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Meet The Professors *Live*

Based on the proceedings of a live tumor panel discussion on the management of early and advanced breast cancer

MODERATOR

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FACULTY

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Breast Cancer® UPDATE

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Meet The Professors Live: Based on the proceedings of a live tumor panel discussion on the management of early and advanced breast cancer

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 Live* uses relevant case-based discussions between community oncologists and clinical investigators to help practicing clinicians incorporate this information into evidence-based management strategies for treating breast cancer.

LEARNING OBJECTIVES

- Appraise the potential utility of genomic assays to aid in the quantification of risk and selection of individualized treatment for select patients with node-positive breast cancer.
- Devise an algorithm for the endocrine treatment of pre- and postmenopausal women with ER-positive early breast cancer, addressing total duration of therapy, management of side effects and concomitant use of bisphosphonates.
- Identify strategies to achieve local and systemic control of symptomatic inflammatory breast cancer.
- Recognize the impact of active pregnancy on the selection, timing and outcome of treatment for patients with early breast cancer.
- Compare and contrast the efficacy and safety of evidence-based combination regimens employed in the management of HER2-positive early and metastatic breast cancer.
- Appraise the clinical value of emerging adjuvant therapeutic approaches for triple-negative early breast cancer.
- Communicate the benefits and risks of the first-line use of bevacizumab for HER2-negative metastatic breast cancer.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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Overview of Audio and Print Program

Case 1: A 29-year-old nursing student underwent a right mastectomy for two 3-cm, Grade III, ER-positive, PR-positive, HER2-positive infiltrating ductal cancers (IDC) in the right breast. Five axillary nodes were positive, and the patient is now being considered for adjuvant systemic therapy *(from the practice of Alan B Astrow, MD)*.

Case 2: A 39-year-old woman at 21 weeks' gestation with her second pregnancy presented with a 4 x 3.1-cm, triple-negative IDC and a palpable lymph node that was positive for malignant cells on FNA. The tumor is BRCA1-positive, and the patient's mother died of breast cancer at the age of 29. The patient desires breast-conserving surgery, but the surgeon states that tumor shrinkage would be required *(from the practice of Mary Ann K Allison, MD)*.

Case 3: A 77-year-old otherwise healthy physician's wife presented with a 5.5-cm, left-sided, ER-positive, PR-positive, HER2-negative infiltrating lobular carcinoma with one of three positive sentinel nodes. The patient wishes to avoid chemotherapy, if possible *(from the practice of Robert A Moss, MD)*.

Case 4: A 61-year-old woman who was treated with adjuvant AC and five years of tamoxifen for left-sided, node-positive breast cancer presented eight years after initial diagnosis with biopsy-proven metastatic disease to the left lung. She was treated with letrozole for three years, then developed symptomatic progression with mediastinal and hilar lymph node metastases, for which she received radiation therapy and fulvestrant. After disease progression, the patient was treated with capecitabine but developed a malignant pericardial effusion, treated with a pericardial window *(from the practice of Dr Astrow)*.

Case 5: A 58-year-old woman with a 4-cm, Grade III, ER-negative, HER2-positive IDC and synchronous bone and liver metastases was enrolled on the TORI B-03 trial of trastuzumab and bevacizumab. She experienced tumor response and disease stabilization for two years, at which time she desired less frequent therapy and was treated off study with trastuzumab alone every three weeks. She received further lines of chemotherapy/anti-HER2 treatment upon disease progression and was intolerant of lapatinib because of intractable diarrhea. She then developed back pain from progressive bone metastases *(from the practice of Dr Allison)*.

Case 6: A 69-year-old emotionally fragile woman who underwent mastectomy and undetermined "low-dose chemotherapy" 14 years earlier for right-sided, node-negative breast cancer presented with a chest wall abnormality. Biopsy revealed a poorly differentiated, ER-positive, PR-negative, HER2-negative adenocarcinoma consistent with primary breast cancer. MRI revealed extensive right chest wall involvement, including skin, pectoral muscles and axillary nodes. The chest wall was indurated, erythematous and pruritic *(from the practice of Dr Moss)*.

Case 7: A 41-year-old nurse who underwent mantle radiation therapy 21 years ago for Stage IIA Hodgkin disease presented with a 1.3-cm, poorly differentiated, triple-negative, p53-positive, node-negative breast cancer *(presented by an audience member)*.

CASE 1: A 29-year-old nursing student underwent a right mastectomy for two 3-cm, Grade III, ER-positive, PR-positive, HER2-positive infiltrating ductal cancers (IDC) in the right breast. Five axillary nodes were positive, and the patient is now being considered for adjuvant systemic therapy *(from the practice of Alan B Astrow, MD)*.

Track 1

DR LOVE: John, which chemotherapy regimen would you consider for this patient and would you offer her participation in the ALTTO trial (1.1)?

PROF CROWN: My belief is that this woman should receive TCH. I would not use an anthracycline in a 29-year-old who is likely to live long enough to possibly experience a delayed onset of cardiomyopathy, because I believe that we would be doing a disservice. The reasons include the approximate equivalence between TCH and the anthracycline- and trastuzumab-containing regimens in terms of the anticancer effect. I see "clear blue water" between the two regimens in terms of the occurrence of severe toxicities (Slamon 2006; [1.2]).

Under no circumstances would I allow her to join the ALTTO trial. Because the ALTTO trial mandates anthracycline-containing therapy, despite the efforts of some of us to allow a nonanthracycline-containing

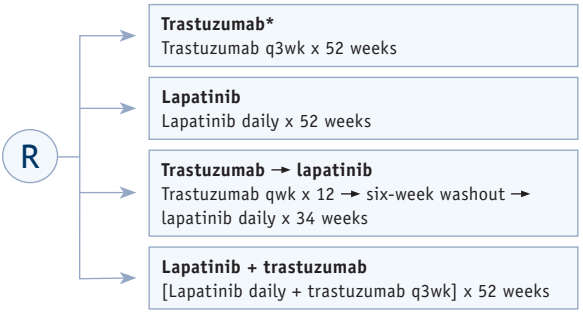
1.1 Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) Trial

Protocol ID: BIG 2-06; Target Accrual: 8,000 (Open)

Eligibility
HER2-positive breast cancer
Node-negative with tumor ≥ 1 cm or node-positive
LVEF ≥ 50%

In Design 1, patients will complete all (neo)adjuvant chemotherapy prior to administration of targeted therapy.

In Design 2, patients will receive weekly paclitaxel concurrently for 12 weeks with targeted therapy after any anthracycline-based (neo)adjuvant chemotherapy.



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

SOURCES: www.breastinternationalgroup.org; www.alttotrials.com.

regimen, this woman would run the risk of receiving an anthracycline, trastuzumab and lapatinib.

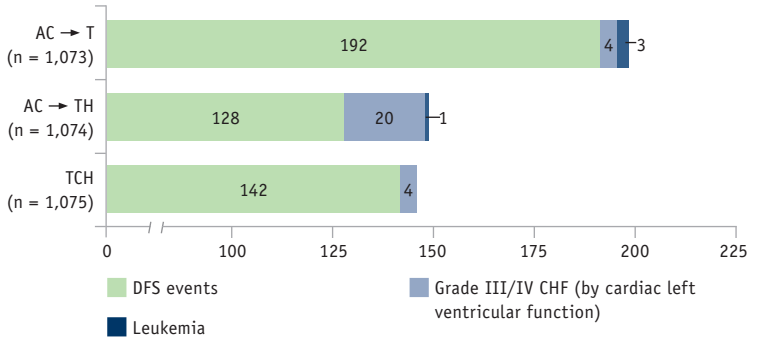
DR LOVE: What about the possibility of her not receiving trastuzumab if she enrolled in the ALTTO trial?

PROF CROWN: I'd be comfortable with that. The data with lapatinib in metastatic disease are reassuring considering the extraordinarily difficult group in whom lapatinib was tested. Compared to patients in the pivotal trastuzumab trial who received first-line therapy with trastuzumab, lapatinib proved its mettle in patients whose disease was resistant to anthracyclines, taxanes and trastuzumab (Geyer 2006).

DR LOVE: Cliff, your group recently published results with dose-dense therapy in combination with trastuzumab (Dang 2008; [1.3]). Which chemotherapy regimen would you consider for this woman?

DR HUDIS: If she had an ejection fraction above 55 percent, I wouldn't hesitate to use doxorubicin. Our series is far greater than what has been published so far. We have about 240 patients who have been treated on three consecutive prospective studies, and 100 percent of them have had pre- and post-AC ejection fractions measured. Notwithstanding the widely repeated notion of a five percent dropout rate after AC, no patients have failed to receive trastuzumab when they enrolled in these studies. We have one case of heart failure in the 240 patients and no long-term declines in ejection fraction to report.

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



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

1.3 Safety of Dose-Dense (dd) Doxorubicin/Cyclophosphamide (AC) Followed by Paclitaxel/Trastuzumab in HER2-Positive Breast Cancer

"Although our pilot study was much smaller than these randomized trials, we observed a CHF rate of only 1.4% (one patient) with no cardiac deaths suggesting that dd therapy is unlikely to add significant cardiac risk to that of conventional anthracycline and taxane sequences. Furthermore, there was no significant asymptomatic LVEF decline after dd AC so that all enrolled patients received trastuzumab."

SOURCE: Dang C et al. *J Clin Oncol* 2008;26(8):1216-22. **Abstract**

DR LOVE: Julie, would you offer zoledronic acid every six months to this young lady, as was done in the Austrian study recently reported at ASCO (Gnant 2008)?

DR GRALOW: In that trial, premenopausal women with ER-positive breast cancer received ovarian suppression for three years and were randomly assigned to also receive either tamoxifen or an aromatase inhibitor. It was a two-by-two study and the second randomization was zoledronic acid, four milligrams every six months for the three years, or not.

Previously, the Austrian Breast Cancer Study Group revealed that bone density was preserved with the addition of zoledronic acid in either arm — tamoxifen or an aromatase inhibitor. At ASCO 2008, they showed that there was no statistically significant difference in efficacy between tamoxifen and an aromatase inhibitor, combined with ovarian suppression.

The surprise was that the addition of zoledronic acid resulted in approximately a 35 percent reduction in recurrences.

I don't think I would offer bisphosphonate therapy to this patient based on the Austrian trial, but I have two patients who mirror those in the study. However, I would offer this patient participation in the Intergroup trial, SWOG-S0307, which compares adjuvant clodronate versus ibandronate versus zoledronic acid.

CASE 2: A 39-year-old woman at 21 weeks' gestation with her second pregnancy presented with a 4 x 3.1-cm, triple-negative IDC and a palpable lymph node that was positive for malignant cells on FNA. The tumor is BRCA1-positive, and the patient's mother died of breast cancer at the age of 29. The patient desires breast-conserving surgery, but the surgeon states that tumor shrinkage would be required *(from the practice of Mary Ann K Allison, MD)*.

Track 2

DR LOVE: John, would you use chemotherapy for this woman in an attempt to shrink the tumor so she could undergo lumpectomy?

PROF CROWN: You can consider arguments for mastectomy in her case. You'd have to go through all the issues with her carefully, regarding whether she would receive induction chemotherapy or undergo mastectomy. You might also obtain a second surgical opinion about whether breast-conserving surgery is feasible right now.

In general, life is a little easier when you're pregnant if you undergo surgery first and delay the chemotherapy until a little later. My default position here would always be trying to perform surgery first and use chemotherapy later.

DR LOVE: Julie, is it safe for the fetus if the mother receives chemotherapy in this situation?

DR GRALOW: I believe reasonable data exist for doxorubicin/cyclophosphamide, not in any studies but with long-term follow-up of both the patients and babies. I don't believe we have the data to use growth factors. I'd probably avoid using a taxane, although they have been accidentally used in some reported cases.

We know she will receive chemotherapy. She has node-positive, triple-negative disease. If we think we might have a chance of converting her surgery to breast conservation, then I believe it's reasonable to start with chemotherapy.

DR LOVE: Kevin, chemotherapy in this situation is basically for cosmesis — it's not a

life-threatening situation. Do we know for sure if chemotherapy is safe to offer here?

DR FOX: At ASCO 2005, the group from MD Anderson presented the largest collection of women who had received chemotherapy for early-stage breast cancer while pregnant (Johnson 2005). They have subsequently published their data. About 55 women received FAC, because that was the regimen in use at the time (Hahn 2006; [2.1]).

They didn't examine the patient outcomes but rather the outcomes of the children who were born. They followed some of them out to seven years. No signals indicated that the children suffered from the chemotherapy or that peripartum mortality or morbidity for the women was increased. The collective opinion was that FAC was safe (Hahn 2006; [2.1]).

So administering doxorubicin/cyclophosphamide to this woman to achieve the surgical goal that she wishes for, I believe, is also safe. I believe it will do her no harm, and it will do her child, in all likelihood, no harm either.

This comes back to John's point earlier. For a young woman with triple-negative breast cancer and a genetic mutation, I would have counseled this patient to take into consideration her long-term concerns and it might have changed her view of breast conservation, although it might not have.

DR HUDIS: The advantage of operating on her and then using conventional postoperative therapy is that she can be induced to deliver when she is closer to 36 weeks. Then she can receive dose-dense therapy or a third-generation regimen, if you prefer one of the others, and you're offering her a state-of-the-art outcome.

DR LOVE: What happened with this patient?

DR ALLISON: She has received three cycles of FAC. She's going to receive her fourth one next week, and then she'll be induced at week 37.

After the first cycle, the tumor shrank from four centimeters to two centimeters. Three weeks ago, only thickening was found — it melted away.

2.1 Outcomes for Children Exposed to Chemotherapy in Utero

"We have described the presentation, treatment, and outcomes for the largest cohort of pregnant patients with breast cancer treated on a prospective clinical trial. Based on our data, pregnant women with breast cancer can be treated with FAC chemotherapy in the second and/or third trimesters with relative safety for both mother and fetus. In our prospective cohort, the majority of children exposed to chemotherapy in utero were reported to be healthy, with no significant developmental problems except for the child with Down syndrome."

SOURCE: Hahn KM et al. *Cancer* 2006;107(6):1219-26. **Abstract**

CASE 3: A 77-year-old otherwise healthy physician's wife presented with a 5.5-cm, left-sided, ER-positive, PR-positive, HER2-negative infiltrating lobular carcinoma with one of three positive sentinel nodes. The patient wishes to avoid chemotherapy, if possible *(from the practice of Robert A Moss, MD)*.

Track 3

DR LOVE: Cliff, can you comment on the data presented at the 2007 San Antonio meeting evaluating the Onco*type* DX® assay for patients with node-positive disease?

DR HUDIS: In 2007, Kathy Albain and colleagues at SWOG presented confirmatory results from a different cohort of patients — postmenopausal women with node-positive disease who were randomly assigned to tamoxifen with or without CAF (Albain 2007; [3.1]).

The one caution is that the numbers in Kathy's trial are small. The absolute differences in the number of events between the patients who did and those who did not receive chemotherapy in the various cohorts of high, intermediate and low are barely in double digits. Thus, one can be forgiven for being extremely conservative in terms of broadly interpreting those data, but they're consistent with the other retrospective data set. For this patient, it would give me the courage to use the test.

DR LOVE: For this patient with node-positive disease, did you recommend Onco*type* DX?

DR MOSS: Yes. This patient did not want to receive adjuvant chemotherapy if it was at all reasonable to avoid it. I ordered the Onco*type* DX and her score was 19, falling in the intermediate range. The fact that it was not in the high-risk range gave me the reassurance I needed to not administer chemotherapy.

DR LOVE: Bob, what kind of hormonal therapy did she receive?

DR MOSS: She was started on anastrozole and has continued on that without any problems.

DR LOVE: Skip, how do you approach the patient who completes five years of adjuvant therapy with an aromatase inhibitor and does not experience problems with arthralgias (3.2)?

DR BURRIS: Based on their prognostic factors, I say to some patients, "We will continue to follow the literature. For now, I am planning on keeping you on this indefinitely." For some patients, you feel as if even five years is too much. It's a lengthy discussion. Until more data are available, I'll often let the patient be the primary driver of the decision.

DR FOX: We invite every patient who is so inclined to participate in NSABP-B-42 (3.3). If they decline participation, we discontinue the aromatase inhibitor. The reason for doing that is based on the experience that some of us went through with tamoxifen. The tendency was to prescribe it ad infinitum for patients, particularly those with a high risk of recurrence, without having established that it was advisable.

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

	10-year disease-free survival estimates	
	Tamoxifen (n = 148)	**CAF → tamoxifen (n = 219)**
Low Recurrence Score (<18)	60%	64%
Intermediate Recurrence Score (18-30)	49%	63%
High Recurrence Score (≥31)	43%	55%

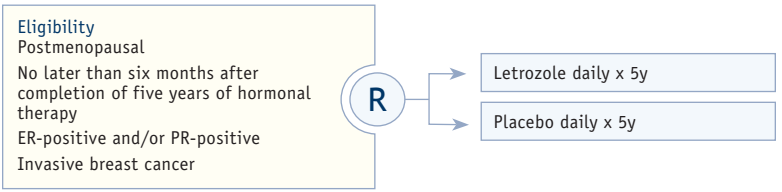
SOURCE: Albain K et al. San Antonio Breast Cancer Symposium 2007;**Abstract 10**.

3.2 Retrospective Analysis of the ATAC Trial: Treatment-Emergent Endocrine Symptoms and Risk of Breast Cancer Recurrence

"The appearance of new vasomotor symptoms or joint symptoms within the first 3 months of treatment is a useful biomarker, suggesting a greater response to endocrine treatment compared with women without these symptoms. Awareness of the relation between early treatment-emergent symptoms and beneficial response to therapy might be useful when reassuring patients who present with them, and might help to improve long-term treatment adherence when symptoms cannot be alleviated effectively."

SOURCE: Cuzick J et al, on behalf of the ATAC Trialists' Group. *Lancet Oncol* 2008;9(12):1143-8. **Abstract**

3.3 NSABP-B-42: A Phase III Trial to Determine Improvement in Disease-Free Survival with Adjuvant Letrozole After Completion of Five Years of Hormonal Therapy with Either an Aromatase Inhibitor or Tamoxifen Followed by an Aromatase Inhibitor



Primary Endpoint

- Disease-free survival

Secondary Endpoints

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

Target Accrual: 3,840 over 5.25 years

Date Activated: August 14, 2006

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

SOURCE: NCI Physician Data Query, November 2008.

CASE 4: A 61-year-old woman who was treated with adjuvant AC and five years of tamoxifen for left-sided, node-positive breast cancer presented eight years after initial diagnosis with biopsy-proven metastatic disease to the left lung. She was treated with letrozole for three years, then developed symptomatic progression with mediastinal and hilar lymph node metastases, for which she received radiation therapy and fulvestrant. After disease progression, the patient was treated with capecitabine but developed a malignant pericardial effusion, treated with a pericardial window *(from the practice of Dr Astrow)*.

Track 4

DR LOVE: Julie, which chemotherapy would you recommend? Would you add bevacizumab in this situation?

DR GRALOW: The key is how much disease she has and how active it is. Did it progress? Was this pericardial tamponade a progression on capecitabine? At some point, I don't believe it would be unreasonable to go back to tamoxifen. She was off of it for several years before her disease relapsed.

With respect to chemotherapy, she's never received a taxane. In the metastatic setting, I like weekly nanoparticle albumin-bound (*nab*) paclitaxel. I would generally try to add bevacizumab early, and I prefer to use it in a first-line setting. I would add it here if I were using chemotherapy as my next step.

DR WOLFF: At Hopkins, we are limited to the FDA-approved label for bevacizumab. I would have used paclitaxel as my first drug of choice for this case. If I were considering bevacizumab at some point, my hand would have been forced to use it in that setting. With her visceral disease, I would definitely have started with paclitaxel and bevacizumab.

PROF CROWN: I believe this woman should receive a taxane. The data, at present, suggest a rough equivalence between weekly paclitaxel and three-weekly docetaxel in the treatment of metastatic disease (Sparano 2008). We don't have *nab* paclitaxel in Europe yet. I would probably add bevacizumab once we were certain she wasn't at risk for postoperative bleeding from her pericardial window.

We now have data with bevacizumab in two randomized trials: the AVADO trial with docetaxel (Miles 2008; [4.1]) and the previous American trial (ECOG-E2100) with paclitaxel (Miller 2007; [4.2]). They both demonstrated an enhanced effect when bevacizumab was added to the taxane.

The magnitude of benefit with bevacizumab in the AVADO trial (Miles 2008; [4.1]) was smaller than the one seen in the trial with paclitaxel (Miller 2007; [4.2]). As a docetaxel fan and aficionado, I would argue that single-agent docetaxel presented a somewhat sterner control group than paclitaxel.

DR LOVE: Kevin, how are you thinking through cases like this?

DR FOX: We've tried to not use bevacizumab in any setting other than as first-line therapy. Here we would have been disinclined to try it.

The taxane we are in the habit of using is *nab* paclitaxel because we have found it to be efficient for patients. The time commitment for the patient is less, which in Philadelphia is a big deal. The toxicity, I believe, is favorable. Conversely, we're

4.1 AVADO Trial: Docetaxel Alone or in Combination with Two Different Doses of Bevacizumab (Bev) as First-Line Therapy for Women with Locally Recurrent or Metastatic Breast Cancer

	Docetaxel + placebo (n = 241)	Docetaxel + bev 7.5 mg/kg (n = 248)	Docetaxel + bev 15 mg/kg (n = 247)
Median PFS	8.0 months	8.7 months	8.8 months
HR (95% CI) vs placebo	—	0.79 (0.63-0.98)	0.72 (0.57-0.90)
p-value	—	0.0318	0.0099

PFS = progression-free survival; HR = hazard ratio; CI = confidence interval

SOURCE: Miles D et al. *Proc ASCO* 2008;**Abstract LBA1011**.

not big fans of docetaxel because the dose often used in clinical trials — 100 mg/m^2 every three weeks — is a little harsh.

Generally, we have not added bevacizumab to a chemotherapy regimen when that regimen has failed. I believe that practice may reflect logic, but we have no data to support it.

I wonder if anybody has had any experience with the risk of bleeding associated with bevacizumab in someone whose pericardium had been violated? I certainly would be a little nervous about using bevacizumab with this particular woman for some time.

DR LOVE: What happened with this patient?

DR ASTROW: I used weekly paclitaxel with bevacizumab. I worried about the pericardial window, so I waited two months before starting bevacizumab. She developed no toxicity from that standpoint.

She received paclitaxel and bevacizumab for six months, when she began to develop peripheral neuropathy and headaches. At that point, I stopped all treatment.

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

	Paclitaxel (n = 326)	Paclitaxel/bevacizumab (n = 347)
Median progression-free survival	5.9 months	11.8 months
	Hazard ratio = 0.60, $p < 0.001$	
Median overall survival	25.2 months	26.7 months
	Hazard ratio = 0.88, $p = 0.16$	
One-year survival	73.4%	81.2%
	$p = 0.01$	
Objective response rate	21.2%	36.9%
	$p < 0.001$	

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

CASE 5: A 58-year-old woman with a 4-cm, Grade III, ER-negative, HER2-positive IDC and synchronous bone and liver metastases was enrolled on the TORI B-03 trial of trastuzumab and bevacizumab. She experienced tumor response and disease stabilization for two years, at which time she desired less frequent therapy and was treated off study with trastuzumab alone every three weeks. She received further lines of chemotherapy/anti-HER2 treatment upon disease progression and was intolerant of lapatinib because of intractable diarrhea. She then developed back pain from progressive bone metastases *(from the practice of Dr Allison)*.

Track 5

DR LOVE: Cliff, can you discuss the German trial that evaluated the continuation of trastuzumab upon disease progression?

DR HUDIS: Von Minckwitz reported the results at ASCO 2008. The trial was closed early when lapatinib became available in Germany. Upon disease progression, patients were switched to capecitabine and were randomly assigned to either continue or discontinue trastuzumab (Von Minckwitz 2008). It's precisely similar to Charlie Geyer's lapatinib study (Geyer 2006), except it's with trastuzumab.

The shock to many of us was the near doubling of the overall response rate and the approximately 50 percent improvement in progression-free survival associated with the continuation of trastuzumab. The trial was underpowered because it was closed prematurely, but it's still the largest experience we have (Von Minckwitz 2008; [5.1]).

DR LOVE: What do you think we would have seen if the trial had included a third arm with lapatinib?

DR HUDIS: My prediction, based on these data, is that the efficacy would have been equivalent — but I don't know. This trial preselected a cohort of patients who tolerated trastuzumab. Some gastrointestinal and skin toxicities are associated with lapatinib, so I believe, by comparison, lapatinib would appear worse.

DR LOVE: Julie, can you discuss the trial evaluating the combination of lapatinib and trastuzumab that was presented by Joyce O'Shaughnessy at ASCO 2008?

DR GRALOW: Joyce presented a trial in which upon disease progression while receiving trastuzumab, patients went on to receive either single-agent lapatinib or lapatinib with the continuation of trastuzumab.

An advantage was demonstrated with the combination for these patients who had received a considerable amount of prior trastuzumab (O'Shaughnessy 2008; [5.2]).

Admittedly, the patients were heavily pretreated and in neither arm did they have a long time before their disease progressed again. They didn't receive any chemotherapy with these drugs (O'Shaughnessy 2008).

So it might be that the combination of lapatinib and trastuzumab is better than either alone, but the addition of some chemotherapy is even superior.

5.1 Phase III Trial of Capecitabine versus Capecitabine/Trastuzumab for Patients with HER2-Positive Metastatic Breast Cancer Progressing During Trastuzumab Therapy

	Capecitabine (n = 78)	Capecitabine/ trastuzumab (n = 78)	*p*-value
Median time to progression	5.6 months	8.2 months	0.03
Median overall survival	20.4 months	25.5 months	0.26
Overall response rate*	27%	48%	0.01
Clinical benefit rate†	54.0%	75.3%	0.007

* Complete response + partial response
† Complete response + partial response + no change for more than 24 weeks

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

DR LOVE: Cliff, what are some of the new anti-HER2 strategies being tested in clinical trials?

DR HUDIS: In patients with trastuzumab-refractory breast cancer, three classes of drugs have above a 20 percent response rate when combined with trastuzumab: T-DM1 (trastuzumab with maytansine), pertuzumab and HSP90 inhibitors.

DR LOVE: John, what is your thinking with regard to this patient?

PROF CROWN: I would go back and treat her the way we would treat a patient with de novo HER2-positive metastatic disease, with a taxane/trastuzumab regimen — either docetaxel/trastuzumab or docetaxel/carboplatin/trastuzumab.

She would have a reasonable chance of responding to one of those regimens, and it might re-establish control of her disease.

DR LOVE: Julie, what about continuing trastuzumab and switching to another chemotherapy?

DR GRALOW: I believe that's on the table too. For this particular patient, we know that she had tried lapatinib, didn't fare well and refused to ever take it again. So that's off the table.

I do believe we have data indicating that capecitabine with the continuation of trastuzumab is better than capecitabine alone (Von Minckwitz 2008; [5.1]). We don't, however, have a head-to-head comparison with capecitabine/lapatinib.

5.2 Lapatinib (L) with or without Trastuzumab (H) for Patients (N = 296) with Heavily Pretreated, HER2-Positive Metastatic Disease Progressing on Trastuzumab

	L	L + H	Odds ratio	*p*-value
Response rate[1]	6.9%	10.3%	1.5	0.46
Clinical benefit ratio[2]	12.4%	24.7%	2.2	0.01
			Hazard ratio	
Median progression-free survival[3]	8.1 weeks	12.0 weeks	0.73	0.008
Median overall survival	39 weeks	51.6 weeks	0.75	0.106
Adjusted overall survival[3]	NR	NR	0.71	0.0596

[1] Confirmed complete response (CR) + partial response (PR)
[2] CR + PR + stable disease ≥ 6 months
[3] Adjusted for extent of disease and performance status (significant baseline covariates)

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

CASE 6: A 69-year-old emotionally fragile woman who underwent mastectomy and undetermined "low-dose chemotherapy" 14 years earlier for right-sided, node-negative breast cancer presented with a chest wall abnormality. Biopsy revealed a poorly differentiated, ER-positive, PR-negative, HER2-negative adenocarcinoma consistent with primary breast cancer. MRI revealed extensive right chest wall involvement, including skin, pectoral muscles and axillary nodes. The chest wall was indurated, erythematous and pruritic *(from the practice of Dr Moss)*.

Track 6

DR LOVE: Had this patient received any endocrine therapy in the past?

DR MOSS: She told us tamoxifen had been prescribed, but she was convinced that it caused cancer, so she never took it. This made me a little nervous about using an oral therapy. She also had not received radiation therapy.

DR LOVE: Kevin, how would you think through an overall strategy for this patient?

DR FOX: You're describing a situation that isn't exactly life threatening but is symptomatically ominous. She itches and is probably fairly miserable. She looks at it in the mirror and is probably in distress.

On the surface, hormonal therapy appears to be appropriate because this is occurring 14 years after the initial diagnosis of ER-positive cancer, and it's likely to be hormone sensitive. This, however, might be a situation in which I would try chemotherapy.

I would probably use paclitaxel/bevacizumab to make her feel better a little faster.

DR LOVE: Cliff, what about the selection of hormonal therapy?

DR HUDIS: I'd typically start with a nonsteroidal aromatase inhibitor. The EFECT study reassured us that after using a nonsteroidal aromatase inhibitor, we could use the steroidal aromatase inhibitor exemestane and obtain equivalent results to those we would obtain with fulvestrant.

I would have thought it would be better to proceed from the nonsteroidal aromatase inhibitor to fulvestrant, but the EFECT trial says it's more or less equivalent to exemestane (Chia 2008; [6.1]).

After that, I would use fulvestrant if the patient remained a good candidate for hormonal therapy. I believe if the disease is hormone responsive, one should eke out a benefit for as long as possible.

I suspect that this case would be likely to progress relatively quickly on hormonal therapy, and I would move on to chemotherapy then.

DR LOVE: Julie, would you discuss the trials that are evaluating the combination of fulvestrant with an aromatase inhibitor?

DR GRALOW: SWOG-S0226 (6.2) is a first-line trial in the metastatic setting that is evaluating an aromatase inhibitor with or without fulvestrant.

In the aromatase inhibitor-alone arm, at disease progression, we strongly encourage sequencing to fulvestrant. We can't mandate it, but we're trying to evaluate the combination versus the sequence of an aromatase inhibitor and fulvestrant.

We're close to completing the accrual of about 690 patients. We're awaiting the results from this and another similar trial to start the next adjuvant trial, in which we're considering evaluating the combination.

DR LOVE: Let's follow up with what happened with this patient.

DR MOSS: My bias is to use chemotherapy for these patients, but I didn't feel that she would tolerate it. I decided to start her on fulvestrant.

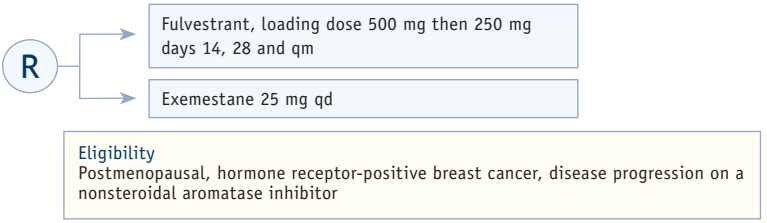
I wanted to avoid pills because I was afraid she wouldn't take them. I used a loading dose of fulvestrant, and she also received radiation therapy. Two to three weeks ago, her disease was in complete remission.

DR LOVE: We don't hear much about responses to fulvestrant. Kevin, it seems as though most people use it pretty late?

DR FOX: I believe that's part of what has cursed fulvestrant's reputation. It's never been used in circumstances in which it had much of a chance to shine. I believe it was a superb choice for this woman because of the concerns about compliance.

6.1 EFECT: Evaluation of Fulvestrant and Exemestane Clinical Trial

Protocol IDs: EFECT, NCT00065325, 9238IL/0048 Accrual: 693 (Closed)



Efficacy results

	Fulvestrant (n = 351)	Exemestane (n = 342)	*p*-value
OR	7.4%	6.7%	0.736
CB	32.2%	31.5%	0.853
Median TTP	3.7 months	3.7 months	0.653
Median DOR	13.5 months	9.8 months	NR
Median DCB	9.3 months	8.3 months	NR

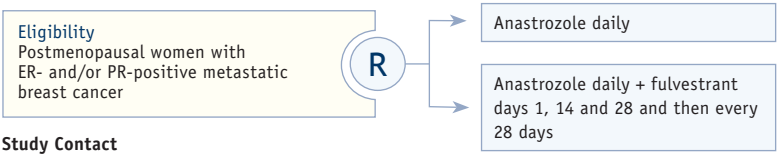
OR = objective response; CB = clinical benefit; TTP = median time to progression; DOR = duration of response; NR = not reported; DCB = duration of clinical benefit

"EFECT is not only one of the largest published trials to date comparing hormonal therapies in HR+ ABC [hormone receptor-positive advanced breast cancer], but also one of the first to specifically address the optimal agent to use in sequence immediately after progression of a nonsteroidal AI. EFECT confirmed efficacy for both fulvestrant and exemestane in this setting, with clinical benefit rates of approximately 32% and a median TTP of 3.7 months for both agents."

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

6.2 Phase III Randomized Study of Anastrozole with or without Fulvestrant as First-Line Therapy for Postmenopausal Women with Metastatic Breast Cancer

Protocol IDs: SWOG-S0226, NCT00075764 Accrual: 690 (Open)



Study Contact
Southwest Oncology Group
Rita Mehta, MD, Study Coordinator
Tel: 714-456-5153

SOURCE: NCI Physician Data Query, November 2008.

CASE 7: A 41-year-old nurse who underwent mantle radiation therapy 21 years ago for Stage IIA Hodgkin disease presented with a 1.3-cm, poorly differentiated, triple-negative, p53-positive, node-negative breast cancer *(presented by an audience member)*.

Track 7

DR WOLFF: Was this patient in any type of breast cancer screening program after her treatment for Hodgkin disease?

DR MAVROTMATIS: She was not.

DR WOLFF: This is an important educational issue for cancer survivors, especially women who have received mantle irradiation. The risk of developing breast cancer is significantly increased, especially for those younger than age 20 receiving radiation therapy. It is high for those receiving radiation therapy between the ages of 20 and 30, and it is essentially nonexistent if she received her mantle irradiation when she was older than age 30. This is someone who should have been referred for screening (7.1).

DR LOVE: Skip, how would you think through this case, considering her history?

DR BURRIS: Everything about this case has a poor prognostic ring. I believe in the setting of prior radiation therapy, you're certainly limited in considering it and would hope not to need to incorporate it.

I like the idea of noncross-resistant sequential therapy. For this patient I'd use four cycles of AC followed by four cycles of a taxane, either dose-dense or weekly paclitaxel.

DR MAVROTMATIS: Would she be eligible for ECOG-E5103 (7.2)?

DR WOLFF: She would be eligible because she has a tumor that is larger than one centimeter.

DR GRALOW: What about her history of Hodgkin disease?

DR WOLFF: I don't recall. It may depend on the time since the diagnosis.

DR BURRIS: I believe enrolling her in one of the adjuvant bevacizumab trials is a great idea.

DR LOVE: What's the design for ECOG-E5103, Antonio?

DR WOLFF: It is a randomized trial of AC → paclitaxel with or without bevacizumab. It is a three-arm study with one arm as the control, one arm using six months of bevacizumab and the other arm using 12 months of bevacizumab. The trial includes patients with node-positive disease and also those with high-risk, node-negative disease. In ECOG-E5103, this patient would have a two-in-three chance

7.1 Analysis of Breast Cancer Risk for Women Previously Treated for Pediatric Hodgkin Disease (HD)

"Women surviving pediatric HD were found to have a 37-fold increase in the risk of breast cancer and a high likelihood of rapidly developing bilateral disease. Early-stage HD and age greater than 12 years at diagnosis of HD were independent risk factors. Higher radiation doses may augment risk, and pelvic radiation may be protective. Breast cancer screening methodology and frequency, plus the role of prophylaxis in patients with unilateral disease, require definition."

SOURCE: Basu SK et al. *Int J Radiat Oncol Biol Phys* 2008;72(1):34-40. **Abstract**

of being randomly assigned to receive bevacizumab.

DR HUDIS: Doesn't her prior mantle radiation therapy exclude her from enrollment?

DR FOX: I don't know whether it disqualifies her, but I would venture to say this woman doesn't have a normal myocardium.

DR LOVE: Would you stay away from an anthracycline?

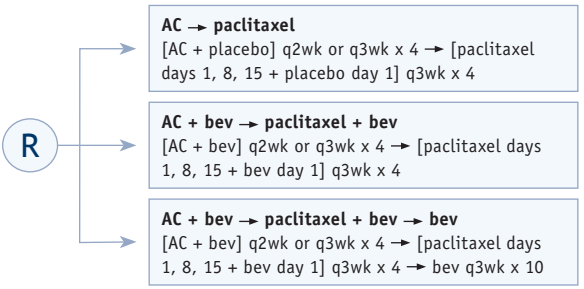
DR FOX: I absolutely would.

DR LOVE: What would you consider using?

DR FOX: TC (docetaxel/cyclophosphamide; [Jones 2006]) would be our standard approach for someone with prior mantle radiation therapy.

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

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



Eligibility

- Pre- or postmenopausal
- ER and PR status known, HER2-negative
- Node-positive or high-risk, node-negative
- Patients enrolled on ECOG-PACCT-1 (TAILORx)

Study Contacts

Eastern Cooperative Oncology Group
Kathy D Miller, MD, Protocol Chair
Tel: 888-600-4822

Ramona Swaby, MD, Protocol Co-Chair
Tel: 888-369-2427

North Central Cancer Treatment Group
Donald Northfelt, MD, Protocol Chair
Tel: 507-538-7623

Cancer and Leukemia Group B
Chau Dang, MD, Protocol Co-Chair
Tel: 800-525-2225

SOURCE: NCI Physician Data Query, November 2008.

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**.

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;112(3):533-43. **Abstract**

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**

Cuzick J et al, on behalf of the ATAC Trialists' Group. **Treatment-emergent endocrine symptoms and the risk of breast cancer recurrence: A retrospective analysis of the ATAC trial.** *Lancet Oncol* 2008;9(12):1143-8. **Abstract**

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**

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.**

Goldstein LJ 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**

Hahn KM et al. **Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero.** *Cancer* 2006;107(6):1219-26. **Abstract**

Johnson PH et al. **The treatment of pregnant women with breast cancer and the outcomes of the children exposed to chemotherapy in utero.** *Proc ASCO* 2005;**Abstract 540**.

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

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**

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

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

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**.

Sparano JA et al. **Weekly paclitaxel in the adjuvant treatment of breast cancer.** *N Engl J Med* 2008;358(16):1663-71. **Abstract**

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**.

Educational Assessment and Credit Form:
Meet The Professors Live Breast, Issue 1, 2008

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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

Studies evaluating continuation of trastuzumab and chemotherapy or lapatinib in patients with HER2-positive metastatic breast cancer progressing on trastuzumab. 4 3 2 1

BETH and ALTTO trials of adjuvant anti-HER2 therapy in early breast cancer 4 3 2 1

Clinical trial results with taxane/bevacizumab for patients with previously untreated HER2-negative metastatic breast cancer . . . 4 3 2 1

Efficacy and duration of therapy with adjuvant aromatase inhibitors for postmenopausal patients with ER/PR-positive early breast cancer 4 3 2 1

Austrian Breast Cancer Study Group (ABCSG-12) data on the antitumor activity of zoledronic acid and ongoing trials of adjuvant bisphosphonates 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

Studies evaluating continuation of trastuzumab and chemotherapy or lapatinib in patients with HER2-positive metastatic breast cancer progressing on trastuzumab. 4 3 2 1

BETH and ALTTO trials of adjuvant anti-HER2 therapy in early breast cancer 4 3 2 1

Clinical trial results with taxane/bevacizumab for patients with previously untreated HER2-negative metastatic breast cancer . . . 4 3 2 1

Efficacy and duration of therapy with adjuvant aromatase inhibitors for postmenopausal patients with ER/PR-positive early breast cancer 4 3 2 1

Austrian Breast Cancer Study Group (ABCSG-12) data on the antitumor activity of zoledronic acid and ongoing trials of adjuvant bisphosphonates 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: . . . . . .

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☐ Yes ☐ No

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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:

- Appraise the potential utility of genomic assays to aid in the quantification of risk and selection of individualized treatment for select patients with node-positive breast cancer. . . . . 4 3 2 1 N/M N/A
- Devise an algorithm for the endocrine treatment of pre- and postmenopausal women with ER-positive early breast cancer, addressing total duration of therapy, management of side effects and concomitant use of bisphosphonates . . . . . 4 3 2 1 N/M N/A
- Identify strategies to achieve local and systemic control of symptomatic inflammatory breast cancer . . . . . 4 3 2 1 N/M N/A
- Recognize the impact of active pregnancy on the selection, timing and outcome of treatment for patients with early breast cancer . . . . . 4 3 2 1 N/M N/A
- Compare and contrast the efficacy and safety of evidence-based combination regimens employed in the management of HER2-positive early and metastatic breast cancer . . . . . 4 3 2 1 N/M N/A
- Appraise the clinical value of emerging adjuvant therapeutic approaches for triple-negative early breast cancer . . . . . 4 3 2 1 N/M N/A
- Communicate the benefits and risks of the first-line use of bevacizumab for HER2-negative metastatic breast cancer . . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials . . . . . 4 3 2 1 N/M N/A

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

.....

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

.....

Additional comments about this activity:

.....

.....

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

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

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

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

Faculty	Knowledge of subject matter				Effectiveness as an educator			
Howard A Burris III, MD	4	3	2	1	4	3	2	1
Professor John Crown, MD	4	3	2	1	4	3	2	1
Kevin R Fox, MD	4	3	2	1	4	3	2	1
Julie R Gralow, MD	4	3	2	1	4	3	2	1
Clifford Hudis, MD	4	3	2	1	4	3	2	1
Antonio C Wolff, 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

Please recommend additional faculty for future activities:

.....

.....

Other comments about the moderator and faculty for this activity:

.....

.....

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