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Breast Cancer® UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

José Baselga, MD, PhD
Kathy S Albain, MD
Denise A Yardley, MD
Rowan T Chlebowski, MD, PhD

EDITOR

Neil Love, MD

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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.
- Use existing and emerging biomarkers to assess risk and individualize therapy for patients with invasive early 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, when appropriate, integrate these findings into clinical practice.
- 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.
- 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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EDITOR

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INTERVIEW

José Baselga, MD, PhD

Dr Baselga is Physician-in-Chief at Memorial Sloan-Kettering Cancer Center in New York, New York.

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Track 4 Efficacy of second-line pertuzumab/trastuzumab in patients with HER2-positive mBC whose disease progresses on trastuzumab-based therapy

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DR LOVE: What is known about the synergy of the combination of the anti-HER2 antibodies pertuzumab and trastuzumab for the treatment of HER2-positive breast cancer?

DR BASELGA: Pertuzumab in combination with trastuzumab is far more effective than trastuzumab alone. These agents target different mechanisms of HER2 activation. Trastuzumab has at least 3 well-defined mechanisms of action. First, it is effective in preventing ligand-independent HER2 receptor activation. Second, it can stimulate an antibody-dependent cellular cytotoxicity response against the tumor. Third, internalization of the trastuzumab-HER2 complex causes downregulation of HER2 on the cell surface.

1.1

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.

Pertuzumab binds to a different HER2 epitope than trastuzumab. It binds to the HER2 dimerization domain and blocks HER2/HER3 heterodimerization. HER2/HER3 heterodimers are the most potent signaling duet in breast cancer. Studies have shown that blockade with both anti-HER2 antibodies in combination with chemotherapy is highly effective.

The Phase III CLEOPATRA trial, which studied the effect of adding pertuzumab to trastuzumab/docetaxel as first-line therapy for patients with HER2-positive metastatic breast cancer, was practice changing. It demonstrated a significant improvement not only in progression-free survival but also in overall survival (Swain 2013; [1.1]). The combination is extremely well tolerated. Minimal additional side effects arise from adding pertuzumab to trastuzumab, although side effects such as rash and diarrhea may be observed in some patients.

DR LOVE: What about the pertuzumab/trastuzumab regimen in the second-line setting and beyond?

DR BASELGA: A Phase II study of pertuzumab added to trastuzumab without chemotherapy for patients who were experiencing disease progression while receiving trastuzumab reported promising results. A clinical benefit rate of 50% and a response rate of 25% were observed (Baselga 2010). A cohort of patients who received pertuzumab alone experienced minimal response. Reintroduction of trastuzumab for patients who experienced disease progression while receiving pertuzumab resulted in a response rate of about 20% (Cortes 2012).

This clearly indicates that the combination of pertuzumab and trastuzumab is more active than monotherapy. One can hypothesize that dual HER2 blockade will be effective across the disease spectrum in the first line, second line and beyond.

DR LOVE: What chemotherapy do you believe should be administered in combination with pertuzumab and trastuzumab?

DR BASELGA: Currently we have data only with the combination of pertuzumab/trastuzumab and taxanes. At Memorial we use paclitaxel. However, I believe that other chemotherapies can also be effective in combination with the anti-HER2 antibodies. It would depend on the preference of the patient and physician.

DR LOVE: You are the chair of the Phase III APHINITY trial, which randomly assigns patients to chemotherapy and trastuzumab or chemotherapy and trastuzumab/pertuzumab in the adjuvant setting (1.2). Any comments on this critical trial?

1.2 **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, July 2013.

DR BASELGA: The study is enrolling patients quickly, but it will take a couple of years to obtain the data. The improvement in survival is so significant with trastuzumab/pertuzumab and chemotherapy in first-line metastatic disease that I believe it will be magnified in the adjuvant disease setting.

Tracks 7-9

DR LOVE: Do you believe we will be able to develop a tumor profile that would indicate which HER2-positive tumors are exquisitely sensitive to targeted therapies without chemotherapy?

DR BASELGA: I believe we will identify a patient population that does not need chemotherapy. We know from the NEOSPHERE data (Gianni 2012) and, most important, from a CLEOPATRA biomarker study that phosphatidylinositol 3-kinase (PI3K) is a major prognostic indicator of response to anti-HER2 therapies (Baselga 2012; [1.3]). PI3K is downstream of HER2, and if the gene is mutated the tumor is less sensitive to inhibition of HER2 upstream. Higher levels of HER2 and HER3 correlate with greater benefit. So I am optimistic that we will develop a signature of HER2 dependency.

DR LOVE: What role do you envision for PI3K inhibitors in the treatment of breast cancer?

DR BASELGA: PI3K is one of the next exciting targets in breast cancer. PI3K mutations are observed in approximately 25% of HER2-positive breast tumors and 40% of

1.3 **Biomarker Analysis in the CLEOPATRA Study: Shorter Median Progression-Free Survival and Maintained Treatment Effect with Mutated PIK3CA**

	Median progression-free survival (mo)		
PIK3CA status	**Ptz + T + D**	**Pla + T + D**	Hazard ratio
Mutated (n = 86, 90)	12.5	8.6	0.64
Wild type (n = 190, 191)	21.8	13.8	0.67
Overall (n = 402, 406)	18.5	12.4	0.62

Ptz = pertuzumab; T = trastuzumab; D = docetaxel; Pla = placebo

Baselga J et al. San Antonio Breast Cancer Symposium 2012;**Abstract S5-1**.

ER-positive, HER2-negative tumors. About 8% of patients with triple-negative cancer also have the mutation.

Targeting the PI3K pathway in breast cancer occurs in 3 ways. Agents that target mTOR, which is downstream of PI3K/AKT, comprise 1 class of PI3K inhibitors. The second class of compounds is the pan-PI3K inhibitors, which block all 4 subunits of the enzyme. BKM120 and GDC-0941 are agents in this class that are in clinical development. A third class of compounds, the PI3K-alpha inhibitors, inhibit only the alpha subunit that is mutated in breast cancer. In the Phase I setting we have reported a high response rate for patients with metastatic disease after therapy with PI3K-alpha inhibitors (Juric 2012). Response rates are 5 times higher than with mTOR inhibitors.

In the future we should be able to identify patients up front who harbor PI3K mutations and offer them therapy with PI3K-alpha inhibitors. These compounds are moving fast in clinical development, and Phase II and Phase III trials should start soon.

DR LOVE: Would you talk about your recent paper evaluating the combination of PI3K and PARP inhibitors in triple-negative breast cancer (Ibrahim 2012)?

DR BASELGA: In triple-negative breast cancer PI3K is required for DNA repair. We hypothesized that inhibiting PI3K would induce DNA damage. The study reported that when xenografts from patients with triple-negative breast cancer were exposed to PI3K inhibitors, a marked increase in DNA damage occurred. We found that PI3K inhibition resulted in a major decrease in the levels of BRCA1 and BRCA2, resembling BRCA1/2-deficient tumors.

This suggested that the combination of PI3K and PARP inhibitors would be effective. When we evaluated the combination in animal models, we found noticeable suppression of the growth of aggressive tumors. A Phase I trial combining the PARP inhibitor olaparib with the PI3K inhibitor BKM120 for patients with triple-negative breast cancer is ongoing, and the early data are promising (NCT01623349).

Tracks 10-11

DR LOVE: What are your thoughts on the recently approved agent ado-trastuzumab emtansine (T-DM1), and how do you see it being used in practice?

DR BASELGA: T-DM1 is trastuzumab that is linked to a derivative of maytansine, which is a potent antimetabolite. When the trastuzumab-maytansine complex selectively enters the tumor cell expressing HER2, the maytansine is released and kills that cell. So T-DM1 is appealing, and clinical data with it show impressive results (1.4). The Phase III EMILIA study comparing T-DM1 to the second-line combination of lapatinib and capecitabine demonstrated that T-DM1 was far superior with fewer side effects (Verma 2012).

The big question is, how will we treat HER2-positive breast cancer with all the options we have, namely trastuzumab, pertuzumab, T-DM1 and lapatinib? Although some physicians may consider using T-DM1 as first-line therapy, the data from the EMILIA study indicated that it was superior to approved therapy in the second-line setting.

In the first-line setting we have trastuzumab and pertuzumab with docetaxel. Although it may be true that this combination is more toxic than T-DM1, docetaxel is administered for a median of only 6 cycles. After that patients can receive pertuzumab/

trastuzumab for many months without any significant side effects. So currently I would administer pertuzumab with trastuzumab in the first-line setting, and I would wait until disease progression to use T-DM1.

DR LOVE: Would you comment on the Phase III MARIANNE trial, which is evaluating T-DM1 with or without pertuzumab versus trastuzumab and a taxane for patients with HER2-positive metastatic breast cancer?

DR BASELGA: This ongoing Phase III study is evaluating T-DM1 in the first-line setting for patients with HER2-positive metastatic breast cancer (1.2, page 5). The combination of T-DM1 with pertuzumab and without chemotherapy is exciting. This would offer the possibility of first-line treatment without chemotherapy for patients with metastatic HER2-positive disease. ■

1.4

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.

SELECT PUBLICATIONS

Baselga J et al. **Biomarker analyses in CLEOPATRA: A Phase III, placebo-controlled study of pertuzumab in HER2-positive, first-line metastatic breast cancer (MBC).** San Antonio Breast Cancer Symposium 2012;**Abstract S5-1**.

Baselga J et al. **Phase II trial of pertuzumab and trastuzumab in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer that progressed during prior trastuzumab therapy.** *J Clin Oncol* 2010;28(7):1138-44.

Cortes J et al. **Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: Activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer.** *J Clin Oncol* 2012;30(14):1594-600.

Gianni L et al. **Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial.** *Lancet Oncol* 2012;13(1):25-32.

Ibrahim YH et al. **PI3K inhibition impairs BRCA1/2 expression and sensitizes BRCA-proficient triple-negative breast cancer to PARP inhibition.** *Cancer Discov* 2012;2(11):1036-47.

Juric D et al. **Phase I study of BYL719, an alpha-specific PI3K inhibitor, in patients with PIK3CA mutant advanced solid tumors: Preliminary efficacy and safety in patients with PIK3CA mutant ER-positive (ER+) metastatic breast cancer (MBC).** San Antonio Breast Cancer Symposium 2012;**Abstract P6-10-07**.

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

Kathy S Albain, MD

Dr Albain is Professor of Medicine at Loyola University Chicago Stritch School of Medicine and Director of the Breast Clinical Research and Thoracic Oncology Programs at Cardinal Bernardin Cancer Center in Maywood, Illinois.

Tracks 1-8

Select Excerpts from the Interview

Tracks 1-2, 4

DR LOVE: Would you discuss the ongoing Phase III adjuvant RxPONDER trial?

DR ALBAIN: The RxPONDER trial is evaluating standard adjuvant endocrine therapy with or without chemotherapy for patients with hormone receptor-positive, HER2-negative breast cancer with an Onco*type* DX Recurrence Score (RS) of 25 or lower and with 1 to 3 positive nodes (2.1).

The RxPONDER trial was originally proposed to include patients with any number of positive nodes, but oncologists may be nervous about offering endocrine therapy only and no chemotherapy to a patient with 6 positive nodes and an RS of 2. In this scenario, the biology indicates that the disease will probably be chemotherapy insensitive, no matter how many nodes are positive. Perhaps clinical trials will show that endocrine therapy with everolimus and no chemotherapy is the correct treatment choice.

We are currently deliberating whether to amend the eligibility criteria for the RxPONDER trial now that it's accruing well by including patients with more than 3 positive nodes. These deliberations are under way, and we must wait for the outcome.

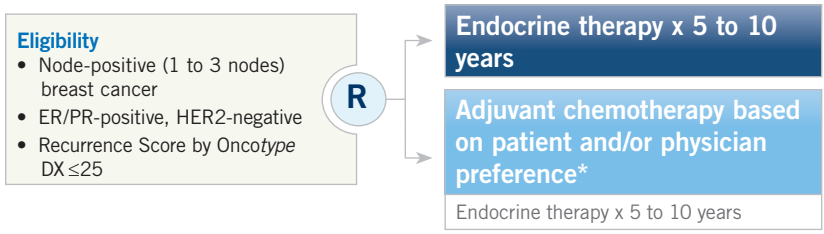
DR LOVE: Would you talk about the design and results of your analysis evaluating the association between metabolic syndrome and the risk of recurrence based on the

2.1

Phase III Randomized Clinical Trial of Adjuvant Endocrine Therapy with or without Chemotherapy in Node-Positive Breast Cancer

Protocol IDs: SWOG-S1007; RxPONDER

Target Accrual: 4,000



* Multiple agents that can be used in various combinations and different schedules, including doxorubicin, epirubicin, 5-FU, cyclophosphamide, paclitaxel, docetaxel and methotrexate

www.clinicaltrials.gov. Identifier NCT01272037, July 2013.

Oncotype DX assay RS for patients with newly diagnosed ER-positive, node-negative breast cancer (Lakhani 2012; [2.2])?

DR ALBAIN: We performed a chart review to determine the relationship between components of metabolic syndrome such as obesity and diabetes and the Oncotype DX RS. We found that although recurrence risk is low in the patient group with the luminal A subtype, a major independent predictor of risk level is the presence or absence of metabolic syndrome. Conducting more aggressive interventional studies may lead to a survival advantage for patients with such tumor characteristics.

We always discuss with patients the benefits of weight loss, diabetes control and exercise. However, a more intensive, prospectively designed approach for this patient population may be warranted. Although this was a small, hypothesis-generating, retro-

2.2

Retrospective Study of Metabolic Syndrome (MS) and Breast Cancer Recurrence within the Oncotype DX Assay Recurrence Score (RS) Risk Categories for Patients with ER-Positive, Lymph Node (LN)-Negative Breast Cancer Treated with Standard Adjuvant Therapy (N = 332)

Oncotype DX risk category	Odds ratio (presence versus absence of MS)	95% CI (odds ratio)
Low risk (RS 0-17)	23.649	2.818-198.435
Intermediate risk (RS 18-30)	3.950	0.984-15.852
High risk (RS 31-100)	0.813	0.063-10.478

Conclusions

- MS is an independent risk factor for breast cancer recurrence among women with low-risk, ER-positive, LN-negative breast cancer treated with standard adjuvant therapy.
- MS has an effect on recurrence for patients with a tumor biology defined by the Oncotype DX assay RS as low risk or, to a lesser extent, intermediate risk.
- No difference in recurrence risk is reported for patients who are at high risk of breast cancer recurrence according to the Oncotype DX assay RS.

Lakhani A et al. San Antonio Breast Cancer Symposium 2012;**Abstract PD10-02**.

spective study, the results are intriguing. We need to validate it with a larger sample size, after which we may be able to propose a new treatment approach.

DR LOVE: Would you comment on other genomic assays being investigated beyond the 21-gene RS?

DR ALBAIN: One is the BluePrint™ assay, which provides the intrinsic breast cancer subtype. Unlike the 21-gene RS, this approach has not been validated in a prospective Phase III trial.

The BluePrint is an 80-gene expression signature that classifies breast cancer into 3 categories: basal, luminal and HER2 types. For patients with breast cancer classified as luminal type with BluePrint, conducting the MammaPrint® assay to assess whether they are at low or high risk of recurrence provides deeper insight into whether they have luminal A- or B-type disease.

We also have the PAM50 assay, which is a paraffin block application of intrinsic molecular subtyping to classify recurrence risk. In the neoadjuvant setting studies indicated that patients at low recurrence risk by the PAM50 assay did not achieve pathologic complete responses (Gomez Pardo 2011). Although all these profiling assays are prognostic, it is uncertain whether they are equally predictive of benefit from chemotherapy.

DR LOVE: Over the 10 years since the Onco*type* DX assay was first developed, many studies have investigated these predictive signatures retrospectively rather than prospectively. What is your perspective on the future clinical approach to validating and expanding on the existing molecular profiling signatures?

DR ALBAIN: The only 2 studies with tamoxifen-only control arms that banked tissue samples were the NSABP-B-20 and SWOG-8814 trials. The newer TAILORx and RxPONDER trials have a rich bank of tumor specimens that will allow studies of the new generation of predictors, which will expand beyond 21 or 70 genes in the near future. We are proposing to conduct a next-generation sequencing analysis of the residual RNA samples from the SWOG-8814 trial. We have enough banked tissue to ask more questions, but we need to be careful about how we expend the remaining resources. ■

SELECT PUBLICATIONS

Albain KS et al. **Prognostic and predictive value of the 21-gene Recurrence Score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: A retrospective analysis of a randomised trial.** *Lancet Oncol* 2010;11(1):55-65.

Dowsett M et al. **Comparison of PAM50 risk of recurrence score with Onco*type* DX and IHC4 for predicting risk of distant recurrence after endocrine therapy.** *J Clin Oncol* 2013;[Epub ahead of print].

Gomez Pardo P et al. **PAM50 intrinsic subtyping and pathologic responses to neoadjuvant trastuzumab-based chemotherapy in HER2-positive breast cancer.** *Proc ASCO* 2011;**Abstract 554**.

Goncalves R, Bose R. **Using multigene tests to select treatment for early-stage breast cancer.** *J Natl Compr Canc Netw* 2013;11(2):174-82.

Lakhani A et al. **Metabolic syndrome and recurrence within the 21-gene Recurrence Score assay risk categories in lymph node negative breast cancer.** San Antonio Breast Cancer Symposium 2012;**Abstract PD10-02**.

Mamounas EP et al. **Association between the 21-gene Recurrence Score (RS) and benefit from adjuvant paclitaxel (Pac) in node-positive (N+), ER-positive breast cancer patients (pts): Results from NSABP B-28.** San Antonio Breast Cancer Symposium 2012;**Abstract S1-10**.

Ramsey SD et al. **Integrating comparative effectiveness design elements and endpoints into a phase III, randomized clinical trial (SWOG S1007) evaluating Onco*type* DX-guided management for women with breast cancer involving lymph nodes.** *Contemp Clin Trials* 2013;34(1):1-9.

INTERVIEW

Denise A Yardley, MD

Dr Yardley is Senior Investigator of Breast Cancer Research at Sarah Cannon Research Institute in Nashville, Tennessee.

Tracks 1-9

Track 1 Everolimus in combination with endocrine treatment for ER-positive mBC: Indications and toxicity management

Track 2 Management of everolimus-associated mucositis

Track 3 Results from a Phase III trial of eribulin versus capecitabine for patients with locally advanced or metastatic BC previously treated with anthracyclines and taxanes

Track 4 Sequencing eribulin and capecitabine in the treatment of mBC

Track 5 Interim safety results of a Phase II trial of eribulin and ramucirumab for mBC

Track 6 Accessing bevacizumab for patients with mBC via participation in early-phase clinical trials

Track 7 Sequencing systemic therapy for older, asymptomatic patients with HER2-positive mBC

Track 8 An ongoing Phase I trial of T-DM1 for patients with HER2-positive mBC and abnormal liver function

Track 9 Selection of patients with mBC for treatment with *nab* paclitaxel

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: Would you discuss your treatment algorithm for patients with ER-positive, HER2-negative metastatic breast cancer?

DR YARDLEY: This is a group of patients who were not embraced initially in many clinical trials or in the development of our understanding of the pathways in metastatic breast cancer. But now as molecular biologists have begun to unravel data with regard to endocrine resistance mediated by the estrogen receptor, we've witnessed the development of the BOLERO-2 trial evaluating the addition of everolimus to the aromatase inhibitor (AI) exemestane. And that approach is now an approved strategy for patients with metastatic breast cancer that has progressed on an AI (Baselga 2012; [3.1]).

I perform biopsies for these patients, not so much to establish disease recurrence but to develop a molecular profile. This initiative provides a wealth of information about the tumor. The probability is high for patients with metastatic ER-positive disease that they harbor PI3K mutations, and we prefer to place such patients on clinical trials if possible. For patients who are not trial candidates or who do not wish to enroll on trials, my preference is to administer everolimus and an AI. I don't typically administer the combination of an AI with fulvestrant.

DR LOVE: What are your experiences with managing everolimus-associated mucositis?

DR YARDLEY: We do not have a "one size fits all" answer because it seems that some patients are susceptible to this side effect and others "sail through" therapy. My approach is this: I meet with patients soon after everolimus therapy begins. The nurses and I inform patients that we want to know about the development of toxicities early on. If needed, I institute rapid dose reductions or even dose delays, let the patient recover and then perhaps drop the dose from 10 mg to 5 mg and work it back up. This is a valuable treatment if you can get the patient over the initial hurdles of some of the toxicities that are so different from those of hormonal therapy alone.

DR LOVE: What is the typical clinical evolution of this mucositis, and how does it compare to chemotherapy-related mucositis?

DR YARDLEY: Mucositis associated with chemotherapy is much more broad and encompassing of the entire mucosa of the oral cavity and can occur throughout the entire gastrointestinal tract. Everolimus-associated mucositis is distinct. The ulcers are discontinuous and have a shallower base, making them more amenable to topical approaches.

Patients can experience mucositis within the first 2 weeks to 28 days of beginning everolimus. Educating patients is key because we want them to realize that we do not have to discontinue this effective agent. We need their help to manage the side effect early on with a dose delay of everolimus while they continue to receive the AI and let the lesions heal. Then we can reinitiate everolimus therapy perhaps with a dose reduction.

3.1

BOLERO-2: A Phase III Trial of 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 or 4**	**All grades**	**Grade 3 or 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.

Tracks 3-5

DR LOVE: What are your thoughts on the results of the Phase III study comparing eribulin to capecitabine for locally advanced or metastatic breast cancer?

DR YARDLEY: This trial was performed in a much earlier clinical setting than that which led to the approval of eribulin. So it was designed to move eribulin up earlier in the metastatic setting and to ascertain whether it was superior to capecitabine. The trial population had a lot of heterogeneity. Patients with HER2-positive breast cancer were allowed on the trial, and as we now start going back and trying to ascertain where the signals were if that subgroup was removed, it is interesting that eribulin appears to have been more effective in patients with HER2-negative disease in addition to those with triple-negative breast cancer (Kaufman 2012; [3.2]).

So even though the trial didn't meet its primary objective, I believe it has a number of interesting facets that we're now trying to channel toward an understanding of a potential molecular target in certain patient subgroups.

DR LOVE: How do you integrate eribulin into your practice outside of a trial setting, and how do you sequence it in relation to capecitabine?

DR YARDLEY: Our practice has openly embraced eribulin since its approval, and I believe in trying to use it in several ways. I sequence it much earlier in my algorithm for patients with metastatic HER2-positive disease. Data on the combination of eribulin and trastuzumab for locally recurrent or metastatic HER2-positive breast cancer were presented by Dr Linda Vahdat at the 2012 San Antonio Breast Cancer Symposium (Vahdat 2012). I have administered this regimen, and it's a well-tolerated combination.

I also integrate eribulin much earlier for patients with HER2-normal disease. I've administered it as second-line therapy. We are awaiting data from a trial of eribulin with ramucirumab as second- or third-line therapy for metastatic breast cancer.

3.2

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

Median OS	Eribulin	Capecitabine	Hazard ratio	*p*-value
Overall (n = 554, 548)	15.9 mo	14.5 mo	0.879	0.056
HER2 status				
HER2-positive	14.3 mo	17.1 mo	0.965	NR
HER2-negative	15.9 mo	13.5 mo	0.838	NR
ER status				
ER-positive	18.2 mo	16.8 mo	0.897	NR
ER-negative	14.4 mo	10.5 mo	0.779	NR
Triple-negative				
Yes	14.4 mo	9.4 mo	0.702	NR
No	17.5 mo	16.6 mo	0.927	NR
Select adverse events	**Eribulin** (n = 544)		**Capecitabine** (n = 546)	
Grade	All	3 or 4	All	3 or 4
Neutropenia	54%	46%	16%	<5%
Leukopenia	31%	15%	10%	<3%

OS = overall survival; NR = not reported

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

Eribulin is also being evaluated in patients who have residual disease after neoadjuvant anthracycline- or taxane-based therapy (3.3).

DR LOVE: Ramucirumab is an novel anti-angiogenic agent with known activity in gastric cancer. Unlike bevacizumab, which binds the ligand, it binds the VEGF receptor. What do we know about this agent in breast cancer?

DR YARDLEY: I believe a particular group of patients clearly benefited from bevacizumab, so when we were approached with a potential trial including ramucirumab in the metastatic setting we were eager to embrace it. Ramucirumab seems to have a little less toxicity in terms of hypertension and some of the other cumbersome toxicities of bevacizumab. We've recently presented the interim safety results from a Phase II study of ramucirumab and eribulin for patients with metastatic disease. Ramucirumab combined well with eribulin, and we did not observe any added features of toxicity (Yardley 2012). ■

3.3

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

Trial identifier	N	Setting	Treatment arms
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
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

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

www.clinicaltrials.gov, July 2013.

SELECT PUBLICATIONS

Campone M et al. **Effect of visceral metastases on the efficacy and safety of everolimus in postmenopausal women with advanced breast cancer: Subgroup analysis from the BOLERO-2 study.** *Eur J Cancer* 2013;49(12):2621-32.

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**.

Vahdat L et al. **Eribulin mesylate + trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer: Results from a Phase 2, multicenter, single-arm study.** San Antonio Breast Cancer Symposium 2012;**Abstract P5-20-04**.

Yardley DA et al. **Interim safety results of eribulin (E) combined with ramucirumab (RAM) in patients (pts) with advanced metastatic breast cancer (MBC).** Breast Cancer Symposium 2012;**Abstract 110**.

INTERVIEW

Rowan T Chlebowski, MD, PhD

Dr Chlebowski is Professor of Medicine at David Geffen School of Medicine at UCLA and Chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center in Torrance, California.

Tracks 1-10

Select Excerpts from the Interview

Tracks 1, 3-4

DR LOVE: What are your thoughts on the results of the ATLAS trial evaluating 5 versus 10 years of adjuvant therapy with tamoxifen for women with early breast cancer?

DR CHLEBOWSKI: In this large trial of continuing adjuvant tamoxifen versus stopping it after 5 years, we observed little effect in years 5 to 10, during the extended tamoxifen administration period — the recurrence rate ratio was 0.90. In years 10 to 15, however, we observed an approximately 30% reduction in risk, resulting in a net statistically significant reduction in breast cancer incidence, breast cancer mortality and overall mortality (Davies 2013; [4.1, 4.2]). This is a spectacular result.

The activity in years 10 to 15 suggests to me that we're not killing cancer cells with hormonal therapy, we're simply controlling them. The disease might require long-term therapy. That's a challenging concept.

DR LOVE: What are the clinical implications of longer-duration adjuvant tamoxifen?

DR CHLEBOWSKI: Significantly fewer coronary heart disease events are reported and no increase in the incidence of strokes is observed, but clinicians should regard the

4.1

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(9869):805-16.

4.2

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(9869):805-16.

data cautiously. Patients who would have been sensitive and more disposed to developing these conditions perhaps would not come forward after 5 years of tamoxifen. In addition, the increased risk of mortality from endometrial cancer was only two tenths of a percent, and we noted a reduction of 3% in the risk of breast cancer mortality. So longer-duration tamoxifen came out ahead with nearly a 3% absolute benefit in terms of survival, which is surprising.

DR LOVE: How are you applying these data in your own practice, and are you administering adjuvant endocrine therapy beyond 10 years?

DR CHLEBOWSKI: We haven't used such an approach. I've been tracking the ATLAS trial for a number of years now, so I've been continuing aromatase inhibitors for at least a couple of years, and the decision of what to do after 7 years or so has not often come

up. But it is a puzzle what one should do if one is to stick strictly to guidelines. It will take years and years to obtain a definitive answer.

Track 5

DR LOVE: It's been 8 years since you presented the data at ASCO from the WINS study evaluating dietary fat and its relation to breast cancer progression in the adjuvant setting (Chlebowski 2006). Where are we today with this concept?

DR CHLEBOWSKI: The LISA (Lifestyle Intervention Study in Adjuvant treatment of early breast cancer) trial in Canada studied dietary fat intake, weight loss and physical activity. The investigators demonstrated the feasibility of successfully encouraging weight loss and increased physical activity with a central approach using telephone calls to patients, and I believe that's moving forward in the cooperative group setting. They hope to accrue about 2,000 patients (NCT00463489).

The ENERGY trial will enroll 800 patients with resected breast cancer, and this trial also will include centrally based intervention for weight loss and increased physical activity (NCT01112839). A similar trial in Germany, the SUCCESS-C trial, has already accrued about 1,000 patients, and DIANA-5 in Italy also targeted weight loss with a Mediterranean diet and physical activity among approximately 1,200 patients. So 2 trials are ongoing and have completed accrual, and 2 are planned studies.

Finally, a meta-analysis that included 107 studies demonstrated a reduction in the risk of recurrence with moderate physical activity — walking 3 to 4 hours a week (Hardefeldt 2012; [4.3]). I tell patients that they should do this. When you study overall patient populations, you see that 50% to 60% of women in the United States report that they are not engaging in any recreational physical activity. We should at least be able to get people to walk 3 or 4 hours a week. ■

4.3

Meta-Analysis of the Effect of Physical Activity and Weight Loss on the Risk of Breast Cancer in Pre- and Postmenopausal Women

Variable (107 studies)	Odds ratio
Physical activity	
Postmenopausal women	0.75
Premenopausal women	0.80
Low-intensity activity	0.82
High-intensity activity	0.78
Weight loss	0.81

Conclusion: "Physical activity and weight loss significantly reduce the risk of breast cancer in both pre- and postmenopausal women. However, the intensity and timing of the physical activity do not affect the protective effect."

Hardefeldt P et al. San Antonio Breast Cancer Symposium 2012;**Abstract P1-11-01**.

SELECT PUBLICATIONS

Chlebowski RT et al. **Dietary fat reduction and breast cancer outcome: Interim efficacy results from the Women's Intervention Nutrition Study.** *J Natl Cancer Inst* 2006;98(24):1767-76.

Cuzick J et al. **Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial.** *Lancet Oncol* 2010;11(12):1135-41.

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(9869):805-16.

Hardefeldt P et al. **Physical activity reduces the risk of breast cancer.** San Antonio Breast Cancer Symposium 2012;**Abstract P1-11-01**.

Van Horn L, Manson J. **The Women's Health Initiative: Implications for clinicians.** *Cleve Clin J Med* 2008;75(5):385-90.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **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. Overall survival
   b. Progression-free survival
   c. Both a and b
   d. None of the above

2. **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

3. **A biomarker analysis of patients in the CLEOPATRA study evaluating pertuzumab versus placebo in combination with trastuzumab and docetaxel reported that patients with HER2-positive metastatic breast cancer who had mutations in PI3KCA experienced a shorter progression-free survival irrespective of treatment.**
   a. True
   b. False

4. **The _____ assay is an 80-gene expression profiling signature that classifies breast cancer into 3 categories of basal-, luminal- and HER2-type breast cancer.**
   a. MammaPrint
   b. Onco*type* DX
   c. PAM50
   d. BluePrint

5. **A retrospective analysis by Lakhani and colleagues indicated that the presence or absence of metabolic syndrome has an effect on recurrence for patients with ER-positive, lymph node-negative breast cancer categorized as _____ by the Onco*type* DX assay RS.**
   a. Low risk
   b. High risk
   c. Both a and b
   d. None of the above

6. **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

7. **Which of the following toxicities was 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

8. **Results from a Phase III randomized study evaluating eribulin versus capecitabine indicated that eribulin was not superior to capecitabine in the overall population of patients with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes.**
   a. True
   b. False

9. **A meta-analysis of 107 studies by Hardefeldt and colleagues demonstrated that _____ significantly reduced the risk of breast cancer in pre- and postmenopausal women.**
   a. Physical activity
   b. Weight loss
   c. Both a and b
   d. None of the above

10. **The Phase III ATLAS trial of 5 versus 10 years of adjuvant tamoxifen therapy 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. Years 1 to 5
    b. Years 5 to 10
    c. Years 10 to 15

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Breast Cancer Update — Issue 2, 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
Tumor subsets and efficacy of eribulin versus capecitabine for patients with metastatic breast cancer previously treated with anthracyclines and taxanes	4 3 2 1	4 3 2 1
Management of mucositis in postmenopausal patients with ER-positive metastatic breast cancer receiving everolimus/exemestane	4 3 2 1	4 3 2 1
Metabolic syndrome and recurrence within the Onco*type* DX assay RS risk categories in node-negative breast cancer	4 3 2 1	4 3 2 1
Incidence of PI3K mutations in ER- and HER2-positive breast cancer	4 3 2 1	4 3 2 1
Ongoing studies of lifestyle factors and their relationship with breast cancer risk	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
- 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
- Evaluate recently presented data supporting the extended use of adjuvant tamoxifen beyond 5 years for patients with ER-positive early breast cancer and, when appropriate, integrate these findings into clinical practice. . . . . 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
- 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

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.....

Would you recommend this activity to a colleague?

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.....

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
José Baselga, MD, PhD	4 3 2 1	4 3 2 1
Kathy S Albain, MD	4 3 2 1	4 3 2 1
Denise A Yardley, MD	4 3 2 1	4 3 2 1
Rowan T Chlebowski, 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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