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Breast Cancer® UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

Sir Richard Peto
Eric P Winer, MD
Sandra M Swain, MD
Matthew J Ellis, MB, BChir, PhD

EDITOR

Neil Love, MD

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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 and expert perspectives on these data sets, 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

- 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.
- Develop evidence-based treatment approaches for patients diagnosed with HER2-positive breast cancer in the neoadjuvant, adjuvant and metastatic settings.
- Utilize existing and emerging biomarkers to assess risk and individualize therapy for patients with invasive early breast cancer.
- Assimilate new clinical trial evidence evaluating the use of mTOR inhibition to reverse endocrine resistance into the therapeutic algorithm for patients with progressive ER-positive metastatic breast cancer.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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EDITOR

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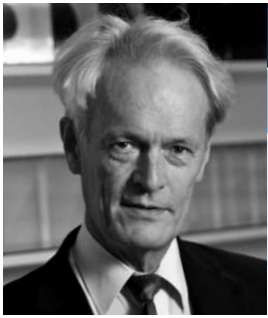

INTERVIEW

Sir Richard Peto

Prof Peto is Professor of Medical Statistics and Co-director of the Clinical Trial Service Unit at the University of Oxford in Oxford, United Kingdom*.

Tracks 1-9

Track 1 Contributors to recent trends in the overall reduction of breast cancer (BC) mortality

Track 2 Background for the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial — Historical data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

Track 3 ATLAS trial design: 5 versus 10 years of adjuvant tamoxifen for women with ER-positive BC

Track 4 Extending the carryover benefit of adjuvant tamoxifen with 10 versus 5 years of treatment

Track 5 Decreased overall vascular mortality with 10 versus 5 years of adjuvant tamoxifen

Track 6 Increased incidence of endometrial cancer in postmenopausal women receiving longer-duration adjuvant tamoxifen

Track 7 Reduction in the risk of second BC with longer-duration adjuvant tamoxifen

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Track 9 Recent improvements in mortality rates in BC versus other solid tumors

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: The ATLAS study was an international Phase III trial that randomly assigned women with early breast cancer who had completed 5 years of tamoxifen to either continue tamoxifen for another 5 years or stop. The findings were one of the major highlights of SABCS 2012 (Davies 2012) and were recently published in *The Lancet* (Davies 2013). Would you discuss the results?

PROF PETO: Previous studies by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated that 5 years of tamoxifen therapy was more effective than 2 years of therapy in women with ER-positive breast cancer (EBCTCG 2005, 2011). The ATLAS trial was designed to answer the question of whether 10 years of tamoxifen was better than 5 years of therapy. We wanted the results of ATLAS to apply globally to all women with ER-positive disease. Hence, we enrolled a large number of patients — approximately 13,000 — onto this study.

In 1995 the NCI issued a "clinical alert" cautioning against continuation of tamoxifen beyond 5 years. After this alert, many physicians and patients wanted to stop tamoxifen at 5 years. However, if they were uncertain whether to continue tamoxifen beyond 5 years, we encouraged them to enroll in our study. The preliminary results of ATLAS demonstrated that 10 years of tamoxifen is better than 5 years of therapy (Davies 2013; [1.1, 1.2]).

*Prof Peto did not receive honoraria funding for participating in this interview.

The EBCTCG had demonstrated that 5 years of tamoxifen is better than no tamoxifen (EBCTCG 2011), but most of the benefit is seen after the treatment is stopped, due to a carryover benefit. Tamoxifen reduces the rate of breast cancer recurrence not only during the treatment period but also throughout the first decade. It reduces breast cancer mortality by about a third throughout the first 15 years.

A similar carryover benefit was observed in the ATLAS trial. The main beneficial effect is observed after the 10 years of treatment have ended. The results in years 10 to 14 are exciting.

Continuing tamoxifen to 10 years results in a 25% reduction in the breast cancer recurrence rate and about a 30% reduction in breast cancer mortality (1.2). Because of the carryover benefit, 10 years of tamoxifen confers protection not only during the decade of treatment but also during the decade after therapy is complete.

1.1

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

	Continue TAM to 10 y (n = 3,428)	Stop TAM at 5 y (n = 3,418)
Recurrence rate		
10 y (treatment end)	13.1%	14.5%
15 y (10 y since study entry)	21.4%	25.1%
Breast cancer mortality		
10 y (treatment end)	5.8%	6.0%
15 y (10 y since study entry)	12.2%	15.0%

Continuing TAM to 10 years reduced the risk of breast cancer recurrence compared to stopping TAM (617 versus 711 recurrences; $p = 0.002$), reduced breast cancer mortality (331 versus 397 deaths; $p = 0.01$) and reduced overall mortality (639 versus 722 deaths; $p = 0.01$).

Davies C et al. *Lancet* 2013;381:805.

1.2

Event Rate Ratios in ER-Positive Disease by Time Period from Diagnosis in Meta-Analyses of Trials of 5 Years of Tamoxifen (TAM) versus None and in the ATLAS Trial

	A. 5-y TAM vs 0: Meta-analyses (n = 10,645)	B. 10-y vs 5-y TAM: ATLAS (n = 6,846)	Estimated effects in a trial of 10-y TAM vs 0 (product of A and B)
Recurrence			
0-4 y	0.53*	1	0.53*
5-9 y	0.68*	0.9	0.61*
≥10 y	0.94	0.75†	0.7†
Breast cancer mortality			
0-4 y	0.71*	1	0.71*
5-9 y	0.66*	0.97	0.64‡
≥10 y	0.73‡	0.71§	**0.52***

* $p < 0.00001$; † $p < 0.01$; ‡ $p = 0.0001$; § $p = 0.0016$

"Taken together with the results from trials of 5 years of tamoxifen versus none, the results from ATLAS show that 10 years of effective endocrine therapy can approximately halve breast cancer mortality during years 10-14 after diagnosis."

Davies C et al. *Lancet* 2013;381:805.

This may not make a big difference if you are diagnosed with cancer at age 80 or 85, but many women are diagnosed with breast cancer when they're 45 or younger. For these women the important question is, what does a decade of tamoxifen do to breast cancer mortality during the decade while you're taking it and during the decade after you're taking it?

Within about 5 years, we'll have data from the long-term follow-up of ATLAS. The aTTom trial, the UK counterpart to ATLAS, has enrolled 7,000 patients (Gray 2008), and follow-up data from that study will likely be presented at the 2013 ASCO meeting. Together, the long-term follow-up of ATLAS and aTTom may show a further small gain as a delayed benefit of continuing tamoxifen to 10 years.

Tracks 5-7

DR LOVE: Would you talk about some of the important adverse events reported in the ATLAS study?

PROF PETO: An important adverse event of continuing tamoxifen to 10 years is the increase in incidence of endometrial cancer (Davies 2013; [1.3]). Tamoxifen binds and stimulates the estrogen receptors in the endometrium. Hence, it can cause endometrial cancer, which can lead to death.

However, the absolute risk of 10 years of tamoxifen causing endometrial cancer is a few per thousand, whereas the absolute benefit is a few percent. So the hazard is 10 times smaller than the benefit.

The data suggest that the risk of endometrial cancer is greater in postmenopausal women. In these women no stimulation from the body's hormones is occurring, so the stimulation from tamoxifen is relevant. Little or no hazard of endometrial cancer exists in premenopausal women or in postmenopausal women who've undergone a hysterectomy before trial entry. Physicians check for evidence of bleeding and, in general, detect endometrial cancer in time for it to be cured. It's generally much easier to cure endometrial cancer than it is to cure breast cancer.

If you consider the overall effect of tamoxifen on the probability of developing a new tumor, the reduction in the risk of developing cancer in the opposite breast is about the

1.3 **ATLAS Trial: Select Adverse Events**

Event	Continue TAM to 10 y	Stop TAM at 5 y	Event rate ratio	*p*-value
Secondary cancer incidence				
Contralateral breast cancer	419	467	0.88	0.05
Endometrial cancer*	116	63	1.74	0.0002
Nonneoplastic disease				
Stroke	130	119	1.06	0.63
Pulmonary embolus	41	21	1.87	0.01
Ischemic heart disease	127	163	0.76	0.02

TAM = tamoxifen
* Mainly endometrial adenocarcinoma but includes all other uterine tumors except cervical cancer; uterine tumors exclude those with recorded hysterectomy at study entry

Davies C et al. *Lancet* 2013;381:805.

same as the increase in the risk of developing cancer of the endometrium. Cancer of the breast is a more dangerous disease than cancer of the endometrium. So, overall, the benefits outweigh the risks.

Although an increase in the incidence of pulmonary embolism was observed, the hazard was small and a decrease in heart disease is likely. The FDA has warned that tamoxifen might cause stroke, but a significant increase of stroke was not observed in either the ATLAS trial or in the old trials of 5 years of tamoxifen versus nothing.

I believe that ATLAS should be viewed as a trial of longer versus shorter endocrine treatment and that the conclusion that 10 years of endocrine treatment is better than 5 years of endocrine treatment is applicable not only to tamoxifen but also to other endocrine therapies (Powles 2012; [1.4]). ■

1.4

Extended Adjuvant Tamoxifen for Breast Cancer — A New Era?

"If the findings from ATLAS are confirmed, what are the best treatment options for postmenopausal women?

… Should these patients be given 10 years of treatment with an aromatase inhibitor? Should they have 5 years of an aromatase inhibitor followed by 5 years of tamoxifen? Would more than 10 years of tamoxifen be even better than 10 years? No data exist to support any of these options.

… In terms of treatment options for premenopausal women for whom tamoxifen is indicated and without notable side-effects, extension of treatment to 10 years would seem to provide added benefit.

… Confirmation of the ATLAS trial by meta-analysis of all extended tamoxifen treatment trials should herald a change of practice, with the standard of care revised to 10 years rather than 5 years of tamoxifen in patients for whom tamoxifen is indicated. This change should open up a whole new era of clinical trials to assess the benefit of extended adjuvant endocrine therapy of breast cancer."

Powles TJ. *Lancet* 2012;381(9869):782-3.

SELECT PUBLICATIONS

Davies C et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. **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;381:805.

Davies C et al. **ATLAS — 10 v 5 years of adjuvant tamoxifen (TAM) in ER+ disease: Effects on outcome in the first and in the second decade after diagnosis.** San Antonio Breast Cancer Symposium 2012;**Abstract S1-2**.

Dowsett M et al. **Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen.** *J Clin Oncol* 2010;28(3):509-18.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials.** *Lancet* 2011;378(9793):771-84.

Early Breast Cancer Trialists' Collaborative Group (EBCTCG). **Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials.** *Lancet* 2005;365(9472):1687-717.

Gray RG et al. **aTTom: Randomized trial of 10 versus 5 years of adjuvant tamoxifen among 6,934 women with estrogen receptor-positive (ER+) or ER untested breast cancer — Preliminary results.** *Proc ASCO* 2008. No abstract available

Peto R. **Five years of tamoxifen — Or more?** *J Natl Cancer Inst* 1996;88(24):1791-3.

Powles TJ. **Extended adjuvant tamoxifen for breast cancer — A new era?** *Lancet* 2012;381(9869):782-3.

INTERVIEW

Eric P Winer, MD

Dr Winer is Thompson Chair in Breast Cancer Research and Chief of the Division of Women's Cancers at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Tracks 1-17

Select Excerpts from the Interview

Tracks 1-2, 11-12, 14-15

DR LOVE: What's going on right now in terms of trials in HER2-positive disease in both the adjuvant and metastatic settings?

DR WINER: In the adjuvant setting, the APHINITY study is randomly assigning patients to chemotherapy and trastuzumab versus chemotherapy and trastuzumab/pertuzumab (2.1). Patients have nothing to lose by enrolling. They would receive

chemotherapy and trastuzumab anyway, and on this study they may be randomly assigned to an additional agent that, as far as we know, doesn't add much toxicity.

I've also been involved in the development of a randomized Phase II study of T-DM1 for patients with high-risk HER2-positive early breast cancer. Patients will likely be randomly assigned to chemotherapy with trastuzumab and probably pertuzumab versus chemotherapy with T-DM1 or chemotherapy with T-DM1 and pertuzumab.

But one of the challenges with any study at this point is that patients with HER2-positive disease fare quite well in the adjuvant setting. It's not as well as we want, but from a trial-design standpoint it presents challenges.

With regard to metastatic HER2-positive disease, the MARIANNE trial is evaluating a taxane/trastuzumab versus T-DM1 alone versus T-DM1 and pertuzumab (2.1). I believe we'll have the results sometime in late 2014.

DR LOVE: What is your current nonprotocol algorithm for metastatic HER2-positive disease?

DR WINER: The first-line regimen will be a taxane with trastuzumab and pertuzumab and the second-line regimen will probably be T-DM1. My fear is that oncologists will start combining T-DM1 with other agents because it has so little toxicity in and of itself. But we don't yet have any data indicating that combining T-DM1 with another agent is better than administering T-DM1 alone, and that kind of approach needs to be left to clinical trials.

Ongoing Phase I trials are now evaluating such combinations, and that's something that will probably be explored in the adjuvant setting. But at the moment, T-DM1 should only be administered as a single agent.

DR LOVE: What new research has emerged with pertuzumab, and what are you combining it with clinically?

DR WINER: We're fairly restricted by insurers and are using it according to the label. We use it in the first-line setting with either docetaxel or weekly paclitaxel with

2.1

Key Ongoing and Proposed Phase II-III Trials for Patients with HER2-Positive Breast Cancer

Trial identifier	Phase	N	Setting	Treatment arms
APHINITY (NCT01358877)	III	3,806	Adjuvant	• Chemotherapy + trastuzumab + pertuzumab • Chemotherapy + trastuzumab + placebo
Proposed[1]	II	—	Adjuvant	• Paclitaxel/trastuzumab/pertuzumab • Chemotherapy/T-DM1 • Chemotherapy/T-DM1/pertuzumab
VELVET (NCT01565083)	II	210	Metastatic	• Pertuzumab + trastuzumab + vinorelbine
MARIANNE (NCT01120184)	III	1,095	Metastatic	• Trastuzumab + taxane • T-DM1/placebo • T-DM1/pertuzumab

www.clinicaltrials.gov, April 2013; [1] Personal communication with Eric P Winer, MD.

trastuzumab. In a handful of cases we've requested permission from insurers to administer pertuzumab to patients who've received multiple prior regimens or 1 or 2 prior regimens but haven't received pertuzumab first line. If the patient hasn't received a taxane, we administer it with a taxane.

We don't have much experience administering it with other agents. However, the VELVET study is evaluating pertuzumab and trastuzumab with vinorelbine (2.1). That's a natural combination because vinorelbine and trastuzumab are administered together commonly, and the combination should be well tolerated.

Tracks 9-10

DR LOVE: What's your take on the Phase III study presented at San Antonio of capecitabine versus eribulin for patients with metastatic breast cancer previously treated with anthracyclines and taxanes?

DR WINER: Some hoped eribulin would be a better agent in this setting, but it appears that the effects are similar with different toxicity profiles (Kaufman 2012; [2.2]). Eribulin is reasonable, but I wouldn't administer it as a substitute for capecitabine.

From a survival standpoint I don't believe it makes a difference whether you administer eribulin first and then capecitabine or capecitabine first and then eribulin.

2.2

Phase III Randomized Study of Eribulin versus Capecitabine for Patients with Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes

Primary efficacy outcomes	Eribulin (n = 554)	Capecitabine (n = 548)	Hazard ratio	*p*-value
Median overall survival	15.9 months	14.5 months	0.879	0.056
Median progression-free survival				
Independent review	4.1 months	4.2 months	1.079	0.305
Investigator review	4.2 months	4.1 months	0.977	0.736
Select adverse events	Eribulin (n = 544)		Capecitabine (n = 546)	
Grade	**All**	**3/4**	**All**	**3/4**
Neutropenia	54%	46%	16%	<5%
Leukopenia	31%	15%	10%	<3%

Kaufman PA et al. San Antonio Breast Cancer Symposium 2012;**Abstract S6-6**.

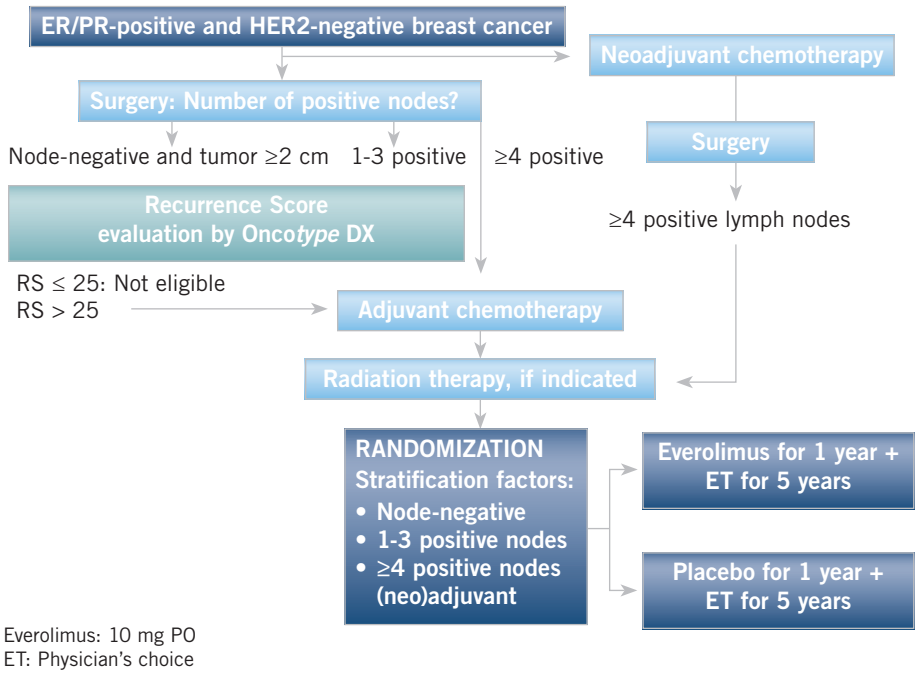
Track 16

DR LOVE: What are your thoughts on the SWOG-S1207 trial, which is evaluating everolimus in the adjuvant setting (2.3)?

DR WINER: After a patient has completed a course of adjuvant chemotherapy and, in most cases, a course of radiation therapy, the choice between endocrine therapy alone and endocrine therapy with everolimus is significant. Though possible, I believe it will be difficult for the patients to complete a full year of everolimus therapy because a fair amount of toxicity is associated with the agent.

2.3

SWOG-S1207: A Phase III Study of Adjuvant Endocrine Therapy (ET) with or without Everolimus for Patients with High-Risk, ER/PR-Positive, HER2-Negative Breast Cancer and an Onco*type* DX Recurrence Score Greater than 25



Chavez-MacGregor M et al. San Antonio Breast Cancer Symposium 2012;**Abstract OT2-2-04**.

Also, at a certain level, this trial is not in keeping with what we know about everolimus. We know that everolimus works in patients with aromatase inhibitor (AI)-refractory disease. However, I understand the rationale of the study and I hope the results will be positive — but it is taking a step beyond what we learned from the BOLERO-2 trial (4.1, page 17). Other everolimus trials for which I understand the appeal are a European study evaluating the use of everolimus after a couple of years of AI therapy and a study in which patients begin their AI therapy with everolimus. ■

SELECT PUBLICATIONS

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

Chavez-MacGregor M et al. **S1207: Phase III randomized, placebo-controlled clinical trial evaluating the use of adjuvant endocrine therapy +/- one year of everolimus in patients with high-risk, hormone receptor-positive and HER2-neu negative breast cancer (NCT01674140).** San Antonio Breast Cancer Symposium 2012;**Abstract OT2-2-04**.

Kaufman PA et al. **A Phase III, open-label, randomized, multicenter study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes.** San Antonio Breast Cancer Symposium 2012;**Abstract S6-6**.

Preston JN, Trivedi MV. **Eribulin: A novel cytotoxic chemotherapy agent.** *Ann Pharmacother* 2012;46(6):802-11.

Scarpace SL. **Eribulin mesylate (E7389): Review of efficacy and tolerability in breast, pancreatic, head and neck, and non-small cell lung cancer.** *Clin Ther* 2012;34(7):1467-73.

INTERVIEW

Sandra M Swain, MD

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

Tracks 1-10

Track 1 Results of the NSABP-B-38 study: Adjuvant dose-dense AC → paclitaxel with or without gemcitabine versus TAC in node-positive BC

Track 2 CALOR (IBCSG 27-02, NSABP-B-37, BIG 1-02) trial: Adjuvant chemotherapy prolongs survival for patients with isolated local or regional recurrence of BC

Track 3 Antitumor effect of adjuvant bone-targeted therapy in BC

Track 4 Utility of the Onco*type* DX assay in node-negative and node-positive early BC

Track 5 Use of the Onco*type* DX assay for premenopausal patients

Track 6 Pertuzumab in combination with trastuzumab and docetaxel as first-line therapy for HER2-positive mBC: Results from confirmatory overall survival analysis in the CLEOPATRA study

Track 7 Clinical experiences with T-DM1 in HER2-positive mBC

Track 8 Ongoing trials evaluating T-DM1 and/or pertuzumab in early-stage and advanced HER2-positive BC

Track 9 Optimal duration of adjuvant trastuzumab

Track 10 Use of anthracycline- and nonanthracycline-containing adjuvant regimens in HER2-positive BC

Select Excerpts from the Interview

Tracks 1-2, 4-5

DR LOVE: Would you discuss the results from your NSABP-B-38 trial, which compared adjuvant TAC to dose-dense AC → paclitaxel with or without gemcitabine for women with node-positive breast cancer?

DR SWAIN: The NSABP-B-38 study was designed to compare TAC to dose-dense regimens, which are frequently used. We also wanted to evaluate whether the addition of gemcitabine could improve the efficacy of the dose-dense regimen. The results from the 3 arms showed no difference in disease-free survival or overall survival (Swain 2012a; [3.1]).

Because the efficacy of these different chemotherapies is not different, the difference in toxicities needs to be examined when deciding how to care for each patient. With the dose-dense regimens more neuropathy is observed, whereas with TAC a higher incidence of febrile neutropenia occurs.

In the past, I often used the TAC regimen and found the toxicities to be manageable. However, some patients experience severe problems with myalgias and asthenia. The dose-dense regimen is considered a standard therapy in the United States.

3.1

NSABP-B-38: Definitive Analysis of an Adjuvant Trial Comparing Dose-Dense (DD) AC → Paclitaxel (P) with Gemcitabine (G) to DD AC → P and to TAC for Patients with Operable, Node-Positive Breast Cancer

Efficacy	DD AC → PG	DD AC → P	TAC
Five-year disease-free survival* (n = 1,613; 1,618; 1,610)	80.6%	82.2%	80.1%
Five-year overall survival* (n = 1,618; 1,624; 1,617)	90.8%	89.1%	89.6%

AC = doxorubicin/cyclophosphamide; TAC = docetaxel/doxorubicin/cyclophosphamide

* *p*-values for AC → P and TAC versus AC → PG were not significant.

Swain SM et al. *Proc ASCO* 2012a;**Abstract LBA1000**.

DR LOVE: What are your thoughts on the CALOR trial reported at San Antonio, which investigated the effect of chemotherapy on the survival of patients with isolated local or regional recurrence of breast cancer?

DR SWAIN: Irene Wapnir, a surgeon who worked with us in the NSABP, urged us to investigate whether patients who had an in-breast or regional recurrence after lumpectomy or mastectomy require chemotherapy. To answer this question, the study randomly assigned these patients to receive chemotherapy or not. Patients could also receive hormone therapy if they had ER-positive tumors. Even though it was supposed to accrue hundreds of patients, the study only accrued a little more than 100. Surprisingly, even with such a small number of patients, a significant disease-free survival benefit was seen, especially for patients with ER-negative disease who received chemotherapy (Aebi 2012; [3.2]). Even though this study was small, I believe these are very important data.

DR LOVE: What are your thoughts on the San Antonio presentation from the NSABP-B-28 trial on the prognostic impact of the Onco*type* DX Recurrence Score for patients with ER-positive, node-positive breast cancer treated with adjuvant chemotherapy (Mamounas 2012; [3.3]), and how do you currently use the Onco*type* DX assay in your practice?

DR SWAIN: I use Onco*type* DX for patients with ER-positive, node-negative disease I would consider for chemotherapy. I routinely use Onco*type* DX for premenopausal

3.2

Results from CALOR: A Phase III Trial Investigating Chemotherapy (Chemo) as Adjuvant Treatment for Isolated Local or Regional Recurrence of Breast Cancer

Survival outcome	Chemo	No chemo	HR	*p*-value
Five-year disease-free survival				
All patients (n = 85, 77)	69%	57%	0.59	0.0455
ER-positive (n = 56, 48)	70%	69%	0.94	0.87
ER-negative (n = 29, 29)	**67%**	**35%**	**0.32**	**0.007**
Five-year overall survival				
All patients (n = 85, 77)	88%	76%	0.41	0.02
ER-positive (n = 56, 48)	94%	80%	0.4	0.12
ER-negative (n = 29, 29)	79%	69%	0.43	0.12

Aebi S et al. San Antonio Breast Cancer Symposium 2012;**Abstract S3-2**.

patients. Studies have shown that the biology of the tumor rather than the age of the patient is relevant. I presented a poster at SABCS 2010 showing that women at low, intermediate and high risk could be identified across all age groups (Shak 2010).

Currently, I do not routinely use the Onco*type* DX assay for patients with node-positive disease. I enroll those patients on the RxPONDER trial (NCT01272037). This is a trial evaluating adjuvant endocrine therapy with or without chemotherapy for patients with 3 or fewer positive nodes who have an Onco*type* DX Recurrence Score of 25 or lower.

3.3

NSABP-B-28 Study: Prognostic Impact of the Onco*type* DX Recurrence Score (RS) in Patients with ER-Positive, Node-Positive Breast Cancer Treated with Adjuvant Chemotherapy

Endpoint	RS low	RS intermediate	RS high	*p*-value
10-year DFS	75.8%	57.0%	48.0%	<0.001
10-year DRFI	80.9%	64.9%	55.8%	<0.001
10-year OS	90.0%	74.7%	63.0%	<0.001

DFS = disease-free survival; DRFI = distant recurrence-free interval; OS = overall survival

Mamounas EP et al. San Antonio Breast Cancer Symposium 2012;**Abstract S1-10**.

Track 6

DR LOVE: With regard to HER2-positive disease, could you talk about the results from the confirmatory overall survival analysis of the CLEOPATRA study that you presented at SABCS 2012?

DR SWAIN: The initial analysis of CLEOPATRA demonstrated about a 6-month benefit in progression-free survival with the addition of pertuzumab to trastuzumab and docetaxel in first-line metastatic breast cancer (Baselga 2012), and the confirmatory survival analysis I presented at SABCS 2012 reported a significant benefit in overall survival with the addition of pertuzumab. It is exciting that treatments for HER2-positive disease have completely changed the natural history of this disease, with patients now surviving longer.

DR LOVE: A Phase II study also reported at San Antonio evaluated pertuzumab/trastuzumab in combination with weekly paclitaxel instead of docetaxel for patients with HER2-positive metastatic breast cancer (Datko 2012). What are your thoughts about the safety of that combination, and what do you use in your practice?

DR SWAIN: In the CLEOPATRA study, a higher incidence of febrile neutropenia, diarrhea and mucositis was observed on the pertuzumab arm. When the mucous membranes are disrupted due to diarrhea or mucositis, the risk of febrile neutropenia is increased. Hence, the addition of pertuzumab results in greater toxicity.

The belief is that if paclitaxel were used as a substitute for docetaxel, these toxicities would be decreased. However, in the Phase II study a significant incidence of diarrhea and mucositis was observed. So it is not clear if that is a better combination. In my own practice, I use docetaxel in combination with pertuzumab/trastuzumab.

DR LOVE: A recent meta-analysis reported that pertuzumab was associated with a significant risk of rash in patients with breast cancer (Drucker 2012). Would you comment on that paper?

DR SWAIN: This publication demonstrated that a number of skin toxicities are associated with pertuzumab. I was surprised with the results because I administer pertuzumab often and have not had the same experience.

Track 7

DR LOVE: Would you discuss the data on T-DM1, which was recently approved for the treatment of metastatic HER2-positive breast cancer?

DR SWAIN: T-DM1 has shown impressive activity in the metastatic setting. The EMILIA study demonstrated a significant survival benefit with T-DM1 versus lapatinib/capecitabine in patients with HER2-positive advanced breast cancer (Verma 2012; [3.4]). The toxicities associated with T-DM1 are manageable and include a decrease of platelet counts and elevation of liver function enzymes.

I had a patient on the capecitabine/lapatinib arm of EMILIA who was quite sick. She did not tolerate the regimen well and was switched to the T-DM1 arm. She responded to T-DM1 and fared extremely well. After the first cycle of treatment, her liver enzyme levels were elevated and her platelet counts decreased, but the dose was reduced and she continued to do well. Her brain metastases did not respond, but she didn't experience disease progression for more than a year. ■

3.4

EMILIA: Results from a Phase III Study of T-DM1 versus Capecitabine and Lapatinib (XL) for HER2-Positive Advanced Breast Cancer

Outcome	T-DM1	XL	HR	*p*-value
Median progression-free survival* (n = 495, 496)	9.6 mo	6.4 mo	0.65	<0.001
Median overall survival† (n = 495, 496)	30.9 mo	25.1 mo	0.68	<0.001
Objective response rate (n = 397, 389)	43.6%	30.8%	—	<0.001

* By independent review; † Second interim analysis results crossed the stopping boundary for efficacy

Verma S et al. *N Engl J Med* 2012;367(19):1783-91.

SELECT PUBLICATIONS

Baselga J et al. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012;366(2):109-19.

Datko F et al. **Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with HER2-overexpressing metastatic breast cancer.** San Antonio Breast Cancer Symposium 2012;**Abstract P5-18-20**.

Drucker AM et al. **Risk of rash with the anti-HER2 dimerization antibody pertuzumab: A meta-analysis.** *Breast Cancer Res Treat* 2012;135(2):347-54.

Shak S et al. **Quantitative gene expression analysis in a large cohort of estrogen-receptor positive breast cancers: Characterization of the tumor profiles in younger patients (≤40 yrs) and in older patients (≥70 yrs).** San Antonio Breast Cancer Symposium 2010;**Abstract P3-10-01**.

INTERVIEW

Matthew J Ellis, MB, BChir, PhD

Dr Ellis is Professor of Medicine and Director of the Breast Cancer Program at Washington University School of Medicine in St Louis, Missouri.

Tracks 16-27

Select Excerpts from the Interview

Tracks 1-2

Case discussion

A 55-year-old woman with ER-positive, HER2-negative breast cancer refractory to endocrine therapy with bone and liver metastases, the latter of which is biopsied and found to exhibit V777L HER2 mutation

DR ELLIS: It has become my practice to biopsy metastases because a small number of these can exhibit changes in the standard ER and HER2 markers. We also now have a clinical trial that focuses on a new finding — the acquisition of mutations in the HER2 gene in either the kinase domain or the heterodimerization interface. We screened this patient, and she was found to have a mutation called V777L in the HER2 kinase domain. This is a known activation mutation for HER2 in vitro, so she was considered for a clinical trial.

We've been aware of the presence of mutations in HER2 for some time, but the screening efforts to understand the exact profile of these mutations in breast cancer awaited the next-generation sequencing bonanza that occurred in 2012. By late 2012, we had identified about 25 mutations in HER2 from The Cancer Genome Atlas, our own sequencing efforts and other publications (Bose 2012; Ellis 2013). We introduced these mutations into indicator cell lines and found that many of them were indeed activating mutations. The question now is, would patients with these mutations respond to targeted therapy?

We performed molecular pharmacology assays, and the small molecule tyrosine kinase inhibitors lapatinib and neratinib are both active against these mutations. Of note, some of the mutations, but not V777L, appear to be natural lapatinib resistance mutations. Obviously, patients with those mutations might be better off with neratinib.

A debate occurred recently as to what the role of trastuzumab might be in the treatment of these mutations. In general, these mutations are occurring in tumors that are not overexpressing HER2. So the questions are, how effective would trastuzumab be, and does it have a contributory pharmacological effect, perhaps in combination with another HER2-targeting agent? We simply don't know at this point.

The challenge for the treatment of HER2-mutant breast cancer is that you must first identify these patients. We don't know the incidence of this mutation class in metastatic breast cancer because, unfortunately, next-generation sequencing efforts have largely focused on primary, untreated breast cancer. In primary breast cancer the incidence rate is about 1.6%, which sounds like a small number, but remember that the denominator for breast cancer is huge.

My first impression is that these mutations are associated with aggressive-type breast cancer because the cases tend to be in patients with brain or liver metastases — almost as if they had untreated HER2-positive breast cancer in the sense that they've never received a HER2-targeting agent. So it may be that in the metastatic setting it's more frequent than 1% or 2%.

We've defined a new disease entity here, and we need to perform rigorous clinical trials to identify the risks and benefits of administering HER2-directed treatment to patients with these mutations. At this point, I would not recommend the treatment of HER2-activating mutations with lapatinib or trastuzumab outside the context of a clinical trial.

DR LOVE: Have any reported cases without HER2 amplification but with one of these mutations been treated and responded?

DR ELLIS: Not yet, but we are conducting a trial evaluating neratinib in this setting (NCT01670877). We are screening patients for these mutations, and I believe we'll know within the next 6 to 9 months whether the first stage of the trial is showing an efficacy signal.

Track 9

DR LOVE: Let's talk about a common problem: ER-positive metastatic disease. In what situations, if any, are you using an AI in combination with fulvestrant versus everolimus when treating ER-positive metastatic breast cancer?

DR ELLIS: I frequently treat ER-positive metastatic breast cancer, and essentially the decisions I'm making are highly personalized in that you must take a number of factors

into account to make a good decision for the patient. Much has to do with my level of confidence that the patient will respond to endocrine therapy. In a relatively asymptomatic patient who has only 1 or 2 bone metastases, I might simply administer an AI. If they have more aggressive disease or low-volume visceral disease, my first-line approach will likely be fulvestrant with anastrozole or another AI.

I reserve everolimus for patients who need "chemo-lite." I've had debates with people regarding everolimus. It's not a targeted therapy because we don't measure mTOR levels in tumors to make decisions about everolimus. It is targeted in that we understand the mechanism, but we're not targeting the drug with a test. I believe we need to develop such tests to make better decisions. So in my practice, the patients for whom I use everolimus would be those who've been through first-line endocrine therapy, as were the patients on the BOLERO-2 trial (Baselga 2012; [4.1]). There, everolimus was basically used as salvage therapy for patients whose disease was becoming symptomatic, and the burdens of the toxicity of everolimus were justified. ■

4.1

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

Efficacy	Everolimus + exemestane (n = 485)	Placebo + exemestane (n = 239)	HR	*p*-value
Median PFS (by central assessment)	10.6 mo	4.1 mo	0.36	<0.001
ORR (by local and central assessment)	9.5%	0.4%	—	<0.001
	Everolimus + exemestane (n = 482)		Placebo + exemestane (n = 238)	
Select adverse events	All grades	Grade 3/4	All grades	Grade 3/4
Stomatitis	56%	8%	11%	1%
Fatigue	33%	<4%	26%	1%
Dyspnea	18%	4%	9%	<2%
Anemia	16%	6%	4%	<2%
Hyperglycemia	13%	<5%	2%	<1%
Pneumonitis	12%	3%	0%	0%

HR = hazard ratio; PFS = progression-free survival; ORR = objective response rate

Baselga J et al. *N Engl J Med* 2012;366(6):520-9.

SELECT PUBLICATIONS

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

Bose R et al. **Activating HER2 mutations in HER2 gene amplification negative breast cancers.** San Antonio Breast Cancer Symposium 2012;**Abstract S5-6**.

Burris HA 3rd et al. **Health-related quality of life of patients with advanced breast cancer treated with everolimus plus exemestane versus placebo plus exemestane in the phase 3, randomized, controlled, BOLERO-2 trial.** *Cancer* 2013;[Epub ahead of print].

Ellis MJ, Perou CM. **The genomic landscape of breast cancer as a therapeutic roadmap.** *Cancer Discov* 2013;3(1):27-34.

Gnant M et al. **Effect of everolimus on bone marker levels and progressive disease in bone in BOLERO-2.** *J Natl Cancer Inst* 2013;[Epub ahead of print].

Ramirez-Fort MK et al. **Rash to the mTOR inhibitor everolimus: Systematic review and meta-analysis.** *Am J Clin Oncol* 2012;[Epub ahead of print].

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The Phase III ATLAS trial of 5 versus 10 years of adjuvant tamoxifen for women with ER-positive early breast cancer demonstrated that the most beneficial effect on breast cancer mortality of continuing tamoxifen to 10 years was observed during which period after diagnosis?**
   a. 0 to 4 years
   b. 5 to 9 years
   c. After 10 years

2. **Which of the following statements is true about the results of the ATLAS trial?**
   a. Continuing adjuvant tamoxifen to 10 years increased the incidence of endometrial cancer
   b. Continuing adjuvant tamoxifen to 10 years decreased the incidence of contralateral breast cancer
   c. Continuing adjuvant tamoxifen to 10 years increased the incidence of pulmonary embolism
   d. All of the above

3. **The ongoing APHINITY trial is evaluating the addition of _____ to chemotherapy/trastuzumab as adjuvant therapy for HER2-positive early breast cancer.**
   a. Bevacizumab
   b. Pertuzumab
   c. T-DM1

4. **The SWOG-S1207 trial is evaluating adjuvant endocrine therapy with or without _____ for patients with high-risk, ER/PR-positive, HER2-negative breast cancer.**
   a. Eribulin
   b. Everolimus
   c. Bevacizumab

5. **Results from a Phase III randomized study of eribulin versus capecitabine indicated that eribulin was not superior to capecitabine in patients with locally advanced or metastatic breast cancer.**
   a. True
   b. False

6. **The Phase III EMILIA study for patients with HER2-positive advanced breast cancer demonstrated a significant increase in _____ with T-DM1 versus capecitabine and lapatinib.**
   a. Progression-free survival
   b. Overall survival
   c. Objective response rate
   d. All of the above

7. **The Phase III CALOR trial evaluating no chemotherapy versus chemotherapy as adjuvant therapy for isolated local or regional recurrence of breast cancer demonstrated a significant improvement in 5-year disease-free and overall survival for patients who received chemotherapy.**
   a. True
   b. False

8. **A retrospective analysis of data from the NSABP-B-28 trial, which compared doxorubicin/cyclophosphamide to doxorubicin/cyclophosphamide followed by paclitaxel, reported that the Onco*type* DX Recurrence Score was a significant predictor of disease-free survival, distant recurrence-free interval and overall survival for patients with ER-positive, node-positive breast cancer treated with adjuvant chemotherapy.**
   a. True
   b. False

9. **Results from the BOLERO-2 Phase III trial of exemestane with or without everolimus for postmenopausal patients with disease refractory to AIs demonstrated significant improvements in response rate and progression-free survival with the addition of everolimus to exemestane.**
   a. True
   b. False

10. **Which of the following toxicities were associated with the addition of everolimus to exemestane for patients with ER/PR-positive metastatic breast cancer refractory to nonsteroidal AIs in the BOLERO-2 trial?**
    a. Stomatitis
    b. Fatigue
    c. Dyspnea
    d. Anemia
    e. All of the above

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 1, 2013

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
ATLAS trial: Benefits and risks associated with 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
Confirmatory overall survival analysis from the CLEOPATRA study of pertuzumab in combination with trastuzumab and docetaxel as first-line therapy for HER2-positive metastatic breast cancer	4 3 2 1	4 3 2 1
SWOG-S1207: A Phase III study of adjuvant endocrine therapy with or without everolimus for patients with high-risk, ER/PR-positive, HER2-negative breast cancer	4 3 2 1	4 3 2 1
Activating HER2 mutations in HER2 gene amplification-negative breast cancer and their potential effects on therapeutic approach	4 3 2 1	4 3 2 1
Results from a Phase III trial of eribulin versus capecitabine for patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes	4 3 2 1	4 3 2 1

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:

- 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
- 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
- Utilize existing and emerging biomarkers to assess risk and individualize therapy for patients with invasive early breast cancer. . . . . 4 3 2 1 N/M N/A
- Assimilate new clinical trial evidence evaluating the use of mTOR inhibition to reverse endocrine resistance into the therapeutic algorithm for patients with progressive ER-positive 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

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
Sir Richard Peto	4 3 2 1	4 3 2 1
Eric P Winer, MD	4 3 2 1	4 3 2 1
Sandra M Swain, MD	4 3 2 1	4 3 2 1
Matthew J Ellis, MB, BChir, 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 faculty and editor for this activity:

.....

.....

.....

REQUEST FOR CREDIT — Please print clearly

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