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Breast Cancer® UPDATE

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

FACULTY INTERVIEWS

Mark D Pegram, MD
Karen A Gelmon, MD
Kathy D Miller, MD
Stephen Chia, MD

EDITOR

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2 Audio CDs
Monograph

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Breast Cancer Update
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OVERVIEW OF ACTIVITY

Breast cancer continues to be 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 and prognostic tools. In order to offer optimal patient care — including the option of clinical trial participation — the practicing cancer clinician must be well informed of these advances. Featuring information on the latest research developments along with expert perspectives, this CME activity is designed to assist medical oncologists, hematologist-oncologists and hematology-oncology fellows with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Develop evidence-based treatment approaches for patients diagnosed with HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings.
- Evaluate recently presented data supporting the extended use of adjuvant tamoxifen beyond 5 years for patients with ER-positive early breast cancer and, where appropriate, integrate these findings into clinical practice.
- Recognize the evolving application of biomarkers and multigene assays in breast cancer management, and effectively use these tools to refine or individualize treatment plans for patients.
- Formulate individualized approaches to first- and later-line therapy for patients with HER2-negative metastatic breast cancer.
- Counsel appropriately selected patients with breast cancer about the supportive and therapeutic role of bisphosphonates in disease management.

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INTERVIEW

Mark D Pegram, MD

Dr Pegram is Susy Yuan-Huey Hung Professor of Medicine, Director of the Breast Oncology Program and Director of the Molecular Therapeutics Program at Stanford University School of Medicine's Stanford Cancer Institute in Stanford, California.

Tracks 1-9

Select Excerpts from the Interview

Track 1

DR LOVE: What are your thoughts on the NSABP-B-50-I trial evaluating T-DM1 versus trastuzumab for patients with HER2-positive breast cancer who have residual disease after preoperative systemic treatment (1.1)?

DR PEGRAM: That study is open and accruing well. It's an interesting and innovative study design for patients who do not achieve a pathologic complete response (pCR) after neoadjuvant trastuzumab and chemotherapy. Patients are randomly assigned to continue a year of adjuvant trastuzumab, which is the current standard, or to complete the year with T-DM1.

It's a promising study that will quickly answer questions in early breast cancer. The study population is unique because it includes only patients who didn't achieve a pCR. If the trial is positive, our enthusiasm for further developing T-DM1 in the adjuvant and neoadjuvant settings will be heightened.

1.1

NSABP-B-50-I (KATHERINE): A Phase III Trial of T-DM1 versus Trastuzumab as Adjuvant Therapy for Patients with HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Nodes After Neoadjuvant Treatment

Protocol ID: NCT01772472

Target Accrual: n = 1,484

Eligibility

- HER2-positive invasive breast cancer
- Clinical Stage T1-4/N0-3/M0 at presentation
- No Stage T1a/bN0 or Stage IV breast cancer allowed

R

T-DM1
3.6 mg/kg every 3 weeks for 14 cycles

Trastuzumab
6 mg/kg every 3 weeks for 14 cycles

www.clinicaltrials.gov. Accessed June 2014.

Tracks 2-3

DR LOVE: Would you discuss the results of the Phase III BETH trial evaluating adjuvant therapy in patients with HER2-positive breast cancer with trastuzumab and chemotherapy with or without bevacizumab (Slamon 2013; [1.2])?

DR PEGRAM: The most important aspect of the BETH trial was whether bevacizumab would add therapeutic benefit. The results were disappointing in that they showed no efficacy signal. This was not entirely surprising because of the results of the NSABP-C-08 trial in the adjuvant colorectal cancer setting (Allegra 2011). As soon as I saw those results, my enthusiasm for adjuvant bevacizumab for human solid tumors was diminished. That said, testing clinical hypotheses in randomized trials, even if the results are negative, provides important findings about the biology of HER2-positive

1.2

Efficacy and Safety Results from the Phase III BETH Trial of Adjuvant Therapy with Trastuzumab (T) and Chemotherapy* with or without Bevacizumab (Bev) for Patients with HER2-Positive Early Breast Cancer

Outcome	Chemo/T (n = 1,757)	Chemo/T/bev (n = 1,752)	Hazard ratio	*p*-value
38-month IDFS	92%	92%	1.00	0.9789
38-month OS	96%	97%	0.87	0.4387
Select Grade 3 or 4 adverse events	**Chemo/T (n = 1,750)**	**Chemo/T/bev (n = 1,722)**	***p*-value**	
Hypertension	4%	19%	<0.0001	
Thromboembolic event	2%	3%	NR	
Bleeding	<1%	2%	<0.0001	
Heart failure	<1%	2.1%	0.0621	
Proteinuria	<1%	1%	<0.0001	

* TCH or TH → FEC
IDFS = invasive disease-free survival; OS = overall survival; NR = not reported

Slamon DJ et al. San Antonio Breast Cancer Symposium 2013;**Abstract S1-03**.

early breast cancer and tells us if we need to redirect our research focus. Although making cross-trial comparisons is problematic, it is reassuring that patients on the control arm of the BETH trial appeared to fare remarkably well with the backbone of docetaxel/carboplatin/trastuzumab (TCH) in the adjuvant setting. This result further bolsters the notion that nonanthracycline-containing regimens are safe and effective in HER2-positive early breast cancer.

Whether anthracyclines are superior or not remains an open question. In my view the BCIRG 006 trial did not answer that question satisfactorily. Although the difference in efficacy between the AC → TH and the TCH arms was statistically insignificant, a visual trend in the graphic analysis favored the anthracycline regimen (Slamon 2011). I always discuss the merits of AC → TH compared to TCH with my patients with lymph node-positive, HER2-positive early breast cancer. I present these results in a balanced and fair way and allow my patients to make as informed a decision as possible after seeing the data.

Tracks 8-9

DR LOVE: What is your view on the recent FDA approval of neoadjuvant pertuzumab?

DR PEGRAM: I applaud the FDA for coming up with new guidelines for accelerated approval that are perhaps paradigm shifting. Pertuzumab is the first drug approved for neoadjuvant breast cancer. The FDA guidance demands, in addition to the use of pCR as an endpoint, commitment to time-to-event Phase III trials in the neoadjuvant and adjuvant settings. The adjuvant APHINITY Phase III trial will compare chemotherapy/trastuzumab to chemotherapy/trastuzumab/pertuzumab head to head (NCT01358877).

Pertuzumab adds little toxicity but increases diarrhea and cutaneous rash. Fortunately it has no effect on left ventricular ejection fraction. The only factor of concern with this accelerated approval is whether the pCR results will hold up in the long term without further adjuvant pertuzumab. We will not have that answer until we obtain the APHINITY trial results.

DR LOVE: In terms of chemotherapeutic backbones for pertuzumab/trastuzumab combinations, what are the options you tend to use?

DR PEGRAM: The FDA label indication and the NCCN guidelines differ in the use of neoadjuvant pertuzumab regimens. On the basis of the NEOSPHERE study the FDA label approves neoadjuvant pertuzumab in combination with docetaxel and trastuzumab. It also mentions that neoadjuvant FEC followed by neoadjuvant docetaxel/trastuzumab/pertuzumab, based on the TRYPHAENA study, may be an option to consider. Additionally, the label indicates that TCH with pertuzumab is a possibility. It specifically states that no safety data exist with doxorubicin-containing regimens. The NCCN guidelines prefer neoadjuvant regimens for HER2-positive disease to include AC → paclitaxel/trastuzumab/pertuzumab. They also suggest that TCH with pertuzumab is a reasonable treatment option. ■

SELECT PUBLICATIONS

Allegra C et al. **Phase III trial assessing bevacizumab in stages II and III carcinoma of the colon: Results of NSABP protocol C-08.** *J Clin Oncol* 2011;29(1):11.

Slamon D et al. **Adjuvant trastuzumab in HER2-positive breast cancer.** *N Engl J Med* 2011;365(14):1273-83.

INTERVIEW

Karen A Gelmon, MD

Dr Gelmon is Professor of Medicine at the University of British Columbia, Medical Oncologist at the BC Cancer Agency Vancouver Cancer Centre and Head of the Division of Medical Oncology at the University of British Columbia in Vancouver, Canada.

Tracks 1-15

Select Excerpts from the Interview

Tracks 2-3, 5

DR LOVE: Would you provide an update on the status of PARP inhibitor research in breast cancer?

DR GELMON: PARP inhibitors have suffered from long delays in development in breast cancer, but we're starting to see some exciting results again. A number of PARP inhibitors are much like olaparib, and many of these agents are entering Phase II studies on

which patients with BRCA1 or BRCA2 mutations are randomly assigned to a PARP inhibitor or best standard care. I believe these studies will rapidly garner much information about the role of PARP inhibitors in the metastatic setting.

Another exciting trial opening in the adjuvant setting is OlympiA (NCT02032823). On this study patients with germline BRCA1/2 mutations and high-risk HER2-negative primary breast cancer are randomly assigned to olaparib or placebo after definitive local therapy and neoadjuvant or adjuvant chemotherapy.

The goal is to determine whether PARP inhibition decreases recurrence rates in BRCA carriers with breast cancer. It will be a long time before we understand whether PARP inhibition has a role in therapy for patients without the BRCA mutation, but that's part of our dissection of the different breast cancer subtypes.

DR LOVE: A presentation at the 2013 San Antonio Breast Cancer Symposium (SABCS) by Hope Rugo on the I-SPY 2 trial reported that the addition of veliparib and carboplatin to standard neoadjuvant therapy increased pCR rates, particularly for the subset of patients with triple-negative breast cancer (Rugo 2013; [2.1]). What are your thoughts on that data set?

DR GELMON: That's an interesting data set. Platinums are looking better and better in the neoadjuvant setting. Whether veliparib made a difference I don't believe we know yet. For now I'd use the adjectives "hypothesis-generating" and "interesting" to describe this study. To make more of it at this point probably would be a mistake.

2.1

First Efficacy Results from the Phase II I-SPY 2 Trial for Patients with High-Risk Breast Cancer: Addition of Veliparib/Carboplatin (V + Carbo) to Standard Neoadjuvant Therapy*

Signature	Estimated pCR rate		Probability V + carbo is superior to control	Predictive probability of success in Phase III trial
	V + carbo	Control*		
All HER2-negative	**33%**	**22%**	**92%**	**55%**
HR-positive/HER2-negative	14%	19%	28%	9%
HR-negative/HER2-negative	**52%**	**26%**	**99%**	**90%**

* Paclitaxel qwk x 12, doxorubicin and cyclophosphamide q2-3wk x 4
pCR = pathologic complete response; HR = hormone receptor

Conclusions: Adaptive randomization successfully identified a biomarker-drug pair for V + carbo on the basis of a modest number of patients. V + carbo has graduated with a triple-negative breast cancer signature, and that is the subset recommended for this regimen's subsequent development. As expected, toxicity is increased with V + carbo, but this was well managed by dose reduction and delay.

Analyses are currently under way to define additional biomarkers that may be predictive of response. The I-SPY 2 standing trial mechanism efficiently evaluates agents/combinations in biomarker-defined patient subsets.

Rugo HS et al. San Antonio Breast Cancer Symposium 2013;**Abstract S5-02**.

Tracks 7-8

DR LOVE: What are your thoughts on the CDK4/6 inhibitor palbociclib for patients with ER-positive metastatic breast cancer (mBC)?

DR GELMON: We were involved in a Phase II trial that randomly assigned postmenopausal women with ER-positive mBC to receive letrozole or letrozole with palboci-

clib. Initial results of this trial were presented almost 2 years ago and demonstrated a remarkable improvement in progression-free survival with the addition of palbociclib to letrozole (Finn 2012).

Final results were recently reported and continue to show an exciting progression-free survival advantage — about 20 months with palbociclib/letrozole versus about 10 months with letrozole alone. A 4-month difference in overall survival also was observed, although it was not statistically significant (Finn 2014; [2.2]).

The large Phase III PALOMA-2 trial (NCT01740427) is evaluating the same design with a few caveats — the study incorporates more pharmacokinetic and safety endpoints. Another Phase III trial called PENELOPE-B (NCT01864746) is evaluating palbociclib after neoadjuvant chemotherapy for patients with ER-positive, HER2-normal primary breast cancer. Patients who do not experience a pCR will receive endocrine therapy with or without palbociclib. A large international trial called PALLAS is also slated to begin enrollment in about 6 months. That trial will evaluate letrozole with or without palbociclib as adjuvant therapy for ER-positive breast cancer.

2.2

PALOMA-1: Final Results of a Phase II Study of Letrozole (L) with or without the CDK4/6 Inhibitor Palbociclib (P) as First-Line Therapy for ER-Positive, HER2-Negative Metastatic Breast Cancer (mBC)

	P + L	L alone	Hazard ratio	*p*-value
Median PFS	20.2 mo	10.2 mo	0.488	0.0004
Median OS	37.5 mo	33.3 mo	0.813	0.2105

PFS = progression-free survival; OS = overall survival

- The most common adverse events on the P + L arm were neutropenia, leukopenia, fatigue and anemia.

Conclusions: "P + L demonstrated a statistically significant improvement in PFS and showed significant clinical benefit as first-line treatment of ER+/HER2- advanced BC. A Phase III study of P + L in this same mBC population is ongoing."

Finn RS et al. *Proc AACR* 2014;**Abstract CT101**.

Tracks 11-13

DR LOVE: What options do you typically discuss with patients with ER-positive mBC who develop resistance to aromatase inhibitor (AI) therapy?

DR GELMON: We see a number of patients who have experienced long responses on hormonal agents but who have now experienced disease progression, and the question is, what's the next treatment? Outside a clinical trial, the major options I would discuss include fulvestrant or the combination of exemestane and everolimus. Benefits for fulvestrant include that it is well tolerated and is administered by intramuscular injection once a month. Most patients fare well with this agent.

However, we have the option of exemestane and everolimus, which is an exciting combination. We know from the BOLERO-2 trial that a significant benefit of about 4 months was seen in progression-free survival with everolimus/exemestane versus exemestane/placebo for patients with advanced breast cancer whose disease recurred or progressed during or after treatment with nonsteroidal AIs (2.3).

At the recent European Breast Cancer Meeting in Glasgow, Martine Piccart presented the overall survival results for BOLERO-2 and, although everolimus/exemestane also had about a 4-month advantage, the difference was not statistically significant (2.3).

We know that patient tolerance to this combination is variable. Some women tolerate it beautifully, whereas others may experience fatigue or mouth sores. I have many patients who sail through it. I have other patients who start at 10 mg but need to be reduced to 5 mg, and then they feel fine. So I believe the toxicity is there, but it's not extensive. I have observed some pulmonary toxicity, however.

We previously performed a randomized Phase II study of everolimus weekly versus daily and observed this pulmonary toxicity to be schedule dependent (Ellard 2009). I have since observed 2 patients with early toxicity with the daily dosing. We have to see these patients at 4 weeks and then again every 6 weeks or so. We can't use our usual algorithm for endocrine therapy. ■

2.3

BOLERO-2: A Phase III Trial of Exemestane and Everolimus in ER/PR-Positive Metastatic Breast Cancer Refractory to Nonsteroidal Aromatase Inhibitors

	Exemestane + everolimus (n = 485)	Exemestane + placebo (n = 239)	Hazard ratio	*p*-value
Median PFS (by central assessment)	11.0 mo	4.1 mo	0.38	<0.0001
Median PFS (by investigator assessment)	7.8 mo	3.2 mo	0.45	<0.0001
ORR (by central assessment)	12.6%	2.1%	—	—
Median OS*	31.0 mo	26.6 mo	0.89	0.14

PFS = progression-free survival; ORR = objective response rate; OS = overall survival

Baselga J et al. *N Engl J Med* 2012;366(6):520-9; Yardley DA et al. *Adv Ther* 2013;30(10):870-84; * Piccart M et al. *Proc European Breast Cancer Conference* 2014;**Abstract LBA1**.

SELECT PUBLICATIONS

Baselga J et al. **Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer.** *N Engl J Med* 2012;366(6):520-9.

Ellard SL et al. **Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC Clinical Trials Group IND.163.** *J Clin Oncol* 2009;27(27):4536-41.

Finn RS et al. **Results of a randomized Phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (BC).** San Antonio Breast Cancer Symposium 2012;**Abstract S1-6**.

O'Shaughnessy J et al. **A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC).** *Proc ASCO* 2011;**Abstract 1007**.

Piccart M et al. **Everolimus plus exemestane for hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (BC): Overall survival results from BOLERO-2.** *Proc European Breast Cancer Conference (EBCC-9)* 2014;**Abstract LBA1**.

Rugo HS et al. **Veliparib/carboplatin plus standard neoadjuvant therapy for high-risk breast cancer: First efficacy results from the I-SPY 2 trial.** San Antonio Breast Cancer Symposium 2013;**Abstract S5-02**.

Yardley DA et al. **Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis.** *Adv Ther* 2013;30(10):870-84.

INTERVIEW

Kathy D Miller, MD

Dr Miller is Co-Director of the IU Simon Cancer Center Breast Cancer Team, Ballvé Lantero Scholar in Oncology and Associate Professor of Medicine in the Department of Personalized Medicine in The Indiana University Melvin and Bren Simon Cancer Center's Division of Hematology/Oncology in Indianapolis, Indiana.

Tracks 1-10

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Track 8 **Second opinion:** Hormonal therapy versus high-dose chemotherapy → radiation therapy for patients with ER-positive, HER2-negative mBC

Track 9 **Case discussion:** A 46-year-old woman who originally received endocrine treatment in 1999 for Stage I, ER-positive IDC presents with ER-negative, HER2-positive recurrent disease and begins treatment with weekly paclitaxel in combination with trastuzumab

Track 10 **Case discussion:** A 68-year-old man who previously received a regimen that included an anthracycline for testicular cancer presents with a 2.4-cm, ER-positive, HER2-positive IDC with 1 positive axillary node

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What are your thoughts on the Phase II APT trial that was presented at the 2013 SABCS by a group from Dana-Farber evaluating adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer (Tolaney 2013; [3.1])?

DR MILLER: This was an important single-arm study that came out of the recognition that a population of patients with smaller, HER2-positive, node-negative breast cancer has been largely excluded from adjuvant trastuzumab trials. The goal of this Phase II trial was to find a treatment that would have an excellent outcome while minimizing the duration, cost and toxicity of therapy. The trial enrolled approximately 400 patients

3.1

Phase II APT Trial of Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Efficacy	Paclitaxel and trastuzumab	
Three-year disease-free survival (DFS)		
All patients (n = 406)	98.7%	
Tumors >1 cm (n = 205)	98.0%	
Tumors ≤1 cm (n = 201)	99.5%	
DFS events		
Any recurrence	2.5%	
Local/regional recurrence (ipsilateral axilla and breast)	0.9%	
Distant recurrence	0.5%	
Select adverse events	All grades	Grade 3 or 4
Neuropathy	13%	3%
Neutropenia	11%	<5%
Leukopenia	9%	2%
Anemia	7%	<1%

Symptomatic congestive heart failure: 0.5%; asymptomatic declines in left ventricular ejection fraction: 3.2%

Tolaney S et al. San Antonio Breast Cancer Symposium 2013;**Abstract S1-04**.

with tumors 3 centimeters or smaller. Patients received paclitaxel and trastuzumab for 12 weeks followed by trastuzumab for 9 months.

The majority of patients had tumors that were between 1 and 2 centimeters in size, and their outcomes were excellent (Tolaney 2013; [3.1]). The side effects, including cardiac toxicity, were minimal. Although questions remain, we now have a fairly large data set we can use in this setting.

DR LOVE: In this study, 19% of the patients had T1a tumors that were 5 millimeters or smaller and may not have experienced a recurrence without treatment. What is your approach for managing these tumors?

DR MILLER: I believe that, even with the most aggressive biology, tumor size still matters. Where you set that bar for treatment is where we differ. I find it difficult to advocate systemic therapy for patients with tumors smaller than 5 millimeters.

I may or may not recommend systemic treatment for tumors in the 5- to 10-mm range, depending on a discussion with the patient. We consider factors such as the size of the tumor, tumor biology and whether the patient is more concerned about recurrence or about the toxicities of therapy.

DR LOVE: What adjuvant therapy do you recommend for patients with node-negative, HER2-positive breast cancer?

DR MILLER: Since participating in the Phase II APT trial, I generally recommend that regimen of paclitaxel and trastuzumab for 12 weeks. It was well tolerated, and I am comfortable recommending that abbreviated regimen to patients outside of a trial setting. I have administered both TCH and anthracyclines followed by paclitaxel/trastuzumab depending on tumor size and nodal burden.

Track 4

DR LOVE: Would you discuss the results from trials reported at SABCS 2013 evaluating the benefits of primary tumor resection for patients with Stage IV breast cancer?

DR MILLER: Two randomized trials — in Turkey and India — were presented at SABCS to address this question (Badwe 2013; Soran 2013). These studies did not report any significant benefits for resection of the primary tumor (3.2).

A subset analysis from one study reported that patients with bone-only metastases had a trend toward longer survival (Soran 2013). I do not generally recommend surgical removal of the primary tumor unless it is symptomatic, and the results from these studies have not affected my practice.

DR LOVE: Dr Seema Khan, the discussant for that session, concluded that locoregional therapy should not be offered to patients with mBC who are at low risk for local recurrence outside the setting of a clinical trial (Khan 2013). Do you agree?

DR MILLER: Dr Khan has been consistent on that front. She has supported the idea that, although surgery might be helpful in some situations, the benefits have not been proven.

It is important to support the ongoing ECOG-E2108 Phase III study (NCT01242800), evaluating early surgery versus standard palliative care for patients with Stage IV breast cancer.

Dr Khan, the principal investigator, has been collaborating with the Turkish and Indian investigators so that they can combine the samples collected in the ECOG trial with their studies. That will allow for a more extensive biobank to identify subsets of patients who might benefit from surgery.

3.2

Results of 2 Phase III Trials Evaluating Primary Tumor Resection for Patients with Stage IV Breast Cancer

Study design	Tata Memorial (India)[1] (n = 350)	MF 07-01 (Turkey)[2] (n = 293)
Initial systemic therapy before randomization	CEF ± taxane	None
Primary endpoint	Overall survival	Overall survival
Efficacy		
Overall survival	LRT vs no LRT HR 1.04, $p = 0.79$	Surgery vs systemic therapy HR 0.76, $p = 0.20$
Bone-only metastases	HR 1.43, p = NR	HR 0.60, $p = 0.15$
Solitary bone metastasis	NR	HR 0.23, $p = 0.02$

CEF = cyclophosphamide/epirubicin/fluorouracil; LRT = locoregional therapy; HR = hazard ratio; NR = not reported

[1] Badwe R et al. San Antonio Breast Cancer Symposium 2013;**Abstract S2-02**; [2] Soran A et al. San Antonio Breast Cancer Symposium 2013;**Abstract S2-03**.

Tracks 5-6

DR LOVE: What are your thoughts on the recent study using the PAM50 assay to predict late distant recurrences in cohorts from the ABCSG-8 and TransATAC studies after 5 years of endocrine treatment?

DR MILLER: Although studies like the ATLAS and aTTom trials have shown that extended adjuvant endocrine therapy is beneficial, the benefit was fairly modest. Considering the cost, side effects and compliance issues associated with long-term therapy, it would be valuable to identify patients who have a high recurrence risk after 5 years of endocrine treatment.

The PAM50 analysis was able to identify groups of patients at different risks of recurrence between 5 years and 10 years after endocrine therapy. The high-risk group had approximately a 17% risk of distant recurrence compared to only about 2% in the low-risk group (Sestak 2013). PAM50 analysis has not affected my personal practice because, although it tells us about risk of recurrence, it does not tell us what treatment would be beneficial.

DR LOVE: A study reported at SABCS 2013 comparing the risk classification among the MammaPrint, Onco*type* DX and Mammostrat assays in early breast cancer demonstrated that these assays classify a large proportion of patients differently. What is your take on these results (Shivers 2013)?

DR MILLER: These assays do classify patients differently, and to an extent that's not surprising. The specific genes incorporated into the different risk-stratifying platforms have little overlap. However, the overlap in the pathways represented by those genes is substantial. Genes involved in ER signaling, proliferation, apoptosis, angiogenesis and invasion are typically represented.

It is important for me to be able not only to determine a patient's risk but also to predict whether a patient will benefit from a specific therapy. Only the Onco*type* DX assay has been validated as a predictor of benefit from chemotherapy in multiple randomized trials, and that's why I use it in my practice. ■

SELECT PUBLICATIONS

Badwe R et al. **Surgical removal of primary tumor and axillary lymph nodes in women with metastatic breast cancer at first presentation: A randomized controlled trial.** San Antonio Breast Cancer Symposium 2013;**Abstract S2-02**.

Khan SA. **Does primary tumor resection improve survival for patients with Stage IV breast cancer?** San Antonio Breast Cancer Symposium 2013;**Abstract S2-04**.

Sestak I et al. **Prediction of late distant recurrence after 5 years of endocrine treatment: A combined analysis of 2485 patients from the ABCSG-8 and transATAC studies using the PAM50 risk of recurrence (ROR) score.** San Antonio Breast Cancer Symposium 2013;**Abstract S6-04**.

Shivers SC et al. **Direct comparison of risk classification between MammaPrint®, Onco*type* DX® and Mammostrat® assays in patients with early stage breast cancer.** San Antonio Breast Cancer Symposium 2013;**Abstract P6-06-02**.

Soran A et al. **Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01).** San Antonio Breast Cancer Symposium 2013;**Abstract S2-03**.

Tolaney S et al. **A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC).** San Antonio Breast Cancer Symposium 2013;**Abstract S1-04**.

INTERVIEW

Stephen Chia, MD

Dr Chia is Medical Oncologist and Associate Professor of Medicine at the University of British Columbia and Chair of the British Columbia Breast Tumour Group in Vancouver, Canada.

Tracks 1-10

Select Excerpts from the Interview

Track 4

DR LOVE: Will you review the issue of the use of extended adjuvant endocrine therapy for patients with hormone-dependent breast cancer?

DR CHIA: The aTTom and ATLAS trial data demonstrated a couple of points. First, 10 years of tamoxifen is better than 5 years, although I believe that the relative risk reduction is fairly modest (4.1). It has not yet been proven that 10 years of an AI is better than 5 years, but a lot of people are trying to make extrapolations.

Studies evaluating that approach have been fully accrued, and we're awaiting those results. In terms of how to select patients, however, we don't yet have a verified or validated predictive profile that says this tumor is more sensitive to 10 years versus 5 years of tamoxifen.

DR LOVE: In what situations do you generally continue tamoxifen beyond 5 years for premenopausal women?

4.1

ATLAS and aTTom Trials: Effect on Breast Cancer Recurrence and Mortality of Continuing Adjuvant Tamoxifen (TAM) to 10 Years versus Stopping at 5 Years

	10 y TAM vs 5 y: **aTTom trial** (n = 6,934 ER+/UK)	10 y TAM vs 5 y: **ATLAS trial*** (n = 10,543 ER+/UK)	10 y TAM vs 5 y: **aTTom and ATLAS combined** (n = 17,477 ER+/UK)
Years 5-9	1.08 (0.85-1.38)	0.92 (0.77-1.09)	0.97 (0.84-1.15)
Years 10+	0.75 (0.63-0.90) $p = 0.007$	0.75 (0.63-0.90) $p = 0.002$	0.75 (0.65-0.86) $p = 0.00004$
All years	0.88 (0.74-1.03) $p = 0.1$	0.83 (0.73-0.94) $p = 0.004$	0.85 (0.77-0.94) $p = 0.001$

* Inverse variance-weighted estimate of the effect in ER-positive disease

- aTTom and ATLAS together provide "proof beyond reasonable doubt" that continuing TAM beyond 5 years reduces recurrence over the following years: No effect in years 5-6, benefit mainly after year 7
- Continuing TAM beyond 5 years also reduces breast cancer mortality: No effect in years 5-9, 25% reduction after year 10
- Main risk: Endometrial cancers (10 y vs 5 y TAM: 2.9% vs 1.3%, $p < 0.0001$)

Gray R et al. *Proc ASCO* 2013;**Abstract 5**; Davies C et al. *Lancet* 2013;381(9869):805-16.

DR CHIA: Where I practice within British Columbia we have our own large clinical outcomes database with which we've evaluated residual risk in premenopausal women with breast cancer after 5 years of tamoxifen. It appears that patients with Stage II disease or greater have a residual risk that would probably warrant an absolute risk reduction of at least 2% if they were to take tamoxifen.

DR LOVE: Are there any situations in which you would consider going beyond 5 years of an AI in the postmenopausal setting?

DR CHIA: I struggle with this. I do believe that the concept of longer hormonal therapy has been proven with the ATLAS and aTTom trials, albeit with tamoxifen. It's difficult to fathom that that wouldn't also be the case with AIs.

The way I approach it is to ask, what is the residual risk for that woman at 5 years? Has she been compliant with her hormonal therapy? What toxicities has she experienced so far? If the patient has experienced few toxicities, her bone mineral density is good and the risk of osteoporosis is low, I would consider continuing the AI. But I'm frank and honest in telling patients that we do not yet have Level 1 evidence in this setting. That could change in a couple of years when the results from the Phase III NSABP-B-42 and MA17R trials of extended use of AIs are reported.

Track 5

DR LOVE: Would you discuss some of the key points of your group's recent publication entitled, "A prospective clinical utility and pharmacoeconomic study of the impact of the 21-gene Recurrence Score (RS) assay in ER-positive, node-negative breast cancer" (Davidson 2013)?

DR CHIA: We've been practicing for many years with the only predictive markers being ER and HER2. But I'm a big fan of predictive assays, and the Onco*type* DX assay is the first but it clearly won't be the last. The aspect about the Onco*type* DX assay

that I believe is positive is that many of the prospective clinical utility studies have had consistent results.

Our clinical utility and pharmacoeconomic study showed a 30% change in the recommendation of chemotherapy by physicians. For 20% of patients we removed the delivery of chemotherapy and for 10% we added it, based on the Onco*type* DX RS (Davidson 2013; [4.2]). Basically this type of proportion was replicated across multiple countries, whether it was in Spain, Germany, Israel, the United States or Australia. So I believe the consistency of that finding is strong.

We also performed a prospective analysis of cost and demonstrated that it was cost effective to add the 21-gene RS to your clinical algorithm. The cost-effectiveness ratio was in the range of about 7,000 Canadian dollars per quality-adjusted life-year gained. And remember, a life-years gain is associated with this. This means that if a high RS is returned for a patient for whom you were not suspecting that or considering chemotherapy, you can prevent a distant metastasis by administering adjuvant chemotherapy.

The treatment of breast cancer recurrence in the metastatic setting is expensive, and clearly it would be great to prevent having to treat in that setting if possible. We see a number of patients and families in our clinic for whom it's extremely difficult to decide whether to proceed with chemotherapy or not. The studies that have been conducted with the 21-gene assay have shown that it reduces decisional conflict. Having the RS result increases the confidence of both the physician and the patient.

4.2

Changes in Physicians' Treatment Recommendations Based on the Onco*type* DX Assay Recurrence Score (RS)

	Chemotherapy + hormonal therapy		Change in recommendation
	Preassay (n)	Postassay (n)	
High RS (n = 36)	24	34	+28%
Intermediate RS (n = 45)	18	13	-11%
Low RS (n = 69)	20	0	-29%
Total (n = 150)	62	47	-10%

- Physicians changed their adjuvant chemotherapy recommendation after receiving the RS result for 45 patients, or 30% of all cases.
  - In two thirds of these situations (20%), chemotherapy was omitted in favor of endocrine therapy alone.
  - In one third of these situations (10%), chemotherapy was added after the oncologist had initially planned to proceed only with endocrine therapy.

Davidson JA et al. *Eur J Cancer* 2013;49(11):2469-75.

Track 8

DR LOVE: What are your thoughts on the meta-analysis presented at SABCS 2013 on the effects of bisphosphonate treatment on recurrence in women with early breast cancer (Coleman 2013)?

DR CHIA: This presentation by Dr Rob Coleman was a surprise in that it showed a reduction in the incidence of bone metastases for postmenopausal women who received adjuvant bisphosphonates regardless of type of bisphosphonate used or treatment

schedule. A benefit also was seen in terms of breast cancer-specific survival (Coleman 2013; [4.3]). I'm hesitant because you're merging all the data and evaluating a subgroup that wasn't initially under consideration and didn't have the biology to support that. This was an afterthought after a couple of the more recent trials suggested that it is the postmenopausal patients who seem to benefit from adjuvant bisphosphonate therapy.

I'm not arguing what this meta-analysis demonstrated, but I would have loved to see a confirmatory trial. One that may come out with time is evaluating denosumab versus placebo (NCT01077154).

So if you have a reason to administer a bisphosphonate — in other words, if you have a postmenopausal woman to whom you're administering at least 5 years of an AI, she has a low bone mineral density and you'll prescribe it to her for bone strength anyway — then, sure, why not? I'm not sure it's a given that you administer it to all postmenopausal women — for instance, in someone with normal bone mineral density without a high risk of recurrence. ■

4.3

Meta-Analysis of the Effects of Bisphosphonate Treatment in Women with Early Breast Cancer

	Number of events	Rate ratio	10-year gain	*p*-value
All women (n = 17,016)				
Breast cancer mortality	2,049	0.91	1.7%	0.04
Breast cancer recurrence	3,284	0.94	1.0%	0.13
Distant recurrence	2,751	0.92	1.3%	0.05
Bone recurrence	825	0.79	1.4%	0.002
Postmenopausal women (n = 10,540)				
Breast cancer mortality	1,107	0.83	3.1%	0.004
Breast cancer recurrence	1,809	0.86	3.0%	0.002
Distant recurrence	1,503	0.83	3.3%	0.0007
Bone recurrence	445	0.65	2.9%	0.00001

Conclusions: Adjuvant bisphosphonate therapy reduces bone recurrences and improves survival for postmenopausal women. Benefits in postmenopausal women were independent of bisphosphonate type, treatment schedule, ER status, nodal involvement or use of concomitant chemotherapy. However, no effects are apparent on disease outcomes for premenopausal women, and no effects on nonbone recurrence were observed regardless of menopausal status.

Coleman R et al. San Antonio Breast Cancer Symposium 2013;**Abstract S4-07**.

SELECT PUBLICATIONS

Coleman R et al. **Effects of bisphosphonate treatment on recurrence and cause-specific mortality in women with early breast cancer: A meta-analysis of individual patient data from randomised trials.** San Antonio Breast Cancer Symposium 2013;**Abstract S4-07**.

Davidson JA et al. **A prospective clinical utility and pharmacoeconomic study of the impact of the 21-gene Recurrence Score assay in oestrogen receptor positive node negative breast cancer.** *Eur J Cancer* 2013;49(11):2469-75.

Davies C et al. **Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.** *Lancet* 2013;381(9869):805-16.

Gray R et al. **aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer.** *Proc ASCO* 2013;**Abstract 5**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The ongoing Phase III NSABP-B-50-I (KATHERINE) trial is evaluating _____ versus trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumor in the breast or axillary nodes after neoadjuvant treatment.**
   a. Pertuzumab/trastuzumab
   b. T-DM1
   c. Chemotherapy/trastuzumab

2. **The Phase III BETH trial of adjuvant therapy with trastuzumab and chemotherapy with or without bevacizumab for HER2-positive early breast cancer demonstrated a statistically significant improvement in _____ with the addition of bevacizumab.**
   a. Invasive disease-free survival
   b. Overall survival
   c. Both a and b
   d. Neither a nor b

3. **Initial efficacy results from the Phase II I-SPY 2 trial evaluating the addition of veliparib/carboplatin to standard neoadjuvant therapy for patients with high-risk breast cancer reported increased rates of pCR with the addition of veliparib/carboplatin in which of the following patient subsets?**
   a. Those with homone receptor (HR)-positive, HER2-negative disease
   b. Those with triple-negative disease
   c. Both a and b
   d. Neither a nor b

4. **Final results of the randomized Phase II PALOMA-1 trial evaluating letrozole with or without palbociclib as first-line therapy for ER-positive, HER2-negative mBC demonstrated statistically significant improvements in _____ for patients receiving the combination.**
   a. Median progression-free survival
   b. Median overall survival
   c. Both a and b
   d. Neither a nor b

5. **Two randomized Phase III trials evaluating the benefits of primary tumor resection for patients with Stage IV breast cancer reported a significant benefit in overall survival in favor of locoregional therapy.**
   a. True
   b. False

6. **The Phase III PENELOPE-B trial is evaluating _____ versus placebo in addition to endocrine therapy for patients with HR-positive, HER2-negative breast cancer with high relapse risk after neoadjuvant chemotherapy.**
   a. Bevacizumab
   b. Olaparib
   c. Palbociclib
   d. All of the above

7. **The Phase II APT trial of adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer reported a 3-year disease-free survival of approximately 99% for the overall population of patients who received this regimen.**
   a. True
   b. False

8. **The OlympiA trial is evaluating _____ versus placebo as adjuvant therapy for patients with germline BRCA1/2 mutations and high-risk HER2-negative primary breast cancer after definitive local therapy and neoadjuvant or adjuvant chemotherapy.**
   a. Olaparib
   b. Iniparib
   c. Veliparib

9. **A publication by Davidson and colleagues on the clinical utility and pharmacoeconomic effects of the Onco*type* DX assay RS in ER-positive, node-negative breast cancer demonstrated that physicians changed their adjuvant chemotherapy recommendation in 30% of cases after receiving a patient's RS.**
   a. True
   b. False

10. **A meta-analysis of the effects of bisphosphonate treatment in women with early breast cancer reported a reduction in bone recurrence and breast cancer mortality among postmenopausal women who received adjuvant bisphosphonate therapy, regardless of _____.**
    a. Treatment schedule
    b. ER status
    c. Nodal involvement
    d. Bisphosphonate type
    e. All of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 1, 2014

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 1 — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

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

	BEFORE	AFTER
Available research data (PALOMA-1) and ongoing Phase III investigation (PENELOPE-B) with the CDK4/6 inhibitor palbociclib (PD-0332991) for ER-positive, HER2-negative breast cancer	4 3 2 1	4 3 2 1
Clinical utility and pharmacoeconomic study of the effects of the Onco*type* DX assay RS in ER-positive, node-negative breast cancer	4 3 2 1	4 3 2 1
Results of 2 recently presented trials evaluating primary tumor resection for patients with Stage IV breast cancer	4 3 2 1	4 3 2 1
ATLAS and aTTom trials: Continuing adjuvant tamoxifen to 10 years versus stopping at 5 years for ER-positive early breast cancer	4 3 2 1	4 3 2 1
Updated efficacy results of the Phase III BOLERO-2 trial: Everolimus in combination with exemestane for ER-positive, HER2-negative advanced breast cancer	4 3 2 1	4 3 2 1
NSABP-B-50-I (KATHERINE): A Phase III trial of T-DM1 versus trastuzumab as adjuvant therapy for patients with HER2-positive breast cancer who have residual tumor in the breast or axillary nodes after neoadjuvant treatment	4 3 2 1	4 3 2 1

Practice Setting:

☐ Academic center/medical school ☐ Community cancer center/hospital ☐ Group practice

☐ Solo practice ☐ Government (eg, VA) ☐ Other (please specify).....

Approximately how many new patients with breast cancer do you see per year? ..... patients

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

☐ Yes ☐ No

If no, please explain:.....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain):.....

If you intend to implement any changes in your practice, please provide 1 or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

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

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

- Develop evidence-based treatment approaches for patients diagnosed with HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings. .....4 3 2 1 N/M N/A
- Evaluate recently presented data supporting the extended use of adjuvant tamoxifen beyond 5 years for patients with ER-positive early breast cancer and, where appropriate, integrate these findings into clinical practice. .....4 3 2 1 N/M N/A
- Recognize the evolving application of biomarkers and multigene assays in breast cancer management, and effectively use these tools to refine or individualize treatment plans for patients. .....4 3 2 1 N/M N/A
- Formulate individualized approaches to first- and later-line therapy for patients with HER2-negative metastatic breast cancer. .....4 3 2 1 N/M N/A
- Counsel appropriately selected patients with breast cancer about the supportive and therapeutic role of bisphosphonates in disease management. .....4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

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 2 — Please tell us about the faculty and editor for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Mark D Pegram, MD	4 3 2 1	4 3 2 1
Karen A Gelmon, MD	4 3 2 1	4 3 2 1
Kathy D Miller, MD	4 3 2 1	4 3 2 1
Stephen Chia, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

.....

.....

REQUEST FOR CREDIT — Please print clearly

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Breast Cancer®
UPDATE

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