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Meet The Professors

A case-based discussion on the management of breast cancer in the adjuvant and metastatic settings

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Meet The Professors: A case-based discussion on the management of breast cancer in the adjuvant and metastatic settings

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. To offer optimal patient care — including the option of clinical trial participation — practicing medical oncologists, hematologists and hematology-oncology fellows must be well informed of these advances. *Meet The Professors* uses relevant case-based discussions between community oncologists and clinical investigators to assist practicing clinicians' incorporation of this information into their management strategies for breast cancer.

LEARNING OBJECTIVES

- Utilize genomic assays to quantify recurrence risk and aid in the selection of appropriate treatment options.
- Counsel pre- and postmenopausal patients with ER/PR-positive breast cancer about the risks and benefits of adjuvant endocrine therapy, addressing agent sequence and duration of treatment.
- Compare and contrast the safety and efficacy of anthracycline- and nonanthracycline-containing adjuvant regimens when recommending chemotherapy for patients with Stage I to Stage III breast cancer.
- Integrate case-based learning into the selection of treatment strategies for patients with HER2-positive early and advanced breast cancer.
- Assess the clinical activity of established and novel anti-HER2 agents in patients with HER2-positive tumors progressing on trastuzumab.
- Communicate the benefits and risks of neoadjuvant systemic therapy to patients with locally advanced breast cancer.
- Appraise the implications of occult axillary lymph node metastases on breast cancer prognosis and the selection of adjuvant systemic therapy.
- Apply the results of emerging research to effectively and safely integrate bevacizumab into the front-line treatment of metastatic breast cancer.
- Counsel appropriately selected patients about participation in ongoing clinical trials.

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CASE 2 *from the practice of Dr Tracy:* A 56-year-old postmenopausal woman with poorly controlled diabetes, hypertension and asymptomatic cardiomyopathy with an LVEF of 49 percent presented with a 5.3- x 4.7-cm, ER-positive, PR-positive, HER2-positive (IHC 3+) invasive ductal carcinoma (IDC) and wishes to have breast conservation (presented to Drs Swain and Hudis).

Track 2

DR LOVE: Sandy, the cardiologist recommended treating the patient's cardiomyopathy and felt she could receive a trastuzumab-based therapy as long as she did not also receive an anthracycline. How do you feel about that recommendation?

DR SWAIN: I agree with the cardiologist. While the data are limited, Dr Yu at MD Anderson examined patients who had received trastuzumab and were then treated for abnormal ejection fractions. He found they could be re-treated with trastuzumab. I believe a trastuzumab-containing regimen would be the best choice with regard to benefit and that his work supports that approach.

I would treat her with a TCH regimen preoperatively, and I would expect a good clinical response if not a pathologic complete response (pCR), considering the data for neoadjuvant trastuzumab-containing regimens. In the NOAH trial, the pCR rate was approximately 40 percent for patients who received neoadjuvant chemotherapy and trastuzumab (Gianni 2008; [1.1]). Also, in Dr Buzdar's neoadjuvant trial, paclitaxel followed by FEC/trastuzumab resulted in pCR rates in the 50 to 60 percent range (Buzdar 2007; [1.2]).

DR LOVE: Cliff, how would you treat this patient?

DR HUDIS: She's not a great candidate for any cytotoxic chemotherapy. From an evidence-based point of view, I believe TCH is the only option, so that's what I would use.

The CALGB has a preoperative trial randomly assigning patients to trastuzumab, lapatinib or both drugs, all with weekly paclitaxel (CALGB-40601). They are evaluating responses in the breast, so

1.1 Neoadjuvant Chemotherapy with Trastuzumab for Patients with Locally Advanced, HER2-Positive Breast Cancer: Primary Efficacy Data

Pathologic complete response rate for primary tumors: Intent-to-treat population

	Chemotherapy + trastuzumab	Chemotherapy	*p*-value
HER2-positive tumors	43%	23%	0.002
Chemotherapy + trastuzumab versus chemotherapy			
Probability	**Hazard ratio (HR)**	**95% CI**	***p*-value**
Event-free survival	0.56	0.36-0.85	0.006*
Overall survival	0.65	0.34-1.23	0.18

* Unadjusted for stratification variables: Adjusted HR = 0.55, $p = 0.0062$; CI = confidence interval

SOURCE: Gianni L et al. San Antonio Breast Cancer Symposium 2008;**Abstract 31**.

the patients go off study at the time of surgery. The recommendation then is for dose-dense AC, followed by finishing a year with trastuzumab, and we are using that approach for patients with larger primary tumors.

I believe that the important question may not be whether these patients need an anthracycline but rather how much chemotherapy they need at all. With trastuzumab, much of our debate about specific chemotherapy regimens may be muted — the trastuzumab effect may be a great leveler.

DR LOVE: Dr Tracy, how did you treat the patient?

DR TRACY: We administered the full regimen of TCH, and the mass shrank clinically and on imaging. She also received cardiac medication and her echocardiogram steadily improved to about 60 percent. She opted for mastectomy, and pathology revealed a 2.3-cm infiltrating ductal cancer with some high-grade DCIS and two positive nodes out of 22.

She then received radiation therapy and began an aromatase inhibitor. It's been four years now, and she is faring well with no evidence of disease and an ejection fraction of 60 percent with only minimal maintenance cardiac medication.

DR LOVE: Cliff, what are some of the promising new approaches to anti-HER2 treatment?

DR HUDIS: This is a remarkably exciting area. We should take great pride in the translational science that has allowed us to understand a target and build appropriate drugs rather than discover them empirically.

We have trial evidence that anti-HER2 drugs such as lapatinib and trastuzumab can be combined, including Dr O'Shaughnessy's study in which patients with HER2-positive metastatic breast cancer previously treated with multiple lines of trastuzumab-containing therapy were randomly assigned to lapatinib with or without trastuzumab (O'Shaughnessy 2008). She reported a modest benefit for the combination, which people use to support continuing trastuzumab and using the combination (1.3).

DR LOVE: What about the strategy of continuous biologic blockade?

DR HUDIS: The German group conducted a trial that essentially duplicated the pivotal capecitabine/lapatinib study except with trastuzumab in place of lapatinib (von Minckwitz 2008). These patients had HER2-positive metastatic disease progressing on trastuzumab and, remarkably, the time to progression was longer with the combination and the response rate was about 50 percent (1.4).

This study was closed early because of accrual problems related to the availability of lapatinib. Nevertheless, it provided this robust signal of activity. Does this mean

1.2 Neoadjuvant Paclitaxel (P) Followed by FEC with or without Concurrent Trastuzumab (H)

		P + FEC + H		
	P + FEC (n = 19)	**First cohort (n = 23)**	**Second cohort (n = 22)**	**Combined (n = 45)**
Pathologic complete response (95% CI)	26.3% (9-51)	65.2% (43-84)	54.5% (32.2-75.6)	60% (44.3-74.3)
One-year disease-free survival (95% CI)	94.7% (85.2-100)	100% (85.2-100)	100% (83.9-100)	100% (92-100)

CI = confidence interval

SOURCE: Buzdar AU et al. *Clin Cancer Res* 2007;13(1):228-33. **Abstract**

that we should continue trastuzumab as we cycle through therapies for patients? That is still difficult to answer. Some patients probably do respond to continued anti-HER2 therapy, but some patients probably do not.

1.3 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]	6.9%	10.3%	OR 1.5	0.46
Clinical benefit rate[2]	12.4%	24.7%	OR 2.2	0.01
Median progression-free survival	8.1 weeks	12.0 weeks	HR 0.73	0.008
Median overall survival[3]	39.0 weeks	51.6 weeks	HR 0.75	0.106

[1] Confirmed complete responses (CR) + partial responses (PR)
[2] CR + PR + stable disease ≥ 6 months
[3] Intent-to-treat population
Odds ratio (OR) > 1, hazard ratio (HR) < 1 favors L + T

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

1.4 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**.

Select publications

Burstein HJ et al. **Neratinib (HKI-272), an irreversible pan erbB receptor tyrosine kinase inhibitor: Phase 2 results in patients with advanced HER2+ breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 37**.

Buzdar AU et al. **Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: An update of the initial randomized study population and data of additional patients treated with the same regimen.** *Clin Cancer Res* 2007;13(1):228-33. **Abstract**

Gianni L et al. **Neoadjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer: Primary efficacy analysis of the NOAH trial.** San Antonio Breast Cancer Symposium 2008;**Abstract 31**.

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**.

CASE 3 *from the practice of Dr Tetreault:* A 62-year-old woman underwent a mastectomy for a 5-cm, ER-positive, PR-negative, HER2-positive IDC with 2/13 positive lymph nodes (presented to Drs Swain and Hudis).

Track 3

DR LOVE: Sandy, how would you treat this woman?

DR SWAIN: This patient's age puts her at a higher risk of experiencing cardiotoxicity with an anthracycline followed by trastuzumab, so I'm a proponent of TCH. I administer it routinely in practice and I believe the BCIRG 006 trial supports its use.

This patient is also a candidate for the BETH trial, which is evaluating chemotherapy with trastuzumab with or without bevacizumab (1.5). For NSABP and CIRG group members, the chemotherapy regimen used is TCH. She could also be considered for the ALTTO trial, evaluating adjuvant lapatinib versus trastuzumab versus the combination or sequence of both agents.

DR LOVE: Cliff, how would you treat this patient on and off study?

DR HUDIS: In my mind, clinical trials always take precedence. I support the BETH trial, and I would also consider the ALTTO study. Off study, if she has a normal ejection fraction, the risk of cardiac problems is less than one percent, so I would use dose-dense AC followed by paclitaxel/trastuzumab.

DR LOVE: How was the patient treated?

DR TETREAULT: She was enrolled on the BETH trial and assigned to the bevacizumab arm. This trial is easy to present to patients. First you discuss with them the TCH data and then you present the trial. Being a nurse, this patient loved the idea of participating in this study.

DR LOVE: Sandy, can you discuss the rationale for the BETH trial?

DR SWAIN: Dennis Slamon and Mark Pegram examined the synergy between various chemotherapy drugs and devised the TCH regimen. People were up in arms when BCIRG 006 was opened and included a nonanthracycline-containing regimen, but the results showed that TCH was highly effective and significantly better than the nontrastuzumab-containing regimen (Slamon 2005).

Examination of approximately 600 tumors showed that patients whose tumors had high VEGF levels and HER2 amplification had the worst prognosis (Konecny 2004). Some laboratory data demonstrated that the combination of bevacizumab and trastuzumab was beneficial, so Pegram conducted Phase I and II studies evaluating the combination. He reported a high response rate simply with these two monoclonal antibodies and no chemotherapy as first-line treatment for HER2-amplified breast cancer (Pegram 2006).

DR LOVE: Can you discuss the cardiac data from the trial combining bevacizumab and trastuzumab that Denise Yardley presented at the San Antonio meeting?

DR SWAIN: Dr Yardley presented preliminary safety data on patients who received TCH with bevacizumab in a Phase II randomized trial of adjuvant bevacizumab with three different docetaxel-containing regimens (1.6). They reported one Grade III/IV cardiac event among the patients who received bevacizumab/trastuzumab but no anthracycline and three events in the anthracycline-containing arms.

The risk of cardiotoxicity is probably not zero when you're dealing with a drug like bevacizumab that causes hypertension, increased afterload and the like, so our recommendation is to critically assess blood pressure and treat elevations aggressively.

DR LOVE: How aggressive are you, Cliff, with regard to blood pressure and bevacizumab?

DR HUDIS: In general, we're treating patients with metastatic disease, in which the long-term consequences are probably far less. That said, we have strict institutional guidelines for monitoring blood pressure and the administration of bevacizumab. For example, we can't administer bevacizumab on any day that the patient's blood pressure is above a set threshold, which I believe is 140/90.

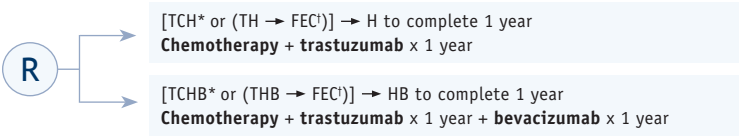
DR LOVE: Do we know to what extent anthracyclines affect a woman's risk of cardiotoxicity?

DR SWAIN: We all know that using anthracyclines, even using one dose, will cause some myocardial necrosis. The Pinder trial examined the Medicare database and showed that among women aged 66 to 70, the incidence of heart failure diagnosis was approximately nine percent higher for those who had received an anthracycline as adjuvant therapy compared to those who received a nonanthracycline-based regimen or no adjuvant chemotherapy (Pinder 2007).

Those are retrospective data using diagnoses in the Medicare database, and they could be biased because physicians knew

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

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



Eligibility

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

Stratification

- Nodal status
- Hormone receptor status

T = docetaxel; C = carboplatin; H = trastuzumab; F = 5-FU; E = epirubicin;
C† = cyclophosphamide; B = bevacizumab
* Chemotherapy used by NSABP/CIRG investigators (Cohort 1)
† Chemotherapy used by independent investigators (Cohort 2)

SOURCE: NCI Physician Data Query, March 2009.

who received anthracyclines and therefore may have been more likely to make that diagnosis. However, the patients did at least present with symptoms that could be heart failure.

We are all considering the risk of cardiotoxicity more in the adjuvant setting because these patients may be cured and we need to consider how it will affect them in 10 to 20 years.

1.6 Grade III/IV Cardiotoxicity with the Addition of Bevacizumab (B) to Three Different Docetaxel Regimens (N = 214)

Patient	Age	Event	No. of treatment cycles received prior to event	Baseline LVEF
Arm A (AC → T + B)				
1	73	CHF	4	52%
2	61	ACS	1	75%
3	49	MI	4	72%
Arm B (TAC + B)				
1	59	CHF	9	54%
2	66	CHF	7	61%
3	62	Cardiomyopathy	4	58%
Arm C (TCH + B)				
1	61	Congestive cardiomyopathy	15	54%

CHF = congestive heart failure; ACS = acute coronary syndrome; MI = myocardial infarction

SOURCE: Yardley DA et al. Poster. San Antonio Breast Cancer Symposium 2008;**Abstract 4107**.

Select publications

Konecny GE et al. **Association between HER-2/neu and vascular endothelial growth factor expression predicts clinical outcome in primary breast cancer patients.** *Clin Cancer Res* 2004;10(5):1706-16. **Abstract**

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**.

Pinder MC et al. **Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer.** *J Clin Oncol* 2007;25(25):3808-15. **Abstract**

Slamon D et al. **Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (AC → T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study.** San Antonio Breast Cancer Symposium 2005. No abstract available

Swain SM et al. **Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trials.** *Cancer* 2003;97(11):2869-79. **Abstract**

Yardley DA et al. **Preliminary safety results: Addition of bevacizumab to 3 docetaxel regimens as adjuvant therapy for early stage breast cancer.** Poster. San Antonio Breast Cancer Symposium 2008;**Abstract 4107**.

CASE 4 *from the practice of Dr Towell:* A 42-year-old woman who recently had a hysterectomy/oophorectomy for heavy bleeding and endometriosis underwent a lumpectomy and axillary dissection for a well-differentiated, 9-mm, ER-positive, PR-negative, HER2-negative breast cancer (BC) with cytokeratin-positive cells in one sentinel node (presented to Drs Swain and Hudis).

Track 4

DR LOVE: Cliff, how would you have treated this patient?

DR HUDIS: First of all, I agree with the decision to perform an axillary dissection. This case failed the sentinel node test, as applied, because the test identified cytokeratin-positive cells in one node.

I suspect that if we entered this patient's information into the Memorial Sloan-Kettering nomogram, which is on the web, we would obtain a 10 to 15 percent probability of finding additional positive nodes.

In a case like this with a 9-mm, ER-positive tumor, I would generally use hormone therapy alone, not chemotherapy, except that we do have the tiny warning — the cytokeratin-positive cells in one node — that her risk may be higher than expected.

DR LOVE: Would you order an Onco*type* DX® assay for this patient?

DR HUDIS: I would have a long conversation with her, and if she were willing to consider chemotherapy, and only in that setting, I would order the Onco*type* DX assay.

I would discuss a prestated plan agreeing that if her score was above a stated threshold, we would use chemotherapy and if her score was below that number, we wouldn't. However, if the test results would not be used to adjudicate our decision, then I wouldn't use it.

DR LOVE: Sandy?

DR SWAIN: I'm not as militant about the use of the Onco*type* DX assay as Cliff. I order the Onco*type* DX assay for any patient who would have been included in the NSABP-B-14 or B-20 analyses.

This patient is a little different in that she had cytokeratin-positive cells, which those studies didn't examine, but she essentially has node-negative disease based on the B-14 and B-20 criteria (Mamounas 2005).

Even though this tumor is well differentiated and more often than not that means we will see a score indicating a low or low-intermediate risk, I would absolutely order an Onco*type* assay.

I believe it's important for the patient to have that information, and I find — except for the 90-year-old with comorbidities — it can change the discussion. When I have this additional information, I find it's easier to talk to the patient about her options.

DR TETREAULT: I agree with Dr Swain that a theoretical discussion with a patient about chemotherapy before you have a Recurrence Score® can suddenly become irrelevant when you have that piece of paper and you say, "Your risk of recurrence is X percent." Patients then make completely different decisions.

DR ASTROW: What do you do when you have a patient with small, strongly ER-positive, Grade I, node-negative breast cancer,

examined by an excellent pathologist whom you trust, and the Onco*type* DX assay results in an intermediate or high score?

DR SWAIN: We all have to decide how to use the Onco*type* DX data, but I believe the biology is important. We can examine the tumor all we want under a microscope. I've been doing this for 25 years and we can be wrong, whereas Onco*type* DX examines the biology of that particular tumor more clearly. I would go with the Onco*type* result.

DR LOVE: Cliff, are you willing to consider Onco*type* results for a patient who clearly has a node-positive tumor?

DR HUDIS: I am. The younger the patient, the less interested I am likely to be in the Recurrence Score to adjudicate this decision.

However, the more undecided a patient is about chemotherapy and, especially as patients age, I believe it's reasonable to extrapolate, with the proviso that all of the node-positive data that we're basing this on is only a small amount (Albain 2007; [1.7]).

DR LOVE: Dr Towell, what happened with this patient?

DR TOWELL: An Onco*type* DX assay was performed and her Recurrence Score was 20, which translated to a 13 percent risk of recurrence. Based on that, she decided to receive chemotherapy. She received four cycles of TC followed by anastrozole.

DR LOVE: Sandy, considering this patient was premenopausal prior to her hysterectomy/oophorectomy, would you have used tamoxifen or an aromatase inhibitor?

DR SWAIN: Tamoxifen has a different mechanism of action, and it may be the correct choice for patients like this. We're testing that in SOFT and other trials. For premenopausal women, I usually recommend tamoxifen, and I would have done so for this patient.

DR LOVE: Cliff, what hormonal therapy would you administer to this patient?

DR HUDIS: I also would probably have used tamoxifen. It seems abrupt to take somebody from menstruating to surgical menopause and then use an aromatase inhibitor.

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

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

CI = confidence interval

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

Select publications

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

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**

Mamounas E et al. **Association between the 21-gene recurrence score assay (RS) and risk of locoregional failure in node-negative, ER-positive breast cancer: Results from NSABP B-14 and NSABP B-20.** San Antonio Breast Cancer Symposium 2005. No abstract available

CASE 7 *from the practice of Dr De Fusco:* A 58-year-old woman presented with symptomatic pleural effusion and ER-positive, PR-borderline, HER2-negative cells consistent with BC 11 years after being diagnosed with an IDC and 14/15 positive nodes. Her primary treatment consisted of neoadjuvant chemotherapy, mastectomy, stem cell transplant and radiation therapy followed by tamoxifen and a bisphosphonate. After five years of tamoxifen, she received letrozole and later anastrozole (presented to Drs Miller, Perez and Winer).

Track 7

DR LOVE: This patient has received three endocrine therapies. Can you discuss the sequence of those agents?

DR DE FUSCO: Initially she received adjuvant tamoxifen. After the MA17 data were released in 2003, we discussed the results and she began letrozole (Goss 2003; [1.8]). However, she experienced insomnia, so we switched to anastrozole and she had no further problems. She has been receiving essentially continuous hormonal therapy.

DR LOVE: Kathy, would you try another endocrine therapy or switch to chemotherapy at this point?

DR MILLER: I see nothing that suggests her disease is refractory to hormones. The disease-free interval was long, and while she has some local symptoms, the disease bulk is limited. I would try another hormonal therapy, probably fulvestrant with a loading dose. Switching to a steroidal aromatase inhibitor would be equally beneficial and reasonable (Chia 2008). I wouldn't use chemotherapy until the disease progressed with the next one or two hormones, or if we encountered difficulty controlling her symptoms.

DR PEREZ: Certainly hormonal therapy is much better tolerated than chemotherapy, but these agents are not as effective after tumor progression on a nonsteroidal aromatase inhibitor. Kathy alluded to the EFECT data, which showed a similar benefit when comparing fulvestrant to exemestane for postmenopausal women with hormone receptor-positive breast cancer progressing on a nonsteroidal aromatase inhibitor (1.9). However, the median time to progression was notably short for both agents, so they were equivalently poor in terms of disease management.

DR LOVE: If you felt her disease was hormone insensitive, what chemotherapy regimen would you use?

DR MILLER: In my mind, we have two alternatives. The first is single-agent capecitabine, which is oral and doesn't cause alopecia or myelosuppression. Given

her history, I would be slightly concerned about her bone marrow reserves and her ability to tolerate myelosuppressive chemotherapy.

The other option is weekly paclitaxel with bevacizumab, as used in the ECOG-E2100 trial (Miller 2007). This was well tolerated and it also does not cause serious myelosuppression. In addition, it may help her pleural effusion because of bevacizumab's effect on vascular permeability.

DR LOVE: How does that relate to why bevacizumab appears to have a positive impact on ascites in the treatment of ovarian cancer?

DR MILLER: The old name for VEGF was vascular permeability factor because one of the first effects identified of that particular protein was an increase in the leakiness of blood vessels. Inhibiting VEGF tends to have the opposite function, so it increases the strength of tight junctions and decreases leakage of lymphatic fluids into the surrounding tissues.

In ovarian cancer, it's been difficult to determine whether bevacizumab is directly affecting the cancer cells, or whether this major clinical improvement occurs because ascites and pleural effusions are major components of that disease.

DR LOVE: Edith, how would you treat this patient considering you felt her disease was hormone resistant?

DR PEREZ: I would look for a clinical trial because we don't have a single best choice for first-line management of metastatic breast cancer. In the absence of an applicable clinical trial, I would go through the menu of options, and Kathy's approach sounds appropriate.

DR LOVE: Eric, what would be your approach?

DR WINER: I agree with Kathy 100 percent both in terms of using a hormone now and in terms of the chemotherapy options. I'm not terribly confident that bevacizumab adds a great deal to capecitabine in metastatic breast cancer. I may be wrong, but at the moment I believe the data suggest that it doesn't. The point of using capecitabine would be the benefit of an oral regimen.

1.8 NCIC-MA17: Late Extended Adjuvant Treatment with Letrozole (LET) — Outcomes for Women Assigned to 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* 2008;26(12):1948-55. **Abstract**

I also agree that paclitaxel/bevacizumab would be a reasonable alternative.

DR LOVE: Kathy, can you comment on the results of the AVADO trial, evaluating docetaxel with or without bevacizumab, and how it compared to the E2100 data?

DR MILLER: Differences between the patient populations of these two studies were minimal. The eligibility criteria were virtually identical. The AVADO trial demonstrated improvements in progression-free survival and response rate by adding bevacizumab to every three-week docetaxel, and the hazard ratios were favorable (Miles 2008).

However, the absolute improvement and the absolute progression-free survival results in the AVADO trial were quite modest compared to the E2100 data (1.10). In addition, the safety profiles were substantially different because of the toxicities associated with every three-week docetaxel.

DR LOVE: Eric, would you tell us about the CALGB-40502 trial?

DR WINER: This study is being led jointly by CALGB and NCCTG. It randomly assigns patients with locally recurrent or metastatic breast cancer to paclitaxel/bevacizumab versus nanoparticle albumin-bound (*nab*) paclitaxel/bevacizumab versus ixabepilone/bevacizumab (1.11).

The design is simple — an antimicrotubule agent in combination with bevacizumab. We are asking a host of correlative questions to determine which tumors respond preferentially to one agent versus another.

DR LOVE: Kathy, would you comment on the association between VEGF genetic polymorphisms and outcome after treatment with paclitaxel/bevacizumab for metastatic breast cancer?

DR MILLER: Brian Schneider from our group examined whether host factors, particularly inherited polymorphisms of either the VEGF gene itself or the VEGF receptor 2 gene, might influence benefit or potential toxicities from bevacizumab. Hypertension was the toxicity selected because other side effects are so infrequent that the numbers simply don't exist to conduct this type of analysis.

He found two VEGF-A polymorphisms that clearly predicted improved overall survival for patients treated with paclitaxel and bevacizumab (Schneider 2008). It was fascinating that those two polymorphisms didn't predict an improvement in response rate or progression-free survival, only overall survival. In addition, these polymorphisms had no effect on overall survival for patients treated with paclitaxel alone.

He also found that two VEGF-A single nucleotide polymorphisms (SNPs) seemed to

1.9 EFECT: Evaluation of Fulvestrant versus Exemestane in Postmenopausal Patients with ER-Positive Metastatic Breast Cancer Progressing on a Nonsteroidal Aromatase Inhibitor

Efficacy results

	Fulvestrant	Exemestane	*p*-value
Objective response	7.4%	6.7%	0.7364
Clinical benefit	32.2%	31.5%	0.8534
Median time to progression	3.7 months	3.7 months	0.6531
Median duration of response	13.5 months	9.8 months	
Median duration of clinical benefit	9.3 months	8.3 months	

SOURCE: Chia S et al. *J Clin Oncol* 2008;26(10):1664-70. **Abstract**

protect patients from developing Grade III or IV hypertension. With only one of those SNPs, only about three to four percent of the patients developed Grade III or IV hypertension.

Perhaps the most interesting finding was that no one who inherited one of the SNPs that portended a better overall survival inherited an SNP that protected them from hypertension. That prompted Brian to investigate whether an association existed between Grade III or IV hypertension and overall survival for the patients who received bevacizumab in the ECOG-E2100 trial, and indeed such an association was apparent.

DR LOVE: Dr De Fusco, would you bring us up to date on this patient?

DR DE FUSCO: After a long discussion with the patient, we decided on chemotherapy, and I prescribed *nab* paclitaxel and bevacizumab.

She began treatment in February and I administered six months of chemotherapy. By October, no disease was evident on PET or CAT scans. I continued her on bevacizumab, but when we restaged her disease last week, the liver lesions had reappeared. The pleural effusion has not reaccumulated and she is asymptomatic, but her disease-free interval was fairly short. I'm considering fulvestrant as our next step.

DR LOVE: Edith, this patient received almost one year of maintenance bevacizumab. Would you continue it?

DR PEREZ: I usually continue the chemotherapy along with the bevacizumab. I do not automatically discontinue chemotherapy at a set number of cycles because the interaction of those two mechanisms of action may be important for added tumor control — unless, of course, the patient is experiencing significant toxicity from the chemotherapy.

When a patient does develop disease progression on bevacizumab, I stop it because we don't have any data suggesting

1.10 E2100 and AVADO: Phase III Randomized Trials of a Taxane with or without Bevacizumab (Bev) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

Study design	**E2100**[1]		**AVADO**[2]		
Treatment	• Paclitaxel (P) + bev until progression or unacceptable toxicity		• Docetaxel (D) for a maximum of 9 cycles duration • Bev until progression		
Study arm crossover	Crossover from P to bev disallowed		Crossover from D to bev + second-line chemotherapy allowed at progression		
Results	**P (n = 326)**	**P + bev (n = 347)**	**D (n = 241)**	**D + bev 7.5* (n = 248)**	**D + bev 15* (n = 247)**
Median PFS	5.9mo	11.8mo	8.0mo	8.7mo	8.8mo
	HR = 0.60, $p < 0.001$			HR = 0.79, $p = 0.0318$	HR = 0.72, $p = 0.01$
Median OS	25.2mo	26.7mo			
	HR = 0.88, $p = 0.16$		NR		
One-year survival	73.4%	81.2%	73%	78%	83%

* mg/kg
PFS = progression-free survival; HR = hazard ratio; OS = overall survival; NR = not reported

SOURCES: [1] Miller K et al. *N Engl J Med* 2007;357(26):2666-76. **Abstract**; [2] Miles D et al. *Proc ASCO* 2008;**Abstract LBA1011**.

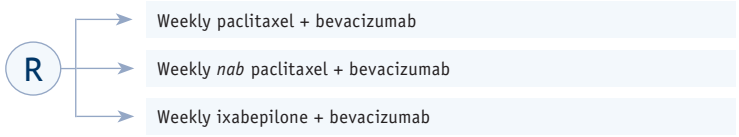
that continuing it is a good approach.

DR LOVE: Edith, if after a year of endocrine therapy her disease progressed, would you consider using bevacizumab with chemotherapy again and, if so, with which agent?

DR PEREZ: Yes I would, and I believe ixabepilone would potentially be a good drug for this patient. We don't have any large trial data on this combination, but the preclinical data with bevacizumab and ixabepilone are excellent. I have used it for patients.

1.11 Phase III Trial of Weekly Paclitaxel Compared to Weekly *Nab* Paclitaxel or Ixabepilone Combined with Bevacizumab as First- or Second-Line Therapy for Locally Recurrent or Metastatic Breast Cancer

Protocol IDs: CALGB-40502, CTSU, NCT00785291; Target Accrual: 900



Eligibility

- Stage IIIB not amenable to local therapy or Stage IV breast cancer
- No preexisting peripheral neuropathy ≥ Grade II
- No recent history of abdominal fistula or intra-abdominal abscess, gastrointestinal perforation or significant bleeding
- No clinically significant cardiovascular disease
- No history of stroke or TIA within previous six months
- No CNS metastases

SOURCE: www.clinicaltrials.gov. Accessed March 2009.

Select publications

Chia S et al. **Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: Results from EFECT.** *J Clin Oncol* 2008;26(10):1664-70. **Abstract**

Goss PE et al. **Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen.** *J Clin Oncol* 2008;26(12):1948-55. **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**

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

CASE 8 *from the practice of Dr Tsarwhas:* A 50-year-old perimenopausal woman underwent bilateral mastectomies for a well-differentiated, 1.4- x 0.7-cm, strongly ER-positive, PR-positive, HER2-negative IDC with a small (>2-mm) focus of metastatic cells in one sentinel node (presented to Drs Miller, Perez and Winer).

Track 8

DR LOVE: Edith, what are your thoughts about the use of the Onco*type* DX assay in this case?

DR PEREZ: Typically I would not order Onco*type* DX for this patient because my usual approach is AC followed by weekly paclitaxel and then hormonal therapy. I would order the assay only if I thought it would change my management.

For example, if the patient were willing to forgo chemotherapy and receive only hormonal therapy if her Recurrence Score was low, I would order it. However, if the decision had already been made to use chemotherapy, then I would not.

DR LOVE: If the sentinel node were completely negative, would you feel differently?

DR PEREZ: Yes, in that case I would order the Onco*type* DX assay. With a 1.4-cm, Grade I, strongly ER-positive, PR-positive tumor, the likelihood of a high Recurrence Score is low, but I believe the information is helpful when treating patients like this.

DR LOVE: Eric, it sounds as though Edith has reservations about the use of the Onco*type* DX assay for patients with positive nodes. What do we know about this assay for patients with node-positive disease?

DR WINER: We know less than we would like, but we do have a moderate amount of information. We have data from Dr Albain's study that randomly assigned postmenopausal patients with ER-positive, node-positive breast cancer to receive tamoxifen with or without CAF (Albain 2001, 2007).

They found the assay was not only prognostic of outcome but also predictive of chemotherapy benefit. For the patients with low Recurrence Scores, the added benefit of CAF was essentially nil.

DR LOVE: What about the TransATAC data that were presented at San Antonio, evaluating Onco*type* DX for patients who received aromatase inhibitors and those who received tamoxifen?

DR WINER: The suggestion had been made that perhaps Onco*type* DX would work differently for patients on aromatase inhibitors than for those receiving tamoxifen.

However, the TransATAC data showed the assay to be prognostic for patients on either endocrine therapy, and some of those patients had node-positive disease (Dowsett 2008; [1.12]).

DR LOVE: How would you treat this patient?

DR WINER: I would not administer chemotherapy to this patient unless she twisted my arm or she had a high Onco*type* DX Recurrence Score. With a strongly ER-positive, PR-positive, low-grade tumor with minimal node involvement, she fits into the category in which the benefit associated with chemotherapy was particularly modest in multiple studies and retrospective analyses.

It's not important to me whether I obtain an Onco*type* score for a patient like this. If the test has been ordered, I'll review it and if the score is high, which I believe is extremely unlikely, I will administer chemotherapy.

However, if the patient said she wouldn't receive chemotherapy anyway, I wouldn't order the test and I'd happily administer

endocrine therapy alone.

DR LOVE: Kathy, what would you do?

DR MILLER: I agree with Eric entirely about not using chemotherapy for this patient. I would order the assay only with the thought that a high score would change my management, but I believe that is unlikely with this patient — although not inconceivable.

DR LOVE: Dr Tsarwhas, was the Onco*type* DX assay performed for this patient?

DR TSARWHAS: Yes. The Recurrence Score was 14, the ER was strongly positive at 8.6 and the PR was 7.5. I treated her with tamoxifen and goserelin. My plan was to administer goserelin for a couple of years because she was perimenopausal at the time of diagnosis, then five years of tamoxifen followed by five years of letrozole.

DR LOVE: How does each of you feel about the choice of hormonal therapy for this patient?

DR WINER: Other than the ABCSG trial, I'm not aware of any data from the adjuvant aromatase inhibitor trials that address using an aromatase inhibitor up front for a woman who is premenopausal at diagnosis. So I would use tamoxifen initially for this patient, regardless of whether she received it alone or with ovarian suppression or even whether she chose to have her ovaries removed.

In the ABCSG trial, the two arms — ovarian suppression with tamoxifen versus ovarian suppression with an aromatase inhibitor — were equivalent with regard to benefit (Gnant 2009). The ongoing SOFT and TEXT studies are both evaluating ovarian suppression with tamoxifen versus suppression with an aromatase inhibitor for premenopausal patients.

DR MILLER: I certainly use ovarian suppression, but I don't do it for everyone because ovarian suppression in a young woman is not easy from a quality-of-life standpoint. I tend to consider it for a patient who is 50 years old and may be menopausal naturally within the next couple of years, although I would also consider it for 30- and 40-year-old patients who are at high risk.

DR PEREZ: In our practice, we would not routinely recommend ovarian suppression for premenopausal women with ER-positive tumors. We strongly believe in conducting the SOFT study, and until it is completed, tamoxifen is our standard outside of a clinical trial.

DR LOVE: Eric, would you consider bisphosphonate therapy for this patient?

DR WINER: Yes, because this is the specific situation that was evaluated in the ABCSG-12 trial. After the bisphosphonate data were presented (1.13), we decided as a group to discuss bisphosphonate therapy with these patients. However, we do not consider the treatment standard.

1.12 TransATAC: Proportion of Patients Treated with Anastrozole or Tamoxifen Who Are Free of Distant Recurrence at Nine Years by Onco*type* DX Recurrence Score (RS) Group: Analysis of Nodal Status

	Low	Int.	High	High vs low	Int. vs low
Node-negative (n = 513, 229, 130)	96%	88%	75%	HR* = 5.2	HR* = 2.5
Node-positive (n = 160, 94, 52)	83%	72%	51%	HR* = 2.7	HR* = 1.8

* HR = hazard ratio for RS group, adjusted for tumor size, grade, age and treatment

SOURCE: Dowsett M et al. San Antonio Breast Cancer Symposium 2008;**Abstract 53**.

1.13 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	10
Secondary cancer	9	10
Death without prior recurrence	0	2

Hazard ratio (95% CI) for DFS, versus no ZDA = 0.64 (0.46-0.91), p = 0.01

SOURCE: Gnant M et al. *N Engl J Med* 2009;360(7):679-91. **Abstract**

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**.

Albain K et al. **Overall survival after cyclophosphamide, Adriamycin, 5-FU, and tamoxifen (CAFT) is superior to T alone in postmenopausal, receptor(+), node(+) breast cancer: New findings from Phase III Southwest Oncology Group Intergroup trial S8814 (INT-0100).** *Proc ASCO* 2001;**Abstract 94**.

Conlin AK, Seidman AD. **Use of the Onco*type* DX 21-gene assay to guide adjuvant decision making in early-stage breast cancer.** *Mol Diagn Ther* 2007;11(6):355-60. **Abstract**

Dowsett M et al. **Risk of distant recurrence using Onco*type* DX in postmenopausal primary breast cancer patients treated with anastrozole or tamoxifen: A TransATAC study.** San Antonio Breast Cancer Symposium 2008;**Abstract 53**.

Gnant M et al. **Endocrine therapy plus zoledronic acid in premenopausal breast cancer.** *N Engl J Med* 2009;360(7):679-91. **Abstract**

Goldstein LJ et al. **Concurrent doxorubicin plus docetaxel is not more effective than concurrent doxorubicin plus cyclophosphamide in operable breast cancer with 0 to 3 positive axillary nodes: North American Breast Cancer Intergroup Trial E2197.** *J Clin Oncol* 2008;26(25):4092-9. **Abstract**

Goldstein L et al. **Prognostic utility of the 21-gene assay in hormone receptor-positive operable breast cancer compared with classical clinicopathologic features.** *J Clin Oncol* 2008;26(25):4063-71. **Abstract**

Henry LR et al. **The influence of a gene expression profile on breast cancer decisions.** *J Surg Oncol* 2009;[Epub ahead of print]. **Abstract**

Mamounas E et al. **Incorporating the Onco*type* DX breast cancer assay into community practice: An expert Q & A and case study sampling.** *Clin Adv Hematol Oncol* 2008;6(2):s1-8. No abstract available

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Meet The Professors Breast Cancer, Issue 1, 2009

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Treatment-emergent endocrine symptoms and risk of BC recurrence 4 3 2 1

Endocrine therapy for premenopausal patients with ER/PR-positive BC 4 3 2 1

Ongoing studies and clinical trial data with chemotherapy/bevacizumab as first-line therapy for metastatic BC 4 3 2 1

Ongoing studies and clinical trial data with HER2-directed therapy in the neoadjuvant, adjuvant and metastatic settings 4 3 2 1

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

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Role of the Oncotype DX assay for patients with ER/PR-positive, node-negative or node-positive early breast cancer (BC) 4 3 2 1

Treatment-emergent endocrine symptoms and risk of BC recurrence 4 3 2 1

Endocrine therapy for premenopausal patients with ER/PR-positive BC 4 3 2 1

Ongoing studies and clinical trial data with chemotherapy/bevacizumab as first-line therapy for metastatic BC 4 3 2 1

Ongoing studies and clinical trial data with HER2-directed therapy in the neoadjuvant, adjuvant and metastatic settings 4 3 2 1

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- Compare and contrast the safety and efficacy of anthracycline- and nonanthracycline-containing adjuvant regimens when recommending chemotherapy for patients with Stage I to Stage III breast cancer ..... 4 3 2 1 N/M N/A
- Integrate case-based learning into the selection of treatment strategies for patients with HER2-positive early and advanced breast cancer ..... 4 3 2 1 N/M N/A
- Assess the clinical activity of established and novel anti-HER2 agents in patients with HER2-positive tumors progressing on trastuzumab ..... 4 3 2 1 N/M N/A
- Communicate the benefits and risks of neoadjuvant systemic therapy to patients with locally advanced breast cancer ..... 4 3 2 1 N/M N/A
- Appraise the implications of occult axillary lymph node metastases on breast cancer prognosis and selection of adjuvant systemic therapy ..... 4 3 2 1 N/M N/A
- Apply the results of emerging research to effectively and safely integrate bevacizumab into the front-line treatment of metastatic breast cancer ..... 4 3 2 1 N/M N/A
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Kathy D Miller, MD	4 3 2 1	4 3 2 1
Edith A Perez, MD	4 3 2 1	4 3 2 1
Sandra M Swain, MD	4 3 2 1	4 3 2 1
Eric P Winer, MD	4 3 2 1	4 3 2 1
Moderator	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

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.....

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