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Breast Cancer® UPDATE

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

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INTERVIEWS

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CME Certified

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Breast Cancer Update
A Continuing Medical Education Audio Series

OVERVIEW OF ACTIVITY

Breast cancer is one of the most rapidly evolving fields in medical oncology. Results from numerous ongoing trials lead to the continual emergence of new therapeutic agents, treatment strategies and diagnostic/prognostic tools. In order to offer optimal patient care — including the option of clinical trial participation — the practicing clinician must be well informed of these advances. Featuring information on the latest research developments along with expert perspectives, this CME program is designed to assist medical oncologists, hematologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Integrate validated genomic assays into the clinical management of hormone receptor (HR)-positive, node-negative or node-positive early breast cancer.
- Apply the results of recent clinical trials and meta-analyses when recommending aromatase inhibitors and/or tamoxifen as primary therapy for postmenopausal women with HR-positive early breast cancer.
- Formulate an evidence-based algorithm for the identification and treatment of localized or metastatic, HER2-positive breast cancer.
- Demonstrate knowledge of ongoing investigational approaches to the management of triple-negative or HER2-positive breast cancer.
- Compare and contrast the efficacy, safety and individualized utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens.
- Appraise the contributory role of oral fluoropyrimidines in the management of early breast cancer.
- Consider the unique benefits and risks associated with novel epothilones and taxanes when selecting and sequencing chemotherapeutic regimens.
- Recall emerging clinical trial results with bevacizumab for metastatic breast cancer, and assess their application to current patient care.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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INTERVIEW

Edith A Perez, MD

Dr Perez is Serene M and Frances C Durling Professor of Medicine, Director of the Cancer Clinical Study Unit and Director of the Breast Cancer Program in the Division of Hematology and Oncology at the Mayo Clinic in Jacksonville, Florida.

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Track 2 Pending report of the HERA trial: Two versus one year of adjuvant trastuzumab

Track 3 Perspective on the role of adjuvant anthracyclines in breast cancer (BC)

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Track 7 RIBBON 1: Chemotherapy (physician's choice) with or without bevacizumab for first-line treatment of mBC

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Tracks 6-7

DR LOVE: Would you summarize where we are currently in terms of clinical research data on bevacizumab for metastatic breast cancer?

DR PEREZ: ECOG-E2100 demonstrated a dramatic improvement in progression-free survival with weekly paclitaxel/bevacizumab as first-line therapy, but no statistical difference in overall survival was seen (Miller 2007; [1.1]). The two agents were continued until disease progression or prohibitive toxic effects occurred.

In the AVADO trial, a statistically significant improvement in median progression-free survival was found for docetaxel/bevacizumab in the first-line setting, but the difference was less than one month (Miles 2008; [1.1]). We can say that the AVADO trial corroborated ECOG-E2100, but it didn't corroborate it to the degree I would have liked.

Potential explanations are related to the differences between the two trials. In the AVADO trial, the patients received up to nine doses of docetaxel. At the beginning, the patients received docetaxel/bevacizumab, and then the physicians had the option of discontinuing docetaxel and continuing bevacizumab as a single agent (Miles 2008).

1.1

ECOG-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	ECOG-E2100[1]		AVADO[2]		
Treatment duration	• P + bev until progression or unacceptable toxicity		• D for a maximum of 9 cycles • Bev until progression		
Study arm crossover	Crossover from P to bev disallowed		Crossover from D to bev + second-line chemotherapy allowed at progression		
Results	Paclitaxel (P) (n = 326)	P + bev (n = 347)	Docetaxel (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	NR		
	HR = 0.88 $p = 0.16$				
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**.

DR LOVE: Another potential issue is related to the choice and schedule of taxanes — weekly paclitaxel versus every three-week docetaxel — and their effectiveness as anti-angiogenic agents.

DR PEREZ: That's possible, because both taxanes have anti-angiogenic properties, but a weekly schedule of administration may be more effective. That's one of the reasons why RIBBON 1 will be so interesting.

Track 5

DR LOVE: Can you comment on the Finnish study that was presented at San Antonio, which added capecitabine to docetaxel followed by an anthracycline in the adjuvant setting (Joensuu 2008)?

DR PEREZ: This was a provocative trial. The follow-up is short, but the study demonstrated that the addition of capecitabine led to an improvement in disease-free survival (Joensuu 2008; [3.3]), which is consistent with the docetaxel/capecitabine data reported in metastatic breast cancer (O'Shaughnessy 2002).

The investigators diminished the dose of docetaxel to 80 mg/m^2 instead of 100 mg/m^2, and they also reduced the dose of capecitabine to 900 mg/m^2 twice per day. This is a good regimen, and it will be interesting to see longer follow-up of that trial.

Track 4

DR LOVE: Joe Sparano presented data at San Antonio from a study of liposomal doxorubicin with docetaxel in patients with advanced breast cancer (Sparano 2008; [1.2]). What are your thoughts about the role of these agents in breast cancer management?

DR PEREZ: Liposomal anthracyclines are important drugs. When the original study was conducted comparing liposomal anthracyclines to standard doxorubicin in a large number of patients, they were able to demonstrate that patients could receive more anthracycline with the pegylated liposomal encapsulation of the drug (O'Brien 2004).

However, it was difficult to demonstrate statistically significant improvements in survival or disease-free survival. Currently, an ongoing randomized trial for patients with HER2-positive breast cancer is evaluating paclitaxel/trastuzumab versus paclitaxel/trastuzumab/liposomal doxorubicin.

This strategy is based on fascinating Phase III data presented by Jose Baselga and colleagues in the neoadjuvant setting, in which a huge response rate to triplet therapy was demonstrated with essentially no cardiac toxicity when the anthracycline was administered concurrently with trastuzumab (Gianni 2008). ■

1.2

DOXIL-BCA-3001: Docetaxel (T) with or without Pegylated Liposomal Doxorubicin (PLD) in Patients with Advanced Breast Cancer Treated with Adjuvant Anthracyclines

Efficacy	T (n = 373)	T + PLD (n = 378)	HR	*p*-value
Median time to progression	7.0mo	9.8mo	0.65	0.000001
Overall response rate	26%	35%	NR	0.0085
Median duration of response	7.4mo	8.8mo	NR	NR
Overall survival	20.7mo	20.6mo	1.03	0.75
Cardiac safety	**T (n = 373)**	**T + PLD (n = 377)**	**HR**	***p*-value**
LVEF decrease*	5%	5%	—	—
≥Grade II cardiac AEs	4%	5%	—	—
Congestive heart failure	1%	1%	—	—

* Absolute decrease ≥15%, or absolute decrease ≥5% and less than lower limit of normal

HR = hazard ratio; NR = not reported; AE = adverse event

SOURCE: Sparano J et al. San Antonio Breast Cancer Symposium 2008;**Abstract 80**.

SELECT PUBLICATIONS

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**.

Joensuu H et al. **Significant improvement in recurrence-free survival (RFS) when capecitabine (X) is integrated into docetaxel (T) → 5-FU + epirubicin + cyclophosphamide (CEF) adjuvant therapy for high-risk early breast cancer (BC): Interim analysis of the FinXX-trial.** San Antonio Breast Cancer Symposium 2008;**Abstract 82**.

Jones S et al. **Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research trial 9735.** *J Clin Oncol* 2009;27(8):1177-83. **Abstract**

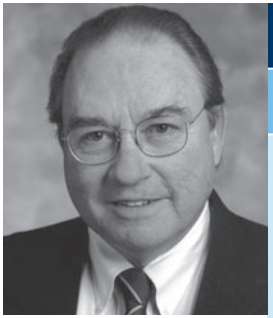
Miles D et al. **Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO.** *Proc ASCO* 2008;**Abstract LBA1011**.

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'Brien ME et al. **Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer.** *Ann Oncol* 2004;15(3):440-9. **Abstract**

O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23. **Abstract**

Sparano J et al. **Pegylated liposomal doxorubicin (PLD) plus docetaxel significantly improves time to progression (TTP) compared with docetaxel (D) monotherapy in patients with advanced breast cancer (ABC) treated with adjuvant anthracycline: Results from a randomized phase 3 study.** San Antonio Breast Cancer Symposium 2008;**Abstract 80**.



INTERVIEW

Stephen E Jones, MD

Dr Jones is Medical Director and Co-Chair of the Breast Cancer Research Committee of US Oncology Research in Houston, Texas and Director of Breast Cancer Research at Baylor-Sammons Cancer Center in Dallas, Texas.

Tracks 1-12

Track 1 Clinical implications of the NSABP-B-30 and BCIRG 005 studies of adjuvant chemotherapy for node-positive BC

Track 2 Adjuvant anthracyclines and long-term risk of congestive heart failure

Track 3 Adjuvant chemotherapy for patients with ER/PR-positive BC

Track 4 Case discussion: A 62-year-old woman with a 1.5-cm, Grade II, strongly ER/PR-positive, HER2-negative, node-negative BC and an Onco*type* DX Recurrence Score® of 41

Track 5 TransATAC: Onco*type* DX predicts distant recurrence risk for postmenopausal patients with node-negative or node-positive BC treated with anastrozole or tamoxifen

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Track 11 Perspective on the ATAC retrospective analysis of treatment-emergent endocrine symptoms and risk of BC recurrence

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Select Excerpts from the Interview

Tracks 4-5

DR LOVE: What is your opinion of the data from the TransATAC study presented at San Antonio on Onco*type* DX?

DR JONES: The Onco*type* DX Recurrence Score proved to be an independent predictor of the risk of distant recurrence in postmenopausal patients with ER-positive, node-negative or node-positive breast cancer treated with either tamoxifen or anastrozole (Dowsett 2008; [2.1]).

The Onco*type* DX data have been consistent in a variety of settings, and we haven't seen any surprises. The assay was consistent in one series with node-positive patients, in which they received tamoxifen or chemotherapy in combination with tamoxifen (Albain 2007). It's been consistent in all the tamoxifen series. Now it's consistent in the ATAC series. That's why I believe this assay is so far along.

This assay humbles us a bit. I consider myself to be an experienced breast oncologist. I've done this for 35 years. I think I can tell who needs chemotherapy and who doesn't. That's my arrogance, but biology and these tests are starting to trump my personal opinion.

2.1

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. Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 53**.

Tracks 10, 12

DR LOVE: In addition to a presentation with the sequencing data for BIG 1-98 (Mouridsen 2008; [2.2]), two other important data sets for adjuvant endocrine therapy were presented on the first morning of the San Antonio meeting (Ingle 2008; Jones 2008). Would you summarize your impressions of the data?

DR JONES: First, Jim Ingle presented a meta-analysis examining two cohorts of patients who were treated with different adjuvant endocrine approaches (Ingle 2008; [2.3]).

The first cohort evaluated up-front aromatase inhibitors versus tamoxifen, comprised predominantly of patients from the ATAC and BIG 1-98 studies. A definite reduction in recurrence rates was evident with the up-front aromatase inhibitors, but no difference in overall survival was noted. The second cohort evaluated switching from two to three years of adjuvant tamoxifen to an aromatase inhibitor. This analysis also demonstrated a reduction in recurrence rates for the switching strategy, but more importantly, an improvement in overall survival.

DR LOVE: I think there has been some confusion about trying to compare the two strategies, because the switching studies focused on patients who

completed two to three years of tamoxifen and did not experience relapse. What was shown in your presentation of the TEAM study comparing up-front tamoxifen to exemestane (Jones 2008; [2.4])?

DR JONES: A message came through loud and clear the first morning of the San Antonio meeting, and I was pleased to be the third one to present that message. The TEAM study has been the missing link in that it was the first study with an up-front comparison of tamoxifen to an aromatase inactivator, which has a different mechanism of action than the other nonsteroidal aromatase inhibitors.

In TEAM, the intent-to-treat hazard ratio was 0.89, or an 11 percent reduction in recurrence. However, when we analyzed the study according to patients who were still receiving the treatment to which they were randomly assigned, the HR was 0.83, or a 17 percent reduction. ■

2.2

BIG 1-98: Letrozole Monotherapy or in Sequence with Tamoxifen as Adjuvant Therapy for Postmenopausal Women with ER-Positive Early Breast Cancer

	Letrozole monotherapy* (n = 1,546)	Letrozole → tamoxifen† (n = 1,540)	Tamoxifen → letrozole† (n = 1,548)
Five-year disease-free survival	87.9%	87.6%	86.2%
Hazard ratio (95% CI) Letrozole versus sequence	—	0.96 (0.76-1.21)	1.05 (0.84-1.32)

* Median follow-up: 71 months; † Median follow-up: 76 months

SOURCE: Mouridsen HT et al. San Antonio Breast Cancer Symposium 2008;**Abstract 13**.

2.3

Meta-Analyses: [1] Adjuvant Trials of Up-Front Aromatase Inhibitors (AIs) versus Tamoxifen (Tam) and [2] Tam for Two to Three Years Followed by AIs versus Continued Tam for Postmenopausal Women with ER-Positive Breast Cancer

	[1] Up-front (8y outcomes)			[2] Switching (6y outcomes)		
	AI (n = 4,954)	Tam (n = 4,902)	*p*-value	Tam → AI (n = 4,508)	Tam (n = 4,507)	*p*-value
Recurrence	15.3%	19.2%	<0.00001	12.6%	16.1%	<0.00001
Breast cancer mortality	10.0%	10.5%	0.1	6.3%	8.0%	0.02
Death without recurrence	9.1%	8.8%	0.9	5.0%	5.7%	0.08
Any death	17.8%	18.0%	0.3	10.8%	13.0%	0.004

SOURCE: Ingle JN et al. San Antonio Breast Cancer Symposium 2008;**Abstract 12**.

2.4

TEAM (Tamoxifen Exemestane Adjuvant Multinational): A Phase III Trial for Postmenopausal Patients with ER-Positive Breast Cancer (N = 9,766)

	Hazard ratio (95% CI)	*p*-value
Disease-free survival	0.89 (0.77-1.03)	0.12
Relapse-free survival	0.85 (0.72-1.00)	0.05
Time to distant metastases	0.81 (0.67-0.98)	<0.03

HR < 1.0 favors exemestane

SOURCE: Jones S et al. San Antonio Breast Cancer Symposium 2008;**Abstract 15**.

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**.

Coombes RC et al. **Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): A randomised controlled trial.** *Lancet* 2007;369(9561):559-70. **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.** Presentation. San Antonio Breast Cancer Symposium 2008;**Abstract 53**.

Eiermann W et al. **BCIRG 005 main efficacy analysis: A phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus doxorubicin and cyclophosphamide followed by docetaxel (AC → T) in women with Her-2/neu negative axillary lymph node positive early breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 77**.

Ingle JN et al. **Aromatase inhibitors versus tamoxifen as adjuvant therapy for postmenopausal women with estrogen receptor positive breast cancer: Meta-analyses of randomized trials of monotherapy and switching strategies.** San Antonio Breast Cancer Symposium 2008;**Abstract 12**.

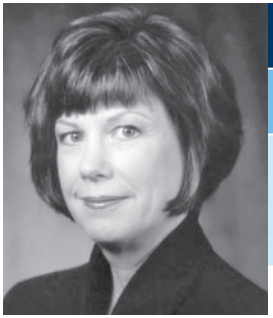
Jakesz R et al. **Tamoxifen and anastrozole as a sequencing strategy in postmenopausal women with hormone-responsive early breast cancer: Updated data from the Austrian breast and colorectal cancer study group trial 8.** San Antonio Breast Cancer Symposium 2008;**Abstract 14**.

Jones S et al. **Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735.** *J Clin Oncol* 2009;27(8):1177-83. **Abstract**

Jones SE et al. **Results of the first planned analysis of the TEAM (Tamoxifen Exemestane Adjuvant Multinational) prospective randomized phase III trial in hormone sensitive postmenopausal early breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 15**.

Mouridsen HT et al. **BIG 1-98: A randomized double-blind phase III study evaluating letrozole and tamoxifen given in sequence as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 13**.

Swain SM et al. **NSABP B-30: Definitive analysis of patient outcome from a randomized trial evaluating different schedules and combinations of adjuvant therapy containing doxorubicin, docetaxel and cyclophosphamide in women with operable, node-positive breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 75**.



INTERVIEW

Sandra M Swain, MD

Dr Swain is Medical Director of the Washington Cancer Institute at Washington Hospital Center and Professor of Medicine at Georgetown University in Washington, DC.

Tracks 1-14

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the recently opened NSABP/CIRG collaborative BETH adjuvant trial for patients with HER2-positive breast cancer?

DR SWAIN: The NSABP has joined with the CIRG to conduct a large adjuvant study for patients with HER2-positive disease. The BETH study is based on Dennis Slamon and Mark Pegram's preclinical data, the Phase I and

Phase II study combining trastuzumab with bevacizumab (Pegram 2006) and the BCIRG 006 study using docetaxel, carboplatin and trastuzumab (TCH; [Slamon 2006]).

The BETH study is open to almost every patient with HER2-positive disease, even those with node-negative disease. Patients will be randomly assigned to TCH with or without bevacizumab (3.1).

DR LOVE: What's the biologic and clinical rationale for this trial?

DR SWAIN: Dennis Slamon examined approximately 600 tumors and showed that those that were HER2-positive and had a high VEGF expression had a worse prognosis (Konecny 2004). After showing synergy with the combination of trastuzumab and bevacizumab in preclinical studies, he evaluated the combination in a Phase II study of HER2-positive advanced breast cancer and the overall response rate was approximately 50 percent (Pegram 2006). So it's nicely going from the bench to the bedside, as Dr Slamon did with the BCIRG 006 study (Slamon 2006).

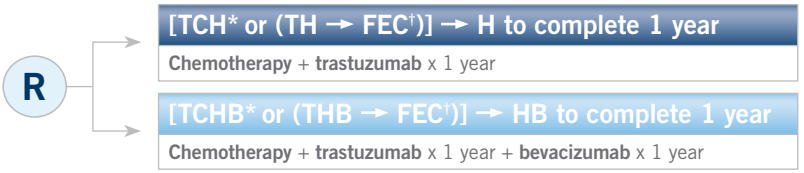
DR LOVE: What do we know about the safety of combining trastuzumab and bevacizumab?

DR SWAIN: In the Phase II study 13 patients had a decrease in ejection fraction (EF), with one severe heart failure. Most of these decreases in EF were Grade I and were not something you would act on. However, hypertension is a known toxicity of bevacizumab, and with a big afterload we may see

3.1

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

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



Eligibility

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

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, February 2009.

more cardiac toxicity in combination with trastuzumab. Denise Yardley in the Sarah Cannon Group presented at San Antonio three different parallel studies evaluating bevacizumab in combination with docetaxel regimens — TAC, AC → T or TCH — to study the cardiac toxicity (Yardley 2008; [3.2]). One heart failure occurred in the study of TCH with bevacizumab, three in the TAC group and three in patients who received AC → T. In the BETH study, we are carefully monitoring EF and are conducting a cardiac analysis of several hundred patients, similar to the B-31 study and the N9831 study, to make sure no excessive cardiac toxicity is incurred.

3.2

Cardiotoxicity with the Addition of Bevacizumab (B) to Three Adjuvant Docetaxel Regimens

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. San Antonio Breast Cancer Symposium 2008;**Abstract 4107**.

Track 14

DR LOVE: Would you discuss the FinXX study evaluating the addition of capecitabine to a taxane/anthracycline base regimen?

DR SWAIN: In this trial, patients were randomly assigned to treatment with three cycles of docetaxel (T) → cyclophosphamide, epirubicin and 5-fluorouracil (CEF) or docetaxel and capecitabine (XT) → cyclophosphamide, epirubicin and capecitabine (CEX; [Joensuu 2008]). It included 1,500 patients with node-positive disease and node-negative tumors.

The results were striking (3.3). Recurrence-free survival was significantly better in the XT → CEX group. It's definitely a positive trial. They found 80 events in the T → CEF arm and 54 events in the capecitabine arm. You can't argue with it. The distant events were 72 versus 42. It appeared to be active.

The design of the FinXX trial was excellent. It was based on previous studies using docetaxel/capecitabine (O'Shaughnessy 2002), so it makes sense that it's beneficial, but it's not enough for me to change my treatment approach now. However, it makes me think about it, and I am anxious to see data from Joyce O'Shaughnessy and the US Oncology trial evaluating AC → T versus AC → XT.

The other point is that evaluating adverse events is where we're headed with the chemotherapy trials. We want the fewest adverse events possible. In the FinXX trial, the TX → CEX arm resulted in less toxicity. Of all the different toxicities, the febrile neutropenia and the myalgias were more prominent in the group that did not receive capecitabine. So I believe that it could be something people will want to use in the future. ■

3.3

FinXX: Docetaxel (T) → CEF versus Docetaxel/ Capecitabine (XT) → CEX for High-Risk Early Breast Cancer

Endpoint	T → CEF (n = 751)	XT → CEX (n = 745)	Hazard ratio	*p*-value
Any recurrence/death	10.7%	7.2%	0.66	0.020
Distant recurrence	9.7%	5.6%	0.64	0.014
Local recurrence	1.6%	0.7%	NR	NR
Death from any cause	5.5%	3.6%	0.66	0.089
Death from breast cancer	4.7%	2.4%	0.51	0.021

NR = not reported

SOURCE: Joensuu H et al. San Antonio Breast Cancer Symposium 2008;**Abstract 82**.

SELECT PUBLICATIONS

Joensuu H et al. **Significant improvement in recurrence-free survival (RFS) when capecitabine (X) is integrated into docetaxel (T) → 5-FU + epirubicin + cyclophosphamide (CEF) adjuvant therapy for high-risk early breast cancer (BC): Interim analysis of the FinXX-trial.** San Antonio Breast Cancer Symposium 2008;**Abstract 82**.

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**

O'Shaughnessy J et al. **Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results.** *J Clin Oncol* 2002;20(12):2812-23. **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**.

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**.

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

INTERVIEW

Ian E Krop, MD, PhD

Dr Krop is Associate Physician at Dana-Farber Cancer Institute and Assistant Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-10

Select Excerpts from the Interview

Track 1

DR LOVE: Would you discuss the recent editorial you published on the evolution of clinical research data with trastuzumab (Krop 2009)?

DR KROP: It has been approximately 10 years since trastuzumab was approved, and we still have a number of unanswered questions that this editorial examined (Krop 2009). First, what is this concept of resistance to trastuzumab? Second, when does the benefit of trastuzumab stop? This is difficult to define because trastuzumab is not typically administered alone.

Two presentations at ASCO 2008 may have provided some clarification to this editorial. In a presentation by Joyce O'Shaughnessy evaluating patients whose disease had progressed on multiple lines of trastuzumab-based therapy, patients were randomly assigned to lapatinib alone or in combination with trastuzumab. Despite the fact that the patients' disease had progressed not on only one but, in most cases, multiple lines of trastuzumab-based therapy, a

significant benefit was seen from continuing trastuzumab with the addition of lapatinib (O'Shaughnessy 2008; [4.1]). Also, a German study by von Minckwitz reported a benefit to continuing trastuzumab in patients treated with capecitabine alone or in combination with trastuzumab after disease progression on trastuzumab therapy (von Minckwitz 2008; [4.2]).

I believe that these two studies indicate that, at least for a significant number of patients, disease progression on a trastuzumab-based regimen was probably due in part to resistance to the agent with which trastuzumab was combined rather than to trastuzumab itself.

4.1

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 > 1, hazard ratio < 1 favors L + T

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

4.2

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**.

Track 5

DR LOVE: Would you discuss the mechanism of action with T-DM1 and the results you presented at the last San Antonio meeting?

DR KROP: T-DM1 is the monoclonal antibody trastuzumab chemically linked to a cytotoxic agent, in this case the antimicrotubule agent DM1. The

antibody specifically targets the cytotoxic agent to the tumor cell. So the idea is that you're able to deliver high amounts of your cytotoxic agent directly to the tumor cell while sparing normal tissue from toxicity.

The Phase I data found encouraging levels of activity — despite the fact that patients had been heavily pretreated — with objective, confirmed response rates in the 40 to 50 percent range (Krop 2008). Another aspect of this drug is how well tolerated it is. The significant toxicities are transient thrombocytopenia and transaminase elevation, but at the maximum tolerated dose, both of those problems are clinically unapparent.

Track 9

DR LOVE: Can you discuss the work conducted by your colleague Nancy Lin, evaluating lapatinib for the treatment of HER2-positive CNS metastases?

DR KROP: CNS metastases develop in approximately 30 to 40 percent of patients with advanced HER2-positive breast cancer (Lin 2008). It's possible that by using a small molecule such as lapatinib we may be able to have an effect on this site of disease.

Nancy Lin and colleagues at Dana-Farber initiated a small study of single-agent lapatinib in patients who had CNS metastases from HER2-positive breast cancer that progressed despite palliative radiation therapy, so we do not have many options for those patients (Lin 2008). She observed a small but significant rate of CNS responses. The study was expanded to combine lapatinib with capecitabine in these patients, and again, a small but significant number of patients benefited (Lin 2009). So currently she's evaluating combining other chemotherapeutic agents, including epothilones, with lapatinib for patients with CNS metastases. ■

SELECT PUBLICATIONS

Krop IE, Winer EP. **Ten years of HER2-directed therapy: Still questions after all these years.** *Breast Cancer Res Treat* 2009;113(2):207-9. No abstract available

Krop IE et al. **A phase I study of weekly dosing of trastuzumab-DM1 (T-DM1) in patients with advanced HER2+ breast cancer.** San Antonio Breast Cancer Symposium 2008;**Abstract 3136**.

Lin NU et al. **Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer.** *Clin Cancer Res* 2009;15(4):1452-9. **Abstract**

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

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**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Which of the following trials demonstrated a statistically significant improvement in progression-free survival with the addition of bevacizumab to chemotherapy as first-line therapy for metastatic breast cancer?**
   a. ECOG-E2100
   b. AVADO
   c. Both a and b
2. **In the BCIRG 005 adjuvant trial comparing four cycles of AC followed by four cycles of docetaxel (AC → T) to six cycles of TAC for patients with node-positive, early breast cancer, the regimens were essentially equivalent in terms of disease-free survival.**
   a. True
   b. False
3. **The BETH trial will evaluate adjuvant chemotherapy/trastuzumab with or without _____ in patients with HER2-positive breast cancer.**
   a. Lapatinib
   b. Bevacizumab
   c. T-DM1
   d. Pertuzumab
4. **In the TransATAC analysis, the Onco*type* DX Recurrence Score predicted the likelihood of distant metastatic disease through nine years of follow-up in patients with node-negative and node-positive breast cancer treated with _____.**
   a. Tamoxifen
   b. Anastrozole
   c. Tamoxifen or anastrozole
5. **In the FinXX trial, patients receiving _____ experienced significantly lower rates of recurrence/death, distant recurrence, death from any cause and death from breast cancer.**
   a. T → CEF
   b. XT → CEX
   c. Rates were the same in both arms
6. **In a randomized study reported by O'Shaughnessy and colleagues, the combination of lapatinib and trastuzumab resulted in equivalent progression-free survival compared to lapatinib alone for heavily pretreated patients with HER2-positive metastatic breast cancer progressing on trastuzumab.**
   a. True
   b. False
7. **In a Phase III study by von Minckwitz and colleagues, continuation of trastuzumab combined with capecitabine resulted in improvements in _____ compared to capecitabine alone in patients with HER2-positive metastatic breast cancer progressing on prior trastuzumab.**
   a. Time to progression
   b. Response rate
   c. Clinical benefit rate
   d. All of the above
8. **In the DOXIL-BCA-3001 study, the addition of pegylated liposomal doxorubicin to docetaxel for patients with advanced breast cancer resulted in significant improvements in _____ with no increase in cardiotoxicity.**
   a. Time to progression
   b. Overall response rate
   c. Overall survival
   d. Both a and b
   e. a, b and c
9. **An ongoing randomized trial is evaluating paclitaxel and trastuzumab with or without pegylated liposomal doxorubicin in patients with HER2-positive early breast cancer.**
   a. True
   b. False

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

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 2, 2009

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

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

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

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

- NSABP-B-30 and BCIRG 005 studies of adjuvant chemotherapy for node-positive early breast cancer (BC) 4 3 2 1
- FinXX: Docetaxel with or without capecitabine → CEF adjuvant therapy for high-risk early BC 4 3 2 1
- TransATAC analysis of the Onco*type* DX assay in node-negative and node-positive BC treated with anastrozole or tamoxifen 4 3 2 1
- US Oncology/NSABP adjuvant trial of TC versus TAC versus TC/bevacizumab 4 3 2 1
- NSABP/CIRG BETH trial: Adjuvant chemotherapy/trastuzumab with or without bevacizumab in HER2-positive BC 4 3 2 1
- Pooled analysis of data for capecitabine with or without ixabepilone in triple-negative mBC 4 3 2 1
- Evidence base for trastuzumab beyond disease progression in mBC 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

- NSABP-B-30 and BCIRG 005 studies of adjuvant chemotherapy for node-positive early breast cancer (BC) 4 3 2 1
- FinXX: Docetaxel with or without capecitabine → CEF adjuvant therapy for high-risk early BC 4 3 2 1
- TransATAC analysis of the Onco*type* DX assay in node-negative and node-positive BC treated with anastrozole or tamoxifen 4 3 2 1
- US Oncology/NSABP adjuvant trial of TC versus TAC versus TC/bevacizumab 4 3 2 1
- NSABP/CIRG BETH trial: Adjuvant chemotherapy/trastuzumab with or without bevacizumab in HER2-positive BC 4 3 2 1
- Pooled analysis of data for capecitabine with or without ixabepilone in triple-negative mBC 4 3 2 1
- Evidence base for trastuzumab beyond disease progression in mBC 4 3 2 1

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

☐ Yes ☐ No

If no, please explain: .....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain: .....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain: .....

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

As a result of this activity, I will be able to:

- Integrate validated genomic assays into the clinical management of hormone receptor (HR)-positive, node-negative or node-positive early breast cancer ..... 4 3 2 1 N/M N/A
- Apply the results of recent clinical trials and meta-analyses when recommending aromatase inhibitors and/or tamoxifen as primary therapy for postmenopausal women with HR-positive early breast cancer. ..... 4 3 2 1 N/M N/A
- Formulate an evidence-based algorithm for the identification and treatment of localized or metastatic, HER2-positive breast cancer. ..... 4 3 2 1 N/M N/A
- Demonstrate knowledge of ongoing investigational approaches to the management of triple-negative or HER2-positive breast cancer. ..... 4 3 2 1 N/M N/A
- Compare and contrast the efficacy, safety and individualized utility of anthracycline- and nonanthracycline-based adjuvant chemotherapy regimens. ..... 4 3 2 1 N/M N/A
- Appraise the contributory role of oral fluoropyrimidines in the management of early breast cancer. ..... 4 3 2 1 N/M N/A
- Consider the unique benefits and risks associated with novel epothilones and taxanes when selecting and sequencing chemotherapeutic regimens. ..... 4 3 2 1 N/M N/A
- Recall emerging clinical trial results with bevacizumab for metastatic breast cancer, and assess their application to current patient care. ..... 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?

.....

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.....

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
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Stephen E Jones, MD	4 3 2 1	4 3 2 1
Sandra M Swain, MD	4 3 2 1	4 3 2 1
Ian E Krop, MD, PhD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the editor and faculty for this activity:

.....

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Breast Cancer® UPDATE

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