatinib
   b. Sunitinib
   c. Bevacizumab
   d. Cetuximab
   e. None of the above

6. **CALGB and NCCTG will be conducting a Phase III randomized trial for women with previously untreated metastatic breast cancer evaluating bevacizumab in combination with which of the following agents?**
   a. Ixabepilone
   b. Paclitaxel
   c. *Nab* paclitaxel
   d. Both b and c
   e. All of the above

7. **In NSABP-B-45, patients with residual invasive breast cancer after neoadjuvant chemotherapy will be randomly assigned to placebo or _____.**
   a. Bevacizumab
   b. Capecitabine
   c. Ixabepilone
   d. Sunitinib

8. **In a randomized study reported by O'Shaughnessy and colleagues, the combination of lapatinib and trastuzumab resulted in no improvement in progression-free survival compared to lapatinib alone for heavily pretreated patients with HER2-positive metastatic breast cancer progressing on trastuzumab.**
   a. True
   b. False

9. **In ECOG-E2100, evaluating paclitaxel with or without bevacizumab in patients with metastatic breast cancer, an association was found between VEGF genotype and _____.**
   a. Overall survival
   b. Grade III/IV hypertension
   c. None of the above
   d. Both a and b

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 6, 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 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Clinical implications of the ABCSG-12 zoledronic acid data 4 3 2 1
- Long-term natural history of ER/PR-positive breast cancer and extended adjuvant hormonal therapy 4 3 2 1
- Potential mechanism(s) of action of anti-angiogenic agents in breast cancer 4 3 2 1
- Association of VEGF and VEGFR-2 genetic polymorphisms, hypertension and outcome with bevacizumab in ECOG-E2100 . . . . . 4 3 2 1
- Study of a novel capecitabine schedule based on the Norton-Simon mathematical model 4 3 2 1
- Safety and efficacy of lapatinib with trastuzumab and/or chemotherapy in HER2-positive 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 = Very good 3 = Above average 2 = Adequate 1 = Suboptimal

- Clinical implications of the ABCSG-12 zoledronic acid data 4 3 2 1
- Long-term natural history of ER/PR-positive breast cancer and extended adjuvant hormonal therapy 4 3 2 1
- Potential mechanism(s) of action of anti-angiogenic agents in breast cancer 4 3 2 1
- Association of VEGF and VEGFR-2 genetic polymorphisms, hypertension and outcome with bevacizumab in ECOG-E2100 . . . . . 4 3 2 1
- Study of a novel capecitabine schedule based on the Norton-Simon mathematical model 4 3 2 1
- Safety and efficacy of lapatinib with trastuzumab and/or chemotherapy in HER2-positive 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 be able to:

- Integrate validated genomic assays into the clinical management of hormone receptor-positive, node-negative and node-positive early breast cancer. . . . . 4 3 2 1 N/M N/A
- Explain the clinical unmet need that underpins ongoing research evaluating therapeutic options for patients with residual disease after neoadjuvant chemotherapy. . . . . 4 3 2 1 N/M N/A
- Communicate the benefits and risks of extended adjuvant endocrine therapy for pre-menopausal and postmenopausal women with ER/PR-positive early breast cancer. . . . . 4 3 2 1 N/M N/A
- Appraise the adjunctive role of bisphosphonates in the management of ER-positive and/or PR-positive early breast cancer, and identify patients who may benefit from this course of therapy . . . . . 4 3 2 1 N/M N/A
- Demonstrate knowledge of existing treatment strategies and ongoing investigational approaches to the management of triple-negative breast cancer. . . . . 4 3 2 1 N/M N/A
- Compare and contrast the efficacy, safety and current clinical utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens, considering HER2 and nodal status of the primary tumor. . . . . 4 3 2 1 N/M N/A
- Implement a therapeutic algorithm for the sequential use of combination and/or single-agent chemotherapy that allows multiple lines of treatment for patients with metastatic breast cancer . . . . . 4 3 2 1 N/M N/A
- Distinguish those patients with advanced breast cancer who may be eligible for first-line treatment with bevacizumab, and recognize the rationale for ongoing investigation of this agent in the adjuvant setting . . . . . 4 3 2 1 N/M N/A
- Develop a strategy for the front-line and subsequent management of HER2-positive metastatic breast cancer, including patients with known CNS involvement . . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about the availability of ongoing clinical trial participation . . . . . 4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

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 editor and faculty for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Paul E Goss, MD, PhD	4 3 2 1	4 3 2 1
Julie R Gralow, MD	4 3 2 1	4 3 2 1
John Mackey, MD	4 3 2 1	4 3 2 1
Erica L Mayer, MD, MPH	4 3 2 1	4 3 2 1
Martine J Piccart-Gebhart, MD, PhD	4 3 2 1	4 3 2 1
Hope S Rugo, MD	4 3 2 1	4 3 2 1
Maria Theodoulou, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the editor and faculty for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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Breast Cancer® UPDATE

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