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Breast Cancer® UPDATE

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

FACULTY INTERVIEWS

Harold J Burstein, MD, PhD
Sunil Verma, MD, MSEd
Ruth O'Regan, MD
Javier Cortes, MD, PhD

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.
- Assimilate new clinical trial evidence evaluating the role of mTOR inhibition in reversing resistance to trastuzumab and endocrine therapy into the therapeutic algorithm for patients with progressive ER-positive metastatic breast cancer.
- 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.
- Use existing and emerging biomarkers to assess risk and individualize therapy for patients with invasive early breast cancer.
- Demonstrate knowledge of emerging research data to guide the selection of chemotherapeutic agents/regimens for patients with metastatic breast cancer.
- Counsel appropriately selected patients with breast cancer about participation in ongoing clinical trials.

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INTERVIEW

Harold J Burstein, MD, PhD

Dr Burstein is Associate Professor of Medicine at the Harvard Medical School Breast Oncology Center at Dana-Farber Cancer Institute in Boston, Massachusetts.

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Track 3

DR LOVE: You were part of an abstract presented recently at ASCO, "Time Trends in the Use of Adjuvant Chemotherapy and Outcomes in Women with T1a,b N0M0 Breast Cancer in the NCCN." Would you discuss the study?

DR BURSTEIN: During the past decade our threshold for administering chemotherapy for small tumors has decreased. Specifically in terms of triple-negative or HER2-positive disease, 10 years ago roughly 20% of patients with subcentimeter tumors were being offered chemotherapy and now it is closer to 65% or 70%. I believe this changed in response to both data and guideline updates. The data on trastuzumab came out in 2005 (Romond 2005), and with that many physicians started offering trastuzumab and chemotherapy to patients with small HER2-positive tumors.

In addition, in reviewing the risk associated with these smaller HER2-positive and triple-negative tumors it became evident that, although they were small tumors, they were biologically aggressive and probably carried more risk than we had anticipated. We started to consider trastuzumab and chemotherapy for 6- to 10-mm HER2-positive tumors or chemotherapy alone for triple-negative disease.

Did that change help patients fare better? The answer seems to be yes (Duarte Luis 2013; [1.1]). In terms of outcomes among women who did not receive chemotherapy for small tumors compared to patients who did, a clear benefit was evident among those who received chemotherapy even if the tumor was 6 to 10 millimeters in size. The recurrence risk for women who did not receive chemotherapy was approximately 15%, and among the patients who did receive chemotherapy it was closer to 10% or less. This suggests that the data and the guidelines were correct — we should be treating these smaller tumors with bad biology more aggressively to see better results.

1.1

Time Trends in the Use of Adjuvant Chemotherapy (CTX) and Outcomes in T1a,b NOMO Breast Cancer in the National Comprehensive Cancer Network

	No CTX or trastuzumab		CTX and/or trastuzumab	
Hormone receptor-positive, HER2-negative	**T1a**	**T1b**	**T1a**	**T1b**
5-year median distant relapse-free survival	97%	96%	100%	95%
5-year median overall survival	98%	97%	100%	98%
Hormone receptor-negative, HER2-negative				
5-year median distant relapse-free survival	90%	90%	95%	93%
5-year median overall survival	94%	91%	100%	96%
Hormone receptor-positive, HER2-positive				
5-year median distant relapse-free survival	93%	91%	100%	95%
5-year median overall survival	95%	95%	100%	99%
Hormone receptor-negative, HER2-positive				
5-year median distant relapse-free survival	89%	81%	89%	94%
5-year median overall survival	93%	100%	100%	95%

Duarte Luis IMV et al. *Proc ASCO* 2013;**Abstract 1006**.

Track 8

DR LOVE: Would you discuss your 62-year-old patient who received tamoxifen, trastuzumab and paclitaxel as first-line treatment for ER-positive, HER2-positive metastatic disease and then experienced progression on tamoxifen/trastuzumab?

DR BURSTEIN: You could consider switching from tamoxifen to fulvestrant. You could argue that her disease never progressed on first-line therapy and you could resume paclitaxel or consider a taxane with trastuzumab and pertuzumab, which is a relatively new option. You could argue that she's already had paclitaxel and trastuzumab and therefore she meets the criteria for getting the newly approved second-line agent T-DM1, or you could consider lapatinib/capecitabine, which is an all-oral regimen, or if the patient fits the population from the BOLERO-3 study, vinorelbine/trastuzumab with or without everolimus would also be a consideration. Thanks to shifts in the past

3 or 4 years, we now have a number of choices that allow patients to experience long runs of treatment with a biologic agent and no chemotherapy (1.2).

I like T-DM1 because the side-effect profile is favorable, and that's what I chose for this lady — it doesn't cause alopecia or other traditional chemotherapy-like side effects such as nausea, vomiting or low blood counts. The other interesting option would be pertuzumab/trastuzumab, without reintroduction of the chemotherapy, in the case of a patient with essentially asymptomatic radiologic progression. We typically limit our pertuzumab use to the FDA label at this juncture, however, which is first line with chemotherapy.

1.2

T-DM1 and the Promise of Antibody-Drug Conjugates

"The pharmacologic properties of trastuzumab emtansine that appear to have been confirmed by this trial [EMILIA] are impressive. Objective evidence of tumor shrinkage indicates, as previously reported in animal models, that HER2 receptor number and function remain intact in most patients in whom clinical resistance to trastuzumab has developed, allowing specific binding of the trastuzumab emtansine conjugate (T-DM1). The remarkable rate of breast-cancer regressions observed at sites of visceral metastases suggests, as originally hypothesized, that the cytotoxic maytansinoid portion of the conjugate is delivered intracellularly at sufficient concentrations to produce cell death (and consequent tumor shrinkage) consistent with mitotic catastrophe, rather than inducing the cytostasis commonly associated with single-agent trastuzumab. The beauty of T-DM1 is that conjugate formation does not preclude the antibody-dependent cellular cytotoxicity or HER2-neutralizing activity of the antibody; thus, T-DM1 retains the functions of trastuzumab and adds the effects of a potent cytotoxic drug."

Teicher BA, Doroshow JH. *N Engl J Med* 2012;367(19):1847-8.

Track 11

DR LOVE: How would you approach a patient with residual disease after neoadjuvant therapy for triple-negative, BRCA1 mutation-positive breast cancer?

DR BURSTEIN: Patients in this setting clearly need more chemotherapy. This is an area that continues to slowly accumulate data. A growing sentiment suggests that platinum-based chemotherapy agents might be particularly valuable in BRCA mutation carriers. The cleanest data come from a neoadjuvant study in Europe that accumulated large numbers of BRCA mutation carriers and reported high rates of complete pathologic response, in the range of 70% to 75%, with cisplatin-based chemotherapy (Byrski 2010).

Thus we are increasingly tempted to try platinum-based therapy for patients with BRCA-1 mutation-positive disease. Whether that's any better than a different alkylator or better than eribulin, ixabepilone or other chemotherapy or whether it improves the natural history remains unclear. But it has led to a resurgence and interest in our group in using platinum for patients with triple-negative breast cancer. I know that this also has been an area of substantial interest around the country. ■

SELECT PUBLICATIONS

Byrski T et al. **Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy.** *J Clin Oncol* 2010;28(3):375-9.

Romond EH et al. **Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.** *N Engl J Med* 2005;353(16):1673-84.

INTERVIEW

Sunil Verma, MD, MSEd

Dr Verma is a Medical Oncologist, Chair of Breast Medical Oncology and Head of Breast Cancer Clinical Trials at Sunnybrook Odette Cancer Centre and is Associate Professor at the University of Toronto in Toronto, Ontario, Canada.

Tracks 1-11

Select Excerpts from the Interview

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Case discussion

A 44-year-old woman who previously received adjuvant chemotherapy/trastuzumab for HER2-positive, node-positive breast cancer presents with bilateral lung metastases

DR VERMA: This patient completed adjuvant treatment in October 2011, and she recently presented with a cough and shortness of breath that was affecting her ability to climb a flight of stairs in her home. The CT revealed a small right pleural effusion in addition to the lung metastases.

She is an otherwise active person and had bounced back nicely after completing trastuzumab in the adjuvant setting, so in terms of treatment options at this point we were considering standard trastuzumab-based treatment with paclitaxel/trastuzumab,

2.1

CLEOPATRA: A Phase III Trial of Pertuzumab, Trastuzumab and Docetaxel as First-Line Therapy for HER2-Positive Metastatic Breast Cancer

	Ptz + T + D (n = 402)	**Pla + T + D** (n = 406)	HR	*p*-value
Median progression-free survival	18.7 mo	12.4 mo	0.69	NR
Median overall survival	Not reached	37.6 mo	0.66	0.0008

Median follow-up: 30 months
Ptz = pertuzumab; T = trastuzumab; D = docetaxel; Pla = placebo; HR = hazard ratio; NR = not reported

Swain SM et al. *Lancet Oncol* 2013;14(6):461-71.

docetaxel/trastuzumab or vinorelbine/trastuzumab. The data are strongest with docetaxel/trastuzumab/pertuzumab as per the CLEOPATRA study (Swain 2013; [2.1]), so we offered her docetaxel/trastuzumab/pertuzumab or paclitaxel/trastuzumab/pertuzumab. We don't have Phase III data with paclitaxel, but the consensus is that the choice of paclitaxel versus docetaxel is not critical for the dual HER2-targeted therapy to be effective. She chose paclitaxel/trastuzumab/pertuzumab. We started treatment 2 weeks ago, and she seems to be faring well.

DR LOVE: If you could have accessed T-DM1, would you have used it in this case?

DR VERMA: On the EMILIA study patients had to experience recurrence within 6 months of completing adjuvant trastuzumab, so this patient would not fit the criteria to receive T-DM1 according to the protocol. The data with T-DM1 are strongest in the first line if patients have experienced a short disease-free interval (Verma 2012; [2.2]). In the CLEOPATRA trial patients were eligible to enroll as long as the adjuvant trastuzumab was completed 1 year ago and the disease-free interval was 1 year or more. For this reason we chose pertuzumab/trastuzumab/taxane. T-DM1 will be an option for this patient at disease progression.

DR LOVE: What do we know in terms of predictors of response to pertuzumab?

DR VERMA: One would think that HER3 expression would be a predictor of response to pertuzumab, considering that the agent blocks the dimerization of HER2, particularly with HER3. However, that's not the case. Prior trastuzumab is potentially a prognostic marker — patient prognosis is slightly worse if they received prior trastuzumab — but we still have not identified any new predictive biomarkers.

2.2

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**	Hazard ratio	*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.

DR LOVE: Do you have any predictions about what we might see in terms of results from the MARIANNE trial (2.3), which is evaluating T-DM1 with or without pertuzumab versus a taxane/trastuzumab for patients with HER2-positive metastatic breast cancer?

DR VERMA: MARIANNE is a pivotal trial, and we're expecting the results in 2014. The combination pertuzumab/T-DM1 arm is of specific interest in terms of improving outcomes, particularly with regard to progression-free survival and what was already achieved in the CLEOPATRA study (2.1). We will see some indirect comparisons between the T-DM1/pertuzumab arm from MARIANNE and the docetaxel/trastuzumab/pertuzumab arm from CLEOPATRA, but what we're hoping for is a progression-free survival of more than 18.5 months.

DR LOVE: What other trials are exploring pertuzumab and T-DM1, particularly in the adjuvant and neoadjuvant settings?

DR VERMA: The APHINITY adjuvant trial (2.3), which is nearing completion of accrual, is evaluating chemotherapy/trastuzumab versus chemotherapy/trastuzumab/pertuzumab. This is a pivotal study investigating whether a benefit exists with the addition of pertuzumab in the adjuvant setting among patients with early-stage breast cancer.

Additional studies in the neoadjuvant setting are being planned and clarified. What exactly the trial arms will require is still being discussed, but the basic premise is that the studies will evaluate chemotherapy/trastuzumab as the control arm versus chemotherapy/trastuzumab/pertuzumab or T-DM1/pertuzumab.

An important consideration when using a targeted approach among patients who may not be receiving chemotherapy, even in the early-stage setting, is the initial HER2 testing. We must be completely confident that we are dealing with HER2-positive disease, so testing is critical.

DR LOVE: What is your clinical perception of the toxicities with pertuzumab and also with T-DM1?

DR VERMA: The toxicity profile with pertuzumab as reported in the CLEOPATRA trial includes an increased rate of rash and an increased risk of diarrhea. Higher febrile neutropenia rates have also been noted.

In terms of T-DM1, it is one of the most effective and least toxic agents in the breast cancer armamentarium. Patients generally "sail through" treatment and usually don't experience toxicities affecting their quality of life. No nausea, vomiting or hair loss occurs, and patients are not at risk for febrile neutropenia or infection.

2.3 **Key Ongoing Phase III Trials for Patients with HER2-Positive Breast Cancer**

Trial identifier	N	Setting	Treatment arms
APHINITY (NCT01358877)	4,800	Adjuvant	• Chemotherapy + trastuzumab + pertuzumab • Chemotherapy + trastuzumab + placebo
MARIANNE (NCT01120184)	1,095	Metastatic	• Trastuzumab + taxane • T-DM1/placebo • T-DM1/pertuzumab

www.clinicaltrials.gov, September 2013.

The toxicities we need to educate our patients about prior to therapy include thrombocytopenia and the potential for nosebleeds, pneumonitis and liver toxicity. One rare side effect is focal nodular hyperplasia, with which patients experience liver toxicity that does not translate into elevations in liver enzymes. Patients may exhibit signs of portal hypertension, varices, splenomegaly or abdominal discomfort, and when this happens treatment likely should be discontinued. Cases of pneumonitis have been reported, which would also be a reason to discontinue therapy.

Track 9

DR LOVE: What are your thoughts on using mTOR inhibitors with endocrine therapy in patients with endocrine-naïve disease?

DR VERMA: A neoadjuvant study suggested that mTOR is an important pathway in breast cancer even in the context of a treatment-naïve patient population (Baselga 2009). Patients were randomly assigned to neoadjuvant letrozole or letrozole/everolimus. The data indicated that the addition of everolimus to letrozole led to an improvement in response and a reduction in Ki-67 expression compared to letrozole alone.

This provides a rationale for studying everolimus in the early setting in addition to the first-line metastatic setting. At least 3 adjuvant trials are under way evaluating everolimus in the adjuvant setting (2.4). One of the challenges of studying this agent in the adjuvant setting is that patients with hormone receptor-positive disease have an excellent prognosis to begin with. We must identify the appropriate patients who are more at risk of disease recurrence and are more likely to have a better risk-benefit analysis. In most cases the trials include patients with significant nodal involvement or those who have a high Recurrence Score (RS) or other adverse prognostic factors, and that is the correct approach. ■

2.4

Ongoing Adjuvant Trials Evaluating Everolimus-Based Therapy for Patients with Breast Cancer

Trial identifier	Phase	N	Treatment arms
SWOG-S1207 (NCT01674140)	III	3,500	• Endocrine therapy + everolimus x 1 year • Endocrine therapy + placebo x 1 year
NCT01805271	III	1,984	• Endocrine therapy x 3 years → everolimus • Endocrine therapy x 3 years → placebo
NCT00930930	II	145	• Cisplatin/paclitaxel + everolimus • Cisplatin/paclitaxel + placebo

www.clinicaltrials.gov, September 2013.

SELECT PUBLICATIONS

Baselga J et al. **Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer.** *J Clin Oncol* 2009;27(16):2630-7.

Swain S et al. **Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study.** *Lancet Oncol* 2013;14(6):461-71.

Verma S et al. **Trastuzumab emtansine for HER2-positive advanced breast cancer.** *N Engl J Med* 2012;367(19):1783-91.

INTERVIEW

Ruth O'Regan, MD

Dr O'Regan is Professor and Vice-Chair for Educational Affairs in the Georgia Cancer Center for Excellence Department of Hematology and Medical Oncology at Grady Memorial Hospital and is the Louisa and Rand Glenn Family Chair in Breast Cancer Research at Winship Cancer Institute of Emory University in Atlanta, Georgia.

Tracks 1-9

Track 1 Background for the development of the BOLERO-3 trial: Trastuzumab/vinorelbine with or without everolimus for HER2-positive locally advanced or metastatic BC

Track 2 Potential incorporation of everolimus into the treatment algorithm for HER2-positive mBC

Track 3 Side-effect management and dose titration with everolimus

Track 4 **Second opinion:** A 59-year-old woman with Stage IV, ER/PR-negative, HER2-positive BC previously treated with TCH followed by 4 years of single-agent trastuzumab presents with liver metastases

Track 5 Selection of patients with mBC for treatment with *nab* paclitaxel

Track 6 Results from a Phase II trial evaluating use of the Onco*type* DX assay RS to select neoadjuvant therapy for ER-positive BC

Track 7 Prognostic impact of the Onco*type* DX RS in patients with Stage IV BC

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Track 9 Perspective on the utility of the Onco*type* DX assay in node-positive BC

Select Excerpts from the Interview

Tracks 1-3

DR LOVE: Would you provide a brief background on the rationale for studying everolimus in HER2-positive breast cancer? Also, would you comment on the results from the Phase III BOLERO-3 trial of everolimus in combination with trastuzumab/vinorelbine in trastuzumab-resistant HER2-positive metastatic breast cancer that you presented at ASCO 2013?

DR O'REGAN: Preclinical data in trastuzumab-resistant breast cancer models have shown an activation of the PI3 kinase pathway. This occurs either through increased signaling through other growth factor receptors rather than HER2, such as HER3 or insulin growth factor receptor 1, or it can occur constitutively or through PTEN loss. We've performed early-phase trials evaluating mTOR inhibition as a means of enhancing the activity of trastuzumab and maybe reversing resistance to trastuzumab.

One such trial evaluated the combination of paclitaxel/trastuzumab administered weekly with everolimus in patients with heavily pretreated trastuzumab-resistant disease. All patients also had prior taxane exposure, and we reported a high clinical benefit rate of more than 70% (Andre 2010).

Several Phase III BOLERO trials are now ongoing in the HER2-positive setting. BOLERO-1 is evaluating the addition of everolimus to paclitaxel/trastuzumab in the first-line setting, and BOLERO-3 is evaluating the proof of principle that inhibiting mTOR with everolimus may improve outcomes for patients with trastuzumab-resistant breast cancer.

Patients on the BOLERO-3 trial were randomly assigned to weekly vinorelbine and trastuzumab with or without everolimus, and the mTOR inhibitor was administered at 5 mg daily because that was the maximum tolerated dose taken forward from the Phase IB trial. BOLERO-3 met its primary endpoint in that the addition of everolimus to trastuzumab/vinorelbine significantly improved progression-free survival by 1.2 months with a hazard ratio of 0.78 (O'Regan 2013; [3.1]).

Numerically the advantage was not that great, but the survival data are not yet mature, though a trend toward a survival advantage is evident. That analysis will be important because these are patients with heavily pretreated disease.

DR LOVE: Do you believe buried in these modest results might be a population of patients who can derive substantial benefit?

DR O'REGAN: The subgroup analysis performed on this study was interesting, so I say absolutely. We are also performing correlative analyses on samples from approximately 40% of patients on the study, including evaluating different parts of the PI3 kinase pathway, mutations of the PI3 kinase pathway, PTEN, et cetera. The results will be reported at ESMO, and we've seen an indication that some subgroups benefit. From the data that we have so far, the most striking thing in my mind was the fact that the benefit was fairly significant in ER/PR-negative cancer, but no difference was observed in the ER-positive/PR-positive group.

3.1

BOLERO-3: A Phase III Trial of Weekly Trastuzumab and Vinorelbine in Combination with Everolimus or Placebo for Trastuzumab-Resistant, HER2-Positive Metastatic Breast Cancer

Efficacy	Everolimus arm (n = 284)	Placebo arm (n = 285)	Hazard ratio	*p*-value
Median progression-free survival	7.0 mo	5.78 mo	0.78	0.0067
Deaths*	36.3%	41.1%	—	—
Overall response rate	40.8%	37.2%	—	—
Clinical benefit rate	59.2%	53.3%	—	0.09
	Everolimus arm (n = 280)		**Placebo arm** (n = 282)	
Select adverse events	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Stomatitis	63%	13%	28%	1%
Pyrexia	39%	3%	23%	1%
Rash	25%	0%	18%	1%
Hyperglycemia	9%	6%	5%	3%
Hyperlipidemia	2%	0%	1%	0%

* Statistical significance not yet reached at interim overall survival analysis

O'Regan R et al. *Proc ASCO* 2013;**Abstract 505**.

DR LOVE: What's the typical side-effect profile for this agent, and how do you advise patients before starting therapy?

DR O'REGAN: I typically outline the more common side effects — mouth sores, rashes, nail changes. You have to be proactive with the mouth sores. Using "magic mouthwash" with steroids appears to be helpful. Also, metabolic abnormalities — hyperglycemia and hyperlipidemia — are some of the tricky aspects. It's difficult to say how we should manage those in general, but I've seen a few patients with diabetes who experienced more elevated blood glucose while receiving everolimus.

Trying to ascertain the right dose for each patient is also an issue. I start with 10 mg for every patient, but I end up reducing the dose to 5 mg or even 2.5 mg a day for patients who can't tolerate the agent. Body mass index appears to play a role in how patients tolerate the drug. Some of my patients with low body mass indexes have experienced more problems. We're working on a pharmacokinetic study to see if we can gain more insight as to what the correct dose is for each patient.

I believe it's important to start with 10 mg in the ER-positive setting because that's what was used in the BOLERO-2 trial, and then you can dose reduce if need be. Some patients may need 10 mg, and you're missing that window by starting at 5 mg.

DR LOVE: In what situations in the metastatic HER2-positive disease setting do you envision using everolimus?

DR O'REGAN: Based on the BOLERO-3 data and if it were approved in this setting, I would lean toward administering it in patients with ER/PR–negative cancer who have gone through the other treatments, including pertuzumab and T-DM1 and perhaps lapatinib. That might be a group for whom you're starting to run out of options.

Tracks 6, 9

DR LOVE: Would you discuss the results of your Phase II study evaluating the use of the Onco*type* DX assay RS to select neoadjuvant therapy for patients with ER-positive breast cancer?

DR O'REGAN: Obviously, the TAILORx study is ongoing and will provide the "gold standard" with regard to use of the Onco*type* DX assay in the adjuvant setting once it is completed. But our Phase II study was initiated a number of years ago because quite often oncologists must administer preoperative treatment.

Similar to the design of the TAILORx trial, we were attempting to use RS to help us select therapies, except this was in the neoadjuvant setting. Patients with an RS of 25 or higher received docetaxel/cyclophosphamide (TC). Those with an RS of 10 or less received neoadjuvant endocrine therapy, and those in the intermediate group were randomly assigned to endocrine therapy or TC.

The number of evaluable patients is somewhat small, but we observed a pathologic complete response rate of approximately 20% in patients with high RS who received TC. Of note, in the intermediate RS group we did not observe any pathologic complete responses among the patients who received TC, although it is clear that chemotherapy can downstage these tumors because radiologically we observed decreases in tumor size (Zelnak 2013; [3.2]).

3.2

Results from a Phase II Trial Evaluating the Use of the Onco*type* DX Assay Recurrence Score (RS) to Select Neoadjuvant Therapy for ER-Positive Breast Cancer

	RS ≤ 10	11 ≥ RS < 25		RS ≥ 25
Clinical response	**Exemestane** (n = 9)	**Exemestane** (n = 9)	**TC x 6** (n = 10)	**TC x 6** (n = 18)
Complete response	33.3%	22.2%	40%	44.4%
Partial response	44.4%	66.7%	50%	44.4%
Radiologic response				
Complete response	0%	0%	40%	11.1%
Partial response	66.7%	66.7%	50%	55.6%
Pathologic CR	0%	0%	0%	22.2%
BCS	28.6%	50%	40%	61.1%

TC = docetaxel/cyclophosphamide; CR = complete response; BCS = breast-conserving surgery

- Results from the Phase III TAILORx and RxPONDER trials will provide additional information regarding use of adjuvant chemotherapy in patients with intermediate RS.
- For patients with ER-positive breast cancer who are referred for preoperative therapy prior to BCS, incorporation of the Onco*type* DX assay RS should be considered.

Zelnak AB et al. *Proc ASCO* 2013;**Abstract 562**.

One of the issues we struggle with in administering preoperative endocrine therapy is not administering it long enough. So we designed this trial so patients received preoperative endocrine therapy for at least 6 months, and we tried to keep them on it until they achieved maximum response. We performed ultrasounds every 2 months on the study. I would say that it's unclear how long you need to administer endocrine therapy in this setting. Of course, another issue was that pathologic complete response is not that important in these ER-positive tumors, particularly luminal A ER-positive disease.

DR LOVE: How do you use the Onco*type* DX assay in the adjuvant setting?

DR O'REGAN: We use the 21-gene RS in virtually all cases of node-negative breast cancer, unless the tumors are tiny. I've actually run into a couple of patients recently for whom one of the surgeons has ordered the assay for a 6-mm tumor and the RS is 24, and I was thinking, "What am I going to do with that information?"

I also order it frequently for patients with 1 to 3 positive lymph nodes, although my preference is to place such patients on the SWOG-S1007 study (RxPONDER). Because our surgeons are proactive about ordering the 21-gene RS, I've been reminding them to send patients over to us first, so we can get them on the study. ■

SELECT PUBLICATIONS

Andre F et al. **Phase I study of everolimus plus weekly paclitaxel and trastuzumab in patients with metastatic breast cancer pretreated with trastuzumab.** *J Clin Oncol* 2010;28(34):5110-5.

Jerusalem G et al. **Phase I trial of oral mTOR inhibitor everolimus in combination with trastuzumab and vinorelbine in pre-treated patients with HER2-overexpressing metastatic breast cancer.** *Breast Cancer Res Treat* 2011;125(2):447-55.

O'Regan R et al. **Phase III, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and vinorelbine in trastuzumab-resistant, advanced breast cancer (BOLERO-3).** *Proc ASCO* 2013;**Abstract 505**.

Zelnak AB et al. **Phase II trial evaluating the use of 21-gene Recurrence Score (RS) to select preoperative therapy in hormone receptor (HR)-positive breast cancer.** *Proc ASCO* 2013;**Abstract 562**.

INTERVIEW

Javier Cortes, MD, PhD

Dr Cortes is Head of the Breast Cancer Program at the Vall d'Hebron Institute of Oncology's Vall d'Hebron University Hospital in Barcelona, Spain.

Tracks 1-10

Select Excerpts from the Interview

Track 3

DR LOVE: What is your perspective on the Phase III CLEOPATRA trial comparing the addition of pertuzumab to trastuzumab and docetaxel as first-line therapy for patients with HER2-positive metastatic breast cancer?

DR CORTES: The CLEOPATRA trial demonstrated that when pertuzumab is added to trastuzumab-based therapy an improvement occurs in all outcomes. Increases were observed in progression-free survival, overall response rate and overall survival, and quality of life improved with no significant increase in toxicity (Swain 2013; [2.1, page 7]; Cortes 2013a).

The hazard ratio for survival with the addition of pertuzumab to trastuzumab/docetaxel was 0.66 in CLEOPATRA, whereas it was 0.80 with the addition of trastuzumab to chemotherapy in the original pivotal trial of trastuzumab (Slamon 2001). So the benefit of adding pertuzumab to trastuzumab/chemotherapy is larger than the original benefit reported with the addition of trastuzumab to chemotherapy, which is amazing.

Tracks 6-7

DR LOVE: Would you discuss the data presented at ASCO 2013 from the Phase III trial comparing eribulin to capecitabine for patients with locally advanced or metastatic breast cancer?

DR CORTES: Eribulin is an antimitotic agent demonstrated to significantly increase overall survival compared to treatment of physician's choice in the late-line setting for patients with metastatic breast cancer (Cortes 2011). It has been considered the standard treatment in that setting.

This recent Phase III trial comparing eribulin to capecitabine was designed to move eribulin up earlier in the metastatic setting for patients who received anthracyclines and taxanes and for whom capecitabine is considered standard therapy. The results showed that eribulin did not improve progression-free or overall survival, the coprimary endpoints of the trial. Even though numerically the hazard ratio for median overall survival favored the eribulin arm, from a statistical point of view the trial was negative (Kaufman 2012). A subgroup analysis of the data at ASCO 2013 reported that in patients with HER2-negative disease and with triple-negative disease, eribulin was superior to capecitabine (Kaufman 2013; [4.1]).

We also presented a study comparing the quality of life for patients receiving eribulin to that of those receiving capecitabine. Overall quality of life was improved with both agents, but it was significantly better with eribulin (Cortes 2013b; [4.2]). I believe that both the antitumor efficacy and side effects of these therapies play a role. When we evaluated the quality of life based on known adverse events associated with these agents, we found that issues related to hair loss favored capecitabine. However, parameters related to gastrointestinal side effects were better with eribulin.

DR LOVE: What were the main side effects observed with eribulin and capecitabine in the Phase III head-to-head trial?

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

Median overall survival	Eribulin	Capecitabine	Hazard ratio
Overall (n = 554, 548)	15.9 mo	14.5 mo	0.88*
HER2 status			
HER2-positive	14.3 mo	17.1 mo	0.97
HER2-negative	15.9 mo	13.5 mo	0.84
ER status			
ER-positive	18.2 mo	16.8 mo	0.9
ER-negative	14.4 mo	10.5 mo	0.78
Triple-negative			
Yes	14.4 mo	9.4 mo	0.7
No	17.5 mo	16.6 mo	0.93

* $p = 0.056$

Prespecified exploratory analysis showed that subgroups of patients with HER2-negative ($p = 0.03$), ER-negative ($p = 0.02$) or triple-negative ($p = 0.01$) disease may have a greater benefit in overall survival with eribulin compared to capecitabine.

Kaufman P et al. *Proc ASCO* 2013;**Abstract 1049**.

4.2

Quality of Life for Patients with Locally Advanced or Metastatic Breast Cancer in a Phase III Study of Eribulin versus Capecitabine

- Global health status and overall quality of life scores improved in both arms but significantly more with eribulin than with capecitabine ($p = 0.048$), suggesting subjective treatment benefit.
- Cognitive functioning improved for patients receiving eribulin compared to capecitabine, whereas emotional functioning improved for patients receiving capecitabine compared to eribulin.
- Advantages in parameters linked to gastrointestinal effects (nausea, vomiting and diarrhea) were observed with eribulin, whereas advantages in parameters related to hair loss were observed with capecitabine.

Cortes J et al. *Proc ASCO* 2013b;**Abstract 1050**.

DR CORTES: Compared to other antimitotic agents, eribulin is well tolerated. Myelosuppression is not a big issue for patients who receive eribulin. Alopecia can be a problem with this agent. One of the major side effects with eribulin is neurotoxicity, with Grade 3 to 4 peripheral neuropathy being reported in 8% of patients.

Capecitabine is generally well tolerated. However, 15% to 20% of patients develop Grade 3 hand-foot syndrome, which may require a dose adjustment.

DR LOVE: What are your thoughts on using eribulin for patients with breast cancer in earlier-stage disease?

DR CORTES: In my opinion, eribulin is as good as or better than capecitabine, especially in HER2-negative disease. I would use eribulin for a patient with triple-negative disease as second-line therapy. However, it is not yet approved in that setting. We are also conducting a clinical trial with single-agent eribulin in the neoadjuvant setting to identify which patients would benefit from this therapy (4.3).

4.3

Key Ongoing Phase II Trials Evaluating Eribulin-Based Therapy for Patients with Breast Cancer

Trial identifier	N	Setting	Treatment arms
SOLTI-1007 (NCT01669252)	200	• Neoadjuvant • HER2-negative	• Eribulin
NCT01593020	152	• Neoadjuvant • HER2-negative	• Eribulin → FAC or FEC • Paclitaxel → FAC or FEC
NCT01388647	56	• Neoadjuvant • HER2-positive	• Eribulin + trastuzumab + carboplatin
NSABP-FB-9 (NCT01705691)	50	• Neoadjuvant • HER2-negative	• Eribulin → AC • Paclitaxel → AC
NCT01439282	67	• Adjuvant • ER-positive, HER2-negative	• Eribulin + capecitabine
NCT01427933	141	• Metastatic • HER2-positive	• Eribulin + ramucirumab • Eribulin
E-VITA/GBG 64 (NCT01534455)	80	• Metastatic • HER2-positive	• Eribulin (1.23 mg) + lapatinib • Eribulin (1.76 mg) + lapatinib

F = 5-FU; A = doxorubicin; C = cyclophosphamide; E = epirubicin

www.clinicaltrials.gov, September 2013.

Track 10

DR LOVE: ATLAS, an international Phase III study, and its United Kingdom counterpart, the aTTom trial, randomly assigned women with early breast cancer who had completed 5 years of adjuvant tamoxifen to either continue or stop tamoxifen. Would you comment on the results of these studies?

DR CORTES: One of the most important presentations at ASCO 2013 was the aTTom trial. The results of aTTom in conjunction with the ATLAS trial demonstrated that 10 years of tamoxifen is a better option for patients than 5 years of therapy (Gray 2013; Davies 2013; [4.4]). The aTTom data reported that the absolute benefit in terms of overall survival was approximately 3%. So for some patients 10 years of tamoxifen would be a good option. I would administer 10 years of tamoxifen for patients who are pre- or perimenopausal with high-risk tumors and node involvement. ■

4.4

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.

SELECT PUBLICATIONS

Cortes J et al. **Health-related quality-of-life assessment in CLEOPATRA, a phase III study combining pertuzumab with trastuzumab and docetaxel in metastatic breast cancer.** *Ann Oncol* 2013a;[Epub ahead of print].

Cortes J et al. **Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): A phase 3 open-label randomised study.** *Lancet* 2011;377 (9769):914-23.

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**.

Slamon D et al. **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001;344(11):783-92.

Swain S et al. **Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): Overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study.** *Lancet Oncol* 2013;14(6):461-71.

QUESTIONS (PLEASE CIRCLE ANSWER):

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

2. **The Phase III CLEOPATRA study demonstrated a statistically significant advantage in _____ with the addition of pertuzumab to trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer.**
   a. Progression-free survival
   b. Overall survival
   c. Both a and b

3. **Data from an NCCN study of T1a,b N0M0 breast tumors indicate that the subgroup of patients with hormone receptor-negative, HER2-positive T1b breast cancer have a higher 5-year median relapse-free survival with chemotherapy/trastuzumab than with no chemotherapy/trastuzumab.**
   a. True
   b. False

4. **The Phase III MARIANNE trial is evaluating _____ with or without pertuzumab versus trastuzumab and a taxane for patients with HER2-positive metastatic breast cancer.**
   a. T-DM1
   b. Lapatinib
   c. Olaparib

5. **A Phase II trial evaluating the use of the _____ to select neoadjuvant therapy for patients with ER-positive breast cancer reported a pathologic complete response rate of approximately 20% for patients with _____ receiving chemotherapy (TC x 6).**
   a. MammaPrint assay; high-risk scores
   b. Onco*type* DX assay RS; high-risk RS (≥25)
   c. PAM50 assay; risk of recurrence high-risk classification

6. **In the BOLERO-3 trial common side effects that were associated with everolimus included _____.**
   a. Hyperglycemia
   b. Hyperlipidemia
   c. Rash
   d. Stomatitis
   e. All of the above

7. **Results of the Phase III BOLERO-3 trial evaluating the addition of everolimus to vinorelbine/trastuzumab for trastuzumab-resistant, HER2-positive metastatic breast cancer indicated a statistically significant improvement in median progression-free survival with the addition of everolimus to vinorelbine/trastuzumab.**
   a. True
   b. False

8. **A Phase III study of eribulin versus capecitabine for patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes reported that patients with HER2-negative, ER-negative or triple-negative disease may experience a greater benefit in overall survival with eribulin compared to capecitabine.**
   a. True
   b. False

9. **Analysis of quality of life in patients with locally advanced or metastatic breast cancer in the Phase III study of eribulin versus capecitabine demonstrated:**
   a. Overall quality of life was improved with both agents but was significantly better with eribulin than with capecitabine
   b. Advantages in parameters linked to gastrointestinal effects with eribulin
   c. Advantages in parameters related to hair loss with capecitabine
   d. All of the above

10. **The ATLAS and aTTom trials investigating the effect of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years demonstrated a 25% reduction in breast cancer mortality after year 10 in patients who continued tamoxifen to 10 years.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 3, 2013

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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 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
Analyses of quality of life, functioning and symptoms with eribulin and capecitabine for metastatic breast cancer in a Phase III trial	4 3 2 1	4 3 2 1
Results from BOLERO-3: A Phase III trial of trastuzumab/vinorelbine with or without everolimus for HER2-positive locally advanced or metastatic breast cancer	4 3 2 1	4 3 2 1
Results from a Phase II trial evaluating use of the Onco*type* DX assay RS to select neoadjuvant therapy for ER-positive breast cancer	4 3 2 1	4 3 2 1
Analysis of adjuvant chemotherapy regimen and outcomes for women with T1N0 breast cancer treated at NCCN cancer centers	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:

- 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
- Assimilate new clinical trial evidence evaluating the role of mTOR inhibition in reversing resistance to trastuzumab and endocrine therapy into the therapeutic algorithm for patients with progressive ER-positive metastatic breast cancer. . . . . 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
- Use 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
- Demonstrate knowledge of emerging research data to guide the selection of chemotherapeutic agents/regimens for patients with 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

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Additional comments about this activity:

.....

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Faculty	Knowledge of subject matter				Effectiveness as an educator			
Harold J Burstein, MD, PhD	4	3	2	1	4	3	2	1
Sunil Verma, MD, MSEd	4	3	2	1	4	3	2	1
Ruth O'Regan, MD	4	3	2	1	4	3	2	1
Javier Cortes, MD, PhD	4	3	2	1	4	3	2	1
Editor	**Knowledge of subject matter**				**Effectiveness as an educator**			
Neil Love, MD	4	3	2	1	4	3	2	1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

.....

.....

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